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Review

Innate immune responses of salmonid fish to viral infections

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ABSTRACT

Viruses are the most serious pathogenic threat to the production of the main aquacultured salmonid species the rainbow trout *Oncorhynchus mykiss* and the Atlantic salmon *Salmo salar*. The viral diseases Infectious Pancreatic Necrosis (IPN), Pancreatic Disease (PD), Infectious Haemorrhagic Necrosis (IHN), Viral Haemorrhagic Septicaemia (VHS), and Infectious Salmon Anaemia (ISA) cause massive economic losses to the global salmonid aquaculture industry every year. To date, no solution exists to treat livestock affected by a viral disease and only a small number of efficient vaccines are available to prevent infection. As a consequence, understanding the host immune response against viruses in these fish species is critical to develop prophylactic and preventive control measures. The innate immune response represents an important part of the host defence mechanism preventing viral replication after infection. It is a fast acting response designed to inhibit virus propagation immediately within the host, allowing for the adaptive specific immunity to develop. It has cellular and humoral components which act in synergy. This review will cover inflammation responses, the cell types involved, apoptosis, antimicrobial peptides. Particular attention will be given to the type I interferon system as the major player in the innate antiviral defence mechanism of salmonids. Viral evasion strategies will also be discussed.

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1. Introduction

The majority of serious diseases in fish farming, causing important economic losses worldwide, have a viral aetiology (OIE, 2012). In most cases, viral infection leads to significant livestock losses. Curative measures are very limited and there is a high risk from new emerging viral diseases (Rimstad, 2010). Traditionally, the research in salmonid immunology has focused mostly on the farmed species including Atlantic salmon *Salmo salar*, Pacific salmon including Chum salmon *Oncorhynchus keta* and Coho salmon *Oncorhynchus kisutch*, and the Rainbow trout *Oncorhynchus mykiss*. According to the FAO tonnage statistics for 2010 (FAO, 2010), salmon production is mainly located in Norway, Chile, UK and Canada, rainbow trout production predominantly occurs in Chile, Iran, Turkey, Norway, US, Denmark and France, and Pacific or Coho salmon production in Chile. Understanding which components of the immune system limit viral replication and are responsible for host recovery is critical in developing adequate prophylactic control strategies. The causative agents of the major salmonid viral diseases include double stranded RNA virus such as Infectious Pancreatic Necrosis Virus (IPNV, Birnaviridae), Piscine Reovirus (PRV) recently renamed as Atlantic Salmon ReoVirus (ASRV, Reoviridae), Piscine MyoCarditis Virus (PMCV, Totiviridae), negative single stranded RNA viruses such as Infectious Haemorrhagic Necrosis Virus (IHNV, Rhabdoviridae), Viral Haemorrhagic Septicaemia Virus (VHSV, Rhabdoviridae), positive single stranded RNA virus Salmonid Alphavirus (SAV, Alphaviridae), negative segmented single stranded RNA virus Infectious Salmon Anaemia Virus (ISAV, Orthomyxoviridae) and DNA virus Epizootic hematopoietic necrosis virus (EHNV, Iridoviridae) (Crane and Hyatt, 2011). Innate immunity is induced quickly after infection and is characterised by an absence of immunological memory, is not specific to the antigen and is modulated by molecules encoded by germ-line genes. A recent study based on paired clonal rainbow trout and fibroblastic cell lines suggest that innate immune factors contribute to a great part of the overall resistance to viral infection (Verrier et al., 2012). In vertebrates, the fast induction of innate defence mechanisms is critical to prevent viral replication before the later more specific adaptive response is established. However innate antiviral defence mechanisms have humoral and cellular components that can directly and, on their own, exclusively eradicate the virus in an infected animal (Takeuchi and Akira, 2009). This chapter will give an update on the current knowledge of the different components of the innate immune system acting against viruses in the main farmed salmonids species.

2. Physical barriers

The first line of defence against viruses occurs at the interface with the external environment on tissues such as skin, gut and the gill representing the main areas where infection can potentially originate. The exact natural port of viral entry is not known for all salmonid viruses but in the case of IHNV it has been suggested using a bioluminescent recombinant virus clone in rainbow trout that the base of the fins is the main entry site (Harmache et al., 2006). For other viruses that infect salmonid fish, experimental infection using cohabitation or immersion routes leads to effective systemic infection but the exact area involved in the physical barrier failure is currently unknown. With the recent progress in reverse genetics and its potential to produce fluorescent fish viral pathogens, we can expect important breakthrough in the identification of viral ports of entry.

It is recognised that the interface between host and pathogens is likely to be responsible for the high fish-to-fish variation observed in intensity of infection even in experimentally controlled environments (Wargo et al., 2012; Peñaranda et al., 2009).

The secretion of mucus on the skin and gills is the first mechanism of defence (Esteban, 2012) and the biochemical composition of the mucus from some salmonid species has been found to contain a number of molecules such as lysozyme, proteases, cathepsin B and alkaline phosphatase involved in immune response (Subramanian et al., 2007; Ingram, 1980; Fast et al., 2002). Antimicrobial peptides present in the fish mucus have been shown to inhibit viral replication (Chinchar et al., 2004; Smith et al., 2009; 2010). The involvement of salmonid antimicrobial peptides in antiviral defenses will be reviewed in more detail in a separate section below.

The gill tissue includes newly described lymphoid tissue, Interbranchial Lymphoid Tissue (ILT), in sea water Atlantic salmon (Haugarvoll et al., 2008) and in rainbow trout (Koppang et al., 2010). Analysis of gene expression levels on micro-dissected tissue and immunohistochemistry staining showed numerous MHCII$^+$ cells potentially macrophages, dendritic cells (DC), T or B lymphocytes. More investigation is required, but it is likely that this tissue is of importance for both innate and adaptive immunity to viruses. Recently, ISAV tropism to hindgut epithelium, as well as to endothelium and gills, was observed, suggesting involvement of the gut tissue in viral immunity (Aamelfot et al., 2012). Gut has been described as an important tissue for immune response (Hart et al., 1988) but its involvement in the innate immunity to viruses has been poorly described as gut is not traditionally sampled from fish suffering from a viral disease. In general, relatively little attention has been given to mucosal tissues mainly because of a lack of good reagents to identify fish cell markers. However, there have been recent progress on the characterisation of the Gut Associated Lymphoid Tissue (GALT) in fish with the recent characterisation of IgT (Zhang et al., 2010; Salinas et al., 2011).

3. Inflammation

An inflammatory reaction is critical to the efficiency of the innate and subsequent adaptive response to any type of infection including viral infections (Hussell and Goulding, 2010). It is characterised by the systemic release of specific cytokines such as IL1β, TNF-α and chemokines such as IL8 and by the chemotactic migration of leukocytes (neutrophils, macrophages) to the site of inflammation. Most of the proinflammatory cytokines have been isolated in salmonid fish and evidence of tissue inflammation was observed in Atlantic salmon following viral infection with example of SAV (Desvignes et al., 2002) and in animals suffering from HSMI (Mikalsen et al., 2012). Following VHSV infection early pro-inflammatory cytokines such as IL1-β1, IL1-β2 and IL-β3 have been found strongly induced in rainbow trout (Cuesta and Tafalla, 2009; Tafalla et al., 2005; Husain et al., 2012), as well as the inducible Nitric Oxide Synthase (iNOS) gene involved in the macrophage oxidative