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Review

The fight between the teleost fish immune response and aquatic viruses

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ABSTRACT

Teleost fish represent a transition point on the phylogenetic spectrum between invertebrates that depend only on innate immunity and mammals that heavily depend on adaptive immunity. The major mechanisms of the teleost fish innate immune response are suggested to be similar to mammals, although fine details of the process require further studies. Within the innate immune response the type I interferon (IFN) system is an essential innate antiviral component that protects fish from some virus infections. The current progress of cloning and functional characterization of fish antiviral genes is promising in further elucidation of the fish antiviral response. The adaptive immune system of fish utilizes cellular components more or less similar to mammals. Teleost fish produce IgM as a primary antibody response and lack isotype switching to mount virus-specific antibodies during the infection process. Despite this, the development of successful fish rhabdoviral vaccines suggest that vaccination may prove to be an effective way of promoting fish adaptive immune responses to viruses. This paper reviews the bony fish antiviral response with specific discussion on the evolutionary mechanisms that allow aquatic viruses to co-exist with their host. Detailed aspects of the teleost type I IFN system are also addressed.

1. Introduction

The immune system is responsible for clearing pathogens that can establish themselves to cause disease. This is implemented by the coordinated use of innate and adaptive immune components of the immune system. Bony fish represent a transition point on the phylogenetic spectrum between species possessing only innate immunity (i.e., invertebrates) and species depending heavily on adaptive immunity (i.e., mammals). Studies of host response to virus infections suggest that mammals and bony fish are more or less similar in the major mechanisms of both innate and adaptive immune responses against viruses.

The winner of the fight between a host and a virus depends on the ability of the host to mount a strong immune response and the capacity of the virus to use its virulence factors that allow the virus to replicate fast enough before the mounting of host responses, or the use of immune evasion mechanisms that allow the virus to replicate in the presence of a potent immune response. Several mammalian viruses have evolved to acquire mechanisms of antagonizing the innate as well as the adaptive immune response. This capacity of viruses to counteract the host immune response can influence the outcome of a disease process by allowing the virus to replicate in the presence of a potent host response. Understanding evolutionary mechanisms involved in aquatic viruses' evasion of the immune response is hardly studied.

Few studies highlight the importance of cold aquatic environments in suppressing the fish immune response. Besides, the gills are under continuous exposure to water that serves as a vehicle of transmission for several viruses. The current review is intended to provide a comprehensive literature on classical and molecular aspects of the bony fish antiviral response with details on the antiviral response and examples of the evolutionary mechanisms that allow aquatic viruses to co-exist with their host. Moreover the review is intended to provide a current understanding of the teleost fish antiviral immune response with an indication of the knowledge gaps that are essential to institute effective control and prevention measures.

2. Viral diseases of significant interest in teleost fish

Almost all virus families except *Bunyaviridae*, *Flaviviridae*, *Parvoviridae*, and *Poxviridae* infect teleost fish (Essbauer and Ahne, 2001). However, the severity of disease, mortality and extent of economic impact varies with different viruses. Table 1 highlights viral diseases of significant economic interest in teleost fish.

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3. Organization of the fish immune system compared to mammals

In mammals the hematopoietic cells of the red bone marrow give rise to immediate progenitors of red blood cells, platelets, and two categories of white blood cells, called myeloid and lymphoid progenitor cells. The myeloid progenitor cells give rise to granulocytes (neutrophils, basophils, and eosinophils), macrophages, dendritic cells and mast cells of the immune system. The common lymphoid progenitor gives rise to lymphocytes and natural killer cells. A minor proportion of dendritic cells originate from the common lymphoid progenitor cells. In mammals the thymus and bone marrow constitute the central lymphoid tissue whereby lymphocytes are generated, whereas lymph nodes, spleen and mucosal associated lymphoid tissues comprise the peripheral lymphoid organs where lymphocytes are maintained and adaptive immune responses are initiated. Red bone marrow and thymus are the central lymphoid organs in mammals. In mammals both B- and T-lymphocytes originate from red bone marrow; however; only T-lymphocytes migrate to the thymus to undergo lymphocyte maturation. Mature lymphocytes migrate to peripheral lymphoid tissue via the blood stream. Pathogens that enter any part of the body are ingested by dendritic cells and macrophages, causing these host cells to mature and migrate to secondary lymphoid tissue where they present antigens to naïve lymphocytes. This is essential for the adaptive immune response (Janeway et al., 2005).

Unlike higher vertebrates teleosts do not have red bone marrow or lymph nodes as primary and secondary lymphoid organs; myelopoiesis occurs in the teleost head kidney (HK) and/or spleen. In teleost fish thymus, HK and spleen are considered the major lymphoid organs (Rombout et al., 2005). The HK of fish exhibits similarity to red bone marrow in terms of morphology and its functional role in haematopoiesis. Thymus and HK are the primary T cell and B cell organs, respectively. The HK serves as a secondary lymphoid organ in the clearance of soluble and particulate antigens from the circulation and it is a major site of antibody production (reviewed in Whyte, 2007). The spleen of teleosts has also been implicated in the clearance of blood-borne antigens and immune complexes in splenic ellipsoids, and also has a role in the antigen presentation and the initiation of the adaptive immune response (reviewed in Whyte, 2007).

The morphological and functional characterization of fish immune cells reveals cells that are equivalent to mammalian macrophages, neutrophils, monocytes, thrombocytes, B cells, plasma cells, T cells, natural killer cells and eosinophils (Manning and Nakanishi, 1996; Whyte, 2007). The adaptive immune response against viruses involves immune cells such as T and B lymphocytes, dendritic cells (DC), macrophages, and NK cells. Morphological and functional evidence shows that teleost fish have all the required components of the adaptive immune response, although detailed immunological characterization of the mechanism is limited (Scapigliati et al., 1999).

4. Antiviral immune response

Teleosts are the most ancestral vertebrate group that has well developed immune and hematopoietic systems (Flajnik, 1996). The immune system comprises two distinct but closely interdependent components: the innate and adaptive immune systems. The innate immune response is responsible for the early detection of invading viral associated molecular patterns (VAMPs) using a set of limited germ line-encoded pattern recognition receptors (PRRs) (Takeuchi and Akira, 2007). The subsequent adaptive immune response relies on enormously diverse receptors generated by random somatic gene rearrangement to detect the pathogens and provides the host an immunological memory (Janeway and Medzhitov, 2002). Teleost fish have both the adaptive and innate immune responses although the adaptive immune response lacks isotype switching to generate virus specific antibodies. In mammals, T-lymphocytes are the principal components of the cell-mediated immune system and can be subdivided into two broad categories on the basis of function and expression of surface antigens. T cells expressing the CD4 surface antigen ($CD4^+$ T-lymphocytes) facilitate B-cell maturation and production of antibodies by B-cells, and are thus termed "helper" T-lymphocytes. T cells expressing the CD8 surface antigen ($CD8^+$ T-lymphocytes) constitute an important component of the specific effector mechanism in immunosurveillance against virus-infected or transformed cells, and are thus termed cytotoxic T-lymphocytes (CTLs). The antigen presenting cells (APCs) that include DCs and macrophages present virus-derived antigenic peptides to naïve $CD8^+$ T cells and $CD4^+$ T cells in association with MHC class I and class II molecules, respectively, although cross-priming is also possible. This antigen presentation is an essential step in the induction of virus-specific immunity by the adaptive immune system (Janeway et al., 2005). Exogenous viral particles and viral antigens are phagocytosed and/or endocytosed by APCs. They are then degraded in lysosomes, and immunogenic peptides are presented in association with MHC class II antigens to naïve $CD4^+$ T cells (Gatti and Pierre, 2003). Studies from several viruses have demonstrated an essential role of virus-specific CTLs in controlling viral replication (Gulzar and Copeland, 2004). For the generation of CTLs, APCs present antigenic peptides derived from the endogenously expressed viral proteins in association with MHC class I molecules to naïve $CD8^+$ T cells. These $CD8^+$ T cells expand and differentiate into virus-specific effector CTLs. The CTLs kill virus-infected cells by recognizing their cognate virus-derived peptides in association with MHC class I molecules (Harty et al., 2000). Specific comparison of the fish and mammalian immune system is dealt in Table 2.

5. Virus replication and sensing of viral associated molecular patterns by pathogen recognition receptors

A viral particle is composed of nucleic acids (RNA or DNA), protein, and, in the case of enveloped viruses, membrane lipids. The proteins include structural components such as capsid pro-

Table 1
Economically important viral diseases of bony fish.

Virus genome	Fish viral disease	Geographical distribution	Susceptible Host	Key references
Negative sense single stranded RNA virus	Infectious Salmon Anemia Virus	Europe, North and south America	Atlantic salmon	Kibenge et al., 2004
	Viral Hemorrhagic Septicemia Virus	North America, Europe, Asia	Several marine and fresh water fish species	
Positive stranded RNA viruses	Viral encephalopathy and retinopathy	Asia, Europe, North America	More than 30 marine species	Munday et al., 2002
	Salmonid alpha viruses	Europe	Salmonids	McLoughlin and Graham, 2007
Double stranded RNA virus	Infectious Pancreatic Necrosis Virus	Europe, North America	Salmonids	Lang et al., 2009