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Editorial

SLAMF receptors and disease

The Signaling Lymphocytic Activation Molecule Family (SLAMF) receptors comprise a group of cell-surface glycoproteins that belong to the immunoglobulin superfamily. These molecules are differentially expressed on a wide variety of hematopoietic cells. Most of the SLAMF members function as homophilic receptors, and unlike the majority of co-signaling molecules, their cytoplasmic tails contain one or more copies of a unique tyrosine motif called the immunoreceptor tyrosine-based switch motif (ITSM) [1–3]. Engagement of SLAMF molecules triggers the phosphorylation of ITSMs, which serve as docking sites for intracellular adapter molecules (SAP and EAT2) or enzymes bearing SH2, that connect these receptors to signal transduction networks. These interactions induce distinct intracellular signals that regulate the development and effector functions of myeloid cells and lymphocytes, including co-stimulation, tolerance, cytokine production, cytotoxicity, antibody responses, as well as, recognition of microbial components. Thus, SLAMF receptors function as cell-cell communicators and microbial sensors, representing a bridge between the innate and adaptive immune responses [4]. We have learned a lot about the biology of this family of immune receptors, however only during the last few years their role in a wide spectrum of diseases has started to emerge.

Thus, the main goal of this Special Issue is to discuss recent findings related to the role played by this receptor family in the pathogenesis of several autoimmune diseases, leukocyte malignancies, infection, and allergy. It also presents recent advances on the use of SLAMF receptor antibody-mediated therapies for the treatment of autoimmunity and malignancies especially chronic lymphocytic leukemia and myeloma.

This issue starts with a paper by Yugit and colleagues that presents a detailed introduction to the SLAMF members and their adaptors SAP and EAT-2. It also describes the functions of SLAMF6 and discusses the promising results that point to SLAMF6 as a target for human malignancies.

The paper by Gordiienko and colleagues describes SLAMF1 (CD150) as a biomarker and its role in regulating malignant cell survival and the tumor microenvironment in Hodgkin's lymphoma and chronic lymphocytic leukemia. They also provide evidences of SLAMF1 as a new target for antibody-based treatment and measles virus oncolytic therapy.

The paper by Shachar and colleagues reviews recent studies regarding SLAMF receptors expression and function in normal and pathological B, and discusses their therapeutic potential.

Pende and colleagues describe the characteristics of X-linked lymphoproliferative disease 1 (XLP1), which is a primary immunodeficiency caused by mutations in the adapter molecule SAP (SH2D1A). XLP1 patient's NK and T cells present an inability to kill EBV-infected B cells with dramatic clinical sequelae such as fulminant mononucleosis or lymphoma. They discuss the key roles of SLAMF6 and 2B4 (CD244) molecules in this immunodeficiency.

The paper by Claus and colleagues explores how SLAMF receptors regulate NK cells. They discuss the cis interactions that these receptors can establish and how these interactions affect NK cell function.

The review by Cuenca and colleagues covers our present understanding of the structure and function of the SLAMF receptor CD84. It discusses its potential as a disease biomarker and therapeutic target in several autoimmune diseases and cancer.

Malaer and colleagues examine the question of the dual effects of SLAMF receptors 2B4 (CD244) and CS1 (SLAMF7) that mediate both activating and inhibitory functions and their role in systemic lupus erythematosus (SLE). They also describe the promising results obtained with anti-CS1 monoclonal antibody Elotuzumab for the treatment of multiple myeloma. In addition, they detail the generation of new CAR-T cells and CAR-NK cells with constructs containing the extracellular domains of CS1 or the signaling domains of 2B4 to treat cancer and autoimmune diseases.

The paper by Conte and colleagues reviews the status of our current knowledge of the contribution of SLAMF receptors to the complex immunopathogenesis of human SLE, and the importance of these molecules as new therapeutic targets.

The review by Pahima and colleagues describes the key role of CD244 (2B4) and CD48 molecules in the context of allergic diseases and their function in the activation of mast cells and eosinophils.

Finally, Olson and colleagues address the characteristics that make CD229 a promising target for anti-multiple myeloma immunotherapy.

I want to dedicate this Special Issue in memoriam to the Ukrainian immunologist Svetlana Sidorenko. Sadly, she passed away when we were preparing this Special Issue. She did seminal contributions to the field of SLAMF molecules. In the early 90s, while working in Ed Clark's laboratory at the University of Washington School of Medicine in Seattle, she produced and characterized the first antibody against the molecule SLAMF1, called IPO-1, and started the study of the ITSM motif [5,6]. She also published a very inspiring review article of SLAMF molecules and viruses that booted the interest in viral homologues of these receptors. [7]. Svetlana will be missed by all the scientists that had the pleasure to work with her.

I hope you will find this collection of reviews interesting and inspiring. I am convinced that the studies of the biology of these molecules and the application of this knowledge will lead, in a next future, to exciting new alternative therapeutic options for our patients.

Pablo Engel

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