MINI-REVIEW

The interactions between the host immunity and intestinal microorganisms in fish

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Abstract

There is a huge quantity of microorganisms in the gut of fish, which exert pivotal roles in maintaining host intestinal and general health. The fish immunity can sense and shape the intestinal microbiota and maintain the intestinal homeostasis. In the meantime, the intestinal commensal microbes regulate the fish immunity, control the extravagant proliferation of pathogenic microorganisms, and ensure the intestinal health of the host. This review summarizes developments and progress on the known interactions between host immunity and intestinal microorganisms in fish, focusing on the recent advances in zebrafish (*Danio rerio*) showing the host immunity senses and shapes intestinal microbiota, and intestinal microorganisms tune host immunity. This review will offer theoretical references for the development, application, and commercialization of intestinal functional microorganisms in fish.

Key points

● *The interactions between the intestinal microorganisms and host immunity in zebrafish*
● *Fish immunity senses and shapes the microbiota*
● *Intestinal microbes tune host immunity in fish*

Keywords Fish · Immunity · Intestinal microorganisms · Interaction · Probiotics

Introduction

In recent years, the world aquaculture is facing the challenge of increasing production, reducing emissions, and saving energy. Therefore, the aquaculture industry has gradually embarked on the road of intensive development. The problems that come with it are environmental deterioration and frequent outbreaks of diseases, causing huge economic losses every year (Assefa and Abunna 2018). In order to control the occurrence of bacterial diseases in fish, large amounts of antibiotics are used, but the effect is not satisfactory due to increasing antibiotic resistance problems (Liu et al. 2021b). At the same time, high stocking density will greatly decrease water quality, reduce function of intestinal barrier, and impair the intestinal health of aquatic animals

(Sundha et al. 2019). Intestinal health has developed into one of the bottleneck constraints, restricting the healthy and sustainable development of world aquaculture. It is urgent to improve the fish intestinal health through nutritional intervention measures in intensive culture mode.

In the intestine, there exists a large number of commensal microbes (Xue et al. 2020), which provide an excellent microecological environment for fish (Liu et al. 2021a). The gut microbes play an important role in gut development, metabolism, immunity, and host health (Ou et al. 2021; Filardy et al. 2023). Recently, growing numbers of studies have begun to focus on the association of intestinal microorganisms with fish immunity and disease resistance (Xiong et al. 2019; Amenyogbe et al. 2022). Interactions between host and intestinal microbiota are the bases for the development of the immunity (Ruff et al. 2020). The host immune system coevolves with host microorganisms, which are very important to host physiology (Kogut et al. 2020), and mucosal and systemic immunity (Gutierrez et al. 2022). The host immune system monitors intestinal microorganisms, maintains the balance of intestinal microbiota and the health of intestinal mucosa, and thus strengthens

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the resistance to potential pathogens (Kinnebrew and Pamer 2012). The host and microorganisms interact with each other and gradually form a dynamic and stable microecological homeostasis in the gut of fish (Diwan et al. 2023). Therefore, understanding the interactions between the host immunity and intestinal microorganisms is very meaningful for maintaining the fish health.

The field on the interactions between the host immunity and microorganisms in fish is interesting and developing so quickly, and several review papers related to this topic have been published in recent years (Langlois et al. 2021; Yu et al. 2021; Diwan et al. 2023; Wang et al. 2023). In 2021, Yu et al. summarized the microbiome composition of teleost mucosa, commensal bacterial dysbiosis in teleost mucosa, crosstalk between commensals and mucosal innate and adaptive immunity, and probiotics contribute to fish immune response (Yu et al. 2021). In 2021, Langlois et al. summarized the host–microbe interactions and the functions of probiotics in salmonid, including salmonid intestinal microbiome, probiotic-mediated regulation of host health, methods of probiotic encapsulation, and delivery (Langlois et al. 2021). In 2023, Wang et al. reviewed the teleost skin microbiome-host immunity focused on the teleost external surface microbiome, including teleost skin microbiome, its modulation of host physiology and immunity, host immune modulation of skin microbiome, and models of skin microbiome-host interaction (Wang et al. 2023). In 2023, Diwan et al. summarized host-microbiome interaction in fish and shellfish, including host-microbiome interaction in fish and shellfish, manipulation of the gut microbiome, and host-microbiome interaction and aquatic environment (Diwan et al. 2023). However, there still exist huge gaps in knowledge of commensal microorganisms and their functions in fish immunity, the molecular mechanisms of the host immunity that can sense and shape intestinal microbiota. Furthermore, the zebrafish has many advantages to explore host-microbe interactions in fish, but previous reviews have lacked a systematic summary of it. Therefore, to complement previous reviews, we summarize developments and progress on the known of interactions between host immunity and intestinal microorganisms in fish, paying specific attention to recent findings in zebrafish. This review will supply theoretical support for the exploitation and application of intestinal functional microorganisms in aquaculture.

The interactions between the host immunity and intestinal microorganisms in zebrafish (*Danio rerio*)

Zebrafish larvae have an innate immune system, while the functional adaptive immune system is not completed until 4 weeks age (Lam et al. 2004), and the adult zebrafish possess the adaptive immune system (Stream and Madigan 2022). The body of zebrafish is transparent at the stage of embryonic development, the fish gut and morphology can be easily observed with a microscope (Teame et al. 2019). It is feasible to study the innate and adaptive immunity of zebrafish by using different developmental periods of zebrafish. Furthermore, zebrafish has several other unique advantages, the ability to image the intestinal microorganisms colonization in vivo for a long time, and the ability to present different phenotype individuals (Ganz 2018). Therefore, zebrafish have become an ideal model for revealing the interactions between the host immunity and intestinal microorganisms (Teame et al. 2019; Zhang et al. 2020b; Nadal et al. 2020; Jia et al. 2021). The summary of interactions between the host immunity and intestinal microorganisms in zebrafish is shown in Table 1.

In zebrafish, the host immunity can effectively sense intestinal microorganisms, for example, the innate immune system mediates toll-like receptor 2 (TLR2) sensing the intestinal colonization of *Exiguobacterium* and *Chryseobacterium* through negative control of myeloid differentiation factor 88 (MyD88) (Koch et al. 2018). Similarly, MyD88 mutant zebrafish are more sensitive to be infected with pathogenic *Edwardsiella tarda* and *Mycobacterium marinum*, and its pro-inflammatory cytokines interleukin-1 beta (IL-1β), activator protein-1 (AP-1), and nuclear factor kappa-B (NF-κB) are dependent on MyD88 during infections (Vaart et al. 2013). Nucleotide-binding oligomerization domain 2 (NOD2) in zebrafish embryonic fibroblasts can sense the muramyl dipeptide of Gram-negative and Gram-positive bacteria, activate NF-κB signaling, and induce antiviral defense response in spring viremia of carp virus infection (Zou et al. 2016).

The host immunity has a close relationship with the gut microbiota in zebrafish, when zebrafish are infected by *Aeromonas hydrophila*, the innate immune response is activated and correspondingly, the intestinal microbial structure is changed, i.e., the proportions of beneficial microorganisms such as *Nitratireductor*, *Enterococcus*, and *Brevundimonas* decrease, while the proportions of harmful microorganisms such as *Halomonas*, *Pelagibacterium*, and *Aeromonas* increase (Yang et al. 2017). When the early adaptive immunity in wild-type zebrafish has not been established, pathogenic *Vibrio* overgrows in the gut. For example, recombination activating gene 1 (Rag1)-deficient zebrafish lack adaptive immunity and have high abundance of *Vibrio* in the intestine, but transferring T lymphocytes rather than B lymphocytes to Rag1-deficient zebrafish can inhibit the growth of intestinal *Vibrio* (Brugman et al. 2014). The intestinal microbiota of 61 rag^{1-} zebrafish (adaptive immunity deficiency, lacking B and T cell receptors) and 68 wild-type zebrafish (functional adaptive immunity) were surveyed to analyze the function of adaptive immunity on

Table 1 The summary of interactions between the host immunity and intestinal microorganisms in zebrafish

Item	Interactions	Source
Host immunity senses gut microbiota		
1	Innate immune system mediated TLR2 sensing *Exiguobacterium* and *Chryseobacterium* through negative control of MyD88	Koch et al. 2018
2	MyD88 mutant zebrafish are more sensitive to pathogenic *Edwardsiella tarda* and *Mycobacterium marinum*, and its pro-inflammatory cytokines expressions are dependent on MyD88 during infections	Vaart et al. 2013
3	NOD2 can sense the MDP of Gram-negative and Gram-positive bacteria, activate NF-κB signaling, and induce antiviral defense response in spring viremia of carp virus (SVCV) infection	Zou et al. 2016
Host immunity shapes the intestinal microbiota		
1	Rag1-deficient zebrafish lack adaptive immunity and have high abundance of intestinal *Vibrio*, but transferring T lymphocytes rather than B lymphocytes to fish can inhibit the growth of intestinal *Vibrio*	Brugman et al. 2014
2	The intestinal microbiota is shaped by intestinal macrophages through IRF8. A reduced number of macrophages was showed with the decreased amounts of *Fusobacteria*, *α-Proteobacteria*, *γ-Proteobacteria*, and the increased amount of *δ-Proteobacteria*	Earley et al. 2018
3	The adaptive immunity makes the intestinal microbiota more personalized	Stagaman et al. 2017
4	When zebrafish are infected by *Aeromonas hydrophila*, the innate immune response is activated and correspondingly, the proportions of beneficial microorganisms such as *Nitratireductor*, *Enterococcus*, and *Brevundimonas* decrease, while the proportions of harmful microorganisms such as *Halomonas*, *Pelagibacterium*, and *Aeromonas* increase	Yang et al. 2017
Intestinal microbes tune host immunity		
1	Intestinal symbiotic microorganisms launch innate immunity through TLRs and MyD88 signaling	Galindo-Villegas et al. 2012
2	*Lactobacillus rhamnosus* could upregulate the expressions of TNF-α, IL-1β, and Becn-1	Gioacchini et al. 2014
3	*Pseudomonas aeruginosa* can induce NF-κB and attenuate the expressions of both SAA and CFB	Kanther et al. 2011
4	*Exiguobacterium* and *Chryseobacterium* regulated the intestinal immune system, decreased the amounts of macrophages, and increased the amounts of neutrophils	Koch et al. 2018
5	*Streptomyces* sp. SH5 could enhance the immune responses and increase the expressions of TLR3, LZM, and NOS2α	Liang et al. 2022
6	*Bacillus amyloliquefaciens* R8 increased the expressions of IL-1β, IL-6, IL-21, TLR1, TLR3, TLR4, and TNF-α, and enhanced the innate immunity	Lin et al. 2018
7	Intestinal microbiota can reduce the expression of suppressor of cytokine signaling-3 and increase the expressions of innate immune-related genes, such as SAA1, CRP, C3, A4, MPO, and GSH-Px	Rawls et al. 2004; Rawls et al. 2007
8	*Bacillus subtilis* WB800N can promote the expressions of TNF-α, IL-10, BF, IL-1β, SAA, and MyD88	Tan et al. 2019a
9	*Lactobacillus plantarum* ST-III enhanced the expressions of immune genes TNF-α, IL-1β, NF-κB, TLR4α, LZM, and IL-10	Zang et al. 2019

the intestinal microbiota. It was found that the existence of adaptive immunity makes the intestinal microbiota of the zebrafish more personalized, but this may be influenced by other conditions, including transmission of microorganisms among hosts (Stagaman et al. 2017). The intestinal microbiota is shaped by intestinal macrophages through interferon regulatory factor 8 (IRF8) in zebrafish. A reduced number of macrophages was showed with reduced expressions of complement genes c1ql, c1qa, c1qb, and c1qc, and severely dysfunctional intestinal symbiotic microbes, *Fusobacteria*, *α-Proteobacteria*, and *γ-Proteobacteria*, decreased, while *δ-Proteobacteria* increased in IRF8-deficient adult zebrafish (Earley et al. 2018).

Studies using specific microorganisms to colonize gnotobiotic zebrafish have shown that symbiotic microorganisms are important for the activation and development of immunity (Murdoch and Rawls 2019; Rawls et al. 2004, 2007). In zebrafish, the intestinal immune system was regulated by *Exiguobacterium* and *Chryseobacterium*, with the amounts of macrophages decreased and the amounts of neutrophils increased (Koch et al. 2018). In transparent gnotobiotic zebrafish, the colonization of *Pseudomonas aeruginosa* was enough to induce NF-κB and attenuate the expressions of both serum amyloid A (SAA) and complement factor B (CFB) (Kanther et al. 2011). Gnotobiotic zebrafish studies show that intestinal microbiota can downregulate the expression of suppressor of cytokine signaling-3 (Rawls et al. 2004) and upregulate the expressions of innate immune-related genes, such as SAA1, C-reactive protein, complement component 3 (C3), angiogenesis 4, myeloperoxidase, and glutathione peroxidase (Rawls et al. 2004, 2007). Intestinal symbiotic microorganisms colonize the gut of newly hatched zebrafish, then launch innate immunity through TLRs and MyD88 signaling (Galindo-Villegas et al. 2012). *Bacillus subtilis* WB800N can promote the expressions of tumor necrosis factor-α (TNF-α), IL-10, CFB, IL-1β, SAA, and MyD88 in gnotobiotic zebrafish (Tan et al. 2019a). Probiotic *Lactobacillus rhamnosus* could upregulate the expressions of TNF-α, IL-1β, and Beclin-1 in the gut of adult zebrafish (Gioacchini et al. 2014). Probiotic *Lactobacillus plantarum* ST-III enhanced the expressions of immune genes TNF-α, IL-1β, NF-κB, TLR4α, lysozyme, and IL-10, increased the diversity of gut microbiota, and attenuated the toxic impacts of triclosan through intestinal microbiota modulation in zebrafish (Zang et al. 2019). *Bacillus amyloliquefaciens* R8 increased the expressions of IL-1β, IL-6, IL-21, TLR1, TLR3, TLR4, and TNF-α and enhanced the innate immunity of zebrafish (Lin et al. 2018). *Streptomyces* sp. SH5 could enhance the immune responses and increase the expressions of TLR3, lysozyme, and nitric oxide synthase 2α in zebrafish (Liang et al. 2022). Through the above studies in zebrafish, we can initially obtain some basic information about the complex interactions of host immunity and

intestinal microorganisms, which give us some reference in commercial fish species.

Host immunity senses gut microbiota

Under evolutionary selective forces, fish have formed innate immunity and an adaptive immune system consisting of B cells and T cells to distinguish opportunistic and commensal microorganisms (Yu et al. 2021). The host immune system exerts a vital function in the recognition and resistance to the invasion of pathogenic microorganisms (Liu et al. 2020b; Lv et al. 2020). The immune mucus layers of intestine, skin, and gill are rich in a large number of immune cells (including lymphocytes, plasma cells, goblet cells, granulocytes, macrophages, and antibody secretory cells) and immune effectors (including lectins, mucins, antimicrobial peptides, and immunoglobulin (Ig)), all of which jointly resist the invasion of pathogenic bacteria (Shephard 1994).

Except for extracellular metabolites, the structural components of microbial cells, especially the cell wall components, are the top layer positions that host immune cells first get in touch with and modulate immune activities (Chapot-Chartier et al. 2010). Host immune cells sense gut microorganisms through pattern recognition receptors (PRRs), which can recognize several microbe-associated molecular patterns (MAMPs), including lipopolysaccharide (LPS), microbial nucleic acid, peptidoglycan (PGN), and flagellin (Lazado and Caipang 2014), and differentially regulate downstream expression of immune molecules and maintain intestinal homeostasis. The host PRRs are microbial sensing elements that have evolved in company with symbiotic commensal microbiota and pathogens, so a similar mechanism might exist in the host immune system sensing gut beneficial microorganisms and pathogens (Murdoch and Rawls 2019). Currently, TLRs, NOD-like receptors (NLRs), C-type lectin receptors (CLRs), and peptidoglycan recognition proteins (PGRPs) are the four PRRs which were found in fish (Boltana et al. 2011).

TLRs are the most largely researched PRRs in fish, which play an important role in identifying the unique molecular patterns of microbes and modulating the innate and adaptive immune system. Fish TLRs can identify pathogen-associated molecular patterns (PAMPs), such as PGN, lipophosphoric acid (LTA), flagellin components, and LPS, activating the downstream expressions of cytokines and immune effector molecules (Ribeiro et al. 2010). For example, *Staphylococcus aureus*-derived PGN activates the expressions of MyD88, TLR2, TNF receptor-associated factor 6, IL-8, and NF-κB in heart cells of *Labeo rohita*, suggesting that TLR2-mediated microbial recognition may depend on MyD88 (Samanta et al. 2012). Recent researchers have found that fish TLRs can mediate immune system

recognizing commensal microbes (Sun et al. 2014). Our previous research showed that live autochthonous *Psychrobacter* sp. SE6 could increase intestinal TLR2, TLR5, MyD88, transforming growth factor-β1 (TGF-β1), IL-1β, and IL-8 expressions in *Epinephelus coioides*, while heat-inactived SE6 only increased the TLR2 expression but did not significantly change the expressions of cytokines and MyD88. This suggests that the intestinal TLR2 signaling pathway is associated with the recognition of *Psychrobacter* sp. SE6, as a probiotic recognition mechanism might be independent of MyD88 (Sun et al. 2014). Hence, there may be some differences in the recognition mechanism of different symbiotic microorganisms based on TLRs in different fish species.

NLRs have crucial functions in identifying fish pathogens and activating innate immune signaling pathways. Studies have demonstrated that fish NLRs can recognize microbial ligands and perceive PAMPs or G-D-glutimyl-meso-diaminopimelic acid (iE-DAP) to activate downstream molecular pathways (Bi et al. 2017). The in vivo and in vitro studies have showed that bacteria or viruses can induce the expression of multiple NLR subfamily receptors in teleost, including NLR-X1, NLR-C3, NLR-C5, NOD1, and NOD2 (Zhang et al. 2018). When Indian major carp (*Cirrhinus mrigala*) were infected with pathogenic *Streptococcus uberis* and *A. hydrophila*, the NOD1 and NOD2 signaling were activated, and the downstream effector molecules IL-1β, IL-8, and interferon-γ (IFN-γ) were induced (Swain et al. 2013). The above studies suggest that NLRs may also play important functions in fish intestinal microbial recognition and immune regulation.

CLRs are produced by dendritic cells, which can recognize microbial antigens and deliver antigen information to T and B lymphocytes, thereby triggering multiple immune responses. It is found that the CLR of tilapia (*Oreochromis niloticus*) is homologous to mammalian natural killer cell receptor (Kikuno et al. 2004). The expression of C-type lectin (Ctl) molecules in gills, spleen, liver, and head kidney was increased significantly after Poly (I: C) and *A. hydrophila* challenge in Qihe crucian carp (*Carassius auratus*) (Wang et al. 2017). In carp (*Cyprinus carpio*) macrophages, CLR receptors can recognize β-dextran and mediate immunomodulatory effects (Petit et al. 2019). However, as far as we know, there are no reports about gut microbes sensed by fish CLRs, which needs further investigation.

PGRPs are the PRRs of the innate immune system and can particularly sense PGN, a peculiar component of the microbial cell wall (Hu et al. 2020). On the basis of the length of the amino acid sequence, PGRPs could be classified into short-PGRPs, intermediate-PGRPs, and long-PGRPs. PGN is an important molecule of the microbial cell wall, including Lys type (L-lysine) and Dap type (diaminoheptanedioic acid), with the PGN in Lys type mainly existing in the cell wall of Gram-positive microbes, while

PGN in Dap type being the main cell wall element of Gram-negative bacteria (Royet and Dziarski 2007). In grass carp (*Ctenopharyngodon idella*), PGRPs can recognize pathogenic *Edwardsiella tarda* by combining bacterial PGN in Lys and Dap types (Li et al. 2014). In rainbow trout (*Oncorhynchus mykiss*), the PGRP negatively regulates the NODs-mediated antimicrobial immune response (Jang et al. 2016), which suggests that, in sensing microbes, different PRRs families also interact with each other.

The sensing of gut microorganisms by the fish intestinal immune system is summarized in Fig. 1. The immune cells sense gut microorganisms through PRRs (TLRs, NLRs, CLRs, and PGRPs), which can recognize MAMPs of microorganisms. Fish TLRs are able to recognize PAMPs, such as LTA, PGN, LPS, and flagellin components. Fish NLRs can recognize PAMPs or iE-DAP, CLRs can recognize microbial antigens, and PGRPs can specifically recognize PGN. The recognition of microorganisms by immune system would further regulate downstream signaling pathways, like mitogen-activated protein kinase (MAPK) or the NF-κB signaling pathway, and activate the downstream expression of cytokines and immune effector molecules.

Host immunity shapes the intestinal microbiota

The immunity of fish consists of innate and adaptive immunity, which are interconnected to clear harmful substances and pathogens, and maintain host health (Fadel et al. 2018). Studies indicate that innate immunity can regulate microbial composition (Cao et al. 2021), i.e., improving the abundance of beneficial microbes and controlling harmful microbes in the intestine of fish (Thaiss et al. 2016). The immunity and intestinal microbes are intimately connected in fish, and in the first part of this review, we have summarized the zebrafish immunity in shaping the intestinal microbiota. Except for zebrafish, the relationships between immunity and gut microbes are also very close in other fish species. Immune responses were closely associated with intestinal microbes in sea cucumber (*Apostichopus japonicus*), the activities of alkaline phosphatase and lysozyme were strongly correlated with *Shewanella*, while the lectin expression levels were significantly negatively associated with *Flavirhabdus* (Song et al. 2019). The increased expression levels of intestinal IFN-induced helicase C domain containing protein 1, TNF-α, IL-1β, and major histocompatibility complex-1 were accompanied by the reduced relative abundances of *Sphingomonas* and *Listonella* and the enhanced relative abundances of *Akkermansia*, *Faecalibacterium*, and *Bifidobacteium* in turbot (*Scophthalmus maximus*) (Guo et al. 2022). In golden pompano (*Trachinotus ovatus*), the enhanced immunity (decreasing epithelial lymphocyte
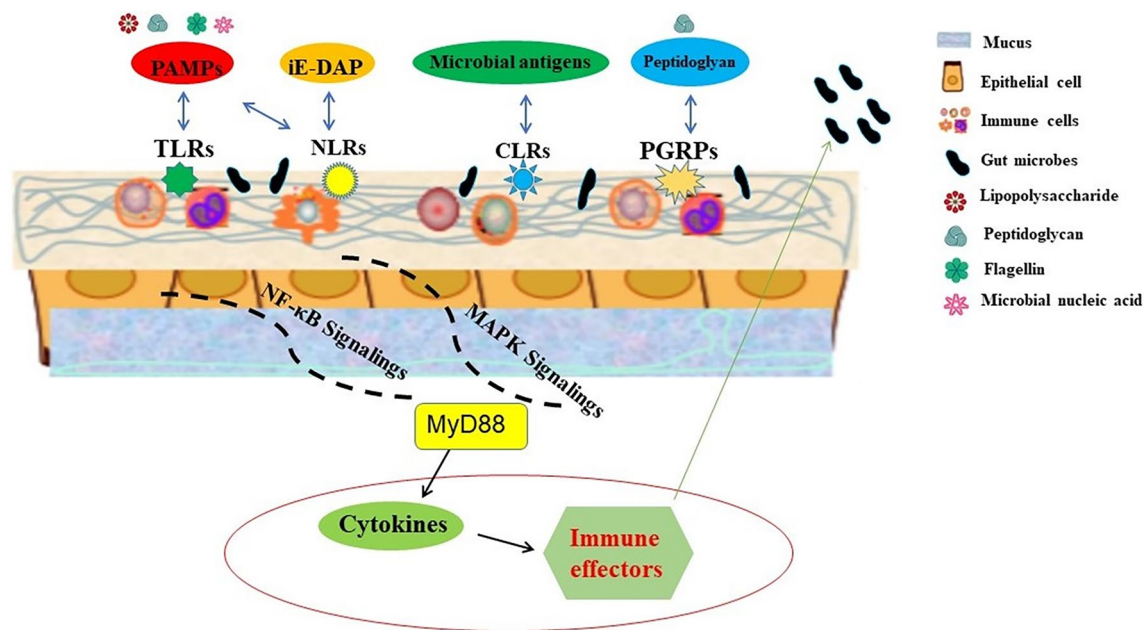
Fig. 1 The fish intestinal immune system senses gut microorganisms. The immune cells sense gut microorganisms through PRRs (TLRs, NLRs, CLRs, and PGRPs), which can recognize MAMPs of microorganisms. Fish TLRs are able to recognize PAMPs (LTA, PG, LPS, and flagellin). Fish NLRs can recognize PAMPs or iE-DAP, CLRs can recognize microbial antigens, and PGRPs can specifically recognize PG. The recognition of microorganisms by immune system would further induce downstream signaling pathways, like MAPK or the NF-κB signaling pathway, then activate the downstream expressions of cytokines and immune effector molecules

numbers and increasing intestinal goblet cells numbers) was accompanied by the improved diversity and richness of gut microbiota, with the relative abundance of harmful microbial taxa decreased, and the abundance of *Firmicutes* and *Actinobacteria* increased (Tan and Sun 2020).

The host immune system exerts key functions in the intestinal homeostasis of homoiothermic animals, and it can shape the microbial structure through the IgA (Petersen et al. 2019). Secretory immunoglobulin A (sIgA), an element of the adaptive immune system, is a vital protector of intestinal epithelial health, and an important factor of intestinal microbiological regulation (Dollé et al. 2016). The host secretes large amounts of IgA into the intestinal cavity, which either react extensively with microorganisms in low affinity or relatively react specifically with microorganism in high affinity, and in some cases binds to several common motifs of bacteria (Lynch and Hsiao 2019). Teleost fish has mucosal IgT, which can recognize mucosal symbiotic microorganisms and bind to their surfaces, playing a similar function as mammalian sIgA in the anti-infection process of parasitic and bacterial pathogens (Xu et al. 2016). Fish lacking IgT are highly sensitive to mucosal parasites and cannot produce compensatory IgM responses in rainbow trout. After the mucosal microbiota was disturbed, the amounts of conditional pathogenic microbes (such as *Bacteroidetes*) increased significantly, the surface microbes translocated, and eventually caused tissue lesions and inflammatory reactions. With

the recovery level of secretory IgT, the proportion and type of IgT-coated microorganisms returned to normal level in mucosal tissue (Xu et al. 2020). This study reveals for the first time that like sIgA in mammalian, fish IgT plays an important role in maintaining intestinal mucosa immunity and microbial homeostasis.

Intestinal microbes tune host immunity

Although zebrafish is recognized as an ideal model for studying host immunity and microbial interaction, most of the current information about intestinal microbes regulating host immunity in fish are from the studies using host-derived intestinal microbes (Table 2). In common carp (*Cyprinus carpio*), commensal *Enterococcus casseliflavus* (EC-001) could significantly improve the immunity, with increased serum total protein (TP), Ig and C3 contents, and skin mucus protease activity (Akbari et al. 2021). In African catfish (*Clarias gariepinus*), host-derived *Lactobicillus plantarum* promoted the immune system, with improved levels of blood parameters, such as hemoglobin and pack cell volume, and white blood cells (Nwanna and Tope-Jegede 2017). In Nile tilapia (*Oreochromis niloticus*), host-derived *Lactobacillus plantarum* N11 and *Bacillus velezensis* H3.1 could promote mucosal and serum immunities, and enhance the serum lysozyme activity (Doan et al. 2018). Three

Table 2 The summary of commensals modulating immune responses in fish

Fish species	Intestinal microorganisms	Immune functions	Source
Clarias gariepinus	Lactobacillus plantarum	Improve levels of blood parameters, such as pack cell volume and hemoglobin, and white blood cells	(Nwanna and Tope-Jegede 2017)
Ctenopharyngodon idellus	Citrobacter freundii GC01	Upregulate many complement system genes, including c3, c4, c5, c7, c8a, c8b, and c1s, trigger the host's innate mucosal immune system	(Xiong et al. 2020)
Cyprinus carpio	Enterococcus casseliflavus EC-001	Increase serum total protein, immunoglobulin content, skin mucus protease, and complement component 3 activity	(Akbari et al. 2021)
Dicentrarchus labrax	Vibrio lentus	Modulate NF-κB pathway and upregulate the downstream molecules	(Schaeck et al. 2017)
Epinephelus coioides	Psychrobacter sp. SE6	Activate the expressions of cytokines (IL-1, IL-8, and TGF-1) and genes in TLR signaling pathways (TLR2, TLR5, MyD88) in the intestinal tract	(Sun et al. 2014)
	Enterococcus faecium MM4 and Lactococcus lactis MM1	Increase serum complement component 3 (C3) levels	(Sun et al. 2012)
	Bacillus clausii DE5 and Bacillus pumilus SE5	Increase leucocyte phagocytic activity, serum lysozyme activity, and serum complement C3 and C4 levels	(Sun et al. 2010)
Gadus morhua	Pseudomonas sp. GP21 and Psychrobacter sp. GP12	Upregulate the expressions of IL-1β and IL-8 in the head kidney leukocytes	(Lazado et al. 2010)
Lateolabrax japonicus	Lactococcus petauri LF3 and Bacillus siamensis LF4	Increase the serum lysozyme activity, downregulate expressions of IL-1β, TNF-α, and IL-8. Upregulate expression of TGF-β1 in the gut	(Yang et al. 2021, 2022b)
Oncorhynchus mykiss	Bacillus subtilis AB1	Stimulate both cellular and humoral immune responses, increase the number of leucocytes, enhance serum phagocytic activity and lysozyme activity	(Newaj-Fyzul et al. 2007)
Oncorhynchus mykiss	Carnobacterium maltaromaticum B26 and Carnobacterium divergens B33	Increase the expressions of TNF-α, TGF-β, IL-1β, and IL-8 in the head kidney	(Kim and Austin 2006)
Oreochromis niloticus	Bacillus velezensis H3.1 and Lactobacillus plantarum N11	Promote mucosal and serum immunity, enhance the serum lysozyme activity	(Doan et al. 2018)
	Bacillus velezensis TPS3N, Bacillus amyloliquefaciens TPS17, and Bacillus subtilis TPS4	Promote the intestinal and skin mucosal immunities, with high LZM, NO, AKP, and IgM activities	(Kuebutornye et al. 2020)
	Rummeliibacillus stabekisii	Elevate expressions of the cytokine genes IL-1β, TNF-α, TGF-β, and hsp 70 in the head kidney	(Tan et al. 2019b)
Paralichthys olivaceus	Lactobacillus plantarum FGL0001	Upregulate gene expressions of IL-6, IL-8, and TNF-α in the intestinal tract	(Beck et al. 2015)
Rachycentron canadum	Pantoea agglomerans RCS2	Upregulate the expressions of IL-1β, TNF-α, and IL-8 in the intestinal tract	(Amenyogbe et al. 2022)
Salmo trutta	L. lactis subsp. lactis CLFP 100 and Leuconostoc mesenteroides CLFP196	Increase the serum complement activity and lysozyme activity Increase the phagocytic activity of the head kidney leukocytes	(Balcázar et al. 2006, 2007, 2009)
Sebastes schlegelii	Bacillus sp. KRF-7	Increase the expressions of IL-10, NF-κB, and B cell activating factors in both the kidney and spleen	(Jang et al. 2021)
Trachinotus ovatus	Bacillus pumilus A97	Improve non-specific immune responses and promote TLR8 expression in the intestinal tract and TLR9 expression in the kidney	(Liu et al. 2020a)

host-associated *Bacillus* species, *Bacillus velezensis* TPS3N, *Bacillus amyloliquefaciens* TPS17, and *Bacillus subtilis* TPS4, were proved to significantly promote the intestinal and skin mucosal immunities of Nile tilapia (*O. niloticus*), with higher lysozyme, alkaline phosphatase activities, and nitric oxide and IgM contents (Kuebutornye et al. 2020). The host-derived *Lactococcus lactis* MM1 and *Enterococcus faecium* MM4 were proved to regulate the immune function and increase serum C3 levels in grouper *E. coioides* (Sun et al. 2012). Isolated from the intestinal tract of the healthy rainbow trout (*O. mykiss*), *Bacillus subtilis* AB1 can activate both humoral and cellular immune responses, increase the number of leucocytes, and enhance serum phagocytic activity and lysozyme activity (Newaj-Fyzul et al. 2007). Isolated from the intestine of *Trachinotus ovatus*, *B. pumilus* A97 could improve the host immune function, promote non-specific immune responses and intestinal TLR8 and TLR9 expressions in the kidney, and enhance the disease resistance (Liu et al. 2020a). Isolated from the intestine of grass carp (*Ctenopharyngodon idellus*), *Citrobacter freundii* GC01 triggers the natural mucosal immune system, induces the increasing expressions of immune system genes, such as c1s, c3, c4, c5, c7, c8a, and c8b, significantly reduces the α- and β-diversity of intestinal microbiota, and improves the relative abundance of *Pasteurellales*, *Enterobacteriales*, *Citrobacter*, and *Neisseriales* in grass carp (Xiong et al. 2020). *L. lactis* CLFP100 and *Leuconostoc mesenteroides* CLFP196 were isolated from the intestinal tract of brown trout (Balcázar et al. 2006), and they could enhance fish serum complement content and lysozyme activity (Balcázar et al. 2007) and activate head-kidney phagocytes (Balcázar et al. 2009). Our research group isolated *B. clausii* DE5 and *B. pumilus* SE5 from the gut of juvenile grouper (*E. coioides*) (Sun et al. 2013). The two probiotics can promote the immune function of grouper, with serum lysozyme activity, leucocyte phagocytic activity, and serum complement C3 and C4 levels increased significantly (Sun et al. 2010). The function of *Bacillus pumilus* SE5 is independent to its viability, as both heat-inactivated *B. pumilus* SE5 (Yan et al. 2016) and live *B. pumilus* SE5 (Yang et al. 2014) could improve the immunity of grouper (*E. coioides*). Our study group also demonstrated that commensal *Psychrobacter* sp. SE6 can regulate intestinal immunity and maintain the balance of intestinal microbiota in grouper (Sun et al. 2014), and commensal *Lactococcus petauri* LF3 and *Bacillus siamensis* LF4 can significantly increase the activity of serum lysozyme (Yang et al. 2021) and regulate the intestinal immunity and microbial structure in Japanese seabass (*Lateolabrax japonicus*) (Yang et al. 2022a, 2022b). It can be concluded that the host-derived beneficial microbes can regulate fish intestinal immune function, control the excessive proliferation of intestinal pathogens, and maintain the intestinal microbial homeostasis.

Cytokines are key signaling molecules for information transmission between cells and are important molecules regulating the immune cascades after the fish intestinal tract has been exposed to different microorganisms. Host-derived beneficial microbes can regulate the expression of gut pro-inflammatory cytokines, such as IL, IFN, and TNF, and anti-inflammatory cytokines, such as TGFs. Isolated from the gut of healthy Atlantic cod, live and heat-inactivated *Pseudomonas* sp. GP21 and *Psychrobacter* sp. GP12 could promote the expressions of IL-1β and IL-8 in the head kidney leukocytes of Atlantic cod (Lazado et al. 2010). *Carnobacterium divergens* B33 and *C. maltaromaticum* B26 are isolated from the intestinal tract of rainbow trout, and they can regulate the expressions of TNF-α, TGF-β, IL-1β, and IL-8 in the head kidney of rainbow trout (Kim and Austin 2006). Isolated from the gut of cobia (*Rachycentron canadum*), *Pantoea agglomerans* RCS2 could upregulate the expressions of IL-1β, TNF-α, and IL-8 in the gut of juvenile cobia (Amenyogbe et al. 2022). Isolated from the intestinal tract of Nile tilapia (*O. niloticus*), *Rummeliibacillus stabekisii* could significantly elevate expressions of the cytokine genes, like heat shock protein 70, TNF-α, IL-1β, and TGF-β in the head kidney of Nile tilapia (Tan et al. 2019b). Isolated from the intestinal tract of olive founder (*Paralichthys olivaceus*), *Lactobacillus plantarum* FGL0001 could significantly upregulate the expressions of TNF-α, IL-6, and IL-8 in the intestinal tract of olive founder (Beck et al. 2015). Isolated from the intestinal tract of Japanese seabass, *L. petauri* LF3 and *B. siamensis* LF4 could significantly reduce the expressions of TNF-α, IL-8, and IL-1β and increase the expression of TGF-β1 in the intestine of Japanese seabass (Yang et al. 2022b).

The intestinal microbes can sense fish PRRs and regulate the expressions of cytokines, then modulate the expressions of key molecules in downstream signaling pathways. Isolated from clinically healthy European seabass (*Dicentrarchus labrax*) larvae, probiotic candidate *Vibrio lentus* can modulate NF-κB pathway and upregulate the downstream molecules NF-κB inhibitor zeta and tyrosine-protein phosphatase non-receptor type 22 in sea bass (Schaeck et al. 2017). Isolated from the gut of rockfish (*Sebastes schlegelii*), *Bacillus* sp. KRF-7 was found to increase the expressions of NF-κB, IL-10, and B cell activating factors in both the kidney and spleen in rockfish (Jang et al. 2021). Our group demonstrated that *B. pumilus* SE5 originated LTA and PGN could enhance the intestinal imunity of grouper (*E. coioides*) by regulating the TLRs/MyD88 signaling (Yang et al. 2019). Based on the above studies, we postulate that fish intestinal microbes may modulate host immunity through TLRs/MyD88/NF-κB and MAPK signaling pathways, but more data are needed to clarify this.

Intestinal commensal bacteria could secrete many metabolites and nutrients, which can be involved in the

development, maturation, function, and homeostasis of the immune system (Brestoff and Artis 2013). In rainbow trout (*O. mykiss*), administration of the shingolipids produced by *Flectobacillus major* can change the percentage of IgT⁺ to IgM⁺ B cells in the head kidney and regulate the mucosal homeostasis (Sepahi et al. 2016). Microorganisms within the *Firmicutes* phylum can generate short-chain fatty acids (SCFAs) that can offer energy for the intestinal mucosal cells (Koh et al. 2016). Adding SCFAs to the diets has beneficial functions by improving the immune systems in aquatic animals (Tran et al. 2020). SCFAs can increase intracellular bactericidal activity of head kidney macrophages via hypoxia inducible factor-1α in turbot (*Scophthalmus maximus* L.) (Zhang et al. 2020a). It is demonstrated that butyrate (0.2%) activated the expressions of IL-1β, IL-6, IL-8, IL-10, and TNF-α in European seabass (*Dicentrarchus labrax* L.) (Rimoldi et al. 2016). Besides secretory metabolites and nutrients, bacterial cell components such as bacterial DNA, LPS, PGN, and LTA have been confirmed as promising immunostimulants in fish (Giri et al. 2018). LPS could activate the innate immune system (O'Hagan et al. 2001), enhance the antibody level (Ackerman et al. 2000; Selvaraj et al. 2006), and induce the expressions of pro-inflammatory cytokines and acute-phase proteins in fish (Swain et al. 2008). Our group demonstrated that commensal *Bacillus pumilus* SE5-derived LTA and PGN could increase the expressions of MyD88, TLR1, TLR2, and TLR5, upregulate the expressions of antimicrobial effectors, and modulate the microbial composition in the intestine of grouper (*E. coioides*) (Yang et al. 2019).

Crosstalk between probiotics, intestinal immunity, and microbiota

Probiotics can improve the activities of the cytokines and innate immune cells on the surface of fish intestinal mucosa, control the proliferation of conditioned pathogens, and effectively prevent disease onset (Fazle Rohani et al. 2022). Also, probiotics can regulate the innate and adaptive immunity of fish, and then establish the correlation between intestinal and systemic immunity of fish by shaping microbial structure. Probiotics can regulate the fish microbiota in the three major mucosal tissues, namely, intestinal-associated lymphoid tissue, gill-associated lymphoid tissue, and skin-associated lymphoid tissue, thus exerting local immune effects (e.g., intestinal immunity) and systemic immune effects (e.g., cellular and humoral immunity) (Lazado and Caipang 2014).

By supplying significant signals for the development and maintenance of the immune system, a healthy microbiota has an important function in host immunophysiologic regulation (Salminen et al. 2005). The intestinal microbial composition in healthy fish is in a dynamic balance, and

the pathogens are surveilled and their amounts are being controlled at an appropriate level. However, the intestinal microbial dysbiosis may disrupt immunomodulatory networks, which are closely related with gut inflammation and other immune-mediated diseases (Maynard et al. 2012). For example, *Vibrio harveyi* colonized in the liver led to a gut-liver immune response and substantially disrupted the intestinal microbiota balance of the pearl gentian grouper (*Epinephelus lanceolatus* ♂ × *E. fuscoguttatus* ♀), with the amounts of *Photobacterium* and *Vibrio* increased and the amounts of *Lactobacillus*, *Blautia*, *Bradyrhizobium*, and *Faecalibaculum* reduced, and causing the death of fish (Deng et al. 2020). In sea cucumbers (*Apostichopus japonicus Selenka*), benzo[a]pyrene exposure decreased the abundance of *Firmicutes* and increased the abundances of *Bacteroidete* and *Proteobacteria*, and caused the immune suppression, i.e., significantly downregulated the relative expressions of lysozyme, Ctl, and NF-κB1, and negatively impacted the gut health (Zhao et al. 2019). Therefore, the dysbiosis of intestinal microbiota could lead to the disorders of intestinal immune system and cause the diseases occurrence in fish (Pérez et al. 2010).

Probiotics are perhaps the most feasible therapeutic strategy to promote the healthy fish physiology by regulating gut microbiota and immunity (Langlois et al. 2021; Vargas-Albores et al. 2021). As one of the crucial regulators in fish immune responses, cytokines are also found to be positively regulated by probiotics (Kim and Austin 2006; He et al. 2013). Probiotic *Clostridium butyricum* could significantly improve the expressions of intestinal immune-related genes (MyD88, TLR2, and IL-10) and improve the diversity of the intestinal microbiota, with the abundance of *Fusobacteria* and *Proteobacteria* decreased and the abundance of *Bacteroidetes* increased in common carp (*Cyprinus carpio* L.) (Meng et al. 2021). *Bacillus subtilis* H2 could upregulate the expressions of IFN-α, colony stimulating factor, FOSB, IL-4, IL-11, IGHV3-11, MAPK12b, and IGHV3-21 in the intestinal tract of grass carp (Shi et al. 2020). Dietary *Lactobacillus rhamnosus* JCM1136 and *L. lactis subsp. lactis* JCM5805 could enhance the expressions of IL-1β, C-type lysozyme (lyzc), and IFN-γ, and shape the intestinal microbiota, with the abundances of *Fusobacteria*, *Bacteroidetes*, and *Actinobacteria* reduced and the abundance of *Proteobacteria* increased in Nile tilapia (Xia et al. 2018). Besides, our previous research discovered that two cell wall components of *B. pumilus* SE5, LTA, and PGN can enhance the expressions TLR1, TLR2, TLR5, and MyD88, activate the expression of immune effector molecules, and modulate the intestinal microbiota, i.e., increase the abundance of *Lactobacillus* and decrease the abundance of *Vibrio* significantly (Yang et al. 2019). Therefore, it is clear that probiotics/commensals can regulate fish intestinal immunity and intestinal microbiota and improve the overall health of host fish.

Summary and outlook

Intestinal microbes can improve the development and response of fish mucosal immune system, and the host immune system monitors and modulates the intestinal microbial balance. This complex interaction is very important to maintain intestinal health of fish. However, it is unclear how the intestinal immune system of fish accurately monitors and regulates the intestinal microbiota and maintains intestinal homeostasis. Existing studies have shown that both TLR and NLRs signaling may play important functions in this process, but more supporting data are needed. Commensals can regulate the immune system and intestinal microbiota of fish, improve the disease resistance, and then promote the feed utilization efficiency and growth performance. However, the molecular mechanisms of the interactions among commensals with host immunity and gut microbiota are still poorly understood. Future studies can use gnotobiotic zebrafish technology, in vitro intestinal epithelial cell culture technology, combined with RNA interference, multi-omics analysis, gene editing, and other biological techniques to further explore these issues. The elucidation of these issues will greatly promote the exploitation and application of intestinal functional microbes in fish.

Declarations

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