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益生菌调控幼龄畜禽消化道微生物研究进展

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摘 要： 益生菌是一类对宿主（人类或动物）有益的活性微生物，包括细菌、真菌（如酵母）等，具有促进动物生长、提高免疫力的作用，是潜在的抗生素替代品。益生菌可能通过与动物消化道微生物互作来发挥益生作用，但具体机制仍不明确。综述了基于高通量测序技术研究益生菌调控幼龄畜禽（仔猪、雏鸡、反刍动物）消化道微生物群落组成的最新进展，并提出了未来研究方向，包括益生菌如何通过与消化道微生物互作影响其功能，益生菌对于幼龄畜禽不同健康状态下肠道微生物的影响，以及宿主因素如何影响益生菌对于幼龄畜禽消化道微生物的作用效果。

关键词： 益生菌；机制；消化道微生物；畜禽；幼龄
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Recent Advance in the Study of the Regulation of Early Life Gut Microbiota by Probiotics in Livestock

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Abstract: Probiotics are defined as live microorganisms that confer a health benefit on the host (human/animals), including bacteria, fungi (i.e., yeasts), etc. Probiotics demonstrate beneficial effects on the animal by improving the growth and immunity, and therefore have been proposed to be a promising alternative to antibiotics. It is suggested that the interaction between probiotics and gut microbiota results in the beneficial effect of probiotics, despite that the mechanisms remain largely unknown. This review summarizes the most recent advances in regulating microbiota in gastrointestinal tract of early age livestock (piglet, chicken, and ruminant) by probiotics based on high-throughput sequencing technology. The paper also highlights the future directions, including how probiotics interact with gut microbiota and affect their functions, how probiotics affect gut microbiota of livestock under different health conditions in early age, and how host factors affect the efficacy of probiotics in terms of regulating gut microbiota of livestock in early age.

Key words: probiotics; mechanism; microbiota in gastrointestinal tract; livestock; early age

随着世界人口和经济的快速增长，人们对于优质动物产品的需求量与日俱增。预计到2050年，对于肉和蛋的需求将增加73%，对奶制品的需求将增加58%[2]。为了满足人们对于优质动物产品的需求，提高畜禽生产性能和效率是畜牧业发展的重中之重。长期以来，抗生素不仅能够预防和治疗动物疾病，还具有促进动物生长的作用[3]。预计2030年，全球动物养殖使用的抗生素总量将提高到105 596 t，且仅在亚洲就将达到51 851 t，占全球使用总量的一半[4]。尽管适量或低剂量的抗生素能够预防疾病或促进动物生产，但仍会导致抗药性病原菌的出现[5-6]。2019年7月，中华人民共和国农业农村部

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发布第 194 号公告，饲料无抗已迫在眉睫，因此寻找合适的抗生素替代品，成为动物生产的一项重要任务。

益生菌是一类对宿主（人类或动物）有益的活性微生物[7]，包括细菌、真菌（如酵母）等，能够有效提高动物生产性能[8-9]和对疾病的抵抗力[10]，同时能够抑制耐药性细菌的生长[11-12]，在畜禽生产中具有替代抗生素的潜力。动物消化道中存在着大量的微生物，包括细菌、原虫、病毒及真菌等[13]。与成年阶段相比，新生或幼龄动物的消化道微生物更易受日粮等因素的影响，且该影响作用持续时间更长久[14]。因此，合理利用益生菌调控消化道微生物和宿主之间建立早期的积极互作，对于促进其消化道免疫功能的建立、提高生产性能具有长效作用[15]。本文介绍了益生菌的潜在作用机制，对近 10 年来利用高通量测序技术研究益生菌调控幼龄畜禽（仔猪、雏鸡和反刍动物）消化道微生物的进展进行了总结和归纳，并提出了未来研究方向，包括益生菌如何通过与消化道微生物互作影响其功能，益生菌对于幼龄畜禽不同健康状态下肠道微生物的影响，以及宿主因素如何影响益生菌对于幼龄畜禽消化道微生物的作用效果。

1 益生菌的潜在作用机制

作为有效的益生菌，必须保证其自身能够耐受消化道的特殊环境（温度、pH 等），能够附着在消化道上皮细胞上，在此基础上，产生抗病原微生物的物质，并在消化道中发挥持续的益生作用[16]。益生菌在动物消化道中发挥作用的潜在机制主要包括 3 个方面：首先，益生菌通过多种途径抑制病原微生物的生长，具体表现在：（1）益生菌与病原微生物竞争有限的营养源、能量以及消化道结合位点，从而限制病原微生物生长。青春双歧杆菌（*Bifidobacterium adolescentis*）S2-1 能够与牙龈卟啉单胞菌（*Porphyromonas gingivalis*）竞争维生素 K，从而抑制其生长[17]。（2）益生菌通过产生抗微生物成分包括细菌素、有机酸、过氧化氢等，抑制病原微生物生长，如卷曲乳杆菌（*Lactobacillus crispatus*）F117 和副干酪乳杆菌（*Lactobacillus paracasei*）F2/F28 均能够通过产生大量的过氧化氢来抑制金黄色葡萄球菌（*Staphylococcus aureus*）的生长[18]。此外，益生菌产生的乳酸、有机酸能够通过降低消化道 pH，从而抑制沙门氏菌和大肠杆菌等病原微生物的生长[19]。其次，益生菌能够作用于宿主消化道上皮细胞和树突细胞，促进上述细胞产生消化道黏液或防御素[20-21]，提高紧密连接以及屏障功能[22]，防止促炎性细胞因子导致的细胞凋亡[23]。主要体现在：乳杆菌[24-25]、链球菌[26]及双歧杆菌[27]等益生菌能够通过纤毛附着在宿主消化道细胞上。在成功黏附后，肽聚糖（革兰氏阳性菌）和脂多糖（革兰氏阴性菌）等益生菌细胞壁成分与消化道上皮细胞和树突细胞模式识别受体相互作用，促使后者产生黏液或防御素[28]。此外，益生菌产生的细菌黏附素如黏液结合蛋白也有利于其结合宿主树突细胞，从而发挥其吞噬作用[29]。第三，益生菌可能通过调控宿主特异性免疫功能来发挥作用，主要表现在乳酸菌对肠淋巴组织的调控作用[30]。乳酸菌的免疫活性不仅体现在调控 Toll 样受体（TLR）表达、激活树突细胞和自然杀伤细菌等非特异性免疫反应，还体现在调控调节性 T 细胞（Treg）应答以及特异性免疫球蛋白 A 的分泌等免疫反应[31]。例如，脆弱拟杆菌（*Bacteroides fragilis*）[32]及梭菌属（*Clostridium*）IV[33-34]等能够提高无菌小鼠结肠 Treg 细胞的数量；婴儿型双歧杆菌（*Bifidobacterium infantis*）能够促进感染沙门氏菌的小鼠消化道 Treg 细胞的生成[35]；健康的人服用婴儿型双歧杆菌 35624 后，其 Treg 细胞表达量提高。此外，其外周血液中的白介素 -10 分泌功能增加[36]。尽管在人类和实验动物上的研究一定程度上揭示了益生菌的作用机制，但上述机制是否同样能够解释益生菌与畜禽消化道微生物的相互作用，还有待于进一步探索。

2 益生菌调控幼龄畜禽消化道微生物的研究进展

基于高通量测序技术研究益生菌调控幼龄畜禽消化道微生物的报道主要集中在近 10 年，但总体研究数量仍比较少。在仔猪和雏鸡上研究应用较多的益生菌包括乳杆菌属、肠球菌属及芽孢杆菌属等；在幼龄反刍动物上研究应用较多的益生菌为酵母。上述益生菌的主要益生作用体现在提高幼龄畜禽消

化道有益微生物的丰度，降低有害微生物的丰度。但在不同动物品种之间，具体益生作用有较大的区别，一方面是由于不同动物使用的益生菌菌种/株存在差异；另一方面是由于不同动物消化道微生物存在差异。因此，本节将围绕不同益生菌对不同品种的幼龄动物（仔猪、雏鸡及反刍动物）消化道微生物组成的影响作具体阐述。

2.1　益生菌调控仔猪消化道微生物的研究

在仔猪上研究应用的益生菌主要包括乳杆菌属（*Lactobacillus*）[37-39]、肠球菌属（*Enterococcus*）[40-43]、芽孢杆菌属（*Bacillus*）[44-45]以及丙酸杆菌属（*Propionibacterium*）[46]（表1）。上述益生菌调控仔猪消化道微生物的主要作用包括提高了普雷沃氏菌科（*Prevotellaceae*）[39]、双歧杆菌科（*Bifidobacteriaceae*）[39]、小杆菌属（*Dialister* spp.）[38]和光冈菌属（*Mitsuokella* spp.）[38]、乳杆菌目/属[40, 42, 44]和梭菌属（*Clostridium*）的相对丰度。其中，普遍认为普雷沃氏菌是畜禽消化道中的一类有益微生物，与分解植物源的饲料成分密切相关[47]；双歧杆菌也是人和动物消化道菌群的重要组成成员之一，其能够分解碳水化合物生成乳酸，对于维持消化道健康和菌群稳定具有重要作用[48]；小杆菌属与消化道短链脂肪酸产量呈正相关，对于维持消化道免疫功能具有重要作用[49]；光冈菌属中的*M. jalaludinii*菌种具有分解植酸磷的作用[50]。除提高有益微生物的相对丰度外，上述益生菌能够降低肠杆菌科（Enterobacteriaceae）[38]、韦荣氏球菌科（Veillonellaceae）[41]、假单胞菌属（*Pseudomonas*）[43]、变形菌门（Proteobacteria）和放线菌门（Actinobacteria）的相对丰度。肠杆菌科包含的大肠杆菌（*Escherichia coli*）存在多个致病性菌株，如大肠杆菌O157：H7和S102-9，可引起动物感染性腹泻或肠炎[51-52]；韦荣氏球菌科可能会引起消化道胆酸浓度过高，影响消化道健康，也是炎症性肠炎的标记物之一[53-54]。然而也有研究表明，添加益生菌对仔猪消化道微生物无显著影响[37, 46]，说明了益生菌和宿主及微生物之间互作的复杂性，受到益生菌的类型、添加方法、剂量及动物因素（如品种、饲养方式和试验周期）

表1　基于高通量测序技术应用益生菌调控仔猪消化道微生物的研究

益生菌类别	益生菌菌种/株	年龄	样品	微生物相对丰度变化	参考文献
乳杆菌属	发酵乳杆菌（*L. fermentum*）I5007	新生	结肠食糜	无显著影响	[37]
	罗伊氏乳杆菌（*L. reuteri*）TMW1.656	21日龄	粪样	肠杆菌科（Enterobacteriaceae）降低，小杆菌属（*Dialister* spp.）和光冈菌属（*Mitsuokella* spp.）升高	[38]
	植物乳杆菌（*L. plantarum*）PFM 105	28日龄	结肠食糜	普雷沃氏菌科（Prevotellaceae）和双歧杆菌科（Bifidobacteriaceae）升高	[39]
肠球菌	屎肠球菌（*E. faecium*）NCIMB11181	28日龄	粪样	乳杆菌属升高，肠杆菌科和韦荣氏球菌科（Veillonellaceae）降低	[40-41]
	屎肠球菌EF1	新生	盲肠食糜	拟杆菌门（Bacteroidetes）和乳杆菌目（Lactobacillales）升高，变形菌门（Proteobacteria）降低	[42]
	粪肠球菌（*E. faecalis*）UC-100	25日龄	粪样	纤维杆菌门（Fibrobacteres）和包含假单胞菌属（*Pseudomonas*）在内的12个菌属降低	[43]
芽孢杆菌	地衣芽孢杆菌（*B. lichiformis*）DSM 5749、枯草芽孢杆菌（*B. subtilis*）DSM 5750	21日龄	结肠粘膜	梭菌属（*Clostridium*）、乳杆菌属升高	[44]
	枯草芽孢杆菌	7日龄	空肠结肠食糜	硬壁菌门（Firmicutes）升高，拟杆菌门、放线菌门（Actinobacteria）、变形菌门降低	[45]
丙酸杆菌	费氏丙酸杆菌（*P. freudennreichii*）BIA129	49日龄	结肠食糜	无显著影响	[46]

等的影响。

2.2 益生菌调控雏鸡消化道微生物的研究

与仔猪上的研究类似，肉鸡饲粮中常用的益生菌包括乳杆菌[55-58]、肠球菌[59-60]、芽孢杆菌[61-63]及多菌种的组合[64-65]（表2）。益生菌对雏鸡消化道微生物的影响主要体现在降低了潜在病原微生物的相对丰度，如罗伊氏乳杆菌KUB-AC5降低了回肠食糜气单胞菌属（*Aeromonas*）和弯曲杆菌目（Campylobacterales）的相对丰度[55]；屎肠球菌（*E. faecium*）NCIMB 10415降低了排泄物中埃希－志贺菌属（*Escherichia-Shigella*）[60]。气单胞菌属和弯曲菌目是鸡肉中常见的病原微生物[66]，弯曲杆菌属是最常见的食物源性病原微生物[67]，能够引起一系列人类消化道疾病，而家禽及其产品是重要的弯曲杆菌感染源[68]。此外，埃希－志贺菌属也包含了大量潜在病原微生物，如上述致病性大肠杆菌（*E. coli* O157：H7、*E. coli* S102-9），因此，降低这些潜在病原微生物的相对丰度，对于降低家禽消化道疾病风险，提高其免疫性能及生产性能具有重要意义。另一方面，添加益生菌后，乳杆菌、瘤胃球菌、肠球菌等丰度升高。上述益生作用可能与益生菌促进消化道免疫功能有关，如添加乳杆菌[58, 69]、肠球菌[59, 70]，梭菌属[71]或复合益生菌能够提高雏鸡血清免疫球蛋白M、A、G的浓度，进而降低了致病菌的数量。此外，添加益生菌能够提高雏鸡空肠黏膜免疫型免疫球蛋白A[72]、杯状细菌数量和中性黏液的产量[73-74]，上述免疫相关物质均能够保护禽类肠黏膜免受有害菌的破坏，从而保持黏膜稳态[70]。

2.3 益生菌调控幼龄反刍动物消化道微生物的研究

幼龄反刍动物由于瘤胃尚未完全发育，其消化道结构类似于单胃动物[75]。研究表明，犊牛出生后1–3 d内，瘤胃中已经存在以变形菌门、硬壁菌门和拟杆菌门为主的大量微生物[76]，说明这些微生物

表2 基于高通量测序技术应用益生菌调控雏鸡消化道微生物的研究

益生菌	菌种/株	年龄	样品	微生物相对丰度变化	参考文献
乳杆菌	罗伊氏乳杆菌（*L. reuteri*）KUB-AC5	一日龄	回肠食糜	气单胞菌属（*Aeromonas*）、弯曲菌目（Campylobacterales）等降低	[55]
	嗜酸乳杆菌（*L. acidophilus*）D2/CSL	一日龄	盲肠食糜	卵形瘤胃球菌（*R. obeum*）、梭状梭菌（*C. clostridioforme*）、消化道罗斯氏菌（*R. intestinalis*）等升高	[56]
	唾液乳杆菌（*L. salivarius*）SMXD51	一日龄	盲肠食糜	空肠弯曲杆菌（*C. jejuni*）降低	[57]
	植物乳杆菌（*L. plantarum*）8	一日龄	排泄物	多个乳杆菌种升高	[58]
肠球菌	屎肠球菌（*E. faecium*）CGMCC 9353	一日龄	盲肠食糜	乳杆菌属和肠球菌属升高	[59]
	屎肠球菌（*E. faecium*）NCIMB 10415	一日龄	排泄物	埃希－志贺菌属（*Escherichia-Shigella*）降低，布劳特氏菌属（*Blautia*）、厌氧棍状菌属（*Anaerotruncus*）、乳杆菌属升高	[60]
芽孢杆菌	枯草芽孢杆菌（*B. subtilis*）CSL2	一日龄	排泄物	乳杆菌属升高，苏黎世杆菌属（*Turicibacter*）、未分类肠球菌科、拟杆菌属（*Bacteroides*）降低	[61]
	枯草芽孢杆菌（*B. subtilis*）DSM 32315	一日龄	回肠食糜 盲肠食糜	瘤胃球菌属升高	[62]
	枯草芽孢杆菌（*B. subtilis*）29784	一日龄	回肠食糜/粘膜 盲肠食糜/粘膜	盲肠瘤胃球菌属、*Lachnoclostridium*、*Anaerostipes* 升高	[63]
组合	戊糖片球菌（*P. pentosaceus*）、蜡状芽胞杆菌乳白变种（*B. cereus* var. *albolactis*）、浸麻芽孢杆菌（*B. macerans*）、枯草芽孢杆菌、植物乳杆菌、东方伊萨酵母（*I. orientalis*）	一日龄	盲肠食糜	拟杆菌属升高，普雷沃氏菌属有升高趋势	[64]
	敏捷乳杆菌（*L. agilis*）、罗伊氏乳杆菌（*L. reuteri*）、*L. ingluviei*	一日龄	盲肠食糜 回肠粘膜	单形拟杆菌（*B. uniformis*）升高，费格森埃希菌（*E. fergusonii*）降低	[65]

可能在瘤胃发育及功能完善的过程中起到重要作用。饲粮因素如益生菌对幼龄反刍动物消化道微生物的研究仍较少，研究表明，代乳粉中添加5种益生菌组合，包括解淀粉芽胞杆菌（*B. amyloliquefaciens*）H57、小孔芽孢杆菌（*B. foraminis*）VTM4R85、坚强芽孢杆菌（*B. firmus*）VTM2R84、地衣芽孢杆菌（*B. licheniformis*）VTM2R66、地衣芽孢杆菌VTM1R74和腐生葡萄球菌（*Staphylococcus saprophyticus bovis*）VTM1R96能够提高新生羔羊瘤胃液中普雷沃氏菌科、瘤胃球菌科相对丰度，降低毛螺菌科的相对丰度[77]；新生犊牛代乳粉中添加布拉迪酵母（*S. boulardii*）CNCM I-1079，瘤胃液中只有瘤胃球菌科UCG-008相对丰度显著降低，其他微生物相对丰度没有变化。此外，布拉迪酵母CNCM I-1079[78]显著降低了盲肠黏膜链球菌属（*Streptococcus*）的相对丰度，链球菌属中有多个菌种具有致病性，如酿脓链球菌（*S. pyogenes*）和肺炎链球菌（*S. pneumoniae*）；降低了回肠黏膜艰难梭菌属（*Peptoclostridium*）的相对丰度，艰难梭菌属是引起腹泻的一种病原菌[79]；提高了回肠黏膜纤维杆菌属（*Fibrobacter*）、罗斯氏菌属（*Roseburia*）和欧氏菌属（*Olsenella*）的相对丰度，罗斯氏菌是一种产丁酸菌，不仅能够为消化道细胞提供能量，而且还具有抗炎症的作用，有利于维持正常免疫功能[80-81]；欧氏菌是一种乳酸菌，具有耐胆汁酸的特性且能够利用黏蛋白[82-83]。但也有研究表明，或布拉迪酵母CNCM I-1079对犊牛粪便微生物无显著影响[84]，这可能是由于粪便微生物并不能够代表整个消化道的微生物变化情况。相比较在仔猪和雏鸡上开展的大量益生菌调控消化道微生物的效果研究，益生菌调控幼龄反刍动物的研究仍处在起步阶段。基于此，有必要进一步开展相关研究，为合理有效使用益生菌促进幼龄反刍动物长期健康和提高其生产性能奠定基础。

3　未来研究方向

大量研究表明，益生菌具有替代抗生素的潜力。但由于目前对于益生菌的作用机制尚未完全明确，因此在一定程度上限制了益生菌的合理有效利用。为解决这一问题，今后需要更多研究来阐明益生菌与消化道微生物互作，以及这种互作如何进一步影响畜禽消化道功能和健康及生产性能。

第一，除了明确益生菌对消化道微生物组成的影响之外，还需要进一步明确其对消化道微生物功能的影响，因为最终在生态系统中起重要作用的是微生物功能，而不是其组成[85]。事实上，已有研究表明环境微生物的功能与其组成相比更具有保守性和相关性[86-87]。由此可推断，益生菌引起的微生物组成上的变化并不一定能够引起或反映功能的变化。因此，今后需要更多基于宏基因组或宏转录组的研究，来探索益生益引起的微生物相关基因或转录因子的变化，从而帮助我们更好地理解益生菌和微生物之间的互作。

第二，益生菌的益生作用不应仅限于在健康动物上的研究，还需要研究在非正常状态（如应激/疾病）下的作用效果，在鸡[88]、猪[89]和犊牛[90]上的研究表明，益生菌对于健康动物消化道微生物的作用效果并不一定能在应激或疾病状态下表现出来，这可能是因为在不同健康状态下动物消化道微生物群落也存在差异，因此需要明确在不同健康状态下动物消化道的核心微生物组成，从而为精确筛选益生菌菌株，有效调控消化道微生物，为治疗疾病或缓解应激奠定基础。

第三，相比在仔猪和雏鸡上面的研究，益生菌对幼龄反刍动物消化道微生物的影响仍较为有限。反刍动物拥有独特的消化道结构，瘤胃微生物能够发酵利用高纤维素含量的饲料[91]；另一方面，由于瘤胃微生物的存在，外源益生菌可能由于竞争或不适应瘤胃特殊的环境（温度、pH）而无法定植[92]，因此有必要充分研究益生菌和瘤胃微生物的互作，从而开发能够适应瘤胃环境且能有效调控瘤胃发酵功能的益生菌。

第四，除微生物因素外，宿主遗传因素以及环境因素也会影响益生菌的作用效果，在小鼠上的研究表明，上述因素是造成微生物个体差异的重要原因[93]。近年来研究也表明了宿主遗传因素对牛瘤胃微生物的个体差异存在显著影响[94-95]，在牛上有些可遗传的微生物与SNP（单核苷酸多态性）存在相关性[96]；当然，也有研究表明鸡的消化道微生物不受宿主遗传因素（SNP）的影响[97]，造成上述研究结果存在差异的原因仍不明确，因此还需要继续探

索环境（如养殖场和饲粮）和宿主遗传因素（如品种和性别）如何决定个体微生物差异，以及后者如何影响益生菌调控效果，从而有针对性地筛选益生菌，促进动物健康和生产性能。

4 小结

益生菌能够有效提高畜禽健康和生长性能，尽管其调控机制尚未明确，但益生菌和消化道微生物互作可能很大程度上决定了益生菌的有益作用效果。目前关于益生菌和幼龄畜禽消化道微生物互作的研究非常有限，在一定程度上限制了益生菌的有效应用。组学技术的发展，为更深入了解益生菌的作用效果和机制提供了可能，因此，今后有必要利用多组学技术，针对性地研究具体的益生菌菌株、宿主因素等如何影响幼龄畜禽消化道微生物的组成和功能。

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