

肠道微生物和宿主肠道干细胞互作机制的研究进展

郭芳申, 甄文瑞, 张祎, 马彦博, 李旺*

河南科技大学 动物科技学院, 河南 洛阳

郭芳申, 甄文瑞, 张祎, 马彦博, 李旺. 肠道微生物和宿主肠道干细胞互作机制的研究进展[J]. 微生物学报, 2026, 66(2): 560-577.
GUO Fangshen, ZHEN Wenrui, ZHANG Yi, MA Yanbo, LI Wang. Advances in the interaction mechanisms between gut microbiota and host intestinal stem cells[J]. *Acta Microbiologica Sinica*, 2026, 66(2): 560-577.

摘要: 肠黏膜上皮细胞种类和数量的稳定维持着肠道形态和功能的正常, 而肠道上皮细胞稳态依赖于位于隐窝处肠道干细胞(intestinal stem cells, ISCs)的不断增殖、分化和迁移。肠道共生微生物与 ISCs 相互作用, 共同维持肠道生态稳定。ISCs 分化形成的肠上皮细胞(intestinal epithelial cells, IECs)通过分泌免疫球蛋白、黏蛋白等调控肠道微生物的组成与功能。肠道共生微生物通过微生物相关分子模式(如脂磷壁酸、脂多糖)及微生物代谢物(如短链脂肪酸、胆汁酸)等构成了独特的肠道微环境, 进而调控宿主 ISCs 功能及成熟细胞亚群稳态。基于肠道微生物靶向调控宿主 ISCs 功能以维护肠道健康已成为当前的研究热点。因此, 本文重点阐述 ISCs 对肠道微生物区系的影响, 以及肠道微生物及其代谢物对宿主 ISCs 增殖分化命运的调控作用, 以期加深对肠道微生物和宿主 ISCs 相互作用的理解, 为肠道功能及健康的调控提供理论参考。

关键词: 肠道干细胞; 肠道微生物; 微生物代谢物

Advances in the interaction mechanisms between gut microbiota and host intestinal stem cells

GUO Fangshen, ZHEN Wenrui, ZHANG Yi, MA Yanbo, LI Wang*

College of Animal Science and Technology, Henan University of Science and Technology, Luoyang, Henan, China

Abstract: The gut structure and functional performance rely on the stable type and quantity of gut mucosal epithelial cells, whose stability depends on continuous proliferation, differentiation, and migration of intestinal stem cells (ISCs) located in the crypts. Interactions between gut microbiota

资助项目: 河南省自然科学基金青年项目(252300421652)

This work was supported by the Henan Provincial Natural Science Foundation Youth Program (252300421652).

*Corresponding author. E-mail: liwang@haust.edu.cn

Received: 2025-08-23; Accepted: 2025-10-04; Published online: 2025-10-30

and ISCs support the homeostasis of the gut ecosystem. Intestinal epithelial cells (IECs) differentiated from ISCs influence the composition and function of gut microbiota through secreting immunoglobulins, mucins, etc. Meanwhile, the microorganism-associated molecular patterns (such as lipoteichoic acid and lipopolysaccharides) and metabolites (such as short-chain fatty acids and bile acids) from gut microbiota form the unique gut microenvironment to regulate the activity of ISCs and the homeostasis of IECs. Regulating the activity of ISCs and gut health by modifying gut microbiota has become a focus of current research. Thus, this review elaborates on the impact of ISCs on the gut microbiota as well as the regulatory roles of gut microbiota and related metabolites on the proliferation and differentiation fate of ISCs, aiming to broaden the understanding of the interaction between gut microbiota and ISCs. It is expected to provide strategies and targets for the regulation on gut health.

Keywords: intestinal stem cells; gut microbiota; microbial metabolites

动物肠道上皮细胞(intestinal epithelial cells, IECs)主要由位于绒毛端的成熟上皮细胞、隐窝处的潘氏细胞与肠道干细胞(intestinal stem cells, ISCs)构成。肠道成熟上皮细胞可分为两大类,即吸收型细胞亚群(如肠细胞和 M 细胞等)和分泌型细胞亚群(如杯状细胞、潘氏细胞、Tuft 细胞、肠内分泌细胞等)^[1]。不同类型的肠道上皮细胞协同发挥消化吸收和屏障防御功能。外界刺激会引起肠道上皮细胞衰老及损伤,因此 ISCs 不断分化产生子代细胞,对于黏膜上皮细胞的更新以及维持肠道形态和功能的正常发挥着不可替代的作用^[2]。作为宿主的“第二基因组”,肠道微生物是调控宿主 ISCs 增殖分化的重要因素^[3]。抗生素干预及无菌条件下动物 ISCs 分化形成子代细胞的能力受损^[4-5]。此外,肠道微生物相关分子模式[如脂磷壁酸(lipoteichoic acid, LTA)、脂多糖(lipopolysaccharide, LPS)等]及微生物代谢物[如色氨酸代谢物、短链脂肪酸(short-chain fatty acids, SCFAs)等]也参与构成可调控 ISCs 功能的干细胞龛^[6]。肠道共生微生物和 ISCs 的相互作用对于保障宿主肠道健康意义重大。因此,了解肠道微生物及其代谢产物和 ISCs 的相互作用,阐明肠道微生物调控 ISCs 增殖分化及肠道更新能力的机制对于利用微生态策略调控宿主肠道健康至关重要。

1 肠道干细胞

1.1 肠道干细胞的分类

20 世纪 70 年代, Cheng 等^[2]发现隐窝底部的潘氏细胞之间存在 1 种细长的细胞,将其命名为隐窝基底柱状细胞;这类细胞可产生子代细胞,并持续沿隐窝-绒毛轴迁移形成新的肠道上皮细胞,因此也被称为肠道干细胞。肠道干细胞可分为 2 类:位于隐窝基底位置,由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)标记的活化 ISCs (Lgr5⁺ ISCs);以及位于隐窝“+4”位置,由 B 细胞特异性白血病病毒插入位点(B cell-specific moloney murine leukemia virus integration site 1, Bmi-1)标记的储备 ISCs (Bmi-1⁺ ISCs)^[1,7]。目前,也有学者使用嗅觉调节素 4 (olfactomedin 4, Olfm4)或 achaete-scute 家族 bHLH 转录因子 2 (achaete-scute family bHLH transcription factor 2, Ascl2)标记 Lgr5⁺ ISCs,使用同源域蛋白同源盒(homeodomain-only protein homeobox, Hopx)、小鼠端粒酶逆转录酶(mouse telomerase reverse transcriptase, mTert)或富亮氨酸的重复序列和免疫球蛋白样结构域 1 (leucine rich repeats and immunoglobulin like domains 1, Lrig1)标记 Bmi-1⁺ ISCs^[7-8]。肠道更新依赖于隐窝底部的 Lgr5⁺ ISCs 的增殖及分化,而位于

隐窝“+4”位置的 $Bmi-1^+$ ISCs 常处于静息状态^[9]。在不利条件下, 当 $Lgr5^+$ ISCs 受到损伤时静息的 $Bmi-1^+$ ISCs 可产生子细胞, 补充受损的 $Lgr5^+$ ISCs 和肠道上皮细胞^[10]。因此, 储备 ISCs 被认为是组织修复的后备干细胞。同时, 在上皮损伤诱发的再生反应中未彻底分化的分泌和吸收型祖细胞也会去分化成为 $Lgr5^+$ ISCs 以维持 ISCs 池稳态^[11]。

1.2 肠道干细胞的调控通路

$Lgr5^+$ ISCs 的增殖分化维持着肠道组织的更新。肠道上皮细胞、间充质细胞、免疫细胞和微生物等产生的调控 ISCs 更新、增殖和分化的

信号分子所组成的微环境被称为干细胞生态位, 主要包括 Notch、Wnt、骨形态发生蛋白(bone morphogenetic protein, BMP)和表皮细胞生长因子(epidermal growth factor, EGF)等信号分子(图 1)^[11]。干细胞之间会竞争肠道生态位, 被“挤出”干细胞区的细胞在接触到不同浓度的分化调控因子时会发生分化^[12]。具体而言, 当 $Lgr5^+$ ISCs 细胞受到 Notch 信号通路效应分子 hes 家族 bHLH 转录因子 1 (hes family bHLH transcription factor 1, Hes1)的刺激后, ISCs 先转化为过渡放大(transit amplify, TA)细胞, 进而分化为肠细胞^[13]。当细胞未受到 Notch 信号通路的刺激时

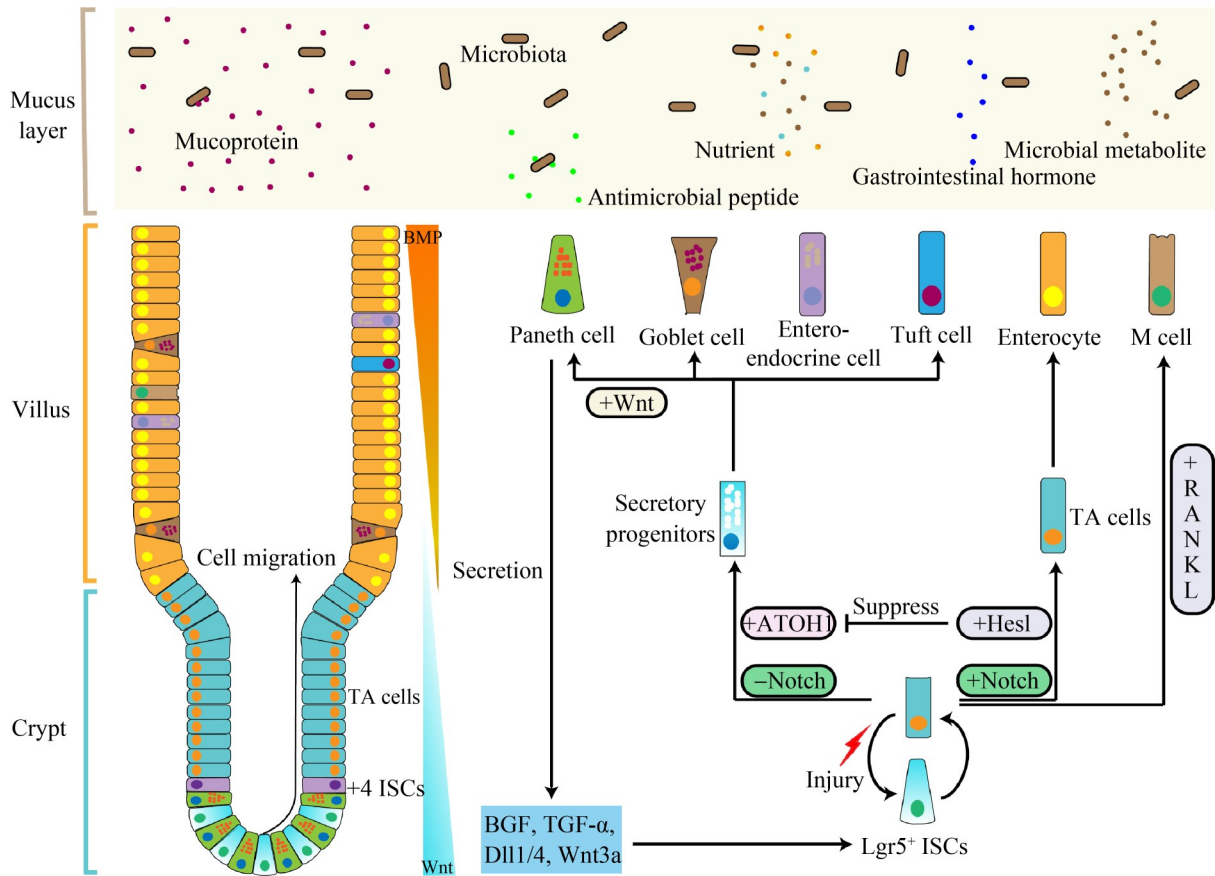


图1 肠道干细胞微环境

Figure 1 Niche factors of intestinal stem cells. ATOH1: Atonal bHLH transcription factor 1; BMP: Bone morphogenetic protein; EGF: Epidermal growth factor; Hes1: Hes family bHLH transcription factor 1; ISCs: Intestinal stem cells; Lgr5: Leucine-rich repeat-containing G-protein coupled receptor 5; RANKL: Receptor activator for nuclear factor-kappa B ligand; TA: Transit amplify; TGF- α : Transforming growth factor- α .

会分化成分泌型肠上皮细胞祖细胞。迁移离开干细胞区的分泌型祖细胞在接收到 Wnt 信号刺激后会在上皮细胞之间的 Eph-ephrin 作用下返回隐窝底部, 成为潘氏细胞^[14]。未受到 Wnt 蛋白刺激的分泌型祖细胞则分化成为杯状细胞、肠内分泌细胞或 Tuft 细胞。M 细胞的分化不受 Notch 和 Wnt 通路的影响, 主要是由派尔集合淋巴结中核因子受体激活因子- κ B 配体(receptor activator for nuclear factor-kappa B ligand, RANKL)直接刺激形成^[1]。

Notch 信号通路是决定 Lgr5⁺ ISCs 分化命运的关键信号通路^[15]。Notch 信号的激活依赖于配体呈递细胞和受体细胞之间的直接接触。因此, Notch 配体如 delta 样配体(delta-like ligand, Dll) 1 和 Dll4 主要由与 ISCs 相邻的间充质细胞和潘氏细胞提供^[16-17]。Notch 配体和受体之间的相互作用会诱导受体细胞内形成 Notch 胞内结构域(Notch intracellular domain, NCID)^[18]。NCID 与细胞核中免疫球蛋白 κ J 区重组信号结合蛋白(recombination signal binding protein for immunoglobulin kappa J region, RBPJ)结合, 从而激活 Hes1 表达; Hes1 通过抑制细胞周期蛋白依赖性激酶抑制剂 p27KIP1 和 p57KIP2 的表达促进 Lgr5⁺ ISCs 和 TA 细胞的快速增殖, 最终使 ISCs 分化成为吸收型肠上皮细胞^[19]。无调性 bHLH 转录因子 1 (atonal bHLH transcription factor 1, ATOH1), 也被称为小鼠无调性同源物 1 (mouse atonal homolog 1, MATH1), 是促进 Lgr5⁺ ISCs 向分泌型肠道上皮细胞分化的转录因子。Notch 信号通路靶基因 Hes1 是 ATOH1 的转录抑制因子, 因此 Notch 的激活会通过抑制 ATOH1 的表达, 进而抑制 Lgr5⁺ ISCs 分化为分泌型肠道上皮细胞^[20]。

Wnt/ β -catenin 与 Notch 信号通路协同调控 Lgr5⁺ ISCs 的增殖分化命运。Wnt 信号通路的激活可以上调 ATOH1 的表达, 诱导 Lgr5⁺ ISCs 分化为分泌型肠道上皮细胞^[21]。潘氏细胞可产生 Wnt3a, 肠道间质细胞如 Foxl1⁺、Gli1⁺ 或

α SMA⁺细胞可以产生 Wnt2b、Wnt4 和 Wnt5a 等激活 Wnt/ β -catenin 信号通路^[22-23]。Wnt 配体与位于 ISCs 细胞膜上的 Frizzled-LDL 受体相关蛋白(LDL receptor related protein, LRP) 5/6 受体复合物结合^[24]。复合物的形成会引起 β -catenin 从 APC/Axin/GSK-3 β 复合体上解离并在胞内聚积; 之后 β -catenin 入核, 与 TCF/LEF 结合进而启动 c-Myc 和 Cyclin D1 等靶基因的表达, 激活 Lgr5⁺ ISCs 的增殖和分化^[25]。

R-spondin 也是 ISCs 生态位的重要组成成分。R-spondin 可与 Lgr5 结合形成 R-spondin-Lgr5 复合物, 该复合物作用于 E3 泛素连接酶 Rnf43 和 ZNRF3, 弱化其对 Frizzled 受体的抑制作用, 从而增强 Wnt 信号通路的激活^[26-27]。与 Wnt 的来源一致, R-spondin 主要由 Foxl1⁺ 细胞分泌^[28]。

EGF 是调节 ISCs 活性的一种外源性因子, 主要由潘氏细胞和基质细胞分泌^[29]。EGF 通过与膜受体酪氨酸激酶家族的 ErbB1-4 结合介导细胞通路转导, 相关配体主要包括 EGF、转化生长因子- α (transforming growth factor- α , TGF- α)、双调节蛋白 (amphiregulin, AREG)、表观原 (epigen, EPGN)、肝素结合 EGF 样生长因子 (heparin-binding epidermal growth factor-like growth factor, HB-EGF)、表皮调节蛋白 (epiregulin, EREG)、 β 细胞蛋白 (betacellulin, BTC) 和神经调节蛋白 (neuregulin, NRG) 等^[30-31]。EGF 配体具有受体结合特异性, 具体而言, EGF、TGF- α 、AREG 和 EPGN 与 ErbB1 受体特异性结合, HB-EGF、EREG 和 BTC 与 ErbB1 和 ErbB4 特异性结合, NRG1 和 NRG2 与 ErbB3 和 ErbB4 特异性结合, NRG3 和 NRG4 与 ErbB4 特异性结合^[32]。EGF 配体同 ErbB 受体结合后, 引起受体细胞特定酪氨酸残基磷酸化^[33]。磷酸化残基通过激活丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK)、磷脂酰肌醇 3 激酶-蛋白激酶 B (phosphatidylinositol 3-kinase-protein kinase B, PI3K-AKT) 和非受体型酪氨酸蛋

白激酶-信号转导及转录激活因子(Janus kinase-signal transducer and activator of transcription, JAK-STAT)等通路, 调控 ISCs 的增殖和分化^[34]。

BMP 属于转化生长因子家族, 由肠道间充质细胞产生, 主要类型为 BMP2 和 BMP4 等。BMP2 和 BMP4 与骨形态发生蛋白受体 1A 型 (bone morphogenetic protein receptor type 1A, BMPRI1A) 结合激活 Smad 蛋白, 抑制 Lgr5⁺ ISCs 增殖, 促进其分化^[35]。同时, 隐窝周围的基质细胞, 包括肌成纤维细胞和平滑肌细胞可分泌 BMP 抑制剂, 如 Noggin、Chordin 和 Gremlin 等, 促进 ISCs 的增殖和更新^[36]。与 Wnt 信号相反, BMP 浓度由隐窝底部至绒毛顶端逐渐升高, 两者以冗余的方式建立 ISCs 分化生态梯度^[1]。

2 肠道干细胞对肠道微生物的影响

Notch 信号通路是决定 ISCs 分化命运的首要因素, 其激活会促进 ISCs 向肠细胞分化^[15]。肠道固有层浆细胞分泌的多聚免疫球蛋白 A (polymeric immunoglobulin A, pIgA) 通过与肠细胞表达的多聚免疫球蛋白受体 (polymeric immunoglobulin receptor, pIgR) 结合运送到上皮细胞顶端膜, 进而转化为分泌型免疫球蛋白 A (secretory immunoglobulin A, sIgA)^[37]。sIgA 可通过凝集或抑制细菌鞭毛蛋白 (flagellin, Flg) 的形成, 进而限制潜在致病菌如分段丝状细菌和变形杆菌的生长; 还可包裹共生菌如阿克曼氏菌属 (*Akkermansia*) 和乳杆菌属 (*Lactobacillus*) 等, 增强其在肠黏膜中的黏附和定殖^[38-40]。肠碱性磷酸酶 (intestinal alkaline phosphatase, IAP) 主要由小肠细胞产生, 通常被认为是肠细胞的标志物^[41]。IAP 可将肠腔内微生物鞭毛蛋白、脂多糖、DNA 中未甲基化的胞嘧啶-磷酸-鸟嘌呤序列 (CpG-DNA) 和腺苷酸二磷酸 (uridine diphosphate, UDP) 等去磷酸化以减弱其抗原活性

和诱发肠道炎症反应的能力^[42-43]。同时, 去磷酸化的 LPS 会阻碍 Toll 样受体 (Toll like receptor, TLR) 信号通路的激活, 下调核因子 κ B (nuclear factor kappa-B, NF- κ B) 和促炎性细胞因子的表达^[44]。IAP 也发挥调控肠道微生物区系组成的作用。IAP 敲除小鼠肠道内好氧性革兰氏阴性细菌和总体细菌数量显著降低, 而补充 IAP 能促进共生细菌的生长并抑制有害细菌的生长^[45-46]。

Notch 信号通路的抑制会促进分泌型肠道上皮细胞亚群的形成^[15]。杯状细胞可分泌黏蛋白 Mucin-2, 参与构成肠道黏膜层^[47]。肠道黏液作为肠道共栖微生物的营养利用与栖息位点, 构成了肠道的微生物屏障^[48-49]。潘氏细胞通过 TLR 和核苷酸结合寡聚化结构域 (nucleotide binding oligomerization domain containing, NOD) 样受体 (NOD-like receptor, NLR) 等模式识别受体 (pattern recognition receptors, PRRs) 感知微生物, 进而释放抗菌肽来增强肠道抗菌防御功能。潘氏细胞主要分泌的抗菌肽是 α -防御素, 其通过破坏细菌的外膜, 改变膜通透性及电导率, 起到杀菌作用^[50]。溶菌酶通过破坏细菌细胞壁肽聚糖中的 β -1,4-糖苷键, 使细胞壁破裂, 从而发挥杀菌作用^[51]。类似地, C 型凝集素可与肽聚糖结合, 产生对革兰氏阳性菌的杀伤作用^[52]。M 细胞是肠道重要的抗原呈递细胞, 其可摄取肠腔内抗原并呈递给免疫细胞如树突状细胞^[53]、巨噬细胞和 B 细胞等, 从而诱导肠道免疫应答反应^[54-55]。总之, ISCs 增殖分化功能相关调控因子通过改变肠道上皮细胞组成发挥对肠道微生物的调控作用。

3 肠道微生物对肠道干细胞的影响

肠道共生微生物对 ISCs 增殖分化和黏膜上皮的更新起重要调控作用。研究表明无菌小鼠和抗生素处理的动物肠道上皮细胞增殖以及迁移活性降低, 肠道成熟细胞亚群如杯状细胞和

肠内分泌细胞数量减少^[56-57]。相反, 无菌果蝇的肠内分泌细胞数量增多, 而成肠细胞数量减少^[58], 这些差异可能由于不同物种间 ISCs 调控通路的不同所致。总而言之, 肠道共生微生物对 ISCs 的增殖分化以及肠道成熟细胞谱系的形成具有重要调控作用。

3.1 微生物相关分子模式对肠道干细胞的影响

细菌细胞壁中的脂磷壁酸、LPS 和胞壁酰二肽(muramyl dipeptide, MDP)等是宿主 ISCs 增殖分化及黏膜上皮细胞更新的重要调节因子(图 2)。TLR 和 NLR 在肠上皮细胞、内分泌细胞、免疫细胞以及 ISCs 中均有表达, 通过识别病原体相关分子模式(pathogen-associated molecular patterns, PAMPs)介导宿主对微生物的应答反应^[59-60]。TLR2 可识别微生物来源的 LTA 和肽聚

糖等^[61]。Riehl 等^[62]发现来自鼠李糖乳杆菌(*L. rhamnosus*)的 LTA 通过 TLR2 刺激环氧合酶-2 (cyclooxygenase-2, COX-2)⁺间充质干细胞分泌前列腺素 E2 (prostaglandin E2, PGE2), 保护 ISCs 免受辐射诱导的肠细胞凋亡。Hou 等^[63]发现枯草芽孢杆菌(*Bacillus subtilis*)以 LTA-TLR2 依赖性方式抑制 Notch 通路激活, 进而促进小鼠肠道分泌型上皮细胞亚群的形成。此外, TLR2 促进葡聚糖硫酸钠(dextran sulphate sodium, DSS)刺激的小鼠肠道杯状细胞的再生, 并通过诱导肠三叶因子 3 (trefoil factor family-3, TFF3)表达抑制天冬氨酸特异性的半胱氨酸蛋白水解酶 (cysteiny aspartate specific proteinase, Caspase)-9 介导的肠黏膜细胞凋亡^[64]。TLR4 信号通路可抑制 Wnt3a 表达和受体 LRP6 的活性, 抑制 Wnt 信号通路的激活^[65]。Sodhi 等^[66]发现 LPS 通过激活 TLR4 促进糖原合成酶激酶-3 β (glycogen

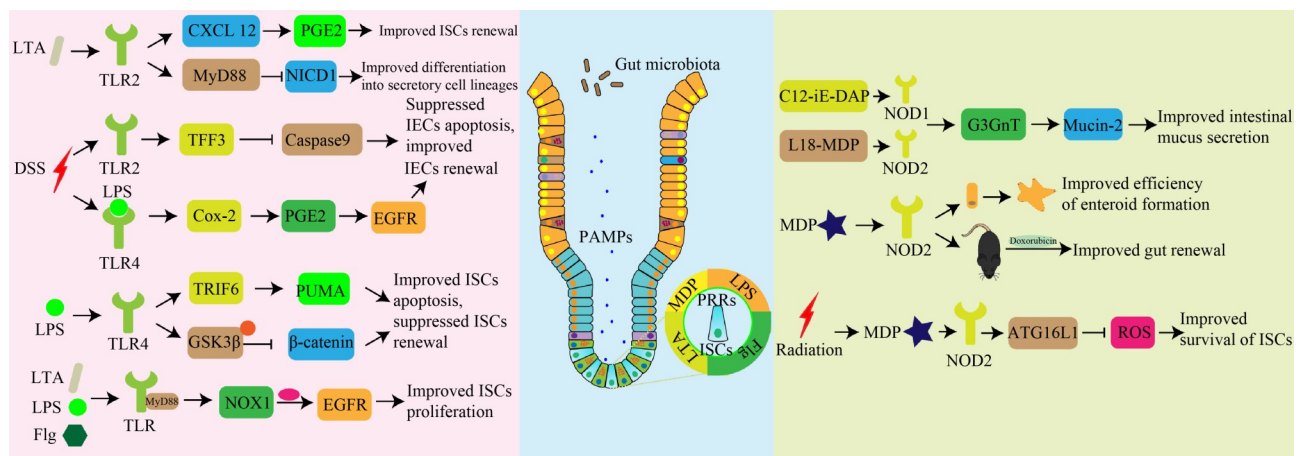


图2 微生物相关分子模式和模式识别受体对ISCs的影响

Figure 2 Impact of microbe-associated molecular patterns and pattern recognition receptors on ISCs. ATG16L1: Autophagy related 16 like 1; Cox2: Cyclooxygenase-2; CXCL12: Chemokine C-X-C motif ligand 12; DSS: Dextran sulfate; EGFR: Epidermal growth factor receptor; Flg: Flagellin; GSK-3 β : Glycogen synthase kinase-3 β ; IECs: Intestinal epithelial cells; ISCs: Intestinal stem cells; LPS: Lipopolysaccharide; LTA: Lipoteichoic acid; MDP: Muramyl dipeptide; MyD88: Myeloid differentiation primary response protein 88; NICD: Notch intracellular domain; NOD: Nucleotide binding oligomerization domain; NOX1: NADPH oxidase 1; PAMPs: Pathogen-associated molecular patterns; PGE2: Prostaglandin E2; PRRs: Pattern recognition receptors; ROS: Reactive oxygen species; TFF3: Trefoil factor family-3; TLR: Toll like receptor; TRAF6: TNF receptor associated factor 6.

synthase kinase-3 β , GSK-3 β)磷酸化, 降低新生小鼠小肠 β -catenin 的表达从而抑制小鼠肠道的增殖活性。此外, LPS 通过 TLR4- β 干扰素 TIR 结构域衔接蛋白 (TIR-domain-containing adaptor inducing interferon- β , TRIF) 依赖方式刺激 p53 上调的凋亡因子 (p53 up-regulated modulator of apoptosis, PUMA) 的表达, 引起 ISC 凋亡^[59]。类似地, 小鼠大肠中定殖于隐窝处的核心微生物群以 TLR4 依赖的方式激活受体相互作用的丝氨酸-苏氨酸激酶 3 (receptor-interacting serine-threonine kinase 3, RIPK3) 介导的坏死性凋亡, 抑制 ISC 增殖^[67]。然而, TLR4 的过表达会导致小鼠 Lgr5⁺ ISC 中 β -catenin 的核积聚, 引起小鼠 ISC 和上皮细胞增殖能力的增加^[68]。类似地, 细菌 LPS、鞭毛蛋白和 LTA 与 TLR 的相互作用可上调 ISC 中 NADPH 氧化酶 1 (NADPH oxidase 1, NOX1) 的表达, 产生活性氧 (reactive oxygen species, ROS) 进而激活表皮生长因子受体 (epidermal growth factor receptor, EGFR) 表达从而引起 ISC 的增殖以及肠黏膜损伤修复^[69-70]。DSS 刺激下, TLR4 通过激活 COX-2/PGE2/EGFR 信号通路从而刺激肠道上皮细胞的增殖^[71-72]。由此可知, 不同来源配体激活的 TLR4 信号通路对 ISC 的调控作用不同, 同时不同生理状态下 ISC 对 TLR 信号通路的响应也有差异。TLR 对 Notch 信号通路的表达也具有调控作用。TLR4 信号通路的沉默会降低小鼠肠道 Notch 配体的活性, 从而导致 Notch 通路靶基因 Hes1 表达的下调^[64,73-74]。细菌鞭毛蛋白是 TLR5 的天然配体。Jones 等^[75]发现, Flg 通过激活 TLR5 上调丝裂原活化蛋白激酶磷酸酶 7 (mitogen-activated protein kinase phosphatases 7, MKP-7) 的表达, 从而缓解小鼠肠黏膜损伤和细胞凋亡。此外, 来自植物乳杆菌 (*L. plantarum*) NCU116 的胞外多糖可以通过增加 ISC 的数量和分化能力, 恢复结肠炎小鼠的肠道稳态^[76]。

核苷酸结合寡聚化结构域 2 (nucleotide binding oligomerization domain containing 2,

NOD2) 是识别细菌胞壁酰二肽 (muramyl-dipeptide, MDP) 的关键受体, 其在肠道潘氏细胞、免疫细胞和 Lgr5⁺ ISC 中均表达^[77]。NOD2 对 ISC 损伤的保护作用依赖微生物来源的 MDP^[78]。Nigro 等^[78]研究发现 MDP 通过 NOD2 提高氧化应激状态下 ISC 的存活和肠上皮再生。类似地, MDP 通过 NOD2 激活自噬相关蛋白 16L1 (autophagy related 16 like 1, ATG16L1), 从而促进辐射诱导的 Lgr5⁺ ISC 线粒体自噬和 ROS 的清除^[79-81]。此外, NOD2 对于肠道黏液的分泌也至关重要。NOD1/2 双突变小鼠的 Mucin-2 表达水平降低, 而 NOD1/2 激动剂的联合使用则促进其表达^[82]。总之, NOD 受体驱动了应激状态下肠道干细胞的存活与黏膜上皮修复。

3.2 微生物代谢物对肠道干细胞的影响

3.2.1 短链脂肪酸

肠道微生物可利用宿主肠道内未消化的碳水化合物发酵产生短链脂肪酸, 主要有乙酸盐、丙酸盐和丁酸盐等^[83]。SCFAs 可通过激活游离脂肪酸受体 (free fatty acid receptor, FFAR) 促进肠道杯状细胞形成、肠道黏液的分泌以及抗菌肽如再生家族成员 3 γ (regenerating family member 3 gamma, RegIII γ) 和 β -防御素等的产生^[84-86]。类似地, 菊粉饲喂的小鼠结肠内乙酸、丙酸和丁酸等 SCFAs 含量显著提高, 同时其结肠 ISC 增殖和分化活性增强^[87]。黏蛋白降解菌嗜黏蛋白阿克曼氏菌 (*A. muciniphila*) 产生的乙酸通过激活 FFAR2 和 FFAR3 促进小鼠 Lgr5⁺ ISC 的增殖以及小肠潘氏细胞和杯状细胞的形成^[56,88]。Bilotta 等^[89]发现, 丙酸能通过抑制组蛋白去乙酰化酶 (histone deacetylase, HDAC)、激活 FFAR2 和 STAT3 等途径增加肠道上皮细胞的极化, 促进成熟谱系细胞沿着隐窝-绒毛轴迁移。此外, 丙酸能刺激肠上皮细胞 Mucin-2 表达, 增强肠道黏液屏障功能^[90-91]。在 DSS 诱导的小鼠结肠炎模型中梭菌 XIV (Clostridia clusters XIV) 分泌的丙酸能缓解 ISC 损伤, 维持黏膜屏障功能^[92]。丁

酸主要由普氏栖粪杆菌 (*Faecalibacterium prausnitzii*) 和罗斯拜瑞氏菌 (*Roseburia*) 等产生^[93]。肠道中多数丁酸盐被肠道上皮细胞用于 β -氧化和三羧酸循环 (tricarboxylic acid cycle, TCA) 以提供能量, 同时降低肠道内氧气含量 (图 3)^[94-95]。Donohoe 等^[96]发现, 添加丁酸能缓解无菌小鼠由于丁酸缺乏导致的 ISC 能量代谢紊乱和细胞自噬。丁酸代谢产生的生理性缺氧微环境可维持肠道缺氧诱导转录因子-1 α (hypoxia inducible factor-1 α , HIF-1 α) 的表达, 进而调控杯状细胞 Mucin-2 的表达和分泌^[95,97]。肠上皮细胞对丁酸的利用可形成代谢屏障, 维持隐窝内低浓度丁酸盐水平^[96]。适宜浓度的丁酸盐可通过抑制 HDAC 提高细胞周期负调节因子 Foxo3 表达, 进而抑制 ISC 的异常增殖^[98]。类似地, 普氏栖粪杆菌 (*F. prausnitzii*) 来源的丁酸可以通过下

调 HDAC3 表达抑制 ISC 向 Tuft 细胞的分化^[99]。此外, 过量的丁酸盐可诱导肠上皮细胞热休克蛋白 (heat shock proteins, HSP) 的表达, 从而干扰 Wnt 信号通路的激活和 ISC 稳态^[100]。在卵清蛋白致敏小鼠模型中丁酸盐抑制肠上皮细胞中 ROS 的产生, 下调 Notch 配体 Jagged1 的表达从而抑制 Notch 通路的激活^[101]。

乳酸和琥珀酸盐等 SCFAs 的中间代谢物也是 ISC 增殖分化的调节分子。乳酸菌产生的乳酸以 G 蛋白偶联受体 81 (G protein-coupled receptor 81, GPR81) 依赖性方式激活 Wnt/ β -catenin 通路, 促进 ISC 的增殖^[102-103]。琥珀酸盐对肠道的影响存在争议。琥珀酸盐可抑制肠上皮增殖, 诱发肠道炎症反应, 进而引起肠道黏膜损伤^[104-106]。然而, 相反的研究结果表明, 肠道微生物来源的琥珀酸盐通过参与 TCA 来诱

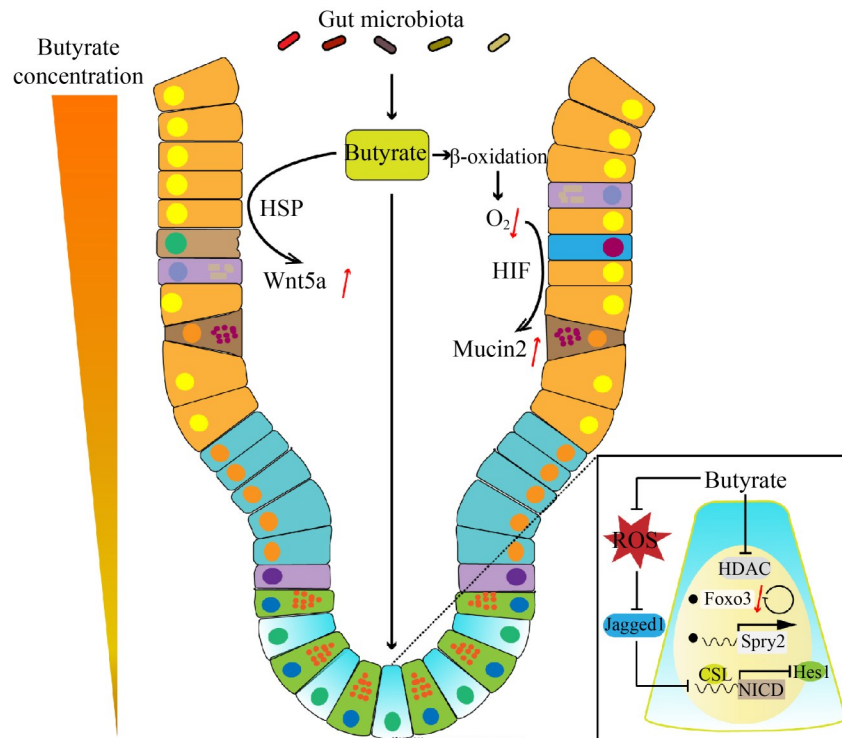


图3 丁酸对ISCs的影响

Figure 3 Impact of butyrate on ISC. CSL: CBF1, suppressor of hairless, Lag-1; HDAC: Histone deacetylase; Hes1: Hes family bHLH transcription factor 1; HIF: Hypoxia-inducible factor; HSP: Heat shock proteins; NICD: Notch intracellular domain; ROS: Reactive oxygen species; Spry2: Sprouty RTK signaling antagonist 2.

导 Tuft 细胞形成, 从而减轻克罗恩病小鼠回肠炎症反应和屏障功能损伤^[107]。类似地, 琥珀酸通过激活琥珀酸受体 1 (succinate receptor 1, SUCNR1), 改善高脂饲喂小鼠肠道杯状细胞的产生和黏液的分泌障碍^[108]。

3.2.2 胆汁酸

胆汁酸是肝脏以胆固醇为原料合成的胆酸物质。在肝细胞中直接合成的胆汁酸称为初级胆汁酸, 包括胆酸(cholic acid, CA)、鹅脱氧胆酸(chenodeoxycholic acid, CDCA)及其与甘氨酸或牛磺酸的结合物^[109]。次级胆汁酸是初级胆汁酸经肠道细菌 7 α -脱羟作用所形成的胆汁酸, 主要包括脱氧胆酸(deoxycholic acid, DCA)和石胆酸(lithocholic acid, LCA)及其与甘氨酸或牛磺酸

的结合物^[110]。根据合成途径和结构的不同, 胆汁酸可分为 12 α -羟基化胆汁酸(12 α -OH BAs, CA、DCA 及其结合物)和非 12 α -OH BAs [CDCA 及其衍生物熊去氧胆酸(ursodeoxycholic acid, UDCA)、石胆酸及其结合物]^[111], 两者对 ISCs 的增殖分化功能具有相反的调控作用(图 4)。在炎症性肠病(inflammatory bowel disease, IBD)个体中胆汁酸通过抑制过氧化物酶体增殖物激活受体 α (peroxisome proliferators-activated receptor α , PPAR α)的活性, 抑制脂肪酸氧化和 Lgr5⁺ ISCs 的自我更新^[112]。奥贝胆酸(obeticholic acid, OCA)可通过法尼醇 X 受体(farnesoid X receptor, FXR)-细胞色素 P450 家族 8 亚家族 B 成员 1 (cytochrome P450 family 8

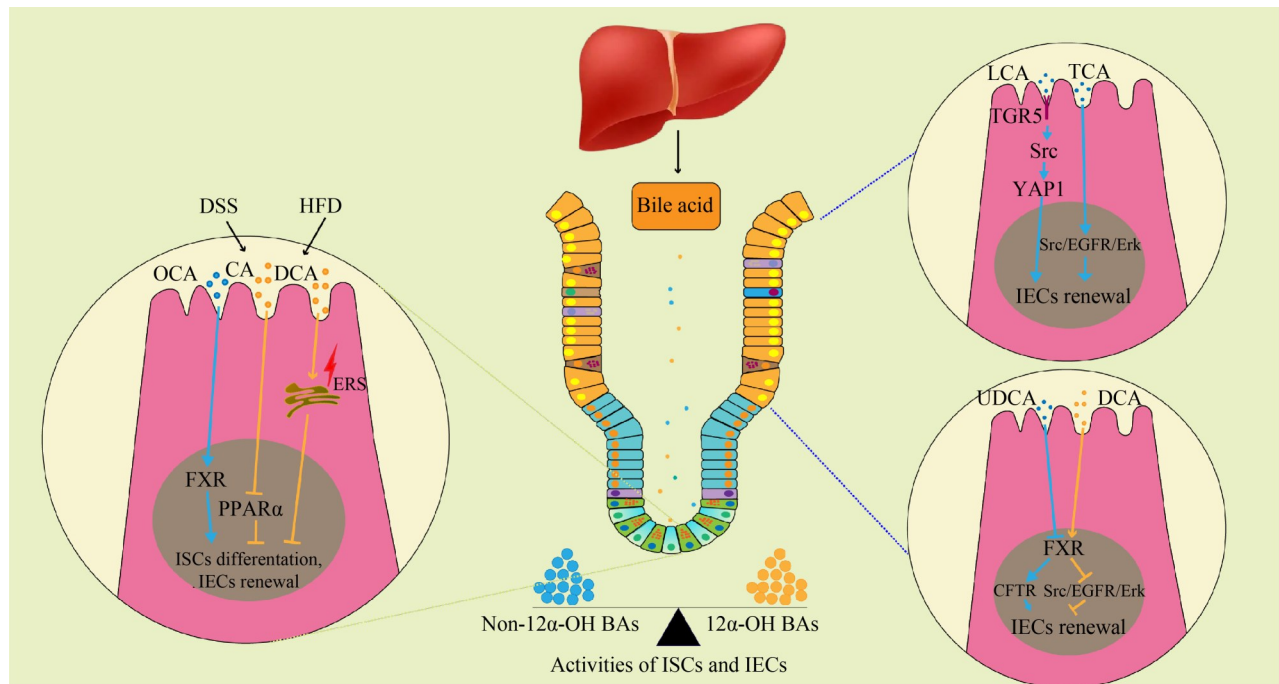


图4 胆汁酸对ISCs的影响

Figure 4 Impact of bile acid on ISCs. 12 α -OH BAs: 12 α -hydroxylated bile acids; CA: Cholic acid; CFTR: Cystic fibrosis transmembrane conductance regulator; DCA: Deoxycholic acid; EGFR: Epidermal growth factor receptor; ERS: Endoplasmic reticulum stress; FXR: Farnesoid X receptor; HFD: High fat diet; IECs: Intestinal epithelial cells; ISCs: Intestinal stem cells; IBD: Inflammatory bowel disease; LCA: Lithocholic acid; OCA: Obeticholic acid; PPAR α : Peroxisome proliferators-activated receptor α ; TCA: Taurocholate acid; TGR5: Takeda G-protein-coupled receptor 5; UDCA: Ursodeoxycholic acid.

subfamily B member 1, CYP8B1)信号通路恢复受损的黏膜上皮更新能力^[112]。高脂饲喂诱发的DCA循环水平提高会引起小鼠肠道内质网应激,从而降低ISCs增殖和分化为杯状细胞的能力^[113]。类似地,DCA可通过FXR依赖机制引起类固醇受体辅激活因子(steroid receptor coactivator, Src)/EGFR/细胞外信号调节激酶(extracellular signal regulated kinases, Erk)蛋白失活从而抑制肠细胞增殖^[114]。与之相反,在受损肠道的上皮再生过程中非12 α -OH胆汁酸LCA通过G蛋白偶联受体TGR5激活Src/Yes相关蛋白(Yes-associated protein, YAP)和下游靶标基因促进ISCs更新和肠内分泌细胞的形成^[115]。类似地,UDCA通过抑制FXR活性并增加结肠上皮细胞囊性纤维化跨膜传导调节因子(cystic fibrosis transmembrane conductance regulator, CFTR)Cl通道的表达,以促进肠黏膜愈合^[116]。Yamada等^[117]发现,一种具有维生素D样活性的石胆酸衍生物可上调肠道类器官发育成熟标志基因CYP3A4的表达。总之,12 α -羟基化胆汁酸如胆酸与非12 α -羟基化胆汁酸如脱氧胆酸和石胆酸等对ISCs增殖和分化功能具有不同的调控作用,两者共同构成维持肠道干细胞稳态的胆汁酸调控微环境。

3.2.3 色氨酸代谢物

色氨酸侧链上的吲哚基团可被宿主和微生物代谢为吲哚衍生物,如色胺、吲哚、3-甲基吲哚、吲哚-3-乳酸(indole-3-lactic acid, ILA)、吲哚-3-乙酸(indole-3-acetic acid, IAA)、吲哚-3-丙酸(indolyl-3-propionic acid, IPA)、吲哚-3-丙烯酸(3-indoleacrylic acid, IA)、吲哚-3-甲醛(indole-3-aldehyde, IAld)和吲哚-3-乙醇(3-indoleethanol, IE)等^[118-119]。这些代谢物可激活芳香烃受体(aryl hydrocarbon receptor, AhR)和孕烷X受体(pregnanane X receptor, PXR)等^[119-120]。AhR在小鼠Lgr5⁺ISCs中高度表达,其可通过上调E3泛素连接酶Rnf43和Znrf3表达进而抑制Wnt/ β -catenin信号通路的激活^[121-122],因此Ahr^{-/-}小鼠

表现出 β -catenin表达异常升高,胃肠道出现炎症反应、增生和肿瘤等情况^[123-124]。在体和离体研究发现,吲哚-3-甲醇(indole-3-carbinol, I3C)以AhR依赖方式调控Wnt信号通路的激活,抑制ISCs的异常增殖^[122,125]。此外,肠道微生物如乳杆菌(*Lactobacillus*)、梭菌(*Clostridium*)和双歧杆菌(*Bifidobacterium*)等可以分解色氨酸,产生吲哚、色胺和IAld等激活AhR,进而产生白细胞介素(interleukin, IL)-22^[118,126-128]。IL-22可以活化STAT3信号通路,刺激Lgr5⁺ISCs增殖分化以修复受损的肠黏膜^[126]。类似地,肠道微生物色氨酸代谢产物IAld通过促进ISCs的增殖来缓解断奶仔猪肠道发育受损^[129]。罗素氏消化链球菌(*Peptostreptococcus russellii*)产生的吲哚-3-丙烯酸可以激活AhR,增强结肠炎小鼠肠道杯状细胞的增殖和Ki67的表达^[130]。近期也有研究发现,色氨酸代谢产物5-羟基吲哚乙酸(5-hydroxyindole acetic acid, 5HIAA)和犬尿氨酸等通过激活AhR信号通路来缓解小鼠结肠炎^[131-132]。别样杆菌属(*Alistipes*)色氨酸代谢物吲哚及其衍生物(吲哚-3-乙醛、吲哚丙酮酸和IAA)激活AhR/ARNT信号通路,上调老龄鼠肠道干细胞标记物Lgr5的表达^[133]。结直肠癌患者相关研究发现,不动杆菌(*Acinetobacter*)分泌的IAA通过AhR-Wnt- β -catenin轴抑制干细胞的更新,维持干细胞稳态^[134]。此外,微生物来源的5-羟色胺通过5-羟色胺2A受体(5-HT2A receptor, HTR2A)和HTR3A激活巨噬细胞产生PGE2,PGE2通过前列腺素E2受体亚型1(PGE2 receptor 1, EP1)和EP4促进ISCs的Wnt/ β -catenin信号表达,以促进ISCs的自我更新^[135]。

3.2.4 多胺

多胺类物质由细菌利用鸟氨酸或精氨酸产生,主要包括腐胺、亚精胺和精胺等^[136-137]。多胺类物质如腐胺可直接作为能量来源促进肠道上皮细胞的更新^[138]。Bardócz等^[138]发现肠细胞摄取的腐胺约30%可转化为琥珀酸参与ISCs能量代谢。同时,多胺类物质可通过抑制TGF- β /

Smads 信号传导, 上调 Wnt 信号通路从而促进 ISC 的增殖^[139-141]。

4 总结与展望

综上所述, ISCs 稳态及宿主肠道健康与肠道共生微生物密切相关。肠道细菌及其代谢物可通过模式识别受体、G 蛋白偶联受体和芳香烃受体等调控肠道干细胞的分化、更新, 以及肠道的发育和损伤后修复等。因此, 加强 ISCs 和肠道菌群相互作用及其机制研究具有重要意义。抗生素干预或无菌动物模型是研究肠道微生物与 ISCs 相互作用的常用方法, 但这些策略通常难以揭示发挥关键作用的核心菌株。通过构建模拟宿主肠道菌群结构和功能的合成微生物群落可为解析特定关键微生物对 ISCs 的调控机制提供有效策略。3D 类器官培养技术和器官芯片的发展为 ISCs 与肠道微生物之间的相互作用提供了新的体外研究途径, 但类器官的封闭性结构对于微生物和 ISCs 的互作研究局限较大。此外, 类器官体外培养体系中缺乏完整的肠道微环境组分, 肠道免疫系统和神经系统等如何调节 ISCs 命运的具体机制还需深入研究。ISCs 是肠道抵御病原体的关键, 不同病原体通过何种策略操控 ISCs 更新和分化活性, 以及肠道共生微生物如何介导这些影响, 相关研究还需深入。

作者贡献声明

郭芳申: 综述撰写与作图; 甄文瑞: 综述修改与润色; 张祎: 辅助作图; 马彦博: 综述构思与写作指导; 李旺: 综述构思与写作。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

参考文献

- [1] BEUMER J, CLEVERS H. Cell fate specification and differentiation in the adult mammalian intestine[J]. *Nature Reviews Molecular Cell Biology*, 2020, 22(1): 39-53.
- [2] CHENG H, LEBLOND CP. Origin, differentiation and renewal of the four main epithelial cell types in the mouse small intestine I. Columnar cell[J]. *American Journal of Anatomy*, 1974, 141(4): 461-479.
- [3] LUO HM, LI MX, WANG F, YANG YF, WANG Q, ZHAO YS, DU FK, CHEN Y, SHEN J, ZHAO QY, ZENG JP, WANG SP, CHEN MJ, LI XB, LI WP, SUN YH, GU L, WEN QL, XIAO ZG, WU X. The role of intestinal stem cell within gut homeostasis: focusing on its interplay with gut microbiota and the regulating pathways[J]. *International Journal of Biological Sciences*, 2022, 18(13): 5185-5206.
- [4] ZHOU Z, YU LZ, CAO JJ, YU JM, LIN ZB, HONG Y, JIANG SB, CHEN C, MI YL, ZHANG CQ, LI J. *Lactobacillus salivarius* promotion of intestinal stem cell activity in hens is associated with succinate-induced mitochondrial energy metabolism[J]. *mSystems*, 2022, 7(6): e0090322.
- [5] SCHOENBORN AA, von FURSTENBERG RJ, VALSARAJ S, HUSSAIN FS, STEIN M, SHANAHAN MT, HENNING SJ, GULATI AS. The enteric microbiota regulates jejunal Paneth cell number and function without impacting intestinal stem cells[J]. *Gut Microbes*, 2019, 10(1): 45-58.
- [6] MA N, CHEN XY, JOHNSTON LJ, MA X. Gut microbiota-stem cell niche crosstalk: a new territory for maintaining intestinal homeostasis[J]. *iMeta*, 2022, 1(4): e54.
- [7] BARKER N, van ES JH, KUIPERS J, KUJALA P, van den BORN M, COZIJNSEN M, HAEGEBARTH A, KORVING J, BEGTHEL H, PETERS PJ, CLEVERS H. Identification of stem cells in small intestine and colon by marker gene *Lgr5*[J]. *Nature*, 2007, 449(7165): 1003-1007.
- [8] MONTGOMERY RK, CARLONE DL, RICHMOND CA, FARILLA L, KRANENDONK MEG, HENDERSON DE, BAFFOUR-AWUAH NY, AMBRUZS DM, FOGLI LK, ALGRA S, BREAU DT. Mouse telomerase reverse transcriptase (*mTert*) expression marks slowly cycling intestinal stem cells[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2011, 108(1): 179-184.
- [9] BLOEMENDAAL ALA, BUCHS NC, GEORGE BD, GUY RJ. Intestinal stem cells and intestinal homeostasis in health and in inflammation: a review[J]. *Surgery*, 2016, 159(5): 1237-1248.
- [10] YU LZ, QI SC, WEI GZ, RAO X, LUO DN, ZOU MY, MI YL, ZHANG CQ, LI J. Krüppel-like factor 5 activates chick intestinal stem cell and promotes mucosal repair after impairment[J]. *Cell Cycle*, 2023, 22(19): 2142-2160.
- [11] AYYAZ A, KUMAR S, SANGIORGI B, GHOSHAL B, GOSIO J, OULADAN S, FINK M, BARUTCU S, TRCKA D, SHEN J, CHAN K, WRANA JL, GREGORIEFF A. Single-cell transcriptomes of the regenerating intestine reveal a revival stem cell[J]. *Nature*, 2019, 569(7754): 121-125.

- [12] RITSMA L, ELLENBROEK SIJ, ZOMER A, SNIPPET HJ, de SAUVAGE FJ, SIMONS BD, CLEVERS H, van RHEENEN J. Intestinal crypt homeostasis revealed at single-stem-cell level by *in vivo* live imaging[J]. *Nature*, 2014, 507(7492): 362-365.
- [13] SHROYER NF, HELMRATH MA, WANG VY, ANTALFFY B, HENNING SJ, ZOGHBI HY. Intestine-specific ablation of mouse atonal homolog 1 (Math1) reveals a role in cellular homeostasis[J]. *Gastroenterology*, 2007, 132(7): 2478-2488.
- [14] BATLLE E, HENDERSON JT, BEGHEL H, van den BORN MMW, SANCHO E, HULS G, MEELDIJK J, ROBERTSON J, van de WETERING M, PAWSON T, CLEVERS H. β -catenin and TCF mediate cell positioning in the intestinal epithelium by controlling the expression of EphB/EphrinB[J]. *Cell*, 2002, 111(2): 251-263.
- [15] FRE S, HUYGHE M, MOURIKIS P, ROBINE S, LOUVARD D, ARTAVANIS-TSAKONAS S. Notch signals control the fate of immature progenitor cells in the intestine[J]. *Nature*, 2005, 435(7044): 964-968.
- [16] SANTOS AJM, LO YH, MAH AT, KUO CJ. The intestinal stem cell niche: homeostasis and adaptations[J]. *Trends in Cell Biology*, 2018, 28(12): 1062-1078.
- [17] DEMITRACK ES, SAMUELSON LC. Notch regulation of gastrointestinal stem cells[J]. *The Journal of Physiology*, 2016, 594(17): 4791-4803.
- [18] BRAY SJ. Notch signalling in context[J]. *Nature Reviews Molecular Cell Biology*, 2016, 17(11): 722-735.
- [19] RICCIO O, van GIJN ME, BEZDEK AC, PELLEGRINET L, van ES JH, ZIMMER-STROBL U, STROBL LJ, HONJO T, CLEVERS H, RADTKE F. Loss of intestinal crypt progenitor cells owing to inactivation of both Notch1 and Notch2 is accompanied by depression of CDK inhibitors p27Kip1 and p57Kip2[J]. *EMBO Reports*, 2008, 9(4): 377-383.
- [20] JENSEN J, PEDERSEN EE, GALANTE P, HALD J, HELLER RS, ISHIBASHI M, KAGEYAMA R, GUILLEMOT F, SERUP P, MADSEN OD. Control of endodermal endocrine development by Hes-1[J]. *Nature Genetics*, 2000, 24(1): 36-44.
- [21] TIAN H, BIEHS B, CHIU C, SIEBEL CW, WU Y, COSTA M, de SAUVAGE FJ, KLEIN OD. Opposing activities of Notch and Wnt signaling regulate intestinal stem cells and gut homeostasis[J]. *Cell Reports*, 2015, 11(1): 33-42.
- [22] FARIN HF, van ES JH, CLEVERS H. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth cells[J]. *Gastroenterology*, 2012, 143(6): 1518-1529.e7.
- [23] VALENTA T, DEGIRMENCI B, MOOR AE, HERR P, ZIMMERLI D, MOOR MB, HAUSMANN G, CANTÙ C, AGUET M, BASLER K. Wnt ligands secreted by subepithelial mesenchymal cells are essential for the survival of intestinal stem cells and gut homeostasis[J]. *Cell Reports*, 2016, 15(5): 911-918.
- [24] GAMMONS MV, RENKO M, JOHNSON CM, RUTHERFORD TJ, BIENZ M. Wnt signalosome assembly by DEP domain swapping of dishevelled[J]. *Molecular Cell*, 2016, 64(1): 92-104.
- [25] LIU JQ, XIAO Q, XIAO JN, NIU CX, LI YY, ZHANG XJ, ZHOU ZW, SHU G, YIN G. Wnt/ β -catenin signalling: function, biological mechanisms, and therapeutic opportunities[J]. *Signal Transduction and Targeted Therapy*, 2022, 7: 3.
- [26] KOO BK, SPIT M, JORDENS I, LOW TY, STANGE DE, van de WETERING M, van ES JH, MOHAMMED S, HECK AJR, MAURICE MM, CLEVERS H. Tumour suppressor RNF43 is a stem-cell E3 ligase that induces endocytosis of Wnt receptors[J]. *Nature*, 2012, 488(7413): 665-669.
- [27] HAO HX, XIE Y, ZHANG Y, CHARLAT O, OSTER E, AVELLO M, LEI H, MICKANIN C, LIU D, RUFFNER H, MAO XH, MA QC, ZAMPONI R, BOUWMEESTER T, FINAN PM, KIRSCHNER MW, PORTER JA, SERLUCA FC, CONG F. ZNRF3 promotes Wnt receptor turnover in an R-spondin-sensitive manner[J]. *Nature*, 2012, 485(7397): 195-200.
- [28] KANG E, YOUSEFI M, GRUENHEID S. R-spondins are expressed by the intestinal stroma and are differentially regulated during *Citrobacter rodentium*- and DSS-induced colitis in mice[J]. *PLoS One*, 2016, 11(4): e0152859.
- [29] SATO T, van ES JH, SNIPPET HJ, STANGE DE, VRIES RG, van den BORN M, BARKER N, SHROYER NF, van de WETERING M, CLEVERS H. Paneth cells constitute the niche for Lgr5 stem cells in intestinal crypts[J]. *Nature*, 2010, 469(7330): 415-418.
- [30] DOWNWARD J, YARDEN Y, MAYES E, SCRACE G, TOTTY N, STOCKWELL P, ULLRICH A, SCHLESSINGER J, WATERFIELD MD. Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences[J]. *Nature*, 1984, 307(5951): 521-527.
- [31] PLOWMAN GD, CULOUSCOU JM, WHITNEY GS, GREEN JM, CARLTON GW, FOY L, NEUBAUER MG, SHOYAB M. Ligand-specific activation of HER4/p180erbB4, a fourth member of the epidermal growth factor receptor family[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 1993, 90(5): 1746-1750.
- [32] ABUD HE, CHAN WH, JARDÉ T. Source and impact of the EGF family of ligands on intestinal stem cells[J]. *Frontiers in Cell and Developmental Biology*, 2021, 9: 685665.
- [33] LEMMON MA, SCHLESSINGER J, FERGUSON KM. The EGFR family: not so prototypical receptor tyrosine kinases[J]. *Cold Spring Harbor Perspectives in Biology*, 2014, 6(4): a020768.
- [34] IWAKURA Y, NAWA H. ErbB1-4-dependent EGF/neuregulin signals and their cross talk in the central nervous system: pathological implications in schizophrenia and Parkinson's disease[J]. *Frontiers in Cellular Neuroscience*, 2013, 7: 4.

- [35] QI Z, LI YH, ZHAO B, XU C, LIU Y, LI HN, ZHANG BJ, WANG XQ, YANG X, XIE W, LI BJ, HAN JJ, CHEN YG. BMP restricts stemness of intestinal Lgr5⁺ stem cells by directly suppressing their signature genes[J]. *Nature Communications*, 2017, 8: 13824.
- [36] KOSINSKI C, LI VSW, CHAN ASY, ZHANG J, HO C, TSUI WY, CHAN TL, MIFFLIN RC, POWELL DW, YUEN ST, LEUNG SY, CHEN X. Gene expression patterns of human colon tops and basal crypts and BMP antagonists as intestinal stem cell niche factors[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2007, 104(39): 15418-15423.
- [37] 吴元霞, 孙静, 葛良鹏, 李周权, 张进威. SIgA与哺乳动物肠道菌群互作研究进展[J]. *生命科学*, 2023, 35(6): 733-742.
WU YX, SUN J, GE LP, LI ZQ, ZHANG JW. Progress in the interaction between SIgA and mammalian gut flora[J]. *Chinese Bulletin of Life Sciences*, 2023, 35(6): 733-742 (in Chinese).
- [38] GOGUYER-DESCHAUMES R, WAECKEL L, KILLIAN M, ROCHEREAU N, PAUL S. Metabolites and secretory immunoglobulins: messengers and effectors of the host-microbiota intestinal equilibrium[J]. *Trends in Immunology*, 2022, 43(1): 63-77.
- [39] MATHIAS A, CORTÉSY B. N-Glycans on secretory component: mediators of the interaction between secretory IgA and Gram-positive commensals sustaining intestinal homeostasis[J]. *Gut Microbes*, 2011, 2(5): 287-293.
- [40] YANG Y, PALM NW. Immunoglobulin A and the microbiome[J]. *Current Opinion in Microbiology*, 2020, 56: 89-96.
- [41] HODIN RA, CHAMBERLAIN SM, MENG S. Pattern of rat intestinal brush-border enzyme gene expression changes with epithelial growth state[J]. *The American Journal of Physiology*, 1995, 269(2 Pt 1): C385-C391.
- [42] HAMARNEH SR, MOHAMED MM, ECONOMOPOULOS KP, MORRISON SA, PHUPITAKPHOL T, TANTILLO TJ, GUL SS, GHAREDAGHI MH, TAO QS, KALIANNAN K, NARISAWA S, MILLÁN JL, van der WILDEN GM, FAGENHOLZ PJ, MALO MS, HODIN RA. A novel approach to maintain gut mucosal integrity using an oral enzyme supplement[J]. *Annals of Surgery*, 2014, 260(4): 706-714.
- [43] CHEN KT, MALO MS, MOSS AK, ZELLER S, JOHNSON P, EBRAHIMI F, MOSTAFA G, ALAM SN, RAMASAMY S, WARREN HS, HOHMANN EL, HODIN RA. Identification of specific targets for the gut mucosal defense factor intestinal alkaline phosphatase[J]. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2010, 299(2): G467-G475.
- [44] GHOSH SS, WANG J, YANNIE PJ, GHOSH S. Intestinal barrier dysfunction, LPS translocation, and disease development[J]. *Journal of the Endocrine Society*, 2020, 4(2): bvz039.
- [45] MALO MS, ALAM SN, MOSTAFA G, ZELLER SJ, JOHNSON PV, MOHAMMAD N, CHEN KT, MOSS AK, RAMASAMY S, FARUQUI A, HODIN S, MALO PS, EBRAHIMI F, BISWAS B, NARISAWA S, MILLÁN JL, WARREN HS, KAPLAN JB, KITTS CL, HOHMANN EL, et al. Intestinal alkaline phosphatase preserves the normal homeostasis of gut microbiota[J]. *Gut*, 2010, 59(11): 1476-1484.
- [46] MIZUMORI M, HAM M, GUTH PH, ENGEL E, KAUNITZ JD, AKIBA Y. Intestinal alkaline phosphatase regulates protective surface microclimate pH in rat duodenum[J]. *The Journal of Physiology*, 2009, 587(14): 3651-3663.
- [47] HANSSON GC. Mucins and the microbiome[J]. *Annual Review of Biochemistry*, 2020, 89: 769-793.
- [48] MOTTA JP, WALLACE JL, BURET AG, DERAISON C, VERGNOLLE N. Gastrointestinal biofilms in health and disease[J]. *Nature Reviews Gastroenterology & Hepatology*, 2021, 18(5): 314-334.
- [49] STAHL M, TREMBLAY S, MONTERO M, VOGL W, XIA LJ, JACOBSON K, MENENDEZ A, VALLANCE BA. The Muc2 mucin coats murine Paneth cell granules and facilitates their content release and dispersion[J]. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2018, 315(2): G195-G205.
- [50] AYABE T, SATCHELL DP, WILSON CL, PARKS WC, SELSTED ME, OUELLETTE AJ. Secretion of microbicidal alpha-defensins by intestinal Paneth cells in response to bacteria[J]. *Nature Immunology*, 2000, 1(2): 113-118.
- [51] YU SY, BALASUBRAMANIAN I, LAUBITZ D, TONG K, BANDYOPADHYAY S, LIN X, FLORES J, SINGH R, LIU Y, MACAZANA C, ZHAO YL, BÉGUET-CRESPEL F, PATIL K, MIDURA-KIELA MT, WANG D, YAP GS, FERRARIS RP, WEI Z, BONDER EM, HÄGGBLUM MM, et al. Paneth cell-derived lysozyme defines the composition of mucolytic microbiota and the inflammatory tone of the intestine[J]. *Immunity*, 2020, 53(2): 398-416.e8.
- [52] DARNAUD M, dos SANTOS A, GONZALEZ P, AUGUI S, LACOSTE C, DESTERKE C, de HERTOIGH G, VALENTINO E, BRAUN E, ZHENG JZ, BOISGARD R, NEUT C, DUBUQUOY L, CHIAPPINI F, SAMUEL D, LEPAGE P, GUERRIERI F, DORÉ J, BRÉCHOT C, MONIAUX N, et al. Enteric delivery of regenerating family member 3 alpha alters the intestinal microbiota and controls inflammation in mice with colitis[J]. *Gastroenterology*, 2018, 154(4): 1009-1023.e14.
- [53] SCHULZ O, PABST O. Antigen sampling in the small intestine[J]. *Trends in Immunology*, 2013, 34(4): 155-161.
- [54] KOMBAN RJ, STRÖMBERG A, BIRAM A, CERVIN J, LEBRERO-FERNÁNDEZ C, MABBOTT N, YRLID U, SHULMAN Z, BEMARK M, LYCKE N. Activated Peyer's patch B cells sample antigen directly from M cells in the subepithelial dome[J]. *Nature Communications*, 2019, 10: 2423.
- [55] REBOLDI A, ARNON TI, RODDA LB, ATAKILIT A, SHEPPARD D, CYSTER JG. IgA production requires B

- cell interaction with subepithelial dendritic cells in Peyer's patches[J]. *Science*, 2016, 352(6287): aaf4822.
- [56] PARK JH, KOTANI T, KONNO T, SETIAWAN J, KITAMURA Y, IMADA S, USUI Y, HATANO N, SHINOHARA M, SAITO Y, MURATA Y, MATOZAKI T. Promotion of intestinal epithelial cell turnover by commensal bacteria: role of short-chain fatty acids[J]. *PLoS One*, 2016, 11(5): e0156334.
- [57] GUO FS, QIAO JN, HU ZQ, HUANG J, BI RC, ABBAS W, ZHEN WR, GUO YM, WANG Z. Yeast cell wall polysaccharides accelerate yet in-feed antibiotic delays intestinal development and maturation *via* modulating gut microbiome in chickens[J]. *Journal of Animal Science and Biotechnology*, 2025, 16(1): 14.
- [58] BRODERICK NA, BUCHON N, LEMAITRE B. Microbiota-induced changes in *Drosophila melanogaster* host gene expression and gut morphology[J]. *mBio*, 2014, 5(3): e01117-14.
- [59] NEAL MD, SODHI CP, JIA HP, DYER M, EGAN CE, YAZJI I, GOOD M, AFRAZI A, MARINO R, SLAGLE D, MA CR, BRANCA MF, PRINDLE T, GRANT Z, OZOLEK J, HACKAM DJ. Toll-like receptor 4 is expressed on intestinal stem cells and regulates their proliferation and apoptosis *via* the p53 up-regulated modulator of apoptosis[J]. *Journal of Biological Chemistry*, 2012, 287(44): 37296-37308.
- [60] HISAMATSU T, SUZUKI M, REINECKER HC, NADEAU WJ, McCORMICK BA, PODOLSKY DK. CARD15/NOD2 functions as an antibacterial factor in human intestinal epithelial cells[J]. *Gastroenterology*, 2003, 124(4): 993-1000.
- [61] LEBEER S, VANDERLEYDEN J, de KEERSMAECKER SCJ. Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens[J]. *Nature Reviews Microbiology*, 2010, 8(3): 171-184.
- [62] RIEHL TE, ALVARADO D, EE XP, ZUCKERMAN A, FOSTER L, KAPOOR V, THOTALA D, CIORBA MA, STENSON WF. *Lactobacillus rhamnosus* GG protects the intestinal epithelium from radiation injury through release of lipoteichoic acid, macrophage activation and the migration of mesenchymal stem cells[J]. *Gut*, 2019, 68(6): 1003-1013.
- [63] HOU QH, JIA JP, LIN J, ZHU LD, XIE S, YU QH, LI YC. *Bacillus subtilis* programs the differentiation of intestinal secretory lineages to inhibit *Salmonella* infection[J]. *Cell Reports*, 2022, 40(13): 111416.
- [64] PODOLSKY DK, GERKEN G, EYKING A, CARIO E. Colitis-associated variant of TLR2 causes impaired mucosal repair because of TFF3 deficiency[J]. *Gastroenterology*, 2009, 137(1): 209-220.
- [65] YI H, PATEL AK, SODHI CP, HACKAM DJ, HACKAM AS. Novel role for the innate immune receptor Toll-like receptor 4 (TLR4) in the regulation of the Wnt signaling pathway and photoreceptor apoptosis[J]. *PLoS One*, 2012, 7(5): e36560.
- [66] SODHI CP, SHI XH, RICHARDSON WM, GRANT ZS, SHAPIRO RA, PRINDLE T, BRANCA M, RUSSO A, GRIBAR SC, MA CR, HACKAM DJ. Toll-like receptor-4 inhibits enterocyte proliferation *via* impaired β -catenin signaling in necrotizing enterocolitis[J]. *Gastroenterology*, 2010, 138(1): 185-196.
- [67] NAITO T, MULET C, de CASTRO C, MOLINARO A, SAFFARIAN A, NIGRO G, BÉRARD M, CLERC M, PEDERSEN AB, SANSONETTI PJ, PÉDRON T. Lipopolysaccharide from crypt-specific core microbiota modulates the colonic epithelial proliferation-to-differentiation balance[J]. *mBio*, 2017, 8(5): e01680-17.
- [68] SANTAOLALLA R, SUSSMAN DA, RUIZ JR, DAVIES JM, PASTORINI C, ESPAÑA CL, SOTOLONGO J, BURLINGAME O, BEJARANO PA, PHILIP S, AHMED MM, KO J, DIRISINA R, BARRETT TA, SHANG LM, LIRA SA, FUKATA M, ABREU MT. TLR4 activates the β -catenin pathway to cause intestinal neoplasia[J]. *PLoS One*, 2013, 8(5): e63298.
- [69] Van der POST S, BIRCHENOUGH GMH, HELD JM. NOX1-dependent redox signaling potentiates colonic stem cell proliferation to adapt to the intestinal microbiota by linking EGFR and TLR activation[J]. *Cell Reports*, 2021, 35(1): 108949.
- [70] ALAM A, LEONI G, WENTWORTH CC, KWAL JM, WU H, ARDITA CS, SWANSON PA, LAMBETH JD, JONES RM, NUSRAT A, NEISH AS. Redox signaling regulates commensal-mediated mucosal homeostasis and restitution and requires formyl peptide receptor 1[J]. *Mucosal Immunology*, 2014, 7(3): 645-655.
- [71] FUKATA M, CHEN AL, KLEPPER A, KRISHNAREDDY S, VAMADEVAN AS, THOMAS LS, XU RL, INOUE H, ARDITI M, DANNENBERG AJ, ABREU MT. Cox-2 is regulated by Toll-like receptor-4 (TLR4) signaling: role in proliferation and apoptosis in the intestine[J]. *Gastroenterology*, 2006, 131(3): 862-877.
- [72] HSU D, FUKATA M, HERNANDEZ YG, SOTOLONGO JP, GOO T, MAKI J, HAYES LA, UNGARO RC, CHEN AL, BREGLIO KJ, XU RL, ABREU MT. Toll-like receptor 4 differentially regulates epidermal growth factor-related growth factors in response to intestinal mucosal injury[J]. *Laboratory Investigation*, 2010, 90(9): 1295-1305.
- [73] SODHI CP, NEAL MD, SIGGERS R, SHO S, MA CR, BRANCA MF, PRINDLE T, RUSSO AM, AFRAZI A, GOOD M, Brower-SINNING R, FIREK B, MOROWITZ MJ, OZOLEK JA, GITTES GK, BILLIAR TR, HACKAM DJ. Intestinal epithelial Toll-like receptor 4 regulates goblet cell development and is required for necrotizing enterocolitis in mice[J]. *Gastroenterology*, 2012, 143(3): 708-718.e5.
- [74] LI WAR, SAKAMOTO K, LEIFER CA. TLR9 is important for protection against intestinal damage and for intestinal repair[J]. *Scientific Reports*, 2012, 2: 574.
- [75] JONES RM, SLOANE VM, WU HX, LUO LP, KUMAR A, KUMAR MV, GEWIRTZ AT, NEISH AS. Flagellin administration protects gut mucosal tissue from irradiation-induced apoptosis *via* MKP-7 activity[J]. *Gut*,

- 2011, 60(5): 648-657.
- [76] ZHOU XT, ZHANG DD, QI WC, HONG T, XIONG T, WU TQ, GENG F, XIE MY, NIE SP. Exopolysaccharides from *Lactobacillus plantarum* NCU116 facilitate intestinal homeostasis by modulating intestinal epithelial regeneration and microbiota[J]. *Journal of Agricultural and Food Chemistry*, 2021, 69(28): 7863-7873.
- [77] PETNICKI-OCWIEJA T, HRNCIR T, LIU YJ, BISWAS A, HUDCOVIC T, TLASKALOVA-HOGENOVA H, KOBAYASHI KS. Nod2 is required for the regulation of commensal microbiota in the intestine[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2009, 106(37): 15813-15818.
- [78] NIGRO G, ROSSI R, COMMERE PH, JAY P, SANSONETTI PJ. The cytosolic bacterial peptidoglycan sensor Nod2 affords stem cell protection and links microbes to gut epithelial regeneration[J]. *Cell Host & Microbe*, 2014, 15(6): 792-798.
- [79] LEVY A, DEUTSCH E, SANSONETTI P, NIGRO G. 74P The bacterial receptor NOD2 mediates LGR5⁺ intestinal stem cells protection against irradiation via mitophagy activation[J]. *Annals of Oncology*, 2019, 30: v21.
- [80] LEVY A, STEDMAN A, DEUTSCH E, DONNADIEU F, VIRGIN HW, SANSONETTI PJ, NIGRO G. Innate immune receptor NOD2 mediates LGR5⁺ intestinal stem cell protection against ROS cytotoxicity via mitophagy stimulation[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2020, 117(4): 1994-2003.
- [81] LEE CS, CHOI C, KANG HS, SHIN SW, KIM SY, PARK HC, HONG SN. NOD2 supports crypt survival and epithelial regeneration after radiation-induced injury[J]. *International Journal of Molecular Sciences*, 2019, 20(17): 4297.
- [82] WANG HQ, KIM JJ, DENOU E, GALLAGHER A, THORNTON DJ, SHAJIB MS, XIA LJ, SCHERTZER JD, GRENCIS RK, PHILPOTT DJ, KHAN WI. New role of nod proteins in regulation of intestinal goblet cell response in the context of innate host defense in an enteric parasite infection[J]. *Infection and Immunity*, 2015, 84(1): 275-285.
- [83] MORRISON DJ, PRESTON T. Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism[J]. *Gut Microbes*, 2016, 7(3): 189-200.
- [84] HOLMBERG SM, FEENEY RH, PRASOODANAN P K V, PUÉRTOLAS-BALINT F, SINGH DK, WONGKUNA S, ZANDBERGEN L, HAUNER H, BRANDL B, NIEMINEN AI, SKURK T, SCHROEDER BO. The gut commensal *Blautia* maintains colonic mucus function under low-fiber consumption through secretion of short-chain fatty acids[J]. *Nature Communications*, 2024, 15: 3502.
- [85] WANG XY, CAI ZL, WANG QL, WU C, SUN YK, WANG ZF, XU XQ, XUE WZ, CAO ZW, ZHANG MC, ZHU YM, LIN HB, ZHANG Y, YUAN MY, ZHAO YX, GAO AB, YU YQ, BI YF, NING G, WANG WQ, et al. *Bacteroides* methylmalonyl-CoA mutase produces propionate that promotes intestinal goblet cell differentiation and homeostasis[J]. *Cell Host & Microbe*, 2024, 32(1): 63-78.e7.
- [86] ZHAO Y, CHEN FD, WU W, SUN MM, BILOTTA AJ, YAO SX, XIAO Y, HUANG XS, EAVES-PYLES TD, GOLOVKO G, FOFANOV Y, D'SOUZA W, ZHAO QH, LIU ZJ, CONG YZ. GPR43 mediates microbiota metabolite SCFA regulation of antimicrobial peptide expression in intestinal epithelial cells via activation of mTOR and STAT3[J]. *Mucosal Immunology*, 2018, 11(3): 752-762.
- [87] CORRÊA RO, CASTRO PR, FACHI JL, NIRELLO VD, EL-SAHHAR S, IMADA S, PEREIRA GV, PRAL LP, ARAÚJO NVP, FERNANDES MF, MATHEUS VA, de SOUZA FELIPE J, dos SANTOS PEREIRA GOMES AB, de OLIVEIRA S, de REZENDE RODOVALHO V, de OLIVEIRA SRM, de ASSIS HC, OLIVEIRA SC, dos SANTOS MARTINS F, MARTENS E, et al. Inulin diet uncovers complex diet-microbiota-immune cell interactions remodeling the gut epithelium[J]. *Microbiome*, 2023, 11(1): 90.
- [88] DUAN CH, WU JH, WANG Z, TAN C, HOU LZ, QIAN W, HAN CQ, HOU XH. Fucose promotes intestinal stem cell-mediated intestinal epithelial development through promoting *Akkermansia*-related propanoate metabolism[J]. *Gut Microbes*, 2023, 15(1): 2233149.
- [89] BILOTTA AJ, MA CY, YANG WJ, YU YB, YU Y, ZHAO XJ, ZHOU Z, YAO SX, DANN SM, CONG YZ. Propionate enhances cell speed and persistence to promote intestinal epithelial turnover and repair[J]. *Cellular and Molecular Gastroenterology and Hepatology*, 2021, 11(4): 1023-1044.
- [90] YAO Y, CAI XY, FEI WD, YE YQ, ZHAO MD, ZHENG CH. The role of short-chain fatty acids in immunity, inflammation and metabolism[J]. *Critical Reviews in Food Science and Nutrition*, 2022, 62(1): 1-12.
- [91] XIA ZB, HAN YJ, WANG K, GUO SK, WU DZ, HUANG XZ, LI ZR, ZHU LB. Oral administration of propionic acid during lactation enhances the colonic barrier function[J]. *Lipids in Health and Disease*, 2017, 16(1): 62.
- [92] BAJIC D, NIEMANN A, HILLMER AK, MEJIAS-LUQUE R, BLUEMEL S, DOCAMPO M, FUNK MC, TONIN E, BOUTROS M, SCHNABL B, BUSCH DH, MIKI T, SCHMID RM, van den BRINK MRM, GERHARD M, STEIN-THOERINGER CK. Gut microbiota-derived propionate regulates the expression of Reg3 mucosal lectins and ameliorates experimental colitis in mice[J]. *Journal of Crohn's and Colitis*, 2020, 14(10): 1462-1472.
- [93] LOUIS P, HOLD GL, FLINT HJ. The gut microbiota, bacterial metabolites and colorectal cancer[J]. *Nature Reviews Microbiology*, 2014, 12(10): 661-672.
- [94] ROEDIGER WE. Utilization of nutrients by isolated epithelial cells of the rat colon[J]. *Gastroenterology*,

- 1982, 83(2): 424-429.
- [95] KELLY CJ, ZHENG L, CAMPBELL EL, SAEEDI B, SCHOLZ CC, BAYLESS AJ, WILSON KE, GLOVER LE, KOMINSKY DJ, MAGNUSON A, WEIR TL, EHRENTAUF SF, PICKEL C, KUHN KA, LANIS JM, NGUYEN V, TAYLOR CT, COLGAN SP. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial HIF augments tissue barrier function[J]. *Cell Host & Microbe*, 2015, 17(5): 662-671.
- [96] DONOHOE DR, GARGE N, ZHANG XX, SUN W, O'CONNELL TM, BUNGER MK, BULTMAN SJ. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon[J]. *Cell Metabolism*, 2011, 13(5): 517-526.
- [97] MA S, YEOM J, LIM YH. Specific activation of hypoxia-inducible factor-2 α by propionate metabolism *via* a β -oxidation-like pathway stimulates MUC₂ production in intestinal goblet cells[J]. *Biomedicine & Pharmacotherapy*, 2022, 155: 113672.
- [98] KAIKO GE, RYU SH, KOUES OI, COLLINS PL, SOLNICA-KREZEL L, PEARCE EJ, PEARCE EL, OLTZ EM, STAPPENBECK TS. The colonic crypt protects stem cells from microbiota-derived metabolites[J]. *Cell*, 2016, 165(7): 1708-1720.
- [99] ESHLEMAN EM, RICE T, POTTER C, WADDELL A, HASHIMOTO-HILL S, WOO V, FIELD S, ENGLEMAN L, LIM HW, SCHUMACHER MA, FREY MR, DENSON LA, FINKELMAN FD, ALENGHAT T. Microbiota-derived butyrate restricts tuft cell differentiation *via* histone deacetylase 3 to modulate intestinal type 2 immunity[J]. *Immunity*, 2024, 57(2): 319-332.e6.
- [100] UCHIYAMA K, SAKIYAMA T, HASEBE T, MUSCH MW, MIYOSHI H, NAKAGAWA Y, HE TC, LICHTENSTEIN L, NAITO Y, ITOH Y, YOSHIKAWA T, JABRI B, STAPPENBECK T, CHANG EB. Butyrate and bioactive proteolytic form of Wnt-5a regulate colonic epithelial proliferation and spatial development[J]. *Scientific Reports*, 2016, 6: 32094.
- [101] SHI JL, MAO WJ, SONG YQ, WANG YX, ZHANG LL, XU Y, GU HW, YAO SY, YAO YH, LIU ZF, RAGHAVAN V, WANG J. Butyrate alleviates food allergy by improving intestinal barrier integrity through suppressing oxidative stress-mediated Notch signaling[J]. *iMeta*, 2025, 4(3): e70024.
- [102] OKADA T, FUKUDA S, HASE K, NISHIUMI S, IZUMI Y, YOSHIDA M, HAGIWARA T, KAWASHIMA R, YAMAZAKI M, OSHIO T, OTSUBO T, INAGAKI-OHARA K, KAKIMOTO K, HIGUCHI K, KAWAMURA YI, OHNO H, DOHI T. Microbiota-derived lactate accelerates colon epithelial cell turnover in starvation-refed mice[J]. *Nature Communications*, 2013, 4: 1654.
- [103] LEE YS, KIM TY, KIM Y, LEE SH, KIM S, KANG SW, YANG JY, BAEK IJ, SUNG YH, PARK YY, HWANG SW, O E, KIM KS, LIU SQ, KAMADA N, GAO N, KWEON MN. Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development[J]. *Cell Host & Microbe*, 2018, 24(6): 833-846.e6.
- [104] FUKUI S, SHIMOYAMA T, TAMURA K, YAMAMURA M, SATOMI M. Mucosal blood flow and generation of superoxide in rat experimental colitis induced by succinic acid[J]. *Journal of Gastroenterology*, 1997, 32(4): 464-471.
- [105] INAGAKI A, ICHIKAWA H, SAKATA T. Inhibitory effect of succinic acid on epithelial cell proliferation of colonic mucosa in rats[J]. *Journal of Nutritional Science and Vitaminology*, 2007, 53(4): 377-379.
- [106] WANG H, HU DQ, CHENG Y, GAO Q, LIU K, MANI NL, TANG AY, IYER R, GAO BX, SUN LY, ZHOU Q, YU Q, WEINBERG SE, ZHANG XY, CONG YZ, DULAI PS, ZHANG YN, LIU Z, FANG DY. Succinate drives gut inflammation by promoting FOXP3 degradation through a molecular switch[J]. *Nature Immunology*, 2025, 26(6): 866-880.
- [107] BANERJEE A, HERRING CA, CHEN B, KIM H, SIMMONS AJ, SOUTHARD-SMITH AN, ALLAMAN MM, WHITE JR, MACEDONIA MC, MCKINLEY ET, RAMIREZ-SOLANO MA, SCOVILLE EA, LIU Q, WILSON KT, COFFEY RJ, WASHINGTON MK, GOETTEL JA, LAU KS. Succinate produced by intestinal microbes promotes specification of tuft cells to suppress ileal inflammation[J]. *Gastroenterology*, 2020, 159(6): 2101-2115.e5.
- [108] LI X, HUANG GW, ZHANG YN, REN YT, ZHANG RF, ZHU WY, YU KF. Succinate signaling attenuates high-fat diet-induced metabolic disturbance and intestinal barrier dysfunction[J]. *Pharmacological Research*, 2023, 194: 106865.
- [109] HEGYI P, MALÉTH J, WALTERS JR, HOFMANN AF, KEELY SJ. Guts and gall: bile acids in regulation of intestinal epithelial function in health and disease[J]. *Physiological Reviews*, 2018, 98(4): 1983-2023.
- [110] RIDLON JM, HARRIS SC, BHOWMIK S, KANG DJ, HYLEMON PB. Consequences of bile salt biotransformations by intestinal bacteria[J]. *Gut Microbes*, 2016, 7(1): 22-39.
- [111] CAI JW, RIMAL B, JIANG CT, CHIANG JYL, PATTERSON AD. Bile acid metabolism and signaling, the microbiota, and metabolic disease[J]. *Pharmacology & Therapeutics*, 2022, 237: 108238.
- [112] CHEN L, JIAO TY, LIU WW, LUO YH, WANG J, GUO XZ, TONG X, LIN ZM, SUN CY, WANG KL, HE YF, ZHANG YW, XU HL, WANG JW, ZUO JP, DING QR, HE SJ, GONZALEZ FJ, XIE C. Hepatic cytochrome P450 8B1 and cholic acid potentiate intestinal epithelial injury in colitis by suppressing intestinal stem cell renewal[J]. *Cell Stem Cell*, 2022, 29(9): 1366-1381.e9.
- [113] HUANG D, XIONG ML, XU XJ, WU XW, XU JX, CAI XB, LU LG, ZHOU H. Bile acids elevated by high-fat feeding induce endoplasmic reticulum stress in intestinal stem cells and contribute to mucosal barrier damage[J]. *Biochemical and Biophysical Research Communications*, 2020, 529(2): 289-295.

- [114]DOSSA AY, ESCOBAR O, GOLDEN J, FREY MR, FORD HR, GAYER CP. Bile acids regulate intestinal cell proliferation by modulating EGFR and FXR signaling[J]. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2016, 310(2): G81-G92.
- [115]SORRENTINO G, PERINO A, YILDIZ E, EL ALAM G, BOU SLEIMAN M, GIOIELLO A, PELLICCIARI R, SCHOONJANS K. Bile acids signal *via* TGR5 to activate intestinal stem cells and epithelial regeneration[J]. *Gastroenterology*, 2020, 159(3): 956-968.e8.
- [116]MROZ MS, LAJCZAK NK, GOGGINS BJ, KEELY S, KEELY SJ. The bile acids, deoxycholic acid and ursodeoxycholic acid, regulate colonic epithelial wound healing[J]. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2018, 314(3): G378-G387.
- [117]YAMADA S, MASUNO H, KAGECHIKA H, TANATANI A, KANDA Y. A novel lithocholic acid derivative upregulates detoxification-related genes in human induced pluripotent stem cell-derived intestinal organoids[J]. *Biological & Pharmaceutical Bulletin*, 2022, 45(11): 1720-1724.
- [118]ROAGER HM, LICHT TR. Microbial tryptophan catabolites in health and disease[J]. *Nature Communications*, 2018, 9: 3294.
- [119]AGUS A, PLANCHAIS J, SOKOL H. Gut microbiota regulation of tryptophan metabolism in health and disease[J]. *Cell Host & Microbe*, 2018, 23(6): 716-724.
- [120]VENKATESH M, MUKHERJEE S, WANG HW, LI H, SUN K, BENECHET AP, QIU ZJ, MAHER L, REDINBO MR, PHILLIPS RS, FLEET JC, KORTAGERE S, MUKHERJEE P, FASANO A, le VEN J, NICHOLSON JK, DUMAS ME, KHANNA KM, MANI S. Symbiotic bacterial metabolites regulate gastrointestinal barrier function *via* the xenobiotic sensor PXR and Toll-like receptor 4[J]. *Immunity*, 2014, 41(2): 296-310.
- [121]PARK JH, CHOI AJ, KIM SJ, CHEONG SW, JEONG SY. AhR activation by 6-formylindolo [3,2-b] carbazole and 2,3,7,8-tetrachlorodibenzo-p-dioxin inhibit the development of mouse intestinal epithelial cells[J]. *Environmental Toxicology and Pharmacology*, 2016, 43: 44-53.
- [122]METIDJI A, OMENETTI S, CROTTA S, LI Y, NYE E, ROSS E, LI V, MARADANA MR, SCHIERING C, STOCKINGER B. The environmental sensor AHR protects from inflammatory damage by maintaining intestinal stem cell homeostasis and barrier integrity[J]. *Immunity*, 2018, 49(2): 353-362.e5.
- [123]FERNANDEZ-SALGUERO PM, WARD JM, SUNDBERG JP, GONZALEZ FJ. Lesions of aryl-hydrocarbon receptor-deficient mice[J]. *Veterinary Pathology*, 1997, 34(6): 605-614.
- [124]KAWAJIRI K, KOBAYASHI Y, OHTAKE F, IKUTA T, MATSUSHIMA Y, MIMURA J, PETERSSON S, POLLENZ RS, SAKAKI T, HIROKAWA T, AKIYAMA T, KUROSUMI M, POELLINGER L, KATO S, FUJII KURIYAMA Y. Aryl hydrocarbon receptor suppresses intestinal carcinogenesis in *Apc*^{Min/+} mice with natural ligands[J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2009, 106(32): 13481-13486.
- [125]PARK JH, LEE JM, LEE EJ, HWANG WB, KIM DJ. Indole-3-carbinol promotes goblet-cell differentiation regulating Wnt and Notch signaling pathways AhR-dependently[J]. *Molecules and Cells*, 2018, 41(4): 290-300.
- [126]HOU QH, YE LL, LIU HF, HUANG LL, YANG Q, TURNER J, YU QH. *Lactobacillus* accelerates ISC regeneration to protect the integrity of intestinal mucosa through activation of STAT3 signaling pathway induced by LPLs secretion of IL-22[J]. *Cell Death & Differentiation*, 2018, 25(9): 1657-1670.
- [127]IHEKWEAZU FD, ENGEVIK MA, RUAN W, SHI ZC, FULTZ R, ENGEVIK KA, CHANG-GRAHAM AL, FREEBORN J, PARK ES, VENABLE S, HORVATH TD, HAIDACHER SJ, HAAG AM, GOODWIN A, SCHADY DA, HYSER JM, SPINLER JK, LIU YY, VERSALOVIC J. *Bacteroides ovatus* promotes IL-22 production and reduces trinitrobenzene sulfonic acid-driven colonic inflammation[J]. *The American Journal of Pathology*, 2021, 191(4): 704-719.
- [128]QIU J, ZHOU L. Aryl hydrocarbon receptor promotes ROR γ ^t Group 3 ILCs and controls intestinal immunity and inflammation[J]. *Seminars in Immunopathology*, 2013, 35(6): 657-670.
- [129]ZHANG JQ, CHEN YH, GUO X, LI X, ZHANG RF, WANG MT, ZHU WY, YU KF. The gut microbial metabolite indole-3-aldehyde alleviates impaired intestinal development by promoting intestinal stem cell expansion in weaned piglets[J]. *Journal of Animal Science and Biotechnology*, 2024, 15(1): 150.
- [130]WLODARSKA M, LUO CW, KOLDE R, D'HENNEZEL E, ANNAND JW, HEIM CE, KRSTEL P, SCHMITT EK, OMAR AS, CREASEY EA, GARNER AL, MOHAMMADI S, O'CONNELL DJ, ABUBUCKER S, ARTHUR TD, FRANZOSA EA, HUTTENHOWER C, MURPHY LO, HAISER HJ, VLAMAKIS H, et al. Indoleacrylic acid produced by commensal *Peptostreptococcus* species suppresses inflammation[J]. *Cell Host & Microbe*, 2017, 22(1): 25-37.e6.
- [131]ZHONG S, SUN YQ, HUO JX, XU WY, YANG YN, YANG JB, WU WJ, LIU YX, WU CM, LI YG. The gut microbiota-aromatic hydrocarbon receptor (AhR) axis mediates the anticolic effect of polyphenol-rich extracts from *Sanguangporus*[J]. *iMeta*, 2024, 3(2): e180.
- [132]WU XY, WEI JJ, RAN W, LIU DJ, YI Y, GONG MX, LIU X, GONG QH, LI HB, GAO JM. The gut microbiota-xanthurenic acid-aromatic hydrocarbon receptor axis mediates the anticolic effects of trilobatin[J]. *Advanced Science*, 2025, 12(10): 2412234.
- [133]WANG DD, WANG H, LI YN, LU J, TANG XL, YANG D, WANG MY, ZHAO DQ, LIU FB, ZHANG S, SUN

- LW. *Alistipes senegalensis* is critically involved in gut barrier repair mediated by *Panax ginseng* neutral polysaccharides in aged mice[J]. *Advanced Science*, 2025, 12(36): e16427.
- [134]ZHANG SN, PENG LH, GOSWAMI S, LI YC, DANG HY, XING SL, FENG PP, NIGRO G, LIU YY, MA YF, LIU TH, YANG JH, JIANG TL, YANG YN, BARKER N, SANSONETTI P, KUNDU P. Intestinal crypt microbiota modulates intestinal stem cell turnover and tumorigenesis *via* indole acetic acid[J]. *Nature Microbiology*, 2025, 10(3): 765-783.
- [135]ZHU PP, LU TK, WU JY, FAN DD, LIU BY, ZHU XX, GUO H, DU Y, LIU F, TIAN Y, FAN ZS. Gut microbiota drives macrophage-dependent self-renewal of intestinal stem cells *via* niche enteric serotonergic neurons[J]. *Cell Research*, 2022, 32(6): 555-569.
- [136]BEKEBREDE AF, KEIJER J, GERRITS WJJ, BOER VCJ. The molecular and physiological effects of protein-derived polyamines in the intestine[J]. *Nutrients*, 2020, 12(1): 197.
- [137]LÖSER C, EISEL A, HARMS D, FÖLSCH UR. Dietary polyamines are essential luminal growth factors for small intestinal and colonic mucosal growth and development[J]. *Gut*, 1999, 44(1): 12-16.
- [138]BARDÓCZ S, GRANT G, BROWN DS, PUSZTAI A. Putrescine as a source of instant energy in the small intestine of the rat[J]. *Gut*, 1998, 42(1): 24-28.
- [139]RAO JN, LI L, BASS BL, WANG JY. Expression of the TGF-beta receptor gene and sensitivity to growth inhibition following polyamine depletion[J]. *American Journal of Physiology Cell Physiology*, 2000, 279(4): C1034-C1044.
- [140]LIU L, SANTORA R, RAO JN, GUO X, ZOU TT, ZHANG HM, TURNER DJ, WANG JY. Activation of TGF-beta-Smad signaling pathway following polyamine depletion in intestinal epithelial cells[J]. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2003, 285(5): G1056-G1067.
- [141]HE XC, ZHANG JW, TONG WG, TAWFIK O, ROSS J, SCOVILLE DH, TIAN Q, ZENG X, HE X, WIEDEMANN LM, MISHINA Y, LI LH. BMP signaling inhibits intestinal stem cell self-renewal through suppression of Wnt-beta-catenin signaling[J]. *Nature Genetics*, 2004, 36(10): 1117-1121.