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Contents

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EDITORIAL

ORIGINAL ARTICLE

Clinical Trials Study

Basic Study

Contents

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EDITORIAL

Gut microbiota modulating intestinal stem cell differentiation

Lin He, Chen Zhu, Xiang-Feng Zhou, Shu-E Zeng, Le Zhang, Kuan Li

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Abstract

Proliferation and differentiation of intestinal stem cell (ISC) to replace damaged gut mucosal epithelial cells in inflammatory states is a critical step in ameliorating gut inflammation. However, when this disordered proliferation continues, it induces the ISC to enter a cancerous state. The gut microbiota on the free surface of the gut mucosal barrier is able to interact with ISC on a sustained basis. Microbiota metabolites are able to regulate the proliferation of gut stem and progenitor cells through transcription factors, while in steady state, differentiated colonocytes are able to break down such metabolites, thereby protecting stem cells at the gut crypt. In the future, the gut flora and its metabolites mediating the regulation of ISC differentiation will be a potential treatment for enteropathies.

Key Words: Intestinal stem cells; Gut microbiota; Gut stem niche; Microenvironment; Probiotics

Core Tip: The dysbiosis may cause intestinal cancer. when the proliferation of the stem cells attempting to repair the loss of integrity of the gut barrier. The correction of the gut stem niche dysbiosis by the assumption of some beneficial microbiota could be a specific therapy of this disease.

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INTRODUCTION

Inflammatory bowel disease and irritable bowel syndrome have become global diseases. In the inflammatory state that occurs, proliferation and differentiation of intestinal stem cells (ISCs) to replace damaged gut mucosal epithelial cells is a critical step in ameliorating gut inflammation[1]. ISCs at the gut crypts have the ability to continuously proliferate and differentiate into different types of gut mucosal epithelium during their migration towards the apical part of the gut villi. The microenvironment in which the ISCs reside is known as the stem cell niche, which directs the function of ISCs in homeostasis and repair processes and influences cancer development. Current studies have shown that intrinsic and extrinsic factors and diet can regulate stem cell niche; ISCs can gain competitive advantages when mutated and can regulate the local microenvironment, which drives tumorigenesis and clonal expansion; tumor stem cells control tumor growth and progression in colorectal cancer, and the function of these cells also depends on the microenvironment in which they reside; mutant stem cells are difficult to eliminate, and an understanding of the interactions between mutant stem cells and their microenvironment could help to develop new technologies for colorectal cancer[2].

STEM CELL NICHE REGULATE ISCS

Competitive inhibition: Mutations in the oncogene *Apc* are present in about 80% of colon cancers, and ISCs carrying the *Apc* mutation have a strong competitive advantage in the face of normal ISCs. This advantage is due to the fact that Apc mutant cells can secrete WNT antagonist factors, which inhibit the activity of the normal ISCs and promote their differentiation; the inhibitory effect of WNT antagonist factors on the normal ISCs is effectively counteracted[3]. Balance of renewal and differentiation: In addition, ISCs promote gut homeostasis through the balance between self-renewal and differentiation, and the secretory matrix protein CCN1 at the base of the crypts interacts with integrins αvβ3/αvβ5 to regulate ISCs homeostasis through two different pathways downstream of it, regulating Notch and Wnt signaling, respectively[4]. T cell-expressed integrin αEβ7 binds to E-cadherin, an adhesion signal expressed by ISCs and transiently proliferating (TA) cells, triggering endocytosis of E-cadherin and modulating Wnt and Notch signaling changes. Blocking Eβ7-E-cadherinα adhesion inhibits Wnt signaling and promotes Notch signaling in ISC and TA cells, leading to defective ISC differentiation. αEβ7+ T cells regulate ISC differentiation at the single-cell level through cell-cell contact-mediated αEβ 7-E-cadherin adhesion signaling, emphasizing the important role of T-cell-stem cell/TA cell contact in maintaining homeostasis in the intestine[5]. Cellular supportive role: ISCs located at the base of the gut crypt are dependent on various factors in their surrounding stem cell niche to function properly, however the cellular source of these factors and how they play a supportive role for ISCs is not fully understood. Identifies two types of cells in the ISCs microenvironment - lymphatic endothelial cells and RSPO3+GREM1+ fibroblasts, which are the main cellular source of RSPO3, a key factor in the ISC microenvironment, and which play an important supportive role for the ISCs under gut homeostasis and during regeneration of the gut epithelium[6].

GUT MICROBIOTA REGULATE STEM CELL NICHE

The gut harbors a large number of microorganisms that interact with epithelial cells to maintain a healthy physiological state in the host. These gut microbiota are involved in the fermentation of non-digestible nutrients and produce beneficial metabolites that regulate the host's homeostasis, metabolism and immune response. *Lactobacillus acidophilus* not only inhibits pathogen invasion, but also determines the fate of the gut epithelium, thereby protecting the gut mucosa from overactivation of the Wnt signaling pathway, aberrant proliferation of crypts, and overconsumption of secretory cells in *Salmonella typhimurium* infection[7]. *Lactobacillus reuteri* stimulates gut epithelial cell proliferation and thereby activating the Wnt/β-catenin pathway, effectively maintaining gut epithelial regeneration and homeostasis *in vivo*, as well as repairing gut damage after pathologic injury[8]. On the other hand, butyric acid, at certain physiological concentrations, is able to inhibit the proliferation of gut stem and progenitor cells in dependence on the transcription factor FoxO3; whereas, at homeostasis, differentiated colonocytes are able to metabolize butyric acid and reduce the concentration of butyric acid in the gut tract, in order to protect stem cells at the gut saphenous fossa[9].

Ha *et al*[10] proposed that restoration of microbial composition, enhancement of gut barrier integrity, induction of apoptosis in cancer cells, inactivation of carcinogens, and modulation of host immune response through probiotics. Reducing the incidence of colorectal cancer, attenuating treatment-related side effects, and enhancing the efficacy of anticancer therapies are key to successful translation into clinical practice. However, before their use in the clinic, it is important to assess the potential risks, optimize the method of administration, and consider the changes in the baseline gut microbiology in the patient's body[10].

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CONCLUSION

In the future single-cell sequencing, cell lineage tracing, and metabolomics approaches effectively reveal the impact of ISCs composition, cellular characteristics, and function, as well as signaling pathway changes in associated cancers, providing new insights into gut microbes modulating ISCs differentiation for the treatment of gastrointestinal tumors [11]. Gut epithelial cells form organoids in the medium of three-dimensional scaffolds containing stem and differentiated cells, and the use of organoids will be effective in revealing the relationship between the complex three-dimensional structure of the intestine and the microphysiological system in gut tumors[12].

FOOTNOTES

Author contributions: He L, Zhu C, Zhou XF, Zeng SE, Zhang L, and Li K contributed to this paper; He L, Zhu C, and Li K designed the overall concept and outline of the manuscript; Zhou XF, Zeng SE, and Zhang L contributed to the discussion and design of the manuscript; Zhu C and Li K contributed to the writing, and editing the manuscript, illustrations, and review of literature.

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