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专论与综述

肠道菌群：肠道干细胞增殖分化的调节者

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摘　要：肠道干细胞(intestinal stem cells, ISCs)是肠道各类上皮细胞的来源，通过平衡增殖与分化维持肠道稳态。同时，肠道菌群及其代谢物在维持宿主肠道稳态中也发挥着重要作用。随着技术的发展，研究者认识到 ISCs 与肠道菌群之间存在相互作用。研究表明，ISCs 对上皮细胞亚型的调控影响肠道菌群的组成，并且肠道菌群及其代谢物也影响 ISCs 介导的上皮发育。本文阐述了 ISCs 分化对肠道菌群的影响，重点总结了肠道菌群及其代谢物调控 ISCs 增殖分化的研究进展，从菌群调控 ISCs 的角度探讨肠道损伤的治疗思路，并对未来可能的研究方向进行讨论。

关键词：肠道菌群；菌群代谢物；肠道干细胞

Gut microbiota: an orchestrator of intestinal stem cell proliferation and differentiation

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Abstract: Intestinal stem cells (ISCs) are the source of intestinal epithelial cells, maintaining intestinal homeostasis by orchestrating proliferation and differentiation. Gut microbiota and their metabolites also play a role in maintaining host intestinal homeostasis. With technological advances, the interaction between ISCs and gut microbiota has drawn increasing attention. Emerging evidence has demonstrated that ISCs regulate the composition of gut microbiota by affecting the subtypes of epithelial cells, while gut microbiota and their metabolites modulate the epithelial development mediated by ISCs. In this review, we elucidate the effects of ISCs

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differentiation on gut microbiota, summarize the progress in the effects of gut microbiota and their metabolites on the proliferation and differentiation of ISCs, and forecast the possible research directions in the future, aiming to give new insights into the therapies for intestinal injury.
Keywords: gut microbiota; microbial metabolites; intestinal stem cells

肠道是机体营养物质消化和吸收的主要场所。小肠上皮由重复的绒毛(villus)-隐窝(crypt)单元组成，结肠上皮仅由隐窝构成。肠道干细胞(intestinal stem cells, ISCs)位于隐窝底部，通过不断分裂实现自我更新，并分化产生各类上皮细胞，维持肠道稳态。目前，肠道上皮细胞(intestinal epithelial cells, IECs)的构建主要基于ISCs 谱系等级模型(图 1)，即 Wnt 与 Notch 信号调控 ISCs 产生祖细胞(progenitor cells)，也称为过渡扩增细胞(transit-amplifying cells, TA cells)，TA 细胞进一步分化形成分泌型细胞(潘氏细胞、内分泌细胞、簇状细胞和杯状细胞)与吸收型细胞(肠上皮细胞)[1]。此外，非典型 Wnt/PCP 信号激活的 ISCs 不经历 TA 细胞的过程，更倾向于分化为肠内分泌细胞或潘氏细胞[2]。ISCs 以富含亮氨酸重复序列的 G 蛋白偶联受体 5 (leucine-rich-repeat-containing G-protein-coupled receptor 5, Lgr5)为标志[3]，可在体外构建出具有完整肠道结构的 3D 类器官[4]，为探究宿主-菌群之间的相互作用提供条件。

肠道菌群是肠道复杂生态的一员，在宿主的正常代谢中发挥着重要作用，当菌群组成和空间位置异常时，可影响各种常见代谢疾病的发生发展，包括肥胖、2 型糖尿病和非酒精性肝病等[5]。肠道菌群已被证实与 IECs 有密切的相互作用，菌群可通过调节上皮细胞的功能及特定细胞亚型的形成来影响肠道健康[6-7]。随着技术的发展，研究者发现肠道菌群可定殖在肠隐窝内[8-10]，并可通过特定物质的分泌维持肠隐窝稳态；此外，特定菌株可通过其本身或代谢物直接或间接地调节 ISCs 功能，从而影响肠道的更新与修复。在此，本文阐述了 ISCs 分化对肠道菌群的影响，重点综述了肠道菌群及其代谢物调控 ISCs 增殖分化的机制，以期从菌群调控 ISCs 的角度探讨肠道损伤的治疗思路，并对未来可能的研究方向进行讨论。

1 肠道干细胞的分化影响肠道菌群组成

ISCs 分化形成的各类上皮细胞在维持肠道稳态与宿主防御中发挥重要作用，其中分泌型细胞可通过合成小分子物质影响肠道菌群的组成：(1) 潘氏细胞通过分泌抗菌肽与防御素维持了肠道菌群构成稳定及防止致病菌入侵[6]。当肠道缺乏抗菌肽 REG3B 或 REG3G 会增加黏膜相关微生物菌群的数量，并促进细菌向肠系膜淋巴结和肝脏的易位[11]。(2) 杯状细胞可通过黏蛋白的分泌促进肠道黏膜屏障稳定，抑制病原菌定殖[12]。葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导的肠道损伤中，黏蛋白 Muc5ac 缺失可增加细菌与上皮的接触，同时促进菌群向肠系膜淋巴结转移[13]。(3) 簇状细胞也可直接或间接地调节肠道微生物群。簇状细胞可通过激活 ILC2s 分泌 IL-13，促进杯状细胞释放黏液，进而清除病原体[6]。最新的研究指出，簇状细胞犁鼻器受体 Vmn2r26 可直接被菌群代谢物激活，进而发挥清除病原菌的作用[14]。综上所述，肠道防御功能的发挥得益于 ISCs 分化的各类型上皮细胞共同协作。这些细胞及其分泌物的功能对于肠道免疫系统的调节和肠道

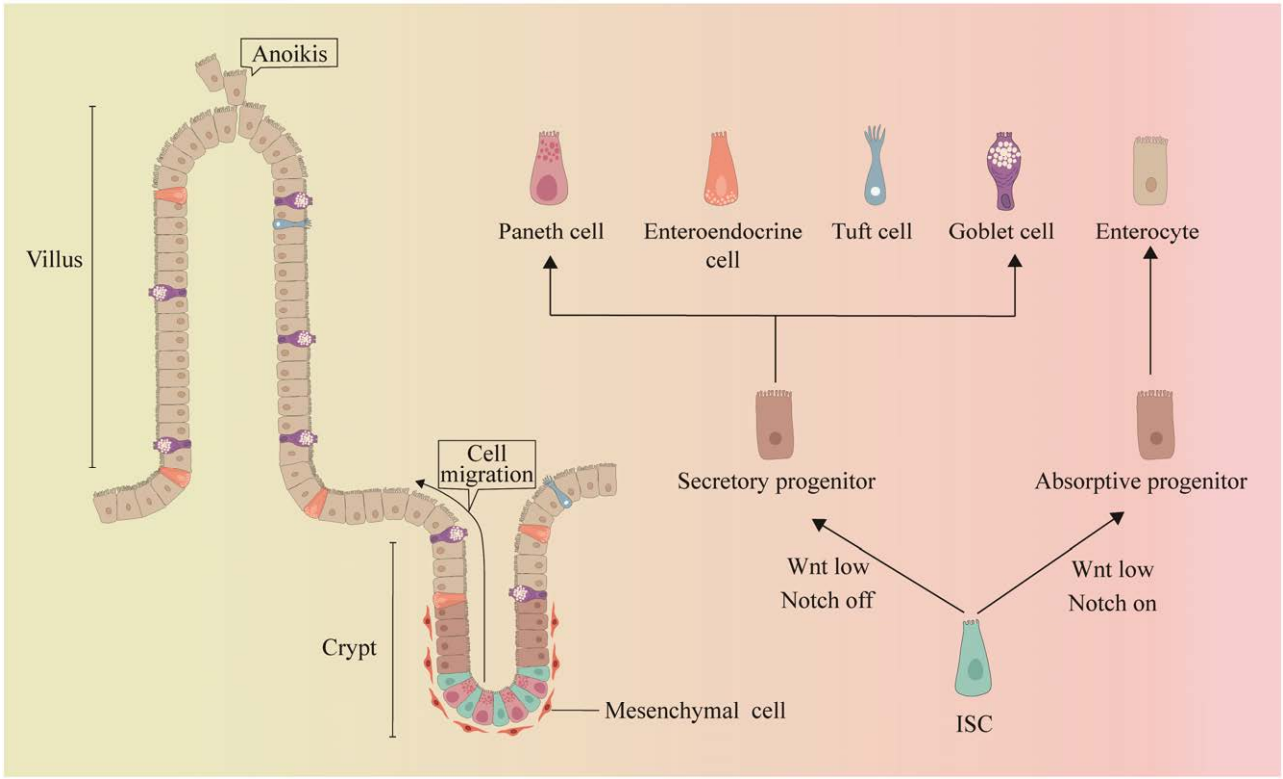

图 1 小肠上皮结构 左：小肠上皮包括了肠绒毛与肠隐窝，ISCs 与潘氏细胞位于隐窝的基部，间充质细胞环绕着隐窝生长，形成 ISCs 的生态位；分化的细胞将沿着隐窝-绒毛的方向迁移到达绒毛顶端，在细胞周期结束时，凋亡进入肠腔. 右：ISCs 分化形成吸收型祖细胞(Notch 信号激活)与分泌型祖细胞(Notch 信号抑制)，吸收型细胞为肠上皮细胞，分泌型细胞包括潘氏细胞、内分泌细胞、簇状细胞和杯状细胞

Figure 1 Structure of small intestinal epithelium. Left: The small intestinal epithelium includes the villus and crypt. ISCs and Paneth cells are located at the base of the crypts, along with mesenchymal cells to form the ISCs niche. The differentiated cells will migrate from the crypt to the tip of the villus, and eventually, apoptosis enters the intestinal lumen. Right: ISCs differentiate into absorptive progenitors (Notch on) and secretory progenitors (Notch off). The absorptive lineage contains enterocytes, and the secretory lineage includes Paneth cells, enteroendocrine cells, tuft cells, and goblet cells.

疾病的防治具有重要意义。未来可结合单细胞测序与空间组学技术深入探索分泌型细胞的作用机制及其与菌群的作用，为肠道疾病的治疗提供理论依据。

2 肠道菌群及其代谢物对肠干细胞功能的调控

肠道稳态需要 ISCs 与肠道菌群共同维持。近年来，研究者发现肠道菌群与 ISCs 之间存在着复杂的关系，菌群及其代谢物在多方面调控 ISCs (图 2)。

2.1 肠道菌群对肠道干细胞功能的调控

2.1.1 无菌环境对肠道干细胞的影响

肠道菌群的定殖情况影响宿主肠道发育。相较于常规饲养小鼠，无菌小鼠的远端小肠绒毛长而细，隐窝深度较浅，并含有较少的增殖

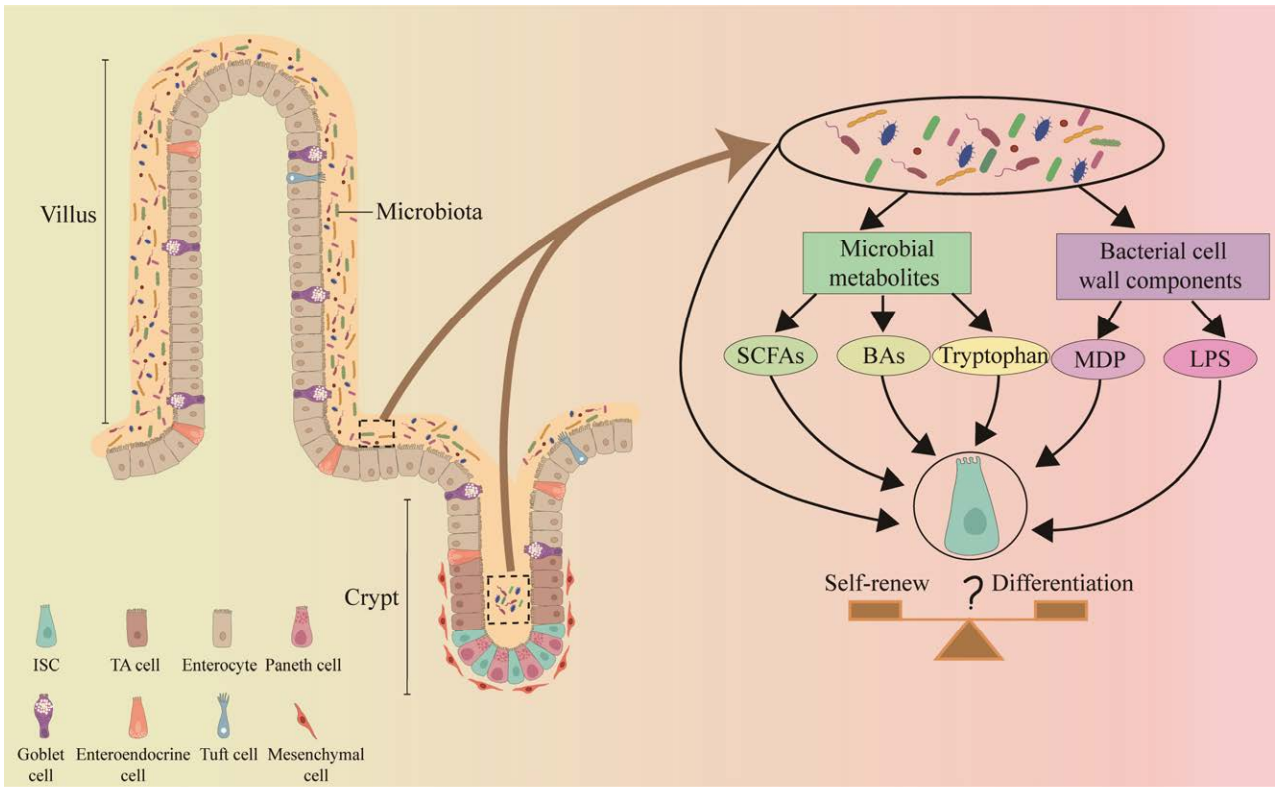

图 2　肠道菌群与其代谢物调控肠道干细胞的命运　左：在肠道黏膜和肠道隐窝内可发现肠道菌群定殖的信号. 右：菌群本身、菌群代谢物(短链脂肪酸、胆汁酸和色氨酸)和菌群细胞壁成分(胞壁酰二肽和脂多糖)影响 ISCs 的增殖与分化

Figure 2　Gut microbiota and its metabolites regulate the fate of intestinal stem cells. Left: Gut microbiota can colonize in the intestinal mucosa and intestinal crypts; Right: Gut microbiota, their metabolites (short-chain fatty acids (SCFAs), bile acids (BAs), and tryptophan), and their cell wall components (muramyl dipeptide (MDP) and lipopolysaccharide (LPS)) affect the ISCs proliferation and differentiation.

干细胞[15-16]。在后来的研究中指出，肠道菌群可以通过调节宿主发育过程中的基因表达来调控 ISCs 的命运[17]。无特定病原体小鼠与无菌小鼠发育过程中有一个高度差异表达的基因——红细胞分化调节因子 1 (erythroid differentiation regulator-1, Erdr1)，菌群通过诱导上皮细胞 Wnt 信号通路调控 Erdr1 介导的 $Lgr5^{+}$ISCs 增加及黏膜损伤后再生[17]。

除了无菌鼠，在其他无菌动物中也发现了肠道菌群与ISCs更新率之间存在着不可分割的关系。相较于普通饲养环境下的同伴，无菌猪与无菌兔具有更长的肠绒毛和更浅的肠隐窝深度[18-20]。类似地，与普通环境饲养下的斑马鱼相比，无菌斑马鱼体内具有更少的增殖细胞[21]。由此可见，对不同类型无菌动物的研究表明，肠道菌群可通过影响ISCs的增殖改变肠道的形态学结构。

2.1.2　特定肠道菌群对肠道干细胞的影响

由于肠隐窝的特殊结构，开口处存在分泌黏蛋白的杯状细胞，而基底部有分泌抗菌肽的潘氏细胞在很长一段时间被认为是无菌的。随着技术的发展，小鼠肠道菌群的荧光 D-型氨基

酸(fluorescent D-amino acid, FDAA)标记法以及激光捕获显微切割(laser capture microdissection, LCM)结合 16S rRNA 基因测序方法，推动了隐窝内肠道菌群的研究。研究指出，在小鼠前端与末端小肠的部分隐窝中可观察到菌群定殖的信号[10]。早在 2012 年便有研究发现隐窝特异性核心菌群(crypt-specific core microbiota, CSCM)定殖于小鼠结肠隐窝中[9]。*Acinetobacter* 为 CSCM 的成员之一，可能通过病原体相关分子模式的表达或脂多糖(lipopolysaccharide, LPS)的释放来影响肠隐窝的稳态[9,22]。

此外，特定菌株丰度的增加可调节 ISCs 功能(表 1)，并在影响 ISCs 介导的上皮发育和肠道稳态的维持中发挥关键作用。一方面，肠道菌群组成的改变导致特异性的肠上皮屏障重组。沙门氏菌(*Salmonella* sp.)感染增加了潘氏细胞与肠上皮细胞的数目，而嗜黏蛋白-阿克曼氏菌(*Akkermansia muciniphila*)丰度上调促进了分泌型细胞分化[24-25]。另一方面，肠道菌群通过多种信号通路调控 ISCs 命运，从而增强黏膜屏障功能。枯草芽孢杆菌(*Bacillus subtilis*)通过激活脂磷壁酸-TLR2-Myd88 通路抑制 ISCs 的 Notch 信号传导，促进分泌型细胞分化，增强黏膜屏障清除病原菌的能力[28]。罗伊氏乳杆菌(*Lactobacillus reuteri*) D8 及乳酸产生菌通过激活 ISCs 的 Wnt/β-catenin 通路促进 ISCs 增殖，从而修复损伤的肠道屏障[29,33]。目前的研究显示微生物疗法在缓解肠道疾病上具有应用前景，但尚缺乏精准调控的方法。肠道菌群的个体差异限制了微生物疗法在肠道疾病治疗中的应用。未来可根据不同的个体开发精准的微生物疗法，发挥菌群调控下 ISCs 对肠道的修复作用，为肠屏障损伤的治疗提供新思路。

2.2 菌群代谢物对肠道干细胞功能的调控

肠道菌群能够将宿主来源的成分转化为多种代谢物，是宿主与菌群互作的重要介质。菌群代谢物，如短链脂肪酸、胆汁酸和吲哚衍生物等已被证明可直接或间接地影响 ISCs 命运(图 2)。

2.2.1 短链脂肪酸

细菌在肠道内对未被消化或仅被部分消化的复杂多糖进行发酵可产生短链脂肪酸(short-chain fatty acids, SCFAs)[36]。乙酸、丙酸和丁酸等主要的 SCFAs 除了在肠上皮细胞的免疫调节和能量供应中发挥作用外[37]，也被证明影响 ISCs 的增殖分化。有研究指出丁酸盐可通过影响基因表达和蛋白质合成促进细胞增殖、分化和成熟，从而促进肠道修复[38]。另一部分研究则认为 SCFAs 可抑制 ISCs 增殖，体外试验发现，丙酸盐及丁酸盐下调了肠类器官的增殖能力，并促进了 ISCs 向 IECs 和分泌型细胞分化[39]。

SCFAs 对 ISCs 的作用受其浓度与肠道生理状态影响。稳态下，小鼠结肠细胞能够代谢丁酸盐，维持隐窝基部的最低丁酸盐浓度，保护 ISCs 和增殖细胞免受丁酸盐抑制[40]。然而当黏膜损伤后，ISCs 暴露于丁酸盐中，丁酸盐通过叉头框家族蛋白 O3 (forkhead box protein O3, FOXO3)负调控细胞周期调节因子，抑制 ISCs 及祖细胞的增殖[40]，延缓了上皮损伤修复[40-41]。目前，SCFAs 对 ISCs 的作用尚无定论，但鉴于 SCFAs 在减轻肠道炎症与抵御病原体中的重要作用[42]，进一步探究 SCFAs 调控 ISCs 的机制将有助于临床肠道损伤修复治疗的发展。

2.2.2 胆汁酸

胆汁酸(bile acids, BAs)可调节肠上皮的稳态，对脂质的消化、吸收以及胆固醇和脂溶性维生素的吸收至关重要[43]，主要包括初级胆汁酸与次级胆汁酸。初级胆汁酸可作为微生物代谢的底物转化为次级游离胆汁酸，主要包括脱氧胆

表 1　特定肠道菌群对肠道干细胞的影响

Table 1　The effects of specific intestinal microbiota on intestinal stem cells

肠道菌群 Microbiota	对肠道干细胞的影响 Effects on ISCs	模型 Model	参考文献 References
沙门氏菌 *Salmonella*	降低 ISCs 标志物 *Lgr5* 和 *Bmi1* 的表达 Decrease the expression of stem cell markers (*Lgr5* and *Bmi1*)	肠类器官 Intestinal Organoids (IOs)	[23]
	减少 ISCs 与 TA 细胞的数目，增加潘氏细胞与肠上皮细胞的比例 Increase the proportion of differentiation cell types (Paneth cells and enterocytes) at the expense of ISCs and TA cells	小鼠 Mouse	[24]
嗜粘蛋白-阿克曼氏菌 *Akkermansia muciniphila*	促进 ISCs 增殖及分泌型细胞分化 Stimulate the ISCs proliferation and the differentiation of secretory cells	小鼠与肠类器官 Mouse and IOs	[25]
	促进 ISCs 的增殖与缓解 DSS 诱导的肠道炎症 Increase the proliferation of ISCs and reduce DSS-induced intestinal inflammation	小鼠与肠类器官 Mouse and IOs	[26]
枯草芽孢杆菌 *Bacillus subtilis*	诱导 ISCs 的增殖，缓解肠黏膜屏障炎症和促进黏膜屏障再生 Induce ISCs proliferation, reduce intestinal mucosal inflammation, and promote mucosal barrier reconstruction	小鼠 Mouse	[27]
	抑制 ISCs 的增殖，促进分泌型细胞分化 Inhibit the proliferation of ISCs and stimulate differentiation towards secretory cells	小鼠与肠类器官 Mouse and IOs	[28]
乳酸产生菌：双歧杆菌和乳酸杆菌 Lactic-acid-producing bacteria (LAB): *Bifidobacterium* and *Lactobacillus* spp.	诱导 ISCs、潘氏细胞和杯状细胞增殖 Elicit ISCs, Paneth cells, and goblet cells proliferation	小鼠与肠类器官 Mouse and IOs	[29]
鼠李糖乳杆菌 *Lactobacillus rhamanosus* GG	减轻炎症，促进 ISCs 增殖 Reduce inflammation and increase stem cells regeneration	小鼠 Mouse	[30]
罗伊氏乳杆菌 *Lactobacillus reuteri*	将棉子糖代谢为果糖，促进 ISCs 增殖 Metabolize raffinose to fructose, which increases ISCs proliferation	小鼠与肠类器官 Mouse and IOs	[31]
罗伊氏乳杆菌 D8 *Lactobacillus reuteri* D8	促进 ISCs 增殖，及肠上皮损伤的修复 Accelerate ISCs proliferation and promote repair of intestinal epithelial injury	小鼠与肠类器官 Mouse and IOs	[32-33]
植物乳杆菌 *Lactobacillus plantarum*	诱导成体中肠祖细胞增殖及肠组织发育 Induce the proliferation of adult midgut progenitor and growth of the intestine	果蝇 Drosophila	[34-35]

酸(deoxycholic acid, DCA)与石胆酸(lithocholic acid, LCA)[44-45]。

BAs 主要通过激活 G 蛋白偶联胆汁酸受体 5 (G-protein-coupled bile acid receptor 5, TGR5)与法尼醇 X 受体(farnesoid X receptor, FXR)参与机体生理代谢过程，包括葡萄糖代谢、脂质代谢、能量代谢和细胞增殖过程等[46]。一项前瞻性临床试验发现，血浆中多种结合的初级和次级胆汁酸的水平与结直肠癌风险呈正相关关系[47]，提示胆汁酸与 ISCs 增殖之间存在关联。BAs 通过激活 ISCs 的 TGR5 促进肠上皮的再生，驱动 SRC 和 YAP 相关蛋白再生级联，从而支持ISCs在稳态和损伤后上皮再生过程中的更新[48]。此外，BAs 可调控 ISCs 分化。研究表明，BAs 抑制 ISCs 向潘氏细胞分化，进而减少抗菌肽合成，这种作用可被 TGR5 抗体逆转[49]。

BAs 可通过 FXR 调节 ISCs 的增殖。研究表明，牛磺酸-β-鼠胆酸和 DCA 水平的增加可拮抗 FXR 功能，诱导 $Lgr5^+$细胞增殖和 DNA 损伤；而选择性激活肠道 FXR 可抑制异常 $Lgr5^+$细胞生长，限制结直肠癌的进程[50]。TGR5 与 FXRs 是肠道疾病发展中的重要因素，探索靶向激活肠道 TGR5 与 FXR 的联合用药，有望成为结直肠癌治疗的新策略。

2.2.3 色氨酸

色氨酸(tryptophan)可作为微生物生胞梭菌(*Clostridium sporogenes*)、消化性链球菌(*Peptostreptococcus* spp.)、乳杆菌(*Lactobacilli* sp.)等的代谢底物发挥支持细胞生长的作用[51]。在菌群的作用下，色氨酸被转化为各种有生物活性的吲哚衍生物，如吲哚、吲哚-3-乙酸、吲哚-3-丙酸和吲哚乙醛等[51]。这些微生物的色氨酸代谢物已被证明是芳基烃受体(aryl hydrocarbon receptor, AHR)的配体[52]。

吲哚衍生物可通过 Wnt 信号通路调控 ISCs 的功能。AHR 在 $Lgr5^+$ ISCs 中高度表达。AHR 激动剂 6-甲酰基吲哚并[3,2-b]咔唑(6-formylindolo[3,2-b]carbazole, FICZ)通过降低 β-catenin 的表达水平导致 Wnt 信号通路传导受阻，从而抑制小鼠肠类器官的发育[53]。此外，益生菌来源的吲哚-3-甲醛(indole-3-aldehyde, I3A)可通过激活 Wnt 信号通路促进 $lgr5^+$ ISCs 的增殖分化，进而修复辐射诱导的肠损伤[54]。

再者，AHR 对上皮细胞再生有重要的影响。肠上皮特异性的 AHR 缺失导致不受控制的 ISCs 增殖和恶性转化[55]。补充 AHR 配体吲哚-3-甲醇(indole-3-carbinol, I3C)可预防肿瘤发生并恢复 Wnt-β-Catenin 通路的调控[55]。最新的研究指出，FICZ 通过激活 AHR 上调参与上皮细胞分化的转录因子，限制再生相关的 Yap/Tead 转录靶点的染色质可及性[56]，提示 AHR 可作为 ISCs 再生与恶性转化过程的调控靶点。

吲哚衍生物也可通过激活其他细胞 AHR 来影响 ISCs 功能。灌胃小鼠罗氏消化链球菌(*Peptostreptococcus russellii*)可导致吲哚丙烯酸(indoleacrylic acid, IA)的产生增加，IA 可激活 DSS 诱导的结肠类器官和巨噬细胞的 AHR，并促进 *Ki67* 的表达和杯状细胞的增殖[57]。此外，罗伊氏乳杆菌 D8 可通过其代谢物 I3A 激活固有层淋巴细胞 AHR，促进 IL-22 分泌，诱导 STAT3 磷酸化，加速 ISCs 再生，从而修复肠黏膜损伤[32]。综上所述，吲哚衍生物可通过 AHR 影响 ISCs 功能，膳食补充 AHR 配体或调控产生 AHR 配体的菌群对上皮细胞分化和肠道屏障修复有积极作用。

2.2.4 细菌细胞壁成分

细菌细胞壁成分提供了各种独特的分子结构，可被机体的固有免疫系统的模式识别受体所识别，并可通过激活 ISCs 上的相应受体影响 ISCs 功能。

胞壁酰二肽(muramyl dipeptide, MDP)已被证明是肽聚糖的最小免疫原性成分[58]，是胞质核苷酸结合寡聚结构域蛋白 2 (nucleotide-binding oligomerization domain-containing protein, NOD2)的配体[59]。MDP 可激活 NOD2，触发对 ISCs 的保护作用[60]。这种细胞保护机制是通过核因子 κB (nuclear factor kappa B, NF-κB)独立通路协调激活 NOD2 和 ATG16L1，并通过线粒体自噬清除过量的活性氧(reactive oxygen species, ROS)分子[61]。

LPS 是革兰氏阴性菌细胞膜的重要结构成分。LPS 通过与 ISCs 表面 TLR4 结合产生 2 种效应：(1) 促进 ISCs 凋亡。ISCs 中 TLR4 信号的激活导致细胞凋亡调控因子 p53 up-regulated modulator of apoptosis (PUMA)诱导的 ISCs 阻滞，进而促进细胞凋亡[62]。靶向 ISCs 的 TLR4-PUMA 轴可能是促进黏膜愈合的一种策略。(2) 维持结肠上皮细胞增殖与分化的平衡。CSCM 来源的 LPS 通过 ripk3 介导的干细胞和 TA 细胞的坏死抑制细胞增殖，同时增强杯状细胞分化[22]。

从治疗的角度来看，调节 ISCs 功能可促进 LPS 介导的肠道损伤修复。抗菌肽 cathelicidin-WA 被证明可逆转 LPS 介导的 ISCs 消融，进而促进肠道上皮细胞再生[63]。此外，岩藻糖(fucose)通过上调 ISCs 岩藻糖基转移酶 2 (fucosyltransferase 2, FUT2)维持了 LPS 介导的肠道损伤中 ISCs 的增殖能力，提高了 ISCs 对内质网应激和炎症损伤的抵抗[64]。因此，研究肠屏障损伤中 ISCs 的反应机制将促进靶向损伤位点的治疗。

3 结论与展望

许多肠道疾病及代谢性疾病与肠道稳态紊乱密切相关，而肠道稳态依赖于 ISCs 在自我更新和分化之间维持平衡。肠道菌群及其代谢物可通过对多种信号的调控影响 ISCs 的功能。鉴于肠道稳态和疾病条件下的优势定殖菌不同，特异性肠道微生物群选择性定殖在隐窝中的原因、肠道菌群对 ISCs 增殖和分化的影响机制、ISCs 如何作出反馈等的肠道菌群与 ISCs 相互作用的问题仍有待进一步探究。以下将对未来可能的研究方向进行讨论和展望。

3.1 肠道菌群可通过调节其他细胞与 ISCs 相互作用

肠道菌群可通过调节其他细胞进而影响 ISCs 的功能。(1) 肠道菌群-嗜酸性粒细胞-ISCs 之间调控的回路可调节上皮更新与稳态维持[65]。(2) 肠道菌群-肠道神经元-ISCs 之间的复杂调控可驱动 ISCs 的自我更新[66]。因此，后续对肠道菌群-肠道免疫细胞、间充质细胞或肠道神经元-ISCs 之间相互作用的探究，将有助于揭示调控 ISCs 的新层面及靶向肠稳态紊乱的治疗。

3.2 从肠道菌群的角度出发探讨作用 ISCs 的新途径

肠道菌群细胞外囊泡(extracellular vesicles, EVs)的释放可作为菌群与 ISCs 之间交流的桥梁[67]。研究表明，肠道菌群 EVs 可以靶向 ISCs 引起遗传变化[67]。但目前关于肠道菌群 EVs-ISCs 之间相互作用的研究较少，该领域还有待进一步探究。未来，研究细菌 EVs 在稳态和疾病条件下对 ISCs 的靶向作用，揭示其调控途径，将有助于探索调节 ISCs 的新机制，为疾病治疗提供新的思路。

3.3 肠道菌群与 ISCs 互作的研究模型

在探究肠道菌群与 ISCs 互作中，小鼠及果蝇模型[68]被广泛应用。随着技术的发展，肠道类器官被广泛应用。肠道类器官代表了 ISCs 的活性，在体外可形成“迷你肠道”，模拟体内的肠道结构与功能。通过显微注射目标菌株于肠类器官内[69-70]，探究肠腔内菌群与 ISCs 或是其

余上皮细胞之间的相互作用；另外，通过微流控系统构建的类器官芯片[71]，解决了传统类器官腔内细胞碎片堆积需每周进行裂解传代的问题，更好地实现了类器官的长时间培养，为观察长期的菌群-宿主肠道之间的相互作用提供了可能。值得注意的是，病人来源的细胞可用于肠类器官的构建[72]，并且通过对病人的粪便样本进行微生物检测与培养，二者的结合将促进精准医学的研究，更好地设计个体化的治疗。

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