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Review

Acquired immunity and vaccination against infectious pancreatic necrosis virus of salmon

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ABSTRACT

Acquired immunity plays an important role in the protection of salmonids vaccinated against infectious pancreatic necrosis virus (IPNV) infections. In recent years, vaccine research has taken a functional approach to find the correlates of protective immunity against IPNV infections. Accumulating evidence suggests that the humoral response, specifically IgM is a correlate of vaccine protection against IPNV infections. The role of IgT on the other hand, especially at the sites of virus entry into the host is yet to be established. The kinetics of CD4+ and CD8+ T-cell gene expression have also been shown to correlate with protection in salmonids, suggesting that other arms of the adaptive immune response e.g. cytotoxic T cell responses and Th1 may also be important. Overall, the mechanisms of vaccine protection observed in salmonids are comparable to those seen in other vertebrates suggesting that the immunological basis of vaccine protection has been conserved across vertebrate taxa.

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1. Introduction

Infectious pancreatic necrosis (IPN) is a disease of juvenile salmonids causing high economic losses in the aquaculture industry (Wolf et al., 1960). The causative agent, IPN virus (IPNV) is the prototype member of the genus *Aquabirnavirus* of the family *Birnaviridae* (Dobos, 1976). It is comprised of two segments of double stranded RNA with segment A encoding a large polyprotein consisting of VP2, VP3 and VP4. This segment also encodes a non-structural protein, VP5, through a separate open reading frame. VP2 is the major immunogenic protein engaged in antibody protection. The second segment (B) encodes a RNA-dependent-RNA-polymerase (Duncan et al., 1991).

Vaccination is one of the foreseeable solutions to reducing recurrence of outbreaks although this is precluded by the general failure to produce highly efficacious vaccines able to eliminate post challenge infections. As a result, there is a growing demand to improve the efficacy of vaccines which calls for good understanding of the immunological basis of vaccine protection.

Building on the infection biology of IPNV at host-pathogen-interaction level, the pathogen can be dissected to identify immunogenic components that are most relevant to initiate protective immunity. Host responses can be used to understand the protective aspect of the adaptive immune system that interacts with the virus in preventing infection progression. At the moment, fish immunology has not yet reached advanced levels where surface markers for different cell-types are commercially available and also knockout models for use in studying different pathways of the adaptive immune response engaged in vaccine protection. Current advances are however opening new insights on elements of the adaptive immune systems engaged in vaccine protection in fish. Much as most of these studies are based on gene expression, indications are that vaccination against IPNV in salmonids can evoke both the humoral and cellular immune responses. In this review, we seek to provide an update on the current level of research on the adaptive immune system of salmonids and its role in providing protective immunity against IPNV infections in vaccinated fish. Unlike previous reviews (Christie, 1997; Gomez-Casado et al., 2011), we seek to provide insights on the mechanisms of vaccine protection and the correlates of protective immunity in an attempt to answer an old enduring challenge that has led some scientists (Reno, 1976; Smith and Munro, 1985) to question the reliability of vaccination as an effective disease control strategy against IPNV infections in salmonids.

2. Viral properties engaged in vaccine protection

Understanding viral properties engaged in host-pathogen interaction is a prerequisite to designing highly efficacious vaccines with the ability to stimulate a strong adaptive immune response. Studies of viral properties of IPNV have evolved from basic virus isolation and characterization using electron microscopy that show the outer surface to be made of a 60 nm diameter, icosahedron capsid to molecular characterization that divides the viral genome into segments A and B (Dobos, 1976; Dobos and Roberts, 1983). This has recently been followed by advances in crystallography that has resolved the crystal structure of the VP2 capsid at 3.4 Å (Coulibaly et al., 2010). At such a high resolution, crystallography facilitates detailed analysis of the structural layout of residues that make the subviral particles (SVP). These in turn form the trimmers whose assemblage results in the icosahedron capsid. Based on crystallography, each SVP is made of three domains whose outermost surface is made of a hypervariable region (HVR) encoding individual residues engaged in host-pathogen interaction. To identify these residues, reverse genetic has been used to determine their positions on the viral genome (Santi et al., 2004) while crystallography has been used to determine their locations on the VP2 capsid (Coulibaly et al., 2010). Using these tools we have recently shown that the immunogenic domain of IPNV is confined to a few residues strategically located on the surface loops of the HVR (Munang'andu et al., 2013c), a refinement to previous studies that pointed to a wider area covering the region between 183 and 351 bp encoding the conserved β-sheets and HVR as immunogenic (Heppell et al., 1995).

2.1. Viral properties underlying virulence and persistent infections

In general, IPNV infections in salmonids can be classified in two broad categories, namely the clinical and subclinical forms of infections. Recent revelations show that these two clinical conditions are coded by specific genetic fingerprints that link virulence with immunogenicity, which could significantly influence the choice of vaccine strains (Munang'andu et al., 2013c; Mutoloki et al., 2013). The clinical form is characterized by lytic infections leading to tissue damage in target organs and mortality in infected fish while the subclinical form is linked to persistent infections (Hedrick et al., 1978; Mangunwiryo and Agius, 1988) in which the virus exists in macrophages and leucocytes of carrier fish without producing lytic infections (Johansen and Sommer, 1995). Studies carried out by Santi et al. (2004), using reverse genetics, showed that genetic determinants of virulence and persistent infections for IPNV are located on positions 217, 221 and 247 of the VP2 capsid. On these positions, the $P_{217}T_{221}$motif codes for persistent infections while the $T_{217}A_{221}$motif codes for virulence. This is supported by a recent study (Mutoloki et al., 2013), in which we showed that clinical and subclinical forms of IPNV infection detected during the fresh and sea water stages of the Atlantic salmon production cycle were coded by the $T_{217}A_{221}$ and $P_{217}T_{221}$ motifs respectively. In another study, Song et al. (2005) confined persistent infections to a single residue, being the T221, while virulence was linked to A221. This observation was recently supported by a study carried out by Gadan et al. (2013) in which we showed that site directed mutagenesis from T221A on the $T_{217}T_{221}$ strain resulted in reversion of the subclinical persistent infection to a virulent variant in Atlantic salmon fry subjected to stress under experimental conditions. Structural analysis of the $T_{217}T_{221}$ and $T_{217}A_{221}$ strains used in this study showed that the former had a stronger binding potential to host cell receptors than the latter. As pointed out by Bauer et al. (1995), too strong an avidity for a receptor could inhibit virus escape from infected cells resulting in less efficient release of virus from the bound receptor. To enhance virus release, viruses like influenza use neuraminidase, which is a receptor-destroying enzyme used to enhance virus release and facilitate rapid replication as a way of enhancing virulence. For IPNV and other viruses that do not have receptor destroying enzymes, mutations that reduce the binding affinity to cell receptors, such as replacing the threonine that has a stronger binding potential at position 221 with a less reactive residue like alanine, would enhance the release of virus leading to increase in replication and virulence. This could account for the observed 1680 fold increase in virus replication for the virulent $T_{217}A_{221}$ strain that reverted from the $T_{217}T_{221}$ during persistent infection (Gadan et al., 2013). Although it is possible that there might be other mechanisms causing persistent infections that are not yet known, current findings show that virulence and persistent infections of IPNV in salmonids are caused by a few amino acid changes in the central region of the VP2 capsid.

2.2. Choice of vaccine strain(s)

Molecular epidemiology studies show antigenic diversity of the immunogenic domain of the VP2 capsid (Heppell et al., 1995;