微生物学报
Acta Microbiologica Sinica
2021, 61(10): 3046–3058
http://journals.im.ac.cn/actamicrocn
DOI: 10.13343/j.cnki.wsxb.20210027

Review 综 述

鱼类肠道微生物与宿主免疫系统相互作用研究进展

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摘要：鱼类肠道中存在大量微生物，对于维持宿主健康具有重要作用。鱼类免疫系统能够监视并调控肠道微生物组成，维持肠道菌群稳态。同时，鱼类肠道共生微生物调节鱼类免疫系统，抑制病原微生物的过度增殖，保证宿主的健康。本文回顾了鱼类肠道微生物与宿主免疫系统相互作用的研究进展，重点介绍了宿主免疫系统识别肠道微生物、塑造肠道菌群以及益生菌对宿主免疫和肠道菌群的调控等，提出了理想的益生菌应该来自动物自身胃肠道，生产中应谨慎选用非宿主来源的益生菌，以期为推动鱼类肠道功能微生物开发和应用提供理论支撑。

关键词：鱼类，肠道微生物，免疫，相互作用，益生菌

根据 FAO 发布的 2020《世界渔业和水产养殖状况》数据，当前水产养殖约占全球渔业总产量的 46%，2030 年鱼类总产量将增至 2.04 亿 t，水产养殖的份额还将进一步增长。近年来，水产养殖业高速发展的同时面临着增产、减排、节能任务，其艰巨性在古今中外绝无仅有，水产养殖业也因此逐渐走上了集约化发展的道路，随之而来的问题是：环境恶化，各种病原微生物引起的疾病频繁暴发，每年造成巨大的经济损失[1]。为了控制鱼类细菌性疾病的发生，养殖业者多大量使用化学药物和抗生素，但效果却并不尽如人意。另外，养殖户为了追求经济效益，不断加大放养密度，增加投喂量，以及在鱼类饲料中大量使用植物蛋白原料，鱼类肠道健康受到很大冲击，肠炎频发，肠道消化不良导致饵料系数升高的问题非常突出，严重影响了养殖效益[2–3]。肠道健康问题已成为制约我国水产养殖业持续健康发展的瓶颈之一，通过营养干预措施改善集约化养殖模式下鱼类肠道功能已经刻不容缓。近年来，越来越多的研究开始关注肠道微生物与鱼类

基金项目：国家自然科学基金(32072990)；福建省高校产学合作项目(2018N5011)；厦门市海洋与渔业发展专项资金(19CZP018HJ04)

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收稿日期：2021-01-11；**修回日期：**2021-03-30；**网络出版日期：**2021-06-21

免疫和疾病的关联[4–5]。基于肠道功能微生物开发的益生菌可以有效改善水产养殖动物的肠道健康，提高动物抗病力，加之其绿色环保的特性，逐渐受到人们的重视[6–8]。

肠道内存在大量的微生物[9]，这些共生或潜在致病微生物，能够被肠道相关淋巴组织识别和区分，启动机体耐受或免疫反应[10]。鱼类肠道微生物和宿主相互作用是免疫系统发展的基础[11]。肠道微生物是刺激宿主“黏膜免疫系统”和“全身免疫系统”成熟的重要因子[12–13]，宿主免疫系统与微生物共同进化，微生物对宿主生理至关重要[14]。宿主与微生物相互合作、相互竞争，逐渐形成了动态的、稳定的微生态系统[15]。稳态条件下，宿主免疫系统监控肠道微生物，维持肠道菌群稳定和肠黏膜的健康，从而增强宿主对病原体的抵抗力[16]。本文对鱼类肠道微生物与宿主免疫互作的研究现状作一综述，为鱼类肠道功能微生物的开发和应用提供理论支撑。

1 宿主免疫系统识别肠道微生物

宿主免疫系统在病原微生物的识别、抵御病原体的入侵过程中起着关键作用[17–18]。脊椎动物的免疫系统主要是指淋巴器官，鱼类作为低等脊椎动物，其免疫系统按淋巴器官可分为：肠道相关淋巴组织(gut associated lymphoid tissue，GALT)、皮肤相关淋巴组织(skin associated lymphoid tissue，SALT)、鳃相关淋巴组织(gill associated lymphoid tissue，GIALT)。这些黏膜表面覆盖的免疫粘液层，是抵御病原体的第一道防线[19]。鱼类肠道、皮肤、鳃和粘液中富含大量的免疫细胞(包括淋巴细胞、浆细胞、粒细胞、巨噬细胞、杯状细胞、抗体分泌细胞等)和免疫因子(包括凝集素、粘蛋白、抗菌肽和免疫球蛋白等)，共同抵御病原菌的侵袭。

除了胞外代谢产物，微生物细胞的结构成分，特别是细胞外膜(例如细胞壁成分)是宿主免疫细胞首先接触的最外层结构，介导免疫调节活性[20]。宿主免疫细胞通过模式识别受体(pattern recognition receptors，PRRs)感知肠道微生物，该类受体能够识别微生物相关分子模式(microbe-associated molecular patterns，MAMPs)，包括脂多糖、肽聚糖、脂磷壁酸、鞭毛蛋白和微生物核酸等[21]。目前，在鱼类中只发现 4 种 PRRs，即 Toll 样受体(Toll-like receptors，TLRs)、NOD 样受体(NOD-like receptors，NLRs)、C 型凝集素受体(C-type lectins receptors，CLRs)和肽聚糖识别蛋白(peptidoglycan recognition proteins，PGRPs)[22]。

Toll 样受体(TLRs)是鱼类研究最多的一类模式识别受体，在先天免疫反应中起着重要的作用，在识别病原菌独特的分子模式以及启动适应性免疫系统方面也起着重要的作用。鱼类 TLRs 能够识别肽聚糖(peptidoglycan，PGN)、脂磷壁酸(lipoteichoic acid，LTA)、脂多糖(lipopolysaccharide，LPS)和鞭毛蛋白成分等病原菌相关分子模式(pathogen-associated molecular patterns，PAMPs)，激活下游细胞因子和免疫效应分子的表达[23]。例如，金黄色葡萄球菌(*Staphylococcus aureus*)来源的肽聚糖可诱导激活南亚野鲮(*Labeo rohita*)心脏细胞 TLR2、MyD88、TRAF6、NF-κB 和 IL-8 的表达，提示南亚野鲮 TLR2 介导的微生物识别可能依赖 MyD88[24]。近期研究发现，鱼类 TLRs

能介导免疫系统识别肠道原籍益生菌[25–26]。本课题组研究表明，饲料添加活性肠道原籍益生菌——嗜冷杆菌(*Psychrobacter* sp.) SE6，石斑鱼(*Epinephelus coioides*)肠道 TLR2、TLR5、MyD88 和细胞因子(IL-1β、IL-8 和 TGF-β1)的表达水平均增强，当饲喂热灭活的 SE6 时，仅 TLR2 的表达增强，MyD88 和细胞因子表达则没有明显变化，这表明石斑鱼肠道 TLR2 信号通路与嗜冷杆菌 SE6 的识别有关，作为一种益生菌识别机制，可能不依赖于 MyD88[26]。然而，Koch 等(2018)发现斑马鱼(*Danio rerio*)先天免疫系统通过负调控 MyD88 介导 TLR2 识别共生微小杆菌(*Exiguobacterium*)和金黄杆菌(*Chryseobacterium*)[27]。因此，不同鱼类基于 Toll 样受体对共生微生物的识别机制可能存在一定差异。

核苷酸结合寡聚结构域(NOD)样受体(NLRs)是一组细胞内病原体识别受体，对识别鱼类病原体和激活天然免疫信号通路起着关键作用。研究发现鱼类 NLRs 能够识别微生物的配体，感知 PAMPs 或 iE-DAP (G-D-glutamyl-meso-diaminopimelic acid)来激活下游分子[28]。在体内和体外，细菌或者病毒可以刺激硬骨鱼类多个 NLR 亚家族成员的表达，包括 NOD1、NOD2、NLR-C3、NLR-C5 和 NLR-X1[29]。乳房链球菌(*Streptococcus uberis*)和嗜水气单胞菌(*Aeromonas hydrophila*)感染麦瑞加拉鲮鱼(*Cirrhinus mrigala*)，会激活 NOD1 和 NOD2 受体，继而诱导下游效应分子 IL-1β、IL-8 和 IFN-γ 的表达[30]。斑马鱼胚胎成纤维细胞 NOD2 可以感知革兰氏阴性和阳性菌的胞壁酰二肽(muramyl dipeptide，MDP)，激活 NF-κB 的表达，诱导 SVCV 感染的抗病毒防御反应[31]。

C 型凝集素受体(CLRs)是树突细胞(dendritic cells，DCs)表达的一类模式识别受体家族，识别微生物抗原，并将抗原信息递呈给 T、B 淋巴细胞，从而触发多种免疫反应。研究发现，尼罗罗非鱼(*Oreochromis niloticus*)的 CLR 与哺乳类 NK 细胞受体同源[32]。嗜水气单胞菌和 Poly(I:C)攻毒后，淇河鲫鱼(*Carassius auratus*)鳃、肝、脾、肾及头肾中的 C 型凝集素受体表达明显上调[33]。在鲤鱼(*Cyprinus carpio*)巨噬细胞中，CLR 受体识别 β-葡聚糖，介导免疫调节作用[34]。

肽聚糖识别蛋白(PGRPs)是一类高度保守的模式识别受体，能够识别细菌细胞壁的主要成分肽聚糖，进而激活并调节机体的先天性免疫反应。目前已报道的鱼类 PGRP 共 23 种，根据氨基酸序列的不同，PGRPs 主要分为 3 类，分别是短型、中型和长型 PGRPs[35]。PGN 是细菌细胞壁的重要成分，包括 L-赖氨酸(Lys 型)和二氨基庚二酸(Dap 型)两种类型，Lys 型 PGN 主要存在于革兰氏阳性菌细胞壁中，而 Dap 型 PGN 是革兰氏阴性菌细胞壁的主要组分[36]。研究表明，鱼类 PGRPs 能通过结合 Lys 型和 Dap 型两种 PGN 来识别病原菌[37–38]，虹鳟(*Oncorhynchus mykiss*)的 PGRP 会负调控 NODs 介导的抗菌免疫应答[39]，表明在感知微生物时，不同模式识别受体家族之间也会相互作用。

2 宿主免疫塑造鱼类肠道菌群

宿主遗传[40]、饮食[41]以及免疫[42]等均会影响鱼类肠道菌群。免疫系统由先天免疫和适应性免疫组成，它们相互联系清除病原体和有害物质，

维持宿主健康[43]。研究发现先天免疫可以调节微生物组成[44–46]，促进肠道有益菌的生长，维持稳定的微生物群落[47]。研究表明，嗜水单胞杆菌感染斑马鱼，可以诱导先天性免疫反应，改变肠道微生物组成：硝化还原菌(*Nitratireductor*)、肠球菌(*Enterococcus*)、短波单胞菌(*Brevundimonas*)等有益微生物减少，盐单胞菌(*Halomonas*)、海洋杆菌(*Pelagibacterium*)、气单胞菌(*Aeromonas*)等有害微生物增加[48]。日粮中添加黄芪多糖可以诱导海参(*Apostichopus japonicus*)的非特异性免疫，改变肠道微生物组成[49]。

宿主免疫系统对肠道菌群平衡起着关键作用，可以通过免疫球蛋白 A(IgA)塑造微生物结构[50]。分泌型免疫球蛋白 A(sIgAs)是适应性免疫系统的组成部分，是肠上皮健康的重要保护者，是肠道微生物调节的重要因子[51]。哺乳动物分泌型 IgA 能够维持黏膜组织微生物稳态，调节微生物定植以及抵御病原的入侵。宿主分泌大量的 IgA 到肠腔内，这些 IgA 要么广泛地与微生物低亲和反应，要么相对特异性地与微生物高亲和反应，并在某些情况下与多个细菌常见的基序结合[52]。

研究表明，低等脊椎动物鱼类中也存在类似功能的黏膜免疫球蛋白 IgT，可以识别黏膜共生微生物并结合到其表面，在抗寄生虫和细菌等病原感染过程中发挥类似哺乳动物 IgA 的功能[53]。在虹鳟中，缺乏 IgT 的鱼对黏膜寄生虫高度敏感，不能产生代偿性 IgM 反应。黏膜组织菌群发生紊乱后，一些条件致病菌(如黄杆菌目细菌)数量显著上升，黏膜组织表面微生物发生易位，最终引发组织病变和炎症反应，随着分泌型 IgT 水平的恢复，黏膜组织中 IgT 包被微生物的比例以及类型也恢复到正常水平[54]。

模式生物斑马鱼的适应性免疫与肠道菌群存在关联，可以通过适应性免疫改变肠道菌群。野生型斑马鱼发育早期适应性免疫尚未建立，肠道弧菌会过度生长。Rag1 缺乏的斑马鱼，缺乏适应性免疫，肠道弧菌丰度很高。通过转移 T 淋巴细胞而不是 B 淋巴细胞到 Rag1 缺乏的斑马鱼可以抑制肠道弧菌的生长[55]。斑马鱼肠道巨噬细胞可以通过干扰素调节因子 IRF8 来塑造肠道菌群。IRF8 缺乏的斑马鱼成鱼表现出巨噬细胞的数量减少，c1qa、c1qb、c1qc 和 c1ql 基因的表达减少，肠道共生微生物严重失调，梭菌(*Fusobacteria*)、α-变形菌(α-*Proteobacteria*)和 γ-变形菌(γ-*Proteobacteria*)减少，而 δ-变形菌(δ-*Proteobacteria*)增多[56]。

鱼类免疫系统调节肠道菌群的同时，肠道微生物也促进了鱼类免疫系统的发育和成熟，并激活宿主免疫反应，控制肠道病原菌过度增殖。斑马鱼是公认的研究宿主免疫和微生物互作的模型[57–58]，利用特定微生物定植无菌斑马鱼的研究表明，共生微生物是鱼类在稳态、感染或损伤状态下免疫系统发育和功能所必需的[59]。肠道共生微生物在新孵化的斑马鱼肠道中定植，通过 TLRs 和 MyD88 启动先天免疫，调节免疫发育，增强斑马鱼抗病毒感染的能力[60]。无菌斑马鱼研究表明，微生物可以上调多个先天免疫相关基因的表达，如血清淀粉样蛋白 A1、C 反应蛋白、补体成分 3、血管生成素 4、谷胱甘肽过氧化物酶和髓过氧化物酶等[61–62]。SWF®主要由鲟鱼胃肠道微生物——枯草芽孢杆菌(*Bacillus subtilis*)、乳酸

乳球菌(*Lactococcus lactis*)和索氏鲸杆菌(*Cetobacterium somerae*)组成，鲟鱼饲喂 SWF®后肠道梭杆菌门(*Fusobacteria*)、厚壁菌门(*Firmicutes*)和变形菌门(*Proteobacteria*)细菌丰度显著增加，而放线菌门(*Actinobacteria*)细菌显著下降；无菌斑马鱼肠道定殖了 SWF®鲟鱼的肠道微生物后，非特异性免疫相关基因 DEFBL-1、C3a 和溶菌酶的表达显著增加，维氏气单胞菌(*Aeromonas veronii*)攻毒后斑马鱼抗病力增强，死亡率显著降低[63]。枯草芽孢杆菌 WB800N 能促进无菌斑马鱼免疫相关基因 IL-10、TNF-α、IL-β、SAA、BF 和 MyD88 的表达[64]。可见，肠道微生物能调节宿主免疫功能，维持肠道菌群稳态，提高宿主抗病力，但是相关机制尚有待进一步研究。

3 益生菌调控鱼类免疫和肠道菌群

益生菌(probiotics)这个词来源于希腊语“pro”和“bios”，意思是“对生命有益(for life)”。益生菌的益生作用及机制在陆地动物中已有大量研究，并极大地支持了益生菌在水生动物中的应用[65]。益生菌有许多潜在的益处，例如调节宿主代谢、维持肠道菌群的平衡[66]、刺激免疫系统的发育、降低疾病发生的风险[67]。对于水产养殖，使用益生菌的主要目的是通过调节动物的微生物群落，改善宿主的健康和抗病力[68]。

益生菌可以调节鱼类的先天免疫和适应性免疫，通过改变微生物结构建立鱼类肠道免疫和全身免疫的相关性。益生菌通过调节鱼类微生物区系进而调控 3 种主要黏膜组织的免疫，即鳃相关淋巴组织(GIALT)、皮肤相关淋巴组织(SALT)和肠道相关淋巴组织(GALT)，从而发挥局部免疫效应(例如肠道)或者全身免疫效应(例如体液)或者两者综合效应[21]。此外，益生菌可以附着在肠道内表面，分泌可溶性因子，激活抗原递呈细胞(antigen-presenting cells，APCs)，进一步调节宿主的肠道免疫和全身免疫反应[69]。

益生菌能够提高鱼类肠道黏膜表面固有的免疫活性细胞和因子，控制病原体数量，有效预防疾病发生。在罗非鱼养殖中，饲喂益生乳酸片球菌(*Pediococcus acidilactici*)，可明显增强全身免疫，如血液白细胞水平和血清溶菌酶活性增加[70]，同时，肠道上皮内白细胞数量升高，但是杯状细胞数量增加不明显[71]。在虹鳟养殖中，饲喂宿主来源益生菌——枯草芽孢杆菌(*Bacillus subtilis*) AB1，可刺激多种免疫反应，先天免疫参数如吞噬活性、血清总蛋白、抗蛋白酶活性和溶菌酶活性均显著提高[72]。

细胞因子是细胞之间传递信号的关键化学信号，是鱼类肠道接触益生菌后免疫调节级联的关键分子。益生菌可以调节鱼类促炎细胞因子的表达，如白细胞介素、肿瘤坏死因子和干扰素，以及抗炎细胞因子如转化生长因子的表达[73−75]。在杂交罗非鱼日粮中添加枯草芽孢杆菌(*B. subtilis*) C-3102 能诱导肠道细胞因子如 IL-1β、TGFβ 和 TNFα 的上调[73]。虹鳟肠道分离出来的麦芽香肉杆菌(*Carnobacterium maltaromaticum*) B26 和广布肉杆菌(*C. divergens*) B33 可以调节虹鳟鱼头肾细胞细胞因子(IL-1β，IL-8，TNF-α 和 TGF-β)的表达[74]。类似地，三种益生菌——鼠李糖乳杆菌(*Lactobacillus rhamnosus*)、屎肠球菌(*Enterococcus*

faecium)和枯草芽孢杆菌(*B. subtilis*)可以促进虹鳟脾脏和头肾 IL-1β、TNF1、TNF2、TGF-β 的上调表达[75]。

益生菌能够激活宿主免疫反应，调节肠道菌群结构。柠檬酸杆菌(*Citrobacter freundii*) GC01 触发了草鱼(*Ctenopharyngodon idellus*)的天然黏膜免疫系统，诱导免疫系统相关基因的表达，包括多个补体系统基因，如 c3、c4、c5、c7、c8a、c8b 和 c1s 的上调表达，显著降低肠道菌群的 α 多样性和 β 多样性，并显著提高肠杆菌目(*Enterobacteriales*)、巴氏杆菌目(*Pasteurellales*)、奈氏球菌目(*Neisseriales*)和柠檬酸菌目(*Citrobacter*)的相对丰度[76]。本课题组近期发现，益生菌细胞组分也能调节鱼类的免疫功能和肠道菌群，石斑鱼肠道功能短小芽胞杆菌(*B. pumilus*) SE5 细胞壁提取物肽聚糖和脂磷壁酸能增强宿主免疫相关基因 TLR1、TLR2、TLR5 和 MyD88 的表达，激活免疫效应分子表达，塑造肠道菌群：变形菌门丰度降低，厚壁菌门丰度增加；弧菌属丰度显著下降，乳酸杆菌属丰度显著上升[77]。益生菌调控鱼类免疫的研究越来越多，但其分子途径，特别是宿主免疫系统对益生菌细胞组分的识别机制和反应级联尚不够清楚，需要进一步研究。

4 宿主与非宿主来源益生菌

过去十年中，益生菌的研究数量惊人，但尚未发现有某一益生菌菌株在所有的动物中都能发挥益生作用。这并非意味着益生菌的作用是针对特定宿主，它仍然可以对多种动物有广泛的作用，只是作用效果不尽相同。大量研究表明，益生菌的来源会影响其效果的最终发挥[78]。目前许多水产上使用的益生菌分离自环境或者陆生动物，这些益生菌往往因为无法在水产动物消化道定植而难以发挥益生效果，因而限制了它们在水产养殖上的应用。大量研究表明，理想的益生菌应该来自动物自身胃肠道[79–80]。

虽然某些其他来源的益生菌可以为水生动物提供益处，但是开发宿主来源的益生菌已经得到学术界的广泛认可[72,74]。宿主共生微生物不仅是一个天然防御系统[81–82]，它还能给宿主带来很多其他益处[83–84]。例如，宿主肠源性益生菌产碱杆菌(*Alcaligenes* sp.) AFG22 和芽孢杆菌(*Bacillus* sp.) AHG22 能促进缓慢生长的似野结鱼(*Tor tambroides*)肥大肌肉生长相关基因的上调表达[85]。当补充产碱杆菌 AFG22 时，似野结鱼的胃肠道中脂肪分解、蛋白分解和纤维素分解的细菌数量显著增加，幼鱼的绒毛长度、绒毛宽度和绒毛面积明显增高，乙酸和丁酸成为肠道的主要挥发性短链脂肪酸。这些结果表明，鱼类肠道功能微生物作为一类重要的益生菌，可提高营养物质的利用率，改善肠道健康，具有极大的开发潜力[86]。

除了改善生长和代谢，宿主来源的益生菌可以抑制病原菌，有利于提升动物免疫力和抗病力。例如，从虹鳟肠道和养殖环境中分离的乳酸菌(lactic acid bacteria)可以抑制格氏乳球菌(*L. garvieae*)等鱼类病原菌[87]。有趣的是，益生菌的抑菌特性在一定的条件下依赖于环境因子，如来自大西洋鳕鱼(*Gadus morhua*)肠道的候选益生菌发光杆菌(*Photobacterium* sp.) GP31 在 13 °C (接近鳕鱼适宜养殖温度)时表现出对病原菌的抑制作用，但这种抑菌活性在 20 °C 时明显减弱[88]。

从褐鳟(*Salmo trutta*)肠道中分离的乳球菌亚种乳杆菌(*L. lactis*) CLFP 100 和肠膜明串珠菌(*Leuconostoc mesenteroides*) CLFP196[89]，可以增强鱼体血清补体和溶菌酶活性[90]，激活头肾吞噬细胞[91]。本课题组从石斑鱼幼鱼肠道中分离出克劳氏芽孢杆菌(*B. clausii*) DE5 和短小芽孢杆菌(*B. pumilus*) SE5[92]，添加到饲料中可以增强鱼体免疫功能，例如白细胞吞噬活性、血清溶菌酶活性、血清补体 C3 和 IgM 水平显著上升[93]。从卵形鲳鲹(*Trachinotus ovatus*)肠道中分离的短小芽孢杆菌(*B. pumilus*) A97 可以增强宿主的免疫功能，促进肠道中 TLR8 和肾脏中 TLR9 的上调表达，提高鱼体的抗病力[94]。

同一宿主来源的不同益生菌菌株作用差异很大。从大菱鲆(*Scophthalmus maximus*)肠黏膜分离到共生菌希瓦氏菌(*Shewanella* sp.) MR-7，该菌发酵后显著地抵消了豆粕诱导的不良影响(降解多种抗营养因子)，增加消化酶活性，抑制炎症反应，减轻大菱鲆肠道微生物群失调[95]。同样是宿主来源益生菌嗜冷杆菌(*Psychrobacter* sp.) 004、葡萄球菌(*Staphylococcus saprophyticus*) 060 和嗜冷杆菌(*Psychrobacter alimentarius*) 094 却不能提高大菱鲆幼鱼对豆粕的消化利用率[96]。这可能是因为希瓦氏菌 MR-7 是从饲喂高豆粕饲料的大菱鲆肠道筛选出来的益生菌，而分离自饲喂正常饲料大菱鲆的嗜冷杆菌和葡萄球菌在这方面则没有特别的优势，这也为将来特定功能益生菌的筛选提供了思路。

从里海拟鲤(*Rutilus rutilus caspicus*)成鱼肠道分离的屎肠球菌(*Enterococcus faecium*) CGMCC 1.2136 比商业的乳酸片球菌(*Pediococcus acidilactici*)在促进鱼体生长和免疫方面更有优势，饲喂宿主来源乳酸菌的鱼体血清免疫参数均显著高于对照组和饲喂商业乳酸菌组，具体体现在碱性磷酸酶活性、总蛋白含量、总免疫球蛋白水平、溶菌酶活性和补体水平等免疫指标显著上升[97]。非宿主益生菌在理论意义上是宿主的一个外来因素，对于非宿主益生菌引起的鱼类免疫反应，不应仓促得出结论。有时，添加益生菌后某些免疫活性的增加可能是鱼体对外来因素的“正常”反应，并不一定表明益生菌增强了动物的免疫功能，所以在非宿主益生菌的选用时应尤其谨慎。

5 小结与展望

肠道微生物可以促进鱼类黏膜免疫系统的发育与应答，同时宿主免疫系统监视并调控肠道菌群平衡，二者之间复杂的相互作用关系对于维持肠道健康十分重要。但是，鱼类肠道免疫系统通过何种机制精准监视并调控肠道菌群结构、维持肠道稳态，目前尚不清楚。现有研究表明，Toll 样受体和 NOD 样受体信号通路可能在此过程中起到重要作用，但还需要更多的数据支撑。益生菌能够调节鱼类免疫系统和肠道菌群结构，提高宿主的抗病力，进而改善动物的生长性能和饲料利用效率。但是，益生菌与宿主免疫系统、肠道微生物相互作用的分子机制目前仍知之甚少。后续研究可以利用无菌斑马鱼技术、肠上皮细胞体外培养技术，结合多组学分析、RNA 干扰、基因编辑等手段对这些问题进行深入探讨。这些问题的阐明必将极大地推动鱼类肠道功能微生物的开发和应用。

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Advances in the interactions between intestinal microorganisms and host immune system in fish

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Abstract: There are a large number of microorganisms in the intestine of fish, which play an key role in maintaining host health. The fish immune system can monitor and regulate the intestinal microbial composition and maintain the homeostasis of intestinal flora. At the same time, the intestinal commensal microorganisms regulate the fish immune system, control the excessive proliferation of pathogenic microorganisms, and ensure the health of the host. This paper reviewed the progress of interactions between intestinal microorganisms and the host immune system in fish, and focusing on the host immune system sensing intestinal microbes, host immune system shaping intestinal microbiota, probiotics regulating host immunity and intestinal microbiota, etc. It is suggested that the ideal probiotics should be derived from the gastrointestinal tract of fish and the non-host derived probiotics should be carefully selected in aquaculture application. This paper would provide theoretical supports for the future researches on the development and application of intestinal functional microbes in fish.

Keywords: fish, intestinal microorganisms, immunity, interactions, probiotics

（本文责编：李磊）

Supported by the National Natural Science Foundation of China (32072990), by the Industry-University Cooperation Project of Fujian Province (2018N5011) and by the Xiamen Marine and Fisheries Development Fund (19CZP018HJ04)
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Received: 11 January 2021; Revised: 30 March 2021; Published online: 21 June 2021