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Review

Advances in research of fish immune-relevant genes: A comparative overview of innate and adaptive immunity in teleosts

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ABSTRACT

Fish is considered to be an important model in comparative immunology studies because it is a representative population of lower vertebrates serving as an essential link to early vertebrate evolution. Fish immune-relevant genes have received considerable attention due to its role in improving understanding of both fish immunology and the evolution of immune systems. In this review, we discuss the current understanding of teleost immune-relevant genes for both innate and adaptive immunity, including pattern recognition receptors, antimicrobial peptides, complement molecules, lectins, interferons and signaling factors, inflammatory cytokines, chemokines, adaptive immunity relevant cytokines and negative regulators, major histocompatibility complexes, immunoglobulins, and costimulatory molecules. The implications of these factors on the evolutionary history of immune systems were discussed and a perspective outline of innate and adaptive immunity of teleost fish was described. This review may provide clues on the evolution of the essential defense system in vertebrates.

Contents

Abbreviations: PRRs, pattern-recognition receptors; PAMPs, pathogen-associated molecular patterns; TLRs, Toll-like receptors; RLRs, RIG-I like receptors; CLRs, C-type lectin receptors; LRR, leucine-rich repeats; TIR, Toll-IL-1 receptor; ssRNA, single-strand RNA; dsRNA, double strand RNA; NF-κB, nuclear factor-κB; cDC, conventional dendritic cells; pDCs, plasmacytoid DCs; RIG-1, retinoic acid-inducible gene I; MDA5, melanoma differentiation-associated gene 5; LGP2, laboratory of genetics and physiology 2; CARD, caspase activation and recruitment domains; RD, repressor domain; CTD, C-terminal domain; ISREs, IFN-stimulated response elements; PGRPs, peptidoglycan recognition proteins; AMPs, antimicrobial peptides; Nramp, natural resistance-associated macrophage protein; NO, nitric oxide; Bf, B factor; Df, D factor; C1INH, complement component 1 inhibitor; CRD, carbohydrate recognition domain; DC-SIGN, DC-specific ICAM-3 grabbing nonintegrin; TCR, T cell receptors; KLH, keyhole limpet hemocyanin; APC, ntigen presenting cells; LECT2, leukocyte cell-derived chemotaxin 2; IFNs, interferons; ILs, interleukins; TNFs, tumor necrosis factors; MBL, mannose-binding lectin; CRP, C-reactive protein; IPNV, infectious pancreatic necrosis virus; PHA, phytoagglutinin; DreIFN B, zebrafish IFN allele B; IFN-γrel, IFN-γ related; IRF, interferon-regulatory transcription factors; DBD, DNA-binding domain; CAB cells, crucian carp blastulae embryonic cells; MITA, The mediator of IRF3 activation; ISGs, interferon-stimulated genes; ICS, IFN-containing supernatant; ICE, interleukin-converting enzyme; THD, TNF homology domain; CRD, cysteine-rich domain; TNFR, TNF receptor; TRAF, TNF receptor-associated factor; DD, death domain; AP-1, activator protein-1; TD, TRAF domain; BAC, bacterial artificial chromosome; MHC, major histocompatibility complex; β-2m, β-2 microglobulin; IgSF, immunoglobulin superfamily; Ii, invariant chain; Igs, immunoglobulins; BCR, B cell receptor; RAG1, recombination-activating gene 1; RAG2, recombination-activating gene 2; RSS, recombination signal sequence; TD, thymus dependent; TGF-β, transforming growth factor-β; MAPK, mitogen-activated protein kinase; STAT, signal transducer and activator of transcription protein; SOCS, suppressors of cytokine signaling; PIAS, protein inhibitor of activated STATs; KIR, kinase inhibitory region; RLD, RING-finger-like zinc-binding; AD, acidic domain; IRAK, including IL-1R-associated kinase; DIGIRR, double-Ig-IL-1R related molecule; SIGIRR, single-Ig-IL-1R related molecule.

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1. Introduction

Immunology has been studied for more than 200 years, starting from the discovery of cowpox in 1796. The majority of what we know today about the composition, function, and modulation of immune systems are mainly derived from works on mammals. From the evolutionary point of view, research on immune systems in lower vertebrates will become indispensable for better understanding of the evolutionary history of immune systems throughout vertebrates as a whole. As an important link to vertebrate evolution, fish is believed to be an excellent model and an indispensable component of comparative immunology. This ancient population, from whom adaptive immunity originates, possesses complicated innate immune networks appropriate for innate immunity investigations. Moreover, it serves as a bridge between innate and adaptive immunity, thus providing insights into the early events in the development of the adaptive immune system. However, immunology in fishes was traditionally less appreciated, largely due to the lack of model organisms for genetic manipulation. The lack of sufficient knowledge in fish immunity limits the investigation of immune system evolution, the development of vaccines, and the selection of disease-resistant breeds. More recently, the emergence of zebrafish (*Danio rerio*) as a new model organism and the advancement in genome sequencing technology and bioinformatics have greatly expedited the discovery and functional delineation of genes associated with immunity in fish (Lieschke and Trede, 2009; Trede et al., 2004; Van Muiswinkel, 2008). In fact, numerous immune-relevant genes for both innate and adaptive immunity, including those encoding cytokines, complements, lectins, immunoglobulins, and certain cell surface molecules, have been characterized from various fish species, with Chinese scientists contributing greatly to these advances. In this review, we attempt to give an overview of the recent advances in fish immune-relevant gene studies by researchers in China and worldwide.

2. Innate immunity relevant genes and signaling

2.1. Pattern recognition receptors

The recognition of microbial pathogens mediated by pattern-recognition receptors (PRRs) is critical to the initiation of innate immune responses. PRRs sense the conserved molecular structure of a pathogen, known as pathogen-associated molecular patterns (PAMPs), and induces subsequent host immunity through multiple signaling pathways that contribute to the eradication of the pathogen (Janeway and Medzhitov, 2002). To date, several classes of PRRs, such as Toll-like receptors (TLRs), RIG-I like receptors (RLRs), NOD-like receptors (NLRs), and C-type lectin receptors (CLRs) have been characterized from many species, including humans, rodents, birds, and teleost fishes (Table 1).

TLRs were the first PRRs to be characterized (Akira et al., 2006). To date, at least 10 and 12 functional TLRs have been characterized in human and mouse, respectively. All of them are type I transmembrane proteins that consist of three parts: an N-terminal ectodomain containing leucine-rich repeats (LRR) that mediate the recognition of PAMPs, a transmembrane region with one α-helix, and a C-terminal intracellular Toll-IL-1 receptor (TIR) domain that activates downstream signaling pathways (Kawai and Akira, 2011). TLR1, TLR2, TLR4, TLR5, and TLR6 are localized on the cell surface and recognize PAMPs of bacteria, fungi, and protozoa, whereas TLR3, TLR7, TLR8, and TLR9 are expressed within intracellular compartments and recognize nucleic acids. Bacterial PAMPs are mainly recognized by TLR1, TLR2, TLR4, TLR5, TLR6, TLR7, and TLR9 (Kumar et al., 2011). Viral nucleic acids, including single-strand RNA (ssRNA), double strand RNA (dsRNA), and DNA, are sensed by TLR7/8, TLR3, and TLR9, respectively (Gerlier and Lyles, 2011). After recognizing the respective PAMPs, TLRs will change their conformation to allow homo- or heterophilic interactions with each other and recruit TIR domain-containing adaptor molecules (TRIF, MyD88, TRAM) to their own TIR domains (Kawai and Akira, 2010). Heterodimers of TLR1-TLR2 and TLR2-TLR6 are expressed on the cell surface and recruit TIRAP and MyD88 to induce nuclear factor-κB (NF-κB) activation, resulting in the production of inflammatory cytokines in conventional dendritic cells (cDC) and macrophages. TLR2 has been found to be expressed in the endosome of inflammatory monocytes. It can induce the production of type I IFN mediated by IRF3 and IRF7 in response to a virus by recruiting TIRAP and MyD88 (Barbalat et al., 2009). TLR3 is the only TLR that cannot recruit MyD88; however, it can recruit TRIF to initiate TRIF-dependent signaling in cDCs and macrophages, leading to the induction of type I IFN and inflammatory cytokines with the help of IRF3 and NF-κB, respectively. TLR4 is the only TLR that activates both the MyD88- and TRIF-dependent pathways (Kawai and Akira, 2010). By recruiting TIRAP and MyD88, TLR4 can activate NF-κB and lead to the production of inflammatory cytokines. Then, it will be transported into phagosomes that contain bacteria and recruit TRAM and TRIF to activate IRF3 and NF-κB for the induction of type I IFN and inflammatory cytokines. TLR5, which is mainly expressed on the cell surface of the lamina propria of DCs, recruits MyD88 to induce NF-κB activation and production of inflammatory cytokines. In cDCs and macrophages, TLR7 and TLR9 heterodimers recruit MyD88 to induce NF-κB-dependent inflammatory cytokine production. While in plasmacytoid DCs (pDCs), TLR7 and TLR9 recruit MyD88 to activate IRF7 and lead to the production of type I IFN. After CpG DNA stimulation, TLR9 moves to the early endosomes and triggers MyD88-dependent NF-κB activation. Afterwards, it will be transported to lysosome-related organelles for IRF7 activation and stimulation of type I IFN production (Sasai et al., 2010).

In recent years, a number of TLRs characterized in teleosts were found to have distinct features and greater diversity compared with