Review Article

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Innate and Adaptive Immunity in Fish: A Review

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Abstract

The fish inhabitant in an aquatic environment so it persists exposure to pathogen and stressor factors so they have a developing immune system similar to that in high vertebrate with some differences points. Head Kidney considered the main and primary hematopoietic organs while spleen, thymus and gut-associated lymphoid tissue represented secondary hematopoietic organs. The immune system divided to the innate immune system doesn't have a memory of previous responses, non-specific cellular as natural killer cells, dendritic cells, neutrophils, basophils and eosinophils with non-specific component these involve complement, lysosomes and acute-phase protein, if the pathogen persists the specific, memory adaptive immunity would be stimulation which composed of two subunits humeral and natural antibodies act for invading extracellular pathogen and the second subunits which are cytokines and T-lymphocyte act for kill intracellular bacterial, parasitic and viral infection. Both subunits (innate and adaptive) of the immune system act each together in the hosts to prevent microorganism's infection and reducer the environmental stressors and give fish immune status. It is concluded from this article review that fish, like mammalians, have an advanced immune system that plays a role in fish resistance to pathological factors and maintaining fish health.

Keywords: Fish, Immunity, Innate, Adaptive.

المناعة الفطرية غير المتخصصة والتكيفية المتخصصة في الاسماك

الخلاصة

تعيش الأسماك في البيئة المائية ولذا فانها تتعرض الى المسببات المرضية وعوامل الاجهاد وعليه تمتلك جهاز مناعي متطور مماثل لذلك الموجود في الفقاريات العالية مع بعض نقاط الاختلاف. تعد الكلية الرأسية من مكونات الأعضاء اللمفاوية الرئيسية والأولية بينما يمثل النسيج الليمفاوي المرتبط بالطحال والتوثة والأمعاء الأعضاء المكونة للدم الثانوية. يقسم الجهاز المناعي الى المناعة الفطرية غير المتخصصة والذي لايتميز بذاكرة للاستجابات السابقة وخلايا غير محددة كالخلايا القاتلة الطبيعية والخلايا المتشجرة والعدلات والقاعدية والحمضة ومكونات غير متخصصة والتي تشمل المكمل والحالات وطور البروتين الحاد إذا استمر العامل الممرض ، فإن المناعة التكيفية المتخصصة للذاكرة ستكون عبارة عن تحفيز يتكون من وحدتين فرعيتين من الأجسام المضادة العضدية والطبيعية تعمل على غزو مسببات الأمراض خارج الخلية والوحدات الفرعية الثانية وهي السيتوكينات واللمفاويات التائية تعمل لقتل العدوى البكتيرية والطفيلية والفيروسية داخل الخلايا. تعمل كل من الوحدتين الفرعيتين (الفطرية والتكيفية) من الجهاز المناعي معًا في المضيف لمنع عدوى الكائنات الحية الدقيقة وتقليل الضغوطات البيئية وإعطاء حالة مناعة الأسماك. يستنتج من مراجعة المقالة هذه بان الأسماك كاللبائن لها جهاز مناعي متقدم يلعب دور مهم في مقاومة الأسماك للعوامل الامراضية والمحافظة على صحة الأسماك.

Introduction

Both animals (vertebrates and invertebrate) with plants have immunsystem (1) which play important function in protect themselves against pathogens(2).The immune system in fish is physiologically and functionally similar to that higher vertebrate which are mainly produce immune cells by cytokines and associated receptors is the main function against pathogen and protecting organisms against diseases (3).

There was some variable features, in fish there is nobone marrow which represented the primary immune organs in other vertebrates, head kidney(HK) in fish represented the organ for hematopoietic cells , myeloid , lymphoid immune cells and produced antibodies (Ab), (4) thymus represented center for T cell maturation (5), also fish lack lymph nodes, blood infiltration is done by Melan macrophage centers which is characterized by assembly macrophages combined to ellipsoid capillaries (5).

Ontogeny of Immune System

The lymphoid tissue is the main unit of immune system in fish because fish lack lymph nodes and bone marrow, although there is 24.0000 fish species was morphological differences but the lymph tissue mainly consisting from reticular cells providing the innate and adaptive immunity as dendritic cells, mononuclear cells, granulocyte, mast cells, thrombocyte and natural killer cells (6).

The fist hematopoietic organ in teleost fish was known as intermediated cells Mas (ICM), in some fish species as Kili *(Psudoepiplatys annulatus)* and Rain Bow Trout hematopoietic persisted for short period and then shift to ICM (7).The lymphoid organs are anterior kidney, thymus, spleen and gut associated lymphoid organs (GALT) were completed before embryonic hatching. (8) refer to variable sequence development of lymphoid organs in marine fish which as kidney ,spleen and thymus with variable function related to stage as spleen in the larval stage has erythropoitic function than hematopoietic. (9) Determined the observative time for each cell, myeloid cell persist around the yolk sac from 24 hours post fertilization(hpf) but not are seen in ICM, neutrophils and myeloblast observation and migrate through blood vessels walls during 34 and 48hpf while granulocytes are presented in blood supply in the connective tissue surround the yolk sac at 34 hpf and at 48 hpf observative near renal tubules.

Immunoglobulins (IgM) and B lymphocyte varies a mong fish species, they are late appearance in marine fish compare to freshwater fish. IgM play roles in phagocytosis, activation complement and it represented nutritional yolk protein (10).

In teleost fish as in higher vertebrate the maternal Abs act to protect eggs against vertical transfer pathogen (11).

Lymphoid Organs

Spleen

The mammal's spleen consist from 2-part white pulp composed mainly from hematopoietic for defense mechanism and red pulp that causes phagocytosis for abnormal and old cells. These features may variable from fish spleen although it persisting in some spp. The fish spleen composed from melanomacrophage (MMC), lymphoid tissue and surrounding with clustered ellipsoid (12), macrophage phagocytize antigen that will culminate in immune memory and then represented for T lymphocyte (13), in zebra fish, spleen describes as small organ contain a large number of enitroblast at 30day post fertilization at three month the lymphoblast antigen , these developmental pattern has been

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detected in Catfish, Grouper and Atlantic salmon(14; 15)

Thymus

It has two lobes mainly consist of thin sheet of oval lymphoid tissue located behind operculum in the dorsolateral position of gill lined with mucosa of pharyngeal epithelium (16), origin of the thymus occur at 24hpf,aggregation of macrophage which are promote encapsulated proliferation T lymphocytes and the capsule surrounding lymphoid tissue are the two main component of fish thymus these structure is variable according to fish in contrast to higher vertebrate it is difficult to recognized medulla from cortex(17).

Thymus responsible for the production and maturation of T lymphocyte as well as the eosinophilic granulocytes and myeloid cells are detected in thymus with Hassal,s corpuscles (7).

Kidney

The kidney in teleost fish are recognized as two lobes anterior and posterior kidney has play roles in blood filtration,urine formation and secretion hormone as renin and angiotensin while anterior kidney equivalent of the bone marrow in vertebrate it is important for production defense cells, reorganization and maturation of B lymphocytes, monocyte and granulocytes(18)

Fish Immune System

As in human and other vertebrates the immune system divided in to two subunit, innate (non-specific) immunity composed of three component (physical barrier, humeral and cellular factors), innate immunity recognised the pathogenic organisms(lipopolysaccharide LPS)in gram negative bacteria, lipoteichoic acid (LTA) in gram positive bacteria, beta -glucan and chitin in fungi and hemagglutinin in viruses by pathogenic associated molecular patterns (PAMPs) (19; 20) after that the phagocytosis process occur, if pathogen persist for long time the innate immunity replace by second subunit adaptive immunity which is more specific and Igs, T cells receptors with major histacompatibility are the main component of it (21; 22).

Innate Immunity

Physical Barrier

In aquatic environment fish is usually direct contact with many types of microorganisms, so the main and first line defense mechanisms is physical barrier which classified to external physical barrier (skin, mucus and gills) and internal barrier represented by intestinal epithelial, the physical and chemical defenses are provided by these barriers (16; 5).

Skin act as first line defense mechanisms and classified as physical and chemical barrier for trapping pathogen (23), variable in structure according fish species in teleosts the skin have have scales known as Leptoid scals and other fish as cat fish lack scales the skin immune components of these types are skin-associated lymphoid tissue(SALT), secreting cells(gobalt cells,granulocytes,macrophage and langerhanse -like cell and T lymphocyte(24)

as well as melanocytes in cartilaginous fish (25). Heimroth et al., (26) refer to present keratinocyte and B cells with granulocytes in skin of Lobe-finned fish, in general skin integrity and epidermal cells hyperplasia with these mononuclear cells and granulocyte is important to prevent entry of pathogen (27)

Gills

Addition to its biological function in keep gas exchanges and osmotic imbalance, gills conserved a physical barrier and having both innate and adaptive immunity which involve macrophage and mononuclear cells and granulocytes(neutrophils and eosinophils)have been detected in gill associated lymphoid tissue (GIALT), also B and T lymphocyte have been observed in some fish as in gill of rainbow trout , cat fish and shark in which B cells transcript to Igs(28; 29) also, expression of B form MHC II has been demonstrated in the gills of Salmonids(30).

Gastrointestinal (GI) tract

The gastrointestinal tract have biological function play roles in absorption of nutrient and also have both innate and adaptive immunity mainly posterior segment and diffuse cells (amyloid and lymphoid) are demonstrated in GALT which are not recognized as in high vertebrate, microflora have roles in development and maturation (31).

Mucus

One of the most important physical barriers is the mucus providing sub molecules which interact and inhibiting entry of pathogen (32). Mucus is more common secretion from skin and gills. In stress the stressor factors considered as stimulator for mucus secretion as microbial agent and chemical assembly, in some cases the mucus reach to 40% of the body weight in case Myxinoids (33). The mucus of fish composed from(i) Lectins are protein present also in eggs and blood their mechanisms is promoting agglutination because their binding to carbohydrate of microorganisms cells wall (ii)Lysins also, present in mucus which are peptide and can destroy membrane of pathogen (iii) Pentarxin (C-reactive protein) is inflammation phase protein has ability to connecting and promoting microorganisms opsonization, complement activation and phagocytosis, mucus have Ig and lysosomes which secreted from (monocytes and neutrophils) act on lysis peptidoglycan of microorganisms cell wall(34; 35).

Cellular Component

Fish possess different cell types as Natural killer cells(NK), dendritic cells, monocytes, granulocyte(mast cells,eosinophilic and neutrophils),leukocyte are produce in head kidney and thymus in bony fish, while in cartilaginous fish the cells are produce in primary sites(epigonal organ, thymus, spleen and leyding organ)(36; 37).Proliferation,survival, differentiation, maturation and biological function are regulated by cytokine act on cell receptors(38).

Toll-Like Receptors (TLRs)

TLRs have been distinguished by reported of (39) in *Carassius auratus auratus,* Pufferfish,zebra fish(40; 41) and in Japanese flounder(*Paralichthys olivaceus*)(42). These TLRs act for recognizing the molecules of the microbes called pathogen associated molecules patterns (PAMPs) this led to inflammation which is the first response of innate immunity (43)

Natural Killer Cells

T cytotoxic are nonspecific classified as innate immunity produced in lymphoid tissues a NK and spleen but rare found in blood (44), like NK in mammals they are small, granular lymphocyte invetidation in Catfish, Rainbow trout, Common carp and *Oreochromis spp.* (45; 46), their function was destroy virus and tumor cells(47; 48).

Denderitic cells

Several cells (thrombocyte) have ability to phagocytize pathogen and exogenous material as well as coagulation function, they have acid phosphatase lead to inflammation (49)

Macrophage is called monocyte in blood circulation and called macrophage in connective tissue,derived from hematopoietic progenitors. In general, is defined as transit cells which have ability to migrate during inflammation through tissue and turn to macrophage, have role in innate and adaptive immunity (50). They play roles in phagocytosis of pathogen, production of reactive oxygen species (ROS), nitric oxide (NO) as well as release pro-inflammation (TNF, IL-1B) these classified as

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subpopulation as M_1 and have roles wound repair, immunosuppression and IL-10M_2(51), while in an adaptive immunity it known professional antigen presenting cell(pAPC) which act for presenting foreign (phagocytic)material to T lymphocyte (52)

The granulocyte cells in fish involve :neutrophils, polymorphonuclear cell, determined in blood, peritoneal cavity and lymphoid tissue,neutrophils play important roles in an innate defense against pathogen(53)that can phagocytosis pathogen or cells by producing extracellular and intracellular granules , they release reactive species, nitric oxide and myleoperoxidses in the cytoplasm which can kill bacteria halide with hydrogenperoxide and cause halogenation of the bacteria cell wall also, have lysosomal and other hydrolytic enzyme (54; 27).

Other granulocytes are eosinophils have acidophilic stain, large elongated homogenous granules found in connective tissue mainly in gill, GIT and blood stream, their function are degranulation and destroyed parasite (55)

Basophilis are uncommon in fish, have a azurophilic grains in their cytoplasm, present in the blood circulation,their function unknown but through to provide and destroyed parasitic fish (56), in mammals have roles in allergy and antiparasitic immunity while in fish it activated be Ab-dependent manner in Fugu(*Takifugu rubripes*) distinguish IgM cross linked to basophils surface lead to degranulation of both two type reddish-purples and dark violet(57) , some materials as papains stimulate degranulation of the reddish purplethis will stimulate migration of other white blood cells while dark violet degranulation by chitin which stimulated series migration of CD+4 T cells.

Other roles in adaptive immunity is interact with T and APCs and endocytosed Ag and expressed MHCII

Humeral and Innate Immunity

Anti-microbial peptide (AMPs)

It is known also as a host defense peptide, they composed of oligopepetide with different amino acid (cathelicidins,hepcidine,histone-derived peptide and specific piscidine),they demonstrated in gills, liver and mucus these AMPs have roles in innate immunity through destruction or forming pore against pathogen membrane (58),there are two type of AMPs(transferrin and squalamine) are distinguish in dog fish shark(*Squalus acanthias*) which act as bactericidal against gram positive and gram negative, other type known as AMPs Kenojeninin has been distinguish in skin of fermented(*R.kenojei*) which act as inhibitory effects on *Bacillus subtilis,* E.coli and *Saccharmoyces cervisiae*(59; 60)

Lysosome

Is one of mediating defense mechanisms, is lytic enzyme cause hydrolyzing for peptidoglycan layer of bacteria (61).Lysosome are present in an invertebrate, plant, bacteriophage microbes, present in saliva ,mucus and blood stream of high vertebrate while in fish they release from neutrophils and macrophage so it present on hematopoietic tissue mainly head kidney and in tissue exposed to pathogen invasion (gills,skin and gut tissue)(16).

There are two types of lysosomes distinguish in vertebrate goose(g)-type and chicken(c)-type, in fish mainly present both type in neutrophilis and less extent in macrophage (62).In highly bacteriolytic activity against some pathogen as *Vibrio anguillarum, Aeromonas hydrophila and Micrococcus lysodeikticus* recomenant (r) between both g- and c- types will be occur(63).

Mode of action of lysosomes are attack lipopolysaccharide layer in pathogen cell all after earlier disruption of wall by complement and other enzyme lead to damage to enter structure, or cause disruption to wall permeability without lysis (32), so leukocyte released enzyme are more activity rather than mammals (64).

Acute phase protein

It is a member of the pentraxin family present in egg, mucus and blood stream, Mantovani *et al.,* (65) identified it as first pattern recognition receptor (PRR), produce in both fish and mammals under factors release from fat cells and immune cells stimulate liver to produce acute phase protein (APP) (66), which have many activities as coagulation factors, transport protein (ferritin),serum amyloid protein(SAP)(67).

Also, another important acute phase protein is C-reactive protein (CRP) have ability to pathogen opsonization, complement and phagocytosis (35), some fish do not possess CRPas Flounder, *Platichthys flesus* and the bacterial endotoxic (LPS) have ability to stimulate liver of fish exposed to pathogen to release CRP (68).

Complement

The complement system is cascade serum protein act in elimination of the pathogen through opsonization and phagocytosis and stimulate inflammation response, it is one of the main humeral components in both innate and adaptive immunity (69), in fish is considered effective than that mammals, but have same mode of action which can activated by three way (i)classical pathway triggered by Ab binding to cell wall of pathogen, is more common in mammals(70)(ii) alternative pathway which is dependent Ab and activated directly by microorganisms or pAMPs this pathway more common in fish than in mammals (71) and finally(iii) lectin pathway in which interaction between lectin(is one components of complement) with sugar(mannose/mannan) present in the surface of pathogen(72).

Complemant activate and neutralize envelop of virus while lipopolysaccaride in the cell wall of G^- stimulate C5a factor which is chemokines to macrophage and C3 was chemokines to neutrophils (73), the biological function of complement are cellular activation,chemotaxis, inflammation reaction and phagocytosis and destroy pathogen through membrane injury and lyse (67)

Natural Antibodies

These types of Abs are present in the serum of fish when there have not infection or lack Ag stimulation of the cells that are equivalent to blood cells (74). They considered initiated key for innate immunity and linked to specific memory; teleost fish have IgM neutral Ab provide protection against different Ags. Species of fish and variable environmental condition represented commonly factors affecting generation and levels of natural Abs (75).

Adaptive Immunity

The adaptive refer to recoganization of specific form from non-specific and specialized responded to pathogen if persist and surviving innate immunity which activated adaptive immunity (76) .The main components of humeral are Abs and cytotoxic T-lymphocyte cells which representing and mainly component of cellular adaptive immunity (77), humeral immunity similar to humeral high vertebrate by Igs structure, function(neutrolization, complement fixation and opsonization also, the cellular which responsible for Abs stimulation but in fish affected by fish species and environment factors.

Antibodies

Known also immunoglobulin Ig, are major component and primary humeral immunity (10),teleost Ab s are found systematically in plasma or may found locally in gills, intestine, bile and mucus (78),gills are more organ direct contact to environment pathogen and stressors factors so the immune response and defense mechanisms are important (79),their function may be explaining as Ag receptors on the surface of b cells or Abs secreted to blood (80).

Types of teleost Abs:

(1) IgM: commonly and predominant Ig in all fish as tetrameric and monomeric, have eight sites for antigenic combining exception that

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coelacanth do not IgM in the genome (81) also, in cartilaginous fish IgM found pentameric and monomeric which play roles in phagocytosis (82)

In bony fish and cartilaginous fish IgM are present in two forms :transmembrane which is shorter than second form which is secreted led to shorter IgM receptors in B cells but these do not affected their function in both innate and adaptive immunity which are Ab-dependent cell- mediated cytotoxicity, opsonization and complement activation (83) .

(2) IgD/IgW:IgD is present in all bon fish, while IgW found in cartilaginous fish(84), coelacanths and lung fish (85)both Igs are phylogenetically old as IgM (86).

IgD have play roles in innat immunity secreted by channel catfish (87) mainly in gill, (88) suggested that IgD /IgM ration in gill much higher than other tissue, also IgN -/IgD + B cell are expressed in the gill.

(3) SPECIEFIC Ab related to species:

IgS:IgNAR, IgZ/T ,IgQ IgZ is firstly identified inzebrafish (89) and IgT in rainbow trout , it specialized for for mucosal immunity and functionally an alogously to mammamls IgA.

The IgT/Z in the serum lower than IgM, in general the ration IgT/Z to IgM higher in the gut than serum (90) IgT +B cell also detecated in fish skin and lymphoid tissue (91)

IgNAR (new/nurse shark antigen receptor) is a heavy chain Ig found in shark, in the serum levels of IgNAR much lower than IgM (92).

Immunological Memory (B cells)

B cells are lymphocytes have avital functions which is responsible for produce Ab, selected as memory B cells which have greater and higher affinity receptors in status of memory response which has faster and larger than primary responsealso the number of Ag-specific B cells in the spleen proportional to B cells – specific Ag (93; 78) also, B cells act as APCs, teleost fish have been lack bone marrow so the main hematopoietic for progenitor B cell and plasma cell is anterior kidney(7) while posterior kidney and spleen representing sites for maturation and activation B cell and plasma blast formation (94;95) and then differentiation in to plasma cells ,these cells migration back to the anterior where have long life span and supporting the storage of larger amount of Ig secreting (96).

Also, B cells found in other organs as in skin of catfish (97), primary gill filaments a long blood vessel in Spotted wolfish (98), in the intestine of carp, sea bass and brain bow trout (99).

T-cells and Cellular cytotoxicity

Lymphocyte mature in to the thymus so it called thymocyte, there are many types involve gamma delta T cell, regulatory Tcell (Treg cell), memory T cell, T helper cells (T_H cell) and T cytotoxic cell (CTL) (100; 101).

CD+8 cytotoxic and CD+3 have ability to recognize and kill virus with derived peptides using MHCI (27), CD+4 T cells have plasticity and heterogeneity (102).There are five types of naive CD+4T cell can recognize to effectors cells (Th1,Th9,Th2,Th22 and Th17). Fischer *et al*., (103) suggested that CD+4 helper and CD+4 CTL in fish similar to higher invertebrate.The presence of T cells is detected at variable time according to fish species As in Sea bass fish (*Dicentrarchus labrax*) T cell was distinguishing in larval stage at five days after incubation (14) and after one week of rainbow trout insemination the CD8+T cells have been distinguish

Cytokines

As modulators of the adaptive immune response there was a little data about teleost cytokines which include:

Interleukine -1B

It detected in both bony and cartilaginous fish, produce by macrophage it is play vital roles as mediator of inflammation and stimulating cortisol secretion (104), other cytokines and regulatory molecules reported in fish with interferon(IFN-g) which are effectors of the Th1 response as(IL-12, IL-18, IL-15)(105; 106; 107) and IL-10 has effectors of T regulatory cells (108)while IL-4 has been relation to Th2 type(109).

Tumor Necrosis Factors (TNF)

TNF- alpha and TNF-beta have been cloned

in all fish species rainbow trout, catfish, *Carassius auratus* and sea bream(*Sparus aurata*) play an important roles in neutrophils migration, phagocytosis and burst activity of macrophage and nitric oxide production as well as induce apoptosis and considered a key factor for neuroimmunoendocrine responses (110; 111; 112).

Interferon (IFN)

There are two types of these cytokines IFN-alpha and INF-beta, both have antiviral activity by inhibition viral nucleic acid replication,also play another role in protecation cells from viral infection by binding to variable receptors lead to induction several genes that are stimulated by INF(ISGs), these genes are encodes antiviral protein as(MX) (113 and 114).

Interferon like peptide has been detection in zebra fish (115), IFN- alpha -1 was recognized in *Atlantic salmon* induces expression of MX and ISGs and with IFN-alpha-2 have activity against infectious pancreatic necrosis virus (116 and 117).

Conclusion

The immune system of fish is sufficient as in mammalian to provide defense against antagonistic pathogens from the environment and improving the safety of the health and disease of fish.

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