Research Progress on the Regulation of Intestinal Stem Cell Function by Energy Metabolism and Preliminary Exploration of Traditional Chinese Medicine Therapeutic Advantages: Postprint

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Abstract

Intestinal stem cells constitute a crucial component in maintaining the stability of intestinal barrier function and are intimately associated with intestinal homeostasis, intestinal epithelial renewal, and the repair of intestinal injury. Normal human physiological activities fundamentally depend on energy intake and metabolism; energy metabolism influences the differentiation fate of stem cells; and impairment of the intestinal barrier is implicated in the pathogenesis and progression of various intestinal diseases. Therefore, this article centers on intestinal stem cells, against the backdrop of energy metabolism and metabolites, to investigate how energy metabolism and metabolites regulate stem cell function and activity, thereby modulating intestinal barrier function to provide therapeutic insights for multiple intestinal diseases. Furthermore, as modern medical research on intestinal barrier protection deepens, the traditional Chinese medicine theory emphasizing the care and protection of the spleen and stomach is gradually demonstrating its scientific validity, aiming to provide directions for subsequent research.

Full Text

Advances in Energy Metabolism Regulation of Intestinal Stem Cell Function and Preliminary Exploration of Traditional Chinese Medicine Therapeutic Advantages

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Abstract

Intestinal stem cells (ISCs) are crucial for maintaining intestinal barrier function stability and are closely associated with intestinal homeostasis, epithelial renewal, and damage repair. Normal physiological activities depend on energy intake and metabolism, which influence stem cell differentiation fate. Impaired intestinal barrier function is implicated in the pathogenesis of numerous intestinal diseases. This review focuses on ISCs against the backdrop of energy metabolism and metabolites, exploring how these factors regulate ISC function and activity to modulate intestinal barrier function, thereby providing insights for treating various intestinal diseases. Furthermore, as modern medical research on intestinal barrier protection deepens, the traditional Chinese medicine (TCM) theory of "protecting the spleen and stomach" is increasingly demonstrating scientific validity, offering new perspectives for future research.

Keywords: Intestinal stem cells; Energy metabolism; Intestinal diseases; Chinese medicine; Review

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The intestinal barrier comprises three components: physical, immune, and microbial, which function to separate the intestinal lumen from the body, dynamically regulate intraluminal balance, and prevent pathogen invasion. Accumulating evidence demonstrates that intestinal diseases are associated with intestinal barrier dysfunction, including irritable bowel syndrome [1], inflammatory bowel disease (ulcerative colitis, Crohn' s disease) [2], and intestinal tumors [3]. Additionally, numerous extraintestinal diseases such as multiple sclerosis [4], cardiovascular disease [5], and autoimmune diseases [6] have been linked to intestinal barrier dysfunction. Intestinal epithelial cells, with a renewal cycle of 3-5 days, constitute a vital component of the barrier, and their renewal depends on the normal proliferation and differentiation of intestinal stem cells (ISCs). Two types of ISCs reside in the intestinal crypts: leucine-rich repeat-containing G-protein coupled receptor 5-positive crypt base columnar cells (Lgr5+ CBCs) and reserve stem cells (RSCs). Under normal conditions, Lgr5+ ISCs continuously maintain epithelial renewal, whereas upon intestinal injury, radiation-resistant RSCs can replenish the cycling CBC pool [7] to preserve intestinal homeostasis. A *Gastroenterology* study confirmed the quiescent nature of human Lgr5+ ISCs [8]. Nevertheless, ISCs can differentiate into various cell types, including Paneth cells, absorptive enterocytes, and enteroendocrine cells, and single Lgr5+ ISCs can form intestinal organoids in vitro [9], collectively demonstrating their robust

stemness.

Energy metabolism sustains life activities, with metabolic pathways and products participating in cell proliferation and differentiation while serving as signaling molecules that regulate cellular signaling cascades.

1. Regulation of Intestinal Stem Cell Stemness and Function by Energy Metabolism

1.1 Appropriate Energy Metabolites Promote Intestinal Stem Cell Proliferation and Differentiation

Fatty acid (FA) metabolism can promote intestinal stem cell self-renewal. A *Nature* study using in situ hybridization for the Lgr5+ ISC marker Olfm4 revealed that mice on a high-fat diet (60% fat content) exhibited a 50% increase in Olfm4+ ISCs. Additionally, intestinal organoids derived from these mice showed lower structural differentiation and higher Lgr5+ ISC frequency [15]. Another study demonstrated that inhibiting fatty acid oxidation with Etomoxir in intestinal organoids caused a dramatic downregulation of Lgr5+ stem cells and their marker transcription levels (including Lgr5, Olfm4, Smoc2, Msi1, and Ascl2) [16]. Furthermore, FA metabolism can drive tumor development by enhancing lipid synthesis, storage, and catabolism. A *Cell* study found that the combination of high-fat diet and Wnt signaling dysregulation altered the intestinal bile acid profile, driving malignant transformation of Lgr5+ cancer stem cells and promoting colorectal cancer progression [17]. Collectively, excessive fat intake exerts substantial pressure and stimulation on the gastrointestinal tract, potentially contributing to certain intestinal diseases through overproduction of fatty acids. However, as an indispensable nutrient and energy source, appropriate fat intake can enhance stem cell vitality, function, and stemness, benefiting disease treatment and prevention.

Bile acids (BAs) circulate between the liver and intestine to maintain adequate and appropriate concentrations [18], and their metabolism drives ISC renewal, proliferation, and regeneration. Farnesoid X receptor (FXR) serves as a crucial regulator of BA metabolism, maintaining dynamic BA homeostasis. To investigate whether FXR modulates ISC proliferation, Fu et al. [17] treated colon cancer model-derived organoids with three different FXR agonists and a chemotherapeutic agent, all of which downregulated ISC gene expression, thereby inhibiting proliferation. In addition to FXR, G protein-coupled bile acid receptor 1 (GPBAR1, TGR5) represents another important BA metabolism regulator. Experimental evidence demonstrates that BAs promote ISC renewal, intestinal epithelial differentiation, and post-injury regeneration via TGR5 activation to maintain intestinal barrier stability [19]. To explore the relationship between BA metabolism and barrier damage, a study using DSS-induced colitis in mice observed significant intestinal injury on day 1 of DSS induction, accompanied by rising cholic acid (CA) concentrations. CA accumulation caused Lgr5+ ISC depletion, which gradually normalized after DSS withdrawal [20]. These findings

underscore the close relationship between ISC function and intestinal barrier integrity, wherein any dysregulation in BA metabolism can alter ISC function or cause ISC loss, consequently impairing barrier function.

Lactate, a glycolysis byproduct, was previously considered a waste product of anaerobic metabolism harmful to the body. However, emerging research identifies lactate as a crucial regulator of systemic metabolism involved in diverse physiological and pathological processes [21]. Most mammalian cells produce substantial lactate even under aerobic conditions. Beyond the tricarboxylic acid (TCA) cycle, lactate metabolism involves urine, feces, and various metabolic enzymes including glycolytic enzymes, monocarboxylate transporters, lactate dehydrogenase, mitochondrial pyruvate carrier, and pyruvate dehydrogenase [22]. Lee et al. [23] demonstrated that lactate treatment increased Lgr5+ ISC numbers, Paneth cell expression, and intestinal organoid growth on days 3 and 5 of culture via the Wnt3/β-catenin pathway. Intestinal lactate production depends on gut microbiota. Leveraging the high similarity between Drosophila and human intestines [24], one study examined *Lactobacillus plantarum* in the Drosophila gut, finding that microbe-derived lactate triggered intestinal damage and stimulated ISC proliferation [25]. As understanding of lactate evolves, it is now recognized not as metabolic waste but as an important metabolite participating in multiple physiological processes. In addition to microbiota-derived lactate, Paneth cells can also produce lactate, influencing neighboring ISC function.

1.2 Energy Metabolism Influences Intestinal Stem Cell Fate Determination

Mitochondria exert broad influence on stem cell function and activity, playing pivotal roles in stem cell activation, fate determination, and aging [26]. One study found that knockout of the metabolic regulator FoxO factor in intestinal organoids followed by bioenergetic analysis revealed reduced mitochondrial respiration, decreased basal glycolysis, and mitochondria displaying both fused and fragmented morphologies [27]. Researchers demonstrated that induced overexpression of miR-484 could partially rescue these mitochondrial functional and morphological defects, suggesting that miR-484 and FoxO factors may constitute a signaling-metabolic axis that modulates stem cell function and activity by regulating mitochondrial status. Earlier research directly established that mitochondrial metabolic regulation correlates with ISC survival [28]. While metabolism was long considered merely a consequence of life activities, current research posits that metabolism itself can determine cellular phenotype and control stem cell fate [29]. Stem cell differentiation and proliferation involve increased oxygen consumption and energy expenditure, processes that depend on mitochondrial function. Therefore, mitochondrial metabolism can regulate ISC function.

Pyruvate serves as a critical hub for glucose metabolism and interconversion of various substances in all living cells. Bensard et al. [30] discovered that during

intestinal tumorigenesis, pyruvate metabolism emerges in early adenomas, preceding the establishment of ischemic tumor microenvironments and correlating with ISC overproliferation. This study also demonstrated that colorectal cancer development associates with downregulation of the mitochondrial pyruvate carrier (MPC), and MPC1 loss promotes colorectal carcinogenesis. MPC1 and MPC2 exhibit low expression in stem cells but increase during differentiation [31], indicating reduced mitochondrial pyruvate oxidation in proliferating cells like stem cells and tumor cells, whereas non-proliferating cells show increased oxidation. Further investigation of MPC function in Drosophila ISCs revealed the lowest expression among all four intestinal cell types in ISCs and the highest in enteroendocrine cells. Beyond intestinal tumors, MPC1 is downregulated in various malignancies including renal, lung, and brain cancers, but not in hematological malignancies like leukemia and lymphoma [32]. Since tumor development involves abnormal stem cell proliferation, these findings establish that pyruvate metabolism correlates with stem cell proliferative capacity and can, under certain conditions, drive pathological proliferation and disease progression.

2. Regulation of Intestinal Stem Cells by Gut Microbiota Metabolites

The intestine represents the primary site for energy absorption and metabolism, and coexisting gut microbiota play essential roles in food digestion and absorption, not only assisting in energy nutrient uptake but also participating in various intestinal physiological and pathological processes. Gut microbiota metabolites can act on the ISC microenvironment and are also implicated in multiple extraintestinal diseases [33]. 5-HT secretion has been closely linked to intestinal diseases [34], with tryptophan as its upstream precursor. Tryptophan is an essential aromatic amino acid that, besides 5-HT, can be converted into indole metabolites through microbial mediation. While no studies have directly demonstrated that indole metabolites regulate ISC stemness, related ligands can inhibit Notch1 signaling to stimulate ISC differentiation [35]. Xing et al. [36] reviewed how common gut microbiota metabolites affect ISC function, revealing that most short-chain fatty acids, lactate, indole-3-aldehyde (IAld), polyamines, low-dose secondary bile acids, and muramyl dipeptide promote ISC proliferation, whereas succinate, indole-3-acetic acid (IAA), high-dose secondary bile acids, and lipopolysaccharide (LPS) inhibit it. Hydrogen sulfide exhibits both proliferative and anti-proliferative effects, with the conditions for each effect remaining unclear but potentially related to exposure duration.

Valeric acid (VA), a gut microbiota metabolite, can promote 5-HT production by intestinal serotonergic neurons to regulate ISC proliferation and differentiation [37]. Observations in germ-free mice revealed reduced ISC numbers, and subsequent treatment with absorbable metabolites showed that VA could promote tryptophan hydroxylase 2 (Tph2) expression, thereby enhancing ISC self-renewal. The mechanism involves VA inhibiting NuRD complex enrichment at the Tph2 promoter, which is suppressed in germ-free mice, thereby restoring

ISC numbers. The symbiotic relationship between gut microbiota and humans is self-evident. Beyond the aforementioned metabolites, many unexplored microbiota metabolites participate not only in intestinal absorption but also regulate ISC proliferation, maintain epithelial integrity, and function as chemical barriers through secreted factors, thereby improving intestinal barrier function through multiple mechanisms.

3. Intestinal Stem Cells and Inflammatory Bowel Disease Treatment: Advantages of Traditional Chinese Medicine

A key pathological feature of inflammatory bowel disease (IBD) is intestinal barrier damage. Current IBD therapies primarily target immune suppression by blocking specific inflammatory cytokines, which carries risks of infection and tumorigenesis. Barrier repair depends on ISC proliferation, prompting researchers to propose direct regenerative stem cell therapy. Hematopoietic stem cells and mesenchymal stem cells have proven effective for IBD treatment [38], restoring barrier function. Studies have shown that transplanting stem cell-derived organoids into colitis models induces crypt regeneration and barrier reconstruction [39]. Culturing stem cells into new tissue for transplantation to damaged mucosal regions represents a novel therapeutic approach. However, as discussed earlier, abnormal ISC proliferation may lead to intestinal tumors, and whether organoid transplantation or ISC regenerative therapy carries tumorigenic risks remains unclear and requires further investigation.

Traditional Chinese Medicine (TCM) does not have a unified disease name for IBD. Based on symptom characteristics, IBD can be classified under "intestinal flux," "abdominal pain," or "diarrhea" in TCM theory, with the disease location in the large intestine and pathogenesis closely related to the liver, spleen, lung, and kidney. During disease progression, "dampness, heat, and stasis" serve as both pathological factors and products, intertwining to cause damp-heat accumulation and intestinal stasis, with deficiency and excess coexisting and creating a protracted condition. TCM emphasizes syndrome differentiation and treatment, prescribing formulas according to disease stage and symptoms, which aligns better with individualized therapy. IBD requires long-term treatment with recurrent symptoms, necessitating safe, effective, and compliance-enhancing therapeutic options. TCM offers clear advantages in being simple, convenient, economical, and effective. Advancing research technologies have provided increasing evidence that active herbal components can regulate ISC-related pathways through different targets. The Wnt and Notch signaling pathways are particularly important in intestinal diseases. For example, in trinitrobenzene sulfonic acid-treated mice, *Astragalus membranaceus* extract astragaloside IV stimulated ISC proliferation via Wnt pathway activation, promoting mucosal healing and alleviating colitis symptoms [40]. Beyond single herbs, TCM formulas such as Gegen Qinlian Decoction maintain colonic mucosal homeostasis in acute and chronic ulcerative colitis by bidirectionally modulating Notch signaling [41]. Qingbai Decoction may enhance mucus and mechanical barrier functions while

suppressing inflammatory cascades through NF- B and Notch pathways, reducing intestinal inflammation and improving barrier function in colitis mice [42]. Shenling Baizhu Powder can alleviate intestinal inflammation by improving barrier function, and gut microbiota metabolism can biotransform Puerariae Flos to improve intestinal inflammation [41]. Future research should further investigate the synergistic effects of multiple signaling pathways regulated by TCM to provide novel insights for preventing and treating intestinal diseases.

The incidence of intestinal diseases such as irritable bowel syndrome, inflammatory bowel disease, and intestinal tumors is increasing, particularly as social pressures intensify, making functional bowel disorders common clinical conditions. ISC-based therapies and organoid technologies represent novel research directions for treating intestinal diseases. Since ISC proliferation and differentiation depend on energy metabolism and related metabolites, modulating ISC function through dietary regulation to promote intestinal barrier repair may offer new clinical therapeutic strategies.

Author Contributions

Zhu Yan, Xiao Jin, and Chen Min conceived the research idea, designed the study, and formulated the research proposition. Yang Yang, Tang Taichun, Wang Shuting, and Chen Siqi conducted literature collection and wrote the Chinese and English abstracts. Zhu Yan drafted the main manuscript. Chen Min revised the final version and takes responsibility for the manuscript.

Conflict of Interest

None declared.

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