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Review

Teleost IgSF immunoregulatory receptors

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ABSTRACT

In all animals innate immunity is the first line of immune defense from invading pathogens. The prototypical innate cellular responses such as phagocytosis, degranulation, and cellular cytotoxicity are elicited by leukocytes in a diverse range of animals including fish, amphibians, birds and mammals reinforcing the importance of such primordial defense mechanisms. In mammals, these responses are intricately controlled and coordinated at the cellular level by distinct subsets of immunoregulatory receptors. Many of these surface proteins belong to the immunoglobulin superfamily and in mammals elaborate immunoregulatory receptor networks play a major role in the control of infectious diseases. Recent examination of teleost immunity has begun to further illustrate the complexities of these receptor networks in lower vertebrates. However, little is known about the mechanisms that control how immunoregulatory receptors influence cellular decision making in ectothermic vertebrates. This review focuses on several families of recently discovered immunoglobulin superfamily members in fish that share structural, phylogenetic and in some cases functional relationships with mammalian immunoregulatory receptors. Further characterization of these teleost innate immune receptor families will provide detailed information regarding the conservation and importance of innate immune defense strategies throughout vertebrate evolution.

Contents

Abbreviations: Ig, immunoglobulin; NK, natural killer; IgSF, immunoglobulin superfamily; TCR, T-cell receptor; BCR, B-cell receptor; Chr, chromosome; FcR, Fc receptor; ADCC, antibody dependent cellular cytotoxicity; MHC I, major histocompatibility class I; KIR, killer Ig-like receptor; LILR, leukocyte Ig-like receptor; LRC, leukocyte receptor complex; CEACAM, carcinoembryonic antigen-related cell adhesion molecule; TREMs, triggering receptors expressed on myeloid cells; NCRs, natural cytotoxicity receptors; Siglec, sialic acid-recognizing IgSF lectin; NITR, novel immune-type receptor; pIgR, polymeric immunoglobulin receptor; NILT, novel Ig-like transcripts; LITR, leukocyte immune-type receptor; pIg, polymeric immunoglobulins; TREM, triggering receptors expressed on myeloid cell; MB, megabases; CHIR, chicken Ig-like receptors; TM, transmembrane; CYT, cytoplasmic; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITAM, immunoreceptor tyrosine-based activatory motif; ITSM, immunotyrosine-based switch motif; J, joining; aa, amino acid; CDR, complementary determining region; IEL, intraepithelial lymphocyte; FCRL, Fc receptor-like; mAb, monoclonal antibody; kDa, kilodaltons; D, domain; β_2M, β-2-microglobulin; SHP, Src homology 2 domain-containing protein tyrosine phosphatases.

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1. Introduction

Immunoregulatory receptors belonging to the immunoglobulin superfamily (IgSF) represent a diverse array of cell surface proteins expressed by immune cells. These receptors can recognize microbial and viral antigens, other immune proteins (e.g. antibodies, complement, and adhesion molecules), or altered/damaged host molecules (i.e. expressed by virus-infected and neoplastic cells). In contrast to the high degree of specific antigen binding receptors generated through the molecular rearrangement mechanisms of immunoglobulin (Ig) and T cell receptor genes, non-TCR and BCR IgSF immunoregulatory receptors are germline encoded and non-rearranging, which limits the potential number of ligands they recognize. In many cases germline encoded IgSF immunoregulatory receptors exist as large gene families consisting of closely related but polymorphic members exhibiting significant intra- and inter-species diversity (Wagtmann et al., 1997; Wende et al., 1999; Martin et al., 2002; Kelley et al., 2005). This diversity is likely due to evolutionary pressures to match rapidly evolving ligands and/or their direct interactions with a diverse range of pathogen products (Khakoo et al., 2000; Parham, 2004; Thananchai et al., 2007; Barrow and Trowsdale, 2008). Both myeloid and lymphoid cell types express IgSF immunoregulatory receptors including macrophages and natural killer (NK) cells. In general, the effector responses of these cells are tightly regulated by a balance of counteracting signals initiated by co-expressed receptors, which are coupled with distinct intracellular signaling modules (Barrow and Trowsdale, 2008; Long, 1999; Brown et al., 2004; Bottino et al., 2005; Takai, 2005; Lanier, 2008).

Surface expression of activating and inhibitory IgSF immunoregulatory receptor-types forms elaborate networks capable of augmenting or abrogating key immunological responses (Kelley et al., 2005; Barrow and Trowsdale, 2008). For example, receptors that bind to the Fc portion of Ig (FcRs) are encoded as a cluster of genes on human chromosome (Chr) 1, which mediate macrophage and NK cell effector functions such as phagocytosis and antibody-dependent cellular cytotoxicity (ADCC) (Takai, 2005; Hulett et al., 1991; Ravetch and Kinet, 1991; Hulett and Hogarth, 1994; Daeron, 1997; Falk and Ravetch RV, 2006; Nimmerjahn and Ravetch, 2007). IgSF immunoregulatory receptors that interact with major histocompatibility class I (MHC I), such as killer cell Ig-like receptors (KIRs) and leukocyte Ig-like receptors (LILRs), are clustered in a region referred to as the leukocyte receptor complex (LRC) on human Chr19 and regulate NK cell cytotoxicity and cytokine secretion (Wende et al., 1999; Martin et al., 2002; Barrow and Trowsdale, 2008; Brown et al., 2004). The central importance of FcR- and KIR/LILR-mediated regulation of these cellular responses is highlighted by studies implicating receptor dysfunctions with increased susceptibility to certain diseases. Thus, unregulated immune cell responses traced to aberrant FcR, KIR, and LILR functions can have destructive biological consequences resulting in autoimmunity, malignancy, and infections (Brown et al., 2004; Takai, 2005; Tsuchiya et al., 2007; Boyton and Altmann, 2007). While the aforementioned proteins exhibit key immunoregulatory roles, they are not the only receptor-types known to participate in shaping mammalian immune cell responses. For example a series of other IgSF immunoregulatory members that serve as co-receptors (e.g.B7 and CD28/CTLA4), adhesion molecules (e.g. CD2 and carcinoembryonic antigen-related cell adhesion molecule [CEACAM]), triggering receptors expressed on myeloid cells (TREMs), natural cytotoxicity receptors (NCRs; e.g. NKp30, NKp44, and NKp46), and sialic acid-recognizing IgSF lectins (Siglecs) are also present on immune cell subsets and have been demonstrated to elicit profound immunomodulatory effects (Driessens et al., 2009; Brandt et al., 2009; Hansen et al., 2009; Zheng et al., 2009; Gray-Owen and Blumberg, 2006; Ford and McVicar, 2009; Biassoni et al., 2001). In addition, many non-IgSF receptors such as CD94/NKG2 and Ly49 C-type lectin family members can influence key immunological responses in mammals (Yokoyama and Plougastel, 2003), reinforcing that a complex array of receptor types participate in dictating immune cell functions.

Repertoires of immunoregulatory receptors have also been discovered in non-mammalian vertebrates (i.e. birds, amphibians, and fish) and the majority of these belong to the IgSF (Hansen et al., 2009; Dennis et al., 2000; Viertlboeck et al., 2009a; Fayngerts et al., 2007; Guselnikov et al., 2008, 2010; Strong et al., 1999; Yoder et al., 2001, 2004; Stet et al., 2005; Stafford et al., 2006a; Panagos et al., 2006; Yoder and Litman, 2011; Ostergaard et al., 2010) and exist as polygenic and polymorphic gene clusters found on different chromosomes. This further emphasizes the complexity of vertebrate immune system regulation and provides some insights into the evolutionary origins of vertebrate immunoregulatory receptor networks. Examination of the signaling pathways initiated by non-mammalian immunoregulatory receptors has also shown that a diverse range of receptor-types engage (or are predicted to engage) evolutionarily conserved signaling pathways necessary for the initiation and termination of immune responses (Guselnikov et al., 2008; Viertlboeck et al., 2004, 2009b; Wei et al., 2007; Montgomery et al., 2008; Mewes et al., 2009).

Over the past two, decades comparative immunologists have collectively contributed to the cloning and molecular characterization of an assortment of immune-related genes from several