

AN INTRODUCTION TO SELECTED INNATE IMMUNE-RELEVANT GENES IN FISH

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(Received 6th Aug 2017; accepted 5th Dec 2017)

Abstract. Aquaculture (aquafarming) especially that related to fish receives a great deal of attention because of its importance to science and economy. To illustrate, aquaculture is a fast growing sector of industry, and a source of many materials, as well as fish act as a good model for scientific research. The immune system has two main arms: innate (non-specific) and adaptive (specific). Innate immunity acts as a firewall not only against pathogens, but also against any foreign bodies, chemical agents or even environmental changes. However, there are many members of such system; but everyone has a particular function, like players in an orchestra. Fish rely mainly on their innate immunity; many studies were done to characterise, determine or understand the behaviour of immune-related genes in normal and disease conditions. To harness the real power beyond natural or innate immunity, we should understand the function of their members or genes. Herein, this review summarises and focuses on some genes related to innate immunity in different fish species.

Keywords: *aquaculture, fish immunity, gene expression, immune-related genes, innate immunity*

Abbreviations: CAS – cellular apoptosis susceptibility; dph – days post-hatching; GST – glutathione S-transferase; IFN – interferon; Ig – immunoglobulin; IL – interleukin; IL1ra –IL1 receptor antagonist; MT – 17 α -methyltestosterone; Mx – myxovirus resistance; NCCs – non-specific cytotoxic cells; NK – nature killer; PAMP – pathogen associated molecular pattern; PRRs – pattern recognition receptors; Th1 – T-helper1; TLR – toll-like receptor; TNF – tumour necrosis factor; VTG – vitellogenin

Introduction

The immune response is a cascade of diverse reactions and proceedings that aims to eliminate the recognised foreign agent. Although specific or non-specific immunity are both important ways of the immune response, the non-specific immune response is the first step and the ready weapon for fighting pathogens. The immune system is very sensitive and they can be affected by exogenous treatment or change. Thus, for instance, it can be inferred that a set of genes related to immunity were greatly disrupted during and after stopping the 17 α -methyltestosterone (MT; commonly used hormone in monosex production) treatment in the Nile tilapia, *Oreochromis niloticus* (Abo-Al-Ela et al., 2017a; Abo-Al-Ela, 2018).

Identification of genes that related to immunity in fish and determination of their expression patterns receive a great attention. Mostly, the increase in the expression of immune genes is usually considered as a sign for immune stimulation or enhanced immune response; however, recently, Nile tilapia received MT for a short period showed an up-regulation in the expression of innate immune genes, but with a marked decrease in the phagocytic activity and index, and genotoxicity. On the other hand, those exposed to vitamin C alone or plus MT showed somewhat normal expression of the same genes with a significant enhancement in several immune parameters (Abo-Al-Ela et al., 2017b).

There are many genes involved in the immune response either via direct or indirect way. This review looks at some of the key elements or genes of innate immunity. It focuses on the potential function of these genes and the change in its gene expression in normal and abnormal cases.

Selected innate immunity-relevant genes

Toll-like receptors (tlr)

The main difference between innate and adaptive immunity is the type of receptors used to recognise pathogens (Medzhitov, 2007). Innate immune recognition depends on number of receptors, including pattern recognition receptors (PRRs) with a broad specificity that have evolved to sense the pathogen associated molecular pattern (PAMPs) (Janeway and Medzhitov, 2002; Medzhitov and Janeway, 2002). There are many functionally distinct classes of PRRs; however, the best characterised are toll-like receptors (TLRs) (reviewed in Alvarez-Pellitero, 2008).

PRRs are classified into two groups: cytosolic and membrane bound receptors. The membrane bound receptors, including the TLRs, detect viral nucleic PAMPs inside the endosomal compartment where numerous viruses lose their coat and expose their genome for replication and transcription. TLR7 and TLR8 sense the single stranded RNA PAMPs and cytosine-phosphate-guanosine motifs of DNA (Kawai et al., 2004; Liu et al., 2011b; Zou and Secombes, 2011; Zhang and Gui, 2012). TLRs found on phagocytic and epithelial cells recognise different pathogen (Akira et al., 2001; Takeda and Akira, 2001; Alvarez-Pellitero, 2008). For example, Tlr7 can recognise viruses (Lee et al., 2013) and initiate an IFN (interferon) response against viruses (Baum and Garcia-Sastre, 2010), bacteria (Kumar et al., 2011) and parasites (Zhao et al., 2013).

The constitutive gene expression of *tlr7* was found in several organs and tissues in zebrafish at different stages of development (Jault et al., 2004), and in other fish species (Tanekhy et al., 2010). Salmon *tlr7* gene expression was sensitive to Ifn and Il (interleukin) 1 β (Lee et al., 2013).

TLR signalling cascades lead to the enhanced production of pro-inflammatory cytokines, such as IL1 β , TNF (tumour necrosis factor), IL8 (Rauta et al., 2014) and IFN molecules, which alert adaptive immune cells to an existing pathogen and mediate direct defence responses (Iwasaki and Medzhitov, 2004; Kawai and Akira, 2010). In addition, triggering TLRs can result in apoptosis (Salaun et al., 2007).

Exogenous IFN α up-regulated *TLR7* mRNA expression in macrophages (Miettinen et al., 2001). It was found that a TLR7 ligands stimulator triggered the expression of *ifna* and *mx*; thus, it potentiated the antiviral activity in Atlantic salmon, *Salmo salar* L. (Kileng et al., 2008; Sun et al., 2009), induced the IFN response in salmonid leukocytes (Palti et al., 2010; Svingerud et al., 2012) and stimulated IFN and TNF secretions from peripheral blood mononuclear cells in rat (Hammerbeck et al., 2007).

Similarly, activation of TLR7 is required to produce imidazoquinoline-inducible IFN by macrophages (Hemmi et al., 2002). In addition, the TLR7/TLR8 agonist stimulated the production of Ifn, Il1 β and Il8 in rainbow trout leukocytes (Palti et al., 2010). These lead to T-helper1 (Th1) immune response and CD4+ T-cell activation, which is vital for the host's antiviral defence (Jault et al., 2004).

Cytokines and chemokines

The immune system of fish contains both non-specific and specific mechanisms, and has cellular and humoral mechanisms to fight pathogens. Mononuclear phagocytes and T-lymphocytes from the non-specific and specific immunity pathways, respectively, are typically the major cell sources of the immune modulators, cytokines. Cytokines, are generally defined as interleukins, lymphokines, members of the TNF family and chemokines, based on the cells from which they are secreted, their functions and their targets (Alejo and Tafalla, 2011); they have a significant function in complement activation, chemotaxis, and pathogen opsonisation in the process of phagocytosis (Secombes et al., 2001; Salaun et al., 2007).

The earliest immune mediators released following virus infection are cytokines, which regulate the induction and maintenance of innate and acquired antiviral responses (Tortorella et al., 2000) and allow the clearance of viral infection (He et al., 2006). The pro-inflammatory cytokines produced by Th1 cells, IFN γ and TNF α/β , induce innate and cell-mediated responses against bacteria, fungi and viruses, resulting in their clearance, as well as having anti-tumour effects (Davidson et al., 1996; Micallef et al., 1996; Wan and Flavell, 2009; Choi et al., 2013; Gerber et al., 2013; Assani et al., 2014; Lai et al., 2014).

Many fish cytokines are identified, such as IL1 β (Zou et al., 1999), IL2 (Bird et al., 2005a), IL4 (Li et al., 2007), IL6 (Bird et al., 2005b), IL8 (Lee et al., 2001), IL10 (Savan et al., 2003), IL11 (Wang et al., 2005), IL12 (Yoshiura et al., 2003), IL15 (Bei et al., 2006), IL17 (Gunimaladevi et al., 2006), IL18 (Zou et al., 2004a), Tnf α (Savan and Sakai, 2004), Ifn γ (Zou et al., 2004b) and myxovirus resistance (Mx) (Staeheli et al., 1989).

Interleukin 1 (il1)

The IL1 family, one of the major IL families in fish and mammals, has four main members: IL1 α , IL1 β , IL18 (interferon-gamma inducing factor) and IL1 receptor antagonist (IL1ra) (Dinarello, 1997; 1999; Mulero et al., 1999; Busfield et al., 2000; Smith et al., 2000; Pan et al., 2001). However, il1 β is the most studied in relation to innate immunity in fish.

Interleukin 1 β (il1 β)

IL1 β is well-characterized cytokine, plays an important role in cellular responses to immunological challenges, infection and inflammation. Macrophages are the primary source of IL1 β , although it is secreted by various other cell types including nature killer (NK) cells, B-cells, Langerhans cells of the skin, peripheral neutrophilic granulocytes, endothelial cells, fibroblasts and microglia cells (Huisling et al., 2004; Tassakka and Sakai, 2004). IL1 β is a key player in the defence against microorganism invasion and tissue injury and is able to induce immune responses by stimulating lymphocytes or by enhancing the release of other cytokines that can activate NK cells, macrophages and lymphocytes (Low et al., 2003).

In fish, *il1 β* is constitutively expressed in several tissues, such as spleen, head kidney and liver, and higher expression has been detected in the spleen (Tafalla et al., 2005; Lu et al., 2008). Moreover, upon administration with recombinant IL1 β , the systemic gene expression of *il1 β* was induced in rainbow trout, *Oncorhynchus mykiss* (Hong et al., 2003), yellowfin sea bream, *Acanthopagrus latus* (Jiang et al., 2008), orange-spotted grouper, *Epinephelus coioides* (Lu et al., 2008) and grass carp, *Ctenopharyngodon idella* (Bo et al., 2015).

The mRNA level of *il1 β* significantly increased in response to bacterial (Mohanty and Sahoo, 2010), viral (Tafalla et al., 2005) and parasitic (Bridle et al., 2006; Mladineo and Block, 2010) infections, indicating its main role as a member in immune system. Furthermore, in chronically stressed fish (Bermejo-Nogales et al., 2007), during the smolting of Atlantic salmon (Ingerslev et al., 2006), as well as in acute stress in common carp, *Cyprinus carpio* L. (Metz et al., 2006) there was an increase in the expression of pro-inflammatory cytokines (*il1 β* , *tnfa*).

Even a change in the dietary components in hybrid tilapia (Zhang et al., 2014b) or the addition of oxytetracycline, formic and propionic acid/salt mixture to the feed of Nile tilapia (Reda et al., 2016) changed the expression of *il1 β* and disease resistance. Intraperitoneal injection of the common carp with the toxic material carbon tetrachloride (CCl₄) up-regulated the gene expressions of inflammatory cytokines, including *il1 β* and *tnfa* (Jia et al., 2014).

Tumour necrosis factor alpha (tnfa)

TNF α was first identified in fish as a single copy gene in the stimulated leukocytes of the Japanese flounder, *Paralichthys olivaceus* (Hirono et al., 2000). TNF α is a central regulatory cytokine in antimicrobial and inflammatory responses (Grayfer et al., 2008). The treatment of *Rhodococcus equi* infected mice with antibodies against IFN γ and TNF α increased the tissue colony counts. Thus, IFN γ and TNF α are involved in cell-mediated immunity against bacterial infection (Nordmann et al., 1993). Furthermore, *Tnfa* has the ability to induce the gene expression of *il1 β* and *il8* (Zou et al., 2003).

TNF α is involved in viral (Purcell et al., 2004) and ectoparasitic (Saurabh et al., 2011) invasions. Moreover, the expression of *tnf* could be considered for the assessment of fry-rearing environment (Lam et al., 2011).

TNF α stimulates the proliferation of trout leucocytes. TNF α and macrophage activating factor synergistically act on rainbow trout macrophages. This synergy causes elevation in respiratory burst activity in trout macrophages and this action is ablated after pre-incubation with neutralising mouse anti-TNF α IgG antibody (Hardie et al., 1994). TNF α can enhance chemotactic responses and phagocytosis in a dose-dependent manner, induce nitric oxide production in primary macrophages, and prime respiratory burst in monocytes (Grayfer et al., 2008).

Tnfa is predominantly expressed in non-specific cytotoxic cells (NCCs) of tilapia (Praveen et al., 2006a). The pro-apoptotic effects of TNF α are mainly responsible for macrophage-mediated cytotoxicity (Goetz et al., 2004). Recombinant tilapia *Tnfa* is highly cytotoxic to mammalian cells (Praveen et al., 2006a), and the trout *Tnfa* markedly stimulated cytotoxicity in murine L929 cells (Qin et al., 2001). In other words, this cytotoxic effect may be because TNF α has the ability to decrease telomerase activity and cause telomeric disturbances (shortening, fusions, and losses) and additional chromosomal aberrations (Beyne-Rauzy et al., 2004).

TNF α plays an important role in regulation of the biosynthesis of steroid hormones (Yan et al., 1993; Zhao et al., 1996). There is possible reciprocal feedback among IL1 β , TNF α and testosterone. The basal secretion of testosterone in purified leydig cells and whole testis cells was stimulated by TNF and IL1 β (Warren et al., 1990). In Nile tilapia, *tnfa* expression showed an early up-regulation and late down-regulation upon treatment with MT (Abo-Al-Ela et al., 2017a). These give us an indication about the interaction between cytokines and sex hormones in fish, which may result in positive or negative action.

Chemokines

Chemokines are a large multifunctional family of cytokines (**Chemotactic cytokines**) (Laing and Secombes, 2004a). They are a diverse group of small cytokines that can be divided into numerous families. Chemokines are structurally related and contain four invariant cysteine residues. Based on the arrangement of these cysteine residues, they are classified into four subfamilies: CXC (α), CC (β), C (γ) and CX3C (δ) (Baggiolini, 1998; Murphy et al., 2000; Alejo and Tafalla, 2011). Furthermore, a new family of chemokines called CX, which includes five members, has been determined in zebrafish, *Danio rerio* (Nomiyama et al., 2008). Interestingly, some microorganisms (especially viruses) appear to have copies of chemokine genes, probably to confuse the immune system of the host (Laing and Secombes, 2004a), which in this way may protect themselves.

CXC-chemokines

The Cys-Xaa-Cys (CXC)-chemokines are a superfamily of the chemotactic cytokines that play a vital role in leucocyte chemotaxis; they are able to recruit various immune cells to infection sites (Kim et al., 2007; Liu et al., 2007), and they are substantial and selective mediators in leukocyte migration to secondary lymphoid organs and inflammatory sites (Vandercappellen et al., 2008). They have been categorized as key regulators of the immune defence, acting as a link between innate and adaptive responses (Alejo and Tafalla, 2011).

In vitro, an CXC-chemokine significantly induces leukocyte recruitment, including granulocytes, lymphocytes, monocytes/macrophages and neutrophils; they have distinct effects on phagocyte activation; they increase respiratory burst activity; they induce a moderate increase in $IL1\beta$; and they up-regulate the expression of a wide range of immune relevant genes, including *il1\beta*, *il8*, *tnfa* and *mx* (Li et al., 2012; van der Aa et al., 2012).

Additionally, CXC-chemokines play an essential role in hepatic injury, recovery and regeneration (Clarke et al., 2009). Macrophage-derived chemokines are capable of inducing both respiratory burst and the release of lysosomal enzyme from macrophages in mouse and enhancing the killing and phagocytic activities of macrophages against *E. coli* (Matsukawa et al., 2000).

CXC-chemokine is expressed in a basal manner and is found most noticeably in immune organs, such as the tissue and phagocytes of the anterior kidney and the spleen (Huisling et al., 2003; Baoprasertkul et al., 2004). CXC-chemokine transcripts and proteins can show a marked increase and play vital roles in the immune response against bacterial (Baoprasertkul et al., 2004), viral (Li et al., 2012) and parasitic (Huisling et al., 2003) infections. During the early stages of turbot embryo development after fertilization, a low expression level of CXC-chemokine was first detected at the somite stage. Interestingly, turbot chemokine expression was markedly and rapidly induced in the spleen, liver and head kidney as well as in turbot embryonic cells after challenge with *Vibrio anguillarum* (Liu et al., 2007).

Interleukin 8 (il8)

The first CXC-chemokine reported in fish was I18 (Najakshin et al., 1999). The role of ELR^+ CXC-chemokines including I18 (CXCL8) is to enhance the adherence of neutrophils to endothelial cells, followed by migration along a gradient of chemokines

conjoined with matrix proteins and cell surfaces towards the inflammatory site (Laing and Secombes, 2004a). I18 is a powerful chemoattractant to neutrophils, cytokine-stimulated eosinophils, basophils and peripheral blood T-lymphocytes (White et al., 1989; Warringa et al., 1991; Baggiolini et al., 1994).

The recombinant I18 induced migration of head kidney lymphocytes and peripheral blood leukocytes, promoted the proliferation of these cells in a dose-dependent manner, and up-regulated the expression of *il1 β* and *il8* in head kidney lymphocyte culture (Hu et al., 2011; Sun et al., 2011). Fish *il8* is expressed in many tissues under normal condition and it is clearly up-regulated after bacteria, viral and external parasitic challenges (Tafalla et al., 2005; Covello et al., 2009; Ming et al., 2013).

CC-chemokine

CC-chemokines are a major subfamily of chemokines, and are essential members of the innate immune system (Hu and Zhang, 2015); they provoke chemotaxis (recruitment, activation and adhesion) of various types of leukocytes under normal physiological and inflammatory conditions (He et al., 2004; Colobran et al., 2007; Peatman and Liu, 2007; Borza et al., 2010). They are also involved in normal developmental processes as well as the maintenance and organization of lymphoid organ architecture (He et al., 2004). They primarily target mononuclear cells rather than the neutrophils that mediate either homeostatic or pro-inflammatory mechanisms (Laing and Secombes, 2004a). CC-chemokines are involved in antibacterial and antiviral immune responses in fish (Su et al., 2012; Kim et al., 2013).

Nakharuthai et al. (2016) isolated a CC-chemokine in Nile tilapia that participate in early immune defences against pathogens such as bacteria, in which many tissues especially the spleen, liver and peripheral blood leukocytes express significantly higher transcript levels than controls. *In vitro*, recombinant CC-chemokine proteins efficiently stimulated phagocytic activity in Nile tilapia (Nakharuthai et al., 2016) and Japanese flounder (Kono et al., 2003).

The chemotactic activity of peripheral blood leucocytes was markedly evoked in response to stimulation by recombinant CC-chemokine protein (Khattiya et al., 2007; Zhang et al., 2008; Li et al., 2011). Moreover, in humans, CC-chemokines can activate macrophages to kill parasites by means of nitric oxide (Villalta et al., 1998). Interestingly, CC-chemokines were secreted following the stimulation of trout macrophage-like cells by recombinant TNF α (Laing and Secombes, 2004b), which indicates an interaction between several cytokines.

CC-chemokines are constitutively expressed in lymphoid-rich tissues, such as liver, head kidney, spleen, gill and peripheral blood leucocytes (Laing and Secombes, 2004b; Khattiya et al., 2007; Li et al., 2011; Su et al., 2012). Their expression was detected during the early developmental stages of the blunt snout bream, before hatching and at 62 h post fertilization, and were strongly induced and quickly up-regulated upon nitrite stress, supporting the possible existence of pro-inflammatory function (Zhang et al., 2014a). More recently, a set of CC-chemokine ligand genes have been identified and characterized from the channel catfish. Many of the identified CC-chemokines were significantly up-regulated following bacterial infection and hypoxia (Fu et al., 2017), supporting the possible effect of external environmental stress as hypoxia on immune-related gene expression.

Interferon (ifn)

Viral diseases are a serious pathogenic threat, and they have an important concern in the fish aquaculture industry (Langevin et al., 2013); thus, fish antiviral responses are the focus of research, especially on species that have commercial value. Innate defences can play a central role in fish resistance to viral infections (Ellis, 2001). The IFN family is a key component of innate and adaptive immunity (Schroder et al., 2004; Collet, 2014). The IFN system is a powerful and a rapid defence mechanism and a hallmark against viral (Samuel, 1991; Verrier et al., 2011) as well as bacterial (Schultz et al., 2004; Chen et al., 2010) and parasitic infections (Stolte et al., 2008) in vertebrates and fish; it is also involved in tumour control (Schroder et al., 2004).

IFN has the ability to inhibit the cellular replication and propagation of different viruses (Sadler and Williams, 2008; Collet, 2014). IFNs are divided into three subfamilies, type I, type II and type III, based on the relevant receptors they interact with and the immune responses initiated by them (Sadler and Williams, 2008; Zou and Secombes, 2011). Homologues of type I and type II *Ifn* have been found in many teleost fish species, including sea bass, *Dicentrarchus labrax* (Casani et al., 2009). IFNs recognise viral PAMPs via an array of PRRs (Pichlmair and Sousa, 2007; Kawai and Akira, 2009).

In mammals, IFN induces the pro-apoptotic genes that result in the destruction of infected cells (Chawla-Sarkar et al., 2003). The recombinant *Ifn γ* of goldfish have been found to stimulate the respiratory burst responses of macrophages and neutrophils, and increase the nitric oxide production and the phagocytic responses of the macrophages (Grayfer and Belosevic, 2009).

Myxovirus resistance (mx)

The *Mx* gene was discovered for the first time in a strain of mice (A2G) that is resistant to influenza viruses type A and type B (Lindenmann, 1962). The first isolated fish *Mx* was in perch (Staeheli et al., 1989).

The *Mx* protein is rapidly accumulated in the cytoplasm or nucleus, and it self-assembles to form oligomers that interfere with virus replication (Lee and Vidal, 2002; Haller et al., 2007). Lin et al. (2005) found that, in Japanese flounder, the *Mx* protein is concentrated in the cell cytoplasm; however, in mouse, *Mx* accumulates in the cell nucleus and inhibits viruses that are known to replicate in that part of the cell (Haller et al., 2007). The possible antiviral mechanisms of *Mx* include blocking the transport of viral nucleocapsids, inhibition of viral RNA transcription or translation and targeting of viral elements, such as viral polymerase complex (Stranden et al., 1993; Kochs and Haller, 1999; Haller et al., 2007).

Constitutive expression of *mx* was found in blood leukocytes, as well as the kidney, liver, spleen, heart, intestine, gills, muscle, brain and peritoneal cavity fluid of many fish species (Lee et al., 2000; Bergan and Robertsen, 2004; Tafalla et al., 2004). The IFN antiviral state is established by the up-regulation of antiviral proteins gene expression, including *mx* (Jensen and Robertsen, 2002). Viral infection clearly induces *ill β* , *tnfa* and *mx* expression in a variety of immune tissues found in fish (Lee et al., 2000; Poisa-Beiro et al., 2008; Kim et al., 2009). On its own, the over-expression of the IFN-induced *Mx* protein can provide complete viral resistance against various viruses in fish (Larsen et al., 2004; Lester et al., 2012).

Disruption of the *Mx* gene caused a repression of innate immunity against viruses and rapid death (Haller et al., 1998). Moreover, in Atlantic salmon, the stress that accompanies the smolting process alerted the basal transcript levels of *mx* (Das et al., 2007).

Immunoglobulin M (IgM)

Immunoglobulin (Ig) genes encode a family of defence proteins known as antibodies. Antibodies are synthesised by B-cells, which undergo a complex series of somatic mutations and chromosomal rearrangements to generate antibodies with high specificity. IgM has a low molecular weight. Ig consists of two heavy chains and two light chains, linked together by disulphide bonds (Warr, 1995). The immune system in fish reported to contain four types of Ig: IgM, IgZ, IgD and IgT (Randelli et al., 2008).

IgM antibodies comprise the major component of the body antibodies, and it is the first category of antibodies generated during a primary antibody response. The IgM antibodies vary from other categories of antibodies in that they are mainly produced by B1 cells, with the apparent lack of stimulation by specific antigens. Most pathogens trigger a humoral immune response that results in an early increase in antigen-specific IgM, followed by a more specific response of antigen-specific antibodies: IgA, IgG and IgE (such as IgT/Z and IgD in fish) (Boes, 2000).

The first appearance of IgM in lymphocytes differs considerably among fish species. In channel catfish and rainbow trout, the first appearance of surface IgM occurs about one week after hatching. The maternal antibody that is transmitted to eggs and embryos has been detected in several species, including tilapia, carp, plaice, sea bass and salmon (Magnadottir et al., 2005). The IgM-like protein levels decreased gradually as yolk was absorbed (12 days post-hatching, dph) during pre-larval stages of tilapia. After yolk utilisation, the feeding and free swimming begins. About this time, the IgM-like protein drops to its lowest levels, but it increases rapidly during the post-larval stages (Takemura, 1993). *IgM* transcripts were also detectable at 5 dph in the striped trumpeters, *Latris lineata* (Covello et al., 2013). However, in chum salmon (*Oncorhynchus keta*), the serum IgM concentrations remained at a low level until 40 dph, and then they increased rapidly at 48 dph (Nagae et al., 1993).

In teleost fishes, IgM is the only member of the specific humoral defence system that is modulated by aquatic environment factors, such as water temperature, salinity and suspended solids (Dominguez et al., 2004). In particular, the levels of plasma IgM were decreased in cold-treated and stressed tilapia (Chen et al., 2002). Hypoxia significantly suppressed *IgM*, *il1 β* gene expression, and it also delayed antibody production in infected Nile tilapia (Gallage et al., 2016).

IgM secretion and expression can be altered in response to chemicals or hormones. In Nile tilapia, the organochlorine insecticide, endosulfan, led to a significant increase in the secretion of IgM; consequently, it may encourage the production of autoantibodies and the development of autoimmune problems after exposure to infection (Tellez-Banuelos et al., 2010), and after short treatment with MT (Abo-Al-Ela et al., 2017b). Furthermore, common carp, exposed to chlorpyrifos (an organophosphate pesticide that is widely used in agricultural) for 7 days, showed an augmentation in *IgM* expression at the earlier stage of exposure, but it was reduced at the later stage (Li et al., 2013).

Vitellogenin (vtg)

The egg-yolk precursor, vitellogenin (Vtg), acts as a nutrient source for developing embryos, and it also participates in innate immunity (Zhang et al., 2011; Lu et al., 2012). Vtg is a multivalent pattern recognition receptor that has the ability to recognise pathogens via interaction with PAMPs (Li et al., 2008; Li et al., 2009), and it has hemagglutinating and antimicrobial activities (Zhang et al., 2005; Liu et al., 2009). It is able to bind virus, lipopolysaccharide, peptidoglycan, lipoteichoic acid and glucan. It can also act as a bactericidal molecule capable of binding to bacteria, inhibiting bacterial activities and damaging bacterial cell walls (Zhang et al., 2011). Vtg is an opsonin that is able to enhance phagocytosis; it significantly up-regulates the expression of pro-inflammatory cytokine genes, *ill β* and *tnfa* (Liu et al., 2011a). It has been reported that Atlantic salmon serum Vtg can neutralise the action of the infectious pancreatic necrosis virus (Garcia et al., 2010). All of these elucidate that Vtg is an immune-relevant protein involved in the host defence process against microbes, including bacteria and viruses (Zhang et al., 2011).

In zebrafish larvae, *vtg* gene transcription was detected during the early stages of development, 7 days after fertilisation (Wang et al., 2011). The treatment of mature female Nile tilapia with high levels of MT resulted in a pronounced decrease in the plasma Vtg levels (Lazier et al., 1996). Hepatic Vtg levels were significantly decreased in female medaka (*Oryzias latipes*) treated with MT at concentrations of 380 ng/L and 188 ng/L for 3 weeks (Kang et al., 2008).

Cellular apoptosis susceptibility (cas)

Apoptosis is the process of cellular death; it is considerably different from necrosis, which is recognised as the classic system of cell death (Cotter et al., 1990). Apoptosis is an important biological process that destroys virus-infected cells, and it is presumed to be an innate response to counteract viral infection (Wrzesien-Kus et al., 2004). Replicating viruses may directly induce suicide of the host cell or promote recognition by natural killer cells and cytolytic T-cells, and these immune effector cells induce apoptosis (Tortorella et al., 2000).

Several genes control the apoptosis process; for example, cellular apoptosis susceptibility (*cas*). CAS is a microtubule-associated protein that links with microtubules and mitotic spindles (Brinkmann et al., 1995; Scherf et al., 1996). Mitotic spindles are cellular organelles, which play a role in chromosome segregation during cell division (Kuriyama and Nislow, 1992). CAS is associated with cell proliferation and apoptosis (Brinkmann, 1998) and in protection against apoptotic cell death (Praveen et al., 2006b). The Cas protein is important in the regulation of teleost immune functions. NCCs are one of the cellular sources for *cas* transcription in tilapia fish. The up-regulated expression of *cas*, following exposure to stress-activated serum, indicates the involvement of *cas* as a protector against apoptotic cell death (Praveen et al., 2006b). Furthermore, NCCs in tilapia treated with recombinant tilapia Tnfa revealed an up-regulation of *cas* expression, indicating that *cas* may act as a mediator for protective effects of Tnfa on NCC (Praveen et al., 2006b).

In many cases, apoptosis can harm virus replication. Therefore, viruses may protect themselves through the inhibition of proteins implicated in the apoptotic process (He et al., 2006).

Glutathione S-transferase (gst)

The glutathione *S*-transferases (GSTs), a multifunctional family of enzymes, are a natural defence system that catalyse the conjugation of many harmful electrophiles with reduced glutathione through formation of a thioether bond (Scott et al., 1992). GST, a main player in the detoxification system and in antioxidant defence (Frova, 2006; Puerto et al., 2011), plays a vital role in immune responses (Wang et al., 2013). Its expression is greatly changed in response to bacterial challenges in the Mediterranean mussel, *Mytilus galloprovincialis* (Wang et al., 2013), and also was in line with the expression of immune-related genes in Nile tilapia (Abo-Al-Ela et al., 2017a).

Interestingly, the treatment of sertoli cells with TNF α induced a decrease in basal GST α transcription levels in a dose-dependent manner. TNF α also inhibited the hormone testosterone-stimulated *GST α* expression (Benbrahim-Tallaa et al., 2002), which give another example for the cross-link between GST α and immune members.

Some GSTs possess peroxidase activity against organic peroxides, thus they can protect from lipid peroxidation, while other specific enzymes can reduce peroxidised DNA, so they may be involved in DNA repair (Scott et al., 1992). In a previous study, tilapia were subjected to cadmium chloride. Significant increases were evident in the detoxification enzymes of liver and kidney, including Gst from the seventh day continuously until the fifteenth day, and then reduced slightly on the thirtieth day of cadmium stress (Basha and Rani, 2003). To this end, oxidative stress could badly affect the immune parameters.

Conclusive remarks

The synergism of the immune system is finely tuned in such a way that each player in this orchestra cooperates to protect the living body. In the last few years, there have been great advances in the field of fish immunology, although diseases continue to cause economic losses to industry's aquaculture sector. This field of study has prompted researchers to investigate the role, function and molecular characterization of other genes that may participate in the immune system. Many of the mentioned references support the theory of the powerful link and interaction between the immune system and body status (hormones, treatment, environment, etc.). However, it will be necessary to gain a deep understanding of the mechanism underlying gene-gene interactions and the molecular bases of immune functions.

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