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Immunoregulation by Inhibitory Receptors

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Accumulating evidence indicates that the immunological reactivity to foreign substances and self tolerance in our periphery is strictly maintained by unique or sometimes redundant functions of various activating and inhibitory receptor pairs expressed on B cells, T cells, dendritic cells and many other lineages of cells in the immune system. In the absence of the one or more such regulatory receptors, our immune system immediately or gradually lost its integrity, which may lead to unresponsiveness, infection, inflammatory, or autoimmune disorders.

The receptors for immunoglobulin (Ig) Fc portion, FcRs, constitutes one of such most important immunoregulatory systems that participate in securing reactivity to foreign antigens while maintaining peripheral tolerance to self tissues. Like other immune regulatory receptor pairs, the FcR system is constituted by activating[1)] and inhibitory receptors[2)] that bind the same ligands, Fc portions of Ig, and their mode of action has been studied extensively in recent years[3)]. Triggering the activating-type IgG FcRs, namely FcγRI and FcγRIII elicit a variety of effector functions, including phagocytosis, antibody-dependent cell-mediated cytotoxicity, and release of inflammatory mediators. On the other hand, a unique inhibitory FcR, FcγRIIB, inhibits cellular activation triggered through binding of IgG immune complexes to activating FcγRs. Disruption of FcγRIIB by gene targeting lenders mice hypersensitive to stimulation with self- and non-self antigens. Accumulating evidence indicates that FcγRIIB physiologically acts as a negative regulator of immune complex-triggered activation and functions to suppress autoimmunity by regulating both B cell responses and effector cell activation. Experimental results from our group and others highlight the role of FcγRIIB in maintaining tolerance and suggest that this unique inhibitory FcR may play a critical role in the pathogenesis of rheumatoid arthritis, Goodpasture's syndrome, systemic lupus erythematosus, and other autoimmune diseases in humans. I will also discuss briefly about recent reports on the roles of FcγRIIB in the therapeutic effects of intravenous immunoglobulin (IVIg) therapy against several inflammatory and autoimmune diseases[4)], and will mention about future directions of FcγRIIB-targeted therapeutic approaches.

Similar to FcRs, Paired Ig-like receptors (PIRs) represent also a typical receptor pair of the Ig-like receptor family[5)]. Activating PIR-A and inhibitory PIR-B are expressed in a wide range of cells in the murine immune system, such as B cells, mast cells, macrophages and dendritic cells, mostly in a pairwise fashion. PIR-A and PIR-B share similar characteristics with human leukocyte Ig-like receptors (LILRs), including activating LILRAs and inhibitory LILRBs. PIRs bind to MHC class I molecules expressed ubiquitously. The unbalanced binding of PIR-A and PIR-B to MHC class I may lead to the perturbation of cell development, regulation and function, such as augmented mast cell functions and anaphylactic responses[6, 7)], exacerbated graft-versus-host disease[8)], and autoimmune glomerulonephritis[9)], as observed in PIR-B-deficient mice. PIRs, PIR-B in particular, can associate constitutively to MHC class I on the surface of cells of the immune system. Thus, the constitutive binding between PIR-B and MHC class I in cis and/or trans configuration has an essential role in regulating inflammation and autoimmunity. Recent analyses revealed the link between human LILRB single nucleotide polymorphisms and rheumatoid arthritis and autoimmune glomerulonephritis[10–12)]. Exploiting such PIR-B (LILRBs)/MHC class I-mediated constitutive inhibitory immunoregulation may well lead to better control for inflammatory and autoimmune disorders.

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