研究进展

仔猪肠道微生物研究进展

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【摘要】 肠道菌群在哺乳动物及人类健康的作用正日益受到重视。仔猪的健康生长需要一个动态平衡的肠道微生态环境。然而,在猪的生命周期中,从食管到直肠的微生物分布与组成存在时间和空间的变化。健康的肠道菌群具有促进猪的营养代谢,维持肠黏膜屏障,调节免疫应答,抑制病原菌感染等功能。多种因素对猪肠道菌群的形成与稳定具有重要的作用,包括分娩方式(经过产道或剖宫产)、幼龄时期饮食(母乳或配方饲料)、抗生素或抗生素样分子的使用等。本文主要从仔猪肠道微生物组成与定植、功能、影响肠道微生物的因素等方面论述了仔猪肠道微生物与仔猪肠道健康的关系,从而加深肠道微生物对维护仔猪肠道健康作用的认识。

【关键词】 肠道微生物菌群;肠道健康;仔猪

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Current understanding of the intestinal microbiota of piglets

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【Abstract】 The role of intestinal microbiota in mammals and humans are gaining increasing attention. The health of piglets requires a dynamically balanced intestinal microbiota. However, there are temporal and spatial changes in the distribution and composition of microbiota from the esophagus to the rectum during the life cycle of the pig. The intestinal microbiota has various beneficial functions in pig, like nutrient metabolism, intestinal mucosal barrier, immune responses and pathogen infection. A variety of factors play an important role in the formation and stabilization of intestinal microbiota, including the ways of delivery (vaginal or caesarean), the diet during infancy (breast milk or formula feeds) and the usage of antibiotics or antibiotic - like molecules. In this review, we mainly discussed the relationship between intestinal microbiota and the intestinal health of piglets from the aspects of the composition and colonization of intestinal microbiota, as well as the functions and influencing factors of intestinal microbiota, so as to further understanding the importance of intestinal microbiota in intestinal function of piglets.

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【**Key words**】 Intestinal microbiota; Intestinal health; Piglets

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哺乳动物的肠道中存在大量的微生物[1-4]。肠道微生物间以及宿主和肠道微生物之间存在着复杂的动态平衡关系。多年来,研究发现单胃动物的肠道生理功能受其肠道菌群的影响[5,6]。仔猪在出生后,通过接触源自外界以及母体的各种微生物,其胃肠道逐渐形成一个复杂的微生态环境。这种复杂的微生态环境对仔猪的健康生长极其重要。保持动态平衡的肠道微生态环境不仅有助于仔猪对营养物质的消化、吸收,还能形成微生物屏障以阻止病原菌的入侵并促进其肠道发挥免疫功能[7]。

营养因素与肠道菌群之间存在复杂的关系[8]。肠道微生物会影响宿主对营养物质的消化和吸收,同时,微生物的发酵产物可为宿主提供营养成分或者干预宿主的健康。此外,某些微生物代谢产物(丁酸)如具有特定的生物活性,可以影响肠道微生物的数量与组成[9],或者对宿主有潜在的不利影响[10]。仔猪出生后,首先通过吮食母乳在肠道内建立一个相对稳定的微生态环境,而在断奶阶段,由于产生断奶应激以及日粮成分发生改变,其肠道内的微生态环境会发生巨大的变化[11]。本文主要从仔猪不同生长阶段和肠道不同部位的微生物组成、定植情况以及影响肠道微生物的因素等方面,阐述仔猪肠道微生物与仔猪肠道健康的关系,旨在为健康养殖和仔猪肠道健康生态营养调控等方面研究提供帮助。

1 仔猪肠道微生物的定植与组成

新生仔猪肠道处于无菌状态,仔猪通过与外界环境和母亲的产道、粪便接触[12],造成需氧、兼性厌氧和专性厌氧菌在其肠道内按照一定次序定植[13]。这是因为随着需氧菌和肠杆菌、肠球菌等兼性厌氧菌的定植,胃肠道的氧气被消耗完毕,继而逐渐形成厌氧环境,导致专性厌氧菌开始定植和生长。仔猪出生 2 d 后,乳酸杆菌等便逐渐替代需氧菌成为其肠道内的优势菌群。整个哺乳期阶段,每克食糜所含乳酸杆菌的数量保持在 $10^7 \sim 10^9$ 范围内[14]。在仔猪的整个生命过程中,由于断奶应激、仔猪日粮营养物质的变化、胃肠道环境在不同生理阶段的改变以及肠道内特定微生物的定植位点发生转变等,其肠道微生物区系的种类和数量也发生变化[13]。据报道,哺乳仔猪肠道中乳酸杆菌的数量较断奶仔猪更高,而大肠杆菌数量则相反[15],这是由于断奶仔猪胃内 pH 值升高,乳酸杆菌减少,使大肠杆菌开始大量增殖,进而抑制乳酸杆菌的生长。哺乳仔猪胃内 pH 值较低,会导致经口病原菌无法像断奶仔猪中的病原菌那样通过胃部而定植于肠道内[16]。Konstantinov 等[17-19]研究发现,仔猪断奶后回肠中乳酸杆菌数量较断奶前相比显着下降,大肠杆菌数量却显着增加。在仔猪断奶后的 2 周,其肠道的生理及微生态环境会发生巨大的变化[20,21]。

有研究表明,仔猪不同胃肠道部分的微生物分布和组成有很大差异。胃和小肠内的优势菌群主要是梭菌 IX 群、链球菌和乳酸杆菌等,而后肠部位分布着多样性更高的菌群,其中盲肠、结肠和直肠内优势菌群以厚壁菌门中的梭菌 IV 群、XIV 群和拟杆菌门细菌为主[22]。

2 肠道微生物功能

宿主的首要任务是抵御肠道微生物引起的持续性感染。尽管肠道微生物具有多种有益于宿主健康的功能,如碳水化合物的消化和发酵、合成维生素、维持肠绒毛的正常功能、调节免疫反应以及保护肠道免受病原菌感染[23,24],然而,肠道微生物也会通过其代谢产物、基因产物或潜在致病性给宿主带来不利影响[25]。因此,肠道微生物的有益功能和对宿主产生的危害之间的平衡取决于其分布、多样性以及代谢产物的总体状态(如图 1)。

2.1 营养物质代谢

日粮碳水化合物是肠道菌群最主要的营养来源。未经近端小肠消化的碳水化合物及结肠内微生物(如拟杆菌属、双歧杆菌属和肠杆菌等)难以消化的寡糖经过发酵生成乙酸、丙酸、丁酸等短链脂肪酸[27,28]。拟杆菌属是参与碳水化合物代谢的主要微生物,它通过表达糖基转移酶、糖苷水解酶和多糖酶等酶来实现这一功能。肠道菌群也通过抑制脂肪细胞的脂肪酶活性对脂质代谢产生积极影响。此外,多形拟杆菌可以通过上调胰脂肪酶消化脂质时所需的辅脂酶的表达来增加脂质的水解效率[29]。

肠道菌群具有有效的蛋白质代谢机制,即通过微生物蛋白酶和肽酶与宿主蛋白酶产生协同作用。一些基因产物可将氨基酸转化成小信号分子和抗微生物肽,如通过细菌 *hdcA* 基因编码的组胺脱羧酶可

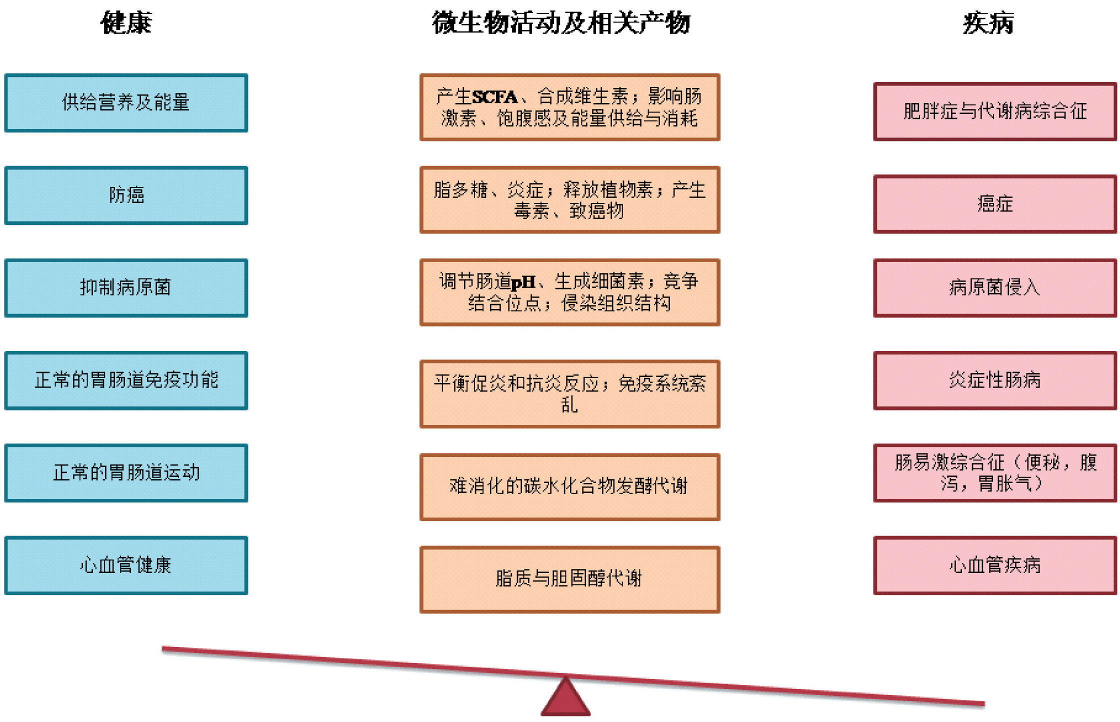

图 1　肠道菌群对肠道及宿主健康的影响[26]

Fig. 1　Effects of intestinal microbiota on intestinal and host health[26]

将 L－组氨酸转化成组胺[30]，通过细菌 *gadB* 基因编码的谷氨酸脱羧酶可将谷氨酸转化为 γ－氨基丁酸[31]。

肠道菌群还能合成维生素 K 和部分维生素 B。研究表明，拟杆菌能合成具有抗糖尿病、抗动脉粥样硬化、降血脂、免疫调节等特性的共轭亚油酸[32－34]。正常的肠道菌群还能增加血清中丙酮酸、柠檬酸、延胡索酸和苹果酸的浓度来促进代谢[35]。

2.2　抗菌保护作用

肠道菌群能够通过提高对病原菌的定植抑制和促进对病原菌的清除这两个作用来减弱肠道病原菌感染[36, 37]。如在长期使用抗生素后，通常伴随着肠道固有菌群的破坏，导致肠道微生物对艰难梭菌的定植抑制作用丧失[37－39]。成功治疗艰难梭菌感染的策略是来自健康个体的粪便微生物移植，在粪便移植后，其肠道菌群结构得以恢复，从而抑制艰难梭菌[40, 41]。肠道菌群还可通过调控宿主先天和获得性免疫应答来影响肠道感染[42, 43]。如无菌小鼠由于其吞噬细胞活化功能及积聚到感染部位的功能受损，导致其对李斯特菌感染非常敏感[43]。本课题组前期研究也表明，肠产毒素性大肠杆菌感染时，肠道 *L. lactis subsp. lactis* 增加，通过产生过量 γ－氨基丁酸而激活 mTORC1－S6K1－EGR－2－GFI－1 信号通路从而促进 IL－17 表达[44]。然而，有一些肠道病原菌感染，肠道菌群在感染期间几乎不会减弱病原菌的感染性或者反而使其增强[45, 46]。因此，肠道菌群在肠道感染中所起的作用可能不仅取决于感染模式还取决于入侵的病原体。

2.3　免疫调节

肠道菌群与宿主免疫系统的发育有关[47]。与正常小鼠相比，无菌小鼠体内 T 细胞数量更少，sIgA 和抗体等水平也较低，而先天免疫反应细胞更活跃且体内溶菌酶活性更强[48, 49]。分节丝状菌可诱导调节性 T 细胞反应[50, 51]，而 $Foxp^{3+}$ T 细胞对肠道炎症反应具有重要的调节作用[52]。肠道微生物对于 $Foxp^{3+}$ T 细胞的正常发育和功能也是必不可少的，然而，这种介导的机制尚不清楚[53, 54]。研究发现，调节性 T 细胞和梭状芽孢杆菌均呈高密度状态分布在近端结肠，而无菌小鼠体内调节性 T 细胞的水平可因梭状芽胞杆菌的定植得以恢复[56]。有报道称细菌中的 LPS 可与其结合蛋白 LBP、CD14 结合形成三联复合物（LPS－LBP－sCD14），作用于 TLR4，激活 MyD－88 依赖性信号通路机制，从而刺激 T 细胞增生[55]。

肠道黏膜相关淋巴组织主要由派伊尔结、孤立淋巴滤泡和肠系膜淋巴结等部分构成[57]。肠道菌

群可作为抗原刺激派伊尔结和肠系膜淋巴结等发育成熟,并且其代谢物及组成也会影响相关淋巴组织产生免疫反应[58-60]。脆弱类拟杆菌等能激活肠道树突状细胞诱导肠道黏膜中的浆细胞产生 sIgA[61]。无菌仔猪体内分泌 IgA 的浆细胞发育不成熟,因此血清中 IgA 水平极低,但在 ASF (altered Schaedler flora) 定植其肠道后,血清 IgA 水平得到极大提升[62,63]。本试验室前期研究表明添加谷氨酰胺可促进含有正常肠道微生物的小鼠分泌 sIgA,然而在抗生素清除肠道微生物的小鼠模型下,则无影响,进一步表明肠道微生物在肠道 sIgA 分泌中的作用[64]。

先天淋巴细胞可快速对上皮细胞产生的信号做出响应[65],具有类似 Th1、Th2 及 Th17 细胞的表达模式,但其分化更依赖于微生物组成而非体细胞重组[66]。肠道微生物可直接或间接地调控先天淋巴细胞,如细菌代谢物吲哚-3-甲醛可通过芳烃受体直接刺激先天淋巴细胞合成 IL-22[67],而间接调控则通过招募其他免疫细胞(如肠巨噬细胞 $CX3CR1^+$)来实现[68]。固有层巨噬细胞的免疫调节作用是在稳定的状态下表达 IL-1β 前体,这有助于在病原体入侵过程中肠道免疫系统迅速产生成熟的 IL-1β。由共生菌群诱导激活的 MyD-88 依赖机制对上述作用至关重要,而微生物菌群调节巨噬细胞产生的 IL-10 则需要 MyD-88 的非依赖机制[69,70]。

2.4 胃肠道结构和肠道屏障的完整性

目前已有足够的证据证明肠道菌群能够维持胃肠功能和结构的完整性。据报道,多形拟杆菌可诱导小富脯氨酸蛋白 2 A 表达,维持上皮绒毛中细胞桥粒正常生长[71]。微生物细胞壁肽聚糖可刺激 TLR2 和维持紧密连接[72]。此外,鼠李糖乳杆菌 GG 可产生 p40 和 p75 这两种可溶性蛋白,其可以避免依赖于上皮细胞生长因子受体 EGFR、蛋白激酶 C 这两条途径的肠上皮细胞发生程序性凋亡[73]。内源性大麻素系统同样能调节肠道菌群以维持肠道屏障功能。例如,革兰氏阴性菌 *Akkermansia muciniphilla* 可通过减少血氧毒素的代谢来增加内源性大麻素的水平,从而控制肠道屏障的功能[74]。

肠道微生物通过诱导与肠道微血管系统发育相关的转录因子血管生成素-3 的生成来促进肠黏膜结构的发育,该结论也已在多个无菌小鼠试验中得到验证[75-79]。肠道菌群也可在细胞表面和亚细胞水平上调节黏膜上微生物附着位点的糖基化模式,如由多形拟杆菌分泌的一种信号分子能刺激位于细胞表面糖缀合物的海藻糖基团的表达[80]。

3 影响仔猪肠道菌群的因素

在仔猪整个动态持续的生命过程中,多种因素会对其肠道菌群的形成与组成造成影响。

3.1 仔猪不同生长阶段

猪肠道菌群是一个非常复杂的生态系统,其组成成分动态且多样,并会随时间及肠段的变化而发生转变[81]。肠道菌群从仔猪出生开始就产生定植,仔猪通过消耗母乳为乳酸菌群体提供营养优势,从而构建乳汁依赖型的菌群[82]。大肠杆菌和链球菌属细菌能够在肠道内建立一个有利于拟杆菌属、乳杆菌属和梭菌属等专性厌氧细菌定植的厌氧环境[83]。依据哺乳动物进行的一项研究表明,母乳喂养和宿主遗传学的转变对肠道菌群的发展形成有很大的影响[84]。因此,哺乳期为肠道菌群的变化提供了一个特殊的渠道窗口。

3.2 日粮营养成分

在断奶阶段,仔猪开始采食谷物和粗蛋白浓度相对较高的饲料。许多研究表明,仔猪断奶时,其肠道中的乳酸菌属细菌含量减少且微生物多样性降低,然而梭菌属、普氏菌属、大肠杆菌和包括变形杆菌科在内的一些兼性厌氧菌含量升高。不同来源和水平的蛋白或纤维会影响断奶仔猪肠道微生物的相对丰度[85,86]。如断奶仔猪采食富含果胶和豆粕的日粮,会导致结肠中乳酸杆菌的相对丰度降低,普氏菌属相对丰度增加[87],而采食富含鱼粉的日粮,则会使得埃希氏菌和志贺氏杆菌的含量增加[88]。许多试验表明,哺乳动物肠道微生物的数量同样受到日粮中不同脂肪来源及成分的影响。刘忠臣[89]发现在日粮中添加椰子油、鱼油和猪油均可扰乱肠道菌群平衡,具体表现为降低盲肠内容物中大肠杆菌的数量,增加乳酸杆菌、双歧杆菌的数量以及乳酸杆菌/大肠杆菌、双歧杆菌/大肠杆菌的比值,但三种不同的脂肪造成的影响具有差异性。本组研究也发现,日粮中单一氨基酸的比例变化(如精氨酸或谷氨酰胺)也显着影响肠道微生物的数量[90,91]。在断奶仔猪日粮中添加高铜能够抑制仔猪肠道有害菌的正常生长,添加氧化锌却可以维持仔猪肠道正常的微生态环境;而在断奶仔猪日粮中添加高锌,则会降低仔猪胃肠道前段及回肠中乳酸杆菌的数量,提高

大肠杆菌和肠球菌的数量[92]。

3.3　抗生素、微生态制剂及其他物质

饲用抗生素具有广谱抗菌性以及潜在的杀死或阻止病原菌和有益微生物生长的能力,可以引起断奶仔猪肠道菌群发生改变[82, 93, 94],微生物群落的多样性可能会进一步下降[93, 95]。长期使用亚治疗剂量的抗生素会导致病原菌在肠道中定植并引发疾病[96]。

胡远亮[97]研究表明,益生菌能增加断奶仔猪肠道微生物的多样性。Mair 等[98]通过给断奶仔猪饲喂肠球菌、乳酸杆菌、双歧杆菌和菊粉得出上述有益菌和菊粉二者组成的合生元制剂可在一定程度上调节仔猪的胃肠道功能,如降低胃、空肠和回肠中的 pH 值,影响其肠道菌群的生长和组成。Ren 等[99]发现褪黑素可提高肠道乳酸杆菌的比例及代谢,并能减少肠产毒素大肠杆菌在肠道的定植。除上述影响因素,其他物质,如酶、植物提取物、酸化剂等通常在仔猪肠道菌群的形成和功能中也发挥着重要的作用[100-102]。

4　展望

驻留在人和动物肠道内的微生物与宿主之间存在着一种复杂的互惠共生关系。目前,虽然有许多研究报道了肠道微生物与宿主健康相关的功能,但是我们只对其中的一些基本功能有一个大致的了解。许多问题都值得我们深入研究,如与宿主营养物质代谢相关的特定微生物的作用机制;微生物组成及其代谢产物与机体免疫细胞种类、数量和分化的关系;机体表面(除肠道外)存在的微生物是否影响宿主健康以及与肠道微生物间是否存在互作关系等。

微生物平衡的破坏可影响肠道的健康进而导致宿主的疾病,通过维持肠道微生物的平衡可以保障肠道的健康,减少仔猪腹泻,从而促进养猪业的健康稳定发展。因此,深入研究肠道微生物与肠道健康相关的调控机制,不仅对维护仔猪健康具有重要的意义,还为我们预防人类相关疾病提供了更宽广的思路。

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