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Commentary

Intestinal Stem Cell Dynamics in Cancer and Homeostasis

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DESCRIPTION

The relationship between Colorectal Cancer (CRC) and Intestinal Stem Cells (ISCs) has been an intense study. Discovery stem cell dynamics in homeostasis and following gaining of oncogenic mutations has provided unparalleled insights into CRC initiation, and it is increasingly obvious that the microenvironment plays an important role in regulating stem cell fate and functionality. So, imbalances in the signaling between the niche and ISCs perturb homeostasis and cause cancer expansion. Furthermore, stem cell-like cells drive growth and progression of established CRCs and these cells also critically rely on microenvironmental contribution.

The adult intestinal tract is created from a pseudostratified epithelium those changes into villus and intervillous domains during late fetal development. Postnatally, crypts form from the proliferative intervillous region and subsequently undergo extension *via* a process known as crypt fission. At the base of the crypts, ISCs that entirely replace the epithelial monolayer every 5–7 days reside, thereby giving rise to all particular cell types of the gut. Every crypt bottom is populated by a limited number of equipotent ISCs (5-16) that collectively work to maintain the balance between differentiated and proliferative cells within the tissue. From a single-cell perspective, these ISCs are engaged in continuously on-going competition for niche occupancy. This process is considered by stochastic loss and replacement proceedings and cause to random expansion and contraction of clones within the intestinal crypts that is referred to as neutral drift. Neutral drift dynamics are defined by the number of functional ISCs per crypt and the rate of replacement, which in turn deeply rely on the microenvironment. Hence, ISC dynamics are influenced by various endogenous and exogenous stimuli, including, for example, diet and the presence of niche factors. Furthermore, neutral drift dynamics are disrupted when an ISC acquires a mutation that confers a competitive advantage. This biased drift results in the preferential expansion of premalignant clones, fixation of the mutation within a crypt, and the subsequent initiation of CRC. Throughout the past decade, the growth of new molecular techniques and comprehensive sequencing studies have led to new insights that greatly contributed to our understanding of stem cell dynamics in health and disease in many organs.

For years, many struggles have been made to clarify the identity of ISCs. The first marker to be functionally allied with ISC features *in vivo* was the Wnt target gene Lgr5. Lgr5+ cells, present solely in the crypt bottom, were verified to be capable of long-term self-renewal and to possess multilineage differentiation potential. Lgr5+ cells are interspersed between Paneth cells, which constitute an important component of the epithelial stem cell niche. This niche is additionally supported by stromal cells and the extracellular matrix that together form a defensive environment for the maintenance of ISCs by secreting signals that are vital for regulating stem cell function and promoting ISC self-renewal. The key signaling pathway controlling ISC function is the Wnt/β-catenin pathway, and Wnt and R-spondin ligands are widely secreted by the niche, reaching the highest levels in the bottom of the crypt. Wnt activity is counteracted by Bone Morphogenetic Protein (BMP) signaling, of which BMP and Grem1 ligands are extremely expressed towards the lumen, and regulates differentiation and apoptosis. Single-cell RNA sequencing identified distinct mesenchymal cell populations that organize the BMP gradient across the crypt–villus axis. Other abundant signaling pathways in the niche include Notch, EGF, and Hedgehog signaling that either directly contributes to regulating ISC fate or indirectly *via* the regulation of the intestinal mesenchyme. A disturbance in any of these tightly controlled signaling gradients therefore substantially affects the ISC compartment, leading to impaired tissue homeostasis and an increased susceptibility to disease. Though the balanced signaling between ISCs and their local microenvironment in upholding tissue homeostasis is a recognized concept, it is becoming progressively evident that this interaction also plays a key role in facilitating tumor initiation.

CONCLUSION

By regulating the number of functional stem cells, the microenvironment dictates the composition of the playing field

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from the first moment an ISC obtains a mutation and crucially influences the spread of mutant clones through the epithelium. Vice versa, mutant ISCs involves in reciprocal signaling with surrounding epithelial and stromal cells to orchestrate a submissive environment for malignant transformation. In established tumors, a similar stem-like hierarchy is maintained in which CSCs control the growth and progression of the tumor and the functionality of these CSCs is greatly influenced by local niche cells. Future challenges remain to uncover mechanisms leading to the role and dichotomy of fibroblasts in these procedures and to arrive at a quantitative understanding of these dynamics in the context of specific genomic aberrations. These discoveries will help guide the development of therapies by shifting the focus to mending the communication between the tumor microenvironment and CSCs, rather than directly targeting CSCs.