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Trans generational immune priming in aquaculture-disease combating potential

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Abstract
Transgenerational immune priming in insects has proven to be effective in producing offsprings that have a superior immune system. The studies have also indicated at the possibility of paternal immune priming, where the male transfers its immunity to the offspring. As a result the immune molecules present in the offspring will be specific to not only the microbes that challenged the mother but also to those that immune challenged the father. The aim of this review article is to explore the possible application of transgenerational immune priming (maternal/paternal/bi-parental) in aquaculture as a method to combat disease outbreaks. The studies reviewed in this article conclude that immune priming has led to healthier offsprings in case of pipefish where both paternal and maternal immune priming was observed. Thus Transgenerational immune priming can be used as an alternative method in aquaculture based on the knowledge of exposing the dominant parent to the prevalent infectious threats. This will result in offspring having a better survival rate compared and can also act as a substitute to vaccination.

Keywords: immune priming, paternal trans-generational immune priming, pipefish, acquired immune response, bi-parental immune priming

1. Introduction

Aquaculture is the farming of aquatic organisms in both coastal and inland areas involving interventions in the rearing process to enhance production. Currently around 567 aquatic species are being farmed globally [1]. These represent a wealth of genetic diversity within and among species. Eighty percent of current aquaculture production is derived from herbivorous, omnivorous fish and mollusk [1]. Commonly farmed fishes include carps, catfish, clams, shrimp, salmon, tilapia etc. [2]. Infectious diseases pose one of the most significant threats to successful aquaculture. The aquaculture faces crowding of large population of fish under stressed condition which provides an environment conducive for the spread of infectious diseases. Moreover, the limited water environment facilitates the spread of pathogens within crowded populations (Fig.1). There are two general categories of fish pathogens:

- Indigenous: diseases caused by pathogens that are native to the local environment
- Exotic: pathogens that normally are not found in that geographical area but make into the environment via eggs or fish imported into the area for breeding purposes [3].

The disease causing agents in fish belong to the class of:

- Bacteria- *Pseudomonas fluorescens, Aeromonas hydrophila*, *Edwardsiella tarda*, *Erysipelothrix rhusiopathiae*, *Streptococcus iniae*, *Vibrio sp., Mycobacterium marinum, Salmonellosis, Clostridium botulinum* etc.
- Fungus and molds- *Lagenidium callinectes*, *Lagenidium marina, Saprolegnia* sp., *Serolpidium* sp., *Fusarium* sp.
- Viral- *Rhabdoviridae,* aquabirnavirus, betanodavirus, infectious hematopoietic necrosis virus, salmonid alphavirus, epizootic hematopoietic necrosis virus, infectious salmon anemia virus, viral hemorrhagic septicemia virus etc.
- Parasites- Copepods, *Ichthyophthirius multifiliis*, Nematodes (*Anisakis simplex*, *Pseudoterranova decipiens)*, cestodes (*Diphyllobothrium*) and digenetic trematodes (*Heterophyidae*, *Opisthorchiidae* and *Nanophyetidae*) Eustrongylide etc. [4]

Some of the commonly employed methods to control infections are use of approved drugs and vaccines along with good management practices like sufficient water flow and avoidance of overcrowding. However vaccinations and drugs aren't effective against all types of pathogens due to the emergence of drug resistant species.

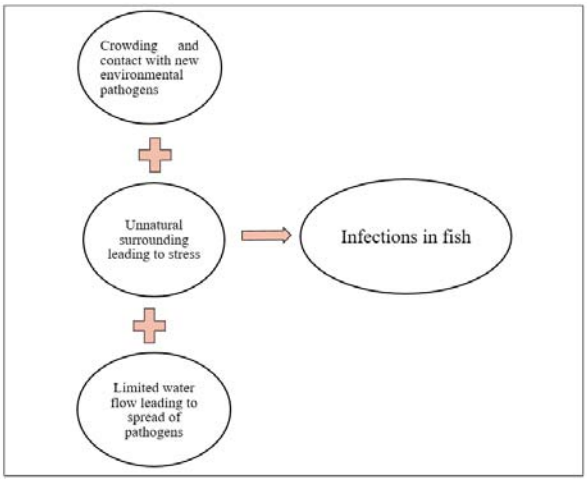

Fig 1: Factors contributing to infections

Some agencies in countries like USA mandate periodic testing of the aquaculture population to ensure that they are disease free. The facility is also tested to ensure there is no pathogen infestation indigenous or exotic. Importation to the area or movement within the area is restricted to fish and fish eggs that have been certified to be free of these pathogens [3]. Invertebrates show immune memory and are more resistant to pathogen infection following previous exposure. This form of memory in an invertebrate is termed as 'immune priming', which is broadly defined as increased protection to a pathogen following previous exposure to a pathogen or an immune elicitor [5-7]. Trans- generational immune priming is the phenomenon in which the offsprings develop immunity against the microbes that immune challenged its parents without actually being exposed to the microbes themselves. While most of these studies focus on maternal transgenerational immune priming, there is now evidence that paternal transgenerational immune priming can occur [9]. Immunostimulants, vaccinations, antibiotics etc. are presently being used for enhancing the immunity of the aquaculture population and decreasing instances of disease in fish. In this article we focus on using Immunomodulation techniques, chiefly immune priming in fish as a possible method to enhance the innate immunity of the aquaculture population [8]. This article investigates the application of maternal and paternal trans-generational immune priming in boosting the immunity of the offspring.

2. Fish Immune System

The fish defense system is basically similar to that described in mammals but there are some physiological differences; the most important one is that in fishes the major lymphoid organs are the head and the kidney as they lack bone marrow and lymph nodes [10, 11]. The immune system is traditionally divided into innate and adaptive/ acquired. However recent studies show that these two systems are not independent of each other [12-15].
The relationship between the two is as follows:
The immune system of fish and mammals are different. Table 1 summarizes some of the differences between mammalian and fish immune system.
It can be concluded from Fig. 2 that the acquired immune response (AIR) depends on the innate immune system i.e. the innate immune system plays a key role in development of the acquired immune response. Table 1 re-iterates the same point that fishes rely more on the innate immune system and their memory response is weak. It can thus be concluded that augmenting the innate immunity of a fish may lead to a higher disease resistance in that fish.

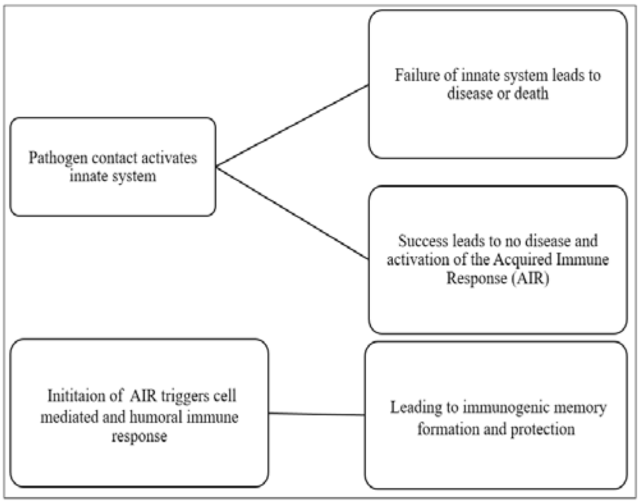

Fig 2: Immune Activation [10].

Table 1: Immune system differences [16].

Features	Fish	Mammal	Conclusion
Ig isotypes	IgM, IgD, IgM, IgA, IgD, IgE, IgG IgM, IgX/IgR, IgW, NAR(C), IgM redox form	IgM, IgA, IgD, IgE, IgG	Fish rely more on innate immunity
Non-specific diversity	Multiple C3 isoforms	No C3 isoforms	Specialization to bind specific surfaces and to increase efficiency to eliminate immunogens in case of fish [17].
Antibody Affinity	Low	High	Mammals have higher immunity
Antibody Response	Slow	Fast	Mammals have a fast responding immune system
Memory Response	Weak	Strong	The adaptive immune system is stronger in mammals compared to fish

3. Immune priming

Increased immune protection following early exposure to bacteria has been found both later in life (within generation priming) and in the next generation (transgenerational priming) in a number of invertebrates. However, it is unclear how immune priming occurs in response to different parasites, including viruses [18].
Transgenerational priming can occur maternally or/and paternally in the case of insects. This process can transfer information from the environment experienced by the parents and can adaptively change their offspring's phenotype without altering its genomic sequence. Therefore, if parasites are

prevalent in the parental environment and offspring are likely to experience the same conditions, the offspring is protected against the same or similar infections from birth itself [19-25].

3.1. Immune priming in insects

The effect of maternal and paternal immune priming was studied in insects by Roth O in 2010. In the study, Red flour beetle (*Tribolium castaneum*) was exposed to two bacteria species, namely *E. coli* (DSM No. 498) and *B. thuringiensis* (DSM No. 2046) and their off springs were studied for immunity to these bacteria [26]. The study population was divided into 2 groups of 4 sub-groups where each group was exposed to one bacteria. The subgroups were as follows:

1- Both sexes were exposed to the bacteria.
2- Male was exposed and female unexposed
3- Female exposed and male unexposed
4- Both sexes unexposed.

The offspring of both the test groups were separated gender wise and were exposed to the bacteria that their parents were exposed to in the initial stage of the study. These offspring were then mated and their offspring were exposed to the same bacteria as their parents. The fertility rate, offspring survival rate, phenol oxidase activity and antimicrobial activity was measured in the offspring to study the extent of priming. Results showed that survival rate was higher in offspring where the parents were exposed to the bacteria to which the offspring were later exposed. Phenol oxidase activity was observed to have been up regulated in the case of offspring from the subgroup where the father was exposed and mother was unexposed in case of *B. thuringiensis*. In case of *E.coli* exposed father, the antimicrobial activity was found to have been down regulated. Fertility was lower in case of offspring where only the father was exposed and mother was unexposed. It was concluded that

1. If maternal immune priming based on transfer of substances via the eggs as has been shown in bumblebees, we could assume this investment to be costly for the female rather than the offspring.
2. Paternal immune priming that is likely to rely on epigenetic changes. Thus the offspring which has to invest would hence likely not induce high costs on the paternal side but mainly for the offspring which consequently have to invest into an up-regulated immune defense.
3. The parasitic experience of both parents transferred can possibly result in offspring better adapted to the local conditions; this would, especially in environmental conditions with high parasitic pressure, improve the fitness of sexually reproducing individuals' significantly.

This study was the first to prove that paternal immune priming also occurs and it has the potential to improve overall health of the offspring [25, 26].

3.2. Immune priming in fish

Maternal immune priming is also observed in birds and fish, however paternal immune priming in fish hasn't been given much thought. To understand immune priming via mother and father in fish it is important to know the modes of reproduction in fish. Table 2 explains the modes of reproduction in fish.

Table 2: Modes of Reproduction in Fish [27, 28].

Mode	Process	Examples	Exposure
Oviparous	1. The females lay the eggs and the males fertilize them by releasing sperm over the eggs. 2. The eggs are laid in a region specific to the species of fish known as the spawning grounds. 3. On hatching the larvae spend the first part of their life as zooplankton and are transported via sea currents to places where they grow into adults. These places are called as a nursery	Herring	The offsprings are exposed to the environments of the spawning grounds and the nursery.
Ovoviviparous (Female bares the offspring)	1. The females retain the eggs in their body. The males bring the sperm into the female's body via a specialized fin in their body. 2. The eggs are retained in the body till the embryo is ready to hatch. 3. The embryo receives all the nutrition via the egg yolk and is not connected to the mother via umbilical cord.	Guppies	The offsprings are exposed to the maternal environment and may or may not be exposed to the paternal environment
Ovoviviparous (Male bares the offspring)	1. The male has a pouch on one side of the body. When it is time to mate the female will deposit eggs into that pouch where it is fertilized. 2. After 45 days the male releases clouds of mini seahorses and mini pipefish from the pouch after which he leaves them alone. 3. It is possible that the female will deposit more eggs into his sack the next day if they mate early in the season the first time	Sea-Horse and pipefish	The offsprings are exposed to the paternal environment. They may or may not be exposed to the maternal environment

In conventional sex role species, female fitness is positively correlated with longevity, whereas males are selected for increasing mating rates. Sexual immune dimorphism suggests that females usually need a greater immune defense than males to efficiently fight parasites and pathogens. Since females play a larger role in reproduction they contribute more to the immune system of the offsprings.

However in species with increased paternal care, these principles may fall. In case of aquatic animals like seahorse it is the male that gives birth to the young. In this case the male has a larger role in reproduction than the female counterpart. With higher paternal investment into offspring like in case of seahorse it is being hypothesized that males may have a greater immune defense. In addition, if offspring are born in paternal environment, paternal trans-generational immune priming will have a stronger influence on the offsprings immune system than the maternal [29].

A study was conducted by Roth *et al.* (2012) to observe the effect of paternal trans-generational immune priming in Pipefish using vibrio bacteria. Groups were created as follows

1- Both sexes were exposed
2- No sex was exposed
3- Only male was exposed
4- Only female was exposed.

Offsprings of these test groups were exposed to the same strain of vibrio bacteria and their response strength was measured by enumeration of immune cells and by measuring mRNA expression levels for specific immune response genes. It was found that the offsprings of group 1 exhibited a strong response to the bacteria. None of the immune parameters tested were affected in offsprings of group 4 but some up regulation was observed in offsprings of group 3.

It was thus concluded that maternal contribution alone is not enough to boost the immune systems of the offsprings. Maternal as well as paternal investment is required to unlock certain characteristics of the immune system which leads to enhanced immunity in the offsprings. The bi -parental investment may lead to activation of some immune cell signaling pathways in the offsprings. Further study needs to be conducted in order to find out parental dependence in development of immune cell signaling pathways in fish Maternal trans-generational immune priming is already studied in fish but not much study has been carried on paternal trans-generational immune priming. Further study on the pipefish model can help unravel the mysteries of male pregnancy and bi parental immune priming.

4. Future research avenues

Since not much is known about the immune system of fish and about parental dependence in development of immunity in offsprings it is important to carry out further studies regarding this paternal trans-generational immune priming in case of oviparous fish must be studied. Once each parent's role in the development of the offsprings immune system is established it will be possible to understand what exactly triggers the immune cell signaling pathway that leads to enhanced immunity in the offsprings against the microbes that immune challenged its parents. Based on this knowledge it is possible to immunize the future offsprings by exposing the dominant parent to the prevalent infectious threats. This will result in offsprings that have a better survival rate compared to their parents. This can act as a substitute to vaccination. This feature can find its application in aquaculture where a lot of money is lost on account of low survival rate of offsprings due to their limited immune system.

Adaptive immunity system of fish and the parental dependence on the development of the same must be researched in order to isolate traits that can be enhanced by treating the maternal or/and paternal contributor. It is possible that fish which invest more on their immune system may face problems in their other systems. It is thus important to study the fertility rate and growth rate of immune primed offsprings.

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