Stem cell retrograde: A new reason why colorectal cancer is more common than small intestinal cancer?

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The intestine is exposed to a dynamic internal environment that is full of physiological stimuli and has a high risk of being invaded by pathogenic factors. It has dynamic fold units referred to as crypts that are composed of epithelial cells to ward off potential damage from gut lumen. Apart from the crypt, the small intestine (SI) contains villi that is covered by functionally differentiated cells, such as absorptive epithelial cells to maintain nutrient exchange with luminal environments. Intestinal stem cells (ISCs) are responsible for self-repair mechanisms of the intestine epithelium. They have the ability to differentiate and proliferate, are well protected, and are located at the bottom of the intestinal crypt structure (Figure 1A).[1] This regenerative mechanism allows stem cells to differentiate and replenish the epithelial cell population to cover the entire gut. Morphologically, the SIs have villi, while the large intestines do not. In addition to this distinction, Azkanaz et al. showed that SI stem cells have a strong retrograde phenomenon, while large intestine stem cells exhibit a weak retrograde phenomenon.

So, what is stem cell retrograde phenomenon? Azkanaz et al. found that in addition to the normally differentiated upward migration movement, stem cells in the crypt of the SI are actively driven by Wnt signaling for retrograde movement toward the crypt center.[2] This phenomenon determines that stem cells in the crypt can maintain long-term proliferation. They found that in large intestine (LI) crypts, marginal *Lgr5*-positive (LGR5+) cells lack retrograde movement and are unable to effectively function for long periods of time.[2] These results suggest that LGR5+ cells can effectively self-renew and further differentiate in the intestines only in a specific environment containing niche cells.

ISCs are located at the base of the crypt and are usually cross-linked with Paneth cells. Normal stem cell proliferation and differentiation is essential to maintain the dynamic intestinal balance. Paneth cells in crypts of the SIs are not found in the LIs. The central role of Wnt signaling is to maintain the functions of ISCs. As a target gene of the Wnt pathway, the LGR5+ cells in stem cells can differentiate to generate various types of epithelial cells.[3] In addition, Wnt signaling plays an important role in Paneth cell differentiation and regulates the normal functions of secretory cells. The Notch pathway maintains intestinal homeostasis by regulating ISCs and promoting stem cell differentiation. The interaction between these two pathways is also important for maintaining a stable cycle of stem cell ecotone and homeostasis in the intestine. On the other hand, the stem cells, intestinal epithelial cells, immune cells, mesenchymal cells, and intestinal microbes together form the stem cell ecological niche that is at the core of intestinal epithelial regeneration.

When LGR5+ stem cells at the bottom of intestinal crypts are transported up the intestinal wall, they differentiate into different cell types via transient amplification. Stem cells can differentiate into various cell types, including secretory and absorbent cells (Figure 1B). After differentiation, cells continue to migrate up intestinal walls to renew the epithelium. However, the number and behavior of stem cells at different locations in the crypt have not been conclusively determined. Azkanaz et al. separately counted crypt stem cells by dividing them into central and marginal regions. They revealed the number of LGR5+ cells in the central and marginal regions of the large and small intestinal crypts. These

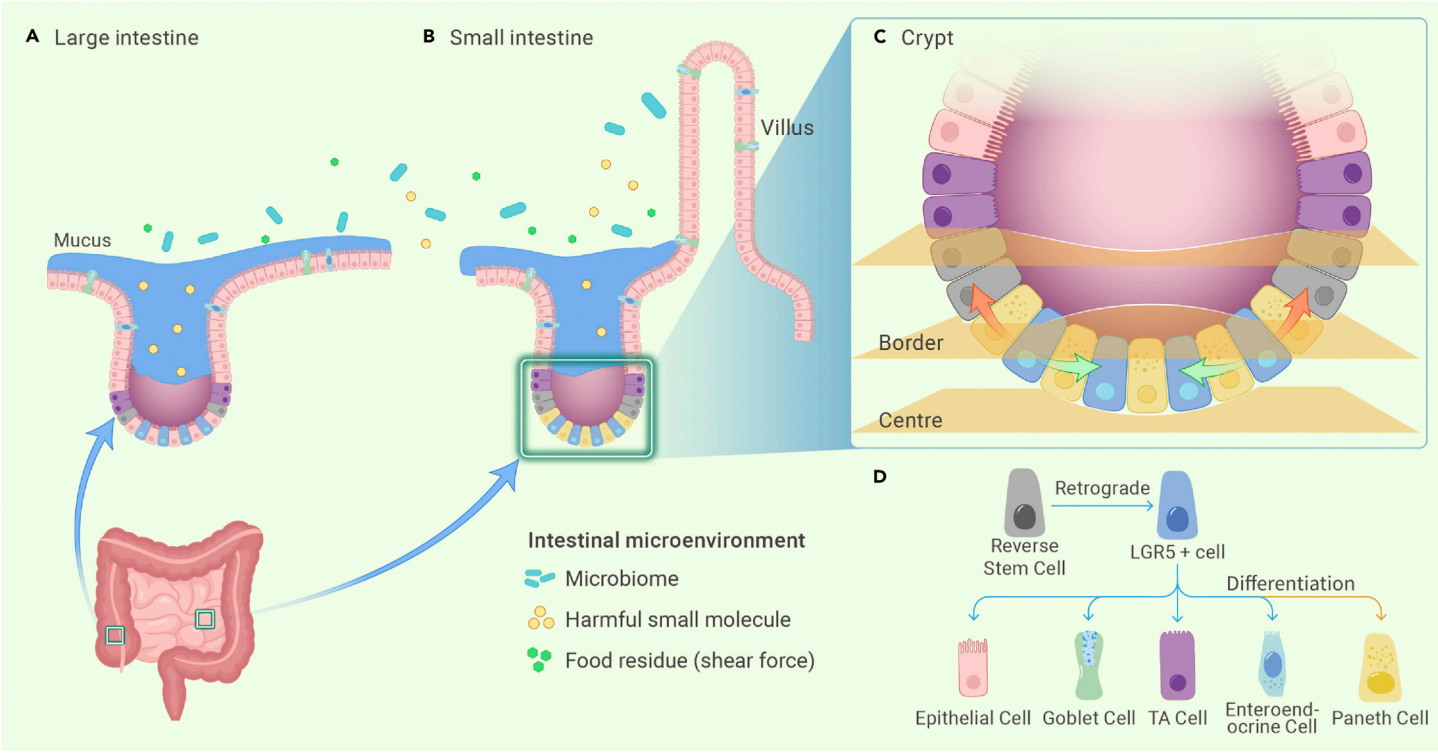

Figure 1. Schematic diagram of intestinal structure and stem cell movement in crypts (A) Model of large intestinal (LI) crypt structure. (B) Model of small intestinal (SI) crypt and villus structure. The green box is enlarged as (C). (C) The red arrows represent the direction in which LGR5+ cells differentiate. The green arrow represents the reverse stem cell proliferation at the edge toward the crypt center. (D) Different types of intestinal epithelium cells and the direction of proliferation and differentiation of ISCs.

LGR5+ cells in the center of the crypt can initiate the differentiation process under the suitable conditions.[2] These results indicate that structural characteristics of all crypts in the whole intestines are consistent with functional roles of LGR5+ cells, implying a stable dynamic repair mechanism in healthy intestines.[2] This is essential for maintenance of the intestinal environment and epithelial functions.

Azkanaz et al. used biophysical cell dynamics to construct quantitative models of intestinal crypts to simulate central drift dynamics around crypts.[2] The ratio between relocalization rate and division rate (*kr*/*kd*) was calculated from experimental data and mathematical models. The *kd* denotes the rate of upward cell division along the crypt-villus axis at the base of the crypt, and the *kr* denotes the rate at which the cells make random movements including retrograde movements, whereby this ratio was used to define the extent of effective stem cell regions in crypts. This further illustrates that ISCs would effectively play the self-renewal role for a long time. This model enriched the understanding of stem cell self-renewal functions.

Stable Wnt signaling is essential for gut development and homeostasis. In addition to its role in Paneth cell differentiation, it can induce ISC migration. Azkanaz et al. further confirmed that Wnt produced by Paneth cells can stimulate and promote LGR5+ cell migrations. These results show that migration activities of LGR5+ cells were activated when exposed to Paneth cells. However, when Wnt secretion was inhibited by the IWP2 inhibitor, the migration behaviors of LGR5+ cells were arrested.[2] Using similar methods, they confirmed that Wnt was positively correlated with the number of effective stem cells, demonstrating that Wnt can induce reverse movement of cells.[2] This finding shows the significance of Wnt signaling in maintenance and proliferation of ISCs and provides a complete theoretical basis for maintaining stem cell functions and repairing stem cell damage in treatment of intestinal diseases.

The lifetime risk for SI cancer in humans is ~0.2% while that of colorectal cancer is ~4.8%, which is 20 times larger. These outcomes might be attributed to (1) the SI containing less bacteria, producing fewer toxic metabolites, and having rapid peristalsis that may reduce the contact time between the SI walls and cancer-inducing factors in intestinal contents; (2) the small intestinal submucosa contains a large number of lymphocytes, thereby reducing the occurrence of tumors; and (3) SI stem cells are surrounded by Paneth cells that are not present in the LIs and are able to release Wnt to promote stem cell retrograde and migration. However, a more important reason may be that colorectal stem cells divide more frequently.[4] Human intestinal epithelial cells can renew once in a few days, but cell division frequencies of stem cells in large and small intestinal crypts differ. Lamprecht et al. found that the frequency of stem cell divisions in the LIs was four times higher than in the SIs, which increases the probability of errors during DNA replication and higher colorectal cancer incidences.[5] But, why do stem cells in the colorectum need to divide more frequently than those in the SIs?

$$\text{Total epithelial cell needed} = \text{Stem cell number} \cdot (1+\text{P})^{n}$$

We set up a simple theoretical mathematical model. In the above equation, n represents the generation of stem cell divisions, while P represents the ratio of stem cell involved in each division, and its value should be between 0% and 100%. If there is a larger P, a smaller n is needed. In the SIs, more stem cells maintain stemness by retrograde migration, which means a lager P.

Stem cell retrograde provides important insights into the higher colorectal cancer incidences relative to small bowel cancer. This implies that the stronger retrograde behaviors of SI stem cells reduce gene mismatch probabilities and decrease the frequency of stem cell abnormal divisions during self-replication. This phenomenon reduces the risk of gene mismatches and abnormal stem cell divisions, as well as the possibility of cancerous lesions due to abnormal lesions in crypts.

The findings by Azkanaz et al. form an important basis for research on prediction and pathogenesis of colorectal carcinogenesis. The mechanisms via which the Wnt and Notch pathways maintain the normal proliferation and differentiation of stem cells have been well established. Azkanaz et al. investigated the role of Wnt in stem cell retrograde processes, particularly in the study where generating inhibitors of Wnt during aging and during early adenomatosis were found to be key factors in inhibiting stem cell motility. Activation of stem cell migration and retrograde motility by exogenous introduction of Wnt reduces gene mismatch risk and abnormal replication during self-replication of colonic stem cells. Inhibition of the binding of the Wnt inhibitor to the receptor at the early stage of adenoma development promotes the normal stem cell migration and retrograde movement. Other factors in the Wnt and Notch pathways also play an indispensable role in migratory movement of ISCs. These factors are potential targets for colorectal cancer prediction and prevention.

In conclusion, the findings by Azkanaz et al. complement the mechanisms by which ISCs maintain their self-renewal abilities and extend our understanding of their functions. Regarding the initiation of intestinal tumor, we hypothesized that in the SI, retrograde migration of stem cells allows more stem cells to remain stemness, and fewer divisive generations lead to a lower mutation rate, which would result in lower chance of cancer. And this logical hypothesis needs further study to confirm or disprove. Elucidation of the relationship between stem cell retrograde and division frequency might provide a new perspective in the future colorectal cancer prevention studies.

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DECLARATION OF INTERESTS

The authors declare no competing interests.