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Slowly cycling versus rapidly cycling intestinal stem cells

Distinct roles or redundancy

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For decades, mammalian stem cells, including those in the intestine, were thought to be maintained as a slowly cycling (largely quiescent) population. While this appears to be the case for the hematopoietic system[1] recent studies by Hans Clevers' laboratory have challenged this notion through the identification of rapidly cycling (*Lgr5*$^+$) stem cells in the intestine and hair follicle.[2] Interestingly, slowly cycling stem cells also exist within the hair follicle[3] raising questions as to the functional role for each of the stem cell populations during tissue homeostasis and in response to injury. In addition, it remains to be determined whether a hierarchy exists between these two populations. Although postulated for many years, definitive proof of a slowly cycling stem cell population within the intestine has remained illusive until now.

Utilizing telomerase (*mTert*) expression as a marker for self-renewal divisions we have recently identified a population of slowly cycling intestinal stem cells (ISCs).[4] This population is long-lived, multipotent and distinct from rapidly cycling *Lgr5*$^+$ ISCs. In addition, under normal homeostasis *mTert*-expressing cells can give rise to *Lgr5*$^+$ cells indicating a lineage relationship between these populations (**Fig. 1**). Interestingly, while *Lgr5*$^+$ cells and putative ISCs present at the traditional "crypt position +4" are sensitive to the effects of ionizing radiation,[5] *mTert*-expressing cells are resistant to high-dose radiation and contribute to the regenerative response following injury.[4] We therefore propose that the intestinal crypt contains a dormant population of self-renewing ISCs that transiently express *mTert* and give rise to terminally differentiated cells via both *Lgr5*-dependent and independent pathways. Understanding the molecular cues that drive these events will be crucial for our understanding of the role each ISC population plays in the intestine.

The identification of slowly cycling telomerase-positive cells stands in contrast to the previously proposed concept that *mTert* expression marks rapidly dividing cells[6] and is essential for maintenance of cellular growth. The lack of *mTert* expression within the rapidly cycling *Lgr5*$^+$ population would indicate that telomerase is not necessarily linked to cycling cells in the intestine. Whereas recent studies have demonstrated that forced expression of mTERT results in activation of quiescent stem cells in skin,[7] highlighting a non-canonical role for this protein, little is known about the role of transient mTERT expression and cell cycle regulation. In fact, our observations suggest that mTERT may play a role in the regulation of quiescent stem cells.

Asymmetric cellular division has been thought to be the main mechanism by which stem cells renew.[8] Recently, two studies have challenged this theory and provide compelling evidence that in the intestine, rapidly cycling stem cells are renewed symmetrically.[9,10] Whether this

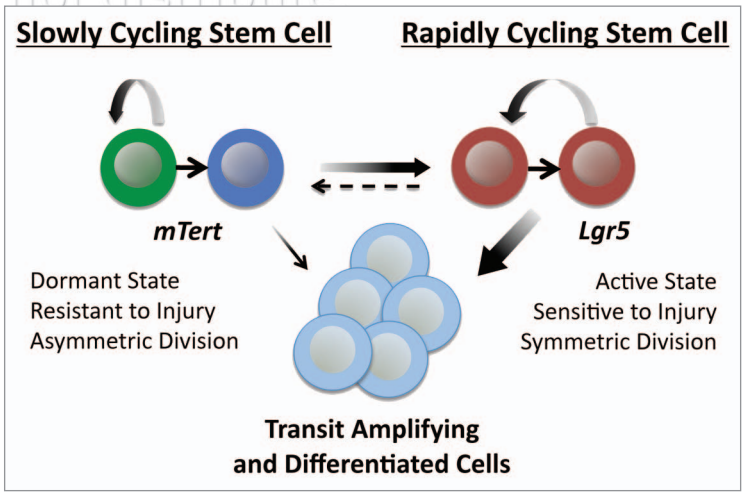

Figure 1. Two stem cell hypothesis of intestinal homeostasis. Schematic illustration of slowly cycling *mTert*$^+$ intestinal stem cells (ISCs) and rapidly cycling *Lgr5*$^+$ ISCs under basal conditions in adult mice. *mTert*-expressing cells represent dormant ISCs that are resistant to injury in contrast to *Lgr5*-expressing cells, which represent active ISCs that are sensitive to injury. Both populations undergo self-renewal divisions with *Lgr5*$^+$ cells dividing symmetrically. *mTert*-expressing cells, in contrast, may undergo asymmetrical division. *mTert*-expressing cells restore *Lgr5*$^+$ cells under basal conditions but can also give rise directly to the transit amplifying population of progenitor cells. It remains to be determined whether *Lgr5*$^+$ cells can give rise to the dormant *mTert*$^+$ population.

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happens in other tissues remains to be determined. Interestingly, these studies focused on rapidly cycling cells and therefore cannot rule out the existence of asymmetric ISC divisions, perhaps by slowly cycling ISCs. The fact that we detect *mTert*-expressing ISCs adjacent to "activated" P-β-catS552^{+} putative ISCs[4] suggests that slowly cycling ISCs may divide asymmetrically. Using *mTert* expression as a marker for quiescent ISCs it may now be possible to establish whether asymmetric divisions underlie intestinal homeostasis.

In summary, we have identified a population of slowly cycling ISCs that co-exists with rapidly cycling stem cells and may suggest a general mechanism shared by other organ systems.[11] The extent to which the function of these two populations is distinct or redundant remains to be established, though emerging data suggest dormant tissue stem cells play an important role in the regenerative response to injury. A detailed understanding of their role in intestinal maintenance as well as their response to regenerative stimuli may ultimately translate into the identification of factors that regulate tissue homeostasis and neoplastic transformation leading to cancer.

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