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Antimicrobial Peptides and the Gastrointestinal Health of Weaned Piglets

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Abstract

In the modern pig industry, the immune function of piglets has not yet been mature when they are weaned at 3 to 4 weeks of age, and piglets are always challenged by postweaning stress. Therefore, in-feed antibiotic use is a common practice for improving growth performance and preventing disease of weaned piglets. However, the problem of drug residues and drug resistance caused by antibiotic abuse has seriously threatened livestock production and human health, forcing people to find alternatives to antibiotics. Antibacterial peptides have become a promising alternative for antibiotics because they have many advantages, such as broad antimicrobial spectrum, not easy to produce drug resistance, and almost non-toxic effects. Recent progresses on antimicrobial peptide in weaned piglets production will be discussed in this review including the reducing susceptibility to disease, growth promoting, ameliorating intestinal microecology, improvement of the intestinal mucosa, improving the immune function of piglets and prospects.

Keywords

Antimicrobial Peptide, Weaned Piglets, Intestinal Tract, Growth, Health

抗菌肽与断奶仔猪的肠道健康

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摘　要

现代养殖模式下，断奶仔猪的免疫功能尚未发育成熟，加之断奶应激的负面影响较大，因此，为了促进断奶仔猪的生长、防治疾病，生产中通常会使用抗生素。但抗生素滥用造成的药物残留、病原微生物的耐药性等问题，严重威胁畜牧生产和人类健康，迫使人类寻找抗生素的替代物。由于抗菌肽具有抗菌谱广、不易产生耐药性、几乎无毒副作用等优点，使其成为了极有希望替代抗生素的物质。本文从抗菌肽抗病、促生长、改善肠道微生态、改善肠道粘膜，以及提高机体免疫功能等方面综述其在断奶仔猪中的研究进展。

关键词

抗菌肽，断奶仔猪，肠道，生长，健康

1. 引言

现代养猪产业模式下，仔猪通常在 3~4 w 即已断奶，而其免疫功能大约到 7 w 后才能发育成熟[1]。因此，断奶仔猪极易受到病原微生物的感染[2] [3] [4]，加之断奶应激会降低仔猪的免疫力、影响肠道的消化吸收功能，从而造成腹泻、生长缓慢、多种疾病，甚至死亡[5] [6]，造成巨大的经济损失。

为了应对断奶对仔猪造成的不良影响，生产中广泛使用抗生素，以增加饲养效率、促进动物生长和预防疾病[7] [8]。不可否认，抗生素对畜牧业的发展起了非常重要的作用，特别是在饲养条件落后的年代和国家地区。但是，由于抗生素的滥用导致畜产品抗生素残留的问题日益突出，同时也产生了大量的耐药菌，甚至超级细菌[9] [10]。更为严峻的是，畜产品中残留的抗生素可以通过食物链传递给人类，威胁人类的健康[11] [12] [13] [14]。因此，开发一些新型、安全、高效的抗菌素替代品显得非常迫切。抗菌肽具有抗菌谱广、无污染、几乎无毒副作用、不易产生耐药性等优点，其俨然已成为抗生素的极佳替代品[15] [16]。

抗菌肽(antimicrobial peptides, AMPs)是一类由几十个氨基酸组成的短链多肽，可从植物、动物和人的组织细胞中提取、分离、纯化得到[17] [18] [19] [20]。抗菌肽具有广泛的抗细菌、抗病毒、抗真菌、抗寄生虫、抗肿瘤以及提高机体免疫力等功能[21]-[28]，在人和动物的先天免疫以及非特异性免疫过程中发挥重要的作用[18]。本文从抗菌肽抗病、促生长、改善肠道微生态、改善肠道粘膜、提高机体免疫功能、抗菌肽与益生菌等方面做一综述。

2. 抗病、促生长

很多研究表明仔猪断奶前后饲料中添加抗菌肽，能够促进其生长发育、增强抗病能力、降低患病率，提高经济效益。Yoon 等在饲料中添加 60 mg·kg^{-1} 人工合成的抗菌肽 A3 或 P5，断奶仔猪的平均日增重和饲料转换率均显著高于对照组的($p < 0.05$) [29]；Yu 等给断奶仔猪饲料中添加 0.5、1.0、2.0 mg·kg^{-1} 的抗菌肽小菌素 J25，同样发现试验组仔猪的平均日增重、平均日采食量和饲料转换率显著提高($p < 0.05$) [30]。Xiong 等给 5 个猪场的饲料中添加乳铁蛋白、天蚕抗菌肽、防御肽和菌丝霉素组成的复合抗菌肽，与对

照组相比，饲料中添加 2 g·kg^{-1} 抗菌肽也可以显著提高断奶仔猪的平均日增重、平均日采食量以及饲料转换率($p < 0.05$) [31]。断奶期间因仔猪肠道发育的不完善，有害菌增多引起的仔猪腹泻是造成经济损失的重要方面。很多研究发现，饲料中添加抗菌肽在提高断奶仔猪生长性能的同时，还能有效地降低仔猪的腹泻率($p < 0.05$) [30] [31] [32]。Zhang 等以断奶仔猪为研究对象，发现爬行动物源的抗菌肽 Cathelicidin-衍生肽对 LPS 引起的肠炎具有保护作用[33]。复合抗菌肽亦能有效地缓解因口服脱氧雪腐镰刀菌烯醇导致的肠道损伤($p < 0.05$)，降低肠道炎症反应[34]。

3. 改善肠道微生态

肠道微生态系统是动物最主要、最复杂的微生态系统，稳定的肠道微生态系统对动物正常生理功能的维持和机体抵抗病原微生物的感染极为重要[35]。研究表明，断奶应激会使仔猪肠道中大肠杆菌数量增加，有益菌数量下降，且越早断奶有益菌下降的幅度越大，这严重破坏了仔猪肠道微生态系统的平衡[36] [37]。更为严峻的是，大幅增加的大肠杆菌等有害菌会产生大量毒素，最终损害肠道健康[38]。而抗菌肽可以抑制或杀死有害菌，并增加益生菌的数量。

早期在小鼠上的研究发现，给小鼠饲喂含 2 mg·mL^{-1} 牛乳铁蛋白的配方奶，可以显著增加其肠道中双歧杆菌的数量($p < 0.05$) [39]。之后，研究人员给仔猪饲喂含 20 mg·g^{-1} 人乳铁蛋白和 2 mg·g^{-1} 牛乳铁蛋白的配方奶，发现同样可以增加仔猪肠道中双歧杆菌的数量($p < 0.05$) [40]；Yoon 等在饲料中添加人工合成的抗菌肽 A3 或 P5，发现断奶仔猪回肠、盲肠以及粪便中的大肠杆菌和梭状芽孢杆菌的数量显著低于对照组的($p < 0.05$) [29]；汪以真(博士论文)研究发现，饲料中添加表达重组乳铁蛋白基因的蚕蛹，可以显著增加仔猪肠道中乳酸杆菌和双歧杆菌的数量($p < 0.05$)，同时抑制仔猪肠道中大肠杆菌和沙门氏菌的生长($p < 0.05$) [41]；Wu 等给仔猪饲喂添加有天蚕菌素的饲料，其回肠中的好氧菌的数量明显降低，同时厌氧菌的数量增加($p < 0.05$) [32]。

4. 改善肠道粘膜

断奶仔猪的肠道粘膜尚未发育完全，断奶应激会引起仔猪肠道黏膜形态结构改变、肠上皮屏障通透性增加、消化吸收功能降低、黏液层厚度下降、免疫功能紊乱等[42] [43]，而研究发现抗菌肽可以在这些方面对肠道粘膜具有很好的改善作用。易宏波(博士论文)以腹泻的断奶仔猪为研究对象，发现腹腔注射 0.6 mg·kg^{-1} 抗菌肽 CWA 可以显著改善断奶仔猪的小肠绒毛形态，缓解结肠水肿现象，并显著增加仔猪空肠和回肠的绒毛高度/隐窝深度比($p < 0.05$) [44]。其他学者在饲料中分别添加抗菌肽天蚕素、A3、P5，发现均可以改善断奶仔猪的小肠绒毛长度以及其与隐窝深度的比值[29] [32]。另外，给予断奶仔猪大肠杆菌攻毒后，灌服 0.25 mg 抗菌肽 buforin II，每日两次并持续 3 w，仔猪小肠的紧密连接蛋白和肠道保护因子表达显著增加($p < 0.05$)，表明了防御素对断奶仔猪肠道黏膜完整性的保护作用[45]。饲粮中添加 60 mg·kg^{-1} 抗菌肽 P5 或 A3 能够显著提高断奶仔猪的全肠道表面消化率和氨基酸回肠末端表面消化率($p < 0.05$) [29] [46]。断奶仔猪腹腔注射 LPS 后再给予腹腔注射抗菌肽 C-BF，仔猪肠道损伤明显减轻，空肠的炎症细胞浸润显著降低($p < 0.05$) [33]。断奶仔猪食用含有脱氧雪腐镰刀菌烯醇(呕吐毒素)的饲料会导致其小肠通透性增大、绒毛损伤、上皮细胞凋亡、以及细胞内蛋白合成的抑制，而饲料中添加复合抗菌肽能够有效地缓解这些影响($p < 0.05$) [34]。

5. 提高机体免疫功能

抗菌肽除了可以抑制并杀死病原微生物，还具有重要的免疫调节功能。在不同物种上的研究证实了抗菌肽具有调节趋化因子表达并招募免疫细胞、调节炎症反应、激活免疫细胞等免疫调节功能[47]。抗菌肽在断奶仔猪上的应用也显示出对其体液免疫、细胞免疫以及细胞因子表达的调节作用。Ren 等在日粮

中添加抗菌肽(猪的防御肽和苍蝇抗菌肽按 1:1 混合)，发现试验组仔猪脾脏中 G0/G1 期细胞显著减少($p < 0.05$)，S 期和 G2+M 期细胞显著增加，细胞增殖指数明显增大($p < 0.05$)，凋亡细胞比例明显降低。另外，外周血 $CD3^+$、$CD3^+CD4^+$、以及 $CD4^+CD8^+$ T 细胞比例均显著增加($p < 0.05$)，说明抗菌肽能够显著提高断奶仔猪脾脏细胞以及 T 细胞的增殖能力，有效改善其细胞免疫功能[48]。Shan 等在饲料中添加 1000 $mg{\cdot}kg^{-1}$ 乳铁蛋白也能显著提高断奶仔猪脾脏淋巴细胞的增殖能力，同时发现血清中 IgG、IgA、IgM 的水平显著升高了($p < 0.05$) [49]。Wu 等给断奶仔猪饲喂添加了天蚕菌素的饲料，发现仔猪的空肠中分泌的 IgA 水平以及血清中 IgA、IgG 水平较对照组显著升高($p < 0.05$) [32]。这些结果表明，抗菌肽对断奶仔猪细胞及体液免疫具有积极的调节作用。细胞因子是动物机体在发生炎症和免疫应答过程中由免疫细胞产生，通过与受体作用参与机体免疫调节作用的小分子蛋白质[50] [51]。很多研究表明，断奶仔猪饲喂含有抗菌肽的日粮能够提高其血清中细胞因子的水平。例如，在 Shan 的研究中即发现乳铁蛋白能够提高仔猪血清中 IL-2 的含量($p < 0.05$) [49]，而在 Wu 的研究中证实天蚕菌素能够提高断奶仔猪血清中 IL-1β 和 Il-6 的水平($p < 0.05$) [32]。袁威等(2015)给予断奶仔猪饲喂添加了复合抗菌肽(猪防御素和苍蝇抗菌肽按 1:1 混合)的日粮 28 d，也发现仔猪血清中 IL-2、IL-4、IL-6、IFNγ 以及 TNFα 的水平显著增加($p < 0.05$) [52]。

6. 抗菌肽与益生菌

在改善人和动物肠道健康方面，益生菌可谓是功不可没。益生菌能调节肠道菌群平衡，防治腹泻，且价格低廉，目前已被广泛应用于医疗保健和畜牧业[53] [54]。另外，益生菌本身就是人和动物胃肠道微生态系统的重要成员，有的益生菌可以分泌乳酸、乙酸、丙酸和丁酸等，从而保持了胃肠道的低 pH 值，进而抑制有害菌的粘附、生长、繁殖，同时还促进其他益生菌的增殖，大部分益生菌还能产生消化酶以促进动物胃肠道的消化吸收。例如，Hou 等将 9 窝仔猪标准化至 8 头哺乳仔猪进行试验，随机分为 3 组，分别进行短期添加(1~5 d，持续 5 d)、早期间歇性添加(从 1 日龄到 17 日龄，每隔 4 d 添加一次) 1.7×10^{10} CFU 罗伊氏乳杆，对照组饲喂 4 ml 0.1%的蛋白胨水。结果显示，在 14 日龄时，处理组仔猪回肠中的双歧杆菌的数目显著高于对照组($p < 0.05$)，短期处理组的仔猪在 7 日龄时以及早期间歇性处理组的仔猪在 14 日龄时，肠道中的乳酸浓度增加、pH 降低($p < 0.05$) [55]。另有研究报道，饲料中添加瑞特乳酸菌 15007，可促进 IPEC-J2 细胞中以及仔猪肠道中 beta-defensin-2、pBD3、pBD114 和 pBD129 等抗菌肽的表达($p < 0.05$)，并且可以通过增加丁酸浓度进而改善仔猪肠道的健康状况[56]。基于抗菌肽和益生菌各自的优势以及相互的促进作用，Xu 等在仔猪饲料中添加表达融合抗菌肽(猪的 beta-defensin-2 和天蚕素 P1 融合肽)的枯草芽孢杆菌，结果发现其可显著促进仔猪的生长($p < 0.05$)，并降低仔猪的腹泻($p < 0.05$) [57]。虽然试验并不能确定到底是枯草芽孢杆菌，还是猪的 beta-defensin-2 和天蚕素 P1 融合肽，亦或是两者的协同作用，最终取得如此好的效果，但作者的研究为我们提供了一个新颖的研究思路。

7. 展望

当下，全面禁抗已进入倒计时。作为抗生素的替代物或新型的饲料添加剂，抗菌肽有诸多优势，但同时也有一些问题值得深入思考和研究。比如，抗菌肽的生产问题，从动植物中提取得率太低，而人工合成的成本又过于昂贵[58]，因此生物工程生产方式将是满足未来需求的最佳途径；再如，抗菌肽的使用问题，如前文所述，不同抗菌肽的使用剂量不同，但投放手段多采取最易操作的饲料添加，然而如何有效避开胃肠道中各种消化酶对抗菌肽的酶解作用以保持其活性仍需大量的研究；人医上有些肠道药物采取肠溶性包衣的形式，比如美沙拉嗪，可保证药物顺利通过胃中的酸性环境，进入肠道，在碱性的肠液中崩解包衣、暴露药物，但此类工艺无疑会加大抗菌肽的生产成本；另外，目前的研究，除了如前所述，抗菌肽可以抑制动物腹泻或炎症外，也有一些报道的结果与之相反。Severino 等在用盲肠结扎和穿刺诱

导的败血症小鼠上发现，敲除抗菌肽 cathelicidin 基因的小鼠比野生型小鼠的存活率高($p < 0.05$) [59]。Hashimoto 等研究发现，给 DSS 诱导的小鼠腹腔注射抗菌肽 HNP-1，会加重小鼠的结肠炎($p < 0.05$) [60]，提示在结肠炎中 HNP-1 可能发挥了促炎作用。另有研究者检测到，溃疡性结肠炎患者的肠道上皮细胞中抗菌肽 hBD-2 和 hBD-3 的表达量分别较正常人的提高了 1000 倍和 300 倍[61] [62]，但不幸的是，如此高水平表达的抗菌肽却无法有效遏制细菌对肠道粘膜的持续入侵[63]。因此，不同种类的抗菌肽与人和动物肠道炎症之间的关系仍需进行广泛而深入的研究。

此外，抗菌肽与益生菌的联合使用也应该得到重视。益生菌有诸多优势，如无致病性、无毒性、无残留、不产生 LPS、价格低廉，因此，将益生菌改造成工程菌用以表达抗菌肽，可谓一举两得。既能体现出前文所述益生菌的优良功效，又可使成功定植在肠道中的益生菌持续表达抗菌肽。目前，类似的研究还很少，但可以预见，将益生菌作为工程菌来表达抗菌肽并添加至饲料或饮水中应该是非常经济高效的生产和投放抗菌肽的方法，其成熟的研究成果势必会更好地为畜牧业以及人类的健康服务。

致　谢

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参考文献

[1] Johnson, J.S. and Lay, D.C. (2017) Evaluating the Behavior, Growth Performance, Immune Parameters, and Intestinal Morphology of Weaned Piglets after Simulated Transport and Heat Stress When Antibiotics Are Eliminated from the Diet or Replaced with L-Glutamine. *Journal of Animal Science*, **95**, 91-102. https://doi.org/10.2527/jas.2016.1070

[2] Heo, J.M., Opapwju, F.O., Pluske, J.R., *et al*. (2013) Gastrointestinal Health and Function in Weaned Pigs: A Review of Feeding Strategies to Control Post-Weaning Diarrhoea without Using In-Feed Antimicrobial Compounds. *Journal of Animal Physiology and Animal Nutrition* (*Berl*), **97**, 207-237. https://doi.org/10.1111/j.1439-0396.2012.01284.x

[3] Britton, R.A. and Young, V.B. (2014) Role of the Intestinal Microbiota in Resistance to Colonization by Clostridium Difficile. *Gastroenterology*, **146**, 1547-1553. https://doi.org/10.1053/j.gastro.2014.01.059

[4] Stensland, I., Kim, J.C., Bowwring, B., *et al*. (2015) A Comparison of Diets Supplemented with a Feed Additive Containing Organic Acids, Cinnamaldehyde and a Permeabilizing Complex, or Zinc Oxide, on Post-Weaning Diarrhoea, Selected Bacterial Populations, Blood Measures and Performance in Weaned Pigs Experimentally Infected with Enterotoxigenic *E. coli*. *Animals* (*Basel*), **5**, 1147-1168. https://doi.org/10.3390/ani5040403

[5] Smith, F., Clark, J.E., Overman, B.L., *et al*. (2010) Early Weaning Stress Impairs Development of Mucosal Barrier Function in the Porcine Intestine. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **298**, G352-G363. https://doi.org/10.1152/ajpgi.00081.2009

[6] Chen, J.S., Li, Y., Tian, Y.N., *et al*. (2015) Interaction between Microbes and Host Intestinal Health: Modulation by Dietary Nutrients and Gut-Brain-Endocrine-Immune Axis. *Current Protein & Peptide Science*, **16**, 592-603. https://doi.org/10.2174/1389203716666150630135720

[7] Lin, J. (2011) Effect of Antibiotic Growth Promoters on Intestinal Microbiota in Food Animals: A Novel Model for Studying the Relationship between Gut Microbiota and Human Obesity. *Frontiers in Microbiology*, **2**, 53. https://doi.org/10.3389/fmicb.2011.00053

[8] Vondruskova, H., Slamova, R., Trckova, M., *et al*. (2010) Alternatives to Antibiotic Growth Promoters in Prevention of Diarrhoea in Weaned Piglets: A Review. *Veterinarni Medicina*, **55**, 199-224. https://doi.org/10.17221/2998-VETMED

[9] Yin, X., Song, F., Gong, Y., *et al*. (2013) A Systematic Review of Antibiotic Utilization in China. *Journal of Antimicrobial Chemotherapy*, **68**, 2445-2452. https://doi.org/10.1093/jac/dkt223

[10] Gill, E.E., Franco, O.L. and Hancock, R.E. (2015) Hancock, Antibiotic Adjuvants: Diverse Strategies for Controlling Drug-Resistant Pathogens. *Chemical Biology & Drug Design*, **85**, 56-78. https://doi.org/10.1111/cbdd.12478

[11] Rakotoharinome, M., Pognon, D., Randriamparany, T., *et al*. (2014) Prevalence of Antimicrobial Residues in Pork Meat in Madagascar. *Tropical Animal Health and Production*, **46**, 49-55. https://doi.org/10.1007/s11250-013-0445-9

[12] Liu, X., Steele, J.C. and Meng, X.Z. (2017) Usage, Residue, and Human Health Risk of Antibiotics in Chinese Aquaculture: A Review. *Environmental Pollution*, **223**, 161-169. https://doi.org/10.1016/j.envpol.2017.01.003

[13] Qin, Y., Jatamunua, F., Zhang, J., *et al*. (2017) Analysis of Sulfonamides, Tilmicosin and Avermectins Residues in Typical Animal Matrices with Multi-Plug Filtration Cleanup by Liquid Chromatography-Tandem Mass Spectrometry Detection. *Journal of Chromatography B*: *Analytical Technologies in the Biomedical and Life Sciences*, **1053**, 27-33. https://doi.org/10.1016/j.jchromb.2017.04.006

[14] Gajda, A., Nowacka-Kozak, E., Gbylik-Sikorska, M., *et al*. (2018) Tetracycline Antibiotics Transfer from Contaminated Milk to Dairy Products and the Effect of the Skimming Step and Pasteurisation Process on Residue Concentrations. *Food Additives & Contaminants*: *Part A*: *Chemistry*, *Analysis*, *Control*, *Exposure & Risk Assessment*, **35**, 66-76. https://doi.org/10.1080/19440049.2017.1397773

[15] Thacker, P.A. (2013) Alternatives to Antibiotics as Growth Promoters for Use in Swine Production: A Review. *Journal of Animal Science and Biotechnology*, **4**, 35. https://doi.org/10.1186/2049-1891-4-35

[16] Fjell, C.D., Hiss, J.A., Hancock, R.E., *et al*. (2011) Designing Antimicrobial Peptides: Form Follows Function. *Nature Reviews Drug Discovery*, **11**, 37-51. https://doi.org/10.1038/nrd3591

[17] Brandwein, M., Bentwich, Z. and Steinberg, D. (2017) Endogenous Antimicrobial Peptide Expression in Response to Bacterial Epidermal Colonization. *Frontiers in Immunology*, **8**, 1637. https://doi.org/10.3389/fimmu.2017.01637

[18] Deng, Z. and Xu, C. (2017) Role of the Neuroendocrine Antimicrobial Peptide Catestatin in Innate Immunity and Pain. *Acta Biochimica et Biophysica Sinica* (*Shanghai*), **49**, 967-972. https://doi.org/10.1093/abbs/gmx083

[19] Fitschen-Oestern, S., Weuster, M., Lippross, S., *et al*. (2017) Hepatocytes Express the Antimicrobial Peptide HBD-2 after Multiple Trauma: An Experimental Study in Human and Mice. *BMC Musculoskeletal Disorders*, **18**, 100. https://doi.org/10.1186/s12891-017-1458-8

[20] Oliveira-Lima, M., Benko-Iseppon, A.M., Neto, J., *et al*. (2017) Snakin: Structure, Roles and Applications of a Plant Antimicrobial Peptide. *Current Protein & Peptide Science*, **18**, 368-374. https://doi.org/10.2174/1389203717666160619183140

[21] Pollini, S., Brunetti, J., Sennati, S., *et al*. (2017) Synergistic Activity Profile of an Antimicrobial Peptide against Multidrug-Resistant and Extensively Drug-Resistant Strains of Gram-Negative Bacterial Pathogens. *Journal of Peptide Science*, **23**, 329-333. https://doi.org/10.1002/psc.2978

[22] He, X., Zhang, H., Shi, Y., *et al*. (2016) A Novel Antimicrobial Peptide Derived from Membrane-Proximal External Region of Human Immunodeficiency Virus Type 1. *Biochimie*, **123**, 110-116. https://doi.org/10.1016/j.biochi.2016.02.006

[23] Rossi, D.C., Munoz, J.E., Carvalho, D.D., *et al*. (2012) Therapeutic Use of a Cationic Antimicrobial Peptide from the Spider *Acanthoscurria gomesiana* in the Control of Experimental Candidiasis. *BMC Microbiology*, **12**, 28. https://doi.org/10.1186/1471-2180-12-28

[24] Jia, J., Zheng, Y., Wang, W., *et al*. (2017) Antimicrobial Peptide LL-37 Promotes YB-1 Expression, and the Viability, Migration and Invasion of Malignant Melanoma Cells. *Molecular Medicine Reports*, **15**, 240-248. https://doi.org/10.3892/mmr.2016.5978

[25] Shah, Y., Sehgal, D. and Valadi, J.K. (2017) Recent Trends in Antimicrobial Peptide Prediction Using Machine Learning Techniques. *Bioinformation*, **13**, 415-416. https://doi.org/10.6026/97320630013415

[26] Mello, C.P., Lima, D.B., Menezes, R.R., *et al*. (2017) Evaluation of the Antichagasic Activity of Batroxicidin, a Cathelicidin-Related Antimicrobial Peptide found in *Bothrops atrox* Venom Gland. *Toxicon*, **130**, 56-62. https://doi.org/10.1016/j.toxicon.2017.02.031

[27] Dong, N., Wang, Z., Chou, S., *et al*. (2017) Antibacterial Activities and Molecular Mechanism of Amino-Terminal Fragments from Pig Nematode Antimicrobial Peptide CP-1. *Chemical Biology & Drug Design*, **91**, 1017-1029. https://doi.org/10.1111/cbdd.13165

[28] Yang, D., Zha, G., Li, X., *et al*. (2017) Immune Responses in the Haemolymph and Antimicrobial Peptide Expression in the Abdomen of *Apis mellifera* Challenged with *Spiroplasma melliferum* CH-1. *Microbial Pathogenesis*, **112**, 279-287. https://doi.org/10.1016/j.micpath.2017.10.006

[29] Yoon, J.H., Ingale, S.L., Kim, J.S., *et al*. (2014) Effects of Dietary Supplementation of Synthetic Antimicrobial Peptide-A3 and P5 on Growth Performance, Apparent Total Tract Digestibility of Nutrients, Fecal and Intestinal Microflora and Intestinal Morphology in Weanling Pigs. *Livestock Science*, **159**, 53-60. https://doi.org/10.1016/j.livsci.2013.10.025

[30] Yu, H.T., Ding, X.L., Li, N., *et al*. (2017) Dietary Supplemented Antimicrobial Peptide Microcin J25 Improves the Growth Performance, Apparent Total Tract Digestibility, Fecal Microbiota, and Intestinal Barrier Function of Weaned Pigs. *Journal of Animal Science*, **95**, 5064-5076. https://doi.org/10.2527/jas2017.1494

[31] Xiong, X., Yang, H.S., Li, L., *et al*. (2014) Effects of Antimicrobial Peptides in Nursery Diets on Growth Performance of Pigs Reared on Five Different Farms. *Livestock Science*, **167**, 206-210. https://doi.org/10.1016/j.livsci.2014.04.024

[32] Wu, S., Zhang, F., Huang, Z., *et al*. (2012) Effects of the Antimicrobial Peptide Cecropin AD on Performance and Intestinal Health in Weaned Piglets Challenged with *Escherichia coli*. *Peptides*, **35**, 225-230. https://doi.org/10.1016/j.peptides.2012.03.030

[33] Zhang, H., Zhang, B., Zhang, X., *et al*. (2017) Effects of Cathelicidin-Derived Peptide from Reptiles on Lipopolysaccharide-Induced Intestinal Inflammation in Weaned Piglets. *Veterinary Immunology and Immunopathology*, **192**, 41-53. https://doi.org/10.1016/j.vetimm.2017.09.005

[34] Xiao, H., Tan, B.E., Wu, M.M., *et al*. (2013) Effects of Composite Antimicrobial Peptides in Weanling Piglets Challenged with Deoxynivalenol: II. Intestinal Morphology and Function. *Journal of Animal Science*, No. 10, 4750-4756. https://doi.org/10.2527/jas.2013-6427

[35] 朱伟云, 余凯凡, 慕春龙, 等. 猪的肠道微生物与畜主营养代谢[J]. 动物营养学报, 2014, 26(10): 3046-3051.

[36] Tao, X., Xu, Z. and Wan, J. (2015) Intestinal Microbiota Diversity and Expression of Pattern Recognition Receptors in Newly Weaned Piglets. *Anaerobe*, **32**, 51-56. https://doi.org/10.1016/j.anaerobe.2014.12.005

[37] Franklin, M.A., Mathew, A.G., Vickers, J.R., *et al*. (2002) Characterization of Microbial Populations and Volatile Fatty Acid Concentrations in the Jejunum, Ileum, and Cecum of Pigs Weaned at 17 vs 24 Days of Age. *Journal of Animal Science*, **80**, 2904-2910. https://doi.org/10.2527/2002.80112904x

[38] 徐子伟. 仔猪肠道损伤修复营养调控及其机制和应用[J]. 动物营养学报, 2014, 26(10): 3033-3045.

[39] Hentges, D.J., Marsh, W.W., Petschow, B.W., *et al*. (1992) Influence of Infant Diets on the Ecology of the Intestinal Tract of Human Flora-Associated Mice. *Journal of Pediatric Gastroenterology and Nutrition*, **14**, 146-152. https://doi.org/10.1097/00005176-199202000-00005

[40] Hu, W., Zhao, J., Wang, J., *et al*. (2012) Transgenic Milk Containing Recombinant Human Lactoferrin Modulates the Intestinal Flora in Piglets. *Biochemistry and Cell Biology*, **90**, 485-496. https://doi.org/10.1139/o2012-003

[41] 汪以真. 猪乳铁蛋白基因克隆、表达及其产物对断奶仔猪生长、免疫和抗菌肽基因表达影响到研究[D]: [博士学位论文]. 杭州: 浙江大学, 2004.

[42] Everaert, N., Van Cruchten, S., Westrom, B., *et al*. (2017) A Review on Early Gut Maturation and Colonization in Pigs, Including Biological and Dietary Factors Affecting Gut Homeostasis. *Animal Feed Science and Technology*, **233**, 89-103. https://doi.org/10.1016/j.anifeedsci.2017.06.011

[43] Flis, M., Sobotka, W., Antoszkiewicz, Z., *et al*. (2017) Fiber Substrates in the Nutrition of Weaned Piglets—A Review. *Annals of Animal Science*, **17**, 627-643. https://doi.org/10.1515/aoas-2016-0077

[44] 易宏波. 抗菌肽 CWA 对断奶仔猪肠道炎症和肠道屏障功能的作用及其机制[D]: [博士学位论文]. 杭州: 浙江大学, 2016.

[45] Tang, Z.R., Deng, H., Zhang, X.L., *et al*. (2013) Effects of Orally Administering the Antimicrobial Peptide Buforin II on Small Intestinal Mucosal Membrane Integrity, the Expression of Tight Junction Proteins and Protective Factors in Weaned Piglets Challenged by Enterotoxigenic *Escherichia coli*. *Animal Feed Science and Technology*, **186**, 177-185. https://doi.org/10.1016/j.anifeedsci.2013.10.012

[46] Yoon, J.H., Ingale, S.L., Kim, J.S., *et al*. (2013) Effects of Dietary Supplementation with Antimicrobial Peptide-P5 on Growth Performance, Apparent Total Tract Digestibility, Faecal and Intestinal Microflora and Intestinal Morphology of Weanling Pigs. *Journal of the Science of Food and Agriculture*, **93**, 587-592. https://doi.org/10.1002/jsfa.5840

[47] 朱健, 刘超群, 刘瑞奇, 等. 抗菌肽免疫调节功能的研究进展[J]. 黑龙江畜牧兽医, 2018(1): 77-79.

[48] Ren, Z.H., Yuan, W., Deng, H.D., *et al*. (2015) Effects of Antibacterial Peptide on Cellular Immunity in Weaned Piglets. *Journal of Animal Science*, **93**, 127-134. https://doi.org/10.2527/jas.2014-7933

[49] Shan, T., Wang, Y., Liu, J., *et al*. (2007) Effect of Dietary Lactoferrin on the Immune Functions and Serum Iron Level of Weanling Piglets. *Journal of Animal Science*, **85**, 2140-2146. https://doi.org/10.2527/jas.2006-754

[50] Worthington, J.J., Reimann, F. and Gribble, F.M. (2018) Enteroendocrine Cells-Sensory Sentinels of the Intestinal Environment and Orchestrators of Mucosal Immunity. *Mucosal Immunology*, **11**, 3-20. https://doi.org/10.1038/mi.2017.73

[51] Drutskaya, M.S., Efimov, G.A., Astrakhantseva, I.V., *et al*. (2018) Making Anti-Cytokine Therapy More Selective: Studies in Mice. *Cytokine*, **101**, 33-38. https://doi.org/10.1016/j.cyto.2016.08.022

[52] 袁威, 任志华, 邓又天, 等. 复合抗菌肽对断奶仔猪生长性能及血清细胞因子含量的影响[J]. 动物营养学报,

2015(3): 885-892.

[53] 崔艳红, 韩庆功, 崔艺佳, 等. 益生菌复合发酵料对断奶仔猪消化环境、血清生化指标和代谢激素水平的影响[J]. 西北农业学报, 2018, 27(1): 16-23.

[54] 范明东, 李元凤, 敖翔, 等. 益生菌和低聚木糖在断奶仔猪上的应用研究[J]. 养猪, 2017(2): 10-16.

[55] Hou, C., Liu, H., Zhang, J., *et al*. (2015) Intestinal Microbiota Succession and Immunomodulatory Consequences after Introduction of *Lactobacillus reuteri* I5007 in Neonatal Piglets. *PLoS ONE*, **10**, e0119505. https://doi.org/10.1371/journal.pone.0119505

[56] Liu, H., Hou, C., Wang, G., *et al*. (2017) *Lactobacillus reuteri* I5007 Modulates Intestinal Host Defense Peptide Expression in the Model of IPEC-J2 Cells and Neonatal Piglets. *Nutrients*, **9**, 559. https://doi.org/10.3390/nu9060559

[57] Xu, J., Zhong, F., Zhang, Y., *et al*. (2017) Construction of *Bacillus subtilis* Strain Engineered for Expression of Porcine Beta-Defensin-2/Cecropin P1 Fusion Antimicrobial Peptides and Its Growth-Promoting Effect and Antimicrobial Activity. *Asian-Australas Journal of Animal Science*, **30**, 576-584. https://doi.org/10.5713/ajas.16.0207

[58] Sun, B.D., Wibowo, D., Middelberg, A.P.J., *et al*. (2018) Cost-Effective Downstream Processing of Recombinantly Produced Pexiganan Peptide and Its Antimicrobial Activity. *AMB Express*, **8**, 6. https://doi.org/10.1186/s13568-018-0541-3

[59] Severino, P., Ariga, S.K., Barbeiro, H.V., *et al*. (2017) Cathelicidin-Deficient Mice Exhibit Increased Survival and Upregulation of Key Inflammatory Response Genes Following Cecal Ligation and Puncture. *Journal of Molecular Medicine*, **95**, 995-1003. https://doi.org/10.1007/s00109-017-1555-z

[60] Hashimoto, S., Uto, H., Kanmura, S., *et al*. (2012) Human Neutrophil Peptide-1 Aggravates Dextran Sulfate Sodium-Induced Colitis. *Inflammatory Bowel Diseases*, **18**, 667-675. https://doi.org/10.1002/ibd.21855

[61] Garcia, J.R., Krause, A., Schulz, S., *et al*. (2001) Human Beta-Defensin 4: A Novel Inducible Peptide with a Specific Salt-Sensitive Spectrum of Antimicrobial Activity. *The FASEB Journal*, **15**, 1819-1821. https://doi.org/10.1096/fj.00-0865fje

[62] Schmid, M., Fellermann, K., Fritz, P., *et al*. (2007) Attenuated Induction of Epithelial and Leukocyte Serine Antiproteases Elafin and Secretory Leukocyte Protease Inhibitor in Crohn's Disease. *Journal of Leukocyte Biology*, **81**, 907-915. https://doi.org/10.1189/jlb.0906581

[63] Arijs, I., De Hertogh, G., Lemaire, K., *et al*. (2009) Mucosal Gene Expression of Antimicrobial Peptides in Inflammatory Bowel Disease before and after First Infliximab Treatment. *PLoS ONE*, **4**, e7984. https://doi.org/10.1371/journal.pone.0007984