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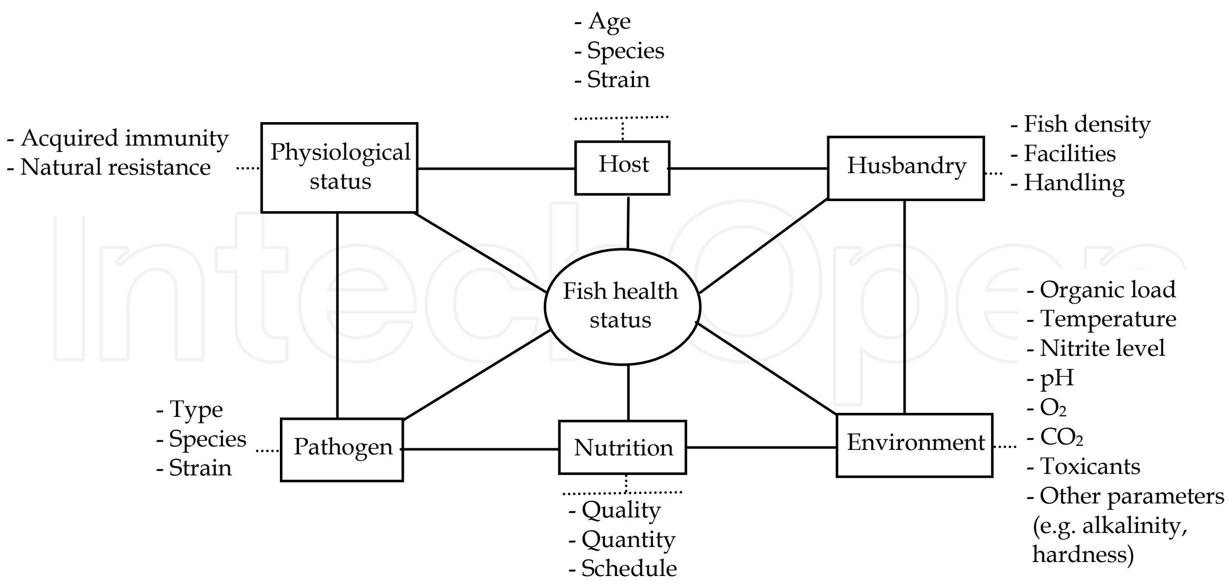
The Immune System Drugs in Fish: Immune Function, Immunoassay, Drugs

Cavit Kum and Selim Sekkin
University of Adnan Menderes, Turkey

1. Introduction

Fish is a heterogeneous group of different organisms which include the agnathans (hagfishes and lampreys), condryctians (sharks and rays) and teleosteans (bony fish). Like in all vertebrates, fish have cellular and humoral immune responses, and central organs whose the main function is involved in immune defence. Fish and mammals show some similarities and some differences regarding immune function (Cabezas, 2006; Nelson, 1994; Tort et al., 2003; Zapata et al., 1996). The fish defence system is basically similar to that described in mammals. For cellular defence systems in fish, teleosts have phagocytic cells similar to macrophages, neutrophils, and natural killer (NK) cells, as well as T and B lymphocytes. Teleosts also have various humoral defence components such as complement (classical and alternative pathways), lysozyme, natural hemolysin, transferrin and C-reactive protein (CRP). The existence of cytokines (such as interferon, interleukin 2 (IL-2), macrophage activating factors (MAF)) has also been reported (Secombes et al., 1996, Sakai, 1999). On the contrary, the morphology of the immune system is quite different between fish and mammals. Most obvious is the fact that fish lack bone marrow and lymph nodes. Instead, the head kidney serves as a major lymphoid organ, in addition to the thymus and spleen (Press & Evensen, 1999). Gut associated lymphoid tissues are also known lymphoid organs, and have been shown to function in eliciting immune responses in carp (Joosten et al., 1996). Some teleosts, such as plaice, have been shown to possess a lymphatic system that is differentiated from the blood vascular system, though the existence of such a system has been challenged in other species (Hølvold, 2007).
Health of fish depends on the interrelationship of some major components of the fish and the environment in which they live (Figure 1). Tolerance of these various factors is dependent on the host and in many case the husbandry practices. The environment may be the most critical component of the fish health matrix because environmental quality influences the fish's physiological well-being, species cultured, feeding regimes, rate of growth, and ability to maintain natural and acquired resistance and immunity. Overall physiological status of the fish host is determined by the husbandry practice, environmental quality, the fish's nutritional well-being and the pathogen, all of which influence the natural resistance and acquired immunity of the host. It is common knowledge that fish stressed by one of these factors are more susceptible to infection (Magnadóttir, 2010; Plumb & Hanson, 2011).



(modified from Magnadóttir, 2006 and Plumb & Hanson, 2011).

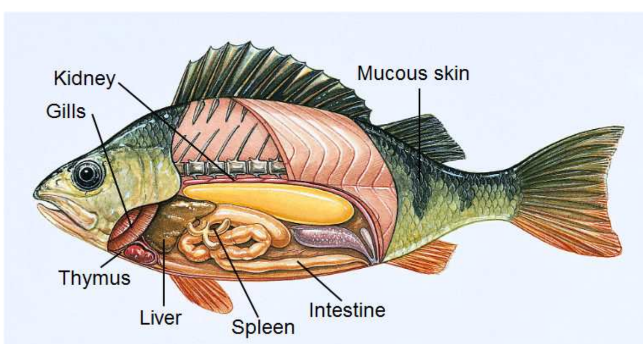
Fig. 1. The relationship of various factors in fish health status.

In addition, in the Food and Drug Administration (FDA) and the European Union (EU) member states, although a limited number of antimicrobial agents are licensed for use in fin fish culture, various drugs such as chemotherapeutics have been used to an increasing levels treat bacterial infections in cultured fish in the last decades years. However, the incidence of drug-resistant (including multiple and cross-resistance) bacteria has become a major problem in fish culture and public health (Alderman & Hasting, 1998; Aoki, 1992; Horsberg, 2003). Vaccination is a useful prophylaxis for infectious diseases of fish and is already commercially available for bacterial infections such as vibriosis, enteric red mouth disease (ERD) and furunculosis and some viral infection such as infectious pancreatic necrosis (IPN). Vaccination may be the most effective method of controlling fish disease. Furthermore, the development of vaccines against intracellular pathogens such as *Renibacterium salmoninarum* has not so far been successful. Therefore, the immediate control of all fish diseases using only vaccines is impossible. Immunostimulants such as synthetic chemicals, bacterial derivatives, polysaccharides or animal and plant extracts increase resistance to infectious disease, not by enhancing specific immune responses, but by enhancing non-specific immune defence mechanisms. Although, there is no memory component and the response is likely to be of short duration. Use of these immunostimulants is an effective means of increasing the immunocompetency and disease resistance of fish. Research into fish immunostimulants is developing and many agents are currently in use in the aquaculture industry (Klesius et al., 2001; Sakai, 1999; Subasinghe, 2009). Besides, the additions of various food additives like vitamins, carotenoids, probiotics, prebiotics, synbiotics and herbal remedies to the fish feed have been tested in fish. Overall the effects have been beneficial such as reducing stress response, increasing the activity of innate parameters and improving disease resistance (Austin & Brunt, 2009; Hoffmann, 2009; Magnadóttir, 2010; Nayak, 2010).

2. Immune system components

2.1 Tissues and cells

Types of immune organs vary between different types of fish. In the jawless fish (hagfishes and lampreys), true lymphoid organs are absent. Instead, these fish rely on region of lymphoid tissue within other organs to produce their immune cells (Zapata et al., 1996). However, genetic differences may be small and some molecular and cellular agents similar, the anatomical and functional organisation such as the structure and form of the immune system (Press & Evensen, 1999; Randeli et al., 2008). The immune system of fish has cellular and humoral immune responses, and organs whose main function is involved in immune defence (Jimeno, 2008). Most of the generative and secondary lymphoid organs present in mammals are also found in fish, except for the lymphatic nodules and the bone marrow (Alvarez-Pellitero, 2008; Jimeno, 2008; Press & Evensen, 1999; Zapata et al., 1996). Instead, the anterior part of kidney usually called head kidney, aglomerular, assumes hemopoietic functions (Jimeno, 2008; Meseguer et al., 1995; Tort et al., 2003), and unlike higher vertebrates is the principal immune organ responsible for phagocytosis (Danneving et al., 1994; Galindo-Villegas & Hosokowa, 2004), antigen processing activity and formation of IgM and immune memory through melanomacrophagic centres (Tort et al., 2003). The most important immunecompetent organs and tissue of fish include the *kidney* (anterior/or head and posterior/or caudal), *thymus*, *spleen*, *liver*, and *mucosa-associated lymphoid tissues* (Figure 2) (Press & Evensen, 1999; Shoemarker et al., 2001). In fish, myelopoiesis generally occurs in the head kidney and/or spleen, whereas thymus, kidney and spleen are the major lymphoid organs (Zapata et al., 2006). Next to the thymus as the primary T cell organ head kidney is considered the primary B cell organ. Also, head kidney and spleen present macrophage aggregates, also known as melano-macrphage centres (Alvarez-Pellitero, 2008).



(modified from http://www.dkimages.com/discover/previews/1171/10686362.JPG).

Fig. 2. Immune structures in teleost fish.

The kidney often referred to as the head kidney tissue is important in hematopoiesis and immunity in fish. And it is predominantly a lympho-myeloid compartment (Press & Evensen, 1999). Early in development, the entire kidney is involved in production of immune cells and the early immune response. As the fish mature, blood flow through the kidney is slow, and exposure to antigens occurs. There appears to be a concentration of melanomacrophage centers are aggregates of reticular cells, macrophages, lymphocytes and plasma cells; they may be involved in antigen trapping and may play a role in immunologic memory (Galindo-Villegas & Hosokowa, 2004; Press et al., 1996; Secombes et al., 1982). The head kidney or anterior kidney (pronephros), the active immune part, is formed with two

Y-arms, which penetrate underneath the gills. In addition, this structure of the kidney has a unique feature, and it is a well innervated organ, and the kidney is also an important endocrine organ, homologous to mammalian adrenal glands, releasing corticosteroids and other hormones. Thus, the kidney is a valuable organ with key regulatory functions and the central organ for immune-endocrine interactions and even neuroimmuno-endocrine connections (Press & Evensen, 1999; Tort et al., 2003).

The thymus is a paired bilateral organ situated beneath the pharyngeal epitelium in the dorso-lateral region of the gill chamber. But it seems that the size of the thymus varies with seasonal changes and hormonal cycles (Galindo-Villegas & Hosokowa, 2004; Meseguer et al., 1995; Press & Evensen, 1999; Zapata et al., 1996). The thymus appears to have no executive function. It is regarded, as a primary lymphoid organ where the pool of virgin lymphocytes in the circulation and other lymphoid organs. However, much of the data supporting this is indirect evidence obtained either by immunizing with T-dependent antigens (Ellsaesser et al., 1988) or by using monoclonal antibodies as cell surface markers (Passer et al., 1996) and functional *in vitro* assay. In addition, trout-labeled blood lymphocytes migrate through the thymus before reaching the spleen and kidney (Tatner & Findlay, 1991). It suggest that teleost thymus, despite its striking morphology, has the same function as in higher vertebrates, that is, it is the main source of immunocomponent T cells (Zapata et al., 1996), and research shows that the thymus is responsible for the development of T-lymphocytes, as in other jawed vertebrates (Alvarez-Pellitero, 2008; Galindo-Villegas & Hosokowa, 2004). In general, the available data support a correlation between the histological maturation of the teleost thymus, appearance of the lymphocytes in peripheral lymphoid organs, and development of the cell-mediated immune response (Zapata et al., 1996).

The spleen is the major peripheral and a secondary lymphoid organ in fish which contains fewer haemopoietic and lymphoid cells than the kidney, being composed mainly of blood held in sinuses, and it is believed to be involved in immune reactivity and blood cell formation (Galindo-Villegas & Hosokowa, 2004; Manning, 1994; Zapata et al., 1996). Most fish spleen is not distinctly organized into red and white pulp, as in mammals, but white and red pulp is identifiable. It contains different sized lymphocytes, numerous developing and mature plasma cells, and macrophages in a supporting network of fibroblastic reticular cells. Lymphocyte and macrophage are present in the spleen of fish, contained in specialized capillary walls, termed ellipsoids. In addition, ellipsoids appear to have a specialised function for plasma filtration and particularly immune complex. Most macrophage is arranged in malanomacrophage centers, and it is defined that they are primarily responsible for the breakdown of erythrocytes. These centers may retain antigens as immune complexes for long periods. Although the lymphoid tissue is poorly developed in the teleost spleen, after antigenic stimulation, increased amount of lymphoid tissue does appear, and indirectly suggesting the presence of T-like and B-like cells in this group fish (Espenes et al., 1995; Galindo-Villegas & Hosokowa, 2004; Zapata et al., 1996). 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 (Alvarez-Pellitero, 2008; Chaves-Pozo et al., 2005; Whyte, 2007).

The liver is included under this chapter, because in mammals, it is responsible for production of components of the complement cascade and acute phase proteins (such as CRP), which are important in the natural resistance of the animal, defined that the liver of

fish plays a similar role (Fletcher, 1981). On the contrary, research to support this claim is lacking (Galindo-Villegas & Hosokowa, 2004; Shoemarker et al., 2001).
The mucosa-associated lymphoid tissues in fish are distributed around the intestine referred to as the gut, skin and gills, thus complementing the physical and chemical protection provided by the structure (Jimeno, 2008; Press & Evensen, 1999; Tort et al., 2003). Teleost lack organized mucosa-associated lymphoid tissues such as Peyer's patches of mammals, though there is evidence that skin, gills and intestine contains populations of leucocytes (Jimeno, 2008; Press & Evensen, 1999) and innate and adaptive immunity act in case of attack of microorganisms (Ellis, 2001; Schluter et al., 1999). This equipment is completed with immunocompetent cells such as leucocytes and intraepithelial plasmatic cells (Dorin et al., 1994; Moore et al., 1998; Tort et al., 2003). Recently, several additional defences have been discovered in fish mucous membranes (Bols et al., 2001), such as the production of nitric oxide by the gill as well as antibacterial peptides and proteins by skin (Campos-Perez et al., 2000; Galindo-Villegas & Hosokowa, 2004; Ebran et al, 1999; Tort et al., 2003). Not only the mucous membranes of these tissues are an important physical barrier in fish, but also contain several components with a role in the host-parasite interaction, and release antimicrobial agents or proteins. Besides that among the epidermal secretions, complement, lysozyme, lectins (or pentraxins), alkaline phosphatase and esterase, trypsin (or trypsin-like), natural antibodies or immunoglobulins are often found, although their amount and activity depend on the species, and hemolysine are among the substances present with biostatic or biocidal activities (Alexander & Ingram, 1992; Alvarez-Pellitero, 2008; Aranishi & Mano, 2000; Arason, 1996; Balfry & Higgs, 2001; Ellis, 1999; Galindo-Villegas & Hosokowa, 2004; Jones, 2001; Fast et al., 2002; Magnadóttir, 2006; Palaksha et al., 2008; Shoemarker et al., 2001; Tort et al., 2003). Most research on the presence of immunoglobulin or antibody in the mucus suggests that mucus immunoglobulin is not a result of the transduction of immunoglobulin from the serum (Shoemarker et al., 2001). Mucous or goblet cells secrete mucus, which has at least three different types of defensive roles: (1) Mucus interrupts establishment of microbes by being continually sloughed off. (2) If establishment is accomplished, mucus acts as a barrier to be crossed. (3) The mucus on skin, and presumably the other surfaces, contains a variety of humoral factors with antimicrobial properties (Galindo-Villegas & Hosokowa, 2004; Tort et al., 2003).
All multicellular organisms possess a selection of cells and molecules that interact in order to ensure production from pathogens (Abbas & Lichtmann, 2006). This collection of highly specialised components makes up the immune system, and poses a physiological defence against microbe invasion (Jimeno, 2008). Fish immune cells show the same main features as those of other vertebrates, and lymphoid and myeloid cell families have been defined. Key cell types involved in non-specific cellular defence responses of teleost fish include the phagocytic cells monocytes/macrophages, non-specific cytotoxic cells (or NK cells), thrombocytes, granulocytes (or neutrophils) and lymphocytes (Table 1) (Buonocore & Scapigliati, 2009; Hamerman et al., 2005; Hølvold, 2007; Magnadóttir, 2006; Jimeno, 2008; Shoemarker et al., 2001).
Epithelial and antigen presenting cell also participate in the innate defence in fish, and some teleost have been reported to have both acidophilic and basophilic granulocytes in the peripheral blood in addition to the neutrophils. Furthermore, recently it has been observed that basophilic granular cells (acidophilic/eosinophilic granule cells or mast cells) of fish Perciformes order, the largest and most evolutionarily advanced order of teleosts, are endowed with histamine (Garcia-Ayala & Chaves-Pozo, 2009; Jimeno, 2008; Magnadóttir,

2006; Murelo et al., 2007; Whyte, 2007). Mononuclear cells in fish include the macrophages (and/or tissue macrophages) and monocytes. These cells are probably the single most important cell in the immune response in fish. Not only are they important in the production of cytokines, but they also are the primary cells involved in phagocytosis and the killing of pathogens upon first recognition and subsequent infection (Buonocore & Scapigliati, 2009; Cabezas, 2006; Clem et al., 1985; Garcia-Ayala & Chaves-Pozo, 2009; Secombes et al., 2001; Shoemarker et al., 2001). Macrophages also play major roles as being the primary antigen-presenting cell in teleost, thus linking the non-specific and acquired immune response (Balfry & Higgs, 2001; Galindo-Villegas & Hosokowa, 2004; Jimeno, 2008; Shoemarker et al., 2001; Vallejo et al., 1992). Thrombocytes are thought to be a nucleated version of the mammalian platelet. These cells are involved in blood clotting and have recently been thought to have phagocytic properties (Balfry & Higgs, 2001; Secombes, 1996).

Cellular components	Functional characteristics and mode of action
Monocytes/Macrophages	Phagocytosis, and phagocyte activation, cytokine production, intracellular killing, antigen processing and presentation, Secretion of growth factors and enzymes to remodel injured tissue, T-lymphocyte stimulation.
Granulocytes (or Neutrophils)	Phagocytosis, secretion and phagocyte activation, cytokine production, extracellular killing, inflammation.
Non-specific cytotoxic cells (or natural killer cells)	Recognition and target cell lysis, induce apoptosis of infected cells, Synthesize and secrete **interferon-gamma** (IFN-γ).

(modified from Hølvold, 2007; Shoemarker et al., 2001).

Table 1. Non-specific immune cells in fish and their functional characteristics and mode of action.

Fish possess polymorph nuclear cells, or granulocytes (especially neutrophils, and eosinophils, and basophils), that contain granules, the contents of which are released upon stimulation (Balfry & Higgs, 2001). These cells are highly mobile cell, phagocytic, produce reactive oxygen species, traveling via the blood and lymphatic systems to sites of infection and injure, thereby playing a vital role in the inflammatory response. Also, neutrophils are the primary cells involved in the initial stages of inflammation in fish, between 12 to 24 hours, and the function of the granulocytes may be cytokine production to recruit immune cells to the area of damage or infection (Galindo-Villegas & Hosokowa, 2004; Manning, 1994; Shoemarker et al., 2001). However, eosinophilic granular cells found in the stratum granuloma of the gut, gills and skin, and surrounding major blood vessels, are not considered to be eosinophils but rather mast cells (Vallejo & Ellis, 1989; Reite, 1998; Galindo-Villegas & Hosokowa, 2004). Cells mediating the lytic cycle to occur and destroy tumour target cells lines following receptor binding in fish have been denominated non-specific cytotoxic cells (Galindo-Villegas & Hosokowa, 2004), and are similar to (or closely related in function) the mammalian NK cells (Shoemarker et al., 2001). These cells capable of be important in protozoan parasites (Evans & Gratzek, 1989; Evans & Jaso-Friedman, 1992), and viral immunity of fish (Hogan et al., 1996), and are found in the blood, lymphoid tissue, and gut of fish (Balfry & Higgs, 2001). Lymphocytes are the cells responsible for the specificity of the specific immune response. The two different classes of lymphocytes (T and B) are the acknowledged cellular pillars of adaptive immunity, and can be distinguished by their cell surface markers and subsequent function (Balfry & Higgs, 2001; Garcia-Ayala &

Chaves-Pozo, 2009; Pancer & Cooper, 2006). T lymphocytes recognize antigen that is presented by antigen-presenting cells such as macrophages, and are primarily responsible for cell-mediated immunity. These cells are also important sources of cytokines, which are particularly important in the inflammatory response (Balfry & Higgs, 2001). On the other hand, B lymphocytes are responsible for humoral immunity, and recognize antigen and produce specific antibodies to that antigen. T and B cells can be worked together and with other types of cells to mediate effective adaptive immunity (Garcia-Ayala & Chaves-Pozo, 2009; Jimeno, 2008; Miller et al., 1998; Pancer & Cooper, 2006). Interestingly, B cells from rainbow trout have high phagocytic capacity, suggesting a transitional period in B lymphocyte evolution during which a cell type important in innate immunity and phagocytosis evolved into a highly specialized component of the adaptive arm of the immune response in higher vertebrates (Jimeno, 2008; Li et al., 2006).

2.2 Humoral molecules

The classification of humoral parameters is commonly based on their pattern recognition specificities or effector function. Most non-specific humoral molecules involved in the natural resistance of fish are presented with composition and mode of action in Table 2 (Magnadóttir, 2006; Shoemarker et al., 2001). These components are act in several ways to kill and/or prevent the growth and spread of pathogens. Other acts as agglutinins (aggregate cells) or precipitins (aggregate molecules). There are also opsonins that bind with the pathogen and, in doing so, facilities its uptake and removal by phagocytic cells. In addition, some of these substances have important role in the inflammatory immune response, such as opsonins, anaphylatoxins, neutrophil, and macrophage chemo-attractants. Briefly, these factors involve various lytic substances/or hydrolase enzymes (lyzosyme, cathepsine L and B, chitinase, chitobiase, trypsin-like), agglutinins /or precipitins (CRP, serum amyloid P (SAP), lectins, α- and natural precipitins, natural antibodies, natural hemagglutinins), enzyme inhibitors (α_2-macroglobulin, serine-/cysteine-/and metal-proteinase inhibitors) and pathogen growth inhibitors (interferon (IFN), myxovirus (Mx)-protein, transferrin, ceruloplasmin, metallothionein). Antimicrobial peptides such as cathelicidins (CATH-1, -2), defesins (DB-1, -2, -3), hepsidins (hepsidinLEAP-1, -2), piscidins (e.g. pleurocidin, epinecidin-1, dicentracin), ribosomal proteins, histone derivates (e.g. parasin, histon H2B, SAMP H1, oncorhyncins, hipposin), which widespread in nature as defence mechanism in plant and animals are also substances that have been identified in the tissue such as mucus, liver, skin and gills of some teleost species, including halibut and flounder (Alvarez-Pellitero, 2008; Aoki et al., 2008; Aranishi & Mano, 2000; Balfry & Higgs, 2001; Buonocore & Scapigliati, 2009; Cole et al., 1997; Ellis, 1999; Ellis, 2001; Galindo-Villegas & Hosokowa, 2004; Hølvold, 2007; Lemaître et al, 1996; Magnadóttir, 2006; Rodriguez-Tovar et al., 2011; Shoemarker et al., 2001; Smith & Fernandes, 2009; Smith et al., 2000; Tort et al., 2003; Whyte, 2007; Yano, 1996).

In addition, in teleost fish, evaluating the complement system as a humoral component is an essential part of the innate immune systems, and can be activated through the two /or three pathways of complement; (1) the classical pathway such as specific immunoglobulin or IgM is triggered by binding of antibody to the cell surface but can also be activated by acute phase proteins such as ligand-bound CRP or directly by viruses, bacteria and virus-infected cells, (2) the alternative pathway such as bacteria cell wall and viral components or surface molecules of parasites is independent of antibody and activated directly by foreign microorganisms, (3) the lectin pathway is elicited by binding of a protein complex consisting mannose-binding lectins to mannans on bacterial cell surfaces. All three pathways converge to the lytic pathway, leading to opsonisation or direct killing of the microorganism (Aoki et al., 2008; Balfry & Higgs, 2001; Ellis, 1999; Ellis, 2001; Galindo-Villegas & Hosokowa, 2004; Holand & Lambris, 2002; Nakao et al., 2003; Randelli et al., 2008; Shoemarker et al., 2001; Tort et al., 2003; Whyte, 2007; Yano, 1996).

Humoral components	**Composition**	**Mode of action**
Antibacterial peptides (*e.g. histone H2B, cecropin P1, pleurocidin, parasin, hipposin, SAMP H1)*	Protein	Constitutive and inducible innate defence mechanism, active against bacteria, defence before development of the specific immune response in the larval fish
Antiproteases (*e.g.* α_1*-anti-protease,* α_2*-anti-plasmin,* α_2*-macroglobulin*)	----	Restricts the ability of bacteria to invade and growth *in vivo*, active against bacteria
Ceruloplasmin	Protein	Copper binding
Complement system (*e.g. C3, C4, C5, C7, C8, C9 and their isoforms, B- and D-factors*)	Protein	Promote binding of microbes to phagocytes, promote inflammation at the of complement activation, cause osmotic lysis or apoptotic death
Interferons (IFNs) /Myxovirus (Mx)-proteins (*e.g. IFN-*$\alpha\beta$*, IFN-*γ)	Glycoprotein /or Protein	Aid in resistance to viral infection, inhibit virus replication, inducible IFN-stimulated genes
Lectins (*e.g. legume and cereal lectins, mannose-binding lectin, C-type lectins, intelectin, cod, ladder lectin*)	Glycoprotein and/or specific sugar binding protein	Induce precipitation and agglutination reactions, recognition, promote binding of different carbohydrates in the presence of Ca^{+2} ions, active complement system, opsonin activity and phagocytosis
Lytic enzymes (*e.g. lysozyme, chitinase, chitobiase*)	Catalytic proteins lysozyme, complement components	Change the surface charge of microbes to facilitate phagocytosis, haemolytic and antibacterial and/or antivirucidal, antiparasitical effects, opsonic activity, inactivation of bacterial endotoxin(s)
Natural antibodies	----	Recognition and removal of senescent and apoptotic cells and other self-antigens, control and coordinate the innate and acquired immune response, activity against haptenated proteins
Pentaxins (*e.g. C-reactive protein, serum amyloid P*)	Protein	Opsonisation or activation of complement, promote binding of polysaccharide structures in the presence of Ca^{+2} ions, induce cytokine release, coast microbes for phagocytosis by macrophage
Proteases (*e.g. cathepsine L and B, trypsin-like*),	----	Defence against bacteria, activity against *Vibrio anguillarum*
Transferrin/Lactoferrin	Glycoprotein	Iron binding, acts as growth inhibitors of bacteria, activates macrophage

(modified from Hølvold, 2007; Shoemarker et al., 2001).

Table 2. Non-specific humoral molecules and their composition and mode of action in fish.

2.3 Cytokines and chemokines

The initiation, maintenance, and amplification of the immune response are regulated by soluble mediators named cytokines. Cytokines are the soluble messengers of the immune system and have the capacity to regulate many different cells in an autocrine, paracrine, and endocrine fashion, and can also be immune effectors (King et al., 2001). In the last few years, much interest has been generated in the study of fish cytokines and chemokines and significant progress, and has been made in isolating these molecules from fish. In recent years, various cytokines have been described in fish, but the major drawback in identifying fish cytokines is the low sequence identity compared to their mammalian counterparts. The low sequence identities also limit the detection of proteins of fish cytokines by using the antibodies of human cytokines (Plouffe et al., 2006). Most of these have been identified in biological assays on the basis of their functional similarity to mammalian cytokine activities. Some have also been detected through their cross-reactivity with mammalian cytokines (Manning & Nakanishi, 1996).

The predominant pro-inflammatory cytokines are interleukins (ILs) (especially IL-1β and IL-6) and tumour necrosis factor-alfa (TNF-α) (Balfry & Higgs, 2001; Bird et al., 2005; Corripio-Miyar et al., 2006; Garcia-Ayala & Chaves-Pozo, 2009; Hølvold, 2007; Jimeno, 2008; King et al., 2001; Magnadóttir, 2010; Randelli et al., 2008; Savan et al., 2005; Tort et al., 2003). These cytokines have a number of systemic effects, including body temperature elevation neutrophil mobilization, and stimulation of acute phase protein production in the liver (Balfry & Higgs, 2001; King et al., 2001; Randelli et al., 2008). Additional several cytokine /or cytokine homologues found in fish include IL-2, IL-4, IL-10, IL-11, IL-12, IL-15, IL-18, IL21, IL22, IL-26 and IFN-γ, (Balfry & Higgs, 2001; Bei et al., 2006; Bird et al., 2004; Buonocore & Scapigliati, 2009; Corripio-Miyar et al., 2006; Garcia-Ayala & Chaves-Pozo, 2009; Hølvold, 2007; Igawa et al., 2006; Inoue et al., 2005; Jimeno, 2008; King et al., 2001; Li et al., 2007; Magnadóttir, 2010; Randelli et al., 2008; Tort et al., 2003; Wang et al., 2005; Whyte, 2007; Yoshiura et al., 2003; Zou et al., 2004), and others cytokines in some fish species include transforming growth factor-β family such as TGF-β_1, -β_2, -β_3, -βA, and –βB, macrophage-migration inhibition factor (MIF), macrophage-colony stimulating (M-CSF or CSF-1; such as CSF-1R or sCSF-1R), chemotactic factor (CF) and plateled activating factor (PAF). However, no antibody markers are at present available for fish TGF-β, M-CFS and PAF (Belosevic et al., 2006; Garcia-Ayala & Chaves-Pozo, 2009; Klesius et al., 2010; Manning & Nakanishi, 1996; Randelli et al., 2008; Tafalla et al., 2003). On the other hand, orthologous cytokines in teleost fish have been classed as Class I, Class II, chemokines, TNF superfamily and IL-1 family (Table 3) (Alvarez-Pellitero, 2008; Aoki et al., 2008; Lutfalla et al., 2003).

IL-1β has been identified in 13 different species of teleost, and is produced by macrophage and also by a variety of other cells such as neutrophilic granulocytes. These ones are play a role in immune regulation through stimulation of T cells which is analogous to mammalian IL-1β. In addition, it is an important mediator of inflammation in response to infection and it has been reported in the trout to directly affect hypothalamic-pituitary-interrenal axis function, stimulating cortisol secretion. Another potentially important cytokines, TNF-α has been cloned in various fish. Besides, TNF-like protein activity has been shown to induce apoptosis, and to enhance neutrophil migration and macrophage respiratory burst activity. The number of studies in fish have provided indirect evidence suggesting that TNF-α is an important macrophage activating factor (MAF) produced by leukocytes. In some fish species, homologous MAF containing supernatants have been shown to induce a typical

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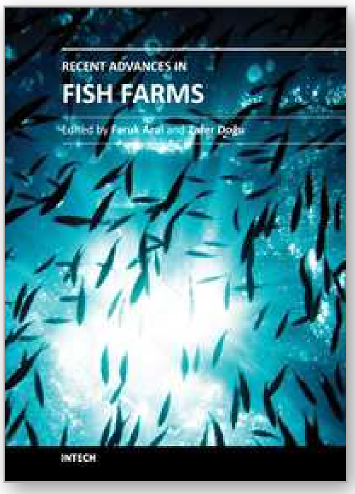

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The world keeps changing. There are always risks associated with change. To make careful risk assessment it is always needed to re-evaluate the information according to new findings in research. Scientific knowledge is essential in determining the strategy for fish farming. This information should be updated and brought into line with the required conditions of the farm. Therefore, books are one of the indispensable tools for following the results in research and sources to draw information from. The chapters in this book include photos and figures based on scientific literature. Each section is labeled with references for readers to understand, figures, tables and text. Another advantage of the book is the "systematic writing" style of each chapter. There are several existing scientific volumes that focus specially on fish farms. The book consists of twelve distinct chapters. A wide variety of scientists, researchers and other will benefit from this book.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821