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Fish Immunology. The modification and manipulation of the innate immune system: Brazilian studies

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ABSTRACT

The understanding of fish immune system structure and function is essential for the development of new technologies and products to improve productivity. This is the first review on immune system of fish with Brazilian studies. Aquaculture in Brazil has shown massive growth in recent years due to methods of culture intensification. However, these procedures led to disease outbreaks, as well as the chemotherapy and the misuse of antibiotics. A viable alternative to avoid the use of chemicals and prevent economic losses is the administration of immunostimulants and prebiotcs, which act by increasing the innate immune system. In Brazil there is a lack of studies on fish immune system, except by some groups that have studied the effects of the immunostimulants administration in various species.

Key words: innate immune system, acquired immune system, immunostimulant, prebiotic.

INTRODUCTION

The Innate and Acquire Immune System of Bony Fish

The immune system is a set of cellular and humoral components to defend the body against foreign substances, such as microorganisms, toxins or malignant cells, responding to factors such as endogenous or exogenous components that stimulate this system. The fish immune system is divided into innate and adaptive (memory), both divided into cell mediated defense and humoral factors (soluble substances), although today it is known that these two systems work together in order to destroy invaders or to trigger defense processes. The innate system includes all components present in the body before the appearance of the pathologic agent, as the first line of defense that acts faster than the specific system. Among these components there is the skin as a physical barrier, the complement system, the antimicrobial enzymes, the interleukins, the interferon and the organic defense cells, such as granulocytes, monocytes, macrophages and natural killers cells (Bayne and Gerwick 2001, Ellis 1999, Magnadottir et al. 2011).

The inflammation is also considered an innate mechanism of immune response, mediated by complex interactions of cellular and humoral compounds. Once a tissue has been penetrated by an infectious agent, mediator factors are released in

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order to extend and make blood capillaries more permeable, allowing the migration of the defense cells. The granulocytes are the first cell type to arrive at the inflammation focus, being responsible for the destruction of pathogens. On the other hand, the remaining pathogenic cells and cellular debris are phagocytosed by macrophages (Magnadottir 2006).

The innate immunity is the oldest system in the phylogenetic scale and probably originated in unicellular organisms during the evolutionary period. By definition, this system recognizes regions in molecules called Pamps - Pathogen Associated Molecular Patterns - from infectious agents or microorganisms of normal microbiota, such as lipopolysaccharide, peptidoglycan, bacterial DNA or viral RNA, or other molecules found in multicellular organisms membranes known as "non-self". The Pamps are usually highly preserved portions during the evolution of species and are found in the greater part of microorganisms. Conversely, the specific system first appeared around 450 million years ago, and can be found in all vertebrates except in fish of the Agnatha class. The acquired system receptors are responsible for detecting the pathogenic agent, and can be found in the cell membrane of T lymphocytes (TCR - T cell receptor) and B lymphocytes (BCR - B cell receptor, also called as well as membrane immunoglobulin) or in serum as free antibody (Abbas and Litchman 2004, Boltaña et al. 2011, Elward and Gasque 2003, Goldsby et al. 2002, Holland and Lambris 2002).

The specific system of defense requires the presence of an antigen, which is a strange molecule or cell that will initiate reactions and culminate in the increase of circulation of specific antibodies, besides promoting immune memory. Antigens that enter the body will be recognized and processed by the innate system by antigen presenting cells (APC - macrophages, dendritic cells and B lymphocytes), to process microorganisms in molecular units, and at first trigger immune response of proliferation, and in a second moment, the response of memory. As a result, the antigen processed by APC will be presented to the T lymphocytes which are the cells of the specific system. T lymphocytes carry the ability to recognize the antigen strictly in the presence of a specific humoral component called major histocompatibility complex molecules, which are glycoprotein receptors coded by genes in a major histocompatibility complex (MHC). After this recognition, the T cell secretes cytokines, which are proteins that activate other cells such as B lymphocytes (responsible for the production of antibodies), cytotoxic lymphocytes, macrophages and other cells in order to destroy the invading agent (Abbas and Lichman 2004, Bernstein et al. 1998, Goldsby et al. 2002, Salinas et al. 2011).

The antibodies recognize and connect to specific microorganisms and consequently activate phagocytosis (component of the innate system, indicating that the specific and innate systems act together). Antibodies may promote agent neutralization or opsonization and may bind to extracellular antigens in addition to complement system. However, if the antigen is established in the intracellular compartment, the defense is conducted by cytotoxic T lymphocytes (Ellis 2001, Goldsby et al. 2002, Salinas et al. 2011).

The Ontogeny of the Immune System

The tissues and organs that structure the immune system of bony fish are classified as lymphoid, and there is no myeloid classification, such as in mammals, because fish lack bone marrow and lymph nodes. The lymphoid organs are the kidneys (the largest lymphoid organ), thymus, spleen and gut associated lymphoid tissues (GALT), formed during larval development. It is known that there are approximately 24,000 fish species thus morphological differences have been found (Nelson 1994, Press and Evensen 1999, Rombout et al. 2010). The lymphoid tissues and organs are usually arranged by reticular cell networks in order to build a structure for the cells of the innate and

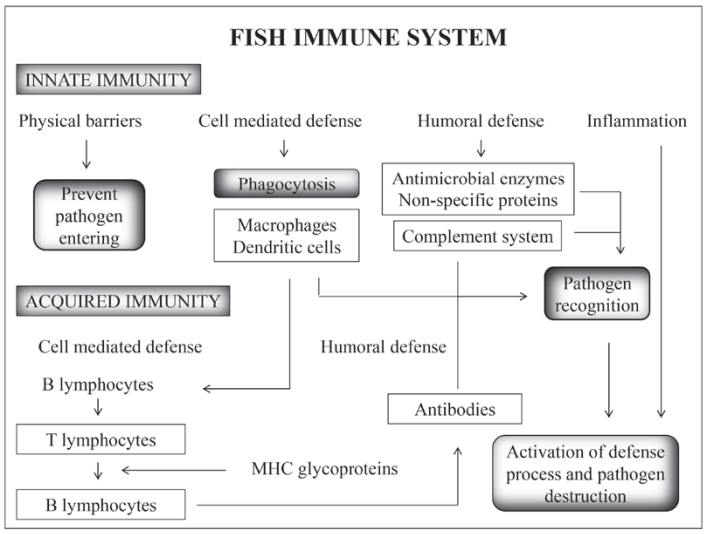

Figure 1 - The concept of fish immune system.

specific defense, such as lymphocytes, monocytes, macrophages, granulocytes and thrombocytes, mast cells, NK cells, cytotoxic cells and dendritic cells. This arrangement is responsible for the production of the immune system components (Miller et al. 1985, Ellis 1977, Salinas et al. 2011).

Thymus is a double organ located behind the operculum in the dorsolateral position of gills. The thymus ontogeny and histology differ according to species, however, in general, their origin occurs 24 hours after fertilization. It is considered an important tissue of T lymphocytes development and maturation (Bowden 2005, Fishelson 1995). Although the involution of the thymus occurs in adult vertebrates, it can differ in bony fish depending on the species. The kidney is very important for fish hematopoiesis and immunity, and could even be compared to the marrow of mammals. It has the function of formation and maturation of red and white blood cells. The kidney displays differences between the anterior and posterior section, both with haemopoietic function. However, the first portion of the organ is more important for the production of defense cells, in addition to differentiation and maturation of leukocytes, including B lymphocytes, monocytes, macrophages and granulocytes (Meseguer et al. 1994, Torroba and Zapata 2003).

The fish spleen contains a white pulp that promotes haematopoiesis with formation of defense cells, and a red pulp that causes phagocytosis of old or defective cells. However, different from mammals, this division in fish is not organized, although it is possible to identify each pulp in various species. The organ concentrates lymphocytes and macrophages, most of which are macrophages arranged in centers that are responsible for phagocytosis that will culminate in immune memory. Once blood flows through spleen, antigens are kept in these centers in order to be processed and presented for T lymphocytes (Press and Evensen 1999, Solem and Stenvik 2006).

GALT includes gastrointestinal mucosa, gills, and skin. These tissues produce mucus containing soluble defense components, such as lysozyme, complement system proteins and immunoglobulins in order to promote the first barrier against pathogen agent. These lymphoid tissues are scattered throughout the mucosa in clusters of defense cells, including macrophages, lymphocytes, mast cells and granulocytes (Georgopoulou and Vernier 1986, Rombout et al. 2010). These cells capture the antigen in order to process and promote immune memory. The liver has the same function as in mammals, of producing humoral compounds such as proteins of the complement system and

acute phase proteins of the inflammatory response (Davidson et al. 1997, Salinas et al. 2011).

Humoral and Cellular Mediated Immunity

The fish immune system is responsible for destroying microorganisms through acquired and innate components, with humoral and cellular process that perform together in an attempt to prevent the outbreak of diseases. The humoral innate system functions through several soluble components in body fluids, while the humoral specific system acts only through antibodies. Fish are susceptible to viral, bacterial, fungal and parasite agents, however, they can resist microbial invasion because of specific and innate mechanisms. The unspecific mechanisms includes the production of numerous antibacterial compounds, proteins of inflammation acute phase, complement activated by alternative pathway, cytokines, phagocytosis and inflammation (Bayne and Gerwick 2001, Ellis 1999, 2001, Lin et al. 2011).

Among the humoral innate components are the inhibitory factors of bacteria growth, such as transferrin, antiproteases, lysozyme, C-reactive protein, antibacterial peptides and complement system proteins, activated through alternative and lectin pathways. The complement system is one of the most important mechanisms since it has lytic activity, chemotaxic, pro-inflammatory and opsonization functions. Defense cells represented by phagocytes, neutrophils and macrophages are very important due to their large quantities of enzymes in lysosomes and reactive oxygen species produced during phagocytosis (Ellis 1999, Magnadottir et al. 2011).

Antiproteases are blood proteins which act against microorganism proteolytic proteins, those ones that make lysis in fish tissues in order to obtain amino acids as sources of energy. Lectins are proteins found in eggs, mucus and blood that promote agglutination due to their high affinity for carbohydrates of the pathogens cell wall. Lysins present in mucus are peptides that attack the membranes of pathogens. Lysozyme is produced by leukocytes (mainly monocytes and neutrophils) and it is found in mucus, eggs, blood and tissues and acts on the peptidoglycan of pathogens cell wall (Arason 1996, Braun et al. 1990, Ellis 1999, 2001, Murray and Fletcher 1976, Magnadottir 2006, Ohta et al. 1990). C-reactive protein from the pentraxin family is found in large concentrations in the blood, egg and mucus. The protein recognize and connect to phosphoryl colin, a component usually found on the walls of various microorganisms such as bacteria, fungi and parasites. The C-reactive protein and the mannose binding lectin are considered inflammation acute phase proteins and receptors of soluble microbial components so that they have ability to connecting and promoting pathogen opsonization, complement activation and phagocytosis. The concentration of acute phase proteins may increase after heat shock (high temperatures), infectious agents and in warm periods of the year (Goldsby et al. 2002, Magnadottir et al. 2011, Nakanishi et al. 1991, Szalai et al. 1994).

The complement system of fish is considered more effective than that of mammals and is one of the most important innate compounds for host protection due to its production of inflammatory mediators (Nonaka et al. 1981, Boshra et al. 2006). The complement system is comprised of soluble and membrane proteins in inactive form or in low levels of spontaneous activation and they are triggered by sequential pathway since the initial stimulus contributes to the proteolysis of the next component. Activation can be triggered by three pathways: i) classical pathway, an antibody-dependent activation by antigen-antibody complex, ii) alternative pathway, prompted by microorganisms Pamps or antigen-antibody complex, iii) lectin pathway, triggered by bacterial surface carbohydrates. The alternative pathway is very efficient on innate recognition and is considered the most important among the three activation pathways, besides it can be easily trigged by various gram-negative

bacteria lipopolysaccharide and cause cytolysis. Alternatively, the classic pathway performs interaction between innate and specific systems (Boltaña et al. 2011, Boshra et al. 2006, Holland and Lambris 2002).

Two complement system components C5a and C3b play a central role in the recruitment of phagocytes and inflammation. C5a and C3b are chemotaxic proteins for neutrophils and macrophages because they remain linked to bacterial wall triggering biological processes of opsonization, phagocytosis, chemotaxis of leukocytes and inactivation of the released bacteria toxin. The complement system is widely used as an immune status indicator due to its contribution to host protection. The function of the complement system regarding cellular activation, phagocytosis, chemotaxis, inflammatory reaction and lise of pathogens cells are well known mainly for their ability to destroy pathogens through membrane injuries, commonly characterized by pores (Bayne and Gerwick 2001, Boshra et al. 2006, Ellis 2001, Secombes 1996).

Innate humoral components increase after outbreak of pathogens such as bacteria, viruses, parasites and fungi, as well as in trauma, necroses, chemicals, heat shock, tumor cells and in some cases increase up to 1000 folds, such as C-reactive protein. These compounds are called acute phase proteins and most of them are synthesized by the liver, however, they can also be synthesized by the brain and leukocytes. The C-reactive protein, serum amyloid A, transferrin, α-2 macroglobulin, C3 complement, lysozyme and lectins are commonly used for the diagnosis of diseases (Bayne and Gerwick 2001, Magnadottir et al. 2011).

The bony fish defense cells are produced by lymphoid tissues such as kidney, thymus, spleen and GALT since they have the same cellular precursor called pluripotent cell. The lymphoid cells production is recognized as hematopoiesis that results in the formation and differentiation of a large quantity of cell types such as erythrocytes, granulocytes, monocytes, lymphocytes, mast cells and thrombocytes (Metcalf and Nicola 1995, Evans 1997, Chettri et al. 2011). The hematopoiesis is regulated by cytokines that act on pluripotent cell receptors controlling their survival, proliferation, differentiation, maturation and function (Hanington et al. 2009). The hematological parameters assessment can be an indicator of physical condition and diseases outbreak of the fish (Stoskopf 1993, Barreda and Belosevic 2009).

Among the defense cells of fish, thrombocytes have phagocytosis capacity besides coagulation function. They have acid phosphatase what leads the cell to be in inflammatory site (Tavares-Dias et al. 1999). Monocytes show phagocytosis and unspecific citotoxic activities and are considered transitory cells in blood because during the inflammatory process they migrate through the connective tissue and turn into macrophages (Mesenguer et al. 1994, Witten et al. 1998, Cuesta et al. 1999). Neutrophils are polymorphonuclear cells found in the blood, lymphoid tissues and peritoneal cavity that can phagocytosis foreign particles or cells and produce superoxide anions that are a bactericidal compound (Plyzycz et al. 1989, Secombes 1996). Eosinophils are distributed by connective tissue, especially in the gastrointestinal tract, gills and bloodstream and provide degranulation when there are parasites infestations. Basophils are unusual in most fish (Hine 1992). The special granulocytic cell are polymorphonuclear cells found in the blood mainly in parasitized fish or injected with inflammatory agents but their exact function is still unknown (Ranzani-Paiva 1996, Martins et al. 2000). The phagocytes described below play an important role in innate immune system modulation since they have phagocytosis ability with consequent pathogen destruction (Chettri et al. 2011, Verlhac and Gabaudan 1997).

T and B lymphocytes are the adaptive immune system cells, however, there are distinct populations of lymphocyte called natural killers or T cytotoxic that have been classified as an innate immune

compound and relies on the ability to destroy injured somatic cells (tumor or viruses infected cells) and produce immune modulation cytokines. (Tizard 2002, Raulet 2004).

Some cells are able to trigger phagocytosis of invading particles, such as microorganisms, cells, cell debris and macromolecules aggregates, in order to destroy or present them to the specific system cells. Phagocytosis is initiated by the connection between the agent and the phagocyte receptor membrane (Neumann et al. 2001). Monocytes, macrophages, dendritic cells and granulocytes are professional phagocytes that may be mobilized to the inflammation site by molecular signals of inflammation (cytokines) released by injured tissue (Stuart and Ezekowitz 2005).

Neutrophils and macrophages destroy microorganisms through phagocytosis with hydrolytic enzymes and reactive oxygen species (ROS). The inflammatory tissue liberates chemotaxis factors that promote cell migration. Neutrophils are the first granulocytes to appear at the injured site, followed by macrophages. Neutrophils migrate from the bloodstream and macrophages are originated from blood monocytes. At the site of injury, these cells trigger the phagocytosis process, in order to destruct invading agents (Hanington et al. 2009, Rowley 1996, Secombes 1996).

During the phagocytosis there is increased oxygen consumption in a molecular mechanism known as leukocyte respiratory burst which result in oxygen reduction with superoxide anion production. The superoxide dismutase enzyme acts over the superoxide anion and generates hydrogen peroxide, in addition myeloperoxidase enzyme released by granular leukocytes react with hydrogen peroxide in order to produce hypochlorite that lead to the production of cloramins. All of these compounds are oxidative substances and can attack microorganism membranes (Verlhac and Gabaudan 1997, Caipang et al. 2012).

The relationship between innate and acquired immune system is made by antigen-presenting cells (dendritic cells and macrophages) that after processing microorganism introduce the processed molecule to T lymphocytes with the help of major histocompatibility complex (MHC), class 2 receptors, thus initiating the acquired response cell mediated (Tizard 2002). Histocompatibility molecules are glycoprotein receptors encoded by a gene complex, which are expressed in almost all organism cells. MHC plays an important role for endogenous and exogenous antigens recognition but lacks in specificity and may recognize several related antigens (Goldsby et al. 2002).

On the other hand, antibodies are glycoproteins, known as well as immunoglobulins (Ig), expressed in the membrane of the B lymphocyte (BCR) or free in body fluids, secreted by plasma cells (B lymphocytes activated by antigen connection) (Goldsby et al. 2002). The immunoglobulin IgM is a tetrameric protein with four sites for antigen recognition well known in fish. However, researchers have observed other immunoglobulins in some species of fish, such as the IgD (Wilson et al. 1997), IgZ (Danilova et al. 2005) and the IgT (Hansen et al. 2005). Immunoglobulins can be found in the serum, body fluids, mucus, eggs and in the gastrointestinal mucosa (Davidson et al. 1993, Ellis 2001, Solem and Stenvik 2006).

The antibodies may develop several roles such as anti-adhesin function which mainly occurs in the epithelium of digestive system surface (Davidson et al. 1993), gills (Davidson et al. 1997, Joosten et al. 1997) and skin (Rombout et al. 1993) so that these antibodies prevent bacteria adherence (Ellis 2001). Anti-toxins antibodies neutralize toxins produced by countless bacteria (Gudmundsdottir and Magnadottir 1997). Anti-invasins antibodies avoid bacteria infiltration into unprotected cells (Magarinos et al. 1996).

Regarding specific immune response, once antigen have been recognized by immunoglobulins receptor of B lymphocyte, it will stimulate endocytosis and proliferation of memory B cells, which activate T lymphocytes, resulting in cytokines release and triggering of B cells, macrophages, among others cells (Tizard 2002). The serum antibodies concentration may differ according to species, age, sexual maturity and physiological events (natural or artificial incident – as smoltification, cortisol boost, etc) and may be increased by artificial immunization or due to chronic infection (Miller et al. 1985, White et al. 1985, Hordvik et al. 1992, van Ginkel et al. 1994, Wilson et al. 1997, Rycyzyn et al. 1996, Wilson et al. 1997, Zhao et al. 2002).

The Modification and Manipulation of the Innate Immune System

Immunostimulants and prebiotics

In Brazil, intensive aquaculture has lead to outbreaks of diseases with substantial damage in production and economic losses (Biller et al. 2013). The misuse of antibiotics in order to reduce diseases has lead to unsatisfactory results, since the prevention and health restore after any chemical uses depends on the appropriate administration and interaction with pathogens. In an attempt to prevent or ban the excessive use of antibiotics and consequent bacterial resistance, several studies have evaluated an alternative to antibiotics administration, such as immunostimulants, probiotics and prebiotics to prevent and control diseases (Verschuere et al. 2000, Nayak 2010, Nikoskelainen et al. 2001).

Among them, there are synthetic chemicals (levamisole, FK-565 – isolated from *Streptomyces olivaceogriseus* cultures), biological substances (bacteria derivates, polysaccharides, animal and plant extract), nutritional factors (C and E vitamins), hormones (prolactin and growth hormone) and cytokines (polypeptides and glycoprotein). These immunostimulants, synthetic or biological extracts enhance the immune system by increasing cellular and humoral production (Raa 1996, Sakai 1999, Fujimoto et al. 2013, Sinha et al. 2011, Sado et al. 2013).

Among the immunostimulants, β-glucan has been defined as a linear polyglucose chain derived from yeast, fungi or fungal mycelium that has demonstrated immune modulation function with anti-tumor, anti-microbial, anti-viral and anti-parasite properties (Caipang et al. 2012, Wasser and Weis 1999). β-glucan with a structure composed of glucose units connected by β 1-3 links and lateral chains by β 1-6 links facilitated the stimulation of mammal and fish innate immune system. β-glucan has activated several functions such as hematopoiesis, lytic proteins production such as lysozyme and complement system protein in addition to promoting phagocytosis activity (Caipang et al. 2012, Di-Luzio 1985, Kiron 2012, Ortuno et al. 2001).

Macrophages play an important role in specific immune response because of the phagocytosis and lymphocyte activation. Macrophages also have specific receptors able to recognize β-glucan so that the immunostimulants increase leukocytes respiratory burst which releases reactive oxygen species, most of them with bactericidal activity (Caipang et al. 2012, Secombes and Fletcher 1992). According to Lin et al. (2012) β-glucan feed inclusion has enhanced growth, survival and immune response of *Cyprinus carpio*. Anderson (1992), Sahoo and Mukherjee (1999) and Sakai (1999) have reported healthy improvement, including increased specific and innate immunity parameters, even after stressor, resulting in protection against pathogen. However, factors such as pathway, dosage and period of immunostimulant administration and species of fish may compromise its efficiency. Regarding the pathway, injection is considered more efficient, yet more invasive, consequently the oral pathway, mainly supplemented in food

is the standard process chosen (Raa et al. 1992, Duncan and Klesius 1996, Sakai 1999, Gannam and Schrock 2001, Lin et al. 2011)

The mannan oligosaccharide (MOS) is an oligosaccharide characterized as a carbohydrate complex derived from glucomannan proteins of yeast wall (Abraham and Beachey 1985). Other oligosaccharides have been used as prebiotics, such as xylo oligosaccharide (XOS), fructo oligosaccharide (FOS), galacto oligosaccharide (GOS), transgalactosylated oligosaccharides (TOS) and inulin. MOS is a component of yeast wall found in the external section, corresponding to approximately 40% of this cellular structure (Hough 1990). Over the last few years several researchers have noted its ability to promote better growth rate, prevent colonization of pathogenic bacteria in the gastrointestinal tract and increase survival rates in a wide variety of species. The results of MOS on growth, systemic immunity and gut mucosa are considered sufficient to avoid the costs of curative measures besides decrease the microbiological problem of the misuse of antibiotics (Newman 1994, Devegowda et al. 1997, Spring 1999, Spring et al. 2000, Liu et al. 2013).

MOS is defined as a prebiotic because it is a non-digestible food ingredient which positively influences the host organism by stimulating growth and activity of one or more bacteria in gut, promoting growth, nutrient utilization and health improvement (Gibson and Roberfroid 1995).

The MOS is a mannose source that has high affinity for gram-negative bacteria. Once bacteria connect to MOS complex, it prevents the colonization of gastrointestinal tract and decrease outbreaks of diseases and the toxins effects, resulting in intact gut with maximum capacity of nutrients absorption and modulation of gut immunity (Ballou 1977, Spring 2000, Ferket et al. 2002).

Brazilian Studies

In Brazil, there is a lack of studies on the manipulation of fish innate immune system, however some groups have already evaluated some growth performance and immunology parameters after the application of immunostimulants and prebiotics.

Abreu (2007) has assessed the effects of β-glucan on innate immunity and in prevention of stress responses in Pacu (*Piaractus mesopotamicus*), and the author has concluded that 100 μg of β-glucan per 100 g body weight injection (Macrogard®), or 0.5% β-glucan in food can stimulate components of the pacu innate immune system. Furthermore, Biller (2008) has evaluated the physiological and immunological effects of β-glucan (Macrogard®) in pacu challenged by *Aeromonas hydrophila*. The β-glucan administration has shown immunity stimulation and decreased mortality from opportunistic pathogens, promoting increased survival in the treated groups, in addition to increasing the immunological parameters such as the number of white blood cells, leucocytes respiratory burst activity, lyzosyme and complement system.

Schorer (2008) has observed pacu fed β-glucan in order to evaluate growth performance, stress indicators, blood profile and survival. Pacu supplied with 0.3% of β-glucan per kg/diet presented greater weight gain, specific growth rate and final weight. In addition 0.1% of β-glucan per kg/diet has led to increased survival after bacterial challenge, as well as the influence on physiopathologic and stress indicators. Conversely, Sado (2008) has utilized mannan oligossacharide and β-glucan supplement (Active-MOS ®) during 60 days in order to assess biological, haematological and biochemical responses of juvenile pacu, and found changes in growth performance, hematology and intestinal morphology of treated fish.

Chagas (2010) has observed the productive performance and physiopathologic responses of tambaqui (*Colossoma macropomum*) fed with β-glucan (Macrogard®) and nucleotides (Biotide®) after *Aeromonas hydrophila* vaccination and challenge and has concluded that the 0.1% of immunostimulant administration increased the resistance against bacterial infection, with survival of 95 to 100% in the treated groups.

Sousa (2010) has assessed the feed supplementation with 0.1% mannan oligossacharide (Active-MOS®) and 0.03% of β-glucan (Macrogard®) for up to 90 days for tilapia in cage. The author found that these compounds promoted improvement on immune system and gut, with increased enzymatic activity and nutrients absorption mainly in β-glucan treated groups. Garcia (2008) has evaluated the homogeneity, growth performance, intestinal structures morphology and the efficiency of food supplementation with 0, 500, 1000 e 2000 mg per kg/diet of mannan oligossacharide and β-glucan supplement (Active-MOS®) in Nile tilapia. Best results were found after administration of 500 mg/kg in the diet of the compound during at least 37 days for cage production due to its improvement in protein utilization and greater integrity of the intestinal surface than the control group. In addition Falcon (2007) has also tested the administration of β-glucan (Macrogard®) for tilapia and determined the best concentration and period of time in order to promote immune stimulation in this species. In his study growth performance, hematologic and immune responses of fish were assessed, and revealed that 0.1% of β-glucan and 600 mg/kg vitamin C in diet for at least 15 days promoted better responses after cold temperature and *A. hydrophila* challenge.

CONCLUSIONS

The knowledge of the structure and function of Brazilian fish immune system is essential for promoting the aquaculture as an economic activity, since the intensification of production often leads to immune suppression, disease outbreak and even death. However, once knowing the immune system, there is a possibility of promoting appropriate stimuli, such as immunostimulants and prebiotcs administration in order to prevent losses during critical periods of cultivation and to avoid the misuse of antibiotics. The study on the modification and manipulation of the innate immune system in Brazil is scarce but this area of knowledge is in successful development because it is crucial for the expansion of Brazilian sustainable aquaculture.

RESUMO

O estudo das estruturas e o funcionamento do sistema imune de peixes são fundamentais para o desenvolvimento de novas tecnologias e produtos para a melhoria da produtividade. Esta é a primeira revisão sobre o sistema imune de peixe ressaltando os estudos realizados no Brasil. A aquicultura no Brasil apresentou grande crescimento nos últimos anos, devido aos métodos de intensificação da cultura. Entretanto estes procedimentos levaram ao aparecimento de diversas enfermidades, bem como ao uso indiscriminado de quimioterápicos e antibióticos. Uma alternativa viável para evitar o uso de fármacos e prevenir as perdas econômicas provocadas por diversos agentes etiológicos é o uso de imunoestimulantes e prebióticos, que atuam aumentando as defesas inespecíficas de peixes. No Brasil os estudos sobre o sistema imune de peixes é escasso, mas alguns grupos já demonstraram benefícios com uso destes compostos em diversas espécies.

Palavras-chave: sistema imune inato, sistema imune adquirido, imunoestimulante, prebiótico.

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