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Review

Molecular regulation of interferon antiviral response in fish

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ABSTRACT

Interferon (IFN) response is the first line of host defense against virus infection. The recent years have witnessed tremendous progress in understanding of fish IFN antiviral response. Varied number of IFN genes has been identified in different fish species but obviously, they do not show a one-to-one orthologous relationship with mammalian IFN homologs. These genes are divided into two groups with different abilities to induce downstream gene expression through binding to different receptor complexes. Consistently, some fish IFN-stimulated genes such as Mx and PKR have been confirmed for their antiviral effects. In this review, we focus on how fish cells respond to IFNs and how fish IFNs are triggered through TLR pathway and RLR pathway. We highlight the roles of IRF3 and IRF7 in activation of fish IFN response. In addition, the unique mechanisms underlying IRF3/7-dependent fish IFN response and auto-regulation of fish IFN gene expression are discussed.

Contents

1. Introduction

The mammalian innate antiviral mechanism involves the actions of interferons (IFNs), a family of cytokines that historically are defined by their ability to block cellular replication of different viruses. Three classes of mammalian IFNs have been identified, including type I IFNs (primarily including IFNα/β), type II IFN (IFNγ) and type III IFNs (including IFNλ1/2/3) (Sadler and Williams, 2008). Type II IFN (IFNγ) promotes cell mediated broad immune responses to intracellular pathogens including viruses, and type III IFNs exhibit a type I IFN-like antiviral response in a restricted

Abbreviations: IFN, interferon; IRF, interferon regulatory factor; IRSE, interferon stimulated response element; ISG, IFN stimulated gene; IKKε, inhibitor of kappaB kinase epsilon; ISGF3, interferon-stimulated gene factor 3; Jak, Janus kinase; Stat, signal transducer and activator of transcription; LGP2, laboratory of genetics and physiology 2; MAVS, mitochondrial antiviral signalling protein; MDA5, melanoma differentiation-associated gene 5; MITA, mediator of IRF3 activation; MyD88, myeloid differentiation primary-response protein 88; poly(I:C), polyinosinic: polycytidylic acid; RIG-I, retinoic acid-inducible gene I; TBK1, TANK-binding kinase 1; TLR, Toll like receptor; TRAF6, TNF receptor-associated factor 6; TRIF, TIR-domain-containing adapter-inducing interferon-β.

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subset of cells (Ank et al., 2006; Zhou et al., 2007). Type III IFN genes were proposed to be the ancestral type I IFNs not only because of the presence of introns but also due to the structure of their cellular receptors (Levraud et al., 2007). In response to virus infection, type I and type III IFNs employ different cellular receptors but function by the same Jak-Stat (Janus kinase-signal transducer and activator of transcription) signaling pathway (Sadler and Williams, 2008).

The activation of mammalian type I IFNs has been well-characterized (Baum and Garcia-Sastre, 2010; Sadler and Williams, 2008; Tamura et al., 2008). In virus-infected cells, type I IFN response is initiated through recognition of viral products by host pattern recognition receptors (PRRs) including Toll-like receptors (TLRs) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). Such recognition events trigger distinct signaling pathways to activate the common transcription factors mainly including IFN-regulatory factor (IRF) 3 and IRF7 that subsequently turn on the transcription of type I IFNs. The produced type I IFNs bind to the cognate receptors activating the Jak-Stat signaling pathway, where Stat1, Stat2 and IRF9 form a transcription factor complex ISGF3 (IFN-stimulated gene factor 3). ISGF3 subsequently translocates from cytoplasm to nucleus and specifically binds to the IFN-stimulated response element (ISRE) in the promoters of downstream genes referred to as IFN-stimulated genes (ISGs). The expression of ISGs confers a cellular environment non-permissive to viral infection.

In the past years, a great attempt to understanding of fish IFN response provides evidence that fish appear to trigger IFN antiviral response by the similar mechanisms to that in mammals, although it is unknown whether these mechanisms are conserved among all fish species. In addition, some unique mechanisms underlying fish IFN antiviral response are observed. In this review, we summarize recent progress on fish IFNs that seem to be more similar to mammalian type I IFNs, focusing on how fish cells respond to IFNs and how fish IFNs are triggered by TLR pathway and RLR pathway. We highlight the roles of IRF3 and IRF7 in activating fish IFN response.

2. Fish IFN responses and Jak-Stat signaling pathway

2.1. Fish IFN genes and receptors

The first fish IFN gene was identified in 2003 by three independent research groups in zebrafish (*Danio rerio*) (Altmann et al., 2003), Atlantic salmon (*Salmo salar*) (Robertsen et al., 2003) and pufferfish (*Tetraodon nigroviridis*) (Lutfalla et al., 2003), and later in a multitude of teleost species (Aggad et al., 2009; Casani et al., 2009; Chang et al., 2009; Kitao et al., 2009; Long et al., 2004; Purcell et al., 2009; Sun et al., 2009a; Yu et al., 2010; Zou et al., 2007). These genes are significantly upregulated by virus infection and other IFN stimuli; overexpression of these genes in fish cells induces an antiviral state against viral infection, suggesting that they are fish homologs of mammalian virus-induced IFN genes. The identified fish IFNs exhibit more homology to mammalian type I IFN molecules based on primary protein sequences and phylogenetic analysis (Zou et al., 2007; Sun et al., 2009a); however, presence of introns and usage of ancestral receptors supports that fish IFN genes are more evolutionally similar to type III IFNs (Levraud et al., 2007). This resulted in a debate on classification of fish virus-induced IFNs (Qi et al., 2010), and some researchers proposed that these fish genes might be referred to as IFNϕ (Stein et al., 2007). Recent evidence indicates that fish IFNs belong to type I IFNs by identification of intron-containing type I IFNs and type III IFNs in amphibians (Qi et al., 2010), and by a crystal structure analyses of zebrafish IFNs, where both zebrafish IFN1 and IFN2 display characteristic type I IFN architecture with a straight F helix rather than typical type III IFN structure with a characteristic bend (Hamming et al., 2011).

Notwithstanding the disputes, it is true that fish IFN genes cannot be simply classified into IFNα or IFNβ (Altmann et al., 2003; Lutfalla et al., 2003). Although vertebrate IFNs all originate from a common ancestor, fish seem to have expanded IFN gene family independent of mammals and birds, since lineage-specific expansion of vertebrate IFN families is revealed by phylogeneitic analyses of vertebrate IFN families (Chang et al., 2009; Stein et al., 2007; Sun et al., 2009a; Zou et al., 2007). Based on protein sequences and phylogenetic analyses, fish IFNs can be classified into two groups: 2 cysteine-containing group I and 4 cysteine-containing group II (Zou et al., 2007). To date group I IFNs have been discovered in all fish species to be investigated, with varied copies, whereas group II is only found in more primitive teleost fishes such as salmonids and cyprinids (Ohtani et al., 2012; Zhu et al., 2012; Zou et al., 2007). Group I IFNs can be further subdivided into subgroup-a and subgroup-d, and group II IFNs into subgroup-c and subgroup-b (Chang et al., 2009; Sun et al., 2009a). Actually, IFNs from the more advanced teleost fishes, such as members of superorder Acanthopterygii, including sea bass, seabream, fugu, green spotted puffer, medaka, and stickleback, belong to subgroup-d of group I IFNs (Chang et al., 2009; Ohtani et al., 2012).

Zebrafish embryos and larvae (before 4–6 weeks) are good models for studying IFN response, because adaptive immune response during these stages is not fully functional (Lam et al., 2004; Trede et al., 2004). A total of four IFNs (IFN1–4) have been found in zebrafish genome (Aggad et al., 2009; Altmann et al., 2003; Stein et al., 2007; Zou et al., 2007). Morpholino-mediated knockdown assays have identified three receptor genes that are essential for four zebrafish IFN signaling. It shows that the receptor usage correlates with the current subdivision of fish IFNs: group I (zebrafish IFN1 and IFN4) binds to a receptor complex comprised of cytokine receptor family B (CRFB) 1 and CRFB5, while group II specifically employs CRFB2 and CRFB5 (Aggad et al., 2009; Levraud et al., 2007). Ectopic expression of either group I or group II IFNs protects zebrafish larvae against infection by spring viremia of carp virus (SVCV) (Lopez-Munoz et al., 2009). Both group IFNs show different ability to induce downstream gene expression. In adult zebrafish, group II IFNs are responsible for a rapid and transient expression of antiviral genes, whereas group I IFNs exert a slow but more powerful induction of several antiviral and proinflammatory genes (Lopez-Munoz et al., 2009).

2.2. Fish IFN-activated Jak-Stat signaling pathway

How fish IFNs mediate their antiviral function downstream of the cellular receptors? Fish genomes contain all key components of the Jak-Stat signaling pathway, including Jak1, Tyr2, Stat1, Stat2 and IRF9 (Stein et al., 2007; Shi et al., 2012; Zhang et al., 2003a,b, 2007). Unlike in mammals, there are two Stat1 genes in zebrafish, encoding two transcripts Stat1a and Stat1b (Stein et al., 2007). Zebrafish Stat1a shares all five domains of human Stat1α but zebrafish Stat1b resembles human Stat1β, a splice variant of human Stat1α (Song et al., 2011). Human Stat1β lacks the last 38 residues in the C-terminal transcriptional activation domain (TAD) of Stat1α but still exhibits a full function on transmitting type I IFN signaling (Shuai et al., 1993). Function analysis showed that zebrafish Stat1a can rescue IFN-mediated growth inhibition in a Stat1-deficient human cell line (Oates et al., 1999). Consistently, Atlantic salmon Stat1a is phosphorylated and transported rapidly into the nucleus following stimulation with Atlantic salon IFN1a (Skjesol et al., 2010), highlighting the role of fish Stat1a in IFN signaling transduction. A recent report showed that zebrafish Stat1b not Stat1a pro-