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MANNAN-OLIGOSACCHARIDE TRIGGERS TRAINED IMMUNITY AND MITIGATES LIVER PATHOLOGY IN TURBOT (*SCOPHTHALMUS MAXIMUS*)

Resume

This study investigated the liver-protective effects of mannan-oligosaccharide (MOS) and its role in inducing trained immunity in turbot (*Scophthalmus maximus*). Using an intraperitoneal MOS injection model, we found that MOS-treated fish mounted faster and stronger inflammatory responses upon secondary bacterial infection. MOS administration also triggered significant metabolic reprogramming, including changes in glycolysis, glutamine metabolism, and fatty acid metabolism, accompanied by epigenetic modifications of histones (H3K4me1, H3K4me3, H3K9me3), hallmarks of trained immunity.

Keywords: Mannan-oligosaccharide, trained immunity, turbot, liver injury, bacterial infection, epigenetic modification, metabolic reprogramming

Abstract

The liver is a central immune organ in fish, responsible for multiple physiological and metabolic processes. Pathological liver damage, often caused by bacterial infections, is a frequent issue in aquaculture. Mannan-oligosaccharide (MOS) has emerged as a promising dietary supplement due to its liver-protective effects, yet the underlying mechanisms remain unclear. In this study, we developed a MOS intraperitoneal injection model in turbot (*Scophthalmus maximus*) and observed that MOS-treated fish exhibited a stronger and faster inflammatory response upon secondary bacterial infection. MOS administration also induced significant alterations in metabolic pathways, including glycolysis, glutamine metabolism, and fatty acid metabolism, alongside epigenetic modifications of histones (H3K4me1, H3K4me3, H3K9me3)—hallmarks of trained immunity. Enhanced bacterial clearance in MOS-treated turbot was associated with reduced liver injury and improved histopathology. Overall, our findings suggest that MOS can induce trained immunity in teleost fish, providing protection against liver damage.

Introduction

The liver is a critical immune and metabolic organ in teleost fish, playing essential roles in energy metabolism, immune defense, digestion, and nutrient absorption. Pathogen-induced liver injury is commonly observed in aquaculture and is characterized by inflammation, congestion, and hyperemia. Severe damage can disrupt the liver-gut axis and increase mortality in farmed fish.

Recently, immunostimulants derived from polysaccharides and oligosaccharides have gained attention as alternatives to antibiotics in aquaculture. These compounds have been shown to support liver and intestinal health, enhance immune responses, and improve growth performance. Among these, mannan-oligosaccharide (MOS), extracted from yeast cell walls, has been widely utilized as a dietary immunomodulator. MOS has been reported to enhance growth, improve feed efficiency, strengthen intestinal barrier integrity, and stimulate mucosal immunity in fish. Furthermore, short-term MOS supplementation can provide long-lasting, non-specific protection against pathogens. However, the precise mechanisms mediating this prolonged protection are not fully understood.

Trained immunity represents a form of innate immune memory, distinct from classical adaptive immunity. It can be triggered by stimuli such as β-glucan or Bacille Calmette-Guérin (BCG), resulting in long-lasting enhancement of the immune response upon secondary exposure. Key features of trained immunity include metabolic reprogramming (e.g., elevated glycolysis and lactate production) and epigenetic modifications (e.g., histone methylation or acetylation). Recent studies suggest that trained immunity can also occur in teleost fish, where neutrophils and macrophages exhibit memory-like responses to stimuli. However, whether MOS can induce trained immunity in fish remains unclear.

In this study, we established a MOS intraperitoneal injection model in turbot and challenged the fish with *Edwardsiella piscicida* to assess immune responses and liver protection. Our results demonstrate that MOS induces a trained immunity phenotype, enhancing inflammatory responses and alleviating liver pathology during bacterial infection.

Materials and methods

Turbot (*Scophthalmus maximus*, 30 ± 5 g) were obtained from Tianyuan Corp. and acclimated in aerated tanks with continuous sand-filtered seawater flow at 15 ± 1 °C and a density of 6 kg/m³ for one week. All experimental procedures complied with the guidelines of the Animal Experiment Committee of East China University of Science and Technology (Protocol No. 2006272)MOS derived from yeast cell walls was administered via intraperitoneal injection (100 μL, 1 mg/mL). Seven days post-injection, turbots were exposed to *Edwardsiella piscicida* through immersion to simulate secondary bacterial infection. Inflammatory cytokine

expression, including il-1β, il-6, and tnf-α, was measured at specific time points post-infection.

Discussion

Our findings indicate that MOS is capable of inducing trained immunity in turbot, as evidenced by rapid and robust inflammatory responses upon secondary bacterial exposure. MOS treatment triggered metabolic reprogramming, including enhanced glycolysis and altered amino acid and lipid metabolism, along with epigenetic histone modifications. These changes resemble mechanisms observed in mammalian trained immunity models, suggesting conserved pathways across vertebrates.

Previous studies have shown that β-glucan and BCG can activate trained immunity through Dectin-1 and NOD2 signaling, promoting Akt-mTOR-HIF1α pathways and cytokine production. Similarly, MOS may engage comparable pathways in teleost fish, leading to heightened immune responsiveness and improved pathogen clearance. Importantly, MOS administration not only enhanced bacterial elimination but also mitigated liver damage, highlighting its dual role as an immunostimulant and hepatoprotective agent.

Conclusion

This study demonstrates that MOS can induce trained immunity in turbot, resulting in accelerated inflammatory responses and improved defense against secondary bacterial infections. MOS-induced metabolic and epigenetic reprogramming likely underlies these effects. Moreover, MOS treatment alleviated liver pathology, emphasizing its potential as an immunopotentiator in aquaculture. These findings provide a foundation for further exploration of trained immunity in fish and offer a promising strategy for enhancing fish health without relying on antibiotics.

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