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EDITORIAL

The ambiguous role of FPR1 in immunity and inflammation

Erika Vacchelli[a,b,c], Julie Le Naour[a,b,c,d], and Guido Kroemer [a,b,c,e,f,g]

[a]Equipe labellisée par la Ligue contre le cancer, Université de Paris, Sorbonne Université, INSERM U1138, Centre de Recherche des Cordeliers, Paris, France; [b]Metabolomics and Cell Biology Platforms, Gustave Roussy Cancer Campus, Villejuif, France; [c]Gustave Roussy Cancer Campus, Villejuif, France; [d]Université Paris Sud, Paris Saclay, Faculty of Medicine Kremlin Bicêtre, Paris, France; [e]Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [f]Suzhou Institute for Systems Medicine, Chinese Academy of Medical Sciences, Suzhou, China; [g]Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital, Stockholm, Sweden

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Formyl peptide receptors (FPRs) are pattern recognition receptors (PPRs) that are involved in multiple pathological processes. These G protein-coupled receptors expressed by immune cells transduce chemotactic signals to trigger cell adhesion, migration, generation of reactive oxygen species (ROS) as well as tissue repair and angiogenesis.[1]

Among the three FPRs known in humans (FPR1, FPR2 and FPR3), most studies have focused on FPR1.[2] Their main ligands, N-formylated peptides, are either produced by invading bacteria or released from degrading mitochondrial proteins contained in dying host cells.[1] Although FPRs are expressed in various immune cells[1,3] among which neutrophils, macrophages, natural killer and dendritic cells, studies on FPR1 functions mostly focus on neutrophils, which often are the leukocytes to migrate toward the site of inflammation.[2]

FPR1 has an ambivalent role in pathogenic processes (Figure 1). In some diseases, FPR1 has a positive effect. In the context of infection by *Escherichia coli*[4] and *Listeria monocytogenes*,[5] a genetic FPR1 deficiency (genotype: *Fpr1*$^{-/-}$) compromises pathogen elimination in mice, therefore, increasing mortality. Indeed, in the context of bacterial infection, FPRs induce trafficking of phagocytes to the site of microbial invasion and increase the phagocytic destruction of the pathogens.[6] In cancers developing on *Fpr1*$^{-/-}$ mice, the recruitment and positioning of dendritic cells into the tumor bed (and not that of neutrophils as in many other scenarios) is reduced in response to chemotherapy, thereby compromising the antitumor immune response required for chemotherapy to be efficient.[7,8] FPR1 has several endogenous ligands including Annexin A1 (ANXA1), cathepsin G (CTSG), family with sequence similarity 19 (chemokine (C-C motif)-like) member A4 (FAM19A4) and N-formylated peptides contained in mitochondria. *In vivo* experiments revealed that only the deletion of the gene coding for *Annexin A1* (ANXA1) compromised the capacity of dying cancer cells to induce anticancer immune responses.[7] Thus, the cancer immunosurveillance-relevant ligand of FPR1 appears to be ANXA1.

In sharp contrast, in many other diseases, FPR1 has negative effects, meaning that its neutralization might be considered as a therapeutic intervention. For example, *Fpr1*$^{-/-}$ mice are protected against infection by *Yersinia pestis*, in line with the discovery that FPR1 acts as the receptor for this pathogen, which is the causative agent of human plague.[9] Moreover, *Fpr1*$^{-/-}$ mice subjected to ischemia-reperfusion damage to the heart present reduced inflammation, cardiomyocyte apoptosis and ventricular remodeling, accompanied by the inhibition of the mitogen-activated protein kinases (MAPK) pathway.[10] Similarly, FPR1 plays a negative role in celiac disease, a highly prevalent autoimmune disorder that can be attenuated but not cured by a gluten-free diet. Indeed, FPR1 promotes the proinflammatory migration of neutrophils into the gut following exposure to gliadin (the pathogenic component of gluten).[11] Acute endotoxin-induce lung injury is also attenuated in *Fpr1*$^{-/-}$ mice commensurate with reduced local neutrophil recruitment.[12] Similarly, *Fpr1*$^{-/-}$ mice are protected from cigarette smoking-induced lung emphysema, coupled to a drastic reduction in the migration of neutrophils and macrophages to the lung after smoke exposure.[13] Indeed, patients with chronic obstructive pulmonary disease exhibiting an increased expression of FPR1 on peripheral neutrophils and in bronchoalveolar fluids.[13] Finally, *Fpr1*$^{-/-}$ mice do not develop pulmonary fibrosis in response to intratracheal bleomycin challenge and failed to recruit neutrophils to the damaged lungs.[2] Adoptive transfer experiments allowed to conclude that the cell type that has to express FPR1 to cause bleomycin-induced lung fibrosis is neutrophils, underscoring the importance of this leukocyte subpopulation for disease pathogenesis.[2]

Of note, more than 200 single nucleotide polymorphisms (SNPs) have been described for FPR1, and this heterogeneity could influence the functional (positive or negative) role of the gene in various diseases. In some cases, such as aggressive periodontitis[14] or exudative age-related macular degeneration and polypoidal choroidal vasculopathy[15] a functional defect of the gene constitutes a potential risk factor. In the context of cancer, the loss-of-function variation rs867228 (G346A affecting the intracellular C-terminus of FPR1) is associated with reduced survival in breast and colorectal cancer patients treated by immunogenic chemotherapy.[7] *FPR1* rs5030880 (R190 W affecting the extracellular loop 2 of FPR1) may constitute plague resistance allele. Indeed, monocytes from individuals bearing this polymorphism exhibit a reduced migration toward formylated peptides or *Y. pestis*.[9]

CONTACT Guido Kroemer kroemer@orange.fr INSERM, U1138, Centre De Recherche Des Cordeliers, 15 Rue De l'Ecole De Medecine, Paris 75006, France

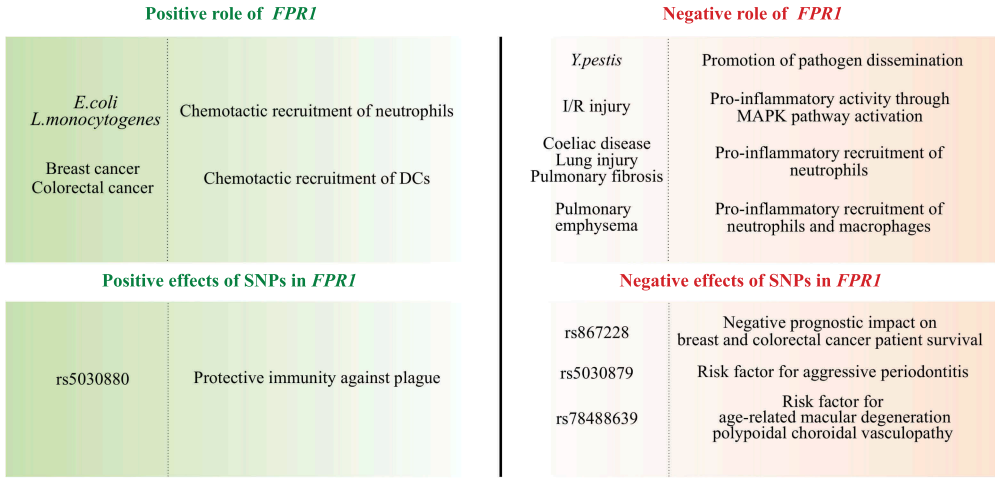

Figure 1. Positive and negative roles of FPR1 in disease pathogenesis.
Abbreviations: DC, dendritic cell; FPR1, formyl peptide receptor 1; I/R, ischemia/reperfusion; MAPK, mitogen-activated protein.

Given the ambiguity of FPR1 in the pathogenesis of disease (Figure 1), from a teleological point of view, it might be important to maintain a heterogeneity in the population that then would constitute an equilibrated mix of individuals some of which, for example, are resistant against some infectious agents (*Y. pestis* and endotoxin-induced lung damage in the case of a loss-of-function allele) at the cost of being more susceptible to other pathogens (*E. coli* and *L. monocytogenes*, for the loss-of-function allele) and *vice versa*. Indeed, rs5030880 occurs in ~12% of Caucasians as well as in ~9% of Africans and Afro-Americans and in ~18% of Asians. Similarly, a sizable fraction of the population (~30% of Caucasians) harbors the loss-of-function allele of rs867228. As an aside, such functionally relevant polymorphisms may impact anticancer immunosurveillance requiring functional dendritic cells[7] as well as chronic inflammation mediated by FPR1 expressing macrophages[3] and neutrophils.[2] It will be important to determine the impact of genetic polymorphisms affecting FPRs and other PRRs in more detail, in a systematic fashion, to understand their importance in the initiation and resolution of inflammatory and immune responses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Abbreviations

ORCID

Guido Kroemer http://orcid.org/0000-0002-9334-4405

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