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Review Article

Mechanistic Basis of the Microbiome-Stem Cell Axis in Aging and Regeneration

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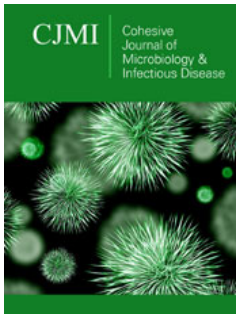

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Abstract

Stem cells and the microbiome coexist in interdependent systems essential for tissue development, regeneration and homeostasis. Dysbiosis and aging both interfere with the stem cell-microbiome axis, resulting in stem cell depletion and tissue degeneration. This short review elucidates the mechanistic basis of microbiome-stem cell interactions, describing how microbial metabolites-such as short-chain fatty acids, bile acids, vitamins and tryptophan derivatives-influence stem cell quiescence and regulate proliferation, differentiation and epigenetic programming through nutrient-sensing pathways, including AMPK-mTOR, NAD^+/SIRT1 and FXR/TGR5. New research shows that bringing microbial balance back or adding microbiome-and metabolite-based factors can make old stem cells younger and improve the ability of an organ to regenerate in a specific way. Taken together, targeting the microbiome-stem cell axis is a new and promising way to improve healthspan and slow down the effects of aging. This review offers an integrative synthesis of mechanistic and metabolic perspectives, highlighting opportunities for precision regenerative and microbiome-based interventions to promote healthy aging.

Keywords: Microbiome stem cells; Aging regeneration; Dysbiosis; Short-chain fatty acids; Epigenetics; Healthspan; Personalized healthcare

Introduction

Stem cells and the microbiome represent two interdependent systems that are central to tissue development, regeneration and homeostasis [1,2]. Investigations into their interaction have revealed mechanisms through which microbial signals modulate stem cell behaviour and, conversely, how stem cells contribute to maintaining niches that support microbial communities [3,4]. Microbial colonization is shaped by perinatal factors, including delivery mode, maternal and infant antibiotic exposure, breastfeeding, nutrition and environmental cues, whereas stem cells progress from pluripotent precursors to lineage-restricted progenitors, exhibiting age-dependent declines in regenerative capacity [5-7].

Metabolites produced by the microbiota, including Short-Chain Fatty Acids (SCFAs), vitamins and tryptophan derivatives, influence chromatin architecture, nutrient sensing, mitochondrial function, autophagy and immune signalling in stem cells [8-10]. Examples of such bidirectional communication are evident in the Gut-Brain Axis (GBA), where microbial metabolites regulate Neural Stem Cell (NSC) proliferation, neurogenesis and synaptic plasticity, while the Enteric Nervous System (ENS) modulates Intestinal Stem Cell (ISC) function [10,11]. These interactions become perturbed during aging and dysbiosis, leading to stem cell exhaustion and consequent tissue degeneration [12,13]. Elucidating these mechanistic pathways provides new opportunities for developing therapeutic interventions that target the microbiome to enhance stem cell-based regeneration and promote healthy aging.

Developmental Intersections of Microbiota and Stem Cells

Birth initiates rapid microbial colonization influenced by the mode of delivery, antibiotic exposure and nutrition [5-7]. Ecological microbial exposures provide critical signals that epigenetically program stem cells [14,15]. In Germ-Free (GF) mice, recolonization with metabolically active microbes such as Akkermansia muciniphila restores epigenetic and immune regulation; conversely, limited microbial exposure impairs the maturation of these stem cells [16,17]. The early gut microbiota is dominated by the families Enterococcaceae, Clostridiaceae, Lactobacillaceae, Bifidobacteriaceae and Streptococcaceae [18]. Human Milk Oligosaccharides (HMOs) in breast milk promote the growth of Bifidobacterium species, while the introduction of solid foods favors the establishment of Bacteroides, Ruminococcus and Clostridium species [19,20]. By approximately two to three years of age, the microbiota assumes an adult-like configuration, coinciding with the maturation of Hematopoietic Stem Cells (HSCs), Mesenchymal Stem Cells (MSCs), NSCs and ISCs [21,22]. Importantly, microbial metabolites such as acetate, propionate and butyrate influence stem cell proliferation, differentiation and gene expression. Butyrate functions as a Histone Deacetylase inhibitor (HDACi), directly linking microbial activity with chromatin modification [23,24]. Such early-life interactions establish the foundation for immune competence, metabolic regulation, neurodevelopment and the long-term functionality of stem cells [25,26].

Dysregulation of the Microbiome-Stem Cell Axis Across the Lifespan

The gut microbiome maintains hematopoietic and immune homeostasis through its metabolites and microbial ligands. During aging, reduced microbial diversity, increased gut permeability and chronic low-grade inflammation collectively impair the maintenance and function of Hematopoietic Stem Cells (HSCs) [27,28]. In GF or antibiotic-treated mice, depletion of the microbiota leads to a reduction in Hematopoietic Stem and Progenitor Cells (HSPCs) [29,30]. Reintroduction of the microbiota or specific microbial ligands, such as Nucleotide-Binding Oligomerization Domain-Containing Protein 1 (NOD1) agonists, restores HSPC proliferation [31,32]. Persistent inflammation skews hematopoiesis toward myeloid lineages, contributing to immune aging [33]. NSCs are similarly influenced through the GBA, as Short-Chain Fatty Acids (SCFAs) cross the blood-brain barrier to promote neurogenesis, mitochondrial activity and neuronal differentiation [34,35]. Dysbiosis disrupts these processes, whereas microbial restoration rejuvenates stem cell function [36,37].

Nutrient Sensing as a Mechanistic Link

Nutrient-sensing pathways, including glucose, lipid and amino acid sensors, are integrated in the regulation of stem cell quiescence, proliferation and differentiation [38,39]. Glucose sensing depends on glucose transporters and glycolytic enzymes, while lipid-sensing mechanisms involve Liver X Receptors (LXRs) and Peroxisome Proliferator-Activated Receptors (PPARs) [40]. Amino acid sensing, particularly of leucine, modulates mechanistic Target of Rapamycin Complex 1 (mTORC1) activity through Sestrin2 and leucyl-tRNA synthetase 1 [41]. These metabolic signals are further amplified by the microbiota through the production of SCFAs, B vitamins and tryptophan metabolites. SCFAs provide an energy source for colonocytes, inhibit Histone Deacetylase (HDAC) activity and stimulate the renewal of Intestinal Stem Cells (ISCs) [42]. Vitamins B2, B9 and B12 support mitochondrial function, nucleotide synthesis and DNA methylation, whereas tryptophan-derived ligands activate Aryl hydrocarbon Receptor (AhR)-dependent pathways that maintain immune and stem cell homeostasis [43,44]. This mechanistic integration ensures coordinated metabolic, immune and regenerative responses.

Microbial Metabolites Directly Modulate Stem Cell Function

Metabolites derived from the microbiota, including SCFAs, bile acids, tryptophan derivatives, vitamins and polyamines, are key regulators of stem cell activity. Gut microbes convert primary bile acids such as cholate and chenodeoxycholate into secondary bile acids, including Deoxycholic Acid (DCA) and Lithocholic Acid (LCA) [45,46]. DCA and LCA regulate the proliferation of both HSCs and ISCs through their receptors, Farnesoid X Receptor (FXR) and G-protein-coupled bile acid receptor 1 (TGR5) [47,48]. Tryptophan-derived indoles, including Indole-3-Acetic Acid (IAA), Indole-3-Propionic Acid (IPA) and Indole-3-Lactic Acid (ILA), activate the Aryl hydrocarbon Receptor (AhR) and Pregnane X Receptor (PXR), maintaining stem cell quiescence and promoting differentiation [49,50]. Microbiome-synthesized vitamins-B2, B9, B12 and niacin-support Nicotinamide Adenine Dinucleotide (NAD^+) metabolism, epigenetic modifications and energy balance. Polyamines, such as spermidine, spermine and putrescine, enhance autophagy, mitochondrial function and stem cell renewal [51,52]. Collectively, these metabolites coordinate proliferation, differentiation, immune regulation and tissue repair across stem cell niches (Table 1). Summarizes key gut microbial metabolites and their regulatory effects on intestinal stem cells, outlining the underlying mechanisms of action and the experimental models employed to elucidate these interactions.

Table 1: Gut microbial metabolites regulating intestinal stem cells: Effects, mechanisms and experimental models. Note: SCFA: Short-Chain Fatty Acid, ISC: Intestinal Stem Cell, LGR5: Leucine-Rich Repeat-Containing G-Protein Coupled Receptor 5, OLFM4: Olfactomedin 4, GPR41 / GPR43: G-Protein Coupled Receptor 41 and 43 (SCFA receptors), HDACs: Histone Deacetylases, FOXO3: Forehead Box O3, AHR: Aryl Hydrocarbon Receptor, ILC3s: Type 3 Innate Lymphoid Cells, IL-22: Interleukin-22, STAT3: Signal Transducer and Activator of Transcription 3, M3R: Muscarinic Acetylcholine Receptor M3, TGR5: Takeda G-Protein-Coupled Receptor 5, FXR: Foresaid X Receptor, T-βMCA: Tauro-β-Muricholic Acid, Wnt (Wingless/Integrated)/β-catenin signalling.

Metabolite	Source	Effects of ISCs	Mechanism of Action	Model/System
Acetate	Generated by gut microbiota (SCFA)	Encourages the development, expansion and budding of intestinal organoids.	Blocks β-oxidation when levels of intracellular acetyl-CoA drop, directing metabolism toward anabolic processes.	Intestinal organoids from mice
Propionate	Generated by gut microbiota and amplified by fucose and *Akkermansia.*	Reverses damage caused by chemicals and reinstates ISC markers (LGR5 and OLFM4).	Stimulates the signaling pathways of GPR41 and GPR43.	Intestinal organoids from mice
Butyrate (Pro-proliferative)	Produced by gut microbiota (SCFA)	Enhances the quantity of Lgr5-positive intestinal stem cells.	Blocks histone deacetylases (HDACs), enhancing the proliferation of stem cells.	Organoids from the small intestine of mice
Butyrate (Anti-proliferative)	Produced by gut microbiota (SCFA)	Inhibits the growth of colonic stem cells.	Functions through transcriptional regulation reliant on FOXO3 at physiological levels.	Colon (*in vivo*)
Lactate	Originating from intestinal microbiota and lactic acid bacteria.	Promotes the growth of epithelial cells and enlarges the size of crypts.	Promotes the proliferation of intestinal stem cells via Wnt/β-catenin signaling.	Cecum of rats, mice that have been starved and then refed
Succinate	Produced by gut bacteria	Suppresses the proliferation of colonic cells, decreases the size of crypts and diminishes barrier integrity.	Causes the production of superoxide and interferes with mucosal blood circulation.	Mice, rats, pigs
Indoleacetic acid	Tryptophan metabolite produced by gut microbiota	Inhibits the growth of ISCs.	Suppresses β-catenin signaling by activating AHR	Mouse model
Indole-3-carbinol	Tryptophan metabolite produced by microbiota	Encourages the specialization of ISCs into secretory lineages.	Activates Wnt/β-catenin signaling and inhibits Notch signaling in a manner that relies on AHR.	Mouse model
Indole-3-aldehyde	Generated by *Lactobacillus species*	Promotes the continued growth of ISCs during times of stress or following an injury.	Activates ILC3s using AHR ligands to produce IL-22, thereby maintaining ISC function through STAT3 signaling.	Mouse model
Deoxycholic acid (DCA)	Secondary bile acid from microbial metabolism	Increases cancer-like stem cell characteristics in colonic epithelial cells.	Triggers the activation of the muscarinic receptor M3R and promotes Wnt/β-catenin signaling.	Human colon cancer cells
Lithocholic acid (LCA)	Secondary bile acid	Comparable impact to DCA in enhancing cancer stemness.	Similar process involving M3R and Wnt/β-catenin signaling.	Human colon cancer cells
Physiological bile acids	Bile acids at normal systemic levels	Encourage the regeneration and healing of ISCs after tissue injury.	Stimulate the bile acid receptor TGR5.	Mouse model
T-βMCA and DCA (at high levels)	Specific bile acid species	Stimulate abnormal ISCs growth and genetic harm in Lgr5-positive cells.	Suppress intestinal FXR signaling, which typically limits proliferation.	Mouse intestinal organoids
Fucose	Dietary sugars processed by intestinal bacteria	Promotes epithelial proliferation	Boosts the production of propionate mediated by *Akkermansia*, which in turn activates GPR41 and GPR43.	Mouse model

Tissue-Specific Mechanisms

Intestinal stem cells

Wnt (wingless-related integration site), β-catenin, Notch and Mechanistic Target of Rapamycin (mTOR) pathways mediate the integration of microbial signals in ISCs [53]. Proliferation and epithelial repair are enhanced by lactic acid-producing bacteria, including Bifidobacterium and Lactobacillus species, through G-Protein-Coupled Receptor 81 (GPR81) and Succinate Receptor 1 (SUCNR1) signalling [54]. Indole derivatives activate the AhR to

promote ISC renewal and maintain barrier integrity. Secondary bile acids further modulate FXR and TGR5 signaling, thereby influencing ISC activity [55,56].

Hematopoietic stem cells

HSCs depend on bone marrow niches modulated by microbial metabolites. SCFAs and tryptophan derivatives maintain quiescence and differentiation [57]. Dysbiosis increases Lipopolysaccharide (LPS) levels, leading to inflammatory induction that biases hematopoiesis toward myeloid lineages [58]. Reconstitution of the microbiome rejuvenated HSCs through the activation of AhR, reduction in oxidative stress and improvement in mitochondrial function [59].

Mesenchymal stem cells

MSCs are responsive to amino acids, fatty acids and micronutrients that modulate pathways such as mTORC1, AMP-activated protein Kinase (AMPK) and NAD^+-dependent deacetylase sirtuin-1 (SIRT1) [60]. SCFAs promote osteogenesis, immune modulation and chromatin remodeling, while MSCs, in turn, support beneficial microbial communities, forming a feedback loop that maintains systemic homeostasis [60,61].

Neural stem cells

SCFAs and tryptophan derivatives modulate the activity of NSCs by influencing mitochondrial activity, the balance of Reactive Oxygen Species (ROS), neurogenesis and synaptic plasticity [62,63]. The microbiota-driven modulation of Brain-Derived Neurotrophic Factor (BDNF) and the maturation of microglia are essential for the maintenance of neurogenic niches and cognitive functions [64,65].

Core Mechanistic Pathways

Microbiota-derived metabolic products regulate energy metabolism, quiescence and epigenetic programming in stem cells through interconnected signaling axes. SCFAs directly activate AMPK, promoting fatty acid oxidation and maintaining stem cell quiescence, while bile acids enhance FXR-and TGR5-dependent AMPK activation, integrating microbial and metabolic signaling with nutrient sensing and cellular energy balance [66]. SCFAs and vitamins elevate NAD^+ levels to activate SIRT1, which governs chromatin remodeling, mitochondrial function and stress resilience-thereby rejuvenating aged stem cells and linking microbial metabolism to epigenetic regulation [67-69]. Collectively, microbial metabolites such as SCFAs, tryptophan derivatives and B vitamins modulate histone acetylation, DNA methylation and noncoding RNA networks that determine stem cell fate, whereas host epigenetic states reciprocally shape microbial communities, establishing a bidirectional microbiome-epigenome-metabolism regulatory circuit that sustains tissue homeostasis and regenerative capacity [70,71].

Future Directions

The integration of multi-omics approaches encompassing transcriptomics, epigenomics, metabolomics and spatial proteomics provides a powerful framework to delineate the mechanistic interactions between the microbiome and stem cells across developmental, adult and aging stages [72]. This strategy enables the identification of key microbial species and metabolites that regulate stem cell maintenance, differentiation and function, thereby informing targeted interventions to preserve tissue homeostasis and regenerative capacity. Harnessing the microbiome-stem cell interplay holds significant potential to enhance healthspan and mitigate age-related diseases. Therapeutically modulating microbial composition or administering specific metabolites, such as SCFAs, B vitamins and tryptophan derivatives, confers protective effects against stem cell exhaustion, chronic inflammation and organ dysfunction. Precision probiotics, postbiotics and engineered microbial therapeutics, used in conjunction with pharmacological targeting of AMPK-mTOR, NAD^+/SIRT1, HDAC and DNA Methyltransferase (DNMT) pathways, may rejuvenate the stem cell compartment while minimizing oncogenic risk.

Furthermore, longitudinal studies integrating microbial profiling with metabolite analyses and functional stem cell assessments could facilitate personalized regenerative strategies tailored to the unique microbiome and stem cell landscape of each individual. Moreover, the microbiome-stem cell axis has critical implications for organ-specific aging clocks [73]. Stem cell function and regenerative potential are central determinants of an organism's biological age and microbial metabolites, including SCFAs, bile acids, vitamins and tryptophan derivatives, directly influence core aspects of stem cell biology, such as quiescence, proliferation, differentiation and epigenetic programming. Dysbiosis accelerates organ aging by impairing stem cell function, heightening inflammation and reducing tissue repair, whereas restoration of microbial balance or supplementation with key metabolites promotes stem cell rejuvenation and delays organ-specific aging. Incorporating microbial composition and metabolite profiles into aging clocks could further enhance predictive accuracy, guide personalized interventions and monitor therapeutic efficacy, thereby directly linking microbial health to tissue-specific biological age and healthspan. Collectively, these mechanistic insights provide a conceptual and translational roadmap for developing microbiome-stem cell-based therapies aimed at restoring tissue function, maintaining organ health and promoting healthy aging, representing a paradigm shift toward preventive and personalized healthcare in aging populations.

Conclusion

The microbiome-stem cell axis serves as a pivotal regulator of tissue development, regeneration and aging, with microbial metabolites such as SCFAs, bile acids, vitamins and tryptophan derivatives modulating stem cell quiescence, proliferation, differentiation and epigenetic programming across diverse tissues. Dysbiosis accelerates stem cell exhaustion and organ-specific aging, whereas restoration of microbial balance or supplementation with key metabolites can rejuvenate stem cells and enhance regenerative capacity, thereby potentially slowing biological aging. These mechanistic insights provide a foundation

for developing interventions aimed at preserving stem cell function, maintaining tissue homeostasis and extending healthspan. Integrating microbiome profiles and stem cell functional readouts into organ-specific aging clocks could improve the precision of biological age prediction, guide personalized therapeutic strategies and enable monitoring of regenerative or microbiome-targeted interventions. Harnessing the microbiome-stem cell axis through microbial modulation, targeted metabolite administration and manipulation of epigenetic or nutrient-sensing pathways offers a promising avenue for preventing age-related diseases, restoring tissue function and promoting healthy aging, thereby representing a paradigm shift in precision regenerative medicine.

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