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The role of type I interferons in innate and adaptive immunity against viruses in Atlantic salmon

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ABSTRACT

Type I IFNs (IFN-I) are cytokines, which play a crucial role in innate and adaptive immunity against viruses of vertebrates. In essence, IFN-I are induced and secreted upon host cell recognition of viral nucleic acids and protect other cells against infection by inducing antiviral proteins. Atlantic salmon possesses an extraordinary repertoire of IFN-I genes encompassing at least six different classes (IFNa, IFNb, IFNc, IFNd, IFNe and IFNf) most of which are encoded by several genes. This review describes recent research on the functions of salmon IFNa, IFNb, IFNc and IFNd. As in mammals, expression of different salmon IFN-I in response to virus infection is dependent on their promoters, properties of the virus and the cell's expression of nucleic acid receptors and interferon regulatory factors (IRFs). While IFNa mainly display local antiviral activity, IFNb and IFNc show systemic antiviral activity. In addition, salmon appears to possess several IFN-I receptors, which show selectivity in binding different IFN-I. This complexity in IFN-I and receptors allows for a large variation in functions of the salmon IFN-I. Studies with intramuscular injection of IFN expression plasmids have recently provided surprising results, which may be of relevance for application of IFN-I in prophylaxis against virus infection. Firstly, injection of IFNc plasmid protected salmon presmolts against virus infection for at least 10 weeks. Secondly, IFN plasmids showed potent adjuvant activity when injected together with a DNA vaccine against infectious salmon anemia virus (ISAV).

1. Introduction

Aquaculture of Atlantic salmon has grown extensively over the last 40 years and reached an annual production of 1.3 million tons in Norway in 2015. Salmon is farmed in dense populations in the open sea and is thus attacked by several different viruses, which represent a continuous threat to the industry. This is highlighted by the devastating effect of the infectious salmon anemia virus (ISAV) epidemic in the Chilean aquaculture of Atlantic salmon in 2007 (Kibenge et al., 2012). Pancreas disease (PD) caused by salmonid alphavirus (SAV) has been one of the most challenging virus diseases in salmon farming in Norway, Ireland and Scotland (McLoughlin and Graham, 2007). Other important viral diseases of salmon are infectious pancreas necrosis (IPN) caused by IPN virus (IPNV), heart skeletal muscle inflammation (HSMI) caused by piscine orthoreovirus (PRV) and cardiomyopathic syndrome (CMS) caused by piscine myocarditis virus (PMCV) (Haugland et al., 2011; Lovoll et al., 2010; Palacios et al., 2010; Smail et al., 1992). All of these viruses are RNA viruses. Commercial vaccines based on inactivated virus (SAV, IPNV) or recombinant virus protein (IPNV) are being used, but do not give satisfactory protection of salmon in the field (Evensen and Leong, 2013).

The problems with viral diseases may leave the impression that Atlantic salmon in nature is quite susceptible to viruses. However, both the exceptional production of farmed fish and recent immunological research suggest that salmon has a high level of innate immunity against viruses. In fact, Atlantic salmon has a very well developed and complex type I interferon (IFN-I) system, which is

Abbreviations: CRFB, class II cytokine receptor family member; HE, hemagglutininesterase; IFN, interferon; IFN-I, type I IFN; IFNAR, mammalian type I IFN receptor; IPNV, infectious pancreatic necrosis virus; IPS-1, interferon promoter stimulating protein; IRF, IFN regulatory factor; ISRE, IFN-stimulated regulatory element; ISAV, infectious salmon anemia virus; ISG15, interferon-stimulated gene 15; MDA5, melanoma differentiation-associated gene 5; MYD88, Myeloid Differentiation Primary Response 88 gene; Mx, myxovirus resistance gene; ORF, open reading frame; pDC, plasmacytoid dendritic cell; PKR, double-stranded RNA-activated protein kinase R; poly I:C, polyinosinic-polycytidylic acid; qPCR, quantitative real time PCR; RIG-I, retinoic acid-inducible gene I; RLR, RIG-I like receptors; TLR, Toll-like receptors; TICAM-1, Toll-Il-1R homology domain-containing adaptor protein 1.

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the most important component in the first line of defence against viruses in vertebrates. This is a review of the recent research on Atlantic salmon IFN-I. The main functions of IFN-I are illustrated in Fig. 1 and functional properties of salmon IFNa, IFNb, IFNc and IFNd are summarized in Table 1.

Large parts of the IFN-I system of Atlantic salmon have been characterized over the last 20 years and antiviral activity of salmon IFN-I against IPNV, ISAV and SAV has been demonstrated. While IFN-I under natural conditions only provides short term protection against virus infection, it was surprising to find that injection of an IFN-I expressing plasmid into salmon provided systemic protection against viruses for at least 10 weeks (Chang et al., 2014). Recently it was also discovered that salmon IFN-I boost the adaptive immune response against ISAV and thus function as adjuvants, which can be of benefit for the development of more effective virus vaccines (Chang et al., 2015). This is in accordance with studies in mammals, which have shown that IFN-I stimulate adaptive immune responses against protein antigens (Fig. 1).

2. Atlantic salmon type I interferons

Interferons are cytokines, which induce antiviral activity in vertebrate cells and are classified into three types according to sequence homology and receptor specificity. Mammalian type I IFNs (IFNα, IFNβ, IFNκ, IFNε, IFNκ, IFNω) and type III IFNs (IFNλ1, IFNλ2, IFNλ3) play important roles in innate immunity against viruses being induced upon host cell recognition of viral nucleic acids, while type II IFN (IFNγ) is a major product of T-cells and has a key role in adaptive immunity against intracellular pathogens (Kotenko et al., 2003; Pestka et al., 2004; Schoenborn and Wilson, 2007). While teleost fish possess type I and type II IFNs, type III IFNs has yet to be found in this group of vertebrates (Robertsen, 2006; Zou and Secombes, 2011). The importance of IFN-I in innate immunity against viruses of vertebrates was first discovered by their ability to induce an antiviral state in cells and was later confirmed by virus infection of mice, which lacked the IFN-receptor (Isaacs and Lindenmann, 1957; Muller et al., 1994). More recently, IFN-I have also been found to play an important role in activation of adaptive immune responses (Le Bon et al., 2001). During virus infection, host cells produce and secrete IFN-I upon recognition of viral nucleic acids (Hoffmann et al., 2015; Yoneyama and Fujita, 2010). These IFNs protect other cells from further viral infection by binding to the IFN-I receptor, which results in induction of hundreds of IFN stimulated genes (ISGs) some of which encode antiviral proteins (Der et al., 1998; Schoggins and Rice, 2011). IFN-α and IFN-β are the predominant mammalian IFN-I (McNab et al., 2015). It is important to note that fish and mammalian IFN-I have evolved quite differently and are thus not orthologs (Robertsen, 2006; Zou and Secombes, 2011). However, they appear to be induced through similar signalling pathways and they apparently induce genes through the same Jak/STAT pathway.

Atlantic salmon IFNa was among the first fish IFN-I to be discovered (Robertsen et al., 2003). Later it was shown that salmon possesses the four subtypes IFNa, IFNb, IFNc and IFNd, which possess 22%–37% amino acid sequence identity (Chang et al., 2009; Sun et al., 2009; Svingerud et al., 2012). With the publication of the Atlantic salmon genome it has become evident that salmon also possesses the IFNe and IFNf classes similar to rainbow trout (Zou

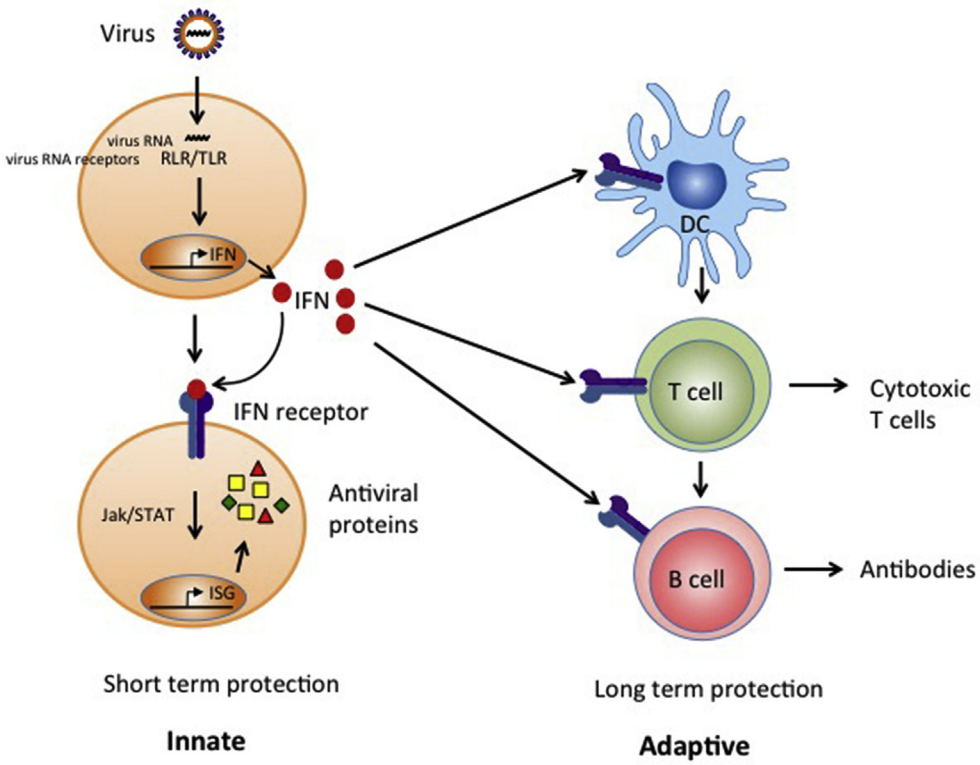

Fig. 1. Overview of the role of type I IFN (IFN-I) in innate and adaptive immune responses. During virus infection, IFN-I is induced and secreted upon host cell recognition of viral RNA by cytoplasmic (RLR) or endosomal receptors (TLR) (Yoneyama and Fujita, 2010). IFN-I bind to IFN-I receptors, which are present on most cells and trigger transcription of IFN-induced genes (ISGs) some of which encode antiviral proteins. This results in protection of cells for a relatively short period of time and represents the innate immune response against viruses. At the same time IFN-I stimulate adaptive immune response against viral antigens by stimulation of antigen presentation in dendritic cells (DC) and by stimulation of B- and T-cells (Le Bon et al., 2006b; Le Bon and Tough, 2008; Longhi et al., 2009). This results in enhanced production of antigen specific antibodies and cytotoxic T-cells. Here, RLR include RIG-I and MDA5 while TLR include TLR3, TLR7 and TLR22.

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