

Immunomodulation in Fishes

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Introduction:

Fish protection against bacterial diseases achieved by specific vaccines has been a practice followed from many years. However, defence mechanisms in lower vertebrates are somewhat different from other mammals hence some immunization techniques do not induce that immune response as is expected from them. Therefore, abundant research has been done to improve the effectiveness and potential of the antigens and how to optimally activate the nonspecific defence as well as specific cellular and humoral immune responses. Fishes are poikilothermic in nature and general they have short life spans. Most of the fishes live in cold water environments, hence when any pathogen invasion occurs in fish it takes longer time for specific immune response to get activated. Therefore, Nonspecific defense mechanism is considered more important than specific one because the latter requires a longer time for build-up and specific cellular activation. While the defense mechanism can be categorized into specific and non-specific groupings, its important to realize that *in vivo* they act in concert with each other as they are inter-dependent in many ways.

1. Nonspecific defense mechanisms.
2. Specific immune response

Non-specific defense barriers and mechanisms:

It suggests by its name that it is not specific to any particular kind of pathogen nor it can be tailored accordingly. This type of defense mechanism is general for all types of disease causing agents. Nonspecific protective mechanisms repel all microorganisms equally. It includes barriers which are already in place e. g physical epithelial shield of the scales, skin and the lytic enzymes of mucus & sera; cellular aspects it includes monocytes, macrophages, neutrophils and cytotoxic cells. When any infectious agent infects fish it gets entrapped in the mucopolysaccharide complexes of the mucus where it may be scraped from fish. Later on this scuffed infectious agent is digested by the mucus lytic enzymes.

Pathogenic organisms are mostly destroyed by digestive and lytic enzymes. The main tools for nonspecific immune response are phagocytes and phagocytosis. These tools act against different pathogenic factors like viruses, bacteria and parasites. In response to the infection, inflammation occurs at the tissue-damage site which results in the migration of leukocytes to wound areas and the elevation of serum component concentrations, including C- reactive protein, transferrin, lysozyme, ceruloplasmine and complement components. Phagocytes are considered to be functionally more effective, especially their ability to kill pathogens is considerable.

Pathogenic antigens get attached to the cell surface which activates cell surface receptors. The cell surface receptors get activated by this attachment and produces immune response. If the membrane does not get activated by attachment of infectious particle then this gets engulfed into phagosome by pseudopods which extend around it. Once inside phagosome, infectious f micparticle gets killed by a battery orobicial mechanism.

In case of viral agents interferons are released by viral infected cells which activate other cells to produce endonucleases that will destroy the genetic material (DNA or RNA) of the virus which will shut down the physiological pathway of virus used for its replication.

Specific immune response:

The specific immune system comprises of different immune cells which are produced against foreign substances like virus or bacteria or against substances produced by these infectious particles called antigens. The cells which are produced against these antigens are called Immunoglobulin (Ig) or antibodies. Specific immune response can be tailored according to the need of the body. Antibody or Immunoglobulin is the primary result of the specific immune response, and unique in the fish physiology because these immunoglobulin molecules are specifically directed against individual antigens. The common Ig in fish is a tetrameric form of antibody and is usually designated as IgM.

Antibody works by making a complex with antigen and initiate other serum proteins to begin a complement cascade in lysing invasive pathogen. It also acts as a communicator to direct circulating cytotoxic cells to recognize and attack pathogenic agents.

The specific immune system in contrast to nonspecific immune system can hold memory. when the animal is attacked again by the same pathogen, antibodies are produced more rapidly and is a magnified quantity.

Uses of immunostimulants in aquaculture:

The fishes which are held in hatcheries, farms, pens, cages etc. are negatively affected by many factors like environmental pollution, stress caused by high stocking density, use of chemotherapeutics and other treatments used. These all factors impair the protective immune system of fish making it more prone to diseases. These factors altogether make a favorable environment for occurrence of infectious agents which leads to disease outbreak in fishes. Therefore, there is an immense need of early detection of immune deficiencies and stimulation or modulation of nonspecific cellular and humoral immunity. The process of regulation or modulation of immune response is called as immunomodulation. The chemicals or substances which are used for that purpose are called immunomodulators.

Immunomodulators have two categories:

- **Immunosuppressants:** Those drugs which suppress immune responses and reduce the risk of rejection of foreign bodies such as transplant organs.
- **Immunostimulants:** Those drugs which stimulate or enhance the immune response by inducing activation or increasing activity of any of its components.

The use of immunostimulants in aquaculture is growing day by day to reduce the declination of fish mortality caused due to disease outbreaks. Growing demand for fish from fish consumers makes it very important to use such drugs which will increase the immunity of the fish making it capable to fight infections. At the same time, there are only few drugs which have been approved by FDA to be used in food fish because of growing concern for consumer liability and for accumulation of substances in the environment. It is well said that Prevention Is Better Than Cure. This Sets the New Stage for the Concept Of disease prevention hence for the use of immunostimulants and vaccines.

Complete Freund's Adjuvant:

Complete Freund's Adjuvant (CFA) was one of the first immunostimulants used in animals and humans to elevate the specific immune response. It's an oil based adjuvant which contains antigens emulsified in mineral oils. It is composed of inactivated and

mycobacteria (usually *Mycobacterium. Tuberculosis*). It has been used in rainbow trout to induce the immune response. It's modified form i.e. MCFA (Modified Complete Freund's Adjuvant) has been used in Coho salmon to increase the protection against pathogens.

Bacterial derivatives as immunostimulants:

Different microbes and their extracts have been used to induce immune response in humans and other organisms. Similarly, these microbes have been found useful in fishes also. Example of bacterial extract used in fishes as immunostimulant is Muramyl dipeptide. It acts by stimulating the polyclonal activity of lymphocytes and activation of macrophages.

Chitin and chitosan:

They act by stimulating the nonspecific immune system. Response produced is short lived in such cases. Chitin is a polysaccharide which constitutes the main component of exoskeletons of crustaceans and insects. It is also present in the cell walls of few fungi. It activates macrophages and provides resistance to the fish from certain bacteria.

Chitosan is a product of chitin derived following its deacetylation. In aquaculture chitosan has been used to provide resistance against certain bacteria and controlled release of vaccine. It has been also used as diet supplement in fish feed.

Yeast derivatives as immunostimulants:

Example of the yeast derivative used in aquaculture are: (β -1, 3- & β -1, 6 glucan) and (β - 1,3glucan). These glucans are the long chain polysaccharides which are extracted from yeast. These are good stimulators of nonspecific defense mechanism. They increase the cellular and noncellular activity in fishes like increment in the activity of lysosomes, phagocytes, along with the bactericidal activity of macrophages.

Plant extracts as immunostimulants:

A number of plant derivatives have been used in aquaculture as immunostimulants. The whole plant or its parts like roots, stem, leaves, seed, flower can be used as immunostimulant. Plant extracts are useful and more economical as compared to other immunostimulants. Different plant extracts or parts used as immunostimulants are; dietary ginger to control *Aeromonas hydrophilla* infection in rainbow trout, use of stinging nettle to increase the disease resistance. Flavonoids from *Allium mangolicum*, curcumin, genistein, limonene, thymol have shown positive effects on growth, nutrient assimilation and

immunity of farmed fish. Methanolic extracts of *Ocimum sanctum*, significantly improved the phagocytic activity, serum bactericidal activity against *Vibrio harveyi*.

Vitamins as immunostimulants:

Among all vitamins, vit C and vit E are considered to have important role in building immunity of an organism. Teleost fishes lack the enzyme for endogenous synthesis of ascorbic acid (vit C) therefore it is given through diet. Effects of dietary vitamin C has been seen on the growth, nutritional quality and immunomodulation in fishes. It has been observed that higher level of dietary vitamin C significantly increases the protection against *Aeromonas hydrophila*.

Vitamin E enhances the specific as well as cell mediated immunity in some fishes and in others it has been seen to increase macrophage phagocytosis eg. Channel catfish.

Other immunostimulants used in aquaculture:

Levamisole; it is an antihelminthic drug that is used to treat parasitic, viral and other infections. It has been observed to have immunostimulant property in humans and animals. In fishes it acts by stimulating the lymphokine production, enhancement of cell mediated cytotoxicity, stimulation of phagocytic activity of macrophages and neutrophils.

Lentianan, Schizophyllan and oligosaccharide are also used as immunostimulants and are believed to increase cellular and non-cellular defense mechanism.

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