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益生菌对鸡抵御沙门氏菌感染作用研究进展

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摘　要: 沙门氏菌病是家禽生产中常见的疾病,其通过水平和垂直传播,导致群体广泛携带,并通过肉、蛋等产品经食物链传染给人类,造成严重的公共卫生安全问题。研究发现,益生菌可有效地抑制病原菌的生长,并通过改善抗氧化能力、肠道功能以及免疫水平等方式,发挥抵御鸡沙门氏菌感染的作用。本文就鸡沙门氏菌的致病机制及益生菌对鸡抵御沙门氏菌感染的作用进行了综述,以期为益生菌应用于鸡沙门氏菌病的防制和健康养殖提供参考。

关键词: 益生菌;沙门氏菌;肠道健康;免疫功能;鸡

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在世界范围内,沙门氏菌病是家禽生产中常见的疾病,以鸡白痢、鸡伤寒等较为典型,给养殖产业造成巨大的经济损失。该病属于人畜共患传染病,很容易通过肉、蛋等途径转移给人类,引起发热、呕吐、腹泻、胃肠炎等症状[1],甚至导致败血症和伤寒,严重威胁着人类的健康。目前,欧洲和美国因具备完善的生物安全体系及严格的生物安全措施,在沙门氏菌净化工作上效果较好,使得其流行率维持在较低水平。国内肉鸡的沙门氏菌感染以鸡白痢为主,且在生产链中广泛存在,并伴随着交叉污染的情况。近年来,随着鸡白痢净化工作的推动,以及“全进全出”的饲养模式的实施和新型疫苗的深入研究,其阳性检出率呈明显下降趋势,我国在防控鸡沙门氏菌感染上已取得一定成绩,但仍有部分地区存在严重的沙门氏菌感染情况[2]。

在集约化家禽生产中,抗生素在防治沙门氏菌感染方面已经取得了很好的效果,但抗生素的滥用致使耐药沙门氏菌逐渐增多,并引发了肉、蛋类产品中耐药性菌和药物残留等一系列问题[3]。随着养殖业对天然抗菌物质的迫切需求,益生菌添加剂作为抗生素的替代品,在家禽生产中已被广泛应用,主要作用体现在促进生长、提高生产性能、增强免疫力、改善肠道健康、降低病原微生物数量及发病率等[4-6]。目前认为,益生菌可通过降低肠道 pH、产生挥发性脂肪酸以及竞争性排斥等方式抑制致病菌,对机体产生积极的作用[7-8]。此外,益生菌在一定程度上调节炎症相关因子、抗体分泌细胞和 T 淋巴细胞的产生,影响先天性和适应性免疫,从而增强机体体液和细胞免疫功能[9-11]。本文就鸡沙门氏菌的致病机制及益生菌在该病防治上的相关研究进行综述,以期为益生菌应用于防治鸡沙门氏菌病提供参考。

1　沙门氏菌病与致病机制

1.1　沙门氏菌病的特点

因雏鸡肠道微生物群没有完全发育,且未能接触到来自母鸡胃肠道的有益菌,机体不能以竞争性排斥的方式对胃肠道提供保护。此外,雏鸡的免疫系统发育不完善,使其易在最初的 24 h 内

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(孵化器中或孵化后的短时间)感染沙门氏菌[12]。感染沙门氏菌的主要临床症状之一是腹泻,并伴随着采食量减少、生长性能下降、肠道结构明显受损[7],其中肠道结构受损表现为肠道通透性增加、肠上皮细胞明显增多、空肠杯状细胞数量减少、盲肠菌群失调[13-14]。此外,鸡在感染沙门氏菌后会产生黏膜、关节和内脏器官病变[15-18],脾脏和法氏囊的相对重量降低,新城疫病毒和传染性法氏囊病毒的抗体滴度降低,机体炎症反应加剧等[14,19]。

1.2　沙门氏菌病的致病机制

沙门氏菌在全身感染过程中主要分为 3 个阶段。首先,沙门氏菌主动入侵宿主上皮细胞并诱导细胞发生自噬,整个自噬过程中,沙门氏菌Ⅲ型分泌系统 1(type Ⅲ secretion system 1,T3SS1)介导了细胞膜完整性的破坏,并将效应蛋白转移至细胞内[20]。然后,沙门氏菌穿过上皮层并被巨噬细胞或树突状细胞所吞噬[21],部分 T3SS 效应器可以将吞噬体转化为含沙门氏菌空泡(*Salmonella*-containing vacuole, SCV),Ⅲ型分泌系统 2(T3SS2)在 SCV 内被激活,促进沙门氏菌在细胞内的存活和复制,并将效应蛋白从细胞内通过 SCV 膜传递到宿主细胞胞浆[22],再通过淋巴系统运输到肝脏和脾脏。最后,机体将死亡或处于持续感染状态。

在整个感染过程中,沙门氏菌诱导半胱氨酸蛋白酶(Caspase)激活产生白细胞介素(IL)-1α、IL-1β、IL-18 等炎性因子[23],通过过度激活 Wnt/β-连环蛋白(Wnt/β-catenin)信号通路,破坏肠黏膜屏障,导致肠细胞凋亡,肠道干细胞异常增殖[24],并影响闭合蛋白-1(claudin-1)、闭锁蛋白(occludin)、闭合小环蛋白-1(*ZO*-1)、黏附蛋白(E-cadherin)的重新分布和表达[25]。此外,沙门氏菌通过促进巨噬细胞的糖酵解水平,诱导其凋亡[26]。

2　益生菌抵御沙门氏菌感染的作用

2.1　益生菌的体外抑菌作用

通过体外试验可以直观地了解益生菌对沙门氏菌的抑制作用。乳酸菌因其耐酸、耐盐,从而可以很好地在家禽胃肠道内发挥作用。大量研究表明,乳酸菌可以抑制沙门氏菌的生长以及生物膜的形成,降低沙门氏菌毒力、运动和黏附相关基因的表达[27-29],竞争性消除沙门氏菌在肠上皮细胞上的定植[30-31]等,其抑菌效果可能与产生的叶酸、核黄素或细菌素等代谢产物有关[32]。枯草芽孢杆菌也被证实具有非常理想的抗沙门氏菌活性,抑制作用在 24 h 时最为明显[33]。刘明刚等[34]进一步验证了枯草芽孢杆菌的抗沙门氏菌能力,发现经共培养 24 h 后,抑菌率可达到 88.5%。除此之外,丁酸梭菌和鼠李糖乳杆菌同样可抑制沙门氏菌的生长,但 2 种菌株联合培养对沙门氏菌生长的抑制并无协同作用[35]。

2.2　益生菌对鸡抗氧化性能的影响

当鸡受到沙门氏菌入侵时,机体会产生大量的活性氧(ROS)和活性氮(RNS)等自由基,这个反应过程也伴随着组织的氧化损伤,从而影响正常生理功能。益生菌能够提高血清过氧化物歧化酶(SOD)活性、增强小肠抗氧化功能、缓解因致病菌感染所造成的氧化应激[36-37]。朱沛霁等[38]指出,饲喂枯草芽孢杆菌可降低雪山草鸡空肠黏膜髓过氧化物酶(MPO)活性及丙二醛(MDA)含量,提高空肠黏膜总抗氧化能力(T-AOC)及总超氧化物歧化酶(T-SOD)、谷胱甘肽转移酶(GSH-Px)活性,减少机体的氧化损伤,进而改善沙门氏菌感染肉鸡的生长和抗氧化状态[8]。由以上研究可见,益生菌通过提高机体抗氧化能力可能是缓解鸡沙门氏菌感染症状的途径之一。

2.3　益生菌对鸡肠道健康的影响

肠道菌群平衡、肠道形态和肠上皮屏障等是衡量肠道健康的重要指标。益生菌的添加已被证明对感染鸡肠道微生物群的稳态具有积极作用,其机制可能是通过竞争性排斥作用以及促进肠道内干扰素-γ(IFN-γ)和肿瘤坏死因子-α(TNF-α)的产生阻止沙门氏菌的定植[39-40]。大量研究表明,枯草芽孢杆菌通过分泌细菌素、有机酸和过氧化氢等物质,发挥抑制病原菌的生长和繁殖的作用,显著降低肠道沙门氏菌数量,增加盲肠微生物群的多样性和组成,缓解沙门氏菌感染引起的肠道菌群失调,这有益于减少家禽之间感染的风险,也保证了禽类食品的安全性[41-43]。

肠道组织结构的完整性对维持肠道屏障及营养物质的消化吸收功能起着重要作用,其损伤会发生肠道渗漏,从而导致细菌移位[44]。沙门氏菌通过早期影响肠道紧密连接复合物的结构以及晚期诱导肠上皮细胞的凋亡来破坏肠上皮细胞屏障的完整性。益生菌能够增强家禽肠道屏障抵御病原菌的能力,减少肠道对分子或细菌的通透性以

及黏液的降解,有效地改善病原菌感染引起的肠道负面影响[45-46]。

芽孢杆菌在抗沙门氏菌感染过程中发挥了较好的保护作用。朱沛霁[36]发现,枯草芽孢杆菌能够改善雪山鸡的肠道形态,促进小肠黏膜生长发育,使空肠黏膜紧密连接蛋白基因的表达上调,增强空肠黏膜物理屏障功能,降低沙门氏菌感染对空肠黏膜的损伤。乳杆菌也被证实具有抑制沙门氏菌生长、黏附和侵袭肠道上皮细胞的能力,并一定程度上缓解沙门氏菌引起的炎症反应和组织损伤[47-48]。Wang 等[13]研究表明,植物乳杆菌消除了肠通透性的升高以及细菌移位,稳定紧密连接基因的表达,调节炎症介质的水平,减少沙门氏菌在肠道内的定植,从而保护雏鸡肠道屏障的完整性。赵效南[49]指出,饲喂丁酸梭菌能够改变肠道微生物组成,增加微生物多样性,缓解由沙门氏菌导致的肠道损伤,进而保证了肠道屏障的完整性,对沙门氏菌引起的感染起到了有效的预防和治疗作用。益生菌对沙门氏菌感染鸡肠道健康的影响研究进展汇总见表 1。

表 1 益生菌对沙门氏菌感染鸡肠道健康的影响研究进展

Table 1 Research progress on effects of probiotics on intestinal health of *Salmonella* infected chickens

分类 Species	益生菌的作用效果 Effects of probiotics	参考文献 Reference
凝结芽孢杆菌 *Bacillus coagulans*	增加盲肠内乳酸杆菌和双歧杆菌的数量,降低大肠杆菌和沙门氏菌的数量,提高空肠绒毛高度与隐窝深度的比值	Zhen 等[14]
植物乳杆菌 *Lactobacillus plantarum*	减少肠道内沙门氏菌数量,减轻肠道形态学损伤,改善了沙门氏菌感染导致的肠道 *ZO*-1、*CLDN*-2 和 *CLDN*-5 mRNA 表达水平的降低	Wang 等[13]
约翰逊乳杆菌 *Lactobacillus johnsonii*	减少肠道内沙门氏菌数量,提高对沙门氏菌的定植抗性	Olnood 等[39]
枯草芽孢杆菌 *Bacillus subtilis*	减少沙门氏菌在盲肠中的定植,增加盲肠微生物多样性、回肠中的共生细菌群数	Hayashi 等[41]
枯草芽孢杆菌 *Bacillus subtilis*	鸡盲肠中沙门氏菌的数量降低了 3 个对数单位	Knap 等[42]
枯草芽孢杆菌 *Bacillus subtilis*	缓解沙门氏菌感染引起的肠道菌群失调,促进肠道中唾液乳杆菌的增殖	李琼燕[43]
枯草芽孢杆菌 *Bacillus subtilis*	增强沙门氏菌感染空肠黏膜的 *CLDN*-1、*OCLN*、*ZO*-1 基因的表达	朱沛霁[36]
丁酸梭菌 *Clostridium butyricum*	减少盲肠内容物中沙门氏菌数量,缓解沙门氏菌感染导致的鸡肠道黏液层厚度下降,增加 *ZO*-1 基因的表达	赵效南[49]

ZO-1:闭合小环蛋白-1 zonula occluden-1;*CLDN*-2:闭合蛋白-2 claudin-2;*CLDN*-5:闭合蛋白-5 claudin-5;*CLDN*-1:闭合蛋白-1 claudin-1;*OCLN*:闭锁蛋白 occludin。

2.4 益生菌对鸡免疫功能的影响

鸡的免疫系统由免疫器官、免疫细胞、免疫因子共同组成。研究发现,通过每千克饲粮中添加 10^9 CFU 枯草芽孢杆菌或通过对 1 日龄雏鸡进行口腔灌服 10^6 CFU/只丁酸梭菌、10^9 CFU/只植物乳杆菌均可显著降低肠炎沙门氏菌在脾脏、盲肠组织的载菌量[13,49-50]。除此之外,Thomas 等[51]也证实了添加乳杆菌可减少海德堡沙门氏菌在火鸡脾脏内的转移和定植。在提高免疫器官指数上,Park 等[50]和 Sadeghi 等[19]研究表明,饲粮中添加枯草芽孢杆菌可增加沙门氏菌感染肉鸡的法氏囊和脾脏的相对重量。由此可见,益生菌可通过减少病原菌的侵袭,促进免疫器官健康发育,从而增强抵御沙门氏菌感染的能力。

益生菌通过调节机体促炎因子和抗炎因子的水平发挥抵御沙门氏菌感染的作用。唐慧琴等[52]发现,枯草芽孢杆菌可诱导机体产生特异性抗沙门氏菌血清免疫球蛋白 G(IgG)和回肠免疫球蛋白 A(IgA),进而激活免疫应答反应,提高机体对沙门氏菌的清除和消灭能力。Wang 等[53]发现,干酪乳杆菌可增强肠道黏膜免疫功能,调节细胞因子水平,有效减轻沙门氏菌感染引起的肠道损伤。赵丽杰等[54]研究表明,饲粮中添加复合乳酸菌制剂在对 SPF 鸡受到沙门氏菌攻击后,可降低

炎症细胞因子的表达水平,缓解机体的炎症反应。Filho 等[55]指出,复合乳杆菌制剂到达肠道后可发挥免疫调节作用,通过减少沙门氏菌的定植和肠黏膜的炎症程度来影响机体先天免疫反应。Zhao 等[56]研究表明,丁酸梭菌能刺激家禽的免疫功能,降低携带沙门氏菌肉鸡体内炎症因子的表达水平,且主要是通过下调肠道组织和肠黏膜上皮细胞中炎症信号通路相关蛋白基因的表达来减轻机体的炎症反应。益生菌对沙门氏菌感染鸡细胞因子的影响研究进展汇总见表 2。

表 2　益生菌对沙门氏菌感染鸡细胞因子的影响研究进展

Table 2　Research progress on effects of probiotics on cytokines in *Salmonella* infected chickens

分类 Species	益生菌的作用效果 Effects of probiotics	参考文献 Reference
干酪乳杆菌 *Lactobacillus casei*	提高空肠 sIgA、IL-10、PCNA 水平,降低 IL-17、TNF-α、IFN-γ 和 TGF-β 水平	Wang 等[53]
复合乳酸菌(乳酸菌、枯草芽孢杆菌、酵母菌及其代谢产物) Compound lactobacillus (*Lactobacillus*, *Bacillus subtilis*, yeast and their metabolites)	抑制 *Myd*88、*TRAF*6、*NF-κB* 的 mRNA 转录,下调 *IL-1β*、*iNOS* 的 mRNA 转录	赵丽杰等[54]
复合乳酸菌(嗜酸乳杆菌、发酵乳杆菌、罗伊乳杆菌、唾液乳杆菌) Compound lactobacillus (*Lactobacillus acidophilus*, *Lactobacillus fermentans*, *Lactobacillus reuteri*, *Lactobacillus salivary*)	直接或间接减轻 $CD8^+$T 细胞和 γδT 细胞对沙门氏菌的炎症反应和细胞毒性免疫反应,降低促炎细胞因子 LITAF 水平,并刺激盲肠扁桃体 *TLR*-2 的表达	Filho 等[55]
丁酸梭菌 *Clostridium butyricum*	降低肠道 IFN-γ、IL-1β、IL-8 和 TNF-α 水平,增加外周血单个淋巴细胞中 $CD4^+$T 细胞百分比和 $CD4^+/CD8^+$的比例	Zhao 等[56]

sIgA:分泌型免疫球蛋白 A secretory immunoglobulin A;IL-10:白细胞介素-10 interleukin-10;PCNA:增殖细胞核抗原 proliferating cell nuclear antigen;IL-17:白细胞介素-17 interleukin-17;TNF-α:肿瘤坏死因子-α tumor necrosis factor-α;IFN-γ:干扰素-γ interferon-γ;TGF-β:转化生长因子-β transforming growth factor-β;*Myd*88:髓样分化因子 88 myeloid differentiation factor 88;*TRAF*6:肿瘤坏死因子受体相关因子 6 TNF receptor associated factor 6;NF-κB:核因子-κB nuclear factor-κB;*IL-1β*:白细胞介素-1β interleukin-1β;*iNOS*:诱导型一氧化氮合酶 inducible nitric-oxide synthase;TLITAF:脂多糖诱导的肿瘤坏死因子-α lipopolysaccharide-induced TNF-α factor;*TLR*-2:Toll 样受体-2 Toll-like receptor-2;IL-8:白细胞介素-8 interleukin-8。

3　小　结

随着国内饲料抗生素全面禁用时代的到来,我国畜牧养殖业将面临不小的挑战。益生菌作为安全有效的抗生素替代物之一,在发挥抑制病原菌生长作用的同时,可维护鸡的肠道健康,具有调节机体抗氧化与免疫功能的作用,必将在畜禽健康高效养殖及疾病防控等方面取得良好的效益。但益生菌种类繁多,同一种类不同菌株的作用效果也有所不同,因此各菌种、各菌株发挥有效抗沙门氏菌感染的剂量也难以统一标准。未来应对复合益生菌制剂是否会比单一菌株更有效,以及益生菌是通过何种益生元件发挥抵御沙门氏菌的作用等问题开展深入系统的研究,为益生菌作为饲料添加剂在疾病防控方面科学合理的应用提供理论依据。

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Research Progress on Probiotics against *Salmonella* Infection in Chickens

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Abstract: *Salmonellosis* is a common disease in poultry production. It spreads horizontally and vertically, leading to widespread population transmission and transmission through food chain to human through meat, eggs and other products, causing serious public health problems. Studies have found that probiotics can effectively inhibit the growth of pathogenic bacteria, and play a role in resisting *Salmonella* infection in chickens by improving antioxidant capacity, intestinal function and immunity. In this paper, the pathogenic mechanism of *Salmonella* and the effect of probiotics on resisting *Salmonellosis* in chickens were reviewed, in order to provide reference for the application of probiotics in the control of chicken *Salmonellosis* and healthy breeding. [***Chinese Journal of Animal Nutrition*, 2021, 33(5):2408-2415**]

Key words: probiotics; *Salmonella*; intestines health; immune function; chickens

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