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Innate immunity of finfish: Primordial conservation and function of viral RNA sensors in teleosts

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ABSTRACT

During the past decade, huge progress has been made in research into teleost PAMPs (pathogen-associated molecule patterns) recognition receptors (PRRs). Numerous fish PRR genes have been identified, and the primordial functions of PRRs involved in the innate immune response to viral infection (especially those responsible for sensing viral RNA) have been increasingly clarified in teleosts. Particular progress has been made in our understanding of Toll-like receptors (TLRs) and retinoic acid inducible gene I (RIG-I)-like receptors (RLRs). However, there are important evolutionary differences between teleosts and mammals; for instance, seven TLR repertoires (TLR5S, -14, -19, -20, -21, -22 and -23) are present in teleosts but not in mammals, indicating that some TLRs likely possess different functions. Thus, comparison of PRRs in teleosts and mammals may help us understand the immune responses triggered by host–pathogen interactions in teleosts. In this article, the evolutionary conservations and divergences in the PRR mechanisms of teleosts and mammals are examined, with a focus on their molecular features and the recognition of viral RNA by fish TLRs and RLRs. In addition, the mechanism of type I interferon gene expression in teleosts, which is enhanced after the recognition of viral RNA by fish TLRs and RLRs, is also introduced.

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1. Introduction: pattern recognition receptors

Innate immunity is more crucial in teleosts than mammals because the adaptive immunity of teleosts is not as diversified; there are only three isotypes of immunoglobulin, and some fish lack one of the major histocompatibility complexes (MHCs) [1–3]. Therefore, fish innate immunity plays a critical role in protecting teleosts against invading pathogens. Our knowledge of innate immunity in teleosts is currently limited, but an improved understanding of this important aspect of immunity could support the development of vaccine adjuvants and the selection of disease-resistant breed stocks in the aquaculture industry.

To initiate an innate immune response against invading pathogens, multicellular organisms generally utilize a variety of germline-encoded pattern recognition receptors (PRRs) [4]. This recognition mechanism relies on the detection of the highly conserved microbial pathogen-associated molecular patterns (PAMPs), which are essential for microbial survival and are structurally conserved among many microorganisms, including bacteria, viruses, yeast and parasites [5–8]. Most PAMPs are unique to microbes, and thus their presence in the host's system indicates microbial invasion. The recognition of PAMPs by PRRs enhances phagocytosis, activates complement cascades, triggers inflammatory cytokine production, and induces dendritic cell maturation [9]. In addition, PRRs also recognize danger signals (*e.g.*, DNA or RNA released by the fragmentation of host cells, heat shock proteins), triggered by host tissue damage due to injury, infection, inflammation, necrotic changes and normal cell death [4,10,11]. PRRs can be functionally divided into three classes: soluble bridging (secreted) PRRs, endocytic PRRs and signaling PRRs [12,13]. The soluble bridging PRRs include the collectins, ficolins and pentraxins, which may opsonize pathogens to trigger their complement-dependent destruction. The endocytic PRRs, which include mannose receptors, scavenger receptors and C-type lectin receptors, are expressed on the cell surface and mediate the recognition and internalization of microbes and/or microbial PAMPs [12,14]. These two PRR types are functionally distinct from

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the signaling PRRs, which are involved in cell activation in response to diverse microbial PAMPs, such as proteins, glycans (*e.g.*, peptidoglycan, PG), lipopolysaccharide (LPS) and nucleic acids (DNA or RNA) [12]. The signaling PRRs include the toll-like receptors (TLRs), retinoic acid inducible gene (RIG)-I-like receptors (RLRs), and nucleotide-oligomerization domain (NOD)-like receptors (NLRs) [15,16]. Over the past decade, research on the signaling PRRs has expanded rapidly, and massive amounts of scientific evidence attest to their importance in innate immunity.

In teleosts, numerous PRR genes have been identified, including 16 TLRs and 3 RLRs, and the primordial functions of PRRs have been studied. The PRR-associated sensing of viral RNA, which leads to antiviral responses via the production of type I interferon (IFN) and inflammatory cytokines, has been studied in some detail in teleosts [17,18]. These fish PRR genes are well conserved, and their functions are conserved among higher vertebrates, albeit with some evolutionary differences. This review examines the evolutionary conservations and divergences in the fish signaling PRRs, particularly TLRs and RLRs, with a focus on the molecular structures and mechanisms of viral RNA sensors in fish. Furthermore, the regulation of type I IFN gene expression in the fish IFN production pathway is also discussed.

2. Evolutionary conservation of PRRs

2.1. Molecular characterization of TLRs

2.1.1. Structural representation of TLRs in teleosts

Unlike cytoplasmic RLRs and NLRs, members of the membrane-bound TLR family are localized at the cell surface or in endosomal compartments, where they recognize a wide range of PAMPs [19]. In teleosts and mammals, TLRs consist of a leucine-rich repeat (LRR) domain for ligand recognition, a transmembrane (TM) domain and a Toll/interleukin 1 receptor (TIR) signaling domain [5,6,17]. The LRR domain plays an important role in the recognition of PAMPs, such as bacterial cell-surface peptidoglycans, lipoproteins, LPS, bacterial flagellin, single-stranded viral RNA (ssRNA), double-stranded viral RNA (dsRNA), and the unmethylated CpG islands of bacterial and viral DNAs [20]. Relatively few studies have examined the specific ligands for fish TLRs (see Section 3.1). However, the LRR domain structure is highly conserved in teleosts and mammals, suggesting that the fish LRR domain may be able to recognize PAMPs similar to those recognized by the mammalian TLRs [17]. In mammals, the LRRs are sandwiched between the LRR N-terminal (LRR-NT) domain and the LRR C-terminal (LRR-CT) domain [21]. The individual TLRs are determined by variations in repeat numbers, sequences and length of LRRs [20]. These variations in LRRs are considered to be related to recognition of specific PAMPs by individulal TLRs [20,21]. Therefore, the LRR domains in various TLRs have different structures that correspond to a variety of PAMPs. The LRR domain possesses a solenoid structure that carries a highly conserved consensus motif of xLxxLxLxxN x*xx*x xxxFxxLx, where "L" is Leu, Ile, Val, or Phe; "N" is Asn, Thr, Ser, or Cys; and "x" is any amino acid. The LRR domains of human TLRs contain amino acid insertions at positions 10 and 15 of the LRR consensus sequence; they provide a concave surface for specific binding surfaces [20,21] and appear to be a characteristic feature of each human TLR. In same subfamily of TLRs, the positions of the LRR insertions are highly conserved from teleosts to human, suggesting that the LRR domains in fish TLRs might be functionally capable of responding to PAMPs of their orthologues in mammals [22,23]. The LRR-CT flanks the LRR on the C-terminal side and possesses a highly conserved consensus motif containing four characteristically spaced Cys residues (xLxxLxLxxN xFxCxCx$_{(24-26)}$Cx$_{(18-21)}$C). The fourth Cys of the LRR-CT is a short distance from the TM domain (2–10 residues), and it is involved in stabilizing the extracellular portion of TLR by disulfide linkage [20]. However, the structural details of the LRR domains in fish TLRs are not yet known.

In zebrafish (*Danio rerio*), the TIR domains of all TLRs contain three conserved regions; they include several hydrophobic residues that are important for TLR function, such as interaction with the TIR domains of adapter molecules [24]. Comparison of TLR amino acid sequences showed that the structures of the TIR domains are highly conserved in teleosts and mammals [24–27]. As in the mammalian TLRs, the fish TLRs (with the sole exception of TLR5 soluble; TLR5S) are structured similar to a typical type I transmembrane glycoprotein, with an extracellular LRR domain at the N-terminus, a TM domain and an intracellular TIR domain at the C-terminus (Fig. 1A) [17]. In mammals, the intracellular TIR domain is homologous to the intracellular region of the Interleukin-1 receptor (IL-1R) family, but the TLR and IL-1R family members differ in their extracellular portions. TLR possesses an extracellular LRR domain, whereas IL-1R uses three immunoglobulin domains for ligand binding. The intracellular TIR domains are composed of roughly 200 amino acid residues and have three highly conserved regions that play a crucial role in initiating signal transduction via an interaction between the TIR domain and its adaptor proteins [28–30]. Upon recognition of a PAMP by the LRR of TLRs, the TIR triggers myeloid differentiation primary-response protein 88 (MyD88)-dependent and -independent signaling, which then lead to the transcription of the genes encoding type I IFN and various inflammatory cytokines [31].

2.1.2. Divergences of TLR repertoires in teleosts

In teleosts, a total of 15 TLRs have been identified, including orthologs of seven mammalian TLRs (TLR1, -2, -3, -5M, -7, -8 and -9) and fish-specific TLRs (TLR5S, -14, -16, -19, -20, -21, -22 and -23) [17,18]. In contrast, only 13 TLRs have been identified in mammals (TLR1 to -10 in human, and TLR1 to -9 and -11 to -13 in mouse) (Table 1) [17,18]. In teleosts, the first report of a fish TLR gene was from an expressed sequence tag (EST) screening of a goldfish (*Carassius auratus*) macrophage in 2003 [32]. In the same year, mammalian TLR homologs and fish-specific TLRs were globally surveyed from the draft genome sequence of Japanese pufferfish (also called as fugu or tiger puffer), *Takifugu rubripes* [17,25]. As in the Japanese pufferfish, the zebrafish genome was found to express various TLR genes via alternative splicing and gene duplication [17,24,33]. TLR genes have also been identified in other fish species, including Japanese flounder (*Paralichthys olivaceus*), rainbow trout (*Oncorhynchus mykiss*), yellow croaker (*Pseudosciaena crocea*), channel catfish (*Ictalurus punctatus*), Atlantic salmon (*Salmo salar* L.), grass carp (*Ctenopharyngodon idella*), common carp (*Cyprinus carpio*), rare minnow (*Gobiocypris rarus*), orange-spotted grouper (*Epinephelus coioides*) and gilthead seabream (*Sparus aurata* L.) (Table 1).

The organization of the exon/intron boundaries in the fish *TLR3* gene is highly conserved between fish and human [23]. In contrast, the Japanese flounder and Japanese pufferfish *TLR2* genes have 11–12 exons; this is far more (>3.6 times) than the number of exons in the mammalian genes, even though the fish *TLR2* genes are much smaller than their mammalian counterparts [26]. The fish *TLR5M* and *TLR9* genes also have completely different numbers of exons in fish species versus mammals [22,27]. It seems that a number of fish *TLR* genes may have experienced insertion of additional introns after the divergence from tetrapods [25].

The TLR1 subfamily is comprised of TLR1, -2, -14 and -16 in fish, but contains TLR1, -2, -6 and -10 in mammals; the encoding genes are located close together on the chromosome, indicating that they arose via tandem duplication [25,33]. There are no homologs of mammalian TLR6 or -10 in teleosts [24,25,33], indicating that they evolved later (Table 1) [25,33]. The fish TLR14 genes have been

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