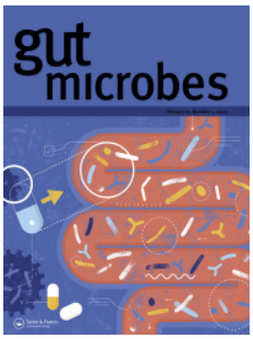

Gut Microbes

ISSN: 1949-0976 (Print) 1949-0984 (Online) Journal homepage: www.tandfonline.com/journals/kgmi20

Impact of gut microbiota on host stem cells across the gastrointestinal tract

Haengdueng Jeong, Yura Lee & Ki Taek Nam

To cite this article: Haengdueng Jeong, Yura Lee & Ki Taek Nam (2026) Impact of gut microbiota on host stem cells across the gastrointestinal tract, Gut Microbes, 18:1, 2606477, DOI: 10.1080/19490976.2025.2606477

To link to this article: https://doi.org/10.1080/19490976.2025.2606477

Published online: 22 Dec 2025.

GUT MICROBES
2025, VOL. 18, NO. 1, 2606477
https://doi.org/10.1080/19490976.2025.2606477

Taylor & Francis
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

Impact of gut microbiota on host stem cells across the gastrointestinal tract

Haengdueng Jeong[a], Yura Lee[b] and Ki Taek Nam[b]

[a]Department of Molecular and Life Science, Hanyang University, Ansan, Republic of Korea; [b]Department of Biomedical Sciences, Brain Korea 21 PLUS Project for Medical Science, Yonsei University College of Medicine, Seoul, Republic of Korea

ABSTRACT

The gut microbiota plays a pivotal role in maintaining gastrointestinal (GI) homeostasis by influencing epithelial integrity, immunity, and metabolism. Recent studies have uncovered that gut microbiota can directly or indirectly modulate the behavior and function of adult stem cells across the GI tract, which are essential for tissue regeneration and disease prevention. Moreover, key microbial metabolites including short-chain fatty acids (SCFAs), tryptophan-derived indoles, succinate, secondary bile acids, and retinoic acid exert diverse effects on stem cell quiescence, proliferation, and differentiation. This review provides current knowledge on the interaction between gut microbiota and host stem cells in the stomach, intestine, and colon.

ARTICLE HISTORY
Received 30 June 2025
Revised 4 November 2025
Accepted 15 December 2025

KEYWORDS
Adult stem cell; gastrointestinal tract; microbiota-derived metabolites

1. Introduction

Microorganisms in the gastrointestinal (GI) tract is collectively referred to as the gut microbiota. This diverse community encompasses bacteria, yeasts, and viruses, of which bacteria are the most enriched. The type and balance of bacteria in the gut are influenced by many factors derived from the host or environment. Bacteria in the gut help break down food, turning it into nutrients that can be used by host cells. They play pivotal roles in modulating both physical and mental health.[1]

With recent advances in high-throughput sequencing involving 16S rRNA sequencing and metagenomic analyzes, it is now possible to characterize microbial communities at the individual level and determine the gene expression and metabolomic profiles of specific microbial taxa. These advances have provided a basis for understanding the link between host cells and specific microbes. A notable finding is that gut microbes impact epithelial cell physiology as well as the behavior and fate of adult stem cells. Given the central role of stem cells in tissue homeostasis, regeneration, and disease, understanding how gut microbiota modulate stem cell biology is of increasing interest.

Recent studies have begun to uncover how microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), tryptophan metabolites, and secondary bile acids, interact with adult stem cells in various segments of the GI tract. These interactions affect stem cell quiescence, proliferation, and differentiation, ultimately affecting tissue integrity and disease susceptibility. Dysbiosis, a disruption of the normal microbial community, has been implicated in the pathogenesis of GI disorders, including inflammatory diseases and cancers, many of which involve alterations in stem cell function. In this review, we summarize the current knowledge on how gut microbiota influence the biology of host adult stem cells across the GI tract. We focus on the impact of the microbial composition and related metabolites on stem cell activity in the stomach, intestine, and colon, highlighting both physiological and pathological contexts.

CONTACT Ki Taek Nam, DVM, PhD kitaek@yuhs.ac Department of Biomedical Sciences, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul, 03722, Republic of Korea

2. Gut microbiota composition and dynamics

The GI tract is divided into two regions. The upper GI tract above the ampulla of Vater generally includes the oral cavity, esophagus, stomach, and proximal part of the small intestine (duodenum).[2] The lower GI tract, the distal part, includes the small intestine (jejunum and ileum), large intestine (colon), and anus.[2] The human gut contains 30–100 trillion microbes, depending on the organ, conferring a diverse bacterial community.[3,4] Generally, the adult human gut microbiota include six main bacterial phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*.[1,5] The composition of the gut microbiota varies across the regions of the digestive tract.[6,7] Microbial richness and heterogeneity are greater in the upper GI tract than in the lower tract.[7]

The human oral cavity is the entry point of food into the GI tract and includes diverse sites, including the teeth, gingival sulcus, tongue, cheeks, tonsils, and hard and soft palates. Six major phyla in the oral cavity, accounting for 96% of the total taxa, have been identified: *Actinobacteria*, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Spirochetes*, and *Fusobacteria*.[8] However, the oral cavity exhibits variation in the microbiota structure depending on the particular site.[9]

The esophagus is a muscular tube that connects the oral cavity to the stomach. Gram-positive *Firmicutes* is the dominant phylum in the healthy esophagus (particularly *Streptococcus* spp., the most abundant genus). Other common phyla and genera are *Firmicutes*, *Bacteroidetes* (*Prevotella* and *Bacteroides*), *Proteobacteria* (*Haemophilus*), and *Actinobacteria* (*Rothia*).[10,11]

Stomach cells are specialized in facilitating food digestion and protecting organs from acidic environments. A limited number of microbes harboring survival mechanisms reside in the acidic conditions of the stomach in mice and humans.[12,13] Common genera in healthy stomachs include *Bacillus*, *Streptococcus*, *Enterobacter*, *Leptotrichia*, *Veillonella*, and *Pseudomonas*.[9,13,14] However, *Helicobacter pylori* infection, a known risk factor for gastric cancer, has striking effects on the general bacterial community of the upper GI tract, including the stomach.[7,15] The eradication of *H. pylori* increases the diversity of the microbiota.[16]

The small intestine plays a crucial role in digestion and nutrient absorption. It is divided into three sections: the duodenum, where bile and pancreatic enzymes aid in breaking down food; the jejunum, characterized by extensive villi and microvilli for maximal nutrient absorption; and the ileum, where vitamin B12 and other nutrients are absorbed.[17,18] The small intestine is also enriched with commensal bacteria, although they are less abundant in this organ than in the colon. The microbial community of the duodenum is similar to that of the stomach, whereas that of the terminal ileum is similar to that of the colon,[7] indicating heterogeneity along the small intestine. Microbial genera, such as *Porphyromonas*, *Alloprevotella*, *Prevotella*, and *Capnocytophaga,* are more abundant in the duodenum than in the terminal ileum, whereas *Bacteroides*, *Odoribacter*, *Parabacteroides*, and *Alistipes* are more abundant in the terminal ileum.[7,13]

The colon plays a vital role in the absorption of water and electrolytes, fermentation of undigested carbohydrates by the gut microbiota, and formation and storage of feces. In the gut, the colon is characterized by the highest bacterial load because of its long transit time, favorable pH, and nutrient availability. In healthy humans, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, *Fusobacteria*, *Actinobacteria*, and *Verrucomicrobia* are present in the colon.[13]

The definition of the "healthy" or "normal" gut microbiota is unclear, as the functions of specific microbial taxa in our body are not fully understood. Nevertheless, microorganisms in healthy individuals can be considered a good microbiota. Numerous factors influence the composition and dynamics of gut microbes, including maternal inheritance, nationality, diet, and disease progression. For example, there is evidence that host age can influence the composition and diversity of the gut microbiota.[5,19] Notably, the microbial community in infants is affected by the type of delivery and maternal microbiota.[5,20,21] Despite inter-individual complexity, the dominant taxa in the gut microbiota in infants include *Akkermansia muciniphila*, *Bacteroidetes*, *Veillonella*, *Clostridium coccoides*, and *Clostridium botulinum*.[5,22] The gut microbiota gradually stabilize after birth, becoming similar in composition to that of elders by the age of 3 years.[22,23] We have recently shown that the young gut microbiota rejuvenate aged mice by enhancing muscle strength and skin hydration through microbial reconstitution.[24] Thus, compared with that of the elderly, the gut microbiota in young individuals can be considered a "healthy" microbiota with respect to host physical function. The dietary and immune systems of the host also affect the composition of the human gut microbiota.[25-27] Even the economic status of countries can impact the diversity and composition of the gut microbiota. For example, in

developed countries, the Bacteroidetes gut type, dominated by *Bacteroides*, *Phocaeicola*, and *Parabacteroides*, is the most common type because citizens typically consume animal-based foods rather than plant-based foods.[25] Therefore, studies on host–microbiota interactions should consider a wide range of factors that can influence the composition of the microbiota.

3. Metabolites produced by the gut microbiota

Microbiota have a remarkably broad capacity to use inorganic and organic molecules as nutritional substrates. In the mammalian gut, they can catabolize plant-derived polysaccharides and resistant starches that otherwise indigestible by the host.[19] Although the effects of microbial metabolites are context-dependent and sometimes contradictory, several studies have revealed that the microbiota and related metabolites play important roles in the characteristics of stem cells in the GI tract. Stem cells directly interact with extrinsic factors, such as gut microbiota-derived metabolites, as well as with intrinsic host factors.[28-33] Specific microbiota and microbiota-derived metabolites have been identified through the integration of metabolomics, sequencing technologies, and *in vivo* studies (Figure 1).

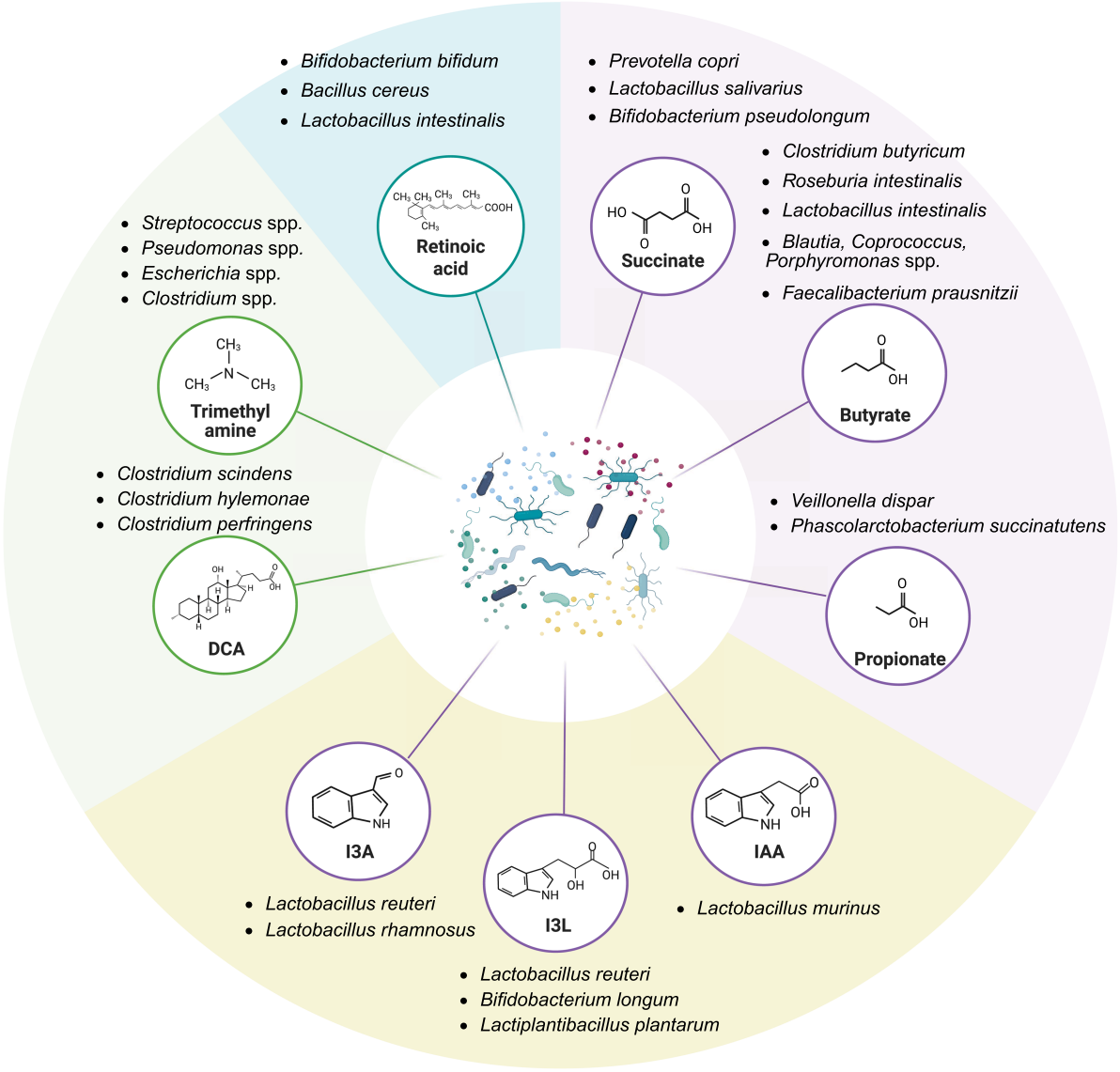

Figure 1. Graphical summary representing the diverse metabolites produced by the gut microbiota, along with specific bacterial species that have been experimentally validated to synthesize each metabolite. Abbreviations: I3A, indole-3-carbaldehyde; I3L, indole-3-lactic acid; IAA, indole-3-acetate; DCA, deoxycholic acid.

3.1. SCFAs

Gut microbes produce and secrete metabolites that are not produced by host cells. SCFAs are metabolites produced via the fermentation of dietary fiber by the gut microbiota. Propionate, butyrate, and acetate are the main SCFAs present in the gut.[34] SCFAs can serve as energy sources and signaling molecules through G protein-coupled receptors in host cells.[35,36] Functionally, these microbiota-derived metabolites can affect diverse physiological processes, development, and immune responses in the host.[37-39] Although most members of the gut microbiota form acetate, only specific, phylogenetically diverse bacterial groups are responsible for butyrate and propionate formation,[40] including some species within the phyla *Bacteroides*, *Firmicutes*, and *Verrucomicrobia*.[41,42]

Butyrate, synthesized via the butyryl-CoA: acetate CoA-transferase pathway, is the most well-studied SCFA owing to its critical roles in gut homeostasis, energy supply, and inflammation. We have recently found that *Lactobacillus intestinalis* (*Firmicutes*), a major gastric microbial species in mice, can produce SCFAs.[12] Among these SCFAs, butyrate produced by *L. intestinalis* plays a key role in switching chief cells from a quiescent state to a proliferative state.[12] A comparison of the bacterial compositions of healthy individuals and patients with Parkinson's disease has revealed *Blautia*, *Coprococcus*, and *Roseburia* (*Firmicutes*) as putative butyrate-producing microbes.[43] *Faecalibacterium prausnitzii* (*Firmicutes*), the most abundant commensal bacterium in the human intestine, produces butyrate and other SCFAs.[44,45] This species exerts protective effects against inflammatory bowel disease.[44,46] *Roseburia intestinalis* (*Firmicutes*) is one of the most abundant butyrate-producing gram-positive anaerobes in the human gut and feces.[47,48] A recent fecal microbiota transplantation study has shown that *R. intestinalis* can ameliorate neuropathic pain via the butyrate and GPR41 (gut–brain) axis.[48] Although there is no direct evidence that *Akkermansia muciniphila* (*Verrucomicrobia*) produces SCFAs, a recent report has shown that mice exposed to maternal *A. muciniphila* exhibit increased levels of serum SCFAs and amino acids.[49] In contrast, another study has revealed that *A. muciniphila* does not produce butyrate.[44] Thus, it is possible that increases in SCFA levels are mediated by interactions with commensal butyrate-producing species.

Phascolarctobacterium succinatutens (*Firmicutes*) produces propionate by utilizing succinate as a source.[50] The symbiosis between succinate-producing bacteria and succinate-consuming SCFA-producing microbes appears to confer metabolic benefits to the host. A recent study has shown that fecal microbiota transplantation from elite athletes into mice results in a high relative abundance of *Phascolarctobacterium succinatutens* and *Prevotella copri* (succinate producers) and improved insulin sensitivity.[51] In addition to the succinate pathway, gut *Veillonella dispar* (*Firmicutes*) can reprogram lactate metabolism to produce acetate and propionate, which are associated with host health.[52] Although the main SCFAs are acetate, propionate, and butyrate, other minor SCFAs, such as lactate, are byproducts of microbial metabolism.[32]

SCFAs are pleiotropic metabolites that can serve as energy source, signaling molecules, or enzyme inhibitors. Hence, their effects on the host are context-dependent rather than uniformly beneficial. Among them, butyrate exhibits particularly diverse and sometimes opposing biological functions. Butyrate can suppress colon cancer cell proliferation through histone deacetylase (HDAC) inhibition.[53] In cancer cells that rely on glycolytic metabolism (known as Warburg effect), butyrate oxidation is limited, leading to its intracellular accumulation and subsequent histone hyperacetylation, resulting in cell cycle arrest and apoptosis.[53] Conversely, microbiota-derived butyrate can also exert antiproliferative effects via GPR43-mediated signaling, independent of HDAC inhibition.[54] In contrast to cancer cells, normal colonocytes metabolize butyrate as an energy source, rendering them resistant to these antiproliferative effects.[53] However, high concentrations of butyrate produced by *Porphyromonas* spp., can provoke senescence-like cell-cycle arrest and a pro-inflammatory secretory phenotype in epithelial cells, potentially promoting colonic tumorigenesis.[55] This dual behavior, often referred to as the "butyrate paradox," highlights the context-dependent nature of SCFA-mediated mechanisms and underscores the complexity of their physiological effects.

3.2. Tryptophan-derived indoles

Although host cells can metabolize tryptophan, an essential aromatic amino acid, through the kynurenine and serotonin pathways, certain gut microbes can also metabolize tryptophan via the indole pathway to produce various derivatives. Indole-3-carbaldehyde (I3A), a tryptophan-derived metabolite of *Lactobacillus reuteri*

(*Firmicutes*), stimulates lamina propria cells to secrete interleukin-22 (IL-22) through the aryl hydrocarbon receptor (AhR) and induces the phosphorylation of signal transducer and activator of transcription 3 (STAT3), thereby promoting the proliferation of intestinal epithelial cells and improving the damaged intestinal mucosa.[56,57] *L. reuteri* produces various tryptophan-derived metabolites, and supplementation with tryptophan increases the levels of I3A and indole-3-lactic acid (I3L).[58] A similar mechanism has been observed in another *Lactobacillus* species, *Lactobacillus rhamnosus GG* (*Firmicutes*), which can metabolize tryptophan and produce AhR ligands, thereby activating the AhR-IL-22 axis.[59]

I3L, a metabolite of breast milk tryptophan, can be produced by *Bifidobacterium longum* (*Actinobacteria*) and exerts an anti-inflammatory effect by reducing IL-1β-induced inflammation.[60] Additionally, *Lactiplantibacillus plantarum* (*Firmicutes*)-derived I3L likely influences the composition of gut microbes.[61] An untargeted metabolomic study of fecal samples revealed that germ-free mice exhibit significantly lower levels of indole-3-acetate (IAA) than their conventionally raised counterparts, suggesting that the majority of IAA is derived from the gut microbiota.[62] Wei et al. recently reported that *Lactobacillus murinus* (*Firmicutes*) can serve as a source of IAA in the gut.[63] Functional tryptophan-derived indole-3-propionic acid and indoleacrylic acid are produced by *Clostridium sporogenes* (*Firmicutes*) and *Parabacteroides distasonis* (*Bacteroidetes*), respectively.[64,65]

3.3. Succinate

The role of succinate in hosts remains poorly understood. This metabolite can be produced by various microbes, including members of the genera *Bacteroides* and *Prevotella*.[66] Vadder et al. suggested that certain gut microbes can utilize dietary fibers to produce succinate instead of SCFAs.[67] Microbiota-derived succinate enhanced intestinal gluconeogenesis by acting as a glucose precursor.[67] *Prevotella copri* (*Bacteroidetes*) is a prominent succinate-producing microbe found in the cecum.[26,67] Moreover, intestinal *Lactobacillus salivarius* (*Firmicutes*) can produce succinate, thereby influencing stem cell activity.[68] Based on transplantation studies and 16S rRNA sequencing, *Bifidobacterium pseudolongum* (*Actinobacteria*) is predicted to be an intestinal succinate producer that promotes tuft cell expansion, thereby suppressing inflammatory diseases.[69]

3.4. Secondary bile acids

Bile acids play key roles in digestion, metabolism, and cellular signaling. They are essential components of the enterohepatic circulation, are produced from cholesterol in the liver, and constitute the main component of mammalian bile.[70] Bile acids are classified into primary bile acids, such as cholic, glycodeoxycholic, and taurocholic acids, and secondary bile acids, such as deoxycholic acid (DCA) and lithocholic acid (LCA).[70] Most primary bile acids secreted into the intestine are reabsorbed in the terminal ileum and transported back to the liver for recirculation. A small portion of primary bile acids that escape reabsorption can be converted into secondary bile acids via the gut microbiota.[71] Bile acids exert biological functions by binding to and activating farnesoid X receptor and the G-protein-coupled bile acid receptor TGR5, thereby initiating downstream signaling pathways.[71] Recent reports have identified specific microbial populations that serve as the producers of secondary bile acids. *Clostridium scindens* (*Firmicutes*) has the bile acid 7α-dehydroxylation pathway and can produce secondary bile acids, which enhance the activity of microbiota-derived antibiotics and thereby suppress pathogenic invasion.[72,73] A recent study has revealed that these major DCA-producing bacteria also influence glucose metabolism in the host.[74] Other *Clostridium* species (*Firmicutes*), such as *Clostridium hylemonae* and *Clostridium perfringens,* also possess enzymes capable of producing DCA.[75,76] In 2021, a Japanese research group identified a novel bile acid biosynthetic pathway and revealed that a strain of *Odoribacter* (*Firmicutes*) produces an LCA isoform with antimicrobial properties.[77]

3.5. Retinoic acid (RA)

RA signaling is primarily mediated by retinoic acid receptors and is involved in diverse biological processes, such as organogenesis, tissue regeneration, and inflammation.[78-80] Retinol (Vitamin A) is primarily converted to retinaldehyde and then oxidized to RA.[81] Although RA is supplied by epithelial cells, it is also produced by specific gut commensals. Woo et al. found that segmented filamentous bacteria

possessing aldehyde dehydrogenase (ALDH) enzymes, including *Bacillus cereus* (*Firmicutes*) and *Bifidobacterium bifidum* (*Actinobacteria*), can convert vitamin A into RA, thereby priming host *Nos2* transcription and contributing to the suppression of pathogenic infections.[82] Additionally, *Lactobacillus intestinalis,* a commensal bacterium of the colon, produces RA via endogenous ALDH and exerts a protective effect against dextran sodium sulfate-induced colitis.[83,84] The ablation of the species results in a marked reduction in retinoid levels, indicating their essential role in vitamin A metabolism. Although RA signaling appears to play an important role in intestinal stem cell differentiation,[85] and epithelial cell proliferation[86] and responses to infection,[82,87] the molecular functions of microbiota-derived RA and its relationship with stem cell behavior are yet to be clearly defined.

3.6. Trimethylamine (TMA) and trimethylamine N-oxide (TMAO)

Dietary nutrients, such as choline and L-carnitine, are metabolized by the gut microbiota into TMA, which is oxidized to TMAO in the host liver.[88] TMA-producing bacteria include various commensal species that harbor the *cutC*, *cutD*, and *cntAB* genes, which encode key enzymes involved in converting dietary components into TMA.[88] The vast majority of TMA-producing genera (*Pseudomonas*, *Streptococcus*, *Escherichia*, and *Clostridium*) belong to *Firmicutes* and *Proteobacteria*.[88] Germ-free mice do not produce TMAO until they are colonized by the normal microbiota, confirming that the microbiota are a crucial producer of TMAO.[89] In contrast to the effects of SCFAs and tryptophan-derived indoles, elevated TMAO levels exert adverse effects on the host. Elevated plasma TMAO levels are associated with increased pro-inflammatory cytokine production and have implications in the development of several inflammation-related diseases, including cardiovascular disease, diabetes, stroke, and metabolic syndrome.[89-91] Notably, reducing TMAO levels by eliminating the gut microbiota can protect mice against diet-induced atherosclerosis.[89] Although there is emerging evidence for a link between microbiota-derived TMAO and host diseases, little is known about the connection between TMAO and stem cell biology. A few studies have demonstrated that microbiota-derived TMAO can activate NF-κB signaling and influence the differentiation of bone marrow mesenchymal stem cells; however, somewhat contradictory results have been reported.[92,93]

4. Adult stem cells in the gut

Stem cells are characterized by the ability to self-renew without losing their developmental potential and to differentiate into multiple specialized cell types. In biology, “quiescence” refers to a temporary and reversible state (G0 phase) in which a cell does not undergo cell cycle progression but retains the capacity to divide upon stimulation (e.g., tissue injury).[94] In the gut, the presence of “quiescent” or “slow cycling” stem cells, retaining potency, was first suggested in the 1970s.[95] Since then, advances in labeling and lineage-tracing technologies using specific and selective molecular markers have revealed that quiescent and active adult stem cells coexist in diverse organs in mammals (Figure 2).[96-98] Actively proliferating stem cells, such as Lgr5 + stem cells, may transiently enter a quiescent state under certain conditions. However, their contributions to regeneration following injury remain unclear. Alternatively, unreserved stem cells are defined by their ability to remain quiescent during homeostasis and become activated upon injury or stress to self-renew and differentiate. Therefore, quiescent stem cells can only be classified as reserve stem cells if they have been functionally validated to contribute to tissue regeneration in response to injury. In this section, we summarize known adult stem cell populations and their markers in the stomach, intestine, and colon to provide a basis for analyzes of links with the microbiota in each segment.

4.1. Host stem cells in the stomach

The gastric epithelium is a continuously self-renewing tissue that maintains homeostasis. All gastric epithelial cells are derived from adult stem cells.[99] The gastric epithelium is composed of two glandular regions, the corpus (also referred to as the body in humans) and antrum, containing distinct, functional epithelial cells and constituting the epithelial lining of the stomach.

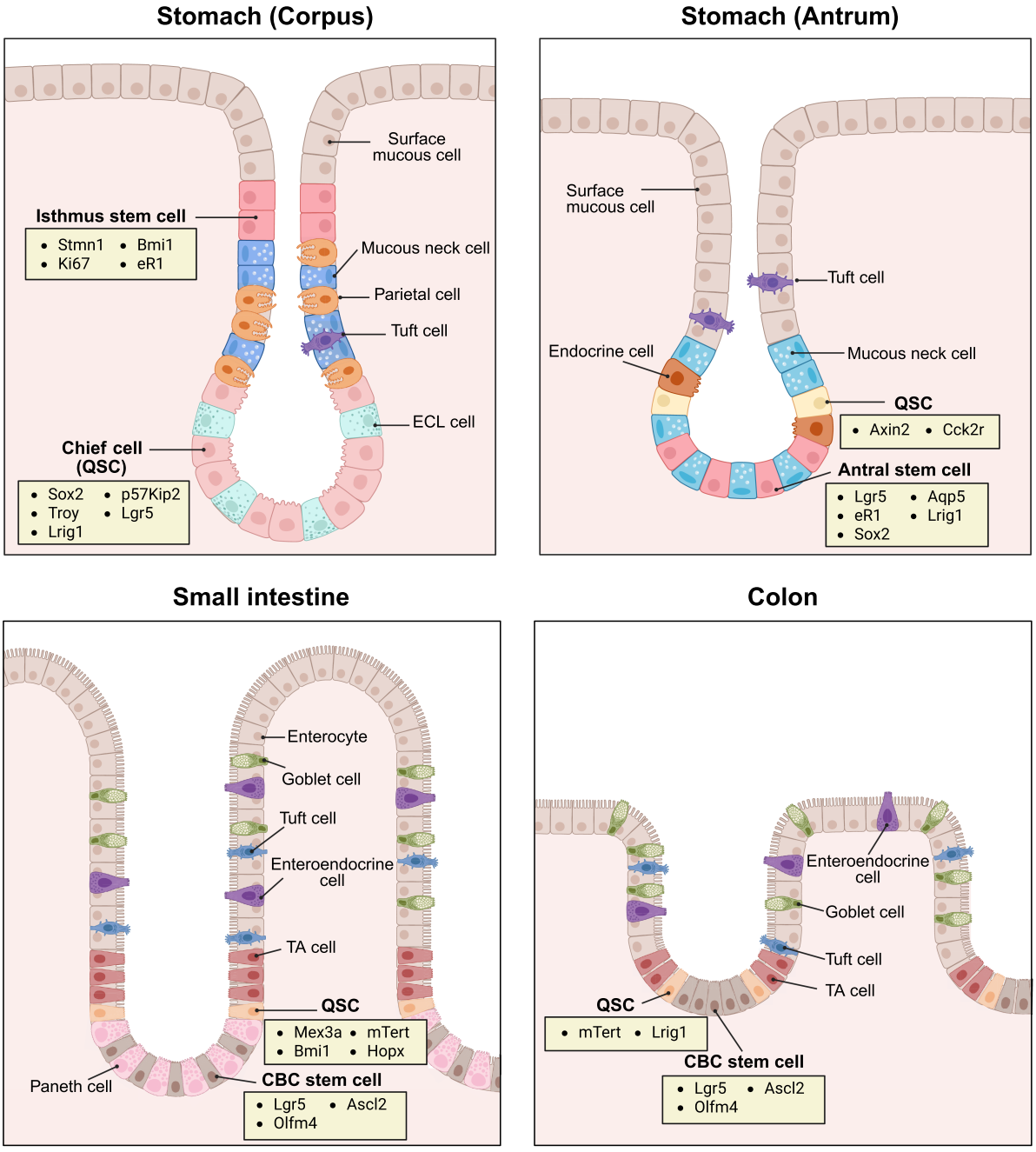

Figure 2. Graphical summary representing the diverse stem cell populations and their representative molecular markers across the stomach corpus, stomach antrum, small intestine, and colon. Abbreviations: QSC, quiescent stem cell; TA cell, transit-amplifying cell; CBC stem cell, crypt base columnar stem cell.

The gastric corpus is the main acid-producing region. It is maintained by two distinct stem cell pools: isthmus stem cells, which are rapidly dividing cells in the isthmus region below the pit region, and chief gastric cells, which are zymogenic enzyme-secreting terminally differentiated cells at the base of the gland that serve as quiescent reserve stem cells.[100,101] Isthmus stem cells continuously produce secondary progenitors committed to the pit, mucous neck, enterochromaffin-like cells, and parietal cells during homeostasis.[102,103] Chief cells present at the base of the corpus gland remain in a quiescent state under homeostatic conditions; however, they can be transdifferentiated and re-enter the cell cycle through conserved cellular reprogramming.[104-106] This cellular plasticity allows some chief cell subsets to generate all epithelial lineages and contribute to regeneration upon injury.[107-109]

Several biomarkers for specific stem cell compartments in the corpus have been identified. Sox2+ cells reside at the base of the corpus gland and function as long-lived stem cells, giving rise to multiple epithelial cell lineages.[110] Using a *Troy*-CreERT2 lineage tracing model, Stange et al. demonstrated that Troy+ chief cells are typically quiescent under homeostatic conditions but can become activated to clonally repopulate the gastric gland upon injury.[101] This finding suggests that Troy marks reserve stem cells in the gastric corpus with multipotent potential.[101] Lgr5+ cells, a subpopulation of antral stem cells, are also present in the corpus glands of humans and mice. In the corpus, Lgr5 is expressed in a subset of the chief cells that function as reserve stem cells.[100] These cells contribute to gland regeneration following high-dose tamoxifen-induced injury, rather than during homeostatic conditions.[100] A recent study has shown that p57Kip2 is highly expressed in chief cells and serves as a key molecular switch for inducing a quiescent and reserved stem cell state.[111]

Actively proliferating stem cells in the isthmus region can be identified using proliferation markers, such as *Stmn1* and *Ki67*.[112] Recent independent lineage-tracing studies using the promoters of these two genes have confirmed that isthmus stem cells can produce functional units during homeostasis.[112] eR1, a Runx1 enhancer element, marks undifferentiated and actively proliferating stem cells in the isthmus.[113] Bmi1-expressing cells in the isthmus exhibit high proliferative activity and generate differentiated progeny.[114]

The gastric antrum shows less heterogeneity than that in the corpus and primarily comprises mucous cells and various types of endocrine cells.[102,103] Stem cells reside at the deep base of the antral gland and give rise to multiple epithelial cells. Various molecular markers have been reported for stem cells in the antrum, such as Lgr5,[115] eR1,[113] CCK2R,[116] and Sox2.[110] Lgr5 was the first stem cell marker identified in the gastric antrum and labels cells located at the base of the antral gland.[115] This cell population represents active stem cells that continuously generate progeny under homeostatic conditions.[115] Aqp5 + cells at the antral base largely overlap with Lgr5 + cells and give rise to all pyloric gland lineages.[117] This stem cell population is present in both humans and mice.[117] However, over the past several years, stem cell markers that do not overlap with Lgr5 have been identified. A subset of Axin2$^+$ cells located at positions + 4 to + 6 in the antral gland are Lgr5$^-$ and can give rise to stem cells upon the depletion of Lgr5 + cells.[118] Antral stem cells regulated by gastrin-secreting G-cells have also been identified. CCK2R + stem cells, located at the + 4 position, rarely express Lgr5, and are relatively quiescent.[116] As in the corpus, eR1 marks stem cells in the antrum. However, these cells appear to be slow cycling and are located higher in the gland than the Lgr5 + cell population.[113] Lrig1 + cells are present at the base of both the corpus and antrum, rarely proliferate, and contribute to the long-term maintenance of the tissue.[119]

4.2. Host stem cells in the intestine

Actively cycling Lgr5 + intestinal stem cells are present at the base of a pocket-like structure called the crypt.[96,120] These actively proliferating stem cells at the crypt base differentiate into two major cell lineages: enterocytes and secretory cells. Wnt target genes, such as *Ascl2* and *Olfm4,* are co-expressed in Lgr5$^+$ actively proliferating stem cells.[121,122] The ablation of Ascl2 leads to the loss of intestinal stem cells, suggesting that the Wnt signaling pathway is essential for maintaining the stem cell population.[121] Intestinal stem cells are likely converted from an active state into a quiescent state. Blocking the EGFR pathway allows the active cycling of Lgr5 + stem cells to transition into quiescent Lgr5 + stem cells, which then give rise to enteroendocrine cells.[123,124] Although intestinal quiescent cells also express Lgr5, as in crypt base cells, their fate is limited; they are committed to the secretory lineages of the Paneth and enteroendocrine cells.[125] Mex3a marks quiescent Lgr5$^+$ stem cells, capable of converting into actively proliferating cells; these Mex3a$^+$ cells are resistant to injury, exhibiting features of reserve-like stem cells.[126] Indeed, after injury, quiescent intestinal cells can survive and reacquire stem cell properties, including clonogenic potential, and generate multiple lineages serving as reserve stem cells that can actively replace cycling stem cells.[125]

Some researchers have argued that quiescent intestinal cells are distinct populations of Lgr5 + stem cells. Bmi1-expressing reserve stem cells in the proximal small intestine (predominantly at the + 4 position) can undergo clonal expansion, exhibit low Ki67 expression, and contribute to the regeneration of the Lgr5 + stem cell pool following the conditional ablation of Lgr5 + cells.[97,127,128] Similarly, mTert and Hopx mark slow-cycling intestinal stem cells at the + 4 position.[129,130] The quiescent intestinal stem

cells at the + 4 position are distinct from Lgr5$^+$ intestinal stem cells, with the two populations functioning in a complementary manner.[129,130] Tuft cells are rare chemosensory and mature secretory cells found in the GI tract. They are conventionally associated with the modulation of immune responses.[131] However, *Clevers* et al. recently suggested that intestinal tuft cells can serve as reserve stem cells capable of giving rise to all epithelial cell types in response to IL-4 and IL-13 stimulation.[132]

4.3. Host stem cells in the colon

Similar to other GI tissues, the colonic epithelium undergoes continuous renewal driven by resident adult stem cells. These stem cells are located at the crypt base and include both actively cycling cells responsible for daily homeostasis and quiescent cells activated in response to injury or stress. Tight regulation of these populations is critical for maintaining epithelial integrity, supporting regeneration, and preventing or initiating tumorigenesis. Colonic stem cells are not only located in a similar niche within the tissue but also express biomarker profiles that closely resemble those of intestinal stem cells. As in the intestine, the best-characterized colonic stem cells are the actively proliferating Lgr5$^+$ stem cells located at the crypt base.[96] Lgr5$^+$ stem cell-derived colonic organoids can be engrafted into recipient mice, generating a functionally normal epithelium that remains stable for more than 6 months.[133] Those Lgr5$^+$ colonic stem cells also express Wnt target genes, such as *Olfm4* and *Ascl2*.[121,122] Colonic quiescent stem cells, similar to those in the small intestine, are marked with mTert.[130] Lrig1$^+$ colonic stem cells are quiescent and characterized by the expression of genes related to cell cycle repression and oxidative stress response, different from proliferative Lgr5$^+$ cells.[134] The loss of Lrig1 or APC in these cells disrupts the regulation of ErbB signaling and promotes tumorigenesis.[134]

5. Microbiota-driven regulation of GI stem cell activity

5.1. Major regulatory pathways for GI stem cell maintenance

GI stem cells are governed by a complex interplay of canonical signaling pathways, including Wnt, Notch, BMP, and Hippo.[135] These major regulatory pathways collectively balance proliferation, differentiation, and quiescence within the crypt and glandular niches. Remarkably, recent studies indicate that microbial communities and their metabolites play integral roles in shaping the major regulatory pathways of GI stem cells.

Wnt signaling pathway plays a crucial role in maintaining stem cell proliferation and determining stem cell fate toward Paneth cells.[135,136] Binding of Wnt ligands to the Frizzled-LRP5/LRP6 receptor complex on GI stem cells suppress consecutive degradation of β-catenin by inhibiting its phosphorylation mediated by destruction complex consist of adenomatous polyposis coli (APC), Axin, and casein kinase I (CK1) and glycogen synthase kinase 3β (GSK 3β).[136] The stabilized β-catenin subsequently translocate into the nucleus, where it regulates expression of target genes involved in stem cell homeostasis.[136] The recent reports have identified that Wnt production from niche cells and its signaling in GI stem cells are controlled by gut microbiota.[32,56,137,138] Notch signaling is a evolutionally conserved pathway that plays a pivotal role in maintaining GI stem cell pool and in balancing between stem cell self-renewal and differentiation.[135,139] To activate Notch signaling, one cell needs to express Notch ligands such as Jagged (Jag-1 and Jag-2) and Delta-like proteins (Dll1, Dll3, and Dll4), while the adjacent stem cell expresses the corresponding receptors (Notch 1-4).[135,139] Upon ligand-receptor binding, Notch intracellular domain (NICD) is cleaved and translocated into the nucleus to promote expression of Notch target genes to maintain GI stem cell homeostasis.[135,139] Although both Wnt and Notch signaling pathways are essential for stem cell self-renewal,[135,140] they play distinct roles in lineage commitment. In contrast to Wnt signaling, which generally leads to secretory lineage differentiation, Notch signaling drives enterocyte differentiation while suppressing the secretory lineage.[140,141] Remarkably, a recent study suggested that epigenetic modifications induced by microbiota-derived SCFAs enable intestinal stem cells to activate Notch signaling, thereby promoting differentiation toward the enterocyte lineage.[142] Although few studies have elucidated that microbiota in GI tracts can influence some major regulatory pathways, evidence linking them to other pathways such as BMP and Hippo signaling remains limited, indicating the need for further investigation. In addition, it should be noted that certain non-canonical signaling pathways, which can influence stem cell, are also subject to regulation by the microbiota.[12,59]

5.2. Impact of the gut microbiota on GI stem cell niche

The GI stem cell niche consists of both epithelial niche cells and subepithelial mesenchymal stromal/immune cells that provide key signals (e.g., Wnt, Notch ligands, BMP modulators) for stem cell homeostasis. As demonstrated by many previous studies, Paneth cells reside adjacent to Lgr5 + intestinal stem cells and secrete crucial factors such as Wnt ligands, EGF, and Notch ligands, which activate Wnt/β-catenin, EGFR/MAPK, and Notch pathways in neighboring stem cells.[143,144] Of note, Paneth cell not only serves as important epithelial niche cells through diverse factor secretion, but also depends on the Wnt pathway for its maturation.[145] Indeed, lactate derived from lactic-acid-producing microbes stimulate Paneth cell to secrete Wnt3 via GPR81 pathway and thereby support intestinal stem cell maintenance and differentiation.[32]

Although Paneth cells are clearly important niche cells for maintaining stemness and supporting differentiation, several key studies have shown that even when Paneth cell–derived niche factors are deficient or absent, they can be compensated by extra-epithelial sources.[146,147] Beneath the epithelium, heterogeneous mesenchymal stromal cells form an essential niche throughout the GI tract, and these stromal cells secrete Wnt ligands and R-spondin as well as BMP inhibitors, thereby establishing a Wnt/BMP gradient within the crypt that sustains stemness.[135] Similar to Paneth cells, Wnt production of the mesenchymal cells can be supported by lactic-acid producing microbiota via GPR81 signaling.[32] Gut microbiota exposure promotes tissue resident macrophage differentiation, which maintains the proliferation of Wnt-producing mesenchymal niche cells and, in turn, activates epithelial Wnt signaling required for stem cell differentiation during the early postnatal period.[137]

Immune cells within the niche also modulate stem cell behavior. Among them, innate lymphoid cells (ILCs) are prominent regulators by secreting specific cytokines such as IL-13 and IL-22.[135,148,149] In particular, IL-22 produced by ILC3 not only promotes intestinal stem cell proliferation, since its receptor is broadly expressed in epithelial cells, but also contributes to Paneth cell maturation.[149,150] Mechanistically, the IL-22–mediated pathway supports stem cell maintenance through STAT3 signaling rather than through canonical Wnt or Notch pathways.[149] A recent study further found that IL-22 production by ILC3 is augmented by microbiota-derived metabolites.[59] Wang et al. demonstrated, using *in vivo* and organoid models, that indoles derived from *Lactobacillus* activate AhR signaling in ILC3, thereby enhancing IL-22 secretion, which in turn promotes the proliferation and development of intestinal stem cells. Although microbiota-dependent regulation of ILC-derived niche factors and their impact on gastric stem cells have not yet been elucidated, a recent study showed that the maintenance and activation of ILC2, the predominant ILC subset in the stomach, are regulated by commensal microbiota.[151]

Taken together, those emerging observations in this section illustrate a putative chain of the gut microbiota influence: microbiota → epithelial/subepithelial niche → GI stem cell. Collectively, gut commensals or microbiota-derived metabolites can shape the GI stem cell niche indirectly affecting the stem cell. Notably, this sequential establishment of the niche environment and the crosstalk between cellular subsets appears to be initiated by tissue-resident immune cells activated by microbiota.[59,137] However, since most experiments have been conducted in the small intestine, it remains unclear whether similar appearance occur in other GI tissues with comparable niches or whether these effects are context-dependent.

5.3. Impact of the gut microbiota on stomach stem cells

SCFAs can modulate the characteristics of chief cells, known as reserve stem cells, in the gastric corpus. In our recent study, the first to introduce crosstalk between a specific microbe and gastric reserve stem cells in mice, we demonstrated that microbiota-derived SCFAs promote the quiescence of gastric chief cells.[12] *L. intestinalis*, which is abundant in the stomach, is capable of producing butyrate and regulates chief cell quiescence through the GPR43 pathway.[12] Germ-free mice exhibit increased chief cell proliferation in the stomach, indicating that microbes normally provide signals that restrain cell cycling in the stomach.[12]

Chief cells can transdifferentiate into metaplastic cells through conserved cellular reprogramming; a subset of these cells subsequently acquire self-renewal and multipotency.[100,101,106] A previous report has shown that metaplastic cells derived from chief cells are responsible for gastric repair following ulceration.[107] Notably, several reports have suggested that probiotic strains can aid ulcer healing through

influencing gastric stem/epithelial cells.[152-155] Mice pre- or post-treatment with probiotics (containing *Lactobacillus* and *Bifidobacterium* species) showed less mucosal damage and increased proliferation of gastric epithelial stem/progenitor cells compared with that in controls.[155] Additionally, *Lactobacillus rhamnosus* GG accelerates the healing of gastric ulcers through attenuating the ratio of cellular apoptosis to proliferation.[153] Although precise molecular mechanisms underlying the effect of probiotics remain to be elucidated, these findings suggest that probiotics may enhance gastric repair through promoting the reprogramming of chief cells or the expansion of stem-like cells.

The pathogenic microbiota can coordinate stem cell activity in the stomach. *H. pylori* (*Campylobacterota*) can colonize the stomach on the surface of the mucosa and in the deep glands, where stem cell compartments exist, contributing to the pathogenesis of gastric cancer.[156] *H. pylori* interacts directly with antral Lgr5 + stem cells, stimulating their proliferation and upregulating stem cell-associated genes.[157] This process occurs during the early stages of infection, before chronic inflammation, and is dependent on *CagA*.[157] Additionally, *H. pylori* induces *Rspo3* expression in myofibroblasts, which is involved in the determination of Lgr5 + stem cell fate and regulation of their antimicrobial properties.[158]

5.4. Impact of the gut microbiota on intestinal stem cells

The intestinal microbiota regulates stem cell differentiation and the niche cells associated with the maintenance of stem cell activity. Studies conducted in the 1960s showed that the loss of the microbiota results in defects in stem cell proliferation.[159,160] The proliferative activity of intestinal stem cells and turnover rate of intestinal epithelial cells are significantly reduced in germ-free mice and in mice treated with an antibiotic mixture.[31] Furthermore, SCFAs produced by gram-positive bacteria play an important role in this process.[31]

Paneth cells play a critical role in intestinal homeostasis by expressing niche factors that contribute to stem cell maintenance.[143] The administration of antibiotics in mice at an early time point results in dysbiosis, which eventually causes defects in the differentiation of intestinal stem cells into Paneth cells.[137] Paneth cell defects can induce necrotizing enterocolitis in newborns,[161] consistent with results for mice with reduced numbers of Paneth cells and in mice with early exposure to antibiotics.[137,162,163] Transplantation of *L. rhamnosus* into mice can rescue the Paneth cell deficiency and necrotizing enterocolitis-like diseases.[137] Intestinal Paneth and stromal cells express GPR81, a lactate G-protein-coupled receptor; therefore, these cells can respond to lactate derived from *Bifidobacterium* and *Lactobacillus* spp., promoting Wnt3A production and thereby facilitating the proliferation of Lgr5 + intestinal stem cells.[32,138] *L. reuteri* contributes to the maintenance of the number of Lgr5 + stem cells and stimulates proliferation through modulating the Wnt/β-catenin pathway.[56]

Dang et al. recently suggested that the maternal microbiota during pregnancy, especially *A. muciniphila*, can shape the characteristics of intestinal stem cells in offspring, contributing to the expansion of secretory lineages.[49] They demonstrated that the maternal microbiota can influence lifelong stem cell function and the physiology of offspring through the mTOR axis.[49] Indeed, the administration of *A. muciniphila* in mice can boost intestinal stem cell proliferation and increase regenerative potential.[164] In contrast, upon physiological stress, *L. murinus* can impair the commitment of secretory lineages through disrupting mitochondrial respiration in Lgr5$^+$ intestinal stem cells.[63] Although the precise mechanism remains unclear, *Lactobacillus acidophilus* (*Firmicutes*) influences the proliferation and differentiation of *Lgr5*$^+$ stem cells and mitigates pathogen-driven inflammation.[165]

The microbiota and their metabolites directly and indirectly influence intestinal stem cells. Microbiota-derived SCFAs serve as HDAC inhibitors, activating Notch signaling in intestinal stem cells.[142] SCFA-induced Notch activation can direct the fate of intestinal stem cells toward enterocytes and improve gut barrier integrity.[142] Using intestinal enteroids, Pearce et al. demonstrated that butyrate and propionate suppress the proliferation of intestinal stem cells and promote cell differentiation; acetate does not affect stem cell proliferation and primarily influences the expression of genes involved in intestinal barrier function.[166] However, Duan et al. recently demonstrated that fucose supplementation increases the abundance of *Akkermansia*, and its metabolite, propionate, promotes the proliferation of Lgr5$^+$ intestinal stem cells in both organoid and mouse models, in a GPR41/GPR43-dependent manner.[167] A metabolomic analysis has revealed that *L. salivarius* produces succinate.[68] This microbiota-derived metabolite can be transported via the SLC13A3 transporter and contributes to the increased expression of *Lgr5* and proliferation markers in host intestinal stem cells.[68]

Lactobacillus spp. can indirectly modulate stem cell characteristics by activating intestinal immune cells. Microbiota-derived indoles activate group 3 innate lymphoid cells (ILC3s), leading to the increased secretion of IL-22, which, in turn, supports intestinal stem cell regeneration and enhances epithelial barrier protection.[59] In contrast, *Lactobacillus*-derived indoles, including IAA and I3L have been implicated in the regulation of intestinal stem cell activity. Wei et al. reported that levels of IAA were elevated under chronic restraint stress condition. In this condition, intestinal crypt exhibited altered expression of genes involved in stem cell fate determination and energy metabolism, including oxidative phosphorylation and the tricarboxylic acid cycle.[63] Furthermore, the increase in indoles lead to inhibition of stem cell differentiation into the secretory lineage, likely mediated via the gut-brain axis.[63] In contrast, Xia et al. demonstrated that cesarean-born offspring are more vulnerable to dextran sulfate sodium induced colitis, exhibiting defective development of ILC3s and subsequently reduced IL-22 level. Supplementation with IAA restored ILC3's niche function through activation of the AhR signaling pathway, leading to enhanced IL-22 production.[168]

Although the effect of succinate on the function of tuft cells as reserve stem cells has not yet been reported,[132] there is evidence that microbiota-derived succinate provides metabolic benefits to *Atoh1*-independent tuft cells and contributes to their expansion.[69] The role of bile acids in intestinal stem cell biology is complex. Bile acid stimulates the proliferation of Lgr5 + intestinal stem cells through activating TGR5, which, in turn, triggers the SRC and YAP signaling pathways and induces the expression of their downstream target genes.[169] However, DCA, a secondary bile acid, can impair ILC3s responsible for IL-22 secretion.[170] Reduced IL-22 levels disrupt intestinal stem cell proliferation and differentiation into secretory lineages.[170] Conversely, a recent study has suggested that DCA directly targets intestinal stem cells, leading to YAP1 phosphorylation and the suppression of their differentiation into secretory lineages.[171] Those reports indicate that secondary bile acids also exert target cell–dependent effects, similar to butyrate.

5.5. Impact of the gut microbiota on colonic stem cells

Although fewer studies have focused on microbiota–stem cell interactions in the colon than in the small intestine, some reports have shown that microbes and their metabolites can influence stem cell function in the colon. The transplantation of the human gut microbiota into germ-free mice can promote a high proliferation rate in the colonic mucosa, suggesting that the microbial composition influences the stem cell-driven renewal of the colonic epithelium.[172] EGFR signaling plays a crucial role in switching gut stem cells from a quiescent to a proliferative state.[124] In this context, the commensal microbiota can upregulate NOX1 expression in colonic stem cells via TLR signaling, and NOX1-derived redox signaling subsequently facilitates proliferation by enhancing EGFR activity.[173]

Microbiota-derived metabolites also affect colonic stem cells. Commensal microbiota-derived I3A can promote the turnover of colonic stem cells and their differentiation into goblet cells in an AhR-IL-10-dependent manner, rather than through the AhR-IL-22 axis.[174] Normal colonocytes can metabolize microbiota-derived butyrate, protecting colonic stem cells from exposure to high butyrate concentrations that can alleviate butyrate-dependent HDAC inhibition and thereby impair stem cell maintenance.[33] On the other hand, a contrasting report showed that patients with colonic atrophy treated with butyrate exhibited upregulation of genes involved in mucosal repair, including Wnt pathway genes and BMP antagonists, which are known to maintain colonic stem cell stemness and proliferation.[175] Indeed, administration of butyrate prevented mucosal inflammation and atrophy in these patients.

6. Cancer development and progression

Although controversial, there is substantial evidence that gut cancers originate from adult stem cells.[109,176-178] Cancer development is associated with drastic changes in the gut microbial diversity, and certain pathogenic or protective microbes can affect cancer progression.[179]

Recently, we demonstrated that adult reserve stem cells (chief cells) located at the base of the gastric corpus strongly express the SCFA receptor GPR43.[12] Consistent with *in vivo* observations, organoids derived from chief cells showed growth suppression in response to butyrate via the GPR43 axis. Since chief cells are well-known precursors of gastric cancer,[100] such metabolite-based growth-suppressive

mechanisms may also operate during gastric carcinogenesis. Notably, *Lactobacillus intestinalis,* introduced in our recent study, can produce microbiota-derived metabolites not only butyrate but also retinoic acid (Figure 1). Thus, its biological relevance in this context warrants particular attention. Therefore, further investigation is urgently required to determine whether gastric microbes and their metabolites suppress the reprogramming of chief cells into precancerous cells or simply modulate their self-renewal capacity under homeostatic conditions.

In some cases, gut microbes may exacerbate the lesion rather than exerting a protective effect. Using human samples, we have demonstrated that the transplantation of the gastric microbiota from patients with metaplasia or gastric cancer into germ-free mice is sufficient to recapitulate precancerous signatures.[179] Additionally, Fu et al. recently demonstrated that *Streptococcus anginosus* (*Firmicutes*), a species enriched in gastric cancer, promotes gastric carcinogenesis.[180] They proposed a new risk factor for carcinogenesis independent of *H. pylori*, showing that the pathogenesis is linked to the TMPC-Annexin A2 axis that enhance its downstream pathway including *p*-ERK, *p*-JNK and *p*-AKT.[180]

Adult stem cells in the esophagus are considered the cellular origin of cancer progression.[181] Although direct evidence linking the esophageal microbiota to stem cell regulation remains limited, previous research has suggested that microbes associated with esophageal cancer can influence gene expression in esophageal epithelial cells.[182] Indeed, specific oral microbes, such as *Campylobacter* spp., *Porphyromonas gingivalis,* and *Streptococcus anginosus,* have been identified in metaplasia or esophageal cancer tissues and are associated with esophageal cancer development.[182,183] Of note, *Porphyromonas gingivalis*, enriched in colorectal cancer, has been shown to accelerate carcinogenesis by producing excessive butyrate that induces cellular senescence of epithelial cells and organoids.[55] *Clostridium butyricum* also produces butyrate, but it activates GPR43-mediated antiproliferative signaling in cancer cell line and simultaneously modulate Wnt/β-catenin signaling and the gut microbiota.[54] This ultimately inhibits colonic tumor development in APC min/ + mice model. Collectively, these contrasting observations suggest that SCFA-mediated pathways may play dual roles in GI carcinogenesis derived from stem cells, with outcomes that depend on the local metabolite concentration, microbial community structure, and the presence of responding receptors or synergistic effects.

Metdji et al. demonstrated that the activation of AhR directly prevents the excessive proliferation of intestinal stem cells and mitigates cancer progression in a murine cancer model; although their study focused specifically on dietary indoles as AhR ligands, these findings suggest that microbiota-derived indoles play a role in preventing cancer progression.[184] In contrast, microbiota-derived TMAO drives the progression of GI cancer. TMAO accelerates the proliferation of colorectal cancer cells and promotes angiogenesis *in vitro* by increasing vascular endothelial growth factor A levels, thereby facilitating carcinogenesis.[185,186] In addition, the production by *Escherichia coli* (*Proteobacteria*) is associated with DNA methylation in colorectal cancer.[88] Recently, a research group conducted a co-culture experiment using human intestinal organoids and a pathogenic strain of *Escherichia coli*. They identified that colibactin, a genotoxic metabolite produced by the pathogen, can directly induce DNA mutation in host cell.[187] This finding suggests that microbiota-derived metabolite may promote cancer progression by inducing DNA modification in GI stem cells. The elevation of secondary bile acids has also been reported in patients with GI cancers.[188] Notably, cancer cells express TGR5, which can be activated by microbiota-derived secondary bile acids to induce various downstream signaling pathways.[189] Secondary bile acid-mediated signaling inhibits apoptosis and promotes cancer cell proliferation, metastasis, invasion, and transformation.[189] Therefore, the targeted manipulation of microbiota capable of producing TMAO and secondary bile acids may serve as a promising strategy for preventing GI cancer.

7. Conclusions

Gut microbes exert direct effects through the colonization and secretion of metabolites, such as SCFAs, succinate, indoles, and secondary bile acids, which may help regulate stem cell characteristics (Table 1). Recent studies have begun to uncover elaborate mechanistic links between specific microbe, its metabolites, and GI stem cell regulation. For example, *Lactobacillus reuteri*–derived fructose has been shown to fuel intestinal stem cell glycolysis and proliferation under stress,[190] while *Lactobacillus murinus*–derived indole-3-acetic acid (IAA) impairs mitochondrial function in intestinal stem cells in an AhR-dependent manner, thereby distorting stem cell differentiation.[63] In the stomach, our recent work first demonstrated

Table 1. Interaction between hots stem cells and gut microbes.

Affected stem cells	Specific bacterial strains	Relevant metabolites	Relevant mechanisms	References
Corpus chief cell	*Lactobacillus intestinalis*	Butyrate	Micorbiota-driven butyrate can promotes proliferation of chief cells via GPR43-dependent pathway	12
Antral Lgr5 + stem cell	*Helicobacter pylori*	Unidentified	*Helicobacter pylori* directly colonizes the surface of stem cells, and then promotes proliferation and expansion of stem cell population	157
	Helicobacter pylori	Unidentified	*Helicobacter pylori* stimulates the production of R-spondin from myofibroblasts, thereby dictating the differentiation of Lgr5+ stem cells.	158
Intestinal Lgr5 + stem cell	*Lactobacillus rhamnosus*	Unidentified	Gut microbiota program the stem cell niche to activate Wnt signaling, thereby promoting the differentiation of stem cells.	137
	Bifidobacterium and *Lactobacillus* spp.	Lactate	Microbiota-derived lactate signal through the GPR81 receptor to niche cells, thereby activating the Wnt3/β-catenin pathway in $Lgr5^+$ intestinal stem cells.	32
	Lactobacillus reuteri	Unidentified	*Lactobacillus reuteri* stimulates the proliferation of intestinal stem cells by upregulating R-spondin expression and activating the Wnt/β-catenin signaling.	56
	Akkermansia muciniphila	SCFAs	Maternal gut microbiota-derived metabolites, such as SCFAs and amino acids, are transferred to the offspring and activate the mTOR signaling in the offspring's stem cells.	49
	Akkermansia muciniphila	N/A	Amuc_1409 promotes the dissociation of the E-cadherin/β-catenin complex through its interaction with E-cadherin, thereby activating the Wnt/β-catenin signaling pathway.	164
	Lactobacillus murinus	IAA	Microbiota-derived indole-3-acetic acid acts on mitochondrial function in stem cells, thereby hindering their commitment to the secretory cell lineage.	63
	Akkermensia spp.	Propionate	Fucose enhances the production of propionic acid in the gut, thereby promoting the proliferation and differentiation of intestinal stem cells via activation of GPR41 and GPR43.	167
	Unidentified	LCA, DCA	Bile acids stimulate intestinal epithelial regeneration by activating TGR5 in intestinal stem cells, which in turn triggers SRC and YAP signaling cascades and upregulates downstream target genes.	169
	Unidentified	DCA	Deoxycholic acid can act directly on intestinal stem cells by inducing YAP1 phosphorylation, thereby inhibiting their commitment to secretory cell fates.	171
Active intestinal stem cell	*Lacbobacillus amylovorus*	Lactate	Microbiota-derived lactate activate Wnt/β-catenin signaling in a GPR81-dependent manner to promote stem cll proliferation.	138
	Lactobacillus acidophilus	Unidentified	*Lactobacillus acidophilus* has been shown to protect the intestinal mucosa and alleviate inflammation by modulating the fate of intestinal epithelial cells.	165
	Unidentified	SCFAs	SCFAs enhance intestinal barrier integrity by promoting the differentiation of absorptive enterocytes through activation of the Notch signaling, which is mediated by HDAC inhibition.	142
	Lactobacillus salivarius	Succinate	Microbiota-derived succiante is transported via SLC13A3 and enhances Lgr5 and proliferation marker expression in intestinal stem cells."	68
	Lactobacillus rhamnosus	I3A, IAA	Microbiota-derived indoles activate ILC3s via the AhR pathway, promoting IL-22 secretion and facilitating intestinal epithelial regeneration.	59
	Unidentified	DCA	Deoxycholic acid suppresses ILC3 function, leading to reduced IL-22 secretion. This reduction impairs intestinal stem cell proliferation and their differentiation into secretory lineages.	170
Intestinal tuft cell	Unidentified	Succinate	Microbiota-derived succinate promotes the expansion of an ATOH1-independent tuft cell population by providing metabolic support.	69
Colonic Lgr5 + stem cell	Unidentified	N/A	Microbiota-derived TLR ligands induce NOX1-dependent ROS production, which amplifies EGFR signaling to enhance Lgr5 + colonic stem cell proliferation	173
	Butyrate	Unidentified	Microbiota-derived butyrate suppresses colonic Lgr5 + stem cell proliferation via HDAC inhibition	33
Active colonuc stem cell	Unidentified	I3A	Microbiota-derived indoles modulate epithelial lineage allocation via AhR-mediated IL-10 signaling, thereby fine-tuning stem differentiation within the crypt niche.	174

that *Lactobacillus intestinalis*–produced butyrate modulates the proliferation of gastric chief cells through GPR43 signaling.[12] Although the major metabolite-producing microbial taxa have recently been identified, many fundamental questions remain unresolved. In particular, the precise and profound molecular mechanisms by which specific microbe and its metabolites modulate the function of diverse adult stem cells along GI tract (Figure 2) remain to be fully elucidated.

Future research should employ integrative approaches such as gnotobiotic germ-free mice, organoid co-cultures with defined metabolites or microbes, metagenomics, single-cell multi-omics, and lineage tracing studies with stem cell marker-expressing mice to identify precise and causal relationships within the stem cell niche. Moreover, inter-individual variability in microbiome composition, diet, and host genetics likely contributes to divergent responses to the same metabolite, underscoring the need for personalized analyzes.

As microbial metabolites exhibit context-dependent and sometimes opposing effects on GI tract's homeostasis and pathogenesis, it is possible that these metabolites similarly exert dual effects on stem cell behavior. Recognizing and addressing these knowledge gaps will not only elucidate how microbial metabolites sustain stem cell homeostasis but also guide the development of microbiota-based strategies for disease prevention.

As summarized in this review, most recent research on host stem cell–microbiota interactions have focused on the lower GI tract, while similar analyzes of the stomach are limited, largely owing to its acidic environment. We have recently identified various microbial species inhabiting the stomach under harsh conditions.[12,179] However, further investigations of the relationship between the gastric microbiota and host stem cells are needed. Gastric adult stem cells are considered a potential cellular origin of gastric cancer; thus, understanding how microbes influence their behavior could provide crucial insights into disease initiation and progression. Furthermore, although the upper GI tract, including the oral cavity and esophagus, harbors stem/progenitor cells, there is a notable lack of studies that directly address the interaction between the microbiota and these stem cell populations. Research in this area may reveal broader principles of microbiota: Stem cell communication along the entire GI tract.

Disclosure statement

The authors declare no conflicts of interest. AI and ChatGPT software were not used in this study.

Funding

This study was supported by a grant (21184MFDS326) from Ministry of Food and Drug Safety in 2025. This study was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF), funded by the Korean government (MSIT). K.T.N. was supported by NRF of Korea grant (No. RS-2022-NR070588, RS-2022-NR067350, RS-2024-00400118, RS-2021-NR057630). H.J. was supported by NRF of Korea grant RS-2022-NR072384. Y.L. was supported by NRF of Korea grant RS-2024-00509487.

ORCID

Haengdueng Jeong 0000-0002-9218-7372
Yura Lee 0000-0002-3744-8138
Ki Taek Nam 0000-0001-5292-1280

References

1. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, Zhu D, Koya JB, Wei L, Li J, et al. Microbiota in health and diseases. Signal Transduct Target Ther. 2022;7(1):135. doi: 10.1038/s41392-022-00974-4.
2. Kim BS, Li BT, Engel A, Samra JS, Clarke S, Norton ID, Li AE. Diagnosis of gastrointestinal bleeding: a practical guide for clinicians. World J Gastrointest Pathophysiol. 2014;5(4):467–478. doi: 10.4291/wjgp.v5.i4.467.
3. Ferranti EP, Dunbar SB, Dunlop AL, Corwin EJ. 20 things you didn't know about the human gut microbiome. J Cardiovasc Nurs. 2014;29(6):479–481. doi: 10.1097/JCN.0000000000000166.
4. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body. PLoS Biol. 2016;14(8):e1002533. doi: 10.1371/journal.pbio.1002533.
5. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, Gasbarrini A, Mele MC. What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms. 2019;7(1):14. doi: 10.3390/microorganisms7010014.

6. Sundin OH, Mendoza-Ladd A, Zeng M, Diaz-Arevalo D, Morales E, Fagan BM, Ordonez J, Velez P, Antony N, McCallum RW. The human jejunum has an endogenous microbiota that differs from those in the oral cavity and colon. BMC Microbiol. 2017;17(1):160. doi: 10.1186/s12866-017-1059-6.
7. Vasapolli R, Schutte K, Schulz C, Vital M, Schomburg D, Pieper DH, Vilchez-Vargas R, Malfertheiner P. Analysis of transcriptionally active bacteria throughout the gastrointestinal tract of healthy individuals. Gastroenterology. 2019;157(4):1081–1092e1083. doi: 10.1053/j.gastro.2019.05.068.
8. Dewhirst FE, Chen T, Izard J, Paster BJ, Tanner AC, Yu WH, Lakshmanan A, Wade WG. The human oral microbiome. J Bacteriol. 2010;192(19):5002–5017. doi: 10.1128/JB.00542-10.
9. Li K, Bihan M, Yooseph S, Methe BA. Analyses of the microbial diversity across the human microbiome. PLoS One. 2012;7(6):e32118. doi: 10.1371/journal.pone.0032118.
10. Zou Q, Feng L, Cai X, Qian Y, Xu L. Esophageal microflora in esophageal diseases. Front Cell Infect Microbiol. 2023;13:1145791. doi: 10.3389/fcimb.2023.1145791.
11. Pei Z, Bini EJ, Yang L, Zhou M, Francois F, Blaser MJ. Bacterial biota in the human distal esophagus. Proc Natl Acad Sci U S A. 2004;101(12):4250–4255. doi: 10.1073/pnas.0306398101.
12. Jeong H, Lee B, Cho SY, Lee Y, Kim J, Hur S, Cho K, Kim KH, Kim SH, Nam KT. Microbiota-derived short-chain fatty acids determine stem cell characteristics of gastric chief cells. Dev Cell. 2024. 10.1016/j.devcel.2024.11.007.
13. Ruan W, Engevik MA, Spinler JK, Versalovic J. Healthy human gastrointestinal microbiome: composition and function after a decade of exploration. Dig Dis Sci. 2020;65(3):695–705. doi: 10.1007/s10620-020-06118-4.
14. Hillman ET, Lu H, Yao T, Nakatsu CH. Microbial ecology along the gastrointestinal tract. Microbes Environ. 2017;32(4):300–313. doi: 10.1264/jsme2.ME17017.
15. Schulz C, Schutte K, Koch N, Vilchez-Vargas R, Wos-Oxley ML, Oxley APA, Vital M, Malfertheiner P, Pieper DH. The active bacterial assemblages of the upper GI tract in individuals with and without Helicobacter infection. Gut. 2018;67(2):216–225. doi: 10.1136/gutjnl-2016-312904.
16. Sung JJY, Coker OO, Chu E, Szeto CH, Luk STY, Lau HCH, Yu J. Gastric microbes associated with gastric inflammation, atrophy and intestinal metaplasia 1 year after Helicobacter pylori eradication. Gut. 2020;69(9): 1572–1580. doi: 10.1136/gutjnl-2019-319826.
17. Collins JT, Nguyen A, Badireddy M. Anatomy, Abdomen and Pelvis, Small Intestine. Treasure Island (FL): StatPearls; 2025
18. Shaw S, Jayatilleke E, Meyers S, Colman N, Herzlich B, Herbert V. The ileum is the major site of absorption of vitamin B12 analogues. Am J Gastroenterol. 1989;84(1):22–26.
19. Ghosh TS, Shanahan F, O'Toole PW. The gut microbiome as a modulator of healthy ageing. Nat Rev Gastroenterol Hepatol. 2022;19(9):565–584. doi: 10.1038/s41575-022-00605-x.
20. Biasucci G, Benenati B, Morelli L, Bessi E, Boehm G. Cesarean delivery may affect the early biodiversity of intestinal bacteria. J Nutr. 2008;138(9):1796S–1800S. doi: 10.1093/jn/138.9.1796S.
21. Dominguez-Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, Fierer N, Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A. 2010;107(26):11971–11975. doi: 10.1073/pnas.1002601107.
22. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007;5(7):e177. doi: 10.1371/journal.pbio.0050177.
23. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, Baldassano RN, Anokhin AP, et al. Human gut microbiome viewed across age and geography. Natur. 2012;486(7402):222–227. doi: 10.1038/nature11053.
24. Kim KH, Chung Y, Huh JW, Park DJ, Cho Y, Oh Y, Jeong H, Yoon J, Kang JH, Shin HS, et al. Gut microbiota of the young ameliorates physical fitness of the aged in mice. Microbiome. 2022;10(1):238. doi: 10.1186/s40168-022-01386-w.
25. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, Ling AV, Devlin AS, Varma Y, Fischbach MA, et al. Diet rapidly and reproducibly alters the human gut microbiome. Natur. 2014;505(7484):559–563. doi: 10.1038/nature12820.
26. Kovatcheva-Datchary P, Nilsson A, Akrami R, Lee YS, De Vadder F, Arora T, Hallen A, Martens E, Bjorck I, Backhed F. Dietary fiber-induced improvement in glucose metabolism is associated with increased abundance of prevotella. Cell Metab. 2015;22(6):971–982. doi: 10.1016/j.cmet.2015.10.001.
27. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. Cell Res. 2020;30(6):492–506. doi: 10.1038/s41422-020-0332-7.
28. Yang LL, Millischer V, Rodin S, MacFabe DF, Villaescusa JC, Lavebratt C. Enteric short-chain fatty acids promote proliferation of human neural progenitor cells. J Neurochem. 2020;154(6):635–646. doi: 10.1111/jnc.14928.
29. Sun M, Wu W, Chen L, Yang W, Huang X, Ma C, Chen F, Xiao Y, Zhao Y, Ma C, et al. Microbiota-derived short-chain fatty acids promote Th1 cell IL-10 production to maintain intestinal homeostasis. Nat Commun. 2018;9(1):3555. doi: 10.1038/s41467-018-05901-2.
30. Bilotta AJ, Ma C, Yang W, Yu Y, Yu Y, Zhao X, Zhou Z, Yao S, Dann SM, Cong Y. Propionate enhances cell speed and persistence to promote intestinal epithelial turnover and repair. Cell Mol Gastroenterol Hepatol. 2021;11(4):1023–1044. doi: 10.1016/j.jcmgh.2020.11.011.

31. Park JH, Kotani T, Konno T, Setiawan J, Kitamura Y, Imada S, Usui Y, Hatano N, Shinohara M, Saito Y, et al. Promotion of intestinal epithelial cell turnover by commensal bacteria: role of short-chain fatty acids. PLoS One. 2016;11(5):e0156334. doi: 10.1371/journal.pone.0156334.
32. Lee YS, Kim TY, Kim Y, Lee SH, Kim S, Kang SW, Yang JY, Baek IJ, Sung YH, Park YY, et al. Microbiota-derived lactate accelerates intestinal stem-cell-mediated epithelial development. Cell Host Microbe. 2018;24(6):833–846e836. doi: 10.1016/j.chom.2018.11.002.
33. 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. Cell. 2016;165(7):1708–1720. doi: 10.1016/j.cell.2016.05.018.
34. Cummings JH, Pomare EW, Branch WJ, Naylor CP, Macfarlane GT. Short chain fatty acids in human large intestine, portal, hepatic and venous blood. Gut. 1987;28(10):1221–1227. doi: 10.1136/gut.28.10.1221.
35. Brown AJ, Goldsworthy SM, Barnes AA, Eilert MM, Tcheang L, Daniels D, Muir AI, Wigglesworth MJ, Kinghorn I, Fraser NJ, et al. The orphan G protein-coupled receptors GPR41 and GPR43 are activated by propionate and other short chain carboxylic acids. J Biol Chem. 2003;278(13):11312–11319. doi: 10.1074/jbc.M211609200.
36. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54(9):2325–2340. doi: 10.1194/jlr.R036012.
37. Smith PM, Howitt MR, Panikov N, Michaud M, Gallini CA, Bohlooly YM, Glickman JN, Garrett WS. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569–573. doi: 10.1126/science.1241165.
38. Kelly CJ, Zheng L, Campbell EL, Saeedi B, Scholz CC, Bayless AJ, Wilson KE, Glover LE, Kominsky DJ, Magnuson A, et al. Crosstalk between microbiota-derived short-chain fatty acids and intestinal epithelial hif augments tissue barrier function. Cell Host Microbe. 2015;17(5):662–671. doi: 10.1016/j.chom.2015.03.005.
39. Sommer F, Backhed F. The gut microbiota--masters of host development and physiology. Nat Rev Microbiol. 2013;11(4):227–238. doi: 10.1038/nrmicro2974.
40. Zhang LS, Davies SS. Microbial metabolism of dietary components to bioactive metabolites: opportunities for new therapeutic interventions. Genome Med. 2016;8(1):46. doi: 10.1186/s13073-016-0296-x.
41. Kircher B, Woltemate S, Gutzki F, Schluter D, Geffers R, Bahre H, Vital M. Predicting butyrate- and propionate-forming bacteria of gut microbiota from sequencing data. Gut Microbes. 2022;14(1):2149019. doi: 10.1080/19490976.2022.2149019.
42. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol. 2017;19(1):29–41. doi: 10.1111/1462-2920.13589.
43. Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, Mutlu E, Shannon KM. Colonic bacterial composition in Parkinson's disease. Mov Disord. 2015;30(10):1351–1360. doi: 10.1002/mds.26307.
44. Lenoir M, Martin R, Torres-Maravilla E, Chadi S, Gonzalez-Davila P, Sokol H, Langella P, Chain F, Bermudez-Humaran LG. Butyrate mediates anti-inflammatory effects of Faecalibacterium prausnitzii in intestinal epithelial cells through Dact3. Gut Microbes. 2020;12(1):1–16. doi: 10.1080/19490976.2020.1826748.
45. Duncan SH, Hold GL, Harmsen HJM, Stewart CS, Flint HJ. Growth requirements and fermentation products of Fusobacterium prausnitzii, and a proposal to reclassify it as Faecalibacterium prausnitzii gen. nov., comb. nov. Int J Syst Evol Microbiol. 2002;52(Pt 6):2141–2146. doi: 10.1099/00207713-52-6-2141.
46. Miquel S, Leclerc M, Martin R, Chain F, Lenoir M, Raguideau S, Hudault S, Bridonneau C, Northen T, Bowen B, et al. Identification of metabolic signatures linked to anti-inflammatory effects of Faecalibacterium prausnitzii. mBio. 2015;6(2), 10.1128/mBio.00300-15.
47. Pryde SE, Duncan SH, Hold GL, Stewart CS, Flint HJ. The microbiology of butyrate formation in the human colon. FEMS Microbiol Lett. 2002;217(2):133–139. doi: 10.1111/j.1574-6968.2002.tb11467.x.
48. Jiang Y, Huang Z, Sun W, Huang J, Xu Y, Liao Y, Jin T, Li Q, Ho IHT, Zou Y, et al. Roseburia intestinalis-derived butyrate alleviates neuropathic pain. Cell Host Microbe. 2025;33(1):104–118e107. doi: 10.1016/j.chom.2024.11.013.
49. Dang H, Feng P, Zhang S, Peng L, Xing S, Li Y, Wen X, Zhou L, Goswami S, Xiao M, et al. Maternal gut microbiota influence stem cell function in offspring. Cell Stem Cell. 2025;32(2):246–262. e248. 10.1016/j.stem.2024.10.003.
50. Watanabe Y, Nagai F, Morotomi M. Characterization of Phascolarctobacterium succinatutens sp. nov., an asaccharolytic, succinate-utilizing bacterium isolated from human feces. Appl Environ Microbiol. 2012;78(2):511–518. doi: 10.1128/AEM.06035-11.
51. Martin D, Bonneau M, Orfila L, Horeau M, Hazon M, Demay R, Lecommandeur E, Boumpoutou R, Guillotel A, Guillemot P, et al. Atypical gut microbial ecosystem from athletes with very high exercise capacity improves insulin sensitivity and muscle glycogen store in mice. Cell Rep. 2025;44(4):115448. doi: 10.1016/j.celrep.2025.115448.
52. Zhang SM, Huang SL. The commensal anaerobe veillonella dispar reprograms its lactate metabolism and short-chain fatty acid production during the stationary phase. Microbiol Spectr. 2023;11(2):e0355822. doi: 10.1128/spectrum.03558-22.
53. Donohoe DR, Collins LB, Wali A, Bigler R, Sun W, Bultman SJ. The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. Mol Cell. 2012;48(4):612–626. doi: 10.1016/j.molcel.2012.08.033.

54. Chen D, Jin D, Huang S, Wu J, Xu M, Liu T, Dong W, Liu X, Wang S, Zhong W, et al. Clostridium butyricum, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota. Cancer Lett. 2020;469:456–467. doi: 10.1016/j.canlet.2019.11.019.
55. Okumura S, Konishi Y, Narukawa M, Sugiura Y, Yoshimoto S, Arai Y, Sato S, Yoshida Y, Tsuji S, Uemura K, et al. Gut bacteria identified in colorectal cancer patients promote tumourigenesis via butyrate secretion. Nat Commun. 2021;12(1):5674. doi: 10.1038/s41467-021-25965-x.
56. Wu H, Xie S, Miao J, Li Y, Wang Z, Wang M, Yu Q. Lactobacillus reuteri maintains intestinal epithelial regeneration and repairs damaged intestinal mucosa. Gut Microbes. 2020;11(4):997–1014. doi: 10.1080/19490976.2020.1734423.
57. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, Zecchi R, D'Angelo C, Massi-Benedetti C, Fallarino F, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity. 2013;39(2):372–385. doi: 10.1016/j.immuni.2013.08.003.
58. Montgomery TL, Eckstrom K, Lile KH, Caldwell S, Heney ER, Lahue KG, D'Alessandro A, Wargo MJ, Krementsov DN. Lactobacillus reuteri tryptophan metabolism promotes host susceptibility to CNS autoimmunity. Microbiome. 2022;10(1):198. doi: 10.1186/s40168-022-01408-7.
59. Wang J, Zhao Y, Cui T, Bao H, Gao M, Cheng M, Sun Y, Lu Y, Guan J, Zhang D, et al. AhR ligands from LGG metabolites promote piglet intestinal ILC3 activation and IL-22 secretion to inhibit PEDV infection. J Virol. 2024;98(8):e0103924. doi: 10.1128/jvi.01039-24.
60. Meng D, Sommella E, Salviati E, Campiglia P, Ganguli K, Djebali K, Zhu W, Walker WA. Indole-3-lactic acid, a metabolite of tryptophan, secreted by Bifidobacterium longum subspecies infantis is anti-inflammatory in the immature intestine. Pediatr Res. 2020;88(2):209–217. doi: 10.1038/s41390-019-0740-x.
61. Zhou Q, Xie Z, Wu D, Liu L, Shi Y, Li P, Gu Q. The effect of indole-3-lactic acid from lactiplantibacillus plantarum zj316 on human intestinal microbiota in vitro. Foods. 2022;11(20):3302. doi: 10.3390/foods11203302.
62. Krishnan S, Ding Y, Saedi N, Choi M, Sridharan GV, Sherr DH, Yarmush ML, Alaniz RC, Jayaraman A, Lee K. Gut microbiota-derived tryptophan metabolites modulate inflammatory response in hepatocytes and macrophages. Cell Rep. 2018;23(4):1099–1111. doi: 10.1016/j.celrep.2018.03.109.
63. Wei W, Liu Y, Hou Y, Cao S, Chen Z, Zhang Y, Cai X, Yan Q, Li Z, Yuan Y, et al. Psychological stress-induced microbial metabolite indole-3-acetate disrupts intestinal cell lineage commitment. Cell Metab. 2024;36(3):466–483e467. doi: 10.1016/j.cmet.2023.12.026.
64. Du L, Qi R, Wang J, Liu Z, Wu Z. Indole-3-propionic acid, a functional metabolite of clostridium sporogenes, promotes muscle tissue development and reduces muscle cell inflammation. Int J Mol Sci. 2021;22(22):12435. doi: 10.3390/ijms222212435.
65. Liu D, Zhang S, Li S, Zhang Q, Cai Y, Li P, Li H, Shen B, Liao Q, Hong Y, et al. Indoleacrylic acid produced by parabacteroides distasonis alleviates type 2 diabetes via activation of AhR to repair intestinal barrier. BMC Biol. 2023;21(1):90. doi: 10.1186/s12915-023-01578-2.
66. Shah HN, Olsen I, Bernard K, Finegold SM, Gharbia S, Gupta RS. Approaches to the study of the systematics of anaerobic, gram-negative, non-sporeforming rods: current status and perspectives. Anaerobe. 2009;15(5):179–194. doi: 10.1016/j.anaerobe.2009.08.003.
67. De Vadder F, Kovatcheva-Datchary P, Zitoun C, Duchampt A, Backhed F, Mithieux G. Microbiota-produced succinate improves glucose homeostasis via intestinal gluconeogenesis. Cell Metab. 2016;24(1):151–157. doi: 10.1016/j.cmet.2016.06.013.
68. Zhou Z, Yu L, Cao J, Yu J, Lin Z, Hong Y, Jiang S, Chen C, Mi Y, Zhang C, et al. Lactobacillus salivarius promotion of intestinal stem cell activity in hens is associated with succinate-induced mitochondrial energy metabolism. mSystems. 2022;7(6):e0090322. doi: 10.1128/msystems.00903-22.
69. Banerjee A, Herring CA, Chen B, Kim H, Simmons AJ, Southard-Smith AN, Allaman MM, White JR, Macedonia MC, McKinley ET, et al. Succinate produced by intestinal microbes promotes specification of tuft cells to suppress ileal inflammation. Gastroenterology. 2020;159(6):2101–2115. e2105. 10.1053/j.gastro.2020.08.029.
70. Blanchet M, Brunel JM. Bile acid derivatives: from old molecules to a new potent therapeutic use: an overview. Curr Med Chem. 2018;25(30):3613–3636. doi: 10.2174/0929867325666180309113737.
71. Ferrebee CB, Dawson PA. Metabolic effects of intestinal absorption and enterohepatic cycling of bile acids. Acta Pharm Sin B. 2015;5(2):129–134. doi: 10.1016/j.apsb.2015.01.001.
72. Kang JD, Myers CJ, Harris SC, Kakiyama G, Lee IK, Yun BS, Matsuzaki K, Furukawa M, Min HK, Bajaj JS, et al. Bile acid 7alpha-dehydroxylating gut bacteria secrete antibiotics that inhibit clostridium difficile: role of secondary bile acids. Cell Chem Biol. 2019;26(1):27–34e24. doi: 10.1016/j.chembiol.2018.10.003.
73. Ridlon JM, Hylemon PB. Identification and characterization of two bile acid coenzyme a transferases from clostridium scindens, a bile acid 7alpha-dehydroxylating intestinal bacterium. J Lipid Res. 2012;53(1):66–76. doi: 10.1194/jlr.M020313.
74. Wahlstrom A, Brumbaugh A, Sjoland W, Olsson L, Wu H, Henricsson M, Lundqvist A, Makki K, Hazen SL, Bergstrom G, et al. Production of deoxycholic acid by low-abundant microbial species is associated with impaired glucose metabolism. Nat Commun. 2024;15(1):4276. doi: 10.1038/s41467-024-48543-3.

75. Doden H, Sallam LA, Devendran S, Ly L, Doden G, Daniel SL, Alves JMP, Ridlon JM. Metabolism of oxo-bile acids and characterization of recombinant 12alpha-hydroxysteroid dehydrogenases from bile acid 7alpha-dehydroxylating human gut bacteria. Appl Environ Microbiol. 2018;84(10), 10.1128/AEM.00235-18.
76. Ridlon JM, Kang DJ, Hylemon PB. Isolation and characterization of a bile acid inducible 7alpha-dehydroxylating operon in Clostridium hylemonae TN271. Anaerobe. 2010;16(2):137–146. doi: 10.1016/j.anaerobe.2009.05.004.
77. Sato Y, Atarashi K, Plichta DR, Arai Y, Sasajima S, Kearney SM, Suda W, Takeshita K, Sasaki T, Okamoto S, et al. Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians. Natur. 2021;599(7885):458–464. doi: 10.1038/s41586-021-03832-5.
78. Niederreither K, Subbarayan V, Dolle P, Chambon P. Embryonic retinoic acid synthesis is essential for early mouse post-implantation development. Nat Genet. 1999;21(4):444–448. doi: 10.1038/7788.
79. Duester G. Retinoic acid synthesis and signaling during early organogenesis. Cell. 2008;134(6):921–931. doi: 10.1016/j.cell.2008.09.002.
80. Grizotte-Lake M, Zhong G, Duncan K, Kirkwood J, Iyer N, Smolenski I, Isoherranen N, Vaishnava S. Commensals suppress intestinal epithelial cell retinoic acid synthesis to regulate interleukin-22 activity and prevent microbial Dysbiosis. Immunity. 2018;49(6):1103–1115e1106. doi: 10.1016/j.immuni.2018.11.018.
81. Kumar S, Duester G. SnapShot: retinoic acid signaling. Cell. 2011;147(6):1422–1422e1421. doi: 10.1016/j.cell.2011.11.034.
82. Woo V, Eshleman EM, Hashimoto-Hill S, Whitt J, Wu SE, Engleman L, Rice T, Karns R, Qualls JE, Haslam DB, et al. Commensal segmented filamentous bacteria-derived retinoic acid primes host defense to intestinal infection. Cell Host Microbe. 2021;29(12):1744–1756e1745. doi: 10.1016/j.chom.2021.09.010.
83. Wang QW, Jia DJ, He JM, Sun Y, Qian Y, Ge QW, Qi YD, Wang QY, Hu YY, Wang L, et al. Lactobacillus intestinalis primes epithelial cells to suppress colitis-related Th17 response by host-microbe retinoic acid biosynthesis. Adv Sci (Weinh). 2023;10(36):e2303457. doi: 10.1002/advs.202303457.
84. Bonakdar M, Czuba LC, Han G, Zhong G, Luong H, Isoherranen N, Vaishnava S. Gut commensals expand vitamin a metabolic capacity of the mammalian host. Cell Host Microbe. 2022;30(8):1084–1092e1085. doi: 10.1016/j.chom.2022.06.011.
85. Gudas LJ. Retinoids induce stem cell differentiation via epigenetic changes. Semin Cell Dev Biol. 2013;24(10-12):701–705. doi: 10.1016/j.semcdb.2013.08.002.
86. Chanchevalap S, Nandan MO, Merlin D, Yang VW. All-trans retinoic acid inhibits proliferation of intestinal epithelial cells by inhibiting expression of the gene encoding Kruppel-like factor 5. FEBS Lett. 2004;578(1-2):99–105. doi: 10.1016/j.febslet.2004.10.079.
87. Snyder LM, Arora J, Kennett MJ, Weaver V, Cantorna MT. Retinoid signaling in intestinal epithelial cells is essential for early survival from gastrointestinal infection. Front Immunol. 2020;11:559635. doi: 10.3389/fimmu.2020.559635.
88. Zhou Y, Zhang Y, Jin S, Lv J, Li M, Feng N. The gut microbiota derived metabolite trimethylamine N-oxide: Its important role in cancer and other diseases. Biomed Pharmacother. 2024;177:117031. doi: 10.1016/j.biopha.2024.117031.
89. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, Dugar B, Feldstein AE, Britt EB, Fu X, Chung YM, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Natur. 2011;472(7341):57–63. doi: 10.1038/nature09922.
90. Nie J, Xie L, Zhao BX, Li Y, Qiu B, Zhu F, Li GF, He M, Wang Y, Wang B, et al. Serum trimethylamine n-oxide concentration is positively associated with first stroke in hypertensive patients. Stroke. 2018;49(9):2021–2028. doi: 10.1161/STROKEAHA.118.021997.
91. Papandreou C, Bullo M, Zheng Y, Ruiz-Canela M, Yu E, Guasch-Ferre M, Toledo E, Clish C, Corella D, Estruch R, et al. Plasma trimethylamine-N-oxide and related metabolites are associated with type 2 diabetes risk in the Prevencion con Dieta Mediterranea (PREDIMED) trial. AJCN. 2018;108(1):163–173. doi: 10.1093/ajcn/nqy058.
92. Wang N, Hao Y, Fu L. Trimethylamine-N-oxide promotes osteoclast differentiation and bone loss via activating ROS-dependent NF-kappaB signaling pathway. Nutrients. 2022;14(19):3955. doi: 10.3390/nu14193955.
93. Lin H, Liu T, Li X, Gao X, Wu T, Li P. The role of gut microbiota metabolite trimethylamine N-oxide in functional impairment of bone marrow mesenchymal stem cells in osteoporosis disease. Ann Transl Med. 2020;8(16):1009–1009. doi: 10.21037/atm-20-5307.
94. Marescal O, Cheeseman IM. Cellular mechanisms and regulation of quiescence. Dev Cell. 2020;55(3):259–271. doi: 10.1016/j.devcel.2020.09.029.
95. Potten CS. Extreme sensitivity of some intestinal crypt cells to X and gamma irradiation. Natur. 1977;269(5628):518–521. doi: 10.1038/269518a0.
96. Barker N, van Es JH, Kuipers J, Kujala P, van den Born M, Cozijnsen M, Haegebarth A, Korving J, Begthel H, Peters PJ, et al. Identification of stem cells in small intestine and colon by marker gene Lgr5. Natur. 2007;449(7165):1003–1007. doi: 10.1038/nature06196.
97. Sangiorgi E, Capecchi MR. Bmi1 is expressed in vivo in intestinal stem cells. Nat Genet. 2008;40(7):915–920. doi: 10.1038/ng.165.
98. Li L, Clevers H. Coexistence of quiescent and active adult stem cells in mammals. Science. 2010;327(5965):542–545. doi: 10.1126/science.1180794.

99. Barker N, Bartfeld S, Clevers H. Tissue-resident adult stem cell populations of rapidly self-renewing organs. Cell Stem Cell. 2010;7(6):656–670. doi: 10.1016/j.stem.2010.11.016.
100. Leushacke M, Tan SH, Wong A, Swathi Y, Hajamohideen A, Tan LT, Goh J, Wong E, Denil S, Murakami K, et al. Lgr5-expressing chief cells drive epithelial regeneration and cancer in the oxyntic stomach. Nat Cell Biol. 2017;19(7):774–786. doi: 10.1038/ncb3541.
101. Stange DE, Koo BK, Huch M, Sibbel G, Basak O, Lyubimova A, Kujala P, Bartfeld S, Koster J, Geahlen JH, Stange DE, et al. Differentiated Troy+ chief cells act as reserve stem cells to generate all lineages of the stomach epithelium. Cell. 2013;155(2):357–368. doi: 10.1016/j.cell.2013.09.008.
102. Karam SM, Leblond CP. Dynamics of epithelial cells in the corpus of the mouse stomach. II. Outward migration of pit cells. Anat Rec. 1993;236(2):280–296. doi: 10.1002/ar.1092360203.
103. Karam SM, Leblond CP. Dynamics of epithelial cells in the corpus of the mouse stomach. III. Inward migration of neck cells followed by progressive transformation into zymogenic cells. Anat Rec. 1993;236(2):297–313. doi: 10.1002/ar.1092360204.
104. Brown JW, Cho CJ, Mills JC. Paligenosis: cellular remodeling during tissue repair. Annu Rev Physiol. 2022;84:461–483. doi: 10.1146/annurev-physiol-061121-035954.
105. Willet SG, Lewis MA, Miao ZF, Liu D, Radyk MD, Cunningham RL, Burclaff J, Sibbel G, Lo HG, Blanc V, et al. Regenerative proliferation of differentiated cells by mTORC1-dependent paligenosis. EMBO J. 2018;37(7). doi: 10.15252/embj.201798311.
106. Nam KT, Lee HJ, Sousa JF, Weis VG, O'Neal RL, Finke PE, Romero-Gallo J, Shi G, Mills JC, Peek RM, et al. Mature chief cells are cryptic progenitors for metaplasia in the stomach. Gastroenterology. 2010;139(6):2028–2037. e2029. 10.1053/j.gastro.2010.09.005.
107. Engevik AC, Feng R, Choi E, White S, Bertaux-Skeirik N, Li J, Mahe MM, Aihara E, Yang L, DiPasquale B, et al. The development of spasmolytic polypeptide/tff2-expressing metaplasia (SPEM) during gastric repair is absent in the aged stomach. Cell Mol Gastroenterol Hepatol. 2016;2(5):605–624. doi: 10.1016/j.jcmgh.2016.05.004.
108. Goldenring JR, Mills JC. Cellular plasticity, reprogramming, and regeneration: metaplasia in the stomach and beyond. Gastroenterology. 2022;162(2):415–430. doi: 10.1053/j.gastro.2021.10.036.
109. Caldwell B, Meyer AR, Weis JA, Engevik AC, Choi E. Chief cell plasticity is the origin of metaplasia following acute injury in the stomach mucosa. Gut. 2022;71(6):1068–1077. doi: 10.1136/gutjnl-2021-325310.
110. Arnold K, Sarkar A, Yram MA, Polo JM, Bronson R, Sengupta S, Seandel M, Geijsen N, Hochedlinger K. Sox2(+) adult stem and progenitor cells are important for tissue regeneration and survival of mice. Cell Stem Cell. 2011;9(4):317–329. doi: 10.1016/j.stem.2011.09.001.
111. Lee JH, Kim S, Han S, Min J, Caldwell B, Bamford AD, Rocha ASB, Park J, Lee S, Wu SS, et al. p57(Kip2) imposes the reserve stem cell state of gastric chief cells. Cell Stem Cell. 2022;29(5):826–839. e829. doi:10.1016/j.stem.2022.04.001.
112. Han S, Fink J, Jorg DJ, Lee E, Yum MK, Chatzeli L, Merker SR, Josserand M, Trendafilova T, Andersson-Rolf A, et al. Defining the identity and dynamics of adult gastric isthmus stem cells. Cell Stem Cell. 2019;25(3):342–356. e347. doi: 10.1016/j.stem.2019.07.008.
113. Matsuo J, Kimura S, Yamamura A, Koh CP, Hossain MZ, Heng DL, Kohu K, Voon DC, Hiai H, Unno M, et al. Identification of stem cells in the epithelium of the stomach corpus and antrum of mice. Gastroenterology. 2017;152(1):218–231. e214. doi: 10.1053/j.gastro.2016.09.018.
114. Yoshioka T, Fukuda A, Araki O, Ogawa S, Hanyu Y, Matsumoto Y, Yamaga Y, Nakanishi Y, Kawada K, Sakai Y, et al. Bmi1 marks gastric stem cells located in the isthmus in mice. J Pathol. 2019;248(2):179–190. doi: 10.1002/path.5244.
115. Barker N, Huch N, Kujala M, van de Wetering P, Snippert M, van Es HJ, Sato JH, Stange DE T, Begthel H, van den Born M, et al. Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro. Cell Stem Cell. 2010;6(1):25–36. doi: 10.1016/j.stem.2009.11.013.
116. Hayakawa Y, Jin G, Wang H, Chen X, Westphalen CB, Asfaha S, Renz BW, Ariyama H, Dubeykovskaya ZA, Takemoto Y, et al. CCK2R identifies and regulates gastric antral stem cell states and carcinogenesis. Gut. 2015;64(4):544–553. doi: 10.1136/gutjnl-2014-307190.
117. Tan SH, Swathi Y, Tan S, Goh J, Seishima R, Murakami K, Oshima M, Tsuji T, Phuah P, Tan LT, et al. AQP5 enriches for stem cells and cancer origins in the distal stomach. Natur. 2020;578(7795):437–443. doi: 10.1038/s41586-020-1973-x.
118. Sigal M, Logan CY, Kapalczynska M, Mollenkopf HJ, Berger H, Wiedenmann B, Nusse R, Amieva MR, Meyer TF. Stromal R-spondin orchestrates gastric epithelial stem cells and gland homeostasis. Natur. 2017;548(7668):451–455. doi: 10.1038/nature23642.
119. Schweiger PJ, Clement DL, Page ME, Schepeler T, Zou X, Sirokmany G, Watt FM, Jensen KB. Lrig1 marks a population of gastric epithelial cells capable of long-term tissue maintenance and growth in vitro. Sci Rep. 2018;8(1):15255. doi: 10.1038/s41598-018-33578-6.
120. Snippert HJ, van der Flier LG, Sato T, van Es JH, van den Born M, Kroon-Veenboer C, Barker N, Klein AM, van Rheenen J, Simons BD, et al. Intestinal crypt homeostasis results from neutral competition between symmetrically dividing Lgr5 stem cells. Cell. 2010;143(1):134–144. doi: 10.1016/j.cell.2010.09.016.

121. van der Flier LG, van Gijn ME, Hatzis P, Kujala P, Haegebarth A, Stange DE, Begthel H, van den Born V, Guryev V, Oving I, et al. Transcription factor achaete scute-like 2 controls intestinal stem cell fate. Cell. 2009;136(5):903–912. doi: 10.1016/j.cell.2009.01.031.
122. van der Flier LG, Haegebarth A, Stange DE, van de Wetering M, Clevers H. OLFM4 is a robust marker for stem cells in human intestine and marks a subset of colorectal cancer cells. Gastroenterology. 2009;137(1):15–17. doi: 10.1053/j.gastro.2009.05.035.
123. Leedham SJ. MAP(K)ing the path to stem cell quiescence and the elusive enteroendocrine cell. Cell Stem Cell. 2017;20(2):153–154. doi: 10.1016/j.stem.2017.01.005.
124. Basak O, Beumer J, Wiebrands K, Seno H, van Oudenaarden A, Clevers H. Induced Quiescence of Lgr5+ stem cells in intestinal organoids enables differentiation of hormone-producing enteroendocrine cells. Cell Stem Cell. 2017;20(2):177–190e174. doi: 10.1016/j.stem.2016.11.001.
125. Buczacki SJ, Zecchini HI, Nicholson AM, Russell R, Vermeulen L, Kemp R, Winton DJ. Intestinal label-retaining cells are secretory precursors expressing Lgr5. Natur. 2013;495(7439):65–69. doi: 10.1038/nature11965.
126. Barriga FM, Montagni E, Mana M, Mendez-Lago M, Hernando-Momblona X, Sevillano M, Guillaumet-Adkins A, Rodriguez-Esteban G, Buczacki SJA, Gut M, et al. Mex3a marks a slowly dividing subpopulation of Lgr5+ intestinal stem cells. Cell Stem Cell. 2017;20(6):801–816e807. doi: 10.1016/j.stem.2017.02.007.
127. Yan KS, Chia LA, Li X, Ootani A, Su J, Lee JY, Su N, Luo Y, Heilshorn SC, Amieva MR, et al. The intestinal stem cell markers Bmi1 and Lgr5 identify two functionally distinct populations. Proc Natl Acad Sci U S A. 2012;109(2):466–471. doi: 10.1073/pnas.1118857109.
128. Tian H, Biehs B, Warming S, Leong KG, Rangell L, Klein OD, de Sauvage FJ. A reserve stem cell population in small intestine renders Lgr5-positive cells dispensable. Natur. 2011;478(7368):255–259. doi: 10.1038/nature10408.
129. Takeda N, Jain R, LeBoeuf MR, Wang Q, Lu MM, Epstein JA. Interconversion between intestinal stem cell populations in distinct niches. Science. 2011;334(6061):1420–1424. doi: 10.1126/science.1213214.
130. Montgomery RK, Carlone DL, Richmond CA, Farilla L, Kranendonk ME, Henderson DE, Baffour-Awuah NY, Ambruzs DM, Fogli LK, Algra S, et al. Mouse telomerase reverse transcriptase (mTert) expression marks slowly cycling intestinal stem cells. Proc Natl Acad Sci U S A. 2011;108(1):179–184. doi: 10.1073/pnas.1013004108.
131. Schneider C, O'Leary CE, Locksley RM. Regulation of immune responses by tuft cells. Nat Rev Immunol. 2019;19(9):584–593. doi: 10.1038/s41577-019-0176-x.
132. Huang L, Bernink JH, Giladi A, Krueger D, van Son GJF, Geurts MH, Busslinger G, Lin L, Begthel H, Zandvliet M, et al. Tuft cells act as regenerative stem cells in the human intestine. Natur. 2024;634(8035):929–935. doi: 10.1038/s41586-024-07952-6.
133. Yui S, Nakamura T, Sato T, Nemoto Y, Mizutani T, Zheng X, Ichinose S, Nagaishi T, Okamoto R, Tsuchiya K, et al. Functional engraftment of colon epithelium expanded in vitro from a single adult Lgr5(+) stem cell. Nat Med. 2012;18(4):618–623. doi: 10.1038/nm.2695.
134. Powell AE, Wang Y, Li Y, Poulin EJ, Means AL, Washington MK, Higginbotham JN, Juchheim A, Prasad N, Levy SE, et al. The pan-ErbB negative regulator Lrig1 is an intestinal stem cell marker that functions as a tumor suppressor. Cell. 2012;149(1):146–158. doi: 10.1016/j.cell.2012.02.042.
135. Zhu G, Hu J, Xi R. The cellular niche for intestinal stem cells: a team effort. Cell Regen. 2021;10(1):1. doi: 10.1186/s13619-020-00061-5.
136. Clevers H, Loh KM, Nusse R. Stem cell signaling. An integral program for tissue renewal and regeneration: Wnt signaling and stem cell control. Science. 2014;346(6205):1248012. doi: 10.1126/science.1248012.
137. Kim JE, Li B, Fei L, Horne R, Lee D, Loe AK, Miyake H, Ayar E, Kim DK, Surette MG, et al. Gut microbiota promotes stem cell differentiation through macrophage and mesenchymal niches in early postnatal development. Immunity. 2022;55(12):2300–2317. e2306. doi: 10.1016/j.immuni.2022.11.003.
138. Wu H, Mu C, Li X, Fan W, Shen L, Zhu W. Breed-driven microbiome heterogeneity regulates intestinal stem cell proliferation via lactobacillus-lactate-Gpr81 signaling. Adv Sci (Weinh). 2024;11(33):e2400058. doi: 10.1002/advs.202400058.
139. Demitrack ES, Samuelson LC. Notch regulation of gastrointestinal stem cells. J Physiol. 2016;594(17):4791–4803. doi: 10.1113/JP271667.
140. van Es JH, van Gijn ME, Riccio O, van den Born M, Vooijs M, Begthel H, Cozijnsen M, Robine S, Winton DJ, Radtke F, et al. Notch/gamma-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Natur. 2005;435(7044):959–963. doi: 10.1038/nature03659.
141. 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. Cell Rep. 2015;11(1):33–42. doi: 10.1016/j.celrep.2015.03.007.
142. Farhadipour M, Arnauts K, Clarysse M, Thijs T, Liszt K, Van der Schueren B, Ceulemans LJ, Deleus E, Lannoo M, Ferrante M, et al. SCFAs switch stem cell fate through HDAC inhibition to improve barrier integrity in 3D intestinal organoids from patients with obesity. iSci. 2023;26(12):108517. doi: 10.1016/j.isci.2023.108517.
143. Sato T, van Es JH, Snippert 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. Natur. 2011;469(7330):415–418. doi: 10.1038/nature09637.

144. Sato T, Vries T, Snippert RG, van de Wetering HJ, Barker M, Stange DE N, van Es JH, Abo A, Kujala P, Peters PJ, Sato T, et al. Single Lgr5 stem cells build crypt-villus structures in vitro without a mesenchymal niche. Natur. 2009;459(7244):262–265. doi: 10.1038/nature07935.
145. van Es JH, Jay P, Gregorieff A, van Gijn ME, Jonkheer S, Hatzis P, Thiele A, van den Born M, Begthel H, Brabletz T, et al. Wnt signalling induces maturation of Paneth cells in intestinal crypts. Nat Cell Biol. 2005;7(4):381–386. doi: 10.1038/ncb1240.
146. Farin HF, Van Es JH, Clevers H. Redundant sources of Wnt regulate intestinal stem cells and promote formation of Paneth cells. Gastroenterology. 2012;143(6):1518–1529. e1517. doi: 10.1053/j.gastro.2012.08.031.
147. Valenta T, Degirmenci B, Moor AE, Herr P, Zimmerli D, Moor MB, Hausmann G, Cantu C, Aguet M, Basler K. Wnt Ligands Secreted by Subepithelial Mesenchymal Cells Are Essential for the Survival of Intestinal Stem Cells and Gut Homeostasis. Cell Rep. 2016;15(5):911–918. doi: 10.1016/j.celrep.2016.03.088.
148. Zhu P, Zhu X, Wu J, He L, Lu T, Wang Y, Liu B, Ye B, Sun L, Fan D, et al. IL-13 secreted by ILC2s promotes the self-renewal of intestinal stem cells through circular RNA circPan3. Nat Immunol. 2019;20(2):183–194. doi: 10.1038/s41590-018-0297-6.
149. Lindemans CA, Calafiore M, Mertelsmann AM, O'Connor MH, Dudakov JA, Jenq RR, Velardi E, Young LF, Smith OM, Lawrence G, et al. Interleukin-22 promotes intestinal-stem-cell-mediated epithelial regeneration. Natur. 2015;528(7583):560–564. doi: 10.1038/nature16460.
150. Gaudino SJ, Beaupre M, Lin X, Joshi P, Rathi S, McLaughlin PA, Kempen C, Mehta N, Eskiocak O, Yueh B, et al. IL-22 receptor signaling in Paneth cells is critical for their maturation, microbiota colonization, Th17-related immune responses, and anti-Salmonella immunity. Mucosal Immunol. 2021;14(2):389–401. doi: 10.1038/s41385-020-00348-5.
151. Satoh-Takayama N, Kato T, Motomura Y, Kageyama T, Taguchi-Atarashi N, Kinoshita-Daitoku R, Kuroda E, Di Santo JP, Mimuro H, Moro K, et al. Bacteria-induced group 2 innate lymphoid cells in the stomach provide immune protection through induction of IgA. Immunity. 2020;52(4):635–649e634. doi: 10.1016/j.immuni.2020.03.002.
152. Elliott SN, Buret A, McKnight W, Miller MJ, Wallace JL. Bacteria rapidly colonize and modulate healing of gastric ulcers in rats. Am J Physiol. 1998;275(3):G425–432. doi: 10.1152/ajpgi.1998.275.3.G425.
153. Lam EK, Yu L, Wong HP, Wu WK, Shin VY, Tai EK, So WH, Woo PC, Cho CH. Probiotic Lactobacillus rhamnosus GG enhances gastric ulcer healing in rats. Eur J Pharmacol. 2007;565(1-3):171–179. doi: 10.1016/j.ejphar.2007.02.050.
154. Khoder G, Al-Menhali AA, Al-Yassir F, Karam SM. Potential role of probiotics in the management of gastric ulcer. Exp Ther Med. 2016;12(1):3–17. doi: 10.3892/etm.2016.3293.
155. Al-Yassir F, Khoder G, Sugathan S, Saseedharan P, Al Menhali A, Karam SM. Modulation of stem cell progeny by probiotics during regeneration of gastric mucosal erosions. Biology (Basel). 2021;10(7):596. doi: 10.3390/biology10070596.
156. Fung C, Tan S, Nakajima M, Skoog EC, Camarillo-Guerrero LF, Klein JA, Lawley TD, Solnick JV, Fukami T, Amieva MR. High-resolution mapping reveals that microniches in the gastric glands control Helicobacter pylori colonization of the stomach. PLoS Biol. 2019;17(5):e3000231. doi: 10.1371/journal.pbio.3000231.
157. Sigal M, Rothenberg ME, Logan CY, Lee JY, Honaker RW, Cooper RL, Passarelli B, Camorlinga M, Bouley DM, Alvarez G, et al. Helicobacter pylori activates and expands Lgr5(+) stem cells through direct colonization of the gastric glands. Gastroenterology. 2015;148(7):1392–1404e1321. doi: 10.1053/j.gastro.2015.02.049.
158. Sigal M, Reines MDM, Mullerke S, Fischer C, Kapalczynska M, Berger H, Bakker ERM, Mollenkopf HJ, Rothenberg ME, Wiedenmann B, et al. R-spondin-3 induces secretory, antimicrobial Lgr5(+) cells in the stomach. Nat Cell Biol. 2019;21(7):812–823. doi: 10.1038/s41556-019-0339-9.
159. Abrams GD, Bauer H, Sprinz H. Influence of the normal flora on mucosal morphology and cellular renewal in the ileum. A comparison of germ-free and conventional mice. Lab Invest. 1963;12:355–364.
160. Lesher S, Walburg HE, Jr., Sacher GA, Jr. Generation Cycle in the Duodenal Crypt Cells of Germ-Free and Conventional Mice. Natur. 1964;202:884–886. doi: 10.1038/202884a0.
161. Coutinho HB, da Mota HC, Coutinho VB, Robalinho TI, Furtado AF, Walker E, King G, Mahida YR, Sewell HF, Wakelin D. Absence of lysozyme (muramidase) in the intestinal Paneth cells of newborn infants with necrotising enterocolitis. J Clin Pathol. 1998;51(7):512–514. doi: 10.1136/jcp.51.7.512.
162. Lueschow SR, Stumphy J, Gong H, Kern SL, Elgin TG, Underwood MA, Kalanetra KM, Mills DA, Wong MH, Meyerholz DK, et al. Loss of murine Paneth cell function alters the immature intestinal microbiome and mimics changes seen in neonatal necrotizing enterocolitis. PLoS One. 2018;13(10):e0204967. doi: 10.1371/journal.pone.0204967.
163. White JR, Gong H, Pope B, Schlievert P, McElroy SJ. Paneth-cell-disruption-induced necrotizing enterocolitis in mice requires live bacteria and occurs independently of TLR4 signaling. Dis Model Mech. 2017;10(6):727–736. doi: 10.1242/dmm.028589.
164. Kang EJ, Kim JH, Kim YE, Lee H, Jung KB, Chang DH, Lee Y, Park S, Lee EY, Lee EJ, et al. The secreted protein Amuc_1409 from Akkermansia muciniphila improves gut health through intestinal stem cell regulation. Nat Commun. 2024;15(1):2983. doi: 10.1038/s41467-024-47275-8.

165. Lu X, Xie S, Ye L, Zhu L, Yu Q. Lactobacillus protects against s. typhimurium-induced intestinal inflammation by determining the fate of epithelial proliferation and differentiation. Mol Nutr Food Res. 2020;64(5):e1900655. doi: 10.1002/mnfr.201900655.
166. Pearce SC, Weber GJ, van Sambeek DM, Soares JW, Racicot K, Breault DT. Intestinal enteroids recapitulate the effects of short-chain fatty acids on the intestinal epithelium. PLoS One. 2020;15(4):e0230231. doi: 10.1371/journal.pone.0230231.
167. Duan C, Wu J, Wang Z, Tan C, Hou L, Qian W, Han C, Hou X. Fucose promotes intestinal stem cell-mediated intestinal epithelial development through promoting Akkermansia-related propanoate metabolism. Gut Microbes. 2023;15(1):2233149. doi: 10.1080/19490976.2023.2233149.
168. Xia Y, Liu C, Li R, Zheng M, Feng B, Gao J, Long X, Li L, Li S, Zuo X, et al. Lactobacillus-derived indole-3-lactic acid ameliorates colitis in cesarean-born offspring via activation of aryl hydrocarbon receptor. iSci. 2023;26(11):108279. doi: 10.1016/j.isci.2023.108279.
169. 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. Gastroenterology. 2020;159(3):956–968. e958. 10.1053/j.gastro.2020.05.067.
170. Xu J, Huang D, Xu X, Wu X, Liu L, Niu W, Lu L, Zhou H. An elevated deoxycholic acid level induced by high-fat feeding damages intestinal stem cells by reducing the ileal IL-22. Biochem Biophys Res Commun. 2021;579:153–160. doi: 10.1016/j.bbrc.2021.09.061.
171. Mao T, Xu X, Liu L, Wu Y, Wu X, Niu W, You D, Cai X, Lu L, Zhou H. ABL1–YAP1 axis in intestinal stem cell activated by deoxycholic acid contributes to hepatic steatosis. J Transl Med. 2024;22(1):1119. doi: 10.1186/s12967-024-05865-6.
172. Brandi G, Calabrese C, Tavolari S, Bridonneau C, Raibaud P, Liguori G, Thomas M, Di Battista M, Gaboriau-Routhiau V, Langella P. Intestinal microbiota increases cell proliferation of colonic mucosa in human-flora-associated (HFA) mice. Int J Mol Sci. 2024;25(11):6182. doi: 10.3390/ijms25116182.
173. 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. Cell Rep. 2021;35(1):108949. doi: 10.1016/j.celrep.2021.108949.
174. Powell DN, Swimm A, Sonowal R, Bretin A, Gewirtz AT, Jones RM, Kalman D. Indoles from the commensal microbiota act via the AHR and IL-10 to tune the cellular composition of the colonic epithelium during aging. Proc Natl Acad Sci U S A. 2020;117(35):21519–21526. doi: 10.1073/pnas.2003004117.
175. Luceri C, Femia AP, Fazi M, Di Martino C, Zolfanelli F, Dolara P, Tonelli F. Effect of butyrate enemas on gene expression profiles and endoscopic/histopathological scores of diverted colorectal mucosa: a randomized trial. Dig Liver Dis. 2016;48(1):27–33. doi: 10.1016/j.dld.2015.09.005.
176. Barker N, Ridgway RA, van Es JH, van de Wetering M, Begthel H, van den Born M, Danenberg E, Clarke AR, Sansom OJ, Clevers H. Crypt stem cells as the cells-of-origin of intestinal cancer. Natur. 2009;457(7229):608–611. doi: 10.1038/nature07602.
177. Schepers AG, Snippert HJ, Stange DE, van den Born M, van Es JH, van de Wetering M, Clevers H. Lineage tracing reveals Lgr5+ stem cell activity in mouse intestinal adenomas. Science. 2012;337(6095):730–735. doi: 10.1126/science.1224676.
178. Hayakawa Y, Nakagawa H, Rustgi AK, Que J, Wang TC. Stem cells and origins of cancer in the upper gastrointestinal tract. Cell Stem Cell. 2021;28(8):1343–1361. doi: 10.1016/j.stem.2021.05.012.
179. Kwon SK, Park JC, Kim KH, Yoon J, Cho Y, Lee B, Lee JJ, Jeong H, Oh Y, Kim SH, et al. Human gastric microbiota transplantation recapitulates premalignant lesions in germ-free mice. Gut. 2022;71(7):1266–1276. doi: 10.1136/gutjnl-2021-324489.
180. Fu K, Cheung AHK, Wong CC, Liu W, Zhou Y, Wang F, Huang P, Yuan K, Coker OO, Pan Y, et al. Streptococcus anginosus promotes gastric inflammation, atrophy, and tumorigenesis in mice. Cell. 2024;187(4):882–896e817. doi: 10.1016/j.cell.2024.01.004.
181. Xian W, Duleba M, Zhang Y, Yamamoto Y, Ho KY, Crum C, McKeon F. The cellular origin of barrett's esophagus and its stem cells. Adv Exp Med Biol. Vol. 11232019; p. 55–69. doi: 10.1007/978-3-030-11096-3_5.
182. Deshpande NP, Riordan SM, Gorman CJ, Nielsen S, Russell TL, Correa-Ospina C, Fernando BSM, Waters SA, Castano-Rodriguez N, Man SM, et al. Multi-omics of the esophageal microenvironment identifies signatures associated with progression of Barrett's esophagus. Genome Med. 2021;13(1):133. doi: 10.1186/s13073-021-00951-6.
183. Liu X, Li B, Liang L, Han J, Mai S, Liu L. From microbes to medicine: harnessing the power of the microbiome in esophageal cancer. Front Immunol. 2024;15:1450927. doi: 10.3389/fimmu.2024.1450927.
184. 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. Immunity. 2018;49(2):353–362. e355. doi: 10.1016/j.immuni.2018.07.010.
185. Zhang W, Qin X, Zhang K, Ma J, Li M, Jin G, Liu X, Wang S, Wang B, Wu J, et al. Microbial metabolite trimethylamine-N-oxide induces intestinal carcinogenesis through inhibiting farnesoid X receptor signaling. Cell Oncol (Dordr). 2024;47(4):1183–1199. doi: 10.1007/s13402-024-00920-2.
186. Yang S, Dai H, Lu Y, Li R, Gao C, Pan S. Trimethylamine N-oxide promotes cell proliferation and angiogenesis in colorectal cancer. J Immunol Res. 2022;2022:7043856. doi: 10.1155/2022/7043856.

187. Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, van Hoeck A, Wood HM, Nomburg J, Gurjao C, Manders F, Dalmasso G, Stege PB, et al. Mutational signature in colorectal cancer caused by genotoxic pks(+) E. coli. Natur. 2020;580(7802):269–273. doi: 10.1038/s41586-020-2080-8.
188. Bernstein H, Bernstein C, Payne CM, Dvorakova K, Garewal H. Bile acids as carcinogens in human gastrointestinal cancers. Mutat Res. 2005;589(1):47–65. doi: 10.1016/j.mrrev.2004.08.001.
189. Yang R, Qian L. Research on gut microbiota-derived secondary bile acids in cancer progression. Integr Cancer Ther. 2022;21:15347354221114100. doi: 10.1177/15347354221114100.
190. Hou Y, Wei W, Guan X, Liu Y, Bian G, He D, Fan Q, Cai X, Zhang Y, Wang G, et al. A diet-microbial metabolism feedforward loop modulates intestinal stem cell renewal in the stressed gut. Nat Commun. 2021;12(1):271. doi: 10.1038/s41467-020-20673-4.