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# Cytokines in oncolytic virotherapy

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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 $\beta_2$-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, $\beta_2$-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$^+$ $T_H1$ 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, $T_H1$ 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

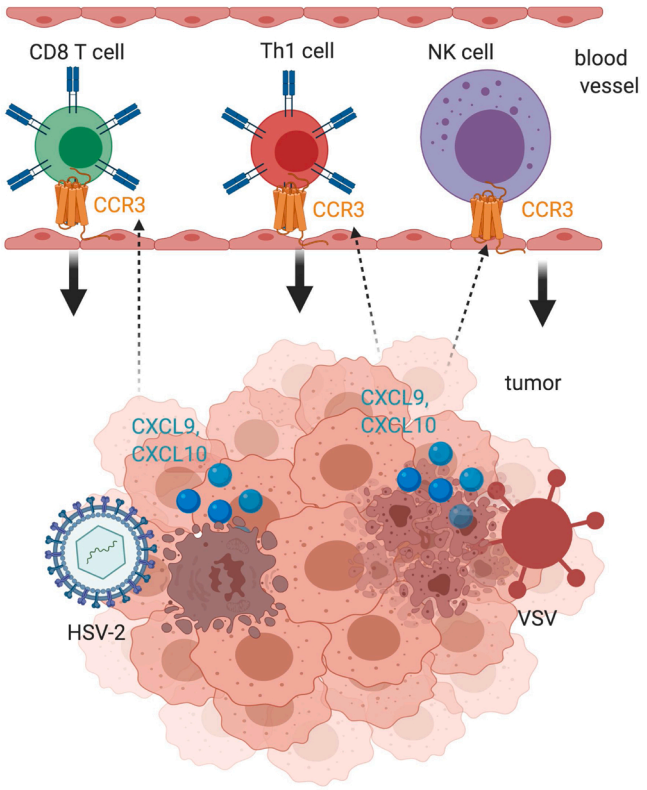


**Fig. 1. Promotion of tumor immunity by chemokines upon oncolytic virotherapy.** Immune cells with antitumor function ($CD4^+$ $T_H1$, $CD8^+$ T lymphocytes and NK cells) require chemokines to exit the blood stream and enter the tumor. Oncolytic viruses promote the release of chemokines such as CXCL9, 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.<br>Transgenes:<br>• **IL-12**<br>• Anti-PD-L1 | i.t. | • Bladder cancer<br>• HNC<br>• Cancer of the Salivary Gland<br>• Lung cancer<br>• Breast cancer<br>• Gastric cancer<br>• Esophageal cancer<br>• CRC<br>• Pancreatic cancer<br>• 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)<br>Deletions:<br>• E3<br>• E4<br>Transgenes:<br>• **CXCL9**<br>• **CXCL10**<br>• **IFNα**<br>• FAP-TAc | i.t.<br>i.v. | • Epithelial tumors | • Chemotherapy<br>• Immune checkpoint inhibitors | 1a/1b | Recruiting | NCT04053283 [67] |
| | ONCOS-102 (Targovax Oy) | Ad5/3-Δ24-GM-CSF<br>Transgene:<br>• **GM-CSF** | i.t. | • Melanoma | • Pembrolizumab<br>• Cyclophosphamide | 1 | Active, not recruiting | NCT03003676 |
| | TILT-123 (TILT Biotherapeutics) | Ad5/3-E2F-d24-hTNFa-IRES-hIL2<br>Mutations:<br>• Insertion of E2F promoter in front of E1AΔ24.<br>Transgenes:<br>• **TNF-a**<br>• **IL-2** | i.t. (?) | • Melanoma | • TILs | 1 | Recruiting | NCT04217473 |
| Herpesvirus | M032 (Catherex) | HSV-1 (F strain)<br>Deletion:<br>• ICP34.5<br>Transgene:<br>• **IL-12** | i.t. | • Glioma | – | 1 | Recruiting | NCT02062827 [154] |
| | ONCR-177 (Oncorus) | HSV-1 (ONCR-159-based vector)<br>Deletions:<br>• 1 out of the 2 copies of ICP34.5<br>• Joint (i.e. internal repeats $IR_L$ & $IR_S$)<br>Other mutations in:<br>• UL37<br>• ICP47<br>miRT for:<br>• miR-1<br>• miR-122<br>• miR-124<br>• miR-126<br>• miR-128<br>• miR-137<br>• miR-143<br>• miR-204 | i.t. | • Skin cancers<br>• HNC<br>• Breast cancer<br>• 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<br>• miR-219<br>Transgenes:<br>• **IL-12**<br>• **CCL4**<br>• **FLT3L**<br>• Anti-PD-1<br>• Anti-CTLA-4 | | | | | | |
| | OrienX010 (Oriengene Biotechnology) | HSV-1 (CL1 strain)<br>Deletions:<br>• ICP34.5<br>• ICP47<br>• ICP6<br>Transgene:<br>• **GM-CSF** | i.t. | • Melanoma | Treprizumab (anti-PD-1)<br>Surgery | 1 | Recruiting | NCT04197882 |
| | | | i.t. | • Melanoma | • Dacarbazine | 2 | Recruiting | NCT04200040 |
| | | | i.t. | • Melanoma | • JS001 (anti-PD-1) | 1b | Recruiting | NCT04206358 |
| | RP1<br>(Replimmune) | HSV-1 (proprietary strain)<br>Deletions:<br>• ICP34.5<br>• ICP47<br>Transgenes:<br>• **GM-CSF**<br>• GALV-GP-R$^-$ | i.t. | • Skin cancers<br>• Bladder cancer<br>• Other solid tumors | • Nivolumab | 1/2 | Recruiting | NCT03767348 |
| | | | i.t. | • SCC | • Cemiplimab | 2 | Recruiting | NCT04050436 |
| | | | i.t. | • SCC | – | 1b | Recruiting | NCT04349436 |
| | T3011<br>(ImmVira Pharma) | HSV-1 (F strain)<br>Deletion:<br>• 15 kbp in the inverted repeat sequences<br>Transgenes:<br>• **IL-12**<br>• Anti-PD-1 | i.t. | • HNC<br>• Sarcoma<br>• Skin cancers<br>• Lung cancer | – | 1 | Recruiting | NCT04370587 |
| | T-VEC<br>(Amgen) | HSV-1 (JS1 strain)<br>Deletions:<br>• ICP34.5<br>• ICP47<br>Transgenes:<br>• **GM-CSF** | i.p. | • Gastrointestinal tumor<br>• 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<br>• Other solid tumors | • Radiotherapy | 2 | Recruiting | NCT02819843 |
| | | | i.t. | • Melanoma<br>• 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<br>• Nivolumab | 1 | Recruiting | NCT04185311 |
| | | | i.t. | • Melanoma | • Surgery | 2 | Recruiting | NCT04427306 |
| | OH2<br>(Wuhan Binhui Biotechnolog) | HSV-2 (HG52 strain)<br>Deletions:<br>• ICP34.5<br>• ICP47 | i.t. | • GI cancers<br>• HNC<br>• Sarcomas | • HX008 (anti-PD-1)<br>• 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 |
| | | Transgene:<br>• **GM-CSF** | i.t. | • Melanoma<br>• GI cancers<br>• Liver cancer<br>• Cervical cancer<br>• HNC | • Pembrolizumab (anti-PD-1) | 1/2 | Recruiting | NCT04386967 [378] |
| Paramyxovirus | MEDI5395 (MedImmune LLC) | NDV (strain 73T-R-198)<br>Transgene:<br>• **GM-CSF** | i.v. | • Breast cancer<br>• CRC<br>• Liver cancer<br>• HNC<br>• Renal cancer<br>• NSCLC<br>• Melanoma | • Durvalumab | 1 | Recruiting | NCT03889275 [379] |
| | ASP9801 (Astellas Pharma) | VV (unknown strain)<br>Transgenes:<br>• **IL-7**<br>• **IL-12** | i.t. | • Skin cancers<br>• Visceral tumors | – | 1 | Recruiting | NCT03954067 |
| | Pexa-Vec / JX-594/ TG6006 (SillaJen; Transgene) | VV (Wyeth strain)<br>Deletion:<br>• TK<br>Transgenes:<br>• **GM-CSF**<br>• LacZ | i.t. | • Solid tumors | • Ipilimumab<br>• Tremelimumab | 1 | Recruiting | NCT02977156 |
| | | | i.t. | • Liver cancer | • Sorafenib | 3 | Active, not recruiting | NCT02562755 |
| Poxvirus | | | i.t.<br>i.v. | • Renal cancer | • REGN2810 (anti-PD-1) | 1b | Recruiting | NCT03294083 |
| | | | i.v. | • CRC | • Durvalumab<br>• Tremelimumab | 1/2 | Recruiting | NCT03206073 |
| | TBio-6517 (Turnstone Biologics) | VV (proprietary strain)<br>Transgenes:<br>• **FLT3L**<br>• **IL-12**<br>• Anti-CTLA-4 | i.t. | • TNBC<br>• MSS-CRC<br>• Other solid tumors | • Pembrolizumab | 1/2 | Recruiting | NCT04301011 |
| | VSV-hIFN-β (Mayo Clinic) | VSV (Indiana strain)<br>Transgene:<br>• **IFN-β** | i.t. | • Liver cancer<br>• Skin cancers<br>• Other solid tumors | – | 1 | Active, not recruiting | NCT01628640 [93] |
| | | | i.t.<br>i.v. | • CRC<br>• Pheochromocytoma<br>• Neuroendocrine cancers | • Avelumab | 1 | Recruiting | NCT02923466 [93] |
| | | | i.v. | • HNC<br>• NSCLC<br>• Other solid tumors | • Pembrolizumab | 1 | Recruiting | NCT03647163 [93] |
| Rhabdovirus | VSV-hIFN-β-TYRP1 (Mayo Clinic) | VSV (Indiana strain)<br>Transgenes:<br>• **IFN-β**<br>• TYRP1 | i.v.<br>i.m. | • Melanoma | – | 1 | Recruiting | NCT03865212 |
| | VSV-hIFN-β-NIS (Mayo Clinic) | VSV (Indiana strain)<br>Transgenes:<br>• **IFN-β**<br>• NIS | i.v. | • Multiple myeloma<br>• Acute myeloid leukemia<br>• 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/$\gamma_c$ - this latter chain being shared with the receptors of IL-4, 7, 9, 15 & 21. The hetero-trimeric complex IL-2Rαβ$\gamma_c$ 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

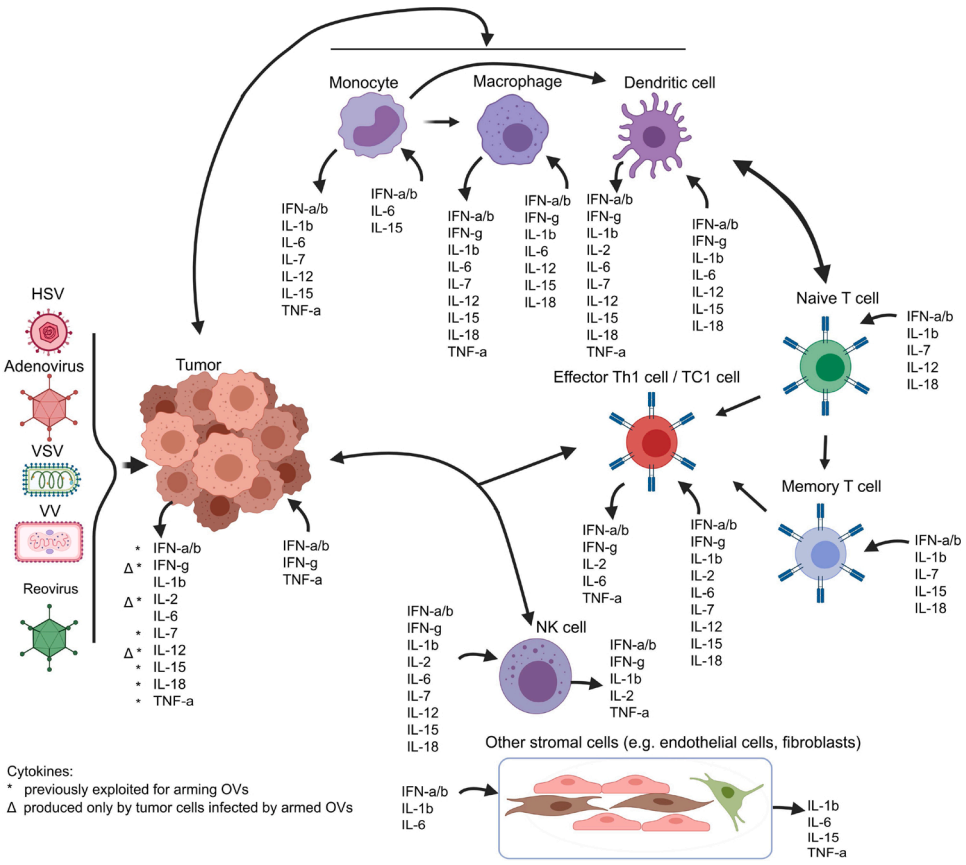


**Fig. 2. Interferons, interleukins, and tumor necrosis factors participating in antitumor immunity described upon oncolytic virotherapy**. Infection of cancer cells by oncolytic Ad, HSV, VSV, VV or reovirus stimulates the release of a plethora of pro-inflammatory cytokines, followed by the recruitment 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/$\gamma_c$, 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/$\gamma_c$ 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 anticancer 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.

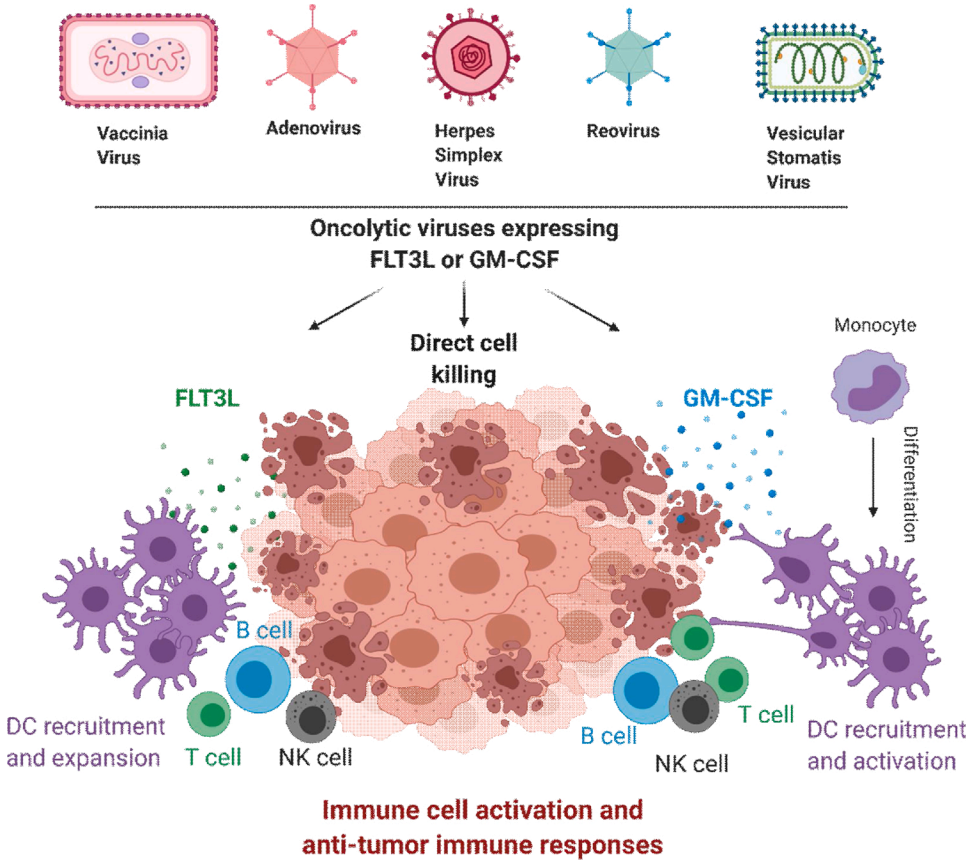


**Fig. 3. Effects of oncolytic viruses expressing growth factors on anti-tumor immunity.** Oncolytic VV, Ad, HSV, reovirus and VSV have been modified to express FLT3L or GM-CSF. This modification aims at combining direct cancer cell killing by OVs with the immune stimulatory actions of FLT3L or GM-CSF. 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 anti-neoplastic 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.

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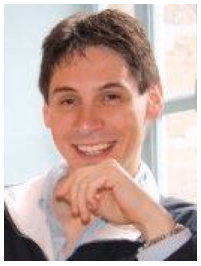

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