NEW ERA AGRICULTURE MAGAZINE

Trained Immunity in Fish: A New Frontier in Aquaculture Disease Management

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Abstract: -

Disease outbreaks are a major constraint to sustainable aquaculture, causing significant economic losses and threatening global fish production. Conventional disease control strategies, particularly the use of antibiotics, have raised concerns regarding antimicrobial resistance and environmental impacts. In this context, trained immunity has emerged as a promising approach for enhancing fish health and disease resistance. Trained immunity refers to the ability of innate immune cells to develop memory-like responses following exposure to specific stimuli, resulting in enhanced protection against subsequent infections. In fish, immunostimulants such as β-glucans, probiotics, and microbial components have been shown to induce trained immune responses through metabolic and epigenetic reprogramming of innate immune cells. These responses can improve disease resistance, reduce antibiotic dependence, and support sustainable aquaculture practices. Although research in this field is still developing, trained immunity offers considerable potential as an innovative tool for disease prevention and health management in aquaculture, contributing to more resilient and environmentally sustainable fish production systems.

Keywords: *Trained immunity, innate immune memory, epigenetic reprogramming, β-glucans etc.*

Understanding Trained Immunity

The immune system of fish, like that of other vertebrates, consists of two major components: innate immunity and adaptive immunity. Innate immunity serves as the first line of defense and provides a rapid, non-specific response against invading pathogens

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through physical barriers, phagocytic cells, antimicrobial molecules, and inflammatory reactions. In contrast, adaptive immunity is characterized by antigen-specific responses and the ability to develop long-term immunological memory through specialized lymphocytes. Traditionally, immune memory was considered a unique feature of the adaptive immune system, while innate immune responses were thought to be short-lived and incapable of remembering previous encounters with pathogens.

This conventional understanding changed with the discovery of **trained immunity**, a phenomenon in which innate immune cells exhibit an enhanced response following an initial stimulation. Unlike adaptive immune memory, trained immunity does not rely on antigen-specific recognition. Instead, it results from functional reprogramming of innate immune cells, enabling them to respond more efficiently when exposed to subsequent infections, even if the second challenge is caused by a different pathogen (Netea et al., 2016).

The concept of trained immunity was first recognized through studies demonstrating that exposure to certain microorganisms or microbial components could induce long-lasting protective effects that could not be explained solely by adaptive immune mechanisms. Subsequent research revealed that innate immune cells such as macrophages, monocytes, and neutrophils can undergo metabolic and epigenetic modifications that enhance their functional capacity. These changes allow the cells to produce stronger inflammatory responses, increased phagocytic activity, and improved antimicrobial defense upon re-exposure to pathogens (Netea et al., 2020).

In fish, trained immunity has attracted increasing attention due to its potential role in disease prevention. Several studies have demonstrated that exposure to immunostimulants such as β-glucans and microbial products can induce enhanced innate immune responses and improve resistance against infectious diseases. Because trained immunity provides broad-spectrum protection rather than targeting a specific pathogen, it represents a promising strategy for strengthening fish health in aquaculture systems where multiple disease-causing agents may be present simultaneously (Petit & Wiegertjes, 2016; Fink et al., 2021).

The recognition of trained immunity has significantly expanded our understanding of host defense mechanisms and has opened new opportunities for developing sustainable approaches to disease management in aquaculture.

Mechanisms Underlying Trained Immunity

The enhanced protective capacity associated with trained immunity is primarily mediated through long-lasting changes in the functional state of innate immune cells. Unlike adaptive immune memory, which depends on antigen-specific lymphocytes, trained immunity is driven by epigenetic and metabolic reprogramming of innate immune cells such as macrophages, monocytes, and neutrophils (Netea et al., 2020).

Epigenetic reprogramming involves modifications in chromatin structure that alter gene expression without changing the DNA sequence. Following exposure to immunostimulants or microbial components, specific regions of the genome become more accessible for transcription, enabling immune-related genes to be activated more rapidly during subsequent pathogen encounters. As a result, trained immune cells exhibit enhanced production of cytokines, antimicrobial molecules, and other defense factors that contribute to improved pathogen clearance (Netea et al., 2016).

In addition to epigenetic changes, trained immunity is accompanied by significant metabolic alterations. Activated innate immune cells undergo shifts in energy metabolism, including increased glucose utilization and enhanced biosynthetic activity. These metabolic adaptations provide the energy and molecular resources required to sustain stronger immune responses upon re-exposure to pathogens. The interaction between metabolic and epigenetic pathways plays a crucial role in establishing and maintaining trained immune responses (Netea et al., 2020).

Induction of Trained Immunity in Fish

Trained immunity can be induced in fish through exposure to various immunostimulatory agents that activate the innate immune system and promote long-lasting functional changes in immune cells. Among these agents, β-glucans are the most extensively studied. β-glucans are naturally occurring polysaccharides derived from the cell walls of yeast, fungi, and certain plants. They are recognized by pattern recognition receptors (PRRs) on immune cells, leading to activation of macrophages, enhanced phagocytosis, and increased production of antimicrobial molecules. Several studies have demonstrated that β-glucan administration can induce long-lasting protection against bacterial and parasitic infections in fish, suggesting the establishment of trained immune responses (Petit & Wiegertjes, 2016).

Another important group of immunostimulants includes probiotics and prebiotics, which can modulate the gut microbiota and influence host immunity. Beneficial microorganisms such as species of *Lactobacillus*, *Bacillus*, and *Enterococcus* have been reported to enhance innate immune functions and improve disease resistance in cultured fish. Through interactions with immune cells and microbial metabolites, probiotics may contribute to the induction of trained immunity and promote long-term health benefits.

Microbial components known as pathogen-associated molecular patterns (PAMPs), including lipopolysaccharides (LPS), peptidoglycans, and flagellin, can also stimulate trained immune responses. These molecules are recognized by innate immune receptors and trigger signaling pathways that result in immune activation and cellular reprogramming. Experimental studies have shown that prior exposure to such microbial products can enhance the ability of fish to respond to subsequent pathogen challenges.

Studies conducted in zebrafish, common carp, tilapia, and other species have demonstrated that fish exposed to immunostimulants exhibit enhanced survival, stronger innate immune responses, and improved resistance to infectious diseases (Fink et al., 2021). These findings highlight the potential of trained immunity-based interventions as sustainable tools for disease prevention and health management in aquaculture.

Applications and Benefits of Trained Immunity in Aquaculture

The application of trained immunity has emerged as a promising strategy for improving fish health and enhancing the sustainability of aquaculture systems. By strengthening the innate immune system, trained immunity enables fish to mount faster and more effective responses against a wide range of pathogens. Unlike conventional vaccines that provide protection against specific diseases, trained immunity offers broad-spectrum resistance, making it particularly valuable in aquaculture environments where multiple pathogens may coexist (Netea et al., 2016).

One of the most significant benefits of trained immunity is its potential to reduce dependence on antibiotics and chemotherapeutic agents. Excessive use of antibiotics in aquaculture has contributed to the development of antimicrobial resistance, which poses risks to animal health, human health, and the environment. By enhancing the natural defense mechanisms of fish, trained immunity can help prevent disease outbreaks and reduce the need for therapeutic interventions (Reverter et al., 2020).

Trained immunity can also contribute to improved growth performance and survival rates. Healthier fish are better able to utilize nutrients, cope with environmental stress, and resist infections, ultimately leading to enhanced productivity and profitability for farmers. The incorporation of immunostimulants such as β-glucans and probiotics into functional feeds offers a practical and cost-effective method for inducing trained immune responses under commercial farming conditions.

Furthermore, trained immunity aligns well with the principles of sustainable aquaculture. It promotes preventive health management rather than disease treatment, minimizes environmental impacts associated with antibiotic use, and supports the production of healthier aquatic products. As consumer demand for environmentally responsible and antibiotic-free aquaculture products continues to increase, trained immunity-based approaches may become an important component of modern fish farming practices (Fink et al., 2021).

Challenges and Research Gaps

Despite the promising potential of trained immunity in aquaculture, several challenges must be addressed before its large-scale application can be achieved. One of the major limitations is the limited understanding of trained immunity across different fish species. Most studies have been conducted in a few model and commercially important species, while information regarding many cultured fish remains scarce. Since immune responses can vary considerably among species, further research is required to determine the effectiveness and consistency of trained immunity under diverse aquaculture conditions (Fink et al., 2021).

Another important research gap concerns the duration and magnitude of trained immune responses. Although several studies have demonstrated enhanced protection following exposure to immunostimulants, the persistence of these effects and the optimal frequency of stimulation remain unclear. Excessive or prolonged immune activation may also lead to physiological stress and increased energy expenditure, potentially affecting fish growth and overall performance (Netea et al., 2020).

The mechanisms underlying trained immunity in fish are still not fully understood. While epigenetic and metabolic reprogramming have been identified as key drivers, the specific molecular pathways involved require further investigation. Advances in genomics, transcriptomics, and epigenetics will be essential for unraveling these mechanisms and identifying reliable biomarkers of trained immunity.

Future Perspectives

The growing understanding of trained immunity has opened new opportunities for developing innovative and sustainable health management strategies in aquaculture. Future research is expected to focus on identifying potent immunostimulants, optimizing their dosage and delivery methods, and evaluating their effectiveness across different fish species and farming systems. Advances in molecular biology, genomics, transcriptomics, and epigenetics will provide deeper insights into the mechanisms regulating trained immunity and facilitate the development of targeted interventions (Netea et al., 2020).

The integration of trained immunity with functional feeds, probiotics, vaccination programs, and precision aquaculture technologies may further enhance fish health management. The use of immune-monitoring tools and data-driven decision-making systems could help optimize the application of immunostimulants and improve disease prevention strategies at the farm level. Additionally, trained immunity may play an important role in strengthening fish resilience to environmental stressors associated with climate change, including temperature fluctuations and deteriorating water quality.

As the aquaculture industry continues to seek alternatives to antibiotics, trained immunity-based approaches offer considerable potential for promoting sustainable production and improving animal welfare. Continued research and field validation will be essential for translating scientific knowledge into practical solutions that can be adopted by the aquaculture sector on a commercial scale (Fink et al., 2021; Wiegertjes et al., 2024).

Conclusion

Trained immunity represents a paradigm shift in our understanding of fish immune responses and offers a promising approach for disease management in aquaculture. By enabling innate immune cells to develop memory-like characteristics, trained immunity enhances the ability of fish to respond rapidly and effectively to pathogen challenges. Immunostimulants such as β-glucans, probiotics, and microbial components have demonstrated significant potential for inducing trained immune responses and improving disease resistance.

The application of trained immunity can contribute to reduced antibiotic usage, improved fish health, enhanced productivity, and more sustainable aquaculture practices. Although several scientific and practical challenges remain, ongoing research continues to reveal new insights into its mechanisms and applications. With further development and validation, trained immunity has the potential to become an important component of future aquaculture health management strategies, supporting resilient and environmentally sustainable fish production systems.

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