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ABSTRACT

Tumors represent a hostile environment for the effector cells of cancer immunosurveillance. Immunosuppressive receptors and soluble or membrane-bound ligands are abundantly exposed and released by malignant entities and their stromal accomplices. As a consequence, executioners of antitumor immunity inefficiently navigate across cancer tissues and fail to eliminate malignant targets. By inducing immunogenic cancer cell death, oncolytic viruses profoundly reshape the tumor microenvironment. They trigger the local spread of danger signals and tumor-associated (as well as viral) antigens, thus attracting antigen-presenting cells, promoting the activation and expansion of lymphocytic populations, facilitating their infiltration in the tumor bed, and reinvigorating cytotoxic immune activity. The present review recapitulates key chemokines, growth factors and other cytokines that orchestrate this ballet of antitumoral leukocytes upon oncolytic virotherapy.

1. Introduction

Emergence of a tumor mass succeeds upon the immunoselection of malignant cell clones that have acquired means of escaping from, or interfering with, cancer immunosurveillance. Immunoescape strategies employed by cancer cells involve defects in antigen expression and/or presentation (e.g. loss of β_2-microglobulin [B2M] or downregulation of class-I major histocompatibility complex [MHC-I], tapasin, or peptide transporters TAP-1 & 2), the local accumulation of metabolites impacting effector T cell activity (e.g. kynurenine, adenosine, lactate), a

Abbreviations: Ad, adenovirus; B2M, β_2-microglobulin; CAFs, Cancer-Associated Fibroblasts; CCL, C-C motif Chemokine Ligand; CTL, Cytotoxic T Lymphocyte; CXCL, C-X-C motif Chemokine Ligand; DAMPs, Damage-Associated Molecular Patterns; DC, Dendritic Cell; FGF, Fibroblast Growth Factor; FGFR, FGF Receptor; FLT3L, FMS-Like Tyrosine Kinase 3 Ligand; GM-CSF, Granulocyte-Macrophage Colony-Stimulating Factor; HSV, Herpes Simplex Virus; ICD, Immunogenic Cell Death; IFN, interferon; IFNAR, Interferon Alpha Receptor; IFNLR, IFN-lambda Receptor; IL, interleukin; IRF, Interferon Regulating Factor; ISG, Interferon-Stimulated Gene; ISGF3, Interferon Simulated Gene Factor 3; JAK1, Janus Activated Kinase 1; MAMPs, Microbe-Associated Molecular Patterns; MAPK, Mitogen Activated Protein Kinase; MDSCs, Myeloid-Derived Suppressor Cell; MHC, Major Histocompatibility Complex; mTOR, Mechanistic Target of Rapamycin; MV, Measles Virus; NDV, Newcastle Disease Virus; NF-κB, Nuclear Factor-Kappa B; NK, Natural Killer; OV, Oncolytic Virus; PD-L1, Programmed Cell Death Ligand 1; PGE2, Prostaglandin E2; PI3K, Phospho-Inositide 3-Kinase; RIG-I, Retinoic Acid-Inducible Gene I; STAT, Signal Transducer and Activation of Transcription; TAM, Tumor-Associated Macrophages; TAP, Transporter Associated with Antigen Processing; T_C1, Type-I cytotoxic T cell; TCR, T Cell Receptor; TGF-β, Transforming Growth Factor beta; T_H1, Type-I Helper T cell; TLR, Toll-Like Receptor; TNF, Tumor Necrosis Factor; TME, Tumor Microenvironment; TYK2, Tyrosine Kinase 2; Treg, Regulatory T cell; VEGF, Vascular Endothelial Growth Factor; VSV, Vesicular Stomatitis Virus; VV, Vaccinia Virus.

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disorganized accretion of extracellular matrix components (e.g. collagens, laminins, fibronectin) that impair immune cell intrusion and mobility in the tumor microenvironment [TME], the exposure of inhibitory immune checkpoints (e.g. programmed cell death 1 ligand 1 [PD-L1], galectin-9), the secretion of immunosuppressive cytokines (e.g. transforming growth factor beta [TGF-β], interleukin [IL]-10, prostaglandin E2 [PGE2]), and the recruitment of protumoral stromal cells through the production of a myriad of chemokines and growth factors (e.g. C-C motif chemokine ligand [CCL] 2, 5, 20 & 22; C-X-C motif chemokine ligand [CXCL] 5, 8 & 12; colony stimulating factor [CSF]-1 & 2; vascular endothelial growth factor [VEGF]; platelet-derived growth factor [PDGF]; TGF-β) [1–13]. These stromal entities include cancer-associated fibroblasts [CAFs] together with myeloid and lymphoid actors, mainly myeloid-derived suppressor cells [MDSCs], "alternatively activated" type-2 tumor-associated macrophages and neutrophils [M2 TAMs and N2 TANs, respectively], as well as regulatory T and B cells [Tregs and Bregs, respectively]. Each of them actively participates in shielding cancer cells from antitumor immunity by supplying immunosuppressive factors [6–8,11,12,14].

Immunotherapies aim at reinstating cancer immunosurveillance by stimulating or supplying tumor-targeting immune effector cells and/or blocking or depleting immunoinhibitory signals and entities. In this line, oncolytic viruses [OVs] preferentially infect malignant cells and trigger immunogenic cell death [ICD], thus igniting an adaptive antitumor response [15–19]. Molecular hallmarks of ICD associated with OV therapy have been poorly investigated to date. Damage-associated molecular patterns [DAMPs] commonly attributed to the ICD phenomenon have been reported together with infection by oncolytic strains of type-1 herpes simplex virus [HSV-1] (e.g. T-VEC, KM100), adenovirus (e.g. Ad5, Ad dl922-947), paramyxovirus (e.g. measle virus [MV], Newcastle disease virus [NDV]), poxvirus (e.g. vaccinia virus [VV]) or togavirus (e.g. Semliki forest virus 4). Among these DAMPs figure calreticulin, a chaperone of the endoplasmic reticulum [ER] which is exposed on the outer layer of the plasma membrane upon ICD. Additionally, ATP, high mobility group box 1 [HMGB1] and some heat shock proteins (e.g. HSP27, 70 & 90) can be freed into the extracellular milieu upon OV therapy [20–37]. Besides the abovementioned DAMPs, microbe-associated molecular patterns [MAMPs] (i.e. viral nucleic acids) provide adjuvant signals and hence contribute to activate immune sentinels like dendritic cells [DCs].

In parallel, OV-induced ICD promotes the spread of tumor-associated antigens. These latter can be ingested by antigen-capturing cells such as immature DCs through pinocytosis, endocytosis, phagocytosis or trogocytosis [38]. In the particular case of OV therapy, the pool of tumor-specific antigens also includes viral proteins whose potent immunogenicity may participate in reversing immune tolerance towards malignant cells [39].

Ultimately, viral MAMPs and host cell-derived DAMPs attract and activate DCs (Clec9A$^+$ conventional, plasmacytoid, myeloid-derived subsets) that undergo maturation along their way to secondary or tertiary lymphoid structures in draining lymph nodes or within the tumor, respectively [40–42]. On site, they will cross-present engulfed tumor and viral antigens to CD8$^+$ T cells, thus priming systemic antitumor and antiviral adaptive responses that target not only infected but also uninfected cancer cells at both primary and metastatic sites [43–46]. Moreover, the establishment of an immune memory compartment may confer protection against disease recurrence [15].

Oncolytic viral agents can promote early targeting of infected malignant cells by innate immune effector cells. In this sense, some oncolytic herpesvirus, reovirus, rhabdovirus and parvovirus have demonstrated an exquisite ability to recruit natural killer [NK] cells. In return, these latter not only mediate cancer cell killing but also support the polarization of TAMs towards an antitumoral "M1" (rather than "M2" protumoral) inflammatory phenotype, as well as the maturation of DCs [47–50].

Altogether, treatment with OVs can dismantle the immunosuppressive network of the TME and restore intrusion and effector functions of cancer-targeting lymphocytes [39,51–54]. The coordination, expansion and activity of the leukocytes involved in the OV-triggered cancer-immunity cycle are regulated by chemokines, growth factors and other cytokines like interferons (IFNs) and interleukins that will be discussed in the present article.

2. Chemokines

Chemokines are small secreted chemotactic cytokines that are best known for their roles in mediating the migration of immune cells between tissues and the positioning and interaction of cells within various tissues. Chemokines influence the host-response to cancer by directing the trafficking of leukocytes into tumor lesions, development of lymphoid tissues and maturation of immune cells. Beyond their direct immune function, chemokines can also modulate tumor progression, metastasis and angiogenesis. Chemokines typically bind to transmembrane spanning G protein-coupled chemokine receptors to trigger intracellular signaling pathways that drive cell polarization, adhesion and migration. Chemokines are divided into four subfamilies based on the position of the first two N-terminal cysteine residues. These include the CC, CXC, CX3C, and XC subfamilies [55]. The chemokine receptors follow a similar nomenclature system, based upon the family of chemokines to which they bind. In the human system, approximately 50 genes coding for chemokines and 20 genes coding for chemokine signaling receptors have been described. In the TME, chemokines are expressed by tumor, immune and non-immune stromal cells. Chemokines play both antitumor and protumor immune-mediated effects. In this review, we focus on OV-induced chemokines participating in the antineoplastic immune response.

2.1. CXCL9, CXCL10, and CXCL11

Adaptive anticancer immunity results from the concerted interaction of antigen-presenting DCs, IFN-γ-expressing CD4$^+$ T$_H$1 cells, CD8$^+$ effector T cells and NK cells within lymphoid organs and the TME. Thus, a constellation of chemokines that facilitate the migration and interaction of these cell types are essential for potent anticancer immunity. Overall, CXCL8 (best known as IL-8), CXCL9, 10, 11 & 14 play key roles in antitumor immunity [11]. CXCL9-11 are mainly produced by cancer cells and stromal immune (e.g. monocytes) and non-immune cells (e.g. fibroblasts, endothelial cells) in the presence of interferons. CXCL9 expression is upregulated by IFN-γ whereas CXCL10 & 11 secretion is stimulated by both IFN-γ and type-I IFNs [56]. Effector CD8$^+$ T cells, T$_H$1 cells and NK cells express CXC-chemokine receptor 3 [CXCR3], the common receptor for the type-1 chemokines CXCL9, CXCL10, CXCL11 [57], and can migrate into tumors in response to these chemokines. Tumors with higher levels of CXCL9, CXCL10 and CXCL11 display increased infiltration by T lymphocytes and prolonged survival. Multiple strains of OVs such as vesicular stomatitis virus [VSV] [58], Maraba virus MG1 [59], HSV-2 [60], Reolysin [61] or chikungunya virus [62] have been reported to drive high expression of these chemokines in infected tumors (Fig. 1). In this line, intratumoral administration of oncolytic HSV-2 is associated with high expression of CXCL9 and CXCL10, and promotes attraction of adoptively transferred T cells into treated lesions [60]. In contrast, despite a remarkable increase of the tumor-to-blood CXCL9 gradient, an oncolytic VSV engineered to express CXCL9 did not further stimulated the recruitment of endogenous or adoptively transferred T cells into the tumor. As a consequence, VSV-mCXCL9 did not show enhanced anticancer activity in comparison to the GFP-expressing control virus [58]. Conversely, intratumoral delivery of CXCL11-expressing VV augmented the *in situ* levels of CXCL11, stimulated the trafficking of adoptively transferred T cells to the malignant tissue, and prolonged survival of tumor-bearing mice [63–66] (Table 1). PsiOxus Therapeutics Ltd is sponsoring a first-in-human clinical trial of NG-641, an oncolytic adenovirus [oAd] that expresses

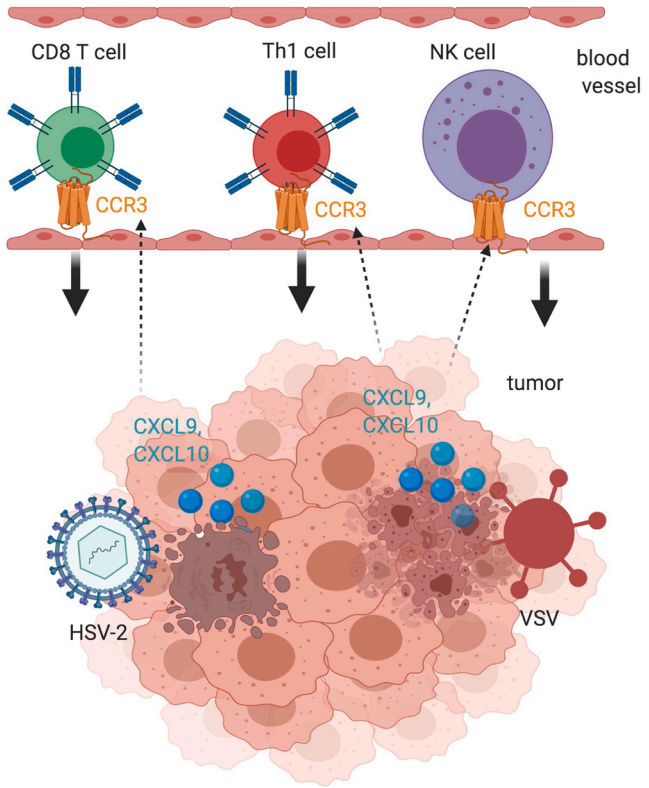

Fig. 1. Promotion of tumor immunity by chemokines upon oncolytic virotherapy. Immune cells with antitumor function ($CD4^+$ T_H1, $CD8^+$ T lymphocytes and NK cells) require chemokines to exit the blood stream and enter the tumor. Oncolytic viruses promote the release of chemokines such as CXCL9, CXCL10 and CXCL11 that all bind to CCR3 receptors on immune cells, thereby promoting their chemotaxis into the tumor. CXCL, C-X-C motif chemokine ligand; NK, natural killer; T_H, T helper.

FAP-Tac, a bi-specific T cell activator, together with an immune enhancer module expressing CXCL9, CXCL10 and IFN-α [67]. The Phase 1 trial initiated in 2020 will evaluate the safety and tolerability of NG-641 in patients with metastatic or advanced epithelial tumors (ClinicalTrials.gov Identifier: NCT04053283) (Table 2).

2.2. CCL5

CCL5 (also known as RANTES) is a chemokine that can bind to the receptors CCR1, CCR3, and CCR5 expressed on several types of effector and regulatory T cells. CCL5 is naturally secreted by antigen-presenting cells and activated T lymphocytes. OV infection has been reported to promote CCL5 production in the TME [59]. For instance, infection of human breast cancer cell lines and patient-derived xenograft models with the oncolytic rhabdovirus Maraba MG1 resulted in the retinoic acid-inducible gene I [RIG-I] and MyD88-dependent induction of *CCL5* mRNA [59]. Reovirus-infected human melanoma cells secreted CCL5, as well as two additional chemokines, CCL3 and CCL4 (also known as MIP-1α and MIP-1β, respectively) [68,69]. Furthermore, direct exposure of murine dendritic cells to reovirus resulted in the secretion of several proinflammatory cytokines, including CCL2, CCL3, CCL12 and CXCL16 [70]. Along this line, increased anticancer efficacy has been documented following treatment with CCL5-armed OVs [71–74] (Table 1). A double-deleted VV [vvDD] expressing CCL5 induced accumulation of NK cells within tumor lesions [71] as well as increased infiltration by T cells with an apparent T_H1 skewing [73]. Interestingly, vvDD-CCL5 also seemed to promote T_H2 immune responses, as illustrated by the local elevation of IL-4 and IL-5 [73]. In combination with a DC-based vaccine, the properties of vvDD-CCL5 translated into a better control of colorectal

Table 1
Cytokine-armed oncolytic viruses that demonstrated therapeutic efficacy in preclinical syngeneic tumor models.

Cytokine	OV backbone	Cancer	Reference
CCL2	HSV	Neuroblastoma	[369]
CCL5	Ad	Lymphoma, mammary tumors	[74]
	VV	CRC	[73]
CCL19	VV	CRC	[370]
CXCL11	VV	CRC, lung cancer, mesothelioma	[63,64,66]
FGF2	Maraba virus	Pancreatic cancer	[245]
FLT3L	Ad	Glioma, lung cancer, mammary tumors	[323,326,327]
	HSV	Glioma	[324]
	VSV	Lymphoma, melanoma	[329]
	VV	Melanoma	[330,331]
GM-CSF	Ad	CRC, glioma, lung cancer, melanoma, pancreatic cancer	[160,300,304,305,306,371,372]
	HSV	Lymphoma, melanoma	[26,281]
	MV	CRC	[314]
	NDV	CRC	[115]
	VSV	CRC, mammary tumor, melanoma	[298,299]
	VV	CRC, glioma, HCC, kidney cancer, mammary tumor, melanoma, pancreatic neuroendocrine cancer, SCC	[286,287,289,290,291,295,296,300]
	Reovirus	Glioma, melanoma, pancreatic cancer	[283,284,297]
IFN-α/β	Ad	Pancreatic cancer	[92]
	VSV	Lung cancer, mesothelioma	[93,97]
	VV	Mammary tumor	[91]
IFN-γ	NDV	CRC	[115]
	VSV	Mammary tumor	[111]
IL-2	Ad	Melanoma, pancreatic cancer	[54,105,129,364]
	HSV	SCC	[133]
	NDV	CRC, HCC, melanoma	[112,115,131]
	VV	CRC	[130]
IL-7	VV	CRC, lung cancer, melanoma, prostate cancer	[146]
IL-12	Ad	Pancreatic cancer, prostate adenocarcinoma, mammary tumor, melanoma	[142,144,145,153,156,160,161,162,236,371,373]
	HSV	B cell lymphoma, CRC, gastric carcinoma, glioblastoma, lung carcinoma, mammary cancer, melanoma, neuroblastoma, prostate cancer, SCC	[109,143,148,150,159,164,165,166,167,168,369,374,375,376]
	Maraba virus	CRC, melanoma	[152]
	MV	CRC, melanoma	[149,151]
	NDV	HCC	[112]
	VSV	SCC	[163]
	VV	CRC, lung cancer, melanoma, prostate cancer	[141,146]
IL-15	Influenza virus	Melanoma	[181]
	MV	CRC, melanoma	[149]
	VSV	CRC	[183]
	VV	CRC, ovarian cancer	[184]
IL-18	Ad	Melanoma	[144]
	HSV	Neuroblastoma, prostate cancer	[166,228]
IL-23	Ad	Melanoma	[355]
IL-24	VV	CRC, mammary tumor, melanoma	[291]
TNF-α	Ad	Melanoma, ovarian cancer, pancreatic cancer,	[45,54,129,362,364,365,366,367,368]
	HSV	Sarcoma	[363]
	NDV	CRC	[115]
	VSV	Mammary tumor, glioblastoma	[361]

Abbreviations Ad, adenovirus; CRC, colorectal carcinoma; FLT3L, Fms-related tyrosine kinase 3 ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HNC, head and neck cancers; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; MV, measle virus; SCC, squamous cell carcinoma; VSV, vesicular stomatitis virus; VV, vaccinia virus.

Table 2
Ongoing clinical trials with cytokine-armed oncolytic viruses.

Oncolytic virus				Clinical trial				
Family	Name (institution)	Description	Delivery route	Cancer	Co-therapy	Phase	Status	Reference
Adenovirus	CAdVEC (Baylor College of Medicine)	Combination of Onc.Ad5/3D24 + HDAdIL12_PDL1. Transgenes: • **IL-12** • Anti-PD-L1	i.t.	• Bladder cancer • HNC • Cancer of the Salivary Gland • Lung cancer • Breast cancer • Gastric cancer • Esophageal cancer • CRC • Pancreatic cancer • Other solid tumors	• HER2-specific CAR T cells	1	Not yet recruiting	NCT03740256 [377]
	NG-641 (PsiOxus Therapeutics)	Variant of the Ad11p/Ad3 enadenotucirev (EnAd) Deletions: • E3 • E4 Transgenes: • **CXCL9** • **CXCL10** • **IFNα** • FAP-TAc	i.t. i.v.	• Epithelial tumors	• Chemotherapy • Immune checkpoint inhibitors	1a/ 1b	Recruiting	NCT04053283 [67]
	ONCOS-102 (Targovax Oy)	Ad5/3-Δ24-GM-CSF Transgene: • **GM-CSF**	i.t.	• Melanoma	• Pembrolizumab • Cyclophosphamide	1	Active, not recruiting	NCT03003676
	TILT-123 (TILT Biotherapeutics)	Ad5/3-E2F-d24-hTNFa-IRES-hIL2 Mutations: • Insertion of E2F promoter in front of E1AΔ24. Transgenes: • **TNF-a** • **IL-2**	i.t. (?)	• Melanoma	• TILs	1	Recruiting	NCT04217473
Herpesvirus	M032 (Catherex)	HSV-1 (F strain) Deletion: • ICP34.5 Transgene: • **IL-12**	i.t.	• Glioma	–	1	Recruiting	NCT02062827 [154]
	ONCR-177 (Oncorus)	HSV-1 (ONCR-159-based vector) Deletions: • 1 out of the 2 copies of ICP34.5 • Joint (i.e. internal repeats IR_L & IR_S) Other mutations in: • UL37 • ICP47 miRT for: • miR-1 • miR-122 • miR-124 • miR-126 • miR-128 • miR-137 • miR-143 • miR-204	i.t.	• Skin cancers • HNC • Breast cancer • Other solid tumors	• Pembrolizumab	1	Recruiting	NCT04348916

(*continued on next page*)

Table 2 (*continued*)

Oncolytic virus				Clinical trial				
Family	Name (institution)	Description	Delivery route	Cancer	Co-therapy	Phase	Status	Reference
		• miR-217 • miR-219 Transgenes: • **IL-12** • **CCL4** • **FLT3L** • Anti-PD-1 • Anti-CTLA-4						
	OrienX010 (Oriengene Biotechnology)	HSV-1 (CL1 strain) Deletions: • ICP34.5 • ICP47 • ICP6 Transgene: • **GM-CSF**	i.t.	• Melanoma	Treprizumab (anti-PD-1) Surgery	1	Recruiting	NCT04197882
			i.t.	• Melanoma	• Dacarbazine	2	Recruiting	NCT04200040
			i.t.	• Melanoma	• JS001 (anti-PD-1)	1b	Recruiting	NCT04206358
	RP1 (Replimmune)	HSV-1 (proprietary strain) Deletions: • ICP34.5 • ICP47 Transgenes: • **GM-CSF** • GALV-GP-R^{-}	i.t.	• Skin cancers • Bladder cancer • Other solid tumors	• Nivolumab	1/2	Recruiting	NCT03767348
			i.t.	• SCC	• Cemiplimab	2	Recruiting	NCT04050436
			i.t.	• SCC	–	1b	Recruiting	NCT04349436
	T3011 (ImmVira Pharma)	HSV-1 (F strain) Deletion: • 15 kbp in the inverted repeat sequences Transgenes: • **IL-12** • Anti-PD-1	i.t.	• HNC • Sarcoma • Skin cancers • Lung cancer	–	1	Recruiting	NCT04370587
	T-VEC (Amgen)	HSV-1 (JS1 strain) Deletions: • ICP34.5 • ICP47 Transgenes: • **GM-CSF**	i.p.	• Gastrointestinal tumor • Ovarian tumors	–	1	Recruiting	NCT03663712
			i.t.	• Liver cancer	• Pembrolizumab	1	Recruiting	NCT02509507
			i.t.	• Breast cancer	–	2	Active, not recruiting	NCT02658812
			i.t.	• Breast cancer	• Paclitaxel	1/2	Active, not recruiting	NCT02779855
			i.t.	• Skin cancers • Other solid tumors	• Radiotherapy	2	Recruiting	NCT02819843
			i.t.	• Melanoma • Lymphomas	• Pembrolizumab	2	Recruiting	NCT02965716
			i.t.	• Non-melanoma skin cancers	• Nivolumab	2	Recruiting	NCT02978625
			i.t.	• Non-melanoma skin cancers	–	1	Recruiting	NCT03458117
			i.t.	• Kaposi sarcoma	–	2	Not yet recruiting	NCT04065152
			i.t.	• SCC	• Pembrolizumab	1	Recruiting	NCT04163952
			i.t.	• Breast cancer	• Ipilimumab • Nivolumab	1	Recruiting	NCT04185311
			i.t.	• Melanoma	• Surgery	2	Recruiting	NCT04427306
	OH2 (Wuhan Binhui Biotechnolog)	HSV-2 (HG52 strain) Deletions: • ICP34.5 • ICP47	i.t.	• GI cancers • HNC • Sarcomas	• HX008 (anti-PD-1) • Irinotecan	1/2	Recruiting	NCT03866525 [378]

(*continued on next page*)

Table 2 (*continued*)

Oncolytic virus				Clinical trial				
Family	Name (institution)	Description	Delivery route	Cancer	Co-therapy	Phase	Status	Reference
Paramyxovirus	MEDI5395 (MedImmune LLC)	Transgene: • **GM-CSF**	i.t.	• Melanoma • GI cancers • Liver cancer • Cervical cancer • HNC	• Pembrolizumab (anti-PD-1)	1/2	Recruiting	NCT04386967 [378]
		NDV (strain 73T-R-198) Transgene: • **GM-CSF**	i.v.	• Breast cancer • CRC • Liver cancer • HNC • Renal cancer • NSCLC • Melanoma	• Durvalumab	1	Recruiting	NCT03889275 [379]
Poxvirus	ASP9801 (Astellas Pharma)	VV (unknown strain) Transgenes: • **IL-7** • **IL-12**	i.t.	• Skin cancers • Visceral tumors	–	1	Recruiting	NCT03954067
	Pexa-Vec / JX-594/ TG6006 (SillaJen; Transgene)	VV (Wyeth strain) Deletion: • TK Transgenes: • **GM-CSF** • LacZ	i.t.	• Solid tumors	• Ipilimumab • Tremelimumab	1	Recruiting	NCT02977156
			i.t.	• Liver cancer	• Sorafenib	3	Active, not recruiting	NCT02562755
			i.t. i.v.	• Renal cancer	• REGN2810 (anti-PD-1)	1b	Recruiting	NCT03294083
			i.v.	• CRC	• Durvalumab • Tremelimumab	1/2	Recruiting	NCT03206073
	TBio-6517 (Turnstone Biologics)	VV (proprietary strain) Transgenes: • **FLT3L** • **IL-12** • Anti-CTLA-4	i.t.	• TNBC • MSS-CRC • Other solid tumors	• Pembrolizumab	1/2	Recruiting	NCT04301011
Rhabdovirus	VSV-hIFN-β (Mayo Clinic)	VSV (Indiana strain) Transgene: • **IFN-β**	i.t.	• Liver cancer • Skin cancers • Other solid tumors	–	1	Active, not recruiting	NCT01628640 [93]
			i.t. i.v.	• CRC • Pheochromocytoma • Neuroendocrine cancers	• Avelumab	1	Recruiting	NCT02923466 [93]
			i.v.	• HNC • NSCLC • Other solid tumors	• Pembrolizumab	1	Recruiting	NCT03647163 [93]
	VSV-hIFN-β-TYRP1 (Mayo Clinic)	VSV (Indiana strain) Transgenes: • **IFN-β** • TYRP1	i.v. i.m.	• Melanoma	–	1	Recruiting	NCT03865212
	VSV-hIFN-β-NIS (Mayo Clinic)	VSV (Indiana strain) Transgenes: • **IFN-β** • NIS	i.v.	• Multiple myeloma • Acute myeloid leukemia • T-cell lymphoma	–	1	Recruiting	NCT03017820

Abbreviations: CCL4, chemokine (C-C motif) ligand 4; CRC, colorectal cancer; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL9/10, chemokine (C-X-C motif) ligand 1; FAP-TAc, fibroblast activation protein-targeting bispecific T-cell activator; FLT3L, Fms-related tyrosine kinase 3 ligand; GALV-GP-R^{-}, truncated fusogenic form of the glycoprotein of gibbon ape leukemia virus; GM-CSF, granulocyte-macrophage colony-stimulating factor; HNC, head and neck cancers; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; i.p., intraperitoneal; i.t., intratumoral; i.v., intravenous; LacZ, gene encoding the β-galactosidase; miRT, microRNA target sequences; MSS, microsatellite stable; NDV, Newcastle disease virus; NIS, sodium iodide symporter; NSCLC, non-small-cell lung cancer; PD-1, programmed cell death 1; SCC, squamous cell carcinoma; TK, thymidine kinase; TNBC, triple negative breast cancer; TYRP1, tyrosinase related protein 1; VSV, vesicular stomatitis virus; VV, vaccinia virus.

tumors. As another example, the oncolytic Ad-RANTES-E1A allowed overexpression of CCL5 in infected tumors and resulted in complete regression of mammary carcinomas and lymphomas. This effect resulted from the massive expansion of activated DCs in the TME, the local and systemic release of the type 1 cytokines IL-12 and IFN-γ, a well as the infiltration of tumor antigen-specific cytotoxic $CD8^+$ T lymphocytes [CTLs] [74].

2.3. CCL20 and CXCL12

T_H17 cells can exert antitumor activity by facilitating the recruitment of $CD8^+$ T cells, NK cells and DCs into the TME. T_H17 cells strongly express CXCR4 and CCR6, two receptors associated with their migration and retention inside the tumor bed. In this line, elevated levels of their respective ligands, CXCL12 and CCL20, facilitate trafficking of T_H17 cells into the tumor. An oncolytic adenovirus co-expressing CCL20 and CD40 ligand (Ad-CCL20-CD40L) [75] exhibited enhanced direct oncolytic activity in vitro and stimulated $CD8^+$ T cell-mediated cancer cell elimination ex vivo. A combination of cytokine-induced killer (CIK) cells and an engineered oAd co-expressing CCL20 and IL-15 (CRAd-C-CL20-IL15) mediated improved antitumor effects against human colon tumor xenografts in mice, as compared to either treatment alone [76]. CXCR4 and its corresponding ligand CXCL12 form a pivotal axis for metastasis of solid tumors such as breast cancer. Overexpression of CXCR4 in breast tumors is related to an aggressive phenotype and to dissemination. Oncolytic VV that expresses the N-terminal region of CXCL12 (CTCE-9908) fused to the murine fragment of IgG (VV-CXCR4-A-mFc), is capable of disrupting the CXCL12/CXCR4 signaling axis, leading to the destruction of intratumoral microvessels, reduction of MDSCs, as well as improved overall survival of tumor-bearing mice [77].

3. Interferons

3.1. Type-I IFNs

In humans, type-I IFNs consist of 13 distinct subtypes of IFN-α (14 in mice) and one IFN-β, as well as the less investigated IFN-ε, κ, and ω (plus IFN-ζ in mice). Type-I IFNs can be synthesized by virtually any nucleated cell upon detection of DAMPs/MAMPs by pattern-recognition receptors [PRRs], with plasmacytoid DCs being the strongest producers [78,79]. Numerous PRRs can sense viral nucleic acids (e.g. cytosolic DNA and double-stranded RNA) such as the cytosolic cyclic GMP–AMP synthase [cGAS], protein kinase R [PKR], retinoic acid-inducible gene I [RIG-I], melanoma differentiation-associated gene 5 [MDA5], or the membrane-bound Toll-like receptors [TLRs] 2, 3, 7, 8 & 9. Activation of these PRRs leads to the phosphorylation of the interferon regulating factors [IRFs] 3 & 7, which in turn trigger transcription of type-I IFN-encoding genes. Once secreted, type-I IFNs bind in an autocrine or paracrine fashion to the ubiquitous interferon alpha receptor [IFNAR], which consists of a heterodimer of IFNAR1 & 2 proteins [80]. These two subunits respectively interact with the cytoplasmic adapters tyrosine kinase 2 [TYK2] and Janus activated kinase 1 [JAK1], the activation of which promotes homo-/hetero-dimerization of signal transducer and activation of transcription [STAT] factors (i.e. STAT1, 2, 3, 4, 5A, 5B & 6). STATs regulate the expression of >300 interferon-stimulated genes [ISGs] [80]. In particular, IFNAR stimulation triggers the association of STAT1 with STAT2, and their subsequent assembly with IRF9. This trimeric complex, known as ISGF3, regulates the expression of ISGs following recognition of cis-regulatory IFN-stimulated response elements [ISREs]. Among the target genes figure some antiviral molecules (e.g. ISG15, MX dynamin-like GTPase 1 [Mx1], 2′-5′-oligoadenylate synthetase [OAS]) and regulatory proteins responsible for positive or negative feedback of the IFN response: virus sensors (e.g. TLR3, RIG-I, MDA5, PKR), components of the interferon signaling cascade (e.g. IFNs, STATs, IRFs), or factors preventing their interaction or precipitating their degradation (e.g. suppressor of cytokine signaling [SOCS] proteins, ubiquitin specific peptidase 18 [USP18]) [81]. Non-STAT proteins can also be activated by TYK2 and/or JAK1 such as CRK-like proto-oncogene adaptor protein [CRKL] and the downstream Rap guanine nucleotide exchange factor 1 [RAPGEF1] and Ras-related protein Rap-1A [RAP1]. IFNAR adapters also phosphorylate the insulin receptor substrates [IRS]-1 & 2 and Vav guanine nucleotide exchange factor 1 [VAV1], thus transducing signal to the phosphoinositide 3-kinase [PI3K], AKT, mechanistic target of rapamycin [mTOR], nuclear factor-kappa B [NF-κB] and mitogen-activated protein kinases [MAPK] pathways [80]. Overall, depending on the abundance of IFNARs, the quality and quantity of its ligands, and the nature of the cell host, the signaling cascades stimulated by type-I IFNs control many different biological processes including cell proliferation, survival, differentiation, migration, as well as innate and adaptive immune effector functions [80].

In addition to mediating resistance to viral infection in normal cells, type-I IFNs also exert antineoplastic activity through cancer cell-intrinsic and extrinsic effects. On one hand, they can inhibit cell cycle progression (e.g. due to increased levels of the cyclin-dependent kinase inhibitors CDKN1B/p27 and CDKN2B/p15, downregulation of MYC), promote apoptosis (due to the expression of FAS, Fas ligand [FASL]), and enhance tumor antigenicity (due to the overexpression of tumor-associated antigens, HLA, B2M and TAP1/2) [80–83]. On the other hand, type-I IFNs inhibit angiogenesis (e.g. due to the downregulation of VEGF) and support cancer immunosurveillance [82,83]. In this sense, type-I IFNs induce the recruitment of $Ly6C^{hi}$ inflammatory monocytes and their differentiation into macrophages or DCs. They also support DC migration, DC maturation, and DC-mediated cross-priming of T cells. Additionally, their presence promotes the secretion of a broad range of proinflammatory cytokines by macrophages such as tumor necrosis factors [TNF], IL-1, 6, 8, 12 & 18, and is required to enhance their phagocytic activity and oxidative burst. Moreover, type-I IFNs control T cell memory differentiation, together with the recruitment, expansion and effector function of the type-I helper (T_H1) and cytotoxic (T_C1/CTL) T cell subsets. Furthermore, type-I IFNs contribute to recruiting and expanding NK cells and enhancing their tumoricidal activity. At last, they prevent the proliferation and immunosuppressive function of Tregs and MDSCs [80,82,83].

Because of these pressuring antineoplastic activities, emerging malignant cell clones tend to accumulate defects in type-I IFN signaling that may have genetic or epigenetic origins [84]. However, defective type-I IFN signaling can be taken advantage of to facilitate the oncoselective replication of numerous OVs that show exquisite, inherent or acquired, sensitivity to type-I IFNs such as the rhabdoviruses VSV and Maraba, NDV, reovirus, the B18R-deleted VV, or the clinically approved ICP34.5-deleted HSV-1 T-VEC [85–91]. Nevertheless, OV infection remains a potent inducer of type-I IFNs within the TME following sensing of virus intrusion by some transformed cell clones and/or normal stromal cells. Intuitively, their production could be seen as a brake to optimal efficacy of OV therapy as it limits the persistence and spread of the oncolytic agent within the TME. Nonetheless, the aforementioned immunostimulatory properties of type-I IFNs amplify indirect oncolysis mediated by cytotoxic immune effectors, thus balancing or even outcompeting the impairment of virus-mediated direct oncolysis. For this reason, transgenes encoding type-I IFNs have been frequently inserted into OVs [91–97] (Table 1). As an illustration, Western Reserve [WR] VV-Δ18RΔTK-IFNb is an oncolytic WR VV engineered to overexpress IFN-β. In preclinical models, this recombinant OV exhibited enhanced tumor-specific replication through enhanced antiviral response together with improved anticancer efficacy, associated with an increased population of tumor-infiltrating lymphocytes and the establishment of an immune memory compartment protecting against tumor rechallenge [91]. Similarly, an oncolytic MV-IFNβ showed improved efficacy associated with anti-angiogenic effects and massive infiltration of the tumor by $CD68^+$ immune cells in human mesothelioma tumors xenografted in

mice [94]. Additionally, a VSV overexpressing IFN-β demonstrated an improved safety profile while maintaining its oncolytic activity and stimulated systemic antitumor immunity following local delivery into murine syngeneic non-small cell lung cancers [93]. VSV-IFN-β also demonstrated improved efficacy against murine syngeneic mesothelioma [97]. This OV is currently evaluated in the clinics against multiple oncological indications (Table 2). More recently, an IFN-α-expressing oncolytic adenovirus (OAd-hamIFN) potentiated the cytotoxic activities of clinically-relevant chemo-radiotherapeutic regimens against pancreatic ductal adenocarcinoma in immunocompetent hamsters [92] (Table 1).

3.2. Type-II IFN

IFN-γ is the sole member of type-II IFNs. It is predominantly secreted by innate and adaptive lymphocytic populations, including NK, NKT, γδ T cells, type 1 innate lymphoid cells [ILC1], innate B cells, $CD4^+$ T_H1 cells, and CTLs. The production of IFN-γ occurs in response to stimulation of activating receptors (e.g. T cell receptor [TCR], natural killer group 2D [NKG2D]), loss of ligand recognition of inhibitory receptors (e.g. killer Ig-like receptors [KIRs]), or by IL-12 alone or in synergy with IL-2, IL-15, IL-18 and/or type-I IFNs [98–103]. Additionally, some myeloid cells (e.g. DCs, macrophages) can secrete IFN-γ. IFN-γ binds as a homodimer to the ubiquitous IFN-γ receptor (IFNGR), which is a tetramer composed of two chains of IFNGR1 and IFNGR2 each [98,99]. These two subunits interact with the cytosolic adapters JAK1 and JAK2, respectively, which in turn phosphorylate STAT1 and STAT3 and trigger their homo-/hetero-dimerization. These activated STATs translocate to the nucleus and promote transcription of ISGs that harbor cis-regulatory interferon-gamma activated sequences (GAS). Target genes include additional transcription factors (e.g. IRF1,2,8,9, JUN and RELA) that will transactivate a secondary wave of IFN-γ-regulated genes. Concomitantly, IFNGR stimulation ignites additional pathways such as PI3K/AKT, mTOR and MAPK signaling [99]. Analogously to type-I IFNs, IFN-γ mediates pleiotropic effects and plays a critical role in both antiviral and anticancer immune responses. Its antineoplastic action results from direct inhibition of malignant cell proliferation, induction of apoptotic or necroptotic cell death, as well as upregulation of MHC-I molecules that facilitate tumor cell recognition by CTLs [101]. IFN-γ also blocks tumor angiogenesis and damages the vasculature of the TME. Moreover, it promotes the recruitment of inflammatory leukocytes, the polarization of TAMs into M1 antitumoral phenotype, supports DC maturation, regulates the differentiation and activation of T_H1 lymphocytes, boosts the cytotoxic activity of CTLs and NK cells, and compromises the survival of intratumoral Tregs [101,104].

However, in specific contexts, prolonged exposure to IFN-γ may support tumor progression, metastasis and resistance to immunotherapies [101]. For example, type-II IFN stimulates the exposure of MHC molecules and that of the programmed cell death 1 [PD-1] ligands, PD-L1 and PD-L2, at the surface of both cancer cells and infiltrating immune cells, thus antagonizing NK cell and CTL cytotoxicity, respectively [101].

Along this line, cancer treatment by OVs has repeatedly been associated with intratumoral (and sometimes systemic) elevation of IFN-γ, together with infiltration by tumor-reactive lymphocytes, increased expression of PD-L1 in the TME, and enhanced sensitivity to anti-PD-1 immune checkpoint inhibitors [25,48,51,105–116]. Accordingly, some groups have armed OV strains with a transgene encoding IFN-γ [111,115,117,118] (Table 1). An oncolytic Ad-IFN-γ showed superior therapeutic efficacy against human nasopharyngeal cancer xenografts thanks to enhanced pro-apoptotic effects [117]. In the same vein, John Bell's group engineered a VSVΔM51-IFNγ with comparable cytopathic activity as its parental backbone but improved proinflammatory efficacy. This recombinant OV enhanced the circulating levels of IFN-γ as well as those of IL-6, TNF-α and CCL2, increased the expansion of activated DCs in the spleen and tumor bed, and amplified the levels of intratumoral IFN-γ together with $CD4^+$ and $CD8^+$ T lymphocytes. In comparison to the parental virus, VSVΔM51-IFNγ demonstrated improved T cell-dependent therapeutic efficacy against syngeneic murine mammary and colon tumors [111] (Table 1).

3.3. Type-III IFNs

Type-III IFNs regroup 4 members in humans: IFN-λ1/IL-29, IFN-λ2/IL-28A, IFN-λ3/IL-28B and IFN-λ4 (only IFN-λ1 & 2 in mice) [119–121]. In response to virus infection or other TLR agonists, most cells seem able to secrete type-III IFNs [122]. These cytokines bind to the IFN-lambda receptor (IFNLR) composed of 2 subunits: IFNLR1 and IL-10R2; the latter being shared with the receptors of other class-II cytokines such as IL-10, 22 & 26. IFNLR seems preferentially expressed on epithelial cells, hepatocytes, as well as in a restricted number of immune subtypes like neutrophils and some DC subsets [123]. IFNLR1 and IL-10R2 interact with the cytosolic adapters JAK1 and TYK2, respectively, thus resulting in overlapping functions between type-I and III IFNs, including antineoplastic effects [119–121]. Recent findings also suggest a non-canonical activation of JAK2 through interaction with IL-10R2, thus complexifying the molecular and cellular outcome of IFNLR stimulation [124].

To our knowledge, IFN-λ has only been attributed a critical involvement in OV therapy mediated by VSV [125,126]. Following intratumoral delivery of VSV Indiana into syngeneic murine melanomas, local sensing of viral infection promoted the recruitment of Gr1-positive cells (likely including plasmacytoid and/or monocyte-derived DCs) and triggered their secretion of IL-28. As a consequence, IFNLR1-expressing malignant cells showed enhanced sensitivity to NK cell killing. Importantly, the *in vivo* neutralization of IL-28 or depletion of NK cells abrogated the therapeutic efficacy of VSV, thus underscoring the negligible role of direct oncolysis in this cancer model. Conversely, melanoma tumors overexpressing the IL-28 receptor showed improved response to VSV treatment [125].

4. Interleukins

4.1. IL-2

Upon antigenic stimulation, IL-2 is predominantly produced by conventional $CD4^+$ T cell subsets as well as, to a lesser extent, by $CD8^+$ effector T lymphocytes [127]. Innate leukocytes of lymphoid and myeloid nature, such as NK, NKT, monocytes and DCs, can also supply IL-2. After its release, the cytokine can bind to its receptor IL-2R. The high affinity receptor is composed of IL2RA/CD25/α, IL2RB/CD122/β, and IL2RG/CD132/γ_c - this latter chain being shared with the receptors of IL-4, 7, 9, 15 & 21. The hetero-trimeric complex IL-2Rα$\beta\gamma_c$ is constitutively expressed on Tregs, transiently exposed on activated/effector T cells, and can be detected on some DC subtypes [127]. Other immune cells, like NK and NKT cells, harbor the intermediate affinity dimeric IL-2Rβγ. Moreover, IL-2R is expressed at the surface of other stromal cells like endothelial cells and, in some tissues, on epithelial cells and fibroblasts [127]. Binding of IL-2 activates the cytosolic adapters JAK1 and JAK3 and the downstream STAT5A & 5B, as well as STAT3 and STAT1, together with the RAS/ERK/AP-1 and PI3K/AKT/mTOR signaling pathways. Depending on the T cell subset, IL-2 regulates the expression of additional cytokines (e.g. production of IFN-γ and TNF-α, repression of IL-17A), receptors (upregulation of IL-2Rα & β as a positive feedback, IL4-Rα, and IL12-Rβ; downregulation of IL-6Rα, IL-7Rα, and CD62 L), regulators of cell proliferation and survival (e.g. MYC, cyclins, B cell lymphoma 2 [BCL2]), pro-apoptotic molecules (e.g. FASL, granzyme B, perforin), or intracellular factors controlling T cell lineage commitment (e.g. upregulation of B lymphocyte-induced maturation protein 1 [BLIMP-1], T-bet, SOCS1/2, and forkhead box P3 [FOXP3]; downregulation of BCL6, and retinoic acid receptor–related orphan nuclear receptor [ROR]γt,). Therefore, IL-2 plays an ambiguous role in

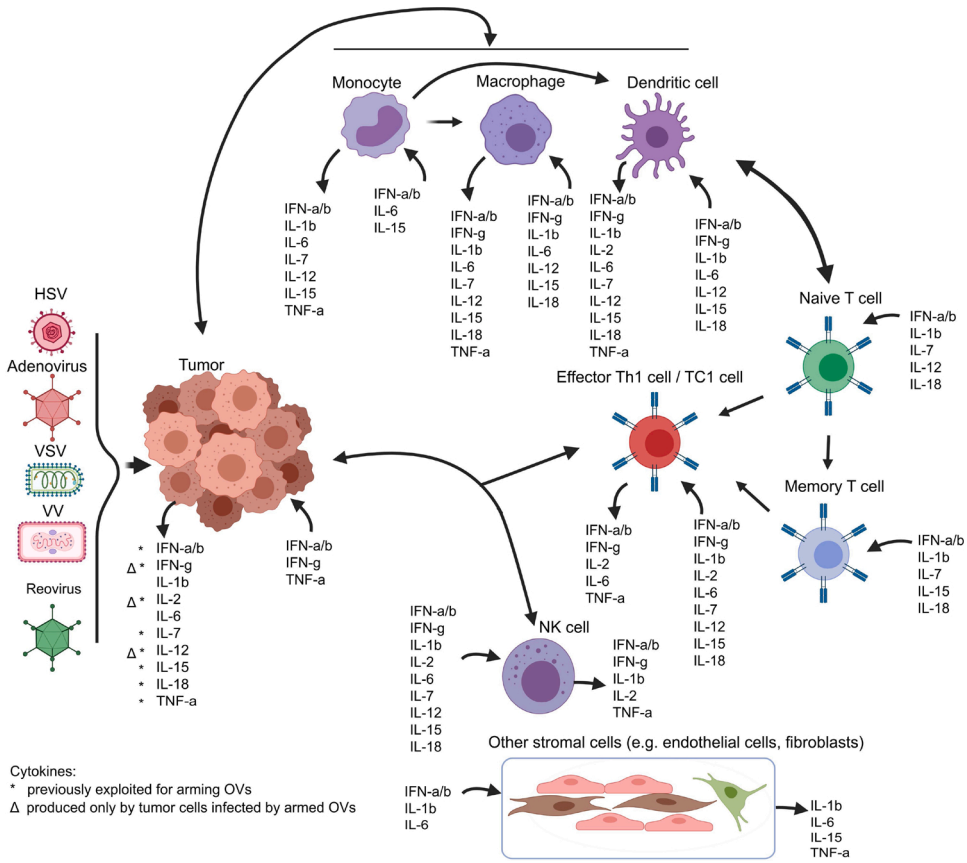

Fig. 2. Interferons, interleukins, and tumor necrosis factors participating in antitumor immunity described upon oncolytic virotherapy. Infection of cancer cells by oncolytic Ad, HSV, VSV, VV or reovirus stimulates the release of a plethora of pro-inflammatory cytokines, followed by the recruitment and activation of myeloid cells and their differentiation into inflammatory macrophages (M1) or DCs. These latter can engulf dying malignant cells and cross-present tumor antigens to naïve T lymphocytes, thus inducing their polarization into memory and effector $CD4^+$ T_H1 or $CD8^+$ T_C1 / CTLs. NK cells can also be recruited and activated. Ultimately, CTLs and/or NK cells infiltrating the malignant tissue drive cancer elimination through direct contact (i.e. release of perforins and granzymes) or secretion of effector cytokines like IFN-γ. Interferons, interleukins, and TNF-α secreted or captured by each cellular player are listed [212]. The initial production of inflammatory cytokines by virus-infected cancer cells can be further enhanced by arming the oncolytic agent with transgenes causing their overexpression. Ad, adenovirus; CTL, cytotoxic T lymphocyte; DC, dendritic cell; HSV, herpes simplex virus; IFN, interferon; IL, interleukin; NK, natural killer; T_C, T cytotoxic; T_H, T helper; TNF, tumor necrosis factor; VSV, vesicular stomatitis virus; VV, vaccinia virus.

cancer immunity. On one side, it determines the differentiation, expansion, survival and immunosuppressive function of peripheral Tregs. On the other side, IL-2 drives the differentiation and expansion of activated T cells towards the Th1/Tc1 lineage, and dictates their orientation towards the effector/cytotoxic (high level of IL-2) *versus* memory (low IL-2) compartments [127].

Detectable levels of intratumoral (and sometimes systemic) IL-2 have rarely been reported along cancer treatment with unarmed OVs [107, 112,116]. In a Phase I trial, five patients with cutaneous T cell lymphoma, relapsing or resistant to conventional therapies, were co-administered with subcutaneous IFN-α prior to intratumoral oncolytic MV injection (Edmonston Zagreb strain, MV-EZ). Treatment resulted not only in a rise in IFN-γ and $CD8^+$ T cells within the tumor bed, but also in a systemic increase of IL-2 (as well as IL-12). As an aside, serum level of IFN-γ remained high in the peripheral blood all along the follow-up. Overall, the approach was well tolerated and resulted in clinical responses [116]. Freedman et al. infected seven malignant prostate biopsy slices with an oncolytic group B adenovirus enadenotucirev (EnAd-SA-controlBiTE). Increased production of IFN-γ and IL-2 were documented in three and two tissue slices, respectively, as compared to uninfected controls [107].

Considering the sustained consumption of IL-2 by Tregs, mathematical predictions and experimental validations revealed the requirement of an elevated local concentration of IL-2 to support (antitumor) effector T cell expansion over (protumor) Tregs' [128]. In order to reach such advantageous threshold, some research teams have armed OVs (e.g. Ad5, Ad5/3, HSV-1 G207, NDV, VV) with an IL-2-encoding transgene and successfully improved the immunotherapeutic versant of these agents [105,112,115,129–134] (Fig. 2, Table 1). In H22 hepatoma tumor-bearing mice topically treated with the unarmed oncolytic NDV rClone30, detectable levels of IL-2, together with IFN-γ and CXCL10, were measured in the malignant tissue. Its IL-2-armed equivalent showed a 3.5-fold increase of the intratumoral level of IL-2, together with an elevation of IFN-γ and CXCL10, translating into a significant improvement of OV therapy [112]. In a recent report, Hemminki's group infected three patient-derived tumor histocultures with the oncolytic adenovirus TILT-123 co-expressing IL-2 & TNF-α (Ad5/3-E2F-d24-hTNFa-IRES-hIL2), and monitored the expression of multiple cytokines along a 7-day period [105]. A clear trend for enhanced expression of T_H1/T_C1-associated IFN-γ, CXCL10, IL-2 and TNF-α, was witnessed and positively correlated with cancer cell mortality [105]. In pancreatic ductal adenocarcinoma xenografted into mice, intratumoral delivery of TILT-123 improved the efficacy of infused mesothelin-redirected chimeric antigen receptor T (meso-CART) lymphocytes. Tumor infection by TILT-123 increased local levels of both IL-2 and TNF-α and dramatically stimulated tumor infiltration by proliferating ($Ki67^+$) and IFN-γ-secreting $CD8^+$ T cells, including an accumulation of meso-CART cells [129]. TILT-123 is currently evaluated in a Phase 1 trial in melanoma patients (Table 2). In syngeneic murine pancreatic ductal adenocarcinoma, a cocktail of two oncolytic Ad5-CMV viruses individually encoding IL-2 or TNF-α (Ad-mTNFa-mIL2) demonstrated superior efficacy than treatment with the parental OV [129]. Furthermore, its association with murine meso-CART resulted in improved control of tumor growth as compared to either approach alone. Tumor infection with Ad-mTNFa-mIL2 raised local levels of chemokines (CCL2 & CXCL10) and M1 macrophages, and promoted the recruitment of both donor and host $CD4^+$ T lymphocytes, as well as donor $CD8^+$ T cells [129]. In mice bearing subcutaneous B16-OVA melanomas, repeated injections of Ad-mTNFa-mIL2 triggered complete responses in 25 % of the animals. Importantly, Ad-mTNFa-mIL2 sensitized the tumors to anti-PD-1 immunotherapy, thus achieving a 100 % cure rate in the hosts receiving the combination regimen [105]. Therapeutic efficacy of Ad-mTNFa-mIL2 coincided with a trend towards an increase of immunostimulatory cytokines (i.e. IFN-γ, TNF-α, IL-2) and a

paralleled decrease of immunosuppressive cytokines (i.e. IL-4, IL-6, IL-10) within the TME, as well as a significant enhancement of tumor-infiltrating activated (i.e. $CD69^+$) $CD8^+$ T lymphocytes [105].

4.2. IL-12

Active IL-12 (which is a heterodimer of IL-12A/p35 and IL-12B/p40) is secreted by antigen-presenting cells (i.e. macrophages, DCs and B cells) and neutrophils following TLR engagement and phagocytosis, or after interaction of CD40 with CD40 L exposed on activated $CD4^+$ T cells [135]. Transmembrane IL-12Rβ1 and IL-12Rβ2 compose the IL-12 receptor and interact with TYK2 and JAK2, respectively. Stimulation of IL-12R, which is preferentially located on activated αβT lymphocytes and innate lymphocytic subsets (e.g. NK, NKT, ILC, γδT cells), mainly phosphorylates STAT4 but also STAT1, 3 & 5 [135–137]. Binding of IL-12 to its receptor controls naïve $CD4^+$ and $CD8^+$ T cell differentiation towards the T_H1 program (e.g. expression of T-bet), promotes cytotoxic activity of CTLs and NK cells (e.g. production of granzyme B and perforin) and stimulates their production of pro-inflammatory cytokines including IFN-γ, TNF-α, IL-2, and CSF-2, best known as granulocyte macrophage-colony stimulating factor [GM-CSF] [136]. Optimal secretion of IL-12 requires a positive feedback by IFN-γ, the docking of CD40L onto CD40, and/or the presence of IL-15 [136]. IL-12 can negatively regulate the secretion of IL-4 and IL-10, which are associated with protumor T_H2 and Tregs [138,139]. Inversely, these latter cytokines, together with TGF-β, inhibit IL-12 synthesis [136]. Additionally, IL-12 exerts powerful antiangiogenic effects, at least through IFN-γ-dependent mechanisms responsible for increased levels of CXCL9 & 10, and reduced release of VEGF and metalloproteinase-9 [MMP-9] [136,140]. Overall, IL-12 is probably the most efficient cytokine in controlling tumor growth in preclinical models [136]. Unfortunately, severe and sometimes lethal toxicity associated with its systemic administration to patients has precluded its clinical translation for cancer immunotherapy [136].

To our knowledge, with the exception of vvDD [73], enhanced intratumor level of IL-12 has never been detected following treatment with unarmed OVs [141–145]. Yet, co-culture of lung carcinoma cells infected by the oncolytic Ad5 OBP-301 (Telomelysin) with DCs stimulated IL-12 production by the latter [33]. Thanks to their oncotropism, OVs have been extensively exploited as vectors for safe tumor-restricted delivery of IL-12 with remarkable tolerability and therapeutic efficacy against a broad range of oncological indications in rodents [109,112, 141–168] (Fig. 2, Table 1). To date, oncolytic herpesviruses (oHSV) have been the backbone of preference for IL-12 transgene insertion [147]. Rabkin's group engineered the oHSV-1 G47Δ (ICP47-deleted) to express IL-12 [143]. In mice bearing intracerebral glioblastoma stem cell (GSC) tumors, intralesional delivery of G47Δ-mIL12 extended median and long-term survivals, while the unarmed virus demonstrated a limited benefit. In comparison to the parental strain, the armed virus led to an acute but remarkable increase of IL-12 in the TME, coinciding with a dramatic enhancement of both intratumor and systemic levels of the T_H1 cytokine IFN-γ. Levels of CXCL10 and VEGF were increased and decreased, respectively, in brain tumors infected with G47Δ-mIL12, and concurred with a reduced vasculature within the TME. Overall, the therapeutic efficacy originated from 1) the oncolytic activity, 2) an antiangiogenic effect and 3) a T cell-dependent and NK cell-independent immunity. Meanwhile, treatment with G47Δ-mIL12 further decreased tumor infiltration by immunosuppressive $CD4^+$ Tregs [143]. Remarkably, the combination of G47Δ-mIL12 with two ICIs, anti-PD-1 plus anti-cytotoxic T-lymphocyte-associated protein 4 [CTLA-4], allowed complete remission in 89 % and 50 % of animals bearing intracranial tumors of 005 GSC or more aggressive CT-2A glioma cells, respectively [150]. This triple therapy significantly improved the ratio of $CD8^+$ T effector cells over Tregs, as compared to G47Δ-mIL12 or the cocktail of ICIs administered separately. Cured mice were protected from cancer rechallenge, indicative of the establishment of a T cell memory compartment [150]. GSC-derived tumors infected with the triple combination of G47Δ-mIL12 plus the two ICIs also harbored an increased population of antitumor M1-like macrophages (positive for inducible nitric oxide synthase $[iNOS]^+$ and phospho-STAT1). Depletion of peripheral macrophages or $CD8^+$ T lymphocytes abrogated the synergy between oHSV and ICIs, thus comforting their well-characterized role in antitumor immunity. More surprisingly, selective depletion of $CD4^+$ T cells annihilated the efficacy of the tritherapy, underscoring their critical involvement in the immune response against glioblastoma [GBM] [150]. Investigations are underway to determine the mechanisms of $CD4^+$ T cell-mediated cancer elimination [169]. Nowadays, several oncolytic strains of HSV, Ad and VV engineered to express human IL-12 are being investigated in the clinics (Table 2).

4.3. IL-15

Various cell types including monocytes, macrophages, DCs, and some non-immune entities (e.g. epithelial cells, fibroblasts) produce IL-15 in inflammatory conditions [170–173]. Target cells that carry the IL-15 receptor [IL-15R] mainly consist of T, B, NK and NKT lymphocytes, monocytes and DCs. The high-affinity IL-15R is a heterotrimer of IL2RB/CD122/β and IL2RG/CD132/γ_c, both shared with IL-2R, together with IL-15Rα [170–173]. Of note, the latter chain is pre-assembled with IL-15 in the cytoplasm of IL-15-expressing cells. This complex then traffics to the plasma membrane where it can be trans-presented to target cells, or be cleaved and released as a soluble IL-15/IL-15Rα dimer [174,175]. The signaling pathways activated upon binding of IL-15 to its receptor are similar to those stimulated by IL-2. IL-15 acts as a major stimulus of the activation, proliferation, survival and cytolytic activity of $CD8^+$ T and NK cells. However, as opposed to IL-2, IL-15 does not interact with Tregs, thus lacking immunosuppressive effects. Moreover, IL-15 promotes the maintenance of the memory T cell compartment, whereas IL-2 prevents its persistence [170–173]. Unsurprisingly, these biological functions of IL-15 appeared critical for enhancing cancer immunosurveillance in preclinical studies [176–179]. Comforting clues have been evidenced in the clinic. Thus, a loss of IL-15 expression in patients affected with colorectal cancer resulted in lower T cell infiltration in the TME and reduced survival [180].

Production of IL-15 has not been reported following infection of cancer cell lines or tumors with unarmed OVs [72,149,181–185]. However, multiple OV backbones have been engineered to overexpress IL-15 [72,149,181–185]. Thus, IL-15-armed influenza A virus [IAV], MV, VSV or VV have proven safety and therapeutic efficacy in diverse syngeneic murine tumor models (Fig. 2, Table 1). Kowalsky et al. developed a vvDD expressing a fusion protein of IL-15 and IL-15Rα [184]. Intravenous delivery of this recombinant OV resulted in detectable levels of IL-15Rα, enhanced infiltration of $CD8^+$ T lymphocytes and NK cells, and expression of the inhibitory immune checkpoint PD-1 in the microenvironment of subcutaneous colorectal tumors. vvDD-IL15-Rα demonstrated a remarkable antitumor activity, translating into complete remission of the majority of mice bearing intraperitoneal colorectal and ovarian tumors. In the challenging model of subcutaneous colorectal cancer (CRC), administration of vvDD-IL15-Rα alone only extended median survival, but reached 100 % cure when combined with PD-1 blockade immunotherapy [184]. Other groups demonstrated comparable efficacy of monotherapies with oncolytic VSV and MV expressing IL-15 in murine CRC models [149,183].

4.4. IL-7

IL-7 is mostly secreted by non-hematopoietic cells (e.g. fibroblasts, epithelial cells) in various organs, including thymus and secondary lymphoid tissues [186]. Some immune cells like monocytes and DCs are also IL-7 producers. The heterodimer of IL-7Rα/CD127 and IL2RG/CD132/γ_c constitutes the IL-7 receptor (IL-7R), which is found at the surface of innate and adaptive lymphocytes. Binding of IL-7 to its

receptor relays the signal to JAK1 & 3 and to the downstream STAT1, 3 & 5, as well as to the mitogenic and pro-survival RAS/ERK/AP-1 and PI3K/AKT/mTOR cascades [186]. Target genes confer to IL-7 a crucial role in thymopoiesis and peripheral T cell homeostasis [186].

In the TME, this cytokine has been involved in the recruitment of effector T lymphocytes, as well as that of NK and NKT cells [186]. Moreover, IL-7 allowed sustained proliferation and survival of tumor-specific CTLs, even in unfavorable conditions (e.g. in the context of limited amounts of antigens and cytokines). Furthermore, adjuvant IL-7 stimulated intratumoral production of effector molecules by CTLs, including IFN-γ and granzyme B. Long-term persistence of central and peripheral memory T cells has also been reported in its presence. In parallel, IL-7 prevents immunosuppression. First, it limits PD-1 expression on activated $CD8^+$ T lymphocytes. Second, because Tregs harbor low levels of IL-7Rα, IL-7 poorly stimulates their proliferation, thus contributing to an increase of the $CD8^+$ T cell/Treg ratio, which favors antitumor immunity [186].

Synergistic effects of IL-7 and IL-12 have been reported on T cell activation [187], prompting Nakao et al. to engineer an oncolytic VV (LC16mO strain) to express either IL-7, or IL-12, or both cytokines [146] (Fig. 2, Table 1). Intratumoral co-administration of hIL-7-VV and mIL-12-VV elicited an increase of the infiltrating populations of $CD8^+$ T, $CD4^+$ T, NK and NKT cells, as compared to mIL-12-VV alone. Delivery of the VV co-expressing IL-7 and IL-12 into colorectal tumors resulted in enhanced concentrations of IFN-γ in the TME and augmented exposure of PD-L1 on cancer cells. This approach led to complete regression of all injected tumors. Interestingly, an abscopal effect was witnessed with a potent growth control of uninfected distant lesions. These latter not only showed an elevated infiltration by effector lymphocytes and an enhanced expression of PD-L1 on malignant cells, but also a stronger recruitment of activated M1 macrophages and $CD11b^+$ DCs, indicative of systemic antitumor immunity. Finally, hIL-7/mIL-12-VV sensitized to anti-PD-1 and anti-CTLA-4, with the combination therapies allowing the eradication of 50 % of untreated distant colorectal cancer lesions [146]. A strain co-expressing the human variant of both cytokines, hIL-7/hIL-12-VV, demonstrated a remarkable efficacy against lung adenocarcinomas in humanized mice [146]. This strain has just entered a Phase I trial under the name ASP9801 (Astellas Pharma) in patients with visceral and skin cancers (Table 2).

4.5. IL-1β

IL-1β together with TNF-α and IL-6 represent the prototypical triad of pro-inflammatory cytokines. Monocytes, macrophages, DCs and neutrophils are the primary sources of IL-1β following PRR activation by MAMPs or DAMPs [188,189]. Two IL-1 receptors exist, namely IL-1R1 and IL-1R2. Binding of IL-1β to one or the other receptor recruits the co-receptor IL-1RAcP [interleukin-1 receptor accessory protein]. However, only the assembly of IL-1β, IL-1R1 and IL-1RAcP relays intracellular signals [188]. This complex recruits the cytosolic adaptor MyD88 which, in cascade, interacts with IRAK4, leads to IRAK1/2 phosphorylation, ignites TRAF6 recruitment, activates TAK1, and ultimately promotes the nuclear translocation of NF-κB and AP-1 [190]. Additionally, IL-1R signaling can modulate STAT1/3 activation [191–193]. IL-1R1 is expressed on virtually all cells and its signaling pathway stimulates the production of molecules involved in systemic inflammation (e.g. IL-1β, IL-6, TNF-α, CCL2, CXCL8, iNOS, COX2) [194–200]. Interestingly, depending on the target cell and inflammatory stimulus, IL-1R1 signaling can also induce genes involved in the type-I IFN response (e.g. IFN-β, IFIT1/2, IRFs). Cumulating evidence suggests a negative feedback of IFN-α/β on the activity of IL-1β [201]. On one hand, type-I IFNs can directly inhibit the transcription and translation of IL-1β. On the other hand, type-I IFNs stimulate the production of anti-inflammatory IL-10, IL-1R2 and IL-1RA (the natural antagonist of the IL-1 receptors) [201]. Overall, IL-1β mediates systemic inflammation and modulates both innate and adaptive immunities [194,200]. First, it induces the production of adhesion molecules and chemokines by endothelial cells to recruit leukocytes [194,200]. In macrophages and DCs, IL-1β stimulates phagocytosis, antigen presentation and cytokine release. In neutrophils, IL-1β triggers the oxidative burst and the release of proteases, extracellular traps, histones and chemokines. In the presence of IL-1β, Th17 and Tγδ17 cells secrete CXCL8, which attracts neutrophils [194,200]. Finally, IL-1β enhances the expansion, migration to non-lymphoid tissues, differentiation towards effector/effector memory subsets (IFN-γ/GrzB-positive) and cytotoxic activity of antigen-primed $CD8^+$ T cells [194,200,202,203].

IL-1β is believed to play a major contribution to carcinogenesis, from its initiation step to metastasis, and can be overexpressed by malignant cells [204]. Its mutagenic role is attributed to the production of reactive oxygen or nitrogen species [ROS or NOS, respectively] by locally activated phagocytes and fibroblasts or other target cells. Moreover, IL-1β can facilitate tumor invasion and dissemination through the production of pro-angiogenic factors, MMPs, integrins and cytokines (e.g. VEGF, MMP-9, integrin β1, CXCL2, hepatocyte growth factor [HGF]) [204–208].

Upregulation of IL-1β has been reported following administration of OVs [26,52–54,70,209] (Fig. 2). For instance, infection of melanoma cell lines with the oHSV-2 ΔPK or the oHSV-1 T-VEC resulted in IL-1β secretion [26,52,53]. Interestingly, T-VEC further enhanced the production of IL-1β in cancer cells lacking the stimulator of interferon genes [STING], supposedly due to the reduced virus sensing and the resulting rise in cell killing and inflammatory signals [26]. Results were confirmed in mice bearing STING-deficient melanoma tumors on both flanks. T-VEC was applied intralesionally to one flank, leaving the other untreated. Remarkably, both treated and untreated tumors showed augmented expression of IL-1β (as well as IL-1α and other cytokines) and infiltration by tumor-specific (and HSV-specific) $CD8^+$ T cells, indicative of the establishment of a systemic antitumor immunity [26]. Repeated intratumoral injections of the oAd TILT-123 resulted in enhanced expression of IL-1β in the bed of pancreatic malignancies [54]. IL-1β secretion depended on the presence of AIM-2 in cancer cells [54]; this latter protein participates in the assembly of the inflammasome, itself involved in the maturation of IL-1β in various cell types [210,211]. Exposure of bone marrow-derived DCs to reovirus also stimulated a plethora of inflammatory cytokines including IL-1β and IL-1α [70]. In a Phase I trial, intravenous delivery of the oAd CG7870 to 23 patients affected with prostate cancer precipitated the release of IL-1β, as well as IL-6 and IL-10, in the bloodstream. These cytokines were acutely detected, peaking at 3−6 h, 6 h and 12−24 h post-infusion, respectively [209]. Conversely, infection of breast cancer cells with Maraba MG1, did not yield detectable levels of secreted IL-1β [59]. Similarly, a study involving the VSV Indiana in murine melanoma tumors demonstrated that the therapeutic efficacy was depending on MyD88 and the type-I IFN response but not on IL-1R [126]. Thus, IL-1β and its signaling may not contribute to the anticancer activity of oncolytic rhabdoviruses.

4.6. IL-6

A variety of immune and stromal cells, including monocytes, macrophages, T and B lymphocytes, endothelial cells and fibroblasts, produces IL-6 following stimulation by IL-1α/β, TNF-α, or IL-17 along tissue damage or infection [212,213]. The IL-6 receptor [IL-6R] is a heterodimer composed of IL-6Rα/gp80 and gp130. Membranous IL-6Rα is only expressed on a limited number of cell types: neutrophils, monocytes, B cells and hepatocytes [212,213]. Nevertheless, soluble IL-6Rα [sIL-6Rα] can be generated by proteolytic cleavage of membranous IL-6Rα at the surface of neutrophils (stimuli of this process include CXCL8 and C-reactive protein [CRP]) or via alternative splicing in neutrophils and monocytes. Thus, sIL-6Rα can bind to IL-6 and assemble in *trans* with gp130, which is ubiquitously expressed on additional targets like endothelial cells and fibroblasts [212,213]. IL-6/IL-6R signaling triggers the activation of JAK1 & 2 and downstream STAT3 & 1, as well as the

RAS/ERK/AP-1 and PI3K/AKT/IKK/NF-κB cascades. In endothelial cells, target genes include adhesion molecules (e.g. ICAM-1, VCAM-1) and cytokines (e.g. CXCL8, CCL2, IL-6) which further attracts leukocytes and fuel inflammation [212,213]. Overall, IL-6 ensures pleiotropic functions by regulating inflammation, acute-phase reactions, hematopoiesis and immune responses [214]. In particular, it participates to the differentiation of naïve $CD4^+$ T cells into Th17 while inhibiting their orientation toward the Tregs lineage [215,216]. This enhanced Th17/Tregs ratio contribute to break peripheral immune tolerance. Moreover, IL-6 promotes the differentiation of $CD8^+$ T cells toward the cytotoxic T cell subset [217].

A broad range of cancer cells express IL-6R and/or IL-6 [204]. Like IL-1β, IL-6 participates in oncogenesis by promoting proliferation, growth, resistance to cell death, differentiation, invasion and dissemination of malignant cells [204]. Accordingly, elevated serum levels of IL-6 are associated with unfavorable prognosis in patients affected with colorectal cancer [218]. Nonetheless, IL-6 has been attributed anti-cancer functions through its contribution to antitumor immunity. On one side, its secretion by DCs in the lymph nodes supports T cell priming and differentiation as mentioned above. On the other side, IL-6 production within the TME contribute to the excavation of $CD8^+$ effector T cells [218]. Therefore, although common knowledge still considers IL-6 as a pro-carcinogenic factor, its local presence might benefit to cancer immunotherapy in specific circumstances.

In a Phase I trial, prostate cancer patients intravenously infused with the oAd CG7870 showed a dose-related elevation of serum IL-6 accompanied by a transient and asymptomatic drop of blood pressure [209]. Administration of oncolytic vvDD and vvCCL5 to immunocompetent mice resulted in IL-6 secretion by splenocytes [73]. Infection of mammary carcinoma or melanoma cell lines by oncolytic Maraba virus MG1, oHSV-2 ΔPK, or MV, potently stimulated IL-6 expression [31,52,53,59,219] Similarly, pancreatic tumors treated with OAd.TNFa-IL2 demonstrated a trend towards a rise in IL-6 levels [54]. Expression of IL-6 was also reported in bone marrow DCs, splenocytes and B16 melanoma tumors following exposure to oncolytic reovirus [70]. Incubation of bone-marrow cells with oVSV stimulated IL-6 secretion in a MyD88-dependent fashion [126]. VSV treatment of melanoma tumors confirmed the stimulation of IL-6 and the requirement of MyD88 signaling for the detection of the cytokine in vivo. Nevertheless, knock-out of IL-6 did not reduce nor extend survival indicating that it does not contribute to the therapeutic efficacy of VSV [126]. Patient-derived urological tumor histocultures spontaneously released IL-6 and this production remained unaffected by infection with the oncolytic TILT-123 (Ad5/3-E2 F-d24-hTNFa-IRES-hIL2) (Table 2) [105]. More surprisingly, treatment of melanoma tumors with this virus seemed to restrict IL-6 production [105]. At last, an oVV engineered to overexpress IL-6 (GLV-1h90) was evaluated in combination with chemotherapy in human pancreatic tumor xenografts. Interestingly, the combination treatment not only mediated enhanced efficacy but also reduced the extent of chemotherapy-induced thrombocytopenia [220]. Thus, levels of pro-inflammatory IL-6 were mostly augmented upon OV therapy and did no compromise treatment efficacy, and at best improved tumor growth control (Fig. 2).

4.7. IL-18

IL-18 belongs to the IL-1 family. This pro-inflammatory cytokine is mostly produced by activated macrophages and DCs, but can also be secreted by some non-hematopoietic entities such as epithelial cells [212]. Like IL-1β, IL-18 is expressed as a precursor whose maturation relies on a proteolytic cleavage catalyzed by caspase-1, which is activated upon assembly of an inflammasome [212]. Target cells include T lymphocytes, NK(T) cells, DCs or macrophages expressing the IL-18 receptor composed of the IL-18Rα and IL-18Rβ subunits [212]. Downstream signaling pathways share some redundancy with the IL-1R system [221]. IL-18 has been ascribed pro-tumorigenic effects (like IL-1β), through its ability to promote the expression of angiogenic factors and adhesion molecules in endothelial cells, to drive NK cell exhaustion and differentiation toward immunosuppressive subsets, or to expand MDSCs in the TME [222]. However, differences exist in the genes stimulated by IL-1β and IL-18 [223]. For instance, IL-18 does not induce COX-2 expression, and thus does not fuel the production of PGE2, an inhibitor of the type-I T cell program [224]. Along this line, IL-18 (as well as IL-1β) synergizes with IL-12 in stimulating the synthesis of IFN-γ by T lymphocytes (independently of the TCR engagement), as well as B, NK, NKT cells, DCs and macrophages [225–227]. Consequently, depending on the qualitative and quantitative signature of cytokines in the TME, IL-18 can support the effector function of T_H1, T_C1 and NK lymphocytes and thus mediate antitumor (and antiviral) activities [222,225].

Oncolytic strains of Ad, HSV-1 and HSV-2 have been engineered to express IL-18 (Fig. 2, Table 1) [52,144,166,228–230]. Disappointingly, an IL-18-armed G47Δ oHSV-1 did not demonstrate improved potency in comparison to the unarmed control following intratumoral injection in a syngeneic model of prostate cancer [228]. One single intralesional delivery of a structurally similar oHSV encoding IL-18 into neuroblastoma tumors allowed acute release of IL-18 within the TME, as well as in the serum [166]. Once again, this vHsv-IL-18 alone was controlling tumor growth but without benefit in comparison to the empty vHsv control or an IL-12-expressing homolog. However, impressive therapeutic efficacy arose from the combination of both vHsv-IL-18 and vHSV-IL-12. This dual treatment triggered a systemic tumor-specific T-cell response that translated into remarkable regression of contralateral untreated lesions (abscopal effect) [166]. Along the same line, Choi and colleagues engineered the oAd RdB to express either IL-18 or IL-12, or both cytokines [144]. In a syngeneic melanoma model, intralesional application of each cytokine-armed OV demonstrated enhanced therapeutic profile in comparison to the unarmed agent. Of note, RdB/IL12/IL18 allowed superior tumor growth control and survival extension as compared to RdB/IL12 or RdB/IL18 monotherapies. The virus-elicited increase of both IL-12 and IL-18 within the TME led to a synergistic elevation of IFN-γ and GM-CSF secretion, as well as to a denser infiltration by $CD4^+$ and $CD8^+$ T lymphocytes and NK cells [144]. Collectively, introducing transgenic IL-18 into OVs can magnify antitumor immunity and provide remarkable benefit, if combined with IL-12.

5. Growth factors

Interactions of cancer cells with their TME comprising stromal and immune cells play an important role in tumor growth and invasion. The fate of these interactions is modulated by various growth factors which directly or indirectly influence the efficacy of OV therapy. For example, OVs can directly interact with various components of the TME and affect the production of growth factors leading to obstruction of tumor growth and invasiveness, as well as impairment of vasculature and angiogenesis. In this section, we discuss how major growth factors play a role in shaping the interactions between OV and TME.

5.1. Transforming growth factor-beta (TGF-β)

TGF-β is a secretory inflammatory ligand and growth factor that can suppress or promote tumor growth, depending on the stage of the tumor [231]. During tumor progression, TGF-β promotes cancer cell migration, invasion, epithelial to mesenchymal transition (EMT) and the formation of an immunosuppressive TME [231]. During OV therapies, TGF-β is produced by cancer cells as well as stromal cells [232] within TME [233]. Engineered versions of oAds infected both cancer cells as well as stellate cells in pancreatic cancer models [234,235] and caused a reduction in the levels of TGF-β that accompanied the process of direct oncolysis of cancer cells and inhibition of stroma [234]. In a prostate cancer model, an adenovirus engineered to target stromal cells and cancer cells resulted in fibroblast depletion, leading to reduced TGF-β production [107]. Several studies have also shown that OV-mediated

reduction of TGF-β in TME is associated with a diminution of regulatory T cells and an overall increase in anti-tumor immunity [233,236,237]. Combination studies using TGF-β inhibition and OV have shown enhanced viral replication, anti-tumor responses, as well as an overall improvement in the efficacy of OV therapy in multiple cancer models [238–241].

While many studies detected beneficial antitumor effects following the combination of TGF-β inhibitors with OV, some studies have contradicted these findings. In a study with a mouse GBM model, TGF-β inhibition resulted in reduced viral titers and overall survival upon oncolytic herpes simplex virus (oHSV) treatment [242]. Pretreating mice with TGF-β1 before oHSV treatment led to improved survival and tumor growth reduction [242], likely resulting from the inhibition of innate immune cells, particularly NK cells, which became less cytolytic against oHSV-infected glioblastoma cells, thus favoring the replication of oHSV [242]. Thus, at least for now, the role of TGF-β in OV therapy remains controversial, and further studies are required to delineate the paradoxical observations reported during the combination therapy with OV and TGF-β inhibition.

5.2. Fibroblast growth factors (FGFs)

FGFs are a family of cell signaling proteins involved in cell growth, survival, differentiation and angiogenesis [243]. In cancer, the role of FGFs and FGF receptors [FGFRs] has been controversial. For example, FGFR1 signaling is implicated in enhanced tumor progression, whereas FGFR2 is associated with decreased tumor progression [244]. Interaction of cells in TME has been shown to affect the levels of TGF-β which indirectly modified the sensitivity of cells to OV infection through FGF2 [245–247]. TGF-β1 secreted by cancer cells was shown to reprogram cancer-associated fibroblasts [CAFs] in a pancreatic cancer model, making them more susceptible to oncolytic VSV (oVSV) infection [245]. This was shown to be in part due to impairment of RIG-I-mediated IFN signaling caused by FGF2. This crosstalk between cancer cells and CAFs resulted in the suppression of antiviral defenses, leading to increased OV mediated oncolysis. Engineering the MG1 strain of the oncolytic Maraba virus (a vesiculovirus with higher oncolytic activity than VSV) to express FGF2 improved therapeutic efficacy in the mouse model compared to parental MG1 (Table 1) [245]. Similarly, the stimulation of human endothelial cells in vitro with FGF2 improved their sensitivity to oncolytic vaccinia virus [oVV] [248]. Increased expression levels of FGF2 have also been correlated with improved survival of glioblastoma patients upon treatment with oAds [15,249]. Contrasting with these findings, a recent study has shown a distinct interaction between CAFs and cancer cells, wherein contact signaling between fibroblasts and cancer cells led to the activation of the STING/IRF3 pathway in stromal fibroblasts, thus further enhancing the expression of IFN-stimulated genes [250]. This resulted in restricted tumor cell infection by oHSV, therefore compromising OV therapy [250]. While there is a complex interplay between CAFs, cancer cells and IFN pathway stimulation, the role of FGF was not evaluated in this study. A prior study showed that blocking FGF/FGFR signaling by combining a dominant-negative FGFR with oHSV improved the killing of tumor cells and endothelial cells in vitro and in an immunosuppressed mouse model [251]. Similarly, in vitro secretome analysis identified FGF16 as a potent inhibitor of VSV replication in multiple cell lines [252]. This latter study also showed a broad antiviral effect for different members of FGF family proteins, and suggested possible negative effects of FGFs on the replication, spread and oncolytic activity of by OVs [252]. Altogether, these findings suggest a paucity of knowledge on the FGF-controlled interactions of CAFs with cancer cells as well as with OVs.

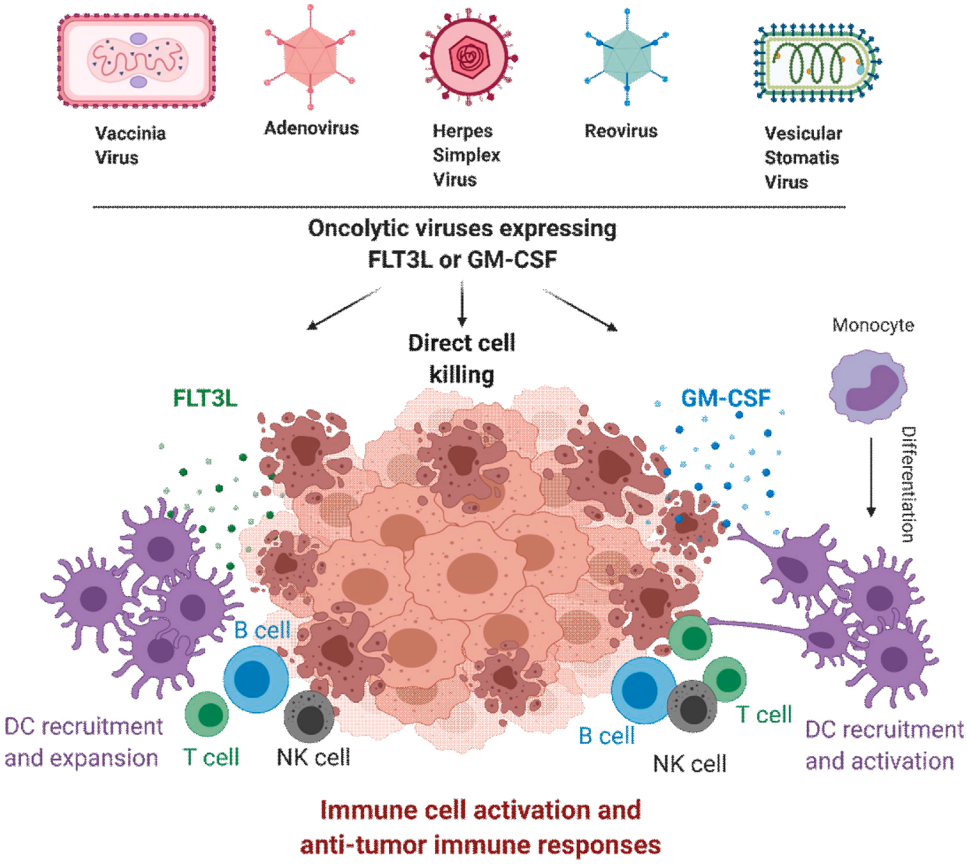

Fig. 3. Effects of oncolytic viruses expressing growth factors on anti-tumor immunity. Oncolytic VV, Ad, HSV, reovirus and VSV have been modified to express FLT3L or GM-CSF. This modification aims at combining direct cancer cell killing by OVs with the immune stimulatory actions of FLT3L or GM-CSF. While GM-CSF favors the differentiation of monocytes into DCs, both FLT3L and GM-CSF are involved in DC activation and recruitment of other immune cell subsets (e.g., T, B and NK cells) to the tumor bed. In this model, OVs kill cancer cells via oncolysis and release otherwise unavailable cancer antigens for their processing by DCs that are primed by FLT3L or GM-CSF. Ultimately, the combination of OV + FLT3L or GM-CSF leads to the induction of anti-tumor immune responses. Ad, adenovirus; DC, dendritic cell; FLT3L, FMS-like tyrosine kinase 3 ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; HSV, herpes simplex virus; NK, natural killer; OV, oncolytic virus; VSV, vesicular stomatitis virus; VV, vaccinia virus.

5.3. Vascular endothelial growth factor (VEGF)

VEGF is a potent growth and angiogenic factor for cancers [253]. It is produced by a wide variety of cells including tumor cells, endothelial cells, fibroblasts, macrophages and platelets [253]. Within TME, VEGF upregulation often contributes to tumor growth and angiogenesis, explaining why the interception of VEGF and VEGF-induced signals has become an important anti-cancer therapeutic strategy [253,254]. Interestingly, VEGF and OVs can impact each other's biology. For example, VEGF/VEGFR signaling sensitizes cells to OV infection [248,255]. In specific cases, VEGF inhibits IFN production in endothelial cells [255] and thus enhances the sensitivity of colon cancer cells to OV infection. This suppression of antiviral responses led to increased viral replication and spread of oVV along with destruction of tumor vasculature [255]. Another study showed that VEGF stimulation of human endothelial cells was important for efficient replication of engineered oVV [248]. A phase II clinical trial containing VEGFR inhibitor-naïve and -refractory patients [248] found disruption of tumor vasculature in advanced VEGF-rich hepatocellular carcinoma (HCC) treated with the oVV JX-594. Thus, VEGF can affect the direct oncolysis caused by OVs in cancer cells. Conversely, OVs themselves can downregulate the expression of VEGF in infected cells [256–260]. An oAd was shown to infect HCC cells in vitro and in vivo, downregulate the expression of VEGF, and reduce tumor vessel formation and angiogenesis [258]. Furthermore, oncolytic NDV was able to infect gastric cancer models and reduce tumor vascularization, which was associated with a reduction in VEGF-A expression at the tumor site [259]. Similarly, oVV infection of breast cancer cells reduced VEGF production from tumor cells in vitro [260], and the levels of VEGF remained suppressed during the period of viral infection. In this mouse model, the tumor vasculature usually recovered after OV clearance, but combining OV with anti-VEGF therapy significantly enhanced the therapeutic outcome [260]. Based on these results, several anticancer strategies are testing VEGF inhibition in the context of OV regimens.

5.4. Granulocyte-macrophage colony-stimulating factor (GM-CSF)

GM-CSF, a 127-amino acid glycoprotein, is an immunomodulatory cytokine produced by several cells including cancer cells, macrophages, epithelial cells, endothelial cells, B and T cells [261,262]. GM-CSF production can be induced or suppressed by pro-inflammatory (e.g., TNFα, IFNγ, IL-2) or anti-inflammatory (e.g., IL-10 and TGFβ) cytokines, respectively [262–265]. GM-CSF regulates survival, proliferation and differentiation of myeloid cells. It has both pro-inflammatory as well as regulatory properties [261,262,266]. Primarily known to stimulate the differentiation of granulocytes and monocytes [261,262,266], GM-CSF also enhances the recruitment and activation of DCs [261,262,267,268]. GM-CSF-primed DCs can stimulate long lasting tumor-specific immune responses by priming $CD8^+$ and $CD4^+$ T cells to recognize tumor-associated antigens [261,269–272]. Interestingly, several studies have observed inhibition of cancer cell proliferation by GM-CSF [273–275]. Accordingly, higher expression of GM-CSF has been correlated with better survival in colorectal cancer patients [276]. GM-CSF may also induce the expansion of other immune cells such as Tregs, T_H9, and NK cells [266,277–279]. Due to these properties, GM-CSF is often used as an adjuvant in cancer therapies and is approved for treatment of hormone refractory prostate cancer as well as melanoma in combination with T cell therapy and OV therapies, respectively [266].

GM-CSF has been widely used in combination with OVs for cancer immunotherapies (Fig. 3). Talimogene laherparepvec (T-VEC), an attenuated HSV-1 engineered to express GM-CSF, is the first OV to be approved for the local treatment of locally advanced melanoma [90]. T-VEC injection into melanoma lesions increased T cell recruitment at the tumor site, enhanced antigen-specific local as well as systemic responses, finally leading to improved durable and objective responses [43,110,280,281]. T-VEC-treated patients displayed a local decrease in Tregs and myeloid-derived suppressive cells (MDSCs) [280], activation of NK cells, maturation of DCs and enhanced cytotoxic T lymphocyte priming [282]. In a murine melanoma model, T-VEC induces immunogenic cell death in vitro as well as in vivo and even can overcome STING deficiency [26]. Of note, oncolytic reovirus has been shown to induce the production of GM-CSF by DCs and to promote DC maturation and migration to the tumor site, thus favoring the DC-mediated initiation of anti-tumor T cell responses [70]. Intratumoral administration of reovirus engineered to express GM-CSF resulted in an increase in DC and T cell activation in a mouse pancreatic cancer model [283]. Moreover, the combination of reovirus and GM-CSF prolonged survival in brain tumor-bearing mice [284]. Based on these promising results, several oncolytic viruses have been modified to express GM-CSF as an adjuvant (Table 1) [115,284–314]. As a result, multiple engineered OVs expressing GM-CSF are being investigated in clinical trials (Table 2).

5.5. FMS-like tyrosine kinase 3 ligand (FLT3L)

Along with GM-CSF, FLT3L is another important growth factor for DCs that can be combined with OVs (Fig. 3, Table 1). In steady state conditions, FLT3L is expressed by $CD34^+$ hematopoietic stem cells and plays a key role in the development and expansion of DCs, NK cells and B cells [315–320]. These immunostimulatory effects of FLT3L have been harnessed for the induction of anti-tumor immune responses by increasing DC numbers, causing complete tumor regression or decreased tumor growth in a murine fibrosarcoma model [321]. Furthermore, FLT3L recruited IFNα-expressing plasmacytoid DCs to brain parenchyma [322], and FLT3L-expressing Ad or HSV improved survival in mouse glioma models [323,324]. Interestingly, FLT3L in combination with HSV-thymidine kinase (TK) has been reported to reverse brain tumor-induced behavioral deficits in a mouse intracranial GBM model [325]. Currently, especially in comparison with GM-CSF, the combination of FLT3L with oncolytic viruses remains poorly studied, requiring further investigation [326–331]. Two oncolytic viruses expressing FLT3L, namely the oHSV ONCR-177 and the oVV TBio-6517, have just entered Phase 1 clinical trials (Table 2).

6. Tumor necrosis factors

6.1. TNF-α

TNF-α is a major proinflammatory cytokine produced primarily during early inflammatory events. Mainly known to be secreted by activated macrophages and monocytes, TNF-α can also be produced by other immune cell types including activated T cells, NK cells, mast cells, as well as by non-immune cells such as endothelial cells and fibroblasts in varying proportions [332–335]. TNF-α can bind to two membrane bound receptors, TNFR1 and TNFR2. TNFR1 is present in the majority of nucleated cells at low levels and can be activated by both the soluble and transmembrane (tm) forms of TNF-α. TNFR2 expression is restricted to astrocytes, microglia and subtypes of T cells such as Tregs and has higher affinity towards tmTNF-α [336].

In general, TNF-α is involved in a wide range of biological processes such as apoptosis, cell proliferation and differentiation. In the context of cancer, TNF-α was originally discovered as an anti-tumor cytokine due to its ability to induce necrotic cell death [337,338]. TNF-α has been involved in several anti-tumor activities including cellular apoptosis, disruption of neo-angiogenesis and collapse of tumor vasculature, activation of T cells by inhibiting Tregs, promoting M1 polarization of tumor-associated macrophages, and stimulation and recruitment of antigen-presenting cells [APCs], neutrophils and monocytes to the tumor site [339–345]. However, some studies have postulated paradoxical roles for TNF-α by assigning both tumor-promoting and tumor-inhibiting properties to this cytokine. TNFR1 activation by TNF-α can result in either cell apoptosis or inflammation and survival depending on the signal strength and activation of downstream

pathways [337,338]. Most of the pro-tumoral properties of TNF-α are mediated by the interaction of recombinant TNF-α with malignant and stromal cells and downstream activation of NF-kB signaling. For this reason, systemic delivery of TNF-α is seldom performed and isolated limb perfusion is the only current clinical application for TNF-α [346, 347]. Efforts have been underway to develop methods to deliver TNF-α locally in order to limit its unwanted cytotoxic effects.

During OV therapies, TNF-α is implicated in OV-mediated cell death, as well as in the stimulation of antitumor immune responses. Studies with oncolytic NDV have shown that the tumor selectivity and antineoplastic activities of the virus are mediated by the induction of TNF-α [348–351]. Oncolytic RSV-mediated infection of cancer cells induces TNF-α production along with TNF-α-mediated apoptosis in lung cancer models [352,353]. It should be noted that injection of OVs results in a modulation of the TME that is associated with TNF-α induction or secretion. A recombinant Ad was shown to induce TNF- α secretion, to activate T cells, and to recruit and activate APCs in syngeneic mouse melanoma and lung cancer models [353–355]. Co-culture of oncolytic reovirus-infected cells with dendritic cells resulted in the secretion of TNF-α and the mediation of DC activation [356]. Likewise, co-culture of oncolytic parvovirus-infected glioma cells with mouse DCs and microglial cells resulted in an enhanced activation of DCs and release of TNF-α into the supernatant [357]. Similarly, mammary or melanoma tumor-bearing mice treated with an HSV-2-based OV therapies caused an increased secretion of TNF-α from Th1 cells, thus entailing an enhanced antitumor immunity [53,358]. Interestingly, a study with mouse GBM model has shown that TNF-α secreted by microglial population in response to oncolytic HSV-1 infection resulted in inhibition of viral replication and induced apoptosis of tumor cells. Herein, transient blockade of TNF-α using blocking antibodies significantly improved virus spread and survival of mice with intracranial GBM tumors [359, 360]. While this could be specific to the OV or cancer type, further investigation is necessary to understand these discrepancies.

Recent studies have combined OVs with TNF-α for their immunostimulatory properties [45,54,361–363] (Fig. 2, Table 1). Combination of a TNF-α-armed oncolytic VSV with inhibitors of apoptosis antagonists improved the survival rate of breast and GBM tumors along with shutdown of tumor vasculature [361]. Oncolytic Ads armed with TNF-α also led to tumor eradication along with induction of antitumor T cell responses in multiple tumor models [362]. Treatment with oAds armed with either TNF-α alone or together with IL-2 reportedly increases MAMPs and DAMPs expression resulting in immunogenic cell death and consequently creating an immunostimulatory antitumor microenvironment [54,362]. This combination also enhanced antitumor immune responses resulting in systemic immunity as indicated by abscopal effect in non-injected tumors [45].

Similarly, recombinant OVs expressing TNF-α combined with other immunotherapies have proven to provide ameliorated anti-tumor benefits. For example, an oAd expressing TNF-α and IL-2 (Ad-TNFα-IL2) along with adoptive T cell therapy acted synergistically in multiple cancer models [129,364–367]. Combination of tumor-infiltrating lymphocyte (TIL) therapy with Ad-TNFα-IL2 in a pancreatic cancer model enhanced the frequency of T cells at the tumor site, augmented splenocyte proliferation, inhibited tumor growth and induced protection from rechallenge [364]. A similar combination treatment of ex vivo human ovarian cancer cultures resulted in modified TME with an increase in clinically relevant TIL activation as well as in proinflammatory signals including T cell-mediated IFN-γ release [367]. Likewise, combining Ad-mTNFα-mIL2 with mesothelin-redirected CAR-T cell (meso-CAR-T) therapy resulted in significant tumor regression of the aggressive pancreatic tumors. This combination also increased the infiltration of CAR-T and host T cells to the immunosuppressive tumor site and modified the immune status of the TME by polarizing macrophages towards the M1 type and by increasing DC maturation [129]. In the B16F10 mouse melanoma model, combination of Ad-mTNFα-mIL2 with PD-1 checkpoint blockade therapy improved the overall survival of mice. Improved melanoma growth control was associated with an increased intratumoral $CD8^+$ and $CD4^+$ T cell infiltrate as well as with a shift towards Th1 cells [368]. As listed in Table 2, the Ad-hTNFα-hIL2 (TILT-123) is currently undergoing clinical trials for advanced melanoma in combination with TIL therapy.

7. Concluding remarks

It is now well-established that OVs are one of the most potent drivers of cytokine responses within TME and in tumor-bearing hosts. As the core constituents of OVs (e.g., viral genome and structural proteins) represent hallmark MAMPs, they interact with pathogen recognition receptors (PRRs) on malignant and non-cancer cells (immune and stromal cells within TME), thus promoting a strong and multivariate cytokine response that overturns the immunosuppressive milieu. The OV-driven cytokine response critically influences the mechanisms through which OVs target cancer cells- via either direct oncolysis or through indirect, immune response-mediated effects. This therapeutically desirable overhaul of the TME driven by OV-induced cytokine responses renders tumors hot (i.e., initiates the infiltration of anticancer immune cells into the TME) and creates a microenvironment conducive to antitumor immunological activities (e.g., aiding killing of malignant cells by the direct actions of cytokines and innate immune cells, promoting antigen presentation by APCs and stimulation of antigen-specific adaptive immunity by T cells). These adjuvant-like actions of OVs enhance the quality of OV-induced antitumor immune activities and act as an indispensable component for OV-induced anticancer activities. It should be noted that, in addition to aiding antitumor immunity, inherent antiviral actions of OV-induced cytokines can negatively affect the replication and spread of OV. Thus, to optimally exploit the therapeutic benefits of OV-induced cytokines, it is imperative to dissect the precise effects of cytokines on antitumor immunity and OV replication. Interestingly, OVs can be engineered to encode a precise set of cytokines and thus have emerged as a suitable platform for configuring the anticancer immune responses at will. Indeed, many currently tested OV platforms are routinely engineered to include one or more cytokines to boost the anticancer effects of OV virotherapy. In conclusion, OV-driven cytokine expression bears multidimensional implications for OV-induced antitumor activities and thus holds major promise for rendering OVs a versatile tool for fighting cancer.

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Author Contributions

JGP, STW, PK, and SG wrote the manuscript. GK edited the manuscript.

Declaration of Competing Interest

JGP is named as inventor on patents for cancer vaccination involving an oncolytic rhabdovirus. These patents have been licensed to Turnstone Biologics of which JGP is shareholder. GK is a cofounder of Samsara Therapeutics, everImmune and Therafast Bio.

References

[1] D.S. Chen, I. Mellman, Elements of cancer immunity and the cancer-immune set point, Nature 541 (7637) (2017) 321–330.
[2] J. Fourcade, Z. Sun, M. Benallaoua, P. Guillaume, I.F. Luescher, C. Sander, J. M. Kirkwood, V. Kuchroo, H.M. Zarour, Upregulation of Tim-3 and PD-1 expression is associated with tumor antigen-specific CD8+ T cell dysfunction in melanoma patients, J. Exp. Med. 207 (10) (2010) 2175–2186.
[3] K. Sideras, K. Biermann, J. Verheij, B.R. Takkenberg, S. Mancham, B.E. Hansen, H.M. Schutz, R.A. de Man, D. Sprengers, S.I. Buschow, M.C. Verseput, P.P. Boor, Q. Pan, T.M. van Gulik, T. Terkivatan, J.N. Ijzermans, U.H. Beuers, S. Sleijfer, M. J. Bruno, J. Kwekkeboom, PD-L1, Galectin-9 and CD8(+) tumor-infiltrating lymphocytes are associated with survival in hepatocellular carcinoma, Oncoimmunology 6 (2) (2017), e1273309.
[4] K. Sideras, R.A. de Man, S.M. Harrington, W.G. Polak, G. Zhou, H.M. Schutz, A. Pedroza-Gonzalez, K. Biermann, S. Mancham, B.E. Hansen, R. Bart Takkenberg, A.J. van Vuuren, Q. Pan, J.N.M. Ijzermans, S. Sleijfer, D. Sprengers, H. Dong, J. Kwekkeboom, M.J. Bruno, Circulating levels of PD-L1 and Galectin-9 are associated with patient survival in surgically treated Hepatocellular Carcinoma independent of their intra-tumoral expression levels, Sci. Rep. 9 (1) (2019) 10677.
[5] E. Henke, R. Nandigama, S. Ergun, Extracellular matrix in the tumor microenvironment and its impact on cancer therapy, Front. Mol. Biosci. 6 (2019) 160.
[6] A. Duray, S. Demoulin, P. Hubert, P. Delvenne, S. Saussez, Immune suppression in head and neck cancers: a review, Clin. Dev. Immunol. 2010 (2010), 701657.
[7] A. Sarvaria, J.A. Madrigal, A. Saudemont, B cell regulation in cancer and anti-tumor immunity, Cell. Mol. Immunol. 14 (8) (2017) 662–674.
[8] Y. Fu, S. Liu, S. Zeng, H. Shen, From bench to bed: the tumor immune microenvironment and current immunotherapeutic strategies for hepatocellular carcinoma, J. Exp. Clin. Cancer Res. 38 (1) (2019) 396.
[9] R. Kalluri, M. Zeisberg, Fibroblasts in cancer, Nat. Rev. Cancer 6 (5) (2006) 392–401.
[10] B. Bierie, H.L. Moses, Tumour microenvironment: TGFbeta: the molecular Jekyll and Hyde of cancer, Nat. Rev. Cancer 6 (7) (2006) 506–520.
[11] N. Nagarsheth, M.S. Wicha, W. Zou, Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy, Nat. Rev. Immunol. 17 (9) (2017) 559–572.
[12] A.E. Vilgelm, A. Richmond, Chemokines modulate immune surveillance in Tumorigenesis, metastasis, and response to immunotherapy, Front. Immunol. 10 (2019) 333.
[13] G. Stoll, J. Pol, V. Soumelis, L. Zitvogel, G. Kroemer, Impact of chemotactic factors and receptors on the cancer immune infiltrate: a bioinformatics study revealing homogeneity and heterogeneity among patient cohorts, Oncoimmunology 7 (10) (2018), e1484980.
[14] L. Ziani, S. Chouaib, J. Thiery, Alteration of the antitumor immune response by cancer-associated fibroblasts, Front. Immunol. 9 (2018) 414.
[15] J.G. Pol, S. Levesque, S.T. Workenhe, S. Gujar, F. Le Boeuf, D.R. Clements, J. E. Fahrner, L. Fend, J.C. Bell, K.L. Mossman, J. Fucikova, R. Spisek, L. Zitvogel, G. Kroemer, L. Galluzzi, Trial Watch, Oncolytic viro-immunotherapy of hematologic and solid tumors, Oncoimmunology 7 (12) (2018), e1503032.
[16] J. Pol, A. Buque, F. Aranda, N. Bloy, I. Cremer, A. Eggermont, P. Erbs, J. Fucikova, J. Galon, J.M. Limacher, X. Preville, C. Sautes-Fridman, R. Spisek, L. Zitvogel, G. Kroemer, L. Galluzzi, Trial Watch-Oncolytic viruses and cancer therapy, Oncoimmunology 5 (2) (2016), e1117740.
[17] J. Pol, N. Bloy, F. Obrist, A. Eggermont, J. Galon, I. Cremer, P. Erbs, J. M. Limacher, X. Preville, L. Zitvogel, G. Kroemer, L. Galluzzi, Trial Watch, Oncolytic viruses for cancer therapy, Oncoimmunology 3 (2014), e28694.
[18] J.G. Pol, J. Rességuier, B.D. Lichty, Oncolytic viruses: a step into cancer immunotherapy, Virus Adapt. Treat. 2012 (4) (2012) 1–21.
[19] B. Cruickshank, M. Giacomantonio, P. Marcato, S. McFarland, J. Pol, S. Gujar, Dying to be noticed: epigenetic regulation of immunogenic cell death for cancer immunotherapy, Front. Immunol. 9 (2018) 654.
[20] S.T. Workenhe, K.L. Mossman, Oncolytic virotherapy and immunogenic cancer cell death: sharpening the sword for improved cancer treatment strategies, Mol. Ther. 22 (2) (2014) 251–256.
[21] A. Lemos de Matos, L.S. Franco, G. McFadden, Oncolytic viruses and the immune system: the dynamic duo, Mol. Ther. Methods Clin. Dev. 17 (2020) 349–358.
[22] S.T. Workenhe, J.G. Pol, B.D. Lichty, D.T. Cummings, K.L. Mossman, Combining oncolytic HSV-1 with immunogenic cell death-inducing drug mitoxantrone breaks cancer immune tolerance and improves therapeutic efficacy, Cancer Immunol. Res. 1 (5) (2013) 309–319.
[23] S.T. Workenhe, G. Simmons, J.G. Pol, B.D. Lichty, W.P. Halford, K.L. Mossman, Immunogenic HSV-mediated oncolysis shapes the antitumor immune response and contributes to therapeutic efficacy, Mol. Ther. 22 (1) (2014) 123–131.
[24] S. Chaurasiya, N.G. Chen, J. Lu, N. Martin, Y. Shen, S.I. Kim, S.G. Warner, Y. Woo, Y. Fong, A chimeric poxvirus with J2R (thymidine kinase) deletion shows safety and anti-tumor activity in lung cancer models, Cancer Gene Ther. 27 (3–4) (2020) 125–135.
[25] J. Ma, M. Ramachandran, C. Jin, C. Quijano-Rubio, M. Martikainen, D. Yu, M. Essand, Characterization of virus-mediated immunogenic cancer cell death and the consequences for oncolytic virus-based immunotherapy of cancer, Cell Death Dis. 11 (1) (2020) 48.
[26] P.K. Bommareddy, A. Zloza, S.D. Rabkin, H.L. Kaufman, Oncolytic virus immunotherapy induces immunogenic cell death and overcomes STING deficiency in melanoma, Oncoimmunology 8 (7) (2019), 1591875.
[27] J.P. van Vloten, S.T. Workenhe, S.K. Wootton, K.L. Mossman, B.W. Bridle, Critical interactions between immunogenic cancer cell death, oncolytic viruses, and the immune system define the rational design of combination immunotherapies, J. Immunol. 200 (2) (2018) 450–458.
[28] T. Ye, K. Jiang, L. Wei, M.P. Barr, Q. Xu, G. Zhang, C. Ding, S. Meng, H. Piao, Oncolytic Newcastle disease virus induces autophagy-dependent immunogenic cell death in lung cancer cells, Am. J. Cancer Res. 8 (8) (2018) 1514–1527.
[29] A. Serrano-Del Valle, A. Anel, J. Naval, I. Marzo, Immunogenic cell death and immunotherapy of multiple myeloma, Front. Cell Dev. Biol. 7 (2019) 50.
[30] Z.S. Guo, Z. Liu, D.L. Bartlett, Oncolytic immunotherapy: dying the right way is a key to eliciting potent antitumor immunity, Front. Oncol. 4 (2014) 74.
[31] O.G. Donnelly, F. Errington-Mais, L. Steele, E. Hadac, V. Jennings, K. Scott, H. Peach, R.M. Phillips, J. Bond, H. Pandha, K. Harrington, R. Vile, S. Russell, P. Selby, A.A. Melcher, Measles virus causes immunogenic cell death in human melanoma, Gene Ther. 20 (1) (2013) 7–15.
[32] T. Yamano, S. Kubo, M. Fukumoto, A. Yano, Y. Mawatari-Furukawa, H. Okamura, N. Tomita, Whole cell vaccination using immunogenic cell death by an oncolytic adenovirus is effective against a colorectal cancer model, Mol. Ther. Oncolytics 3 (2016) 16031.
[33] Y. Endo, R. Sakai, M. Ouchi, H. Onimatsu, M. Hioki, S. Kagawa, F. Uno, Y. Watanabe, Y. Urata, N. Tanaka, T. Fujiwara, Virus-mediated oncolysis induces danger signal and stimulates cytotoxic T-lymphocyte activity via proteasome activator upregulation, Oncogene 27 (17) (2008) 2375–2381.
[34] B. Huang, R. Sikorski, D.H. Kirn, S.H. Thorne, Synergistic anti-tumor effects between oncolytic vaccinia virus and paclitaxel are mediated by the IFN response and HMGB1, Gene Ther. 18 (2) (2011) 164–172.
[35] A. Gauvrit, S. Brandler, C. Sapede-Peroz, N. Boisgerault, F. Tangy, M. Gregoire, Measles virus induces oncolysis of mesothelioma cells and allows dendritic cells to cross-prime tumor-specific CD8 response, Cancer Res. 68 (12) (2008) 4882–4892.
[36] Z.S. Guo, A. Naik, M.E. O'Malley, P. Popovic, R. Demarco, Y. Hu, X. Yin, S. Yang, H.J. Zeh, B. Moss, M.T. Lotze, D.L. Bartlett, The enhanced tumor selectivity of an oncolytic vaccinia lacking the host range and antiapoptosis genes SPI-1 and SPI-2, Cancer Res. 65 (21) (2005) 9991–9998.
[37] L. Bai, J. Koopmann, C. Fiola, P. Fournier, V. Schirrmacher, Dendritic cells pulsed with viral oncolysates potently stimulate autologous T cells from cancer patients, Int. J. Oncol. 21 (4) (2002) 685–694.
[38] F.M. Cruz, J.D. Colbert, E. Merino, B.A. Kriegsman, K.L. Rock, The biology and underlying mechanisms of cross-presentation of exogenous antigens on MHC-I molecules, Annu. Rev. Immunol. 35 (2017) 149–176.
[39] S. Gujar, J.G. Pol, Y. Kim, P.W. Lee, G. Kroemer, Antitumor benefits of antiviral immunity: an underappreciated aspect of oncolytic virotherapies, Trends Immunol. 39 (3) (2018) 209–221.
[40] Y. Kim, D.R. Clements, A.M. Sterea, H.W. Jang, S.A. Gujar, P.W. Lee, Dendritic cells in oncolytic virus-based anti-cancer therapy, Viruses 7 (12) (2015) 6506–6525.
[41] H. Salmon, J. Idoyaga, A. Rahman, M. Leboeuf, R. Remark, S. Jordan, M. Casanova-Acebes, M. Khudoynazarova, J. Agudo, N. Tung, S. Chakarov, C. Rivera, B. Hogstad, M. Bosenberg, D. Hashimoto, S. Gnjatic, N. Bhardwaj, A. K. Palucka, B.D. Brown, J. Brody, F. Ginhoux, M. Merad, Expansion and activation of CD103(+) dendritic cell progenitors at the tumor site enhances tumor responses to therapeutic PD-L1 and BRAF inhibition, Immunity 44 (4) (2016) 924–938.
[42] J.G. Pol, J. Le Naour, G. Kroemer, FLT3LG - a biomarker reflecting clinical responses to the immunogenic cell death inducer oxaliplatin, Oncoimmunology 9 (1) (2020), 1755214.
[43] R.H. Andtbacka, H.L. Kaufman, F. Collichio, T. Amatruda, N. Senzer, J. Chesney, K.A. Delman, L.E. Spitler, I. Puzanov, S.S. Agarwala, M. Milhem, L. Cranmer, B. Curti, K. Lewis, M. Ross, T. Guthrie, G.P. Linette, G.A. Daniels, K. Harrington, M.R. Middleton, W.H. Miller Jr., J.S. Zager, Y. Ye, B. Yao, A. Li, S. Doleman, A. VanderWalde, J. Gansert, R.S. Coffin, Talimogene laherparepvec improves durable response rate in patients with advanced melanoma, J. Clin. Oncol. 33 (25) (2015) 2780–2788.
[44] H.L. Kaufman, T. Amatruda, T. Reid, R. Gonzalez, J. Glaspy, E. Whitman, K. Harrington, J. Nemunaitis, A. Zloza, M. Wolf, N.N. Senzer, Systemic versus local responses in melanoma patients treated with talimogene laherparepvec from a multi-institutional phase II study, J. Immunother. Cancer 4 (2016) 12.
[45] R. Havunen, J.M. Santos, S. Sorsa, T. Rantapero, D. Lumen, M. Siurala, A. J. Airaksinen, V. Cervera-Carrascon, S. Tahtinen, A. Kanerva, A. Hemminki, Abscopal effect in non-injected tumors achieved with cytokine-armed oncolytic adenovirus, Mol. Ther. Oncolytics 11 (2018) 109–121.
[46] L. Kuryk, A.W. Moller, M. Jaderberg, Abscopal effect when combining oncolytic adenovirus and checkpoint inhibitor in a humanized NOG mouse model of melanoma, J. Med. Virol. 91 (9) (2019) 1702–1706.

[47] R. Bhat, J. Rommelaere, Emerging role of natural killer cells in oncolytic virotherapy, Immunotargets Ther. 4 (2015) 65–77.
[48] J.G. Pol, M.J. Atherton, B.W. Bridle, K.B. Stephenson, F. Le Boeuf, J.L. Hummel, C.G. Martin, J. Pomoransky, C.J. Breitbach, J.S. Diallo, D.F. Stojdl, J.C. Bell, Y. Wan, B.D. Lichty, Development and applications of oncolytic Maraba virus vaccines, Oncolytic Virother. 7 (2018) 117–128.
[49] C.A. Alvarez-Breckenridge, B.D. Choi, C.M. Suryadevara, E.A. Chiocca, Potentiating oncolytic viral therapy through an understanding of the initial immune responses to oncolytic viral infection, Curr. Opin. Virol. 13 (2015) 25–32.
[50] C.A. Alvarez-Breckenridge, J. Yu, B. Kaur, M.A. Caligiuri, E.A. Chiocca, Deciphering the multifaceted relationship between oncolytic viruses and natural killer cells, Adv. Virol. 2012 (2012), 702839.
[51] S. Gujar, J.G. Pol, G. Kroemer, Heating it up: oncolytic viruses make tumors 'hot' and suitable for checkpoint blockade immunotherapies, Oncoimmunology 7 (8) (2018), e1442169.
[52] L. Aurelian, D. Bollino, A. Colunga, The oncolytic virus DeltaPK has multimodal anti-tumor activity, Pathog. Dis. 74 (5) (2016).
[53] D. Bollino, A. Colunga, B. Li, L. Aurelian, DeltaPK oncolytic activity includes modulation of the tumour cell milieu, J. Gen. Virol. 97 (2) (2016) 496–508.
[54] C. Heiniö, R. Havunen, J. Santos, K. de Lint, V. Cervera-Carrascon, A. Kanerva, A. Hemminki, TNFa and IL2 encoding oncolytic adenovirus activates pathogen and danger-associated immunological signaling, Cells 9 (4) (2020) 798.
[55] M.T. Chow, A.D. Luster, Chemokines in cancer, Cancer Immunol. Res. 2 (12) (2014) 1125–1131.
[56] R. Tokunaga, W. Zhang, M. Naseem, A. Puccini, M.D. Berger, S. Soni, M. McSkane, H. Baba, H.J. Lenz, CXCL9, CXCL10, CXCL11/CXCR3 axis for immune activation - a target for novel cancer therapy, Cancer Treat. Rev. 63 (2018) 40–47.
[57] P.J. Hensbergen, P.G. Wijnands, M.W. Schreurs, R.J. Scheper, R. Willemze, C. P. Tensen, The CXCR3 targeting chemokine CXCL11 has potent antitumor activity in vivo involving attraction of CD8+ T lymphocytes but not inhibition of angiogenesis, J. Immunother. 28 (4) (2005) 343–351.
[58] E.C. Eckert, R.A. Nace, J.M. Tonne, L. Evgin, R.G. Vile, S.J. Russell, Generation of a tumor-specific chemokine gradient using oncolytic vesicular stomatitis virus encoding CXCL9, Mol. Ther. Oncolytics 16 (2020) 63–74.
[59] M.C. Bourgeois-Daigneault, D.G. Roy, A.S. Aitken, N. El Sayes, N.T. Martin, O. Varette, T. Falls, L.E. St-Germain, A. Pelin, B.D. Lichty, D.F. Stojdl, G. Ungerechts, J.S. Diallo, J.C. Bell, Neoadjuvant oncolytic virotherapy before surgery sensitizes triple-negative breast cancer to immune checkpoint therapy, Sci. Transl. Med. 10 (422) (2018).
[60] X. Fu, A. Rivera, L. Tao, X. Zhang, An HSV-2 based oncolytic virus can function as an attractant to guide migration of adoptively transferred T cells to tumor sites, Oncotarget 6 (2) (2015) 902–914.
[61] J.S. Carew, C.M. Espitia, W. Zhao, M.M. Mita, A.C. Mita, S.T. Nawrocki, Oncolytic reovirus inhibits angiogenesis through induction of CXCL10/IP-10 and abrogation of HIF activity in soft tissue sarcomas, Oncotarget 8 (49) (2017) 86769–86783.
[62] R. Abraham, P. Mudaliar, A. Padmanabhan, E. Sreekumar, Induction of cytopathogenicity in human glioblastoma cells by chikungunya virus, PLoS One 8 (9) (2013), e75854.
[63] E.K. Moon, L.S. Wang, K. Bekdache, R.C. Lynn, A. Lo, S.H. Thorne, S.M. Albelda, Intra-tumoral delivery of CXCL11 via a vaccinia virus, but not by modified T cells, enhances the efficacy of adoptive T cell therapy and vaccines, Oncoimmunology 7 (3) (2018), e1395997.
[64] Z. Liu, R. Ravindranathan, J. Li, P. Kalinski, Z.S. Guo, D.L. Bartlett, CXCL11-Armed oncolytic poxvirus elicits potent antitumor immunity and shows enhanced therapeutic efficacy, Oncoimmunology 5 (3) (2016), e1091554.
[65] B.A. Jonas, Combination of an oncolytic virus with PD-L1 blockade keeps cancer in check, Sci. Transl. Med. 9 (386) (2017).
[66] L. Francis, Z.S. Guo, Z. Liu, R. Ravindranathan, J.A. Urban, M. Sathaiah, D. Magge, P. Kalinski, D.L. Bartlett, Modulation of chemokines in the tumor microenvironment enhances oncolytic virotherapy for colorectal cancer, Oncotarget 7 (16) (2016) 22174–22185.
[67] B.R. Champion, M. Besneux, M. Patsalidou, A. Silva, M. Zonca, N. Marino, G. d. Genova, S. Illingworth, S. Fedele, L. Slater, F. Lilley, D. Plumb, K. West, P. Cockle, A. Brown, Abstract 5013: NG-641: an oncolytic T-SIGn virus targeting cancer-associated fibroblasts in the stromal microenvironment of human carcinomas, Cancer Res. 79 (13 Supplement) (2019) 5013.
[68] L. Steele, F. Errington, R. Prestwich, E. Ilett, K. Harrington, H. Pandha, M. Coffey, P. Selby, R. Vile, A. Melcher, Pro-inflammatory cytokine/chemokine production by reovirus treated melanoma cells is PKR/NF-kappaB mediated and supports innate and adaptive anti-tumour immune priming, Mol. Cancer 10 (2011) 20.
[69] F. Errington, C.L. White, K.R. Twigger, A. Rose, K. Scott, L. Steele, L.J. Ilett, R. Prestwich, H.S. Pandha, M. Coffey, P. Selby, R. Vile, K.J. Harrington, A. A. Melcher, Inflammatory tumour cell killing by oncolytic reovirus for the treatment of melanoma, Gene Ther. 15 (18) (2008) 1257–1270.
[70] S.A. Gujar, P. Marcato, D. Pan, P.W. Lee, Reovirus virotherapy overrides tumor antigen presentation evasion and promotes protective antitumor immunity, Mol. Cancer Ther. 9 (11) (2010) 2924–2933.
[71] F. Li, Y. Sheng, W. Hou, P. Sampath, D. Byrd, S. Thorne, Y. Zhang, CCL5-armed oncolytic virus augments CCR5-engineered NK cell infiltration and antitumor efficiency, J. Immunother. Cancer 8 (1) (2020).
[72] N. Nishio, I. Diaconu, H. Liu, V. Cerullo, I. Caruana, V. Hoyos, L. Bouchier-Hayes, B. Savoldo, G. Dotti, Armed oncolytic virus enhances immune functions of chimeric antigen receptor-modified T cells in solid tumors, Cancer Res. 74 (18) (2014) 5195–5205.
[73] J. Li, M. O'Malley, J. Urban, P. Sampath, Z.S. Guo, P. Kalinski, S.H. Thorne, D. L. Bartlett, Chemokine expression from oncolytic vaccinia virus enhances vaccine therapies of cancer, Mol. Ther. 19 (4) (2011) 650–657.
[74] N. Lapteva, M. Aldrich, D. Weksberg, L. Rollins, T. Goltsova, S.Y. Chen, X. F. Huang, Targeting the intratumoral dendritic cells by the oncolytic adenoviral vaccine expressing RANTES elicits potent antitumor immunity, J Immunother 32 (2) (2009) 145–156.
[75] G.Y. Liu, Z.J. Li, Q.L. Li, Y. Jin, Y.H. Zhu, Y.H. Wang, M.Y. Liu, Y.G. Li, Y. Li, Enhanced growth suppression of TERT-positive tumor cells by oncolytic adenovirus armed with CCL20 and CD40L, Int. Immunopharmacol. 28 (1) (2015) 487–493.
[76] J.F. Ye, W.X. Qi, M.Y. Liu, Y. Li, The combination of NK and CD8+T cells with CCL20/IL15-armed oncolytic adenoviruses enhances the growth suppression of TERT-positive tumor cells, Cell. Immunol. 318 (2017) 35–41.
[77] M. Gil, M. Seshadri, M.P. Komorowski, S.I. Abrams, D. Kozbor, Targeting CXCL12/CXCR4 signaling with oncolytic virotherapy disrupts tumor vasculature and inhibits breast cancer metastases, Proc. Natl. Acad. Sci. U. S. A. 110 (14) (2013) E1291–300.
[78] V. van Pesch, H. Lanaya, J.C. Renauld, T. Michiels, Characterization of the murine alpha interferon gene family, J. Virol. 78 (15) (2004) 8219–8228.
[79] M. Swiecki, M. Colonna, Type I interferons: diversity of sources, production pathways and effects on immune responses, Curr. Opin. Virol. 1 (6) (2011) 463–475.
[80] S. Hervas-Stubbs, J.L. Perez-Gracia, A. Rouzaut, M.F. Sanmamed, A. Le Bon, I. Melero, Direct effects of type I interferons on cells of the immune system, Clin. Cancer Res. 17 (9) (2011) 2619–2627.
[81] C.F. Yu, W.M. Peng, M. Schlee, W. Barchet, A.M. Eis-Hubinger, W. Kolanus, M. Geyer, S. Schmitt, F. Steinhagen, J. Oldenburg, N. Novak, SOCS1 and SOCS3 target IRF7 degradation to suppress TLR7-Mediated type I IFN production of human plasmacytoid dendritic cells, J. Immunol. 200 (12) (2018) 4024–4035.
[82] M. Musella, G. Manic, R. De Maria, I. Vitale, A. Sistigu, Type-I-interferons in infection and cancer: unanticipated dynamics with therapeutic implications, Oncoimmunology 6 (5) (2017), e1314424.
[83] L. Zitvogel, L. Galluzzi, O. Kepp, M.J. Smyth, G. Kroemer, Type I interferons in anticancer immunity, Nat. Rev. Immunol. 15 (7) (2015) 405–414.
[84] O.V. Matveeva, P.M. Chumakov, Defects in interferon pathways as potential biomarkers of sensitivity to oncolytic viruses, Rev. Med. Virol. 28 (6) (2018) e2008.
[85] D.F. Stojdl, B. Lichty, S. Knowles, R. Marius, H. Atkins, N. Sonenberg, J.C. Bell, Exploiting tumor-specific defects in the interferon pathway with a previously unknown oncolytic virus, Nat. Med. 6 (7) (2000) 821–825.
[86] J. Brun, D. McManus, C. Lefebvre, K. Hu, T. Falls, H. Atkins, J.C. Bell, J. A. McCart, D. Mahoney, D.F. Stojdl, Identification of genetically modified Maraba virus as an oncolytic rhabdovirus, Mol. Ther. 18 (8) (2010) 1440–1449.
[87] P.Y. Huang, J.H. Guo, L.H. Hwang, Oncolytic Sindbis virus targets tumors defective in the interferon response and induces significant bystander antitumor immunity in vivo, Mol. Ther. 20 (2) (2012) 298–305.
[88] F. Allagui, C. Achard, C. Panterne, C. Combredet, N. Labarriere, B. Dreno, A. B. Elgaaied, D. Pouliquen, F. Tangy, J.F. Fonteneau, M. Gregoire, N. Boisgerault, Modulation of the type I interferon response defines the sensitivity of human melanoma cells to oncolytic measles virus, Curr. Gene Ther. 16 (6) (2017) 419–428.
[89] S. Elankumaran, V. Chavan, D. Qiao, R. Shobana, G. Moorkanat, M. Biswas, S. K. Samal, Type I interferon-sensitive recombinant newcastle disease virus for oncolytic virotherapy, J. Virol. 84 (8) (2010) 3835–3844.
[90] J. Pol, G. Kroemer, L. Galluzzi, First oncolytic virus approved for melanoma immunotherapy, Oncoimmunology 5 (1) (2016), e1115641.
[91] D.H. Kirn, Y. Wang, F. Le Boeuf, J. Bell, S.H. Thorne, Targeting of interferon-beta to produce a specific, multi-mechanistic oncolytic vaccinia virus, PLoS Med. 4 (12) (2007) e353.
[92] A.O. Salzwedel, J. Han, C.J. LaRocca, R. Shanley, M. Yamamoto, J. Davydova, Combination of interferon-expressing oncolytic adenovirus with chemotherapy and radiation is highly synergistic in hamster model of pancreatic cancer, Oncotarget 9 (26) (2018) 18041–18052.
[93] M.R. Patel, B.A. Jacobson, Y. Ji, J. Drees, S. Tang, K. Xiong, H. Wang, J.E. Prigge, A.S. Dash, A.K. Kratzke, E. Mesev, R. Etchison, M.J. Federspiel, S.J. Russell, R. A. Kratzke, Vesicular stomatitis virus expressing interferon-beta is oncolytic and promotes antitumor immune responses in a syngeneic murine model of non-small cell lung cancer, Oncotarget 6 (32) (2015) 33165–33177.
[94] H. Li, K.W. Peng, D. Dingli, R.A. Kratzke, S.J. Russell, Oncolytic measles viruses encoding interferon beta and the thyroidal sodium iodide symporter gene for mesothelioma virotherapy, Cancer Gene Ther. 17 (8) (2010) 550–558.
[95] E.V. Shashkova, M.N. Kuppuswamy, W.S. Wold, K. Doronin, Anticancer activity of oncolytic adenovirus vector armed with IFN-alpha and ADP is enhanced by pharmacologically controlled expression of TRAIL, Cancer Gene Ther. 15 (2) (2008) 61–72.
[96] E.V. Shashkova, J.F. Spencer, W.S. Wold, K. Doronin, Targeting interferon-alpha increases antitumor efficacy and reduces hepatotoxicity of E1A-mutated spread-enhanced oncolytic adenovirus, Mol. Ther. 15 (3) (2007) 598–607.
[97] C.L. Willmon, V. Saloura, Z.G. Fridlender, P. Wongthida, R.M. Diaz, J. Thompson, T. Kottke, M. Federspiel, G. Barber, S.M. Albelda, R.G. Vile, Expression of IFN-beta enhances both efficacy and safety of oncolytic vesicular stomatitis virus for therapy of mesothelioma, Cancer Res. 69 (19) (2009) 7713–7720.

[98] M. Mojic, K. Takeda, Y. Hayakawa, The dark side of IFN-gamma: its role in promoting cancer immunoevasion, Int. J. Mol. Sci. 19 (1) (2017).
[99] M.Y. Bhat, H.S. Solanki, J. Advani, A.A. Khan, T.S. Keshava Prasad, H. Gowda, S. Thiyagarajan, A. Chatterjee, Comprehensive network map of interferon gamma signaling, J. Cell Commun. Signal. 12 (4) (2018) 745–751.
[100] J.D. Marshall, D.S. Heeke, C. Abbate, P. Yee, G. Van Nest, Induction of interferon-gamma from natural killer cells by immunostimulatory CpG DNA is mediated through plasmacytoid-dendritic-cell-produced interferon-alpha and tumour necrosis factor-alpha, Immunology 117 (1) (2006) 38–46.
[101] M.R. Zaidi, The interferon-gamma paradox in cancer, J. Interferon Cytokine Res. 39 (1) (2019) 30–38.
[102] C. Chester, K. Fritsch, H.E. Kohrt, Natural killer cell immunomodulation: targeting activating, inhibitory, and Co-stimulatory receptor signaling for cancer immunotherapy, Front. Immunol. 6 (2015) 601.
[103] L. Malmgaard, S.R. Paludan, Interferon (IFN)-alpha/beta, interleukin (IL)-12 and IL-18 coordinately induce production of IFN-gamma during infection with herpes simplex virus type 2, J. Gen. Virol. 84 (Pt 9) (2003) 2497–2500.
[104] A.E. Overacre-Delgoffe, M. Chikina, R.E. Dadey, H. Yano, E.A. Brunazzi, G. Shayan, W. Horne, J.M. Moskovitz, J.K. Kolls, C. Sander, Y. Shuai, D. P. Normolle, J.M. Kirkwood, R.L. Ferris, G.M. Delgoffe, T.C. Bruno, C. J. Workman, D.A.A. Vignali, Interferon-gamma drives treg fragility to promote anti-tumor immunity, Cell 169 (6) (2017) 1130–1141, e11.
[105] V. Cervera-Carrascon, D.C.A. Quixabeira, J.M. Santos, R. Havunen, S. Zafar, O. Hemminki, C. Heiniö, E. Munaro, M. Siurala, S. Sorsa, T. Mirtti, P. Järvinen, M. Mildh, H. Nisen, A. Rannikko, M. Anttila, A. Kanerva, A. Hemminki, Tumor microenvironment remodeling by an engineered oncolytic adenovirus results in improved outcome from PD-L1 inhibition, OncoImmunology 9 (1) (2020), 1761229.
[106] F.F. Lang, C. Conrad, C. Gomez-Manzano, W.K.A. Yung, R. Sawaya, J.S. Weinberg, S.S. Prabhu, G. Rao, G.N. Fuller, K.D. Aldape, J. Gumin, L.M. Vence, I. Wistuba, J. Rodriguez-Canales, P.A. Villalobos, C.M.F. Dirven, S. Tejada, R.D. Valle, M. M. Alonso, B. Ewald, J.J. Peterkin, F. Tufaro, J. Fueyo, Phase I study of DNX-2401 (delta-24-RGD) oncolytic adenovirus: replication and immunotherapeutic effects in recurrent malignant glioma, J. Clin. Oncol. 36 (14) (2018) 1419–1427.
[107] J.D. Freedman, M.R. Duffy, J. Lei-Rossmann, A. Muntzer, E.M. Scott, J. Hagel, L. Campo, R.J. Bryant, C. Verrill, A. Lambert, P. Miller, B.R. Champion, L. W. Seymour, K.D. Fisher, An oncolytic virus expressing a T-cell engager simultaneously targets cancer and immunosuppressive stromal cells, Cancer Res. 78 (24) (2018) 6852–6865.
[108] K. Twumasi-Boateng, J.L. Pettigrew, Y.Y.E. Kwok, J.C. Bell, B.H. Nelson, Oncolytic viruses as engineering platforms for combination immunotherapy, Nat. Rev. Cancer 18 (7) (2018) 419–432.
[109] V. Leoni, A. Vannini, V. Gatta, J. Rambaldi, M. Sanapo, C. Barboni, A. Zaghini, P. Nanni, P.L. Lollini, C. Casiraghi, G. Campadelli-Fiume, A fully-virulent retargeted oncolytic HSV armed with IL-12 elicits local immunity and vaccine therapy towards distant tumors, PLoS Pathog. 14 (8) (2018), e1007209.
[110] A. Ribas, R. Dummer, I. Puzanov, A. VanderWalde, R.H.I. Andtbacka, O. Michielin, A.J. Olszanski, J. Malvehy, J. Cebon, E. Fernandez, J.M. Kirkwood, T.F. Gajewski, L. Chen, K.S. Gorski, A.A. Anderson, S.J. Diede, M.E. Lassman, J. Gansert, F.S. Hodi, G.V. Long, Oncolytic virotherapy promotes intratumoral t cell infiltration and improves anti-PD-1 immunotherapy, Cell 170 (6) (2017) 1109–1119, e10.
[111] M.C. Bourgeois-Daigneault, D.G. Roy, T. Falls, K. Twumasi-Boateng, L.E. St-Germain, M. Marguerie, V. Garcia, M. Selman, V.A. Jennings, J. Pettigrew, S. Amos, J.S. Diallo, B. Nelson, J.C. Bell, Oncolytic vesicular stomatitis virus expressing interferon-gamma has enhanced therapeutic activity, Mol. Ther. Oncolytics 3 (2016) 16001.
[112] G. Ren, G. Tian, Y. Liu, J. He, X. Gao, Y. Yu, X. Liu, X. Zhang, T. Sun, S. Liu, J. Yin, D. Li, Recombinant newcastle disease virus encoding IL-12 and/or IL-2 as potential candidate for hepatoma carcinoma therapy, Technol. Cancer Res. Treat. 15 (5) (2016) NP83–NP94.
[113] R. Bhat, S. Dempe, C. Dinsart, J. Rommelaere, Enhancement of NK cell antitumor responses using an oncolytic parvovirus, Int. J. Cancer 128 (4) (2011) 908–919.
[114] S. Grekova, M. Aprahamian, N. Giese, S. Schmitt, T. Giese, C.S. Falk, L. Daeffler, C. Cziepluch, J. Rommelaere, Z. Raykov, Immune cells participate in the oncosuppressive activity of parvovirus H-1PV and are activated as a result of their abortive infection with this agent, Cancer Biol. Ther. 10 (12) (2010) 1280–1289.
[115] A. Vigil, M.S. Park, O. Martinez, M.A. Chua, S. Xiao, J.F. Cros, L. Martinez-Sobrido, S.L. Woo, A. Garcia-Sastre, Use of reverse genetics to enhance the oncolytic properties of Newcastle disease virus, Cancer Res. 67 (17) (2007) 8285–8292.
[116] L. Heinzerling, V. Kunzi, P.A. Oberholzer, T. Kundig, H. Naim, R. Dummer, Oncolytic measles virus in cutaneous T-cell lymphomas mounts antitumor immune responses in vivo and targets interferon-resistant tumor cells, Blood 106 (7) (2005) 2287–2294.
[117] R.Y. Liu, Y.H. Zhu, L. Zhou, P. Zhao, H.L. Li, L.C. Zhu, H.Y. Han, H.X. Lin, L. Kang, J.X. Wu, W. Huang, Adenovirus-mediated delivery of interferon-gamma gene inhibits the growth of nasopharyngeal carcinoma, J. Transl. Med. 10 (2012) 256.
[118] C. Su, L. Peng, J. Sham, X. Wang, Q. Zhang, D. Chua, C. Liu, Z. Cui, H. Xue, H. Wu, Q. Yang, B. Zhang, X. Liu, M. Wu, Q. Qian, Immune gene-viral therapy with triplex efficacy mediated by oncolytic adenovirus carrying an interferon-gamma gene yields efficient antitumor activity in immunodeficient and immunocompetent mice, Mol. Ther. 13 (5) (2006) 918–927.
[119] H.M. Lazear, J.W. Schoggins, M.S. Diamond, Shared and distinct functions of type I and type III interferons, Immunity 50 (4) (2019) 907–923.
[120] E.V. Mesev, R.A. LeDesma, A. Ploss, Decoding type I and III interferon signalling during viral infection, Nat. Microbiol. 4 (6) (2019) 914–924.
[121] A.I. Wells, C.B. Coyne, Type III interferons in antiviral defenses at barrier surfaces, Trends Immunol. 39 (10) (2018) 848–858.
[122] N. Ank, M.B. Iversen, C. Bartholdy, P. Staeheli, R. Hartmann, U.B. Jensen, F. Dagnaes-Hansen, A.R. Thomsen, Z. Chen, H. Haugen, K. Klucher, S.R. Paludan, An important role for type III interferon (IFN-lambda/IL-28) in TLR-induced antiviral activity, J. Immunol. 180 (4) (2008) 2474–2485.
[123] L. Ye, D. Schnepf, P. Staeheli, Interferon-lambda orchestrates innate and adaptive mucosal immune responses, Nat. Rev. Immunol. 19 (10) (2019) 614–625.
[124] C. Odendall, J.C. Kagan, The unique regulation and functions of type III interferons in antiviral immunity, Curr. Opin. Virol. 12 (2015) 47–52.
[125] P. Wongthida, R.M. Diaz, F. Galivo, T. Kottke, J. Thompson, J. Pulido, K. Pavelko, L. Pease, A. Melcher, R. Vile, Type III IFN interleukin-28 mediates the antitumor efficacy of oncolytic virus VSV in immune-competent mouse models of cancer, Cancer Res. 70 (11) (2010) 4539–4549.
[126] P. Wongthida, R.M. Diaz, F. Galivo, T. Kottke, J. Thompson, A. Melcher, R. Vile, VSV oncolytic virotherapy in the B16 model depends upon intact MyD88 signaling, Mol. Ther. 19 (1) (2011) 150–158.
[127] J.G. Pol, P. Caudana, J. Paillet, E. Piaggio, G. Kroemer, Effects of interleukin-2 in immunostimulation and immunosuppression, J. Exp. Med. 217 (1) (2020).
[128] D. Busse, M. de la Rosa, K. Hobiger, K. Thurley, M. Flossdorf, A. Scheffold, T. Hofer, Competing feedback loops shape IL-2 signaling between helper and regulatory T lymphocytes in cellular microenvironments, Proc. Natl. Acad. Sci. U. S. A. 107 (7) (2010) 3058–3063.
[129] K. Watanabe, Y. Luo, T. Da, S. Guedan, M. Ruella, J. Scholler, B. Keith, R. M. Young, B. Engels, S. Sorsa, M. Siurala, R. Havunen, S. Tahtinen, A. Hemminki, C.H. June, Pancreatic cancer therapy with combined mesothelin-redirected chimeric antigen receptor T cells and cytokine-armed oncolytic adenoviruses, JCI Insight 3 (7) (2018).
[130] Z. Liu, Y. Ge, H. Wang, C. Ma, M. Feist, S. Ju, Z.S. Guo, D.L. Bartlett, Modifying the cancer-immune set point using vaccinia virus expressing re-designed interleukin-2, Nat. Commun. 9 (1) (2018) 4682.
[131] D. Zamarin, A. Vigil, K. Kelly, A. Garcia-Sastre, Y. Fong, Genetically engineered Newcastle disease virus for malignant melanoma therapy, Gene Ther. 16 (6) (2009) 796–804.
[132] M. Janke, B. Peeters, H. Zhao, O. de Leeuw, R. Moorman, A. Arnold, Y. Ziouta, P. Fournier, V. Schirrmacher, Activation of human T cells by a tumor vaccine infected with recombinant Newcastle disease virus producing IL-2, Int. J. Oncol. 33 (4) (2008) 823–832.
[133] J.F. Carew, D.A. Kooby, M.W. Halterman, S.H. Kim, H.J. Federoff, Y. Fong, A novel approach to cancer therapy using an oncolytic herpes virus to package amplicons containing cytokine genes, Mol. Ther. 4 (3) (2001) 250–256.
[134] H. Zhao, M. Janke, P. Fournier, V. Schirrmacher, Recombinant Newcastle disease virus expressing human interleukin-2 serves as a potential candidate for tumor therapy, Virus Res. 136 (1–2) (2008) 75–80.
[135] E.D. Tait Wojno, C.A. Hunter, J.S. Stumhofer, The immunobiology of the interleukin-12 family: room for discovery, Immunity 50 (4) (2019) 851–870.
[136] S. Tugues, S.H. Burkhard, I. Ohs, M. Vrohlings, K. Nussbaum, J. Vom Berg, P. Kulig, B. Becher, New insights into IL-12-mediated tumor suppression, Cell Death Differ. 22 (2) (2015) 237–246.
[137] G. Trinchieri, Interleukin-12 and the regulation of innate resistance and adaptive immunity, Nat. Rev. Immunol. 3 (2) (2003) 133–146.
[138] X.L. Yin, N. Wang, X. Wei, G.F. Xie, J.J. Li, H.J. Liang, Interleukin-12 inhibits the survival of human colon cancer stem cells in vitro and their tumor initiating capacity in mice, Cancer Lett. 322 (1) (2012) 92–97.
[139] J.D. Marshall, H. Secrist, R.H. DeKruyff, S.F. Wolf, D.T. Umetsu, IL-12 inhibits the production of IL-4 and IL-10 in allergen-specific human CD4+ T lymphocytes, J. Immunol. 155 (1) (1995) 111–117.
[140] X. Shi, S. Cao, M. Mitsuhashi, Z. Xiang, X. Ma, Genome-wide analysis of molecular changes in IL-12-induced control of mammary carcinoma via IFN-gamma-independent mechanisms, J. Immunol. 172 (7) (2004) 4111–4122.
[141] Y. Ge, H. Wang, J. Ren, W. Liu, L. Chen, H. Chen, J. Ye, E. Dai, C. Ma, S. Ju, Z. S. Guo, Z. Liu, D.L. Bartlett, Oncolytic vaccinia virus delivering tethered IL-12 enhances antitumor effects with improved safety, J. Immunother. Cancer 8 (1) (2020).
[142] P. Wang, X. Li, J. Wang, D. Gao, Y. Li, H. Li, Y. Chu, Z. Zhang, H. Liu, G. Jiang, Z. Cheng, S. Wang, J. Dong, B. Feng, L.S. Chard, N.R. Lemoine, Y. Wang, Re-designing Interleukin-12 to enhance its safety and potential as an anti-tumor immunotherapeutic agent, Nat. Commun. 8 (1) (2017) 1395.
[143] T.A. Cheema, H. Wakimoto, P.E. Fecci, J. Ning, T. Kuroda, D.S. Jeyaretna, R. L. Martuza, S.D. Rabkin, Multifaceted oncolytic virus therapy for glioblastoma in an immunocompetent cancer stem cell model, Proc. Natl. Acad. Sci. U. S. A. 110 (29) (2013) 12006–12011.
[144] I.K. Choi, J.S. Lee, S.N. Zhang, J. Park, C.H. Sonn, K.M. Lee, C.O. Yun, Oncolytic adenovirus co-expressing IL-12 and IL-18 improves tumor-specific immunity via differentiation of T cells expressing IL-12Rbeta2 or IL-18Ralpha, Gene Ther. 18 (9) (2011) 898–909.
[145] Y.S. Lee, J.H. Kim, K.J. Choi, I.K. Choi, H. Kim, S. Cho, B.C. Cho, C.O. Yun, Enhanced antitumor effect of oncolytic adenovirus expressing interleukin-12 and B7-1 in an immunocompetent murine model, Clin. Cancer Res. 12 (19) (2006) 5859–5868.
[146] S. Nakao, Y. Arai, M. Tasaki, M. Yamashita, R. Murakami, T. Kawase, N. Amino, M. Nakatake, H. Kurosaki, M. Mori, M. Takeuchi, T. Nakamura, Intratumoral expression of IL-7 and IL-12 using an oncolytic virus increases systemic sensitivity to immune checkpoint blockade, Sci. Transl. Med. 12 (526) (2020).

[147] H.M. Nguyen, K. Guz-Montgomery, D. Saha, Oncolytic virus encoding a master pro-inflammatory cytokine interleukin 12 in cancer immunotherapy, Cells 9 (2) (2020).
[148] F. Alessandrini, L. Menotti, E. Avitabile, I. Appolloni, D. Ceresa, D. Marubbi, G. Campadelli-Fiume, P. Malatesta, Eradication of glioblastoma by immuno-virotherapy with a retargeted oncolytic HSV in a preclinical model, Oncogene 38 (23) (2019) 4467–4479.
[149] P.S. Backhaus, R. Veinalde, L. Hartmann, J.E. Dunder, L.M. Jeworowski, J. Albert, B. Hoyler, T. Poth, D. Jager, G. Ungerechts, C.E. Engeland, Immunological effects and viral gene expression determine the efficacy of oncolytic measles vaccines encoding IL-12 or IL-15 agonists, Viruses 11 (10) (2019).
[150] D. Saha, R.L. Martuza, S.D. Rabkin, Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade, Cancer Cell 32 (2) (2017) 253–267, e5.
[151] R. Veinalde, C. Grossardt, L. Hartmann, M.C. Bourgeois-Daigneault, J.C. Bell, D. Jager, C. von Kalle, G. Ungerechts, C.E. Engeland, Oncolytic measles virus encoding interleukin-12 mediates potent antitumor effects through T cell activation, Oncoimmunology 6 (4) (2017), e1285992.
[152] A.A. Alkayyal, L.H. Tai, M.A. Kennedy, C.T. de Souza, J. Zhang, C. Lefebvre, S. Sahi, A.A. Ananth, A.B. Mahmoud, A.P. Makrigiannis, G.O. Cron, B. Macdonald, E.C. Marginean, D.F. Stojdl, J.C. Bell, R.C. Auer, NK-cell recruitment is necessary for eradication of peritoneal carcinomatosis with an IL12-expressing maraba virus cellular vaccine, Cancer Immunol. Res. 5 (3) (2017) 211–221.
[153] J. Poutou, M. Bunuales, M. Gonzalez-Aparicio, E. Garcia-Aragoncillo, J. I. Quetglas, R. Casado, C. Bravo-Perez, P. Alzuguren, R. Hernandez-Alcoceba, Safety and antitumor effect of oncolytic and helper-dependent adenoviruses expressing interleukin-12 variants in a hamster pancreatic cancer model, Gene Ther. 22 (9) (2015) 696–706.
[154] J.C. Roth, K.A. Cassady, J.J. Cody, J.N. Parker, K.H. Price, J.M. Coleman, J. O. Peggins, P.E. Noker, N.W. Powers, S.D. Grimes, S.L. Carroll, G.Y. Gillespie, R. J. Whitley, J.M. Markert, Evaluation of the safety and biodistribution of M032, an attenuated herpes simplex virus type 1 expressing hIL-12, after intracerebral administration to aotus nonhuman primates, Hum. Gene Ther. Clin. Dev. 25 (1) (2014) 16–27.
[155] W. Zhang, G. Fulci, H. Wakimoto, T.A. Cheema, J.S. Buhrman, D.S. Jeyaretna, A. O. Stemmer Rachamimov, S.D. Rabkin, R.L. Martuza, Combination of oncolytic herpes simplex viruses armed with angiostatin and IL-12 enhances antitumor efficacy in human glioblastoma models, Neoplasia 15 (6) (2013) 591–599.
[156] S.O. Freytag, K.N. Barton, Y. Zhang, Efficacy of oncolytic adenovirus expressing suicide genes and interleukin-12 in preclinical model of prostate cancer, Gene Ther. 20 (12) (2013) 1131–1139.
[157] L.A. Gillory, M.L. Megison, J.E. Stewart, E. Mroczek-Musulman, H.C. Nabers, A. M. Waters, V. Kelly, J.M. Coleman, J.M. Markert, G.Y. Gillespie, G.K. Friedman, E. A. Beierle, Preclinical evaluation of engineered oncolytic herpes simplex virus for the treatment of neuroblastoma, PLoS One 8 (10) (2013), e77753.
[158] B.J. Passer, T. Cheema, S. Wu, C.L. Wu, S.D. Rabkin, R.L. Martuza, Combination of vinblastine and oncolytic herpes simplex virus vector expressing IL-12 therapy increases antitumor and antiangiogenic effects in prostate cancer models, Cancer Gene Ther. 20 (1) (2013) 17–24.
[159] J.J. Cody, P. Scaturro, A.B. Cantor, G. Yancey Gillespie, J.N. Parker, J.M. Markert, Preclinical evaluation of oncolytic deltagamma(1)34.5 herpes simplex virus expressing interleukin-12 for therapy of breast cancer brain metastases, Int. J. Breast Cancer 2012 (2012), 628697.
[160] S.N. Zhang, I.K. Choi, J.H. Huang, J.Y. Yoo, K.J. Choi, C.O. Yun, Optimizing DC vaccination by combination with oncolytic adenovirus coexpressing IL-12 and GM-CSF, Mol. Ther. 19 (8) (2011) 1558–1568.
[161] J.H. Huang, S.N. Zhang, K.J. Choi, I.K. Choi, J.H. Kim, M.G. Lee, H. Kim, C. O. Yun, Therapeutic and tumor-specific immunity induced by combination of dendritic cells and oncolytic adenovirus expressing IL-12 and 4-1BBL, Mol. Ther. 18 (2) (2010) 264–274.
[162] S. Bortolanza, M. Bunuales, I. Otano, G. Gonzalez-Aseguinolaza, C. Ortiz-de-Solorzano, D. Perez, J. Prieto, R. Hernandez-Alcoceba, Treatment of pancreatic cancer with an oncolytic adenovirus expressing interleukin-12 in Syrian hamsters, Mol. Ther. 17 (4) (2009) 614–622.
[163] E.J. Shin, G.B. Wanna, B. Choi, D. Aguila 3rd, O. Ebert, E.M. Genden, S.L. Woo, Interleukin-12 expression enhances vesicular stomatitis virus oncolytic therapy in murine squamous cell carcinoma, Laryngoscope 117 (2) (2007) 210–214.
[164] B.G. Derubertis, B.M. Stiles, A. Bhargava, N.J. Gusani, M. Hezel, M. D'Angelica, Y. Fong, Cytokine-secreting herpes viral mutants effectively treat tumor in a murine metastatic colorectal liver model by oncolytic and T-cell-dependent mechanisms, Cancer Gene Ther. 14 (6) (2007) 590–597.
[165] S. Varghese, S.D. Rabkin, R. Liu, P.G. Nielsen, T. Ipe, R.L. Martuza, Enhanced therapeutic efficacy of IL-12, but not GM-CSF, expressing oncolytic herpes simplex virus for transgenic mouse derived prostate cancers, Cancer Gene Ther. 13 (3) (2006) 253–265.
[166] Y. Ino, Y. Saeki, H. Fukuhara, T. Todo, Triple combination of oncolytic herpes simplex virus-1 vectors armed with interleukin-12, interleukin-18, or soluble B7-1 results in enhanced antitumor efficacy, Clin. Cancer Res. 12 (2) (2006) 643–652.
[167] R.J. Wong, M.K. Chan, Z. Yu, R.A. Ghossein, I. Ngai, P.S. Adusumilli, B.M. Stiles, J.P. Shah, B. Singh, Y. Fong, Angiogenesis inhibition by an oncolytic herpes virus expressing interleukin 12, Clin. Cancer Res. 10 (13) (2004) 4509–4516.
[168] J.N. Parker, G.Y. Gillespie, C.E. Love, S. Randall, R.J. Whitley, J.M. Markert, Engineered herpes simplex virus expressing IL-12 in the treatment of experimental murine brain tumors, Proc. Natl. Acad. Sci. U. S. A. 97 (5) (2000) 2208–2213.
[169] O.A. Haabeth, A.A. Tveita, M. Fauskanger, F. Schjesvold, K.B. Lorvik, P. O. Hofgaard, H. Omholt, L.A. Munthe, Z. Dembic, A. Corthay, B. Bogen, How do CD4(+) T cells detect and eliminate tumor cells that either lack or express MHC class II molecules? Front. Immunol. 5 (2014) 174.
[170] S. Ikemizu, M. Chirifu, S.J. Davis, IL-2 and IL-15 signaling complexes: different but the same, Nat. Immunol. 13 (12) (2012) 1141–1142.
[171] Q. Hu, X. Ye, X. Qu, D. Cui, L. Zhang, Z. Xu, H. Wan, L. Zhang, W. Tao, Discovery of a novel IL-15 based protein with improved developability and efficacy for cancer immunotherapy, Sci. Rep. 8 (1) (2018) 7675.
[172] T.A. Waldmann, S. Dubois, Y. Tagaya, Contrasting roles of IL-2 and IL-15 in the life and death of lymphocytes: implications for immunotherapy, Immunity 14 (2) (2001) 105–110.
[173] T.A. Waldmann, The biology of interleukin-2 and interleukin-15: implications for cancer therapy and vaccine design, Nat. Rev. Immunol. 6 (8) (2006) 595–601.
[174] E. Mortier, T. Woo, R. Advincula, S. Gozalo, A. Ma, IL-15Ralpha chaperones IL-15 to stable dendritic cell membrane complexes that activate NK cells via trans presentation, J. Exp. Med. 205 (5) (2008) 1213–1225.
[175] C. Bergamaschi, J. Bear, M. Rosati, R.K. Beach, C. Alicea, R. Sowder, E. Chertova, S.A. Rosenberg, B.K. Felber, G.N. Pavlakis, Circulating IL-15 exists as heterodimeric complex with soluble IL-15Ralpha in human and mouse serum, Blood 120 (1) (2012) e1–8.
[176] R.M. Santana Carrero, F. Beceren-Braun, S.C. Rivas, S.M. Hegde, A. Gangadharan, D. Plote, G. Pham, S.M. Anthony, K.S. Schluns, IL-15 is a component of the inflammatory milieu in the tumor microenvironment promoting antitumor responses, Proc. Natl. Acad. Sci. U. S. A. 116 (2) (2019) 599–608.
[177] P. Yu, J.C. Steel, M. Zhang, J.C. Morris, R. Waitz, M. Fasso, J.P. Allison, T. A. Waldmann, Simultaneous inhibition of two regulatory T-cell subsets enhanced Interleukin-15 efficacy in a prostate tumor model, Proc. Natl. Acad. Sci. U. S. A. 109 (16) (2012) 6187–6192.
[178] C.A. Klebanoff, S.E. Finkelstein, D.R. Surman, M.K. Lichtman, L. Gattinoni, M. R. Theoret, N. Grewal, P.J. Spiess, P.A. Antony, D.C. Palmer, Y. Tagaya, S. A. Rosenberg, T.A. Waldmann, N.P. Restifo, IL-15 enhances the in vivo antitumor activity of tumor-reactive CD8+ T cells, Proc. Natl. Acad. Sci. U. S. A. 101 (7) (2004) 1969–1974.
[179] M.A. Curran, T.L. Geiger, W. Montalvo, M. Kim, S.L. Reiner, A. Al-Shamkhani, J. C. Sun, J.P. Allison, Systemic 4-1BB activation induces a novel T cell phenotype driven by high expression of Eomesodermin, J. Exp. Med. 210 (4) (2013) 743–755.
[180] B. Mlecnik, G. Bindea, H.K. Angell, M.S. Sasso, A.C. Obenauf, T. Fredriksen, L. Lafontaine, A.M. Bilocq, A. Kirilovsky, M. Tosolini, M. Waldner, A. Berger, W. H. Fridman, A. Rafii, V. Valge-Archer, F. Pages, M.R. Speicher, J. Galon, Functional network pipeline reveals genetic determinants associated with in situ lymphocyte proliferation and survival of cancer patients, Sci. Transl. Med. 6 (228) (2014), 228ra37.
[181] K. Hock, J. Laengle, I. Kuznetsova, A. Egorov, B. Hegedus, B. Dome, T. Wekerle, M. Sachet, M. Bergmann, Oncolytic influenza A virus expressing interleukin-15 decreases tumor growth in vivo, Surgery 161 (3) (2017) 735–746.
[182] M. van Rikxoort, M. Michaelis, M. Wolschek, T. Muster, A. Egorov, J. Seipelt, H. W. Doerr, J. Cinatl Jr., Oncolytic effects of a novel influenza A virus expressing interleukin-15 from the NS reading frame, PLoS One 7 (5) (2012), e36506.
[183] K.B. Stephenson, N.G. Barra, E. Davies, A.A. Ashkar, B.D. Lichty, Expressing human interleukin-15 from oncolytic vesicular stomatitis virus improves survival in a murine metastatic colon adenocarcinoma model through the enhancement of anti-tumor immunity, Cancer Gene Ther. 19 (4) (2012) 238–246.
[184] S.J. Kowalsky, Z. Liu, M. Feist, S.E. Berkey, C. Ma, R. Ravindranathan, E. Dai, E. J. Roy, Z.S. Guo, D.L. Bartlett, Superagonist IL-15-Armed oncolytic virus elicits potent antitumor immunity and therapy that are enhanced with PD-1 blockade, Mol. Ther. 26 (10) (2018) 2476–2486.
[185] D.C. Gaston, C.I. Odom, L. Li, J.M. Markert, J.C. Roth, K.A. Cassady, R.J. Whitley, J.N. Parker, Production of bioactive soluble interleukin-15 in complex with interleukin-15 receptor alpha from a conditionally-replicating oncolytic HSV-1, PLoS One 8 (11) (2013), e81768.
[186] J. Gao, L. Zhao, Y.Y. Wan, B. Zhu, Mechanism of action of IL-7 and its potential applications and limitations in cancer immunotherapy, Int. J. Mol. Sci. 16 (5) (2015) 10267–10280.
[187] P.T. Mehrotra, A.J. Grant, J.P. Siegel, Synergistic effects of IL-7 and IL-12 on human T cell activation, J. Immunol. 154 (10) (1995) 5093–5102.
[188] J.K. Fields, S. Gunther, E.J. Sundberg, Structural basis of IL-1 family cytokine signaling, Front. Immunol. 10 (2019) 1412.
[189] L. Iula, I.A. Keitelman, F. Sabbione, F. Fuentes, M. Guzman, J.G. Galletti, P. P. Gerber, M. Ostrowski, J.R. Geffner, C.C. Jancic, A.S. Trevani, Autophagy mediates Interleukin-1beta secretion in human neutrophils, Front. Immunol. 9 (2018) 269.
[190] C.A. Dinarello, Immunological and inflammatory functions of the interleukin-1 family, Annu. Rev. Immunol. 27 (2009) 519–550.
[191] G. Biffi, T.E. Oni, B. Spielman, Y. Hao, E. Elyada, Y. Park, J. Preall, D.A. Tuveson, IL1-induced JAK/STAT signaling is antagonized by TGFbeta to shape CAF heterogeneity in pancreatic ductal adenocarcinoma, Cancer Discov. 9 (2) (2019) 282–301.
[192] R. Basu, S.K. Whitley, S. Bhaumik, C.L. Zindl, T.R. Schoeb, E.N. Benveniste, W. S. Pear, R.D. Hatton, C.T. Weaver, IL-1 signaling modulates activation of STAT transcription factors to antagonize retinoic acid signaling and control the TH17 cell-iTreg cell balance, Nat. Immunol. 16 (3) (2015) 286–295.
[193] S.T. Ahmed, L.B. Ivashkiv, Inhibition of IL-6 and IL-10 signaling and Stat activation by inflammatory and stress pathways, J. Immunol. 165 (9) (2000) 5227–5237.

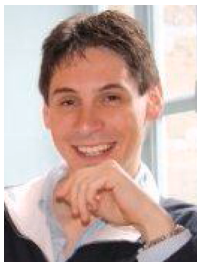
[194] C. Garlanda, C.A. Dinarello, A. Mantovani, The interleukin-1 family: back to the future, Immunity 39 (6) (2013) 1003–1018.
[195] L.D. Aarreberg, C. Wilkins, H.J. Ramos, R. Green, M.A. Davis, K. Chow, M. Gale Jr., Interleukin-1beta signaling in dendritic cells induces antiviral interferon responses, mBio 9 (2) (2018).
[196] M.H. Orzalli, A. Smith, K.A. Jurado, A. Iwasaki, J.A. Garlick, J.C. Kagan, An antiviral branch of the IL-1 signaling pathway restricts immune-evasive virus replication, Mol. Cell 71 (5) (2018) 825–840, e6.
[197] G. Chevillard, A. Derjuga, D. Devost, H.H. Zingg, V. Blank, Identification of interleukin-1beta regulated genes in uterine smooth muscle cells, Reproduction 134 (6) (2007) 811–822.
[198] S.K. Biswas, A. Sica, C.E. Lewis, Plasticity of macrophage function during tumor progression: regulation by distinct molecular mechanisms, J. Immunol. 180 (4) (2008) 2011–2017.
[199] E. Molina-Holgado, S. Ortiz, F. Molina-Holgado, C. Guaza, Induction of COX-2 and PGE(2) biosynthesis by IL-1beta is mediated by PKC and mitogen-activated protein kinases in murine astrocytes, Br. J. Pharmacol. 131 (1) (2000) 152–159.
[200] H.J. Anders, Of Inflammasomes and Alarmins: IL-1beta and IL-1alpha in Kidney Disease, J. Am. Soc. Nephrol. 27 (9) (2016) 2564–2575.
[201] K.D. Mayer-Barber, B. Yan, Clash of the Cytokine Titans: counter-regulation of interleukin-1 and type I interferon-mediated inflammatory responses, Cell. Mol. Immunol. 14 (1) (2017) 22–35.
[202] S.Z. Ben-Sasson, A. Hogg, J. Hu-Li, P. Wingfield, X. Chen, M. Crank, S. Caucheteux, M. Ratner-Hurevich, J.A. Berzofsky, R. Nir-Paz, W.E. Paul, IL-1 enhances expansion, effector function, tissue localization, and memory response of antigen-specific CD8 T cells, J. Exp. Med. 210 (3) (2013) 491–502.
[203] S.Z. Ben-Sasson, J. Hu-Li, J. Quiel, S. Cauchetaux, M. Ratner, I. Shapira, C. A. Dinarello, W.E. Paul, IL-1 acts directly on CD4 T cells to enhance their antigen-driven expansion and differentiation, Proc. Natl. Acad. Sci. U. S. A. 106 (17) (2009) 7119–7124.
[204] S. Setrerrahmane, H. Xu, Tumor-related interleukins: old validated targets for new anti-cancer drug development, Mol. Cancer 16 (1) (2017) 153.
[205] C.Y. Cheng, C.T. Kuo, C.C. Lin, H.L. Hsieh, C.M. Yang, IL-1beta induces expression of matrix metalloproteinase-9 and cell migration via a c-Src-dependent, growth factor receptor transactivation in A549 cells, Br. J. Pharmacol. 160 (7) (2010) 1595–1610.
[206] T. Watanabe, T. Hashimoto, T. Sugino, S. Soeda, H. Nishiyama, Y. Morimura, H. Yamada, S. Goodison, K. Fujimori, Production of IL1-beta by ovarian cancer cells induces mesothelial cell beta1-integrin expression facilitating peritoneal dissemination, J. Ovarian Res. 5 (1) (2012) 7.
[207] I. Kogan-Sakin, M. Cohen, N. Paland, S. Madar, H. Solomon, A. Molchadsky, R. Brosh, Y. Buganim, N. Goldfinger, H. Klocker, J.A. Schalken, V. Rotter, Prostate stromal cells produce CXCL-1, CXCL-2, CXCL-3 and IL-8 in response to epithelia-secreted IL-1, Carcinogenesis 30 (4) (2009) 698–705.
[208] J. Ma, X. Sun, T. Guo, H. Su, Q. Chen, Z. Gong, J. Qi, X. Zhao, Interleukin-1 receptor antagonist inhibits angiogenesis via blockage IL-1alpha/PI3K/NF-kappabeta pathway in human colon cancer cell, Cancer Manag. Res. 9 (2017) 481–493.
[209] E.J. Small, M.A. Carducci, J.M. Burke, R. Rodriguez, L. Fong, L. van Ummersen, D. C. Yu, J. Aimi, D. Ando, P. Working, D. Kirn, G. Wilding, A phase I trial of intravenous CG7870, a replication-selective, prostate-specific antigen-targeted oncolytic adenovirus, for the treatment of hormone-refractory, metastatic prostate cancer, Mol. Ther. 14 (1) (2006) 107–117.
[210] C. Colarusso, M. Terlizzi, A. Molino, P. Imitazione, P. Somma, R. Rega, A. Saccomanno, R.P. Aquino, A. Pinto, R. Sorrentino, AIM2 inflammasome activation leads to IL-1alpha and TGF-beta release from exacerbated chronic obstructive pulmonary disease-derived peripheral blood mononuclear cells, Front. Pharmacol. 10 (2019) 257.
[211] K.J. Hupa, K. Stein, R. Schneider, M. Lysson, B. Schneiker, V. Hornung, E. Latz, Y. Iwakura, J.C. Kalff, S. Wehner, AIM2 inflammasome-derived IL-1beta induces postoperative ileus in mice, Sci. Rep. 9 (1) (2019) 10602.
[212] M. Akdis, A. Aab, C. Altunbulakli, K. Azkur, R.A. Costa, R. Crameri, S. Duan, T. Eiwegger, A. Eljaszewicz, R. Ferstl, R. Frei, M. Garbani, A. Globinska, L. Hess, C. Huitema, T. Kubo, Z. Komlosi, P. Konieczna, N. Kovacs, U.C. Kucuksezer, N. Meyer, H. Morita, J. Olzhausen, L. O'Mahony, M. Pezer, M. Prati, A. Rebane, C. Rhyner, A. Rinaldi, M. Sokolowska, B. Stanic, K. Sugita, A. Treis, W. van de Veen, K. Wanke, M. Wawrzyniak, P. Wawrzyniak, O.F. Wirz, J.S. Zakzuk, C. A. Akdis, Interleukins (from IL-1 to IL-38), interferons, transforming growth factor beta, and TNF-alpha: receptors, functions, and roles in diseases, J. Allergy Clin. Immunol. 138 (4) (2016) 984–1010.
[213] T.C. Barnes, M.E. Anderson, R.J. Moots, The many faces of interleukin-6: the role of IL-6 in inflammation, vasculopathy, and fibrosis in systemic sclerosis, Int. J. Rheumatol. 2011 (2011), 721608.
[214] T. Tanaka, M. Narazaki, T. Kishimoto, IL-6 in inflammation, immunity, and disease, Cold Spring Harb. Perspect. Biol. 6 (10) (2014), a016295.
[215] T. Korn, E. Bettelli, M. Oukka, V.K. Kuchroo, IL-17 and Th17 cells, Annu. Rev. Immunol. 27 (2009) 485–517.
[216] E. Bettelli, Y. Carrier, W. Gao, T. Korn, T.B. Strom, M. Oukka, H.L. Weiner, V. K. Kuchroo, Reciprocal developmental pathways for the generation of pathogenic effector TH17 and regulatory T cells, Nature 441 (7090) (2006) 235–238.
[217] M. Okada, M. Kitahara, S. Kishimoto, T. Matsuda, T. Hirano, T. Kishimoto, IL-6/BSF-2 functions as a killer helper factor in the in vitro induction of cytotoxic T cells, J. Immunol. 141 (5) (1988) 1543–1549.
[218] D.C. Chonov, M.M.K. Ignatova, J.R. Ananiev, M.V. Gulubova, IL-6 activities in the tumour microenvironment. Part 1, Open Access Maced. J. Med. Sci. 7 (14) (2019) 2391–2398.
[219] J.F. Fonteneau, J.B. Guillerme, F. Tangy, M. Gregoire, Attenuated measles virus used as an oncolytic virus activates myeloid and plasmacytoid dendritic cells, Oncoimmunology 2 (5) (2013), e24212.
[220] J.B. Sturm, M. Hess, S. Weibel, N.G. Chen, Y.A. Yu, Q. Zhang, U. Donat, C. Reiss, S. Gambaryan, G. Krohne, J. Stritzker, A.A. Szalay, Functional hyper-IL-6 from vaccinia virus-colonized tumors triggers platelet formation and helps to alleviate toxicity of mitomycin C enhanced virus therapy, J. Transl. Med. 10 (2012) 9.
[221] D.A.B. Rex, N. Agarwal, T.S.K. Prasad, R.K. Kandasamy, Y. Subbannayya, S. M. Pinto, A comprehensive pathway map of IL-18-mediated signalling, J. Cell Commun. Signal. 14 (2) (2020) 257–266.
[222] K.J. Baker, A. Houston, E. Brint, IL-1 family members in cancer; two sides to every story, Front. Immunol. 10 (2019) 1197.
[223] J.K. Lee, S.H. Kim, E.C. Lewis, T. Azam, L.L. Reznikov, C.A. Dinarello, Differences in signaling pathways by IL-1beta and IL-18, Proc. Natl. Acad. Sci. U. S. A. 101 (23) (2004) 8815–8820.
[224] L.L. Reznikov, S.H. Kim, J.Y. Westcott, J. Frishman, G. Fantuzzi, D. Novick, M. Rubinstein, C.A. Dinarello, IL-18 binding protein increases spontaneous and IL-1-induced prostaglandin production via inhibition of IFN-gamma, Proc. Natl. Acad. Sci. U. S. A. 97 (5) (2000) 2174–2179.
[225] K. Yasuda, K. Nakanishi, H. Tsutsui, Interleukin-18 in health and disease, Int. J. Mol. Sci. 20 (3) (2019).
[226] K. Nakanishi, Unique action of Interleukin-18 on t cells and other immune cells, Front. Immunol. 9 (2018) 763.
[227] K. Tominaga, T. Yoshimoto, K. Torigoe, M. Kurimoto, K. Matsui, T. Hada, H. Okamura, K. Nakanishi, IL-12 synergizes with IL-18 or IL-1beta for IFN-gamma production from human T cells, Int. Immunol. 12 (2) (2000) 151–160.
[228] H. Fukuhara, Y. Ino, T. Kuroda, R.L. Martuza, T. Todo, Triple gene-deleted oncolytic herpes simplex virus vector double-armed with interleukin 18 and soluble B7-1 constructed by bacterial artificial chromosome-mediated system, Cancer Res. 65 (23) (2005) 10663–10668.
[229] J.N. Zheng, D.S. Pei, L.J. Mao, X.Y. Liu, F.H. Sun, B.F. Zhang, Y.Q. Liu, J.J. Liu, W. Li, D. Han, Oncolytic adenovirus expressing interleukin-18 induces significant antitumor effects against melanoma in mice through inhibition of angiogenesis, Cancer Gene Ther. 17 (1) (2010) 28–36.
[230] C. Yang, H. Cao, N. Liu, K. Xu, M. Ding, L.J. Mao, Oncolytic adenovirus expressing interleukin-18 improves antitumor activity of dacarbazine for malignant melanoma, Drug Des. Devel. Ther. 10 (2016) 3755–3761.
[231] S. Colak, P. Ten Dijke, Targeting TGF-beta signaling in cancer, Trends Cancer 3 (1) (2017) 56–71.
[232] C. Groeneveldt, T. van Hall, S.H. van der Burg, P. Ten Dijke, N. van Montfoort, Immunotherapeutic potential of TGF-beta inhibition and oncolytic viruses, Trends Immunol. 41 (5) (2020) 406–420.
[233] K. Harrington, D.J. Freeman, B. Kelly, J. Harper, J.C. Soria, Optimizing oncolytic virotherapy in cancer treatment, Nat. Rev. Drug Discov. 18 (9) (2019) 689–706.
[234] E. Eriksson, I. Milenova, J. Wenthe, R. Moreno, R. Alemany, A. Loskog, IL-6 signaling blockade during CD40-mediated immune activation favors antitumor factors by reducing TGF-beta, collagen type I, and PD-L1/PD-1, J. Immunol. 202 (3) (2019) 787–798.
[235] E. Eriksson, I. Milenova, J. Wenthe, M. Stahle, J. Leja-Jarblad, G. Ullenhag, A. Dimberg, R. Moreno, R. Alemany, A. Loskog, Shaping the tumor stroma and sparking immune activation by CD40 and 4-1BB signaling induced by an armed oncolytic virus, Clin. Cancer Res. 23 (19) (2017) 5846–5857.
[236] E. Oh, I.K. Choi, J. Hong, C.O. Yun, Oncolytic adenovirus coexpressing interleukin-12 and decorin overcomes Treg-mediated immunosuppression inducing potent antitumor effects in a weakly immunogenic tumor model, Oncotarget 8 (3) (2017) 4730–4746.
[237] K.C. Soares, A.A. Rucki, V. Kim, K. Foley, S. Solt, C.L. Wolfgang, E.M. Jaffee, L. Zheng, TGF-beta blockade depletes T regulatory cells from metastatic pancreatic tumors in a vaccine dependent manner, Oncotarget 6 (40) (2015) 43005–43015.
[238] N.L. Denton, C.Y. Chen, B. Hutzen, M.A. Currier, T. Scott, B. Nartker, J.L. Leddon, P.Y. Wang, R. Srinivas, K.A. Cassady, W.F. Goins, T.P. Cripe, Myelolytic treatments enhance oncolytic herpes virotherapy in models of ewing sarcoma by modulating the immune microenvironment, Mol. Ther. Oncolytics 11 (2018) 62–74.
[239] S. Esaki, F. Nigim, E. Moon, S. Luk, J. Kiyokawa, W. Curry Jr., D.P. Cahill, A. S. Chi, A.J. Iafrate, R.L. Martuza, S.D. Rabkin, H. Wakimoto, Blockade of transforming growth factor-beta signaling enhances oncolytic herpes simplex virus efficacy in patient-derived recurrent glioblastoma models, Int. J. Cancer 141 (11) (2017) 2348–2358.
[240] B. Hutzen, C.Y. Chen, P.Y. Wang, L. Sprague, H.M. Swain, J. Love, J. Conner, L. Boon, T.P. Cripe, TGF-beta inhibition improves oncolytic herpes viroimmunotherapy in murine models of Rhabdomyosarcoma, Mol. Ther. Oncolytics 7 (2017) 17–26.
[241] Y. Li, F. Xiao, A. Zhang, D. Zhang, W. Nie, T. Xu, B. Han, P. Seth, H. Wang, Y. Yang, L. Wang, Oncolytic adenovirus targeting TGF-beta enhances anti-tumor responses of mesothelin-targeted chimeric antigen receptor T cell therapy against breast cancer, Cell. Immunol. 348 (2020), 104041.
[242] J. Han, X. Chen, J. Chu, B. Xu, W.H. Meisen, L. Chen, L. Zhang, J. Zhang, X. He, Q. E. Wang, E.A. Chiocca, B. Kaur, M.A. Caligiuri, J. Yu, TGFbeta treatment enhances glioblastoma virotherapy by inhibiting the innate immune response, Cancer Res. 75 (24) (2015) 5273–5282.
[243] M. Presta, P. Chiodelli, A. Giacomini, M. Rusnati, R. Ronca, Fibroblast growth factors (FGFs) in cancer: FGF traps as a new therapeutic approach, Pharmacol. Ther. 179 (2017) 171–187.

[244] M. Korc, R.E. Friesel, The role of fibroblast growth factors in tumor growth, Curr. Cancer Drug Targets 9 (5) (2009) 639–651.
[245] C.S. Ilkow, M. Marguerie, C. Batenchuk, J. Mayer, D. Ben Neriah, S. Cousineau, T. Falls, V.A. Jennings, M. Boileau, D. Bellamy, D. Bastin, C.T. de Souza, A. Alkayyal, J. Zhang, F. Le Boeuf, R. Arulanandam, L. Stubbert, P. Sampath, S. H. Thorne, P. Paramanthan, A. Chatterjee, R.M. Strieter, M. Burdick, C. L. Addison, D.F. Stojdl, H.L. Atkins, R.C. Auer, J.S. Diallo, B.D. Lichty, J.C. Bell, Reciprocal cellular cross-talk within the tumor microenvironment promotes oncolytic virus activity, Nat. Med. 21 (5) (2015) 530–536.
[246] M.J.F. Crupi, J.C. Bell, R. Singaravelu, Concise review: targeting cancer stem cells and their supporting niche using oncolytic viruses, Stem Cells 37 (6) (2019) 716–723.
[247] A. Marchini, L. Daeffler, V.I. Pozdeev, A. Angelova, J. Rommelaere, Immune conversion of tumor microenvironment by oncolytic viruses: the protoparvovirus H-1PV case study, Front. Immunol. 10 (2019) 1848.
[248] C.J. Breitbach, R. Arulanandam, N. De Silva, S.H. Thorne, R. Patt, M. Daneshmand, A. Moon, C. Ilkow, J. Burke, T.H. Hwang, J. Heo, M. Cho, H. Chen, F.A. Angarita, C. Addison, J.A. McCart, J.C. Bell, D.H. Kirn, Oncolytic vaccinia virus disrupts tumor-associated vasculature in humans, Cancer Res. 73 (4) (2013) 1265–1275.
[249] M.M. Alonso, M. García-Moure, M. Gonzalez-Huarriz, M. Marigil, R. Hernandez-Alcoceba, M. Buñales, S. Hervás, J. Gallego, C. Gomez-Manzano, J. Fueyo, F. F. Lang, J.J. Peterkin, R. Diez-Valle, S. Tejada, Abstract CT027: oncolytic virus DNX-2401 with a short course of temozolomide for glioblastoma at first recurrence: clinical data and prognostic biomarkers, Cancer Res. 77 (2017) CT027.
[250] E.N. Arwert, E.L. Milford, A. Rullan, S. Derzsi, S. Hooper, T. Kato, D. Mansfield, A. Melcher, K.J. Harrington, E. Sahai, STING and IRF3 in stromal fibroblasts enable sensing of genomic stress in cancer cells to undermine oncolytic viral therapy, Nat. Cell Biol. 22 (7) (2020) 758–766.
[251] T.-C. Liu, T. Zhang, H. Fukuhara, T. Kuroda, T. Todo, X. Canron, A. Bikfalvi, R. L. Martuza, A. Kurtz, S.D. Rabkin, Dominant-negative fibroblast growth factor receptor expression enhances antitumoral potency of oncolytic herpes simplex virus in neural tumors, Clin. Cancer Res. 12 (2006) 6791–6799.
[252] S.D. van Asten, M. Raaben, B. Nota, R.M. Spaapen, Secretome screening reveals fibroblast growth factors as novel inhibitors of viral replication, J. Virol. 92 (16) (2018).
[253] A.M. Duffy, D.J. Bouchier-Hayes, J.H. Harmey, Vascular Endothelial Growth Factor (VEGF) and Its Role in Non-Endothelial Cells: Autocrine Signalling by VEGF, Madame Curie Bioscience Database [Internet] (Landes Bioscience), 2013.
[254] M. Shibuya, Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) signaling in angiogenesis: a crucial target for anti- and pro-angiogenic therapies, Genes Cancer 2 (12) (2011) 1097–1105.
[255] R. Arulanandam, C. Batenchuk, F.A. Angarita, K. Ottolino-Perry, S. Cousineau, A. Mottashed, E. Burgess, T.J. Falls, N. De Silva, J. Tsang, G.A. Howe, M. C. Bourgeois-Daigneault, D.P. Conrad, M. Daneshmand, C.J. Breitbach, D.H. Kirn, L. Raptis, S. Sad, H. Atkins, M.S. Huh, J.S. Diallo, B.D. Lichty, C.S. Ilkow, F. Le Boeuf, C.L. Addison, J.A. McCart, J.C. Bell, VEGF-mediated induction of PRD1-BF1/Blimp1 expression sensitizes tumor vasculature to oncolytic virus infection, Cancer Cell 28 (2) (2015) 210–224.
[256] P.K. Bommareddy, M. Shettigar, H.L. Kaufman, Integrating oncolytic viruses in combination cancer immunotherapy, Nat. Rev. Immunol. 18 (8) (2018) 498–513.
[257] Y. Ikeda, T. Kojima, S. Kuroda, Y. Endo, R. Sakai, M. Hioki, H. Kishimoto, F. Uno, S. Kagawa, Y. Watanabe, Y. Hashimoto, Y. Urata, N. Tanaka, T. Fujiwara, A novel antiangiogenic effect for telomerase-specific virotherapy through host immune system, J. Immunol. 182 (3) (2009) 1763–1769.
[258] Z. Ye, X. Wang, S. Hao, J. Zhong, J. Xiang, J. Yang, Oncolytic adenovirus-mediated E1A gene therapy induces tumor-cell apoptosis and reduces tumor angiogenesis leading to inhibition of hepatocellular carcinoma growth in animal model, Cancer Biother. Radiopharm. 21 (3) (2006) 225–234.
[259] H. Sui, K. Wang, R. Xie, X. Li, K. Li, Y. Bai, X. Wang, B. Bai, D. Chen, J. Li, B. Shen, NDV-D90 suppresses growth of gastric cancer and cancer-related vascularization, Oncotarget 8 (21) (2017) 34516–34524.
[260] W. Hou, H. Chen, J. Rojas, P. Sampath, S.H. Thorne, Oncolytic vaccinia virus demonstrates antiangiogenic effects mediated by targeting of VEGF, Int. J. Cancer 135 (5) (2014) 1238–1246.
[261] I.S. Hong, Stimulatory versus suppressive effects of GM-CSF on tumor progression in multiple cancer types, Exp. Mol. Med. 48 (7) (2016) e242.
[262] P. Bhattacharya, I. Budnick, M. Singh, M. Thiruppathi, K. Alharshawi, H. Elshabrawy, M.J. Holterman, B.S. Prabhakar, Dual role of GM-CSF as a pro-inflammatory and a regulatory cytokine: implications for immune therapy, J. Interferon Cytokine Res. 35 (8) (2015) 585–599.
[263] R. Lari, A.J. Fleetwood, P.D. Kitchener, A.D. Cook, D. Pavasovic, P.J. Hertzog, J. A. Hamilton, Macrophage lineage phenotypes and osteoclastogenesis–complexity in the control by GM-CSF and TGF-beta, Bone 40 (2) (2007) 323–336.
[264] Y. Ogawa, E.A. Duru, B.T. Ameredes, Role of IL-10 in the resolution of airway inflammation, Curr. Mol. Med. 8 (5) (2008) 437–445.
[265] J.A. Hamilton, Colony-stimulating factors in inflammation and autoimmunity, Nat. Rev. Immunol. 8 (7) (2008) 533–544.
[266] M. Dougan, G. Dranoff, S.K. Dougan, GM-CSF, IL-3, and IL-5 family of cytokines: regulators of inflammation, Immunity 50 (4) (2019) 796–811.
[267] G. Miller, V.G. Pillarisetty, A.B. Shah, S. Lahrs, Z. Xing, R.P. DeMatteo, Endogenous granulocyte-macrophage colony-stimulating factor overexpression in vivo results in the long-term recruitment of a distinct dendritic cell population with enhanced immunostimulatory function, J. Immunol. 169 (6) (2002) 2875–2885.
[268] A.K. Mausberg, S. Jander, G. Reichmann, Intracerebral granulocyte-macrophage colony-stimulating factor induces functionally competent dendritic cells in the mouse brain, Glia 57 (12) (2009) 1341–1350.
[269] Y. Chu, L.X. Wang, G. Yang, H.J. Ross, W.J. Urba, R. Prell, K. Jooss, S. Xiong, H. M. Hu, Efficacy of GM-CSF-producing tumor vaccine after docetaxel chemotherapy in mice bearing established Lewis lung carcinoma, J Immunother 29 (4) (2006) 367–380.
[270] N. Mach, S. Gillessen, S.B. Wilson, C. Sheehan, M. Mihm, G. Dranoff, Differences in dendritic cells stimulated in vivo by tumors engineered to secrete granulocyte-macrophage colony-stimulating factor or Flt3-ligand, Cancer Res. 60 (12) (2000) 3239–3246.
[271] S. Zarei, F. Schwenter, P. Luy, M. Aurrand-Lions, P. Morel, M. Kopf, G. Dranoff, N. Mach, Role of GM-CSF signaling in cell-based tumor immunization, Blood 113 (26) (2009) 6658–6668.
[272] G. Goyal, K. Wong, C.J. Nirschl, N. Souders, D. Neuberg, N. Anandasabapathy, G. Dranoff, PPARgamma contributes to immunity induced by cancer cell vaccines that secrete GM-CSF, Cancer Immunol. Res. 6 (6) (2018) 723–732.
[273] M.R. Ruff, W.L. Farrar, C.B. Pert, Interferon gamma and granulocyte/macrophage colony-stimulating factor inhibit growth and induce antigens characteristic of myeloid differentiation in small-cell lung cancer cell lines, Proc. Natl. Acad. Sci. U. S. A. 83 (17) (1986) 6613–6617.
[274] Y. Yamashita, N. Nara, N. Aoki, Antiproliferative and differentiative effect of granulocyte-macrophage colony-stimulating factor on a variant human small cell lung cancer cell line, Cancer Res. 49 (19) (1989) 5334–5338.
[275] W.L. Yan, K.Y. Shen, C.Y. Tien, Y.A. Chen, S.J. Liu, Recent progress in GM-CSF-based cancer immunotherapy, Immunotherapy 9 (4) (2017) 347–360.
[276] R.G. Urdinguio, A.F. Fernandez, A. Moncada-Pazos, C. Huidobro, R.M. Rodriguez, C. Ferrero, P. Martinez-Camblor, A.J. Obaya, T. Bernal, A. Parra-Blanco, L. Rodrigo, M. Santacana, X. Matias-Guiu, B. Soldevilla, G. Dominguez, F. Bonilla, S. Cal, C. Lopez-Otin, M.F. Fraga, Immune-dependent and independent antitumor activity of GM-CSF aberrantly expressed by mouse and human colorectal tumors, Cancer Res. 73 (1) (2013) 395–405.
[277] I.K. Kim, C.H. Koh, I. Jeon, K.S. Shin, T.S. Kang, E.A. Bae, H. Seo, H.J. Ko, B. S. Kim, Y. Chung, C.Y. Kang, GM-CSF promotes antitumor immunity by inducing Th9 cell responses, Cancer Immunol. Res. 7 (3) (2019) 498–509.
[278] B. Kubista, K. Trieb, I. Herbacek, M. Micksche, Effect of granulocyte-macrophage colony-stimulating factor on natural-killer cell mediated cytotoxicity, Int. J. Biochem. Cell Biol. 35 (7) (2003) 1056–1060.
[279] G. van den Bosch, F. Preijers, A. Vreugdenhil, J. Hendriks, F. Maas, T. De Witte, Granulocyte-macrophage colony-stimulating factor (GM-CSF) counteracts the inhibiting effect of monocytes on natural killer (NK) cells, Clin. Exp. Immunol. 101 (3) (1995) 515–520.
[280] H.L. Kaufman, D.W. Kim, G. DeRaffele, J. Mitcham, R.S. Coffin, S. Kim-Schulze, Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with stage IIIc and IV melanoma, Ann. Surg. Oncol. 17 (3) (2010) 718–730.
[281] B.L. Liu, M. Robinson, Z.Q. Han, R.H. Branston, C. English, P. Reay, Y. McGrath, S.K. Thomas, M. Thornton, P. Bullock, C.A. Love, R.S. Coffin, ICP34.5 deleted herpes simplex virus with enhanced oncolytic, immune stimulating, and anti-tumour properties, Gene Ther. 10 (4) (2003) 292–303.
[282] V.A. Jennings, G.B. Scott, A.M.S. Rose, K.J. Scott, G. Migneco, B. Keller, K. Reilly, O. Donnelly, H. Peach, D. Dewar, K.J. Harrington, H. Pandha, A. Samson, R. G. Vile, A.A. Melcher, F. Errington-Mais, Potentiating oncolytic virus-induced immune-mediated tumor cell killing using histone deacetylase inhibition, Mol. Ther. 27 (6) (2019) 1139–1152.
[283] V. Kemp, D.J.M. van den Wollenberg, M.G.M. Camps, T. van Hall, P. Kinderman, N. Pronk-van Montfoort, R.C. Hoeben, Arming oncolytic reovirus with GM-CSF gene to enhance immunity, Cancer Gene Ther. 26 (9–10) (2019) 268–281.
[284] A. Samson, K.J. Scott, D. Taggart, E.J. West, E. Wilson, G.J. Nuovo, S. Thomson, R. Corns, R.K. Mathew, M.J. Fuller, T.J. Kottke, J.M. Thompson, E.J. Ilett, J. V. Cockle, P. van Hille, G. Sivakumar, E.S. Polson, S.J. Turnbull, E.S. Appleton, G. Migneco, A.S. Rose, M.C. Coffey, D.A. Beirne, F.J. Collinson, C. Ralph, D. Alan Anthoney, C.J. Twelves, A.J. Furness, S.A. Quezada, H. Wurdak, F. Errington-Mais, H. Pandha, K.J. Harrington, P.J. Selby, R.G. Vile, S.D. Griffin, L.F. Stead, S. C. Short, A.A. Melcher, Intravenous delivery of oncolytic reovirus to brain tumor patients immunologically primes for subsequent checkpoint blockade, Sci. Transl. Med. 10 (422) (2018).
[285] K.J. Harrington, M. Hingorani, M.A. Tanay, J. Hickey, S.A. Bhide, P.M. Clarke, L. C. Renouf, K. Thway, A. Sibtain, I.A. McNeish, K.L. Newbold, H. Goldsweig, R. Coffin, C.M. Nutting, Phase I/II study of oncolytic HSV GM-CSF in combination with radiotherapy and cisplatin in untreated stage III/IV squamous cell cancer of the head and neck, Clin. Cancer Res. 16 (15) (2010) 4005–4015.
[286] J.H. Kim, J.Y. Oh, B.H. Park, D.E. Lee, J.S. Kim, H.E. Park, M.S. Roh, J.E. Je, J. H. Yoon, S.H. Thorne, D. Kirn, T.H. Hwang, Systemic armed oncolytic and immunologic therapy for cancer with JX-594, a targeted poxvirus expressing GM-CSF, Mol. Ther. 14 (3) (2006) 361–370.
[287] J.H. Lee, M.S. Roh, Y.K. Lee, M.K. Kim, J.Y. Han, B.H. Park, P. Trown, D.H. Kirn, T.H. Hwang, Oncolytic and immunostimulatory efficacy of a targeted oncolytic poxvirus expressing human GM-CSF following intravenous administration in a rabbit tumor model, Cancer Gene Ther. 17 (2) (2010) 73–79.
[288] B.H. Park, T. Hwang, T.C. Liu, D.Y. Sze, J.S. Kim, H.C. Kwon, S.Y. Oh, S.Y. Han, J. H. Yoon, S.H. Hong, A. Moon, K. Speth, C. Park, Y.J. Ahn, M. Daneshmand, B. G. Rhee, H.M. Pinedo, J.C. Bell, D.H. Kirn, Use of a targeted oncolytic poxvirus, JX-594, in patients with refractory primary or metastatic liver cancer: a phase I trial, Lancet Oncol. 9 (6) (2008) 533–542.

[289] H.J. Chon, W.S. Lee, H. Yang, S.J. Kong, N.K. Lee, E.S. Moon, J. Choi, E.C. Han, J. H. Kim, J.B. Ahn, J.H. Kim, C. Kim, Tumor microenvironment remodeling by intratumoral oncolytic vaccinia virus enhances the efficacy of immune-checkpoint blockade, Clin. Cancer Res. 25 (5) (2019) 1612–1623.
[290] M. Kim, M. Nitschke, B. Sennino, P. Murer, B.J. Schriver, A. Bell, A. Subramanian, C.E. McDonald, J. Wang, H. Cha, M.C. Bourgeois-Daigneault, D.H. Kirn, J.C. Bell, N. De Silva, C.J. Breitbach, D.M. McDonald, Amplification of oncolytic vaccinia virus widespread tumor cell killing by sunitinib through multiple mechanisms, Cancer Res. 78 (4) (2018) 922–937.
[291] L. Deng, X. Yang, J. Fan, Y. Ding, Y. Peng, D. Xu, B. Huang, Z. Hu, An oncolytic vaccinia virus armed with GM-CSF and IL-24 double genes for Cancer Targeted therapy, Onco. Ther. 13 (2020) 3535–3544.
[292] S.H. Park, C.J. Breitbach, J. Lee, J.O. Park, H.Y. Lim, W.K. Kang, A. Moon, J. H. Mun, E.M. Sommermann, L. Maruri Avidal, R. Patt, A. Pelusio, J. Burke, T. H. Hwang, D. Kirn, Y.S. Park, Phase 1b trial of biweekly intravenous pexa-vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus in colorectal cancer, Mol. Ther. 23 (9) (2015) 1532–1540.
[293] T.P. Cripe, M.C. Ngo, J.I. Geller, C.U. Louis, M.A. Currier, J.M. Racadio, A. J. Towbin, C.M. Rooney, A. Pelusio, A. Moon, T.H. Hwang, J.M. Burke, J.C. Bell, D.H. Kirn, C.J. Breitbach, Phase 1 study of intratumoral Pexa-Vec (JX-594), an oncolytic and immunotherapeutic vaccinia virus, in pediatric cancer patients, Mol. Ther. 23 (3) (2015) 602–608.
[294] M. Moehler, J. Heo, H.C. Lee, W.Y. Tak, Y. Chao, S.W. Paik, H.J. Yim, K.S. Byun, A. Baron, G. Ungerechts, D. Jonker, L. Ruo, M. Cho, A. Kaubisch, H. Wege, P. Merle, O. Ebert, F. Habersetzer, J.F. Blanc, O. Rosmorduc, R. Lencioni, R. Patt, A.M. Leen, F. Foerster, M. Homerin, N. Stojkowitz, M. Lusky, J.M. Limacher, M. Hennequi, N. Gaspar, B. McFadden, N. De Silva, D. Shen, A. Pelusio, D.H. Kirn, C.J. Breitbach, J.M. Burke, Vaccinia-based oncolytic immunotherapy Pexastimogene Devacirepvec in patients with advanced hepatocellular carcinoma after sorafenib failure: a randomized multicenter Phase IIb trial (TRAVERSE), Oncoimmunology 8 (8) (2019), 1615817.
[295] C.R. de Vries, C.E. Monken, E.C. Lattime, The addition of recombinant vaccinia HER2/neu to oncolytic vaccinia-GMCSF given into the tumor microenvironment overcomes MDSC-mediated immune escape and systemic anergy, Cancer Gene Ther. 22 (3) (2015) 154–162.
[296] M.K. Kim, C.J. Breitbach, A. Moon, J. Heo, Y.K. Lee, M. Cho, J.W. Lee, S.G. Kim, D.H. Kang, J.C. Bell, B.H. Park, D.H. Kirn, T.H. Hwang, Oncolytic and immunotherapeutic vaccinia induces antibody-mediated complement-dependent cancer cell lysis in humans, Sci. Transl. Med. 5 (185) (2013), 185ra63.
[297] E. Ilett, T. Kottke, J. Thompson, K. Rajani, S. Zaidi, L. Evgin, M. Coffey, C. Ralph, R. Diaz, H. Pandha, K. Harrington, P. Selby, R. Bram, A. Melcher, R. Vile, Prime-boost using separate oncolytic viruses in combination with checkpoint blockade improves anti-tumour therapy, Gene Ther. 24 (1) (2017) 21–30.
[298] I. Bergman, J.A. Griffin, Y. Gao, P. Whitaker-Dowling, Treatment of implanted mammary tumors with recombinant vesicular stomatitis virus targeted to Her2/neu, Int. J. Cancer 121 (2) (2007) 425–430.
[299] C.G. Lemay, J.L. Rintoul, A. Kus, J.M. Paterson, V. Garcia, T.J. Falls, L. Ferreira, B. W. Bridle, D.P. Conrad, V.A. Tang, J.S. Diallo, R. Arulanandam, F. Le Boeuf, K. Garson, B.C. Vanderhyden, D.F. Stojdl, B.D. Lichty, H.L. Atkins, K.A. Parato, J. C. Bell, R.C. Auer, Harnessing oncolytic virus-mediated antitumor immunity in an infected cell vaccine, Mol. Ther. 20 (9) (2012) 1791–1799.
[300] X. Lun, J. Chan, H. Zhou, B. Sun, J.J. Kelly, O.O. Stechishin, J.C. Bell, K. Parato, K. Hu, D. Vaillant, J. Wang, T.C. Liu, C. Breitbach, D. Kirn, D.L. Senger, P. A. Forsyth, Efficacy and safety/toxicity study of recombinant vaccinia virus JX-594 in two immunocompetent animal models of glioma, Mol. Ther. 18 (11) (2010) 1927–1936.
[301] L. Kuryk, E. Haavisto, M. Garofalo, C. Capasso, M. Hirvinen, S. Pesonen, T. Ranki, L. Vassilev, V. Cerullo, Synergistic anti-tumor efficacy of immunogenic adenovirus ONCOS-102 (Ad5/3-D24-GM-CSF) and standard of care chemotherapy in preclinical mesothelioma model, Int. J. Cancer 139 (8) (2016) 1883–1893.
[302] V. Cerullo, S. Pesonen, I. Diaconu, S. Escutenaire, P.T. Arstila, M. Ugolini, P. Nokisalmi, M. Raki, L. Laasonen, M. Sarkioja, M. Rajecki, L. Kangasniemi, K. Guse, A. Helminen, L. Ahtiainen, A. Ristimaki, A. Raisanen-Sokolowski, E. Haavisto, M. Oksanen, E. Karli, A. Karioja-Kallio, S.L. Holm, M. Kouri, T. Joensuu, A. Kanerva, A. Hemminki, Oncolytic adenovirus coding for granulocyte macrophage colony-stimulating factor induces antitumoral immunity in cancer patients, Cancer Res. 70 (11) (2010) 4297–4309.
[303] J. Chang, X. Zhao, X. Wu, Y. Guo, H. Guo, J. Cao, Y. Guo, D. Lou, D. Yu, J. Li, A Phase I study of KH901, a conditionally replicating granulocyte-macrophage colony-stimulating factor: armed oncolytic adenovirus for the treatment of head and neck cancers, Cancer Biol. Ther. 8 (8) (2009) 676–682.
[304] M. Robinson, B. Li, Y. Ge, D. Ko, S. Yendluri, T. Harding, M. VanRoey, K. R. Spindler, K. Jooss, Novel immunocompetent murine tumor model for evaluation of conditionally replication-competent (oncolytic) murine adenoviral vectors, J. Virol. 83 (8) (2009) 3450–3462.
[305] N. Lei, F.B. Shen, J.H. Chang, L. Wang, H. Li, C. Yang, J. Li, D.C. Yu, An oncolytic adenovirus expressing granulocyte macrophage colony-stimulating factor shows improved specificity and efficacy for treating human solid tumors, Cancer Gene Ther. 16 (1) (2009) 33–43.
[306] T. Du, G. Shi, Y.M. Li, J.F. Zhang, H.W. Tian, Y.Q. Wei, H. Deng, D.C. Yu, Tumor-specific oncolytic adenoviruses expressing granulocyte macrophage colony-stimulating factor or anti-CTLA4 antibody for the treatment of cancers, Cancer Gene Ther. 21 (8) (2014) 340–348.
[307] N. Ramesh, Y. Ge, D.L. Ennist, M. Zhu, M. Mina, S. Ganesh, P.S. Reddy, D.C. Yu, CG0070, a conditionally replicating granulocyte macrophage colony-stimulating factor–armed oncolytic adenovirus for the treatment of bladder cancer, Clin. Cancer Res. 12 (1) (2006) 305–313.
[308] L. Wang, J. Zheng, Q. He, X. Yu, X. Hu, S. Deng, S. Chang, F. Shen, TOA02, a recombinant adenovirus with tumor-specific granulocyte macrophage colony-stimulating factor expression, has limited biodistribution and low toxicity in rhesus monkeys, Hum. Gene Ther. Methods 26 (2) (2015) 62–70.
[309] T. Ranki, S. Pesonen, A. Hemminki, K. Partanen, K. Kairemo, T. Alanko, J. Lundin, N. Linder, R. Turkki, A. Ristimaki, E. Jager, J. Karbach, C. Wahle, M. Kankainen, C. Backman, M. von Euler, E. Haavisto, T. Hakonen, R. Heiskanen, M. Jaderberg, J. Juhila, P. Priha, L. Suoranta, L. Vassilev, A. Vuolanto, T. Joensuu, Phase I study with ONCOS-102 for the treatment of solid tumors - an evaluation of clinical response and exploratory analyses of immune markers, J. Immunother. Cancer 4 (2016) 17.
[310] M. Janke, B. Peeters, O. de Leeuw, R. Moorman, A. Arnold, P. Fournier, V. Schirrmacher, Recombinant Newcastle disease virus (NDV) with inserted gene coding for GM-CSF as a new vector for cancer immunogene therapy, Gene Ther. 14 (23) (2007) 1639–1649.
[311] S. Burke, A. Shergold, M.J. Elder, J. Whitworth, X. Cheng, H. Jin, R.W. Wilkinson, J. Harper, D.K. Carroll, Oncolytic Newcastle disease virus activation of the innate immune response and priming of antitumor adaptive responses in vitro, Cancer Immunol. Immunother. 69 (6) (2020) 1015–1027.
[312] B.S. Rush, M.L. Coughlin, G. Sanyal, In vitro infectivity of oncolytic Newcastle Disease Virus: correlation between plaque and fluorescent focus assays, J. Virol. Methods 251 (2018) 69–74.
[313] D. Grote, R. Cattaneo, A.K. Fielding, Neutrophils contribute to the measles virus-induced antitumor effect: enhancement by granulocyte macrophage colony-stimulating factor expression, Cancer Res. 63 (19) (2003) 6463–6468.
[314] C. Grossardt, C.E. Engeland, S. Bossow, N. Halama, K. Zaoui, M.F. Leber, C. Springfeld, D. Jaeger, C. von Kalle, G. Ungerechts, Granulocyte-macrophage colony-stimulating factor-armed oncolytic measles virus is an effective therapeutic cancer vaccine, Hum. Gene Ther. 24 (7) (2013) 644–654.
[315] Y. Chen, Y. Pan, Y. Guo, W. Zhao, W.T. Ho, J. Wang, M. Xu, F.C. Yang, Z.J. Zhao, Tyrosine kinase inhibitors targeting FLT3 in the treatment of acute myeloid leukemia, Stem Cell Investig. 4 (2017) 48.
[316] S.G. Shaw, A.A. Maung, R.J. Steptoe, A.W. Thomson, N.L. Vujanovic, Expansion of functional NK cells in multiple tissue compartments of mice treated with Flt3-ligand: implications for anti-cancer and anti-viral therapy, J. Immunol. 161 (6) (1998) 2817–2824.
[317] H. Karsunky, M. Merad, A. Cozzio, I.L. Weissman, M.G. Manz, Flt3 ligand regulates dendritic cell development from Flt3+ lymphoid and myeloid-committed progenitors to Flt3+ dendritic cells in vivo, J. Exp. Med. 198 (2) (2003) 305–313.
[318] P. Guermonprez, J. Helft, C. Claser, S. Deroubaix, H. Karanje, A. Gazumyan, G. Darasse-Jeze, S.B. Telerman, G. Breton, H.A. Schreiber, N. Frias-Staheli, E. Billerbeck, M. Dorner, C.M. Rice, A. Ploss, F. Klein, M. Swiecki, M. Colonna, A. O. Kamphorst, M. Meredith, R. Niec, C. Takacs, F. Mikhail, A. Hari, D. Bosque, T. Eisenreich, M. Merad, Y. Shi, F. Ginhoux, L. Renia, B.C. Urban, M. C. Nussenzweig, Inflammatory Flt3l is essential to mobilize dendritic cells and for T cell responses during Plasmodium infection, Nat. Med. 19 (6) (2013) 730–738.
[319] M. Candolfi, J.F. Curtin, K. Yagiz, H. Assi, M.K. Wibowo, G.E. Alzadeh, D. Foulad, A.K. Muhammad, S. Salehi, N. Keech, M. Puntel, C. Liu, N.R. Sanderson, K. M. Kroeger, R. Dunn, G. Martins, P.R. Lowenstein, M.G. Castro, B cells are critical to T-cell-mediated antitumor immunity induced by a combined immune-stimulatory/conditionally cytotoxic therapy for glioblastoma, Neoplasia 13 (10) (2011) 947–960.
[320] C.E. Marroquin, J.A. Westwood, R. Lapointe, A. Mixon, J.R. Wunderlich, D. Caron, S.A. Rosenberg, P. Hwu, Mobilization of dendritic cell precursors in patients with cancer by flt3 ligand allows the generation of higher yields of cultured dendritic cells, J Immunother 25 (3) (2002) 278–288.
[321] D.H. Lynch, A. Andreasen, E. Maraskovsky, J. Whitmore, R.E. Miller, J.C. Schuh, Flt3 ligand induces tumor regression and antitumor immune responses in vivo, Nat. Med. 3 (6) (1997) 625–631.
[322] J.F. Curtin, G.D. King, C. Barcia, C. Liu, F.X. Hubert, C. Guillonneau, R. Josien, I. Anegon, P.R. Lowenstein, M.G. Castro, Fms-like tyrosine kinase 3 ligand recruits plasmacytoid dendritic cells to the brain, J. Immunol. 176 (6) (2006) 3566–3577.
[323] S. Ali, J.F. Curtin, J.M. Zirger, W. Xiong, G.D. King, C. Barcia, C. Liu, M. Puntel, S. Goverdhana, P.R. Lowenstein, M.G. Castro, Inflammatory and anti-glioma effects of an adenovirus expressing human soluble Fms-like tyrosine kinase 3 ligand (hsFlt3L): treatment with hsFlt3L inhibits intracranial glioma progression, Mol. Ther. 10 (6) (2004) 1071–1084.
[324] Z. Barnard, H. Wakimoto, C. Zaupa, A.P. Patel, J. Klehm, R.L. Martuza, S. D. Rabkin, W.T. Curry Jr., Expression of FMS-like tyrosine kinase 3 ligand by oncolytic herpes simplex virus type I prolongs survival in mice bearing established syngeneic intracranial malignant glioma, Neurosurgery 71 (3) (2012) 741–748, discussion 748.
[325] G.D. King, K.M. Kroeger, C.J. Bresee, M. Candolfi, C. Liu, C.M. Manalo, A. K. Muhammad, R.N. Pechnick, P.R. Lowenstein, M.G. Castro, Flt3L in combination with HSV1-TK-mediated gene therapy reverses brain tumor-induced behavioral deficits, Mol. Ther. 16 (4) (2008) 682–690.
[326] K.M. Bernt, S. Ni, A.T. Tieu, A. Lieber, Assessment of a combined, adenovirus-mediated oncolytic and immunostimulatory tumor therapy, Cancer Res. 65 (10) (2005) 4343–4352.
[327] R. Edukulla, N. Woller, B. Mundt, S. Knocke, E. Gurlevik, M. Saborowski, N. Malek, M.P. Manns, T. Wirth, F. Kuhnel, S. Kubicka, Antitumoral immune response by recruitment and expansion of dendritic cells in tumors infected with telomerase-dependent oncolytic viruses, Cancer Res. 69 (4) (2009) 1448–1458.

[328] J.S. Kim, S.D. Lee, S.J. Lee, M.K. Chung, Development of an immunotherapeutic adenovirus targeting hormone-independent prostate cancer, Onco. Ther. 6 (2013) 1635–1642.
[329] S. Leveille, M.L. Goulet, B.D. Lichty, J. Hiscott, Vesicular stomatitis virus oncolytic treatment interferes with tumor-associated dendritic cell functions and abrogates tumor antigen presentation, J. Virol. 85 (23) (2011) 12160–12169.
[330] A. Dyer, R. Baugh, S.L. Chia, S. Frost, Iris, E.J. Jacobus, H. Khalique, T. D. Pokrovska, E.M. Scott, W.K. Taverner, L.W. Seymour, J. Lei, Turning cold tumours hot: oncolytic virotherapy gets up close and personal with other therapeutics at the 11th Oncolytic Virus Conference, Cancer Gene Ther. 26 (3–4) (2019) 59–73.
[331] W. Wang, P. Dai, N. Yang, S. Shuman, W. Yan, T. Merghoub, J.D. Wolchok, L. Deng, Oncolytic vaccinia virus expressing immune checkpoint blockade antibody as cancer immunotherapeutics, Proc. Natl. Acad. Sci. U. S. A. 78 (2018). Abstract nr LB-306.
[332] E.A. Carswell, L.J. Old, R.L. Kassel, S. Green, N. Fiore, B. Williamson, An endotoxin-induced serum factor that causes necrosis of tumors, Proc. Natl. Acad. Sci. U. S. A. 72 (9) (1975) 3666–3670.
[333] S. Green, A. Dobrjansky, E.A. Carswell, R.L. Kassel, L.J. Old, N. Fiore, M. K. Schwartz, Partial purification of a serum factor that causes necrosis of tumors, Proc. Natl. Acad. Sci. U. S. A. 73 (2) (1976) 381–385.
[334] D. Pennica, G.E. Nedwin, J.S. Hayflick, P.H. Seeburg, R. Derynck, M.A. Palladino, W.J. Kohr, B.B. Aggarwal, D.V. Goeddel, Human tumour necrosis factor: precursor structure, expression and homology to lymphotoxin, Nature 312 (5996) (1984) 724–729.
[335] J.V. Falvo, A.V. Tsytsykova, A.E. Goldfeld, Transcriptional control of the TNF gene, Curr. Dir. Autoimmun. 11 (2010) 27–60.
[336] M.F. Mercogliano, S. Bruni, P.V. Elizalde, R. Schillaci, Tumor necrosis factor alpha blockade: an opportunity to tackle breast cancer, Front. Oncol. 10 (2020) 584.
[337] X. Wang, Y. Lin, Tumor necrosis factor and cancer, buddies or foes? Acta Pharmacol. Sin. 29 (11) (2008) 1275–1288.
[338] F. Balkwill, Tumour necrosis factor and cancer, Nat. Rev. Cancer 9 (5) (2009) 361–371.
[339] F.J. Lejeune, D. Lienard, M. Matter, C. Ruegg, Efficiency of recombinant human TNF in human cancer therapy, Cancer Immun. 6 (2006) 6.
[340] Y. Qiao, X. Huang, S. Nimmagadda, R. Bai, V. Staedtke, C.A. Foss, I. Cheong, M. Holdhoff, Y. Kato, M.G. Pomper, G.J. Riggins, K.W. Kinzler, L.A. Diaz Jr., B. Vogelstein, S. Zhou, A robust approach to enhance tumor-selective accumulation of nanoparticles, Oncotarget 2 (1-2) (2011) 59–68.
[341] H. Nie, Y. Zheng, R. Li, T.B. Guo, D. He, L. Fang, X. Liu, L. Xiao, X. Chen, B. Wan, Y.E. Chin, J.Z. Zhang, Phosphorylation of FOXP3 controls regulatory T cell function and is inhibited by TNF-alpha in rheumatoid arthritis, Nat. Med. 19 (3) (2013) 322–328.
[342] X. Valencia, G. Stephens, R. Goldbach-Mansky, M. Wilson, E.M. Shevach, P. E. Lipsky, TNF downmodulates the function of human CD4+CD25hi T-regulatory cells, Blood 108 (1) (2006) 253–261.
[343] S. Hoving, A.L. Seynhaeve, S.T. van Tiel, G. aan de Wiel-Ambagtsheer, E.A. de Bruijn, A.M. Eggermont, T.L. ten Hagen, Early destruction of tumor vasculature in tumor necrosis factor-alpha-based isolated limb perfusion is responsible for tumor response, Anticancer Drugs 17 (8) (2006) 949–959.
[344] F. Mackay, H. Loetscher, D. Stueber, G. Gehr, W. Lesslauer, Tumor necrosis factor alpha (TNF-alpha)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55, J. Exp. Med. 177 (5) (1993) 1277–1286.
[345] S.F. Josephs, T.E. Ichim, S.M. Prince, S. Kesari, F.M. Marincola, A.R. Escobedo, A. Jafri, Unleashing endogenous TNF-alpha as a cancer immunotherapeutic, J. Transl. Med. 16 (1) (2018) 242.
[346] A.M. Eggermont, J.H. de Wilt, T.L. Ten Hagen, Current uses of isolated limb perfusion in the clinic and a model system for new strategies, Lancet Oncol. 4 (7) (2003) 429–437.
[347] D. Lienard, P. Ewalenko, J.J. Delmotte, N. Renard, F.J. Lejeune, High-dose recombinant tumor necrosis factor alpha in combination with interferon gamma and melphalan in isolation perfusion of the limbs for melanoma and sarcoma, J. Clin. Oncol. 10 (1) (1992) 52–60.
[348] R.M. Lorence, P.A. Rood, K.W. Kelley, Newcastle disease virus as an antineoplastic agent: induction of tumor necrosis factor-alpha and augmentation of its cytotoxicity, J. Natl. Cancer Inst. 80 (16) (1988) 1305–1312.
[349] M. Aghi, R.L. Martuza, Oncolytic viral therapies - the clinical experience, Oncogene 24 (52) (2005) 7802–7816.
[350] Y. Liao, H.X. Wang, X. Mao, H. Fang, H. Wang, Y. Li, Y. Sun, C. Meng, L. Tan, C. Song, X. Qiu, C. Ding, RIP1 is a central signaling protein in regulation of TNF-alpha/TRAIL mediated apoptosis and necroptosis during Newcastle disease virus infection, Oncotarget 8 (26) (2017) 43201–43217.
[351] G. Kazimirsky, W. Jiang, S. Slavin, A. Ziv-Av, C. Brodie, Mesenchymal stem cells enhance the oncolytic effect of Newcastle disease virus in glioma cells and glioma stem cells via the secretion of TRAIL, Stem Cell Res. Ther. 7 (1) (2016) 149.
[352] Z. Jiang, M. Kunimoto, J.A. Patel, Autocrine regulation and experimental modulation of interleukin-6 expression by human pulmonary epithelial cells infected with respiratory syncytial virus, J. Virol. 72 (3) (1998) 2496–2499.
[353] I. Echchgadda, S. Kota, I. DeLa Cruz, A. Sabbah, T. Chang, R. Harnack, V. Mgbemena, B. Chatterjee, S. Bose, Anticancer oncolytic activity of respiratory syncytial virus, Cancer Gene Ther. 16 (12) (2009) 923–935.
[354] I. Diaconu, V. Cerullo, M.L. Hirvinen, S. Escutenaire, M. Ugolini, S.K. Pesonen, S. Bramante, S. Parviainen, A. Kanerva, A.S. Loskog, A.G. Eliopoulos, S. Pesonen, A. Hemminki, Immune response is an important aspect of the antitumor effect produced by a CD40L-encoding oncolytic adenovirus, Cancer Res. 72 (9) (2012) 2327–2338.
[355] I.K. Choi, Y. Li, E. Oh, J. Kim, C.O. Yun, Oncolytic adenovirus expressing IL-23 and p35 elicits IFN-gamma- and TNF-alpha-co-producing T cell-mediated antitumor immunity, PLoS One 8 (7) (2013), e67512.
[356] R.J. Prestwich, F. Errington, E.J. Ilett, R.S. Morgan, K.J. Scott, T. Kottke, J. Thompson, E.E. Morrison, K.J. Harrington, H.S. Pandha, P.J. Selby, R.G. Vile, A.A. Melcher, Tumor infection by oncolytic reovirus primes adaptive antitumor immunity, Clin. Cancer Res. 14 (22) (2008) 7358–7366.
[357] S.P. Grekova, Z. Raykov, R. Zawatzky, J. Rommelaere, U. Koch, Activation of a glioma-specific immune response by oncolytic parvovirus Minute Virus of Mice infection, Cancer Gene Ther. 19 (7) (2012) 468–475.
[358] H. Li, A. Dutuor, X. Fu, X. Zhang, Induction of strong antitumor immunity by an HSV-2-based oncolytic virus in a murine mammary tumor model, J. Gene Med. 9 (3) (2007) 161–169.
[359] W.H. Meisen, E.S. Wohleb, A.C. Jaime-Ramirez, C. Bolyard, J.Y. Yoo, L. Russell, J. Hardcastle, S. Dubin, K. Muili, J. Yu, M. Caligiuri, J. Godbout, B. Kaur, The impact of macrophage- and microglia-secreted TNFalpha on oncolytic HSV-1 therapy in the glioblastoma tumor microenvironment, Clin. Cancer Res. 21 (14) (2015) 3274–3285.
[360] K.B. Pointer, R.R. Zhang, J.S. Kuo, Oncolytic herpes simplex virus glioblastoma therapy is potentiated by tumor necrosis factor-alpha inhibition, Neurosurgery 77 (2) (2015) N18–20.
[361] S.T. Beug, S.J. Pichette, M. St-Jean, J. Holbrook, D.E. Walker, E.C. LaCasse, R. G. Korneluk, Combination of IAP antagonists and TNF-alpha-Armed oncolytic viruses induce tumor vascular shutdown and tumor regression, Mol. Ther. Oncolytics 10 (2018) 28–39.
[362] M. Hirvinen, M. Rajecki, M. Kapanen, S. Parviainen, N. Rouvinen-Lagerstrom, I. Diaconu, P. Nokisalmi, M. Tenhunen, A. Hemminki, V. Cerullo, Immunological effects of a tumor necrosis factor alpha-armed oncolytic adenovirus, Hum. Gene Ther. 26 (3) (2015) 134–144.
[363] Z.Q. Han, M. Assenberg, B.L. Liu, Y.B. Wang, G. Simpson, S. Thomas, R.S. Coffin, Development of a second-generation oncolytic Herpes simplex virus expressing TNFalpha for cancer therapy, J. Gene Med. 9 (2) (2007) 99–106.
[364] R. Havunen, M. Siurala, S. Sorsa, S. Gronberg-Vaha-Koskela, M. Behr, S. Tahtinen, J.M. Santos, P. Karell, J. Rusanen, D.M. Nettelbeck, A. Ehrhardt, A. Kanerva, A. Hemminki, Oncolytic adenoviruses armed with tumor necrosis factor alpha and Interleukin-2 enable successful adoptive cell therapy, Mol. Ther. Oncolytics 4 (2017) 77–86.
[365] M. Siurala, R. Havunen, D. Saha, D. Lumen, A.J. Airaksinen, S. Tahtinen, V. Cervera-Carrascon, S. Bramante, S. Parviainen, M. Vaha-Koskela, A. Kanerva, A. Hemminki, Adenoviral delivery of tumor necrosis factor-alpha and Interleukin-2 enables successful adoptive cell therapy of immunosuppressive melanoma, Mol. Ther. 24 (8) (2016) 1435–1443.
[366] J.M. Santos, V. Cervera-Carrascon, R. Havunen, S. Zafar, M. Siurala, S. Sorsa, M. Anttila, A. Kanerva, A. Hemminki, Adenovirus coding for Interleukin-2 and tumor necrosis factor alpha replaces lymphodepleting chemotherapy in adoptive t cell therapy, Mol. Ther. 26 (9) (2018) 2243–2254.
[367] J.M. Santos, C. Heinio, V. Cervera-Carrascon, D.C.A. Quixabeira, M. Siurala, R. Havunen, R. Butzow, S. Zafar, T. de Gruijl, H. Lassus, A. Kanerva, A. Hemminki, Oncolytic adenovirus shapes the ovarian tumor microenvironment for potent tumor-infiltrating lymphocyte tumor reactivity, J. Immunother. Cancer 8 (1) (2020).
[368] V. Cervera-Carrascon, M. Siurala, J.M. Santos, R. Havunen, S. Tahtinen, P. Karell, S. Sorsa, A. Kanerva, A. Hemminki, TNFa and IL-2 armed adenoviruses enable complete responses by anti-PD-1 checkpoint blockade, Oncoimmunology 7 (5) (2018), e1412902.
[369] J.N. Parker, S. Meleth, K.B. Hughes, G.Y. Gillespie, R.J. Whitley, J.M. Markert, Enhanced inhibition of syngeneic murine tumors by combinatorial therapy with genetically engineered HSV-1 expressing CCL2 and IL-12, Cancer Gene Ther. 12 (4) (2005) 359–368.
[370] J. Li, M. O'Malley, P. Sampath, P. Kalinski, D.L. Bartlett, S.H. Thorne, Expression of CCL19 from oncolytic vaccinia enhances immunotherapeutic potential while maintaining oncolytic activity, Neoplasia 14 (12) (2012) 1115–1121.
[371] K.J. Choi, S.N. Zhang, I.K. Choi, J.S. Kim, C.O. Yun, Strengthening of antitumor immune memory and prevention of thymic atrophy mediated by adenovirus expressing IL-12 and GM-CSF, Gene Ther. 19 (7) (2012) 711–723.
[372] K.J. Choi, J.H. Kim, Y.S. Lee, J. Kim, B.S. Suh, H. Kim, S. Cho, J.H. Sohn, G.E. Kim, C.O. Yun, Concurrent delivery of GM-CSF and B7-1 using an oncolytic adenovirus elicits potent antitumor effect, Gene Ther. 13 (13) (2006) 1010–1020.
[373] S.O. Freytag, Y. Zhang, F. Siddiqui, Preclinical toxicology of oncolytic adenovirus-mediated cytotoxic and interleukin-12 gene therapy for prostate cancer, Mol. Ther. Oncolytics 2 (2015).
[374] R.J. Wong, S.G. Patel, S. Kim, R.P. DeMatteo, S. Malhotra, J.J. Bennett, M. St-Louis, J.P. Shah, P.A. Johnson, Y. Fong, Cytokine gene transfer enhances herpes oncolytic therapy in murine squamous cell carcinoma, Hum. Gene Ther. 12 (3) (2001) 253–265.
[375] R. Yan, X. Zhou, X. Chen, X. Liu, Y. Tang, J. Ma, L. Wang, Z. Liu, B. Zhan, H. Chen, J. Wang, W. Zou, H. Xu, R. Lu, D. Ni, B. Roizman, G.G. Zhou, Enhancement of oncolytic activity of oHSV expressing IL-12 and anti PD-1 antibody by concurrent administration of exosomes carrying CTLA-4 miRNA, Immunotherapy (Los Angel) 5 (2) (2019).
[376] R.J. Wong, M.K. Chan, Z. Yu, T.H. Kim, A. Bhargava, B.M. Stiles, B.C. Horsburgh, J.P. Shah, R.A. Ghossein, B. Singh, Y. Fong, Effective intravenous therapy of murine pulmonary metastases with an oncolytic herpes virus expressing interleukin 12, Clin. Cancer Res. 10 (1 Pt 1) (2004) 251–259.

[377] A. Rosewell Shaw, C.E. Porter, N. Watanabe, K. Tanoue, A. Sikora, S. Gottschalk, M.K. Brenner, M. Suzuki, Adenovirotherapy delivering cytokine and checkpoint inhibitor augments CAR t cells against metastatic head and neck cancer, Mol. Ther. 25 (11) (2017) 2440–2451.
[378] Y. Wang, J. Jin, Z. Wu, S. Hu, H. Hu, Z. Ning, Y. Li, Y. Dong, J. Zou, Z. Mao, X. Shi, H. Zheng, S. Dong, F. Liu, Z. Fang, J. Wu, B. Liu, Stability and anti-tumor effect of oncolytic herpes simplex virus type 2, Oncotarget 9 (37) (2018) 24672–24683.
[379] X. Cheng, W. Wang, Q. Xu, J. Harper, D. Carroll, M.S. Galinski, J. Suzich, H. Jin, Genetic modification of oncolytic newcastle disease virus for cancer therapy, J. Virol. 90 (11) (2016) 5343–5352.



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