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Review on Intestinal Stem Cell

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Abstract: The intestine performs the functions of absorption and protection. Located in the intestine, the intestinal stem cells play an important role in sustaining the intestinal homeostasis. The niche environment affects the intestinal stem cells functions via signaling, structural, and immune pathways. Active intestinal stem cells can differentiate into other intestinal cells and replenish them. This process is regulated by various signaling pathways, including Wnt, BMP, EGF and so on. In addition, other impact factors like aging and microbiota may also influence the intestinal homeostasis through affecting intestinal stem cells. Colorectal cancer, originating from abnormal intestinal stem, may be treated by multiple therapies.

Keywords: Intestinal stem cell, homeostasis, CLC

1. Introduction

The intestine contains the small intestine and large intestine. The small intestine is made up of the duodenum, the jejunum, and the ileum. The large intestine consists of the cecum, appendix, colon, rectum, and anal canal. The intestine has two major functions: absorption and protection. It takes in nutrients and withstands the various pH and bacteria. These functions are managed by the crypt-villus structure and the proliferation of cells. The intestinal stem cells enable the proliferation and are essential for maintenance of intestinal homeostasis. [1]

2. Location

The intestinal epithelium contains millions of crypt-villus structures. The villi take in nutrients and transfer them to capillaries. However, the intestinal environment which contains various pH and bacteria causes abrasion. This leads to the short life of intestinal epithelial cells. [1]

The crypt base columnar (CBC) cells divide and act as intestinal stem cells. The +4 cells are also considered reverse stem cells according to some research. These cells are located at the bottom of crypts, which is called the stem cell zone. They are protected by Paneth cells. Above the stem cell zone is the transit amplifying zone, where progenitor cells divide rapidly. When the cells are mature, they are on the top of the villi and do their jobs. The whole process is called intestinal turnover. This process solves the problem of short-living intestinal epithelial cells. [1]

The maintenance of intestinal stem cells is determined by a specialized microenvironment called stem cell niche. The intestinal stem cell niche consists of the epithelial cells, the mesenchymal cells, and the immune cells. The epithelial niche is abundant with Paneth cells, which touch the LGR5+ ISC to protect the stem cells. In addition, Paneth cells are essential for stem cell signaling which

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contributes to the maintenance of ISC homeostasis. Paneth cells can express signaling molecules such as WNT3, EGF, Tgf-a, and so on. Depletion of Paneth cells will lead to intestinal stem cell function ablation and even loss of ISC. The mesenchymal niche containing myofibroblasts, fibroblasts, pericytes, neural cells, and smooth muscle cells forms the structure of the ISC environment and provides soluble signals. The signaling factors in mesenchymal niche regulate the regenerative capacity of ISC. [1] Immune cells affect the ISC self-renewal and differentiation via cytokines and stimulatory factors, preventing pathogen invasion. [2]

3. The Fate of Intestinal Stem Cell

There are mainly two kinds of cells that have stemness in the intestine: the crypt base columnar and the +4 cells. LGR5+ CBC cells enable the regeneration of intestinal epithelium. Once they are blocked, the regeneration fails. The +4 cells contribute to the repopulation of stem cells. It was also found that the cells containing H2B–YFP can revert into CBC cells if needed. [1] Active intestinal stem cells can migrate upwards and differentiate into transit-amplifying cells in the TA zone. The TA cells can differentiate into absorptive or secretory progenitors. The absorptive progenitors can further become enterocytes while secretory progenitors will become Paneth cells, goblet cells, or enteroendocrine cells. The transition between reserve ISCs and active ISCs is regulated by mixed signaling pathways and may be affected by diseases. [3]

Many secretory cells can revert to stem cells. This ability was observed from Bmi1–GFP and Prox1-GFP reporter mice, but the real cause remains unclear. Whether most mature cells or the cells labeled with Bmi1–GFP and Prox1-GFP have this ability needs to be studied. Moreover, many absorptive cells can revert to stem cells.

If a stem cell experiences damage, stem cell competition can limit the reproduction ability of this cell. The daughter cells grow symmetrically, competing for a space in the niche. Those cells that contain bad mutations will be pushed out of the stem cell zone. This decreases the rate of producing tumors and ensures the production of healthy intestinal epithelia.

4. Signaling Pathways

The differentiation and self-renewal of the ISCs are controlled by the extrinsic niche-derived signaling pathway and intrinsic epigenetic regulation. The extrinsic niche regulation consists of several regulators, including Wnt, bone morphogenetic protein (BMP), notch, epidermal growth factor (EGF), JAK/STAT1, PI3K/AKT, and Hippo signaling. The intrinsic epigenetic regulation contains DNA methylation, histone modification, and chromatin remodeling. [3]

Wnt signaling controls intestinal stem cell renewal. It acts as a short-range cellular signal between adjacent cells by tethering to the cell membrane. Wnt signals transduction can proceed with or without beta-catenin. In the pathway with beta-catenin, Wnt ligands bind to Frizzled receptors and LRP5/6 receptors. Thus, this combination results in LRP phosphorylation which further inhibits glycogen synthase kinase 3 (GSK3) and binds with axin. Without Wnt signals, axin, adenomatous polyposis coli (APC), and GSK3 will form a destruction complex and phosphorylate beta-catenin. Therefore, beta-catenin will be degraded by proteasome. When Wnt signals are transferred, the formation of the destruction complex will be inhibited, promoting beta-catenin accumulation in the nucleus. Beta-catenin can regulate the transcription of targeted genes in the cell nucleus, such as Lgr5 and Axin2. Lgr5 in CBC can generate intestinal cell differentiation. Hence, Wnt signaling pathways can regulate ISC differentiation. Wnt signals can also transduce without beta-catenin, for instance, during morphogenetic movement. [4]

Bone morphogenetic protein (BMP) is a kind of transforming growth factor beta (TGF-beta). BMP signaling is important to stem cell homeostasis, including cell proliferation, differentiation, and

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apoptosis. BMPs bind to BMP receptors (BMPR) in a homodimer or heterodimer form. After binding BMPR, BMPs regulate cells through the Smad pathway and non-Smad pathways such as PI3K/AKT, p38, and JNK. From the tip of the villus to the bottom of the crypt, BMP signaling activity decreases because the crypt expresses BMP antagonists Noggin and Gremlin 1. BMP signaling suppresses intestinal cell proliferation. [5]

Epidermal growth factors (EGF) produced by Paneth cells interact with the ERBB1 receptors. The negative regulator LRIG1 is co-expressed with ERBB1. [1] EGF signaling activates proliferation and suppresses apoptosis of intestinal stem cells, guaranteeing the survival of undifferentiated ISCs. [6]

The notch signaling pathway regulates the differentiation of ISCs into secretory and absorptive cells. It also prevents apoptosis of the ISCs. [7] The notch signal consists of receptors, ligands and DNA binding proteins. The majority of notch receptor Notch1 resides in the intestine. Jagged-1/3 and notch interact with the receptor followed by activation of TNF-alpha-converting enzymes. Notch enters the nucleus and regulates gene expression. Notch signaling promotes ISC differentiation into the absorptive lineage and inhibits differentiation into the secretory lineage. [8]

Wnt/beta-catenin signaling and BMP signaling counteract each other. Wnt ligands are secreted by the niche and highly concentrated at the bottom of the crypt. BMP ligands reach the highest level in the lumen. Wnt signaling, BMP signaling, and other signaling pathways regulate ISC apoptosis and renewal directly or indirectly, contributing to the homeostasis of the ISC. [9]

5. Impact Factors on ISCs

While aging, tissues may show characteristics like impaired regenerative response, loss of tissue homeostasis and maintenance. Aging affects both the architecture and the functions of the intestinal tissue. Although the change in ISC number remains controversial, ISC regeneration and proliferation capacity were found to be reduced upon aging. When aging, intrinsically, canonical Wnt signaling decreases. Beta-catenin is affected, followed by changes in the expression of Ascl (achaete-scute-like 2) which controls ISC function. Notch1 gene expression is also reduced, causing a reduction of Olfactomedin-4 gene expression which regulates the function of ISCs. The expression of Atoh1 increases, resulting in ISC differentiating more into secretory cells. Extrinsically, abnormal Paneth cells that appear frequently upon aging lead to unwanted immune responses, altering gut microbiota and may cause Crohn disease. Providing Wnts, fasting, and targeting aged ISC pharmacologically may enhance the function of ISC and reduce the influence of aging. [10]

ISC differentiation affects gut microbes. Immunoglobulin A (IgA) secreted by absorptive cells can prohibit pathogens from entering and protect cells from infections. Paneth cells can secrete Wnt signals that stimulate the Pspo3-Lgr5 axis, therefore inducing antibacterial protein secretion. Colonizing bacteria in germ-free (GF) animals can reverse the reduction of proliferation rate and cells. Gut microbes can activate the immune system and regulate the epithelial cell renewal rate. In the early life, microbiota contributes to the intestine homeostasis. Microbiota regulates ISC homeostasis via toll-like receptors (TLPs) and nucleotide-binding oligomerization domain (NOD)-like receptors. TLPs recognize the microbes by their molecular patterns and further affect ISC differentiation Wnt and Notch pathway. NOD2 activates ISCs' survival through NOD2 signaling, stabilizing the ISC homeostasis against cell death. Some bacterial-related products like tryptophan metabolites and short-chain fatty acids mediate intestinal epithelial regeneration. These bacterial-related products may be potential targets for curing intestinal diseases. [8]

6. Colorectal Cancer

Colorectal cancer is one of the deadliest cancers in the world, leading to 900,000 deaths in a year. Both genetic and environmental factors can cause colorectal cancer. Behaviors, diets, and lifestyles

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can affect the incidence of colorectal cancer. People who have a family history of colorectal cancer and a previous history of bowel disease will have a higher risk for colorectal cancer. Variations of the oncogenes in intestinal stem cells result in colorectal cancer, such as APC, Kras, and PIK3CA. These mutations cause ISCs to become increasingly competitive, leading to a phenomenon called biased drift. Mutant ISCs take advantage of the normal ISCs and replace them. There are mainly two pathways of colorectal cancer development: the adenoma-carcinoma pathway and the serrated neoplasia pathway. The adenoma-carcinoma pathway is often caused by APC mutation, leading to microsatellite stable colorectal cancer. APC mutations result in increasing secretion of Wnt antagonists which promote the differentiation of ISCs. [9]

The serrated neoplasia pathway is initiated by RAS and RAF mutation, resulting in microsatellite stable and unstable colorectal cancer. [11] Kras mutations often initiate crypt fission and extra-glandular expansion. The ISCs with mutant Kras tend to secrete BMP ligands and activate ISC differentiation, followed by a decreasing number of ISCs [9].

The treatment for colorectal cancers is mainly chemotherapy, apart from that, surgery and some new methods are conducted. Endoscopic resection is also a proper option for large polyps and T1 cancers [11]. Systemic treatments including chemotherapy, targeted treatment, and immunotherapy can provide individual treatments based on the attributes of the cancer [12]. The chemotherapy regimens are DNA-damaging agents which are highly toxic to cells. Yet the targeted therapy can recognize the targeted site and limit the side effects. Immunotherapy ceases the development of cancer by immune checkpoint blockade drugs. Innovated therapies, for instance, CAR-T cell immunotherapy and bacterial delivery systems may be put into use in the future [13].

7. Discussion

Gut microbiota greatly affects intestinal homeostasis. Regulating the microbiota may be a potential target to treat the host's diseases, including cancers. It is known that fecal microbiota transplantation (FMT) from healthy people to patients is beneficial for treating intestinal disorders. Alternations in bacterial diversity and abundance were observed in patients with gastric cancer. Studies show that shifts in gut microbiota from healthy people to patients could improve the gut condition in CRC patients. [14] Further research on how to transform this discovery into systematical treatment is needed.

8. Conclusion

Regulation of intestinal stem cells is essential for replenishing the intestinal epithelium and maintaining the balance of the intestine. By understanding how intestinal homeostasis is regulated by signaling pathways, niche environment, aging, microbiota, and other environmental factors, better treatments for intestinal stem cell diseases can be discovered to promote gut function and health.

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