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Laurence Zitvogel, Guido Kroemer. Cross-reactivity between cancer and microbial antigens. *OncoImmunology*, 2021, 10 (1), pp.1877416. 10.1080/2162402X.2021.1877416 . hal-03134502

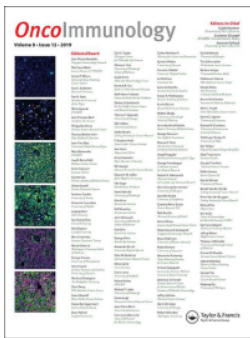
HAL Id: hal-03134502

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Submitted on 8 Feb 2021

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To cite this article: Laurence Zitvogel & Guido Kroemer (2021) Cross-reactivity between cancer and microbial antigens, *Oncolmmunology*, 10:1, 1877416, DOI: [10.1080/2162402X.2021.1877416](https://doi.org/10.1080/2162402X.2021.1877416)

To link to this article: <https://doi.org/10.1080/2162402X.2021.1877416>



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Published online: 20 Jan 2021.



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Cross-reactivity between cancer and microbial antigens

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ARTICLE HISTORY Received 12 January 2021; Revised 13 January 2021; Accepted 13 January 2021

The intestinal microbiota constitute the largest accumulation of alien organisms present on or in the human body, providing a major contribution to the meta-organism.¹ Indeed, the gut ecosystem composed of archae, bacteria, parasites, phages and viruses outnumbers the host in the number of (1) cells, (2) genes/proteins, and (3) enzymatic reactions generating metabolites.

While most microbial metabolites close-to-freely diffuse through the gut barrier to reach the liver for a first round of chemical transformation and detoxification (but reportedly constitute a substantial fraction of mass spectrometry-detectable metabolites in the peripheral circulation), in physiological conditions, microbial organisms are efficiently retained in the lumen in the gut. Thus, the translocation of live microbes into the portal circulation (filtered by the liver), the local lymphoid system (filtered by the mesenteric lymph nodes, mLNs) or beyond only occurs in pathological circumstances.

Microbial macromolecules may activate the local and systemic immune systems through two fundamentally different pathways. On one hand, microbe-associated molecular patterns (MAMPs), often also called pathogen-associated molecular patterns (PAMPs), may activate pathogen recognition receptors (PRRs) to elicit pro-inflammatory reactions. A prominent example of MAMPs/PAMPs is bacterial lipopolysaccharide (LPS) that stimulates Toll-like receptor 4 (TLR4), thus eliciting adaptive responses by intestinal epithelial cells and local myeloid cells if present in the gut. However, when it trespasses the gut barrier, LPS elicits pathogenic signals that may ignite pancreatitis, liver inflammation or even participate in the pathogenesis of septic shock.² Microbial proteins may either elicit PRRs (one prominent example is flagellin, which stimulates TLR5) or act as antigens. Thus, on the other hand, bacterial structures may be recognized by T cell receptors or antibodies. Indeed, specific dendritic cells can sample proteins from the microbiota and then present such antigens to T cells, either locally, in the Peyer patches or in mLNs to elicit a cognate immune response by T lymphocytes or B cells. Here, to maintain homeostasis, the organisms should mount a graduated and appropriate immune response that confers

tolerance (instead of allergy) to commensal bacteria, yet eliminates pathogens (such as enteropathic viruses and bacteria) and simultaneously avoids noxious cross-reactivity with self-antigens that would lead to the development of autoimmune diseases.

There are multiple instances in which this fine line between beneficial and pathogenic immune responses is trespassed, as exemplified in several recent high-profile reports (Table 1). Thus, autoimmune diseases may be favored by intestinal bacteria that elicit MHC class II-restricted autoantigen-cross-reactive CD4⁺ T cell responses. For instance, antiphospholipid syndrome (APS) correlates with the presence of *Roseburia intestinalis*-specific antibodies in APS patients, knowing that *R. intestinalis* possesses proteins that cross-react with the APS self-antigen β 2-glycoprotein I (β 2GPI), both at the level of patient-derived autoantibodies and memory CD4⁺ Th1 cells (in particular in the context of a disease-associated HLA class II allele). In BALB/c mice, immunization with *R. intestinalis* induces antibodies that recognize human β 2GPI, and gavage of autoimmunity-prone (NZW \times BXSB)F₁ hybrid mice induces antihuman β 2GPI IgG antibodies and lethal thromboses, establishing a cause-effect relationship between the presence of *R. intestinalis* in the gut and the development of APS.³ An inflammatory cardiopathy has been causally related to *Bacteroides* species producing a β -galactosidase cross-reactive with an HLA-DQB1*-restricted peptide from human myosin heavy chain 6.⁶ Multiple sclerosis (MS) has been epidemiologically associated with the presence of *Akkermansia muciniphila* in the gut, and HLA-DR15-restricted CD4⁺ T cells from MS patients can recognize peptides encoded by the *A. muciniphila* genome.⁷ Finally, in the context of systemic lupus erythematosus (SLE), HLA-DR3 and HLA-DR15-restricted human Ro60 autoantigen-specific CD4 memory T cell clones are activated by bacteria that express an Ro60 orthologue.⁹ As an alternative, bacteria may interact with host cells to elicit the expression of autoimmunity-relevant autoantigens, as documented for rheumatoid arthritis, in which leukotoxic *Aggregatibacter actinomycetemcomitans* strains involved in periodontitis cause neutrophils to produce and

Table 1. Examples of cross-reactivities between microbial and self-antigens.

Pathology	Microbial antigen or modification of self-antigen	Self-antigen	MHC class I + observations	Reference
Antiphospholipid syndrome (APS)	Proteins from <i>Roseburia intestinalis</i> stimulate β 2GPI-reactive memory CD4 ⁺ Th1 Cells from APS patients, and one protein (DNMT) crossreacts with a patient-derived anti- β 2GPI mAb	T and B cell autoepitopes in the APS autoantigen β 2-glycoprotein I (β 2GPI)	HLA-DRB4*0103 (serotype DR53) APS patients have high levels of <i>intestinalis</i> – specific IgG antibodies. Oral gavage of susceptible (NZW \times BXSb)F ₁ mice with <i>R. intestinalis</i> induces anti-human β 2GPI autoantibodies and lethal thromboses	3
Cancer: Multiple transplantable mouse cancers	TSLARFANI contained in the TMP1 protein expressed by an enterococcal phage	GSLARFRNI contained in PSMB4 protein	Mouse K ^b Colonization with <i>Enterococcus hirae</i> or <i>Escherichia coli</i> expressing the TMP1 epitope improves control of MCA205 fibrosarcomas	4
Cancer: Lung adenocarcinoma + kidney cancer	KLAKFASVW contained in the TMP1 expressed by an enterococcal phage	KLQKFASTV contained in GPD1-L protein	HLA-A*0201 Cross-reactive T cells found in non-small cell lung cancer patients. Presence of TMP1 associated to good prognosis in patients treated with PD-1 blockade	4
Cancer: melanoma	SVYRYYGL expressed by <i>Bifidobacterium breve</i>	SIYRYYGL artificially introduced into B16 melanoma cells	Mouse K ^b Colonization with <i>B. breve</i> allows for melanoma control	5
	Multiple melanoma antigen-homologous peptides identified by bioinformatics within the human intestinal microbiota	EAAGIGILTV present in the MART-1 protein and TLNDECWPA present in MELOE1	HLA-A*0201 In vitro evidence of cross-reactive T cells with defined TCR sequences	4
Inflammatory cardiomyopathy	FLILMAALTATFASAQ contained in β -galactosidase from <i>Bacteroides thetaiotaomicron</i> and <i>B. faecis</i>	SLKLMATLFFSSYATAD from human myosin heavy chain 6 (MYH6)	HLA-DQB1* <i>Bacteroides</i> -specific CD4 ⁺ T cell and B cell responses found in human myocarditis patients. <i>B. thetaiotaomicron</i> monocolonization expressing the β -galactosidase epitope favors myocarditis development in mice expressing a MYH6-specific T cell receptor on more than 95% of their CD4 ⁺ T cells.	6
Multiple sclerosis (MS)	<i>Akkermansia muciniphila</i> Epstein Barr virus (EBV)	HLA-DR15 DR2a and Dr2b presenting peptides derived from themselves	HLA-DR15 cross-reactive responses between autoreactive CD4 ⁺ T cells from an MS patients and peptides derived from <i>A. muciniphila</i> or EBV, which are both epidemiologically associated with MS	7
Rheumatoid arthritis (RA)	Citrullination of host proteins following periodontitis by leukotoxic <i>Aggregatibacter actinomycetemcomitans</i> (Aa) strains	Citrullinated host proteins in neutrophils	Shared epitope (SE)-containing HLA-DRB1 alleles. Epidemiological association between anti-Aa antibodies, anti-citrullinated protein antibodies and rheumatoid factor	8
Systemic lupus erythematosus (SLE)	Skin and mucosal bacteria expressing Ro60, in particular species of <i>Corynebacterium</i> , <i>Propionibacterium</i> , and <i>Bacteroides</i>	Ro60 autoantigen	HLA-DR3 and HLA-DR15 Human Ro60 autoantigen-specific CD4 memory T cell clones from lupus patients are activated by Ro60-containing bacteria. Germ-free mice colonized with a Ro60 ortholog-containing <i>Bacteroides thetaiotaomicron</i> develop T and B cell response against anti-human Ro60, as well as glomerular immune complex deposits.	9
	<i>Enterococcus gallinarum</i> , which is found in the liver from autoimmune patients and translocates from the gut to the liver in genetically lupus-prone (NZW \times BXSb)F ₁ hybrid mouse	Increased expression of autoantigens ERV gp70 and β 2GPI by hepatocytes cultured with <i>E. gallinarum</i>	SLE patients have increased antibodies against <i>E. gallinarum</i> RNA. Germ-free C57Bl/6 mice colonized with <i>E. gallinarum</i> allow for translocation of the bacterium and induces autoantibodies. Intramuscular vaccination of (NZW \times BXSb)F ₁ mice with heat-inactivated <i>E. gallinarum</i> attenuates autoimmunity.	10

release citrullinated proteins,⁸ and SLE, in which *Enterococcus gallinarum* translocates from the gut into the liver and causes hepatocytes to express the autoantigens ERV gp70 and β 2GPI (Table 1).¹⁰

In the context of cancer, cross-reactivities have been documented for MHC Class I-restricted CD8⁺ cytotoxic T lymphocytes that recognize both tumor-associated antigens and bacterial antigens expressed by intestinal commensals (Table 1). In a pioneering report, Bessel et al. demonstrated that a peptide expressed by *Bifidobacterium breve* can cross-react with a tumor antigen that

was artificially induced into B16 melanoma cells.⁵ A more recent study from our laboratories demonstrated that a peptide (within the tape measure protein TMP1) encoded by the genome of a 39.2-kb prophage from the *Siphoviridae* bacteriophage family, which lysogenizes *Enterococci*, can cross-react with a peptide contained in a natural protein (PSMB4, which is an oncogenic proteasome subunit) expressed by mouse fibrosarcomas and lung cancers.⁴ The relevance of this cross-reactivity for tumor control was demonstrated by several lines of evidence, including the observations that (1) only *Enterococci* harboring the bacteriophage-encoded TMP1 epitope

favor immune control of tumors; (2) point mutations of the bacteriophage-encoded TMP1 epitope abolished such an immune control; (3) transfer of the TMP1 epitope into *Escherichia coli* conferred antitumor immunity-inducing properties to this usually inert bacterium if it was orally administered to mice; (4) mutation of the PSMB4 epitope in tumor cells rendered them resistant to TMP1-encoding bacteriophage-elicited immunosurveillance.⁴ For human cancer, cross-reactivity between bacterial and tumor antigens has also been documented. Thus, TMP1 codes for another peptide that is cross-reactive with the human suppressor gene glycerol 3-phosphate dehydrogenase 1 like (GPD1-L) protein. In patients with non-small cell lung cancer, TMP1/GPD1-L cross-reactive CD8⁺ T cells were detected. Moreover, the presence of the bacteriophage coding for TMP1 in the gut could be correlated with therapeutic responses of lung and kidney cancer patients to PD-1 blockade.⁴ Finally, two non-mutated human melanoma antigens (MART-1 and MELOE1) elicit CD8⁺ T cell responses in patients that are cross-reactive with peptides encoded by the human gut microbiota.⁴

Altogether, the aforementioned results support the notion that the microbiota, in particularly the gut microflora, has a major impact on the T cell repertoire, with far-reaching implications for pathogenic autoimmunity and homeostatic immunosurveillance. We suspect that future research will unveil the detailed mechanisms explaining how specific microbes elicit tumor-relevant immune responses.

Disclosure of potential conflicts of interest

LZ and GK are scientific cofounders of EverImmune.

Funding

LZ and GK are supported by the Ligue Contre le Cancer (équipe labellisée); Agence National de la Recherche (ANR) – Projets blancs; AMMICA US23/CNRS UMS3655; Association pour la Recherche sur le Cancer (ARC); Association “Ruban Rose”; Cancéropôle Ile-de-France; Fondation pour la Recherche Médicale (FRM); a donation by Elior; Equipex Onco-Pheno-Screen; European Joint Programme on Rare Diseases (EJPRD); Gustave Roussy Odyssey, the European Union Horizon 2020 Projects Oncobiome and Crimson; Fondation Carrefour; High-end Foreign Expert Program in China [GDW20171100085], Institut National du Cancer (INCa); Inserm (HTE); Institut Universitaire de France; LabEx Immuno-Oncology [ANR-18-IDEX-0001]; the RHU Torino Lumière; Seerave Foundation; SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); and SIRIC Cancer Research and Personalized Medicine (CARPEM). This study contributes to the IdEx Université de Paris ANR-18-IDEX-0001.

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