Review

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Plasticity within stem cell hierarchies in mammalian epithelia

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Tissue homeostasis and regeneration are fueled by resident stem cells that have the capacity to self-renew, and to generate all the differentiated cell types that characterize a particular tissue. Classical models of such cellular hierarchies propose that commitment and differentiation occur unidirectionally, with the arrows 'pointing away' from the stem cell. Recent studies, all based on genetic lineage tracing, describe various strategies employed by epithelial stem cell hierarchies to replace damaged or lost cells. While transdifferentiation from one tissue type into another ('metaplasia') appears to be generally forbidden in nonpathological contexts, plasticity within an individual tissue stem cell hierarchy may be much more common than previously appreciated. In this review, we discuss recent examples of such plasticity in selected mammalian epithelia, highlighting the different modes of regeneration and their implications for our understanding of cellular hierarchy and tissue self-renewal.

Epithelial tissue homeostasis and regeneration

Cells lost through physiological ageing or as a result of environmental insults must be continuously replaced to preserve the 'cellular status quo' of an organism. This homeostasis is achieved by undifferentiated, self-renewing stem cells that can generate all cell types of the tissue (Figure 1). Some adult tissues, such as the epithelia of intestine, stomach, and skin, are exposed to mechanical wear-and-tear and are continuously self-renewing. Epithelia of other internal organs, such as liver, pancreas, or kidneys, are typically self-renewing at a low rate. Although some general rules may apply across these tissues, each appears to employ uniquely designed stem cell hierarchies and, correspondingly, unique tissue architectures to fulfill specific physiologic demands.

Plasticity refers to the ability of cells to adopt an alternate cellular fate in response to extrinsic or intrinsic factors. When this plasticity involves a differentiated cell changing into another differentiated cell of another lineage within a given tissue, we term this transdifferentiation. Dedifferentiation is a form of plasticity in which a differentiated cell reverts to a less differentiated cell within the same tissue lineage. Of note, this 'working definition' of plasticity excludes epithelial–mesenchymal transitions observed during embryogenesis and tumorigenesis.

Although tissue stem cells are generally viewed as the major drivers of tissue regeneration after damage, endogenous dedifferentiation and transdifferentiation of non-stem cell populations has been observed to play a key role in tissue replacement in planarians, amphibians, fishes, and even some nonepithelial tissues in mammals, (reviewed elsewhere [1–3]). Emerging evidence from mammalian systems implies that differentiated epithelial cells can function as reserve stem cells upon tissue damage, implying that this might be a universal phenomenon adopted by multicellular organisms to replenish lost cells. This has important implications for the definition of what constitutes a stem cell and for our views on cellular hierarchies in homeostasis, regeneration, and in pathologies such as cancer. In this review, we discuss recent examples of endogenous plasticity (without genetic/epigenetic manipulation) in the epithelia of organs of the gastrointestinal tract, lung, kidney, and adrenal cortex, and highlight different regenerative strategies. Notably, we focus on the intestinal epithelium as an excellent genetic model of plasticity due to the extensive characterization of stem and differentiated cell populations, which enable *bona fide* cell fate conversions to be established.

The intestine as a model of plasticity

Although the liver and pancreas are much more renowned for regeneration, their suitability as model systems to study epithelial plasticity is laden with controversies surrounding the existence of stem/progenitor cells during homeostasis and regeneration [4–7]. In the single-layered intestine epithelium, however, the localization of all stem cell populations and differentiated cells is known, all cell lineages have been extensively characterized, and multiple mouse models based on stem cell marker genes exist, as well as well-defined injury models that allow the elimination of specific cell types.

Stem cell populations in intestinal homeostasis

The intestinal epithelium is the fastest self-renewing tissue in mammals. The rapid cellular turnover of the intestinal epithelium is propelled by daily proliferation of stem cells located at crypt bottoms to generate rapidly dividing daughter cells (Figure 2A). These in turn differentiate into secretory cells (Paneth cells, goblet cells, and enteroendocrine cells) or absorptive enterocytes, which make up the bulk of the villus epithelium (Figure 2B).

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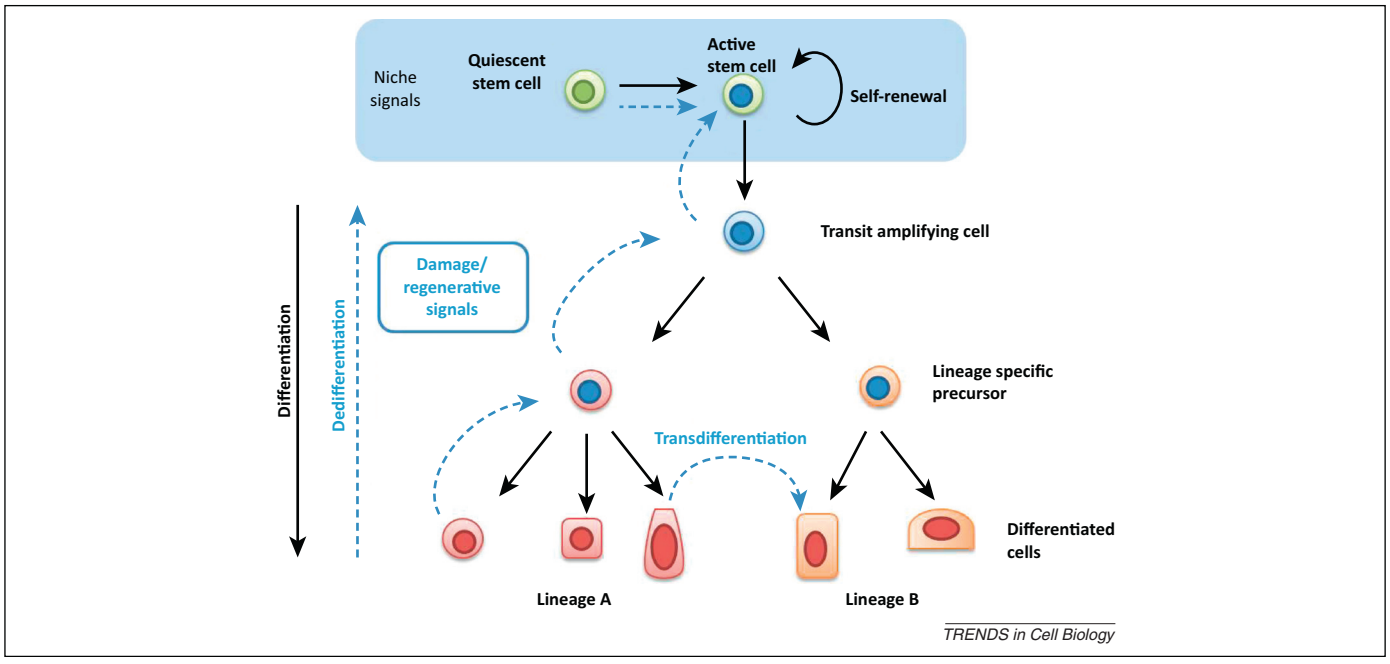

Figure 1. Stem cell hierarchy in homeostasis and regeneration. Niche signals drive stem cell self-renewal and differentiation to generate the specialized lineage populations that maintain the tissue during homeostasis. Cellular dynamics during homeostasis is indicated by black arrows. During damage and regeneration (blue arrows), cells can be replenished by mobilization of quiescent stem cells and increased proliferation of surviving stem cells. Alternatively committed cells can dedifferentiate and re-enter the cell cycle. Lost cells can also be replenished via transdifferentiation into another differentiated cell lineage. Proliferating cells are indicated with a blue nucleus, differentiated cells are represented with a red nucleus.

Cheng and Leblond proposed crypt base columnar (CBC) cells interposed between Paneth cells as the stem cells driving crypt homeostasis [8–10], which was later incorporated in the stem cell zone model of Bjerknes and Cheng [11,12]. The *leucine-rich repeat containing G-protein coupled receptor 5* gene (*Lgr5*) has been identified as a specific marker of CBCs. Genetic lineage tracing (Box 1) in mice harboring a targeted insertion of an expression cassette of

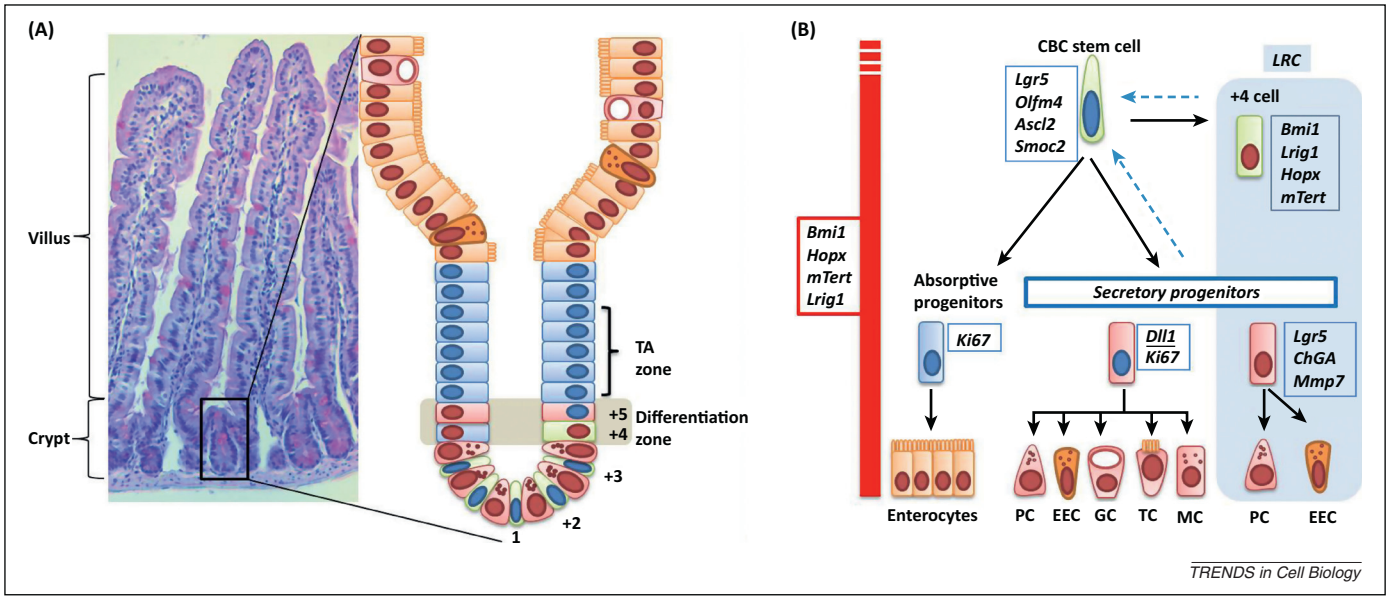

Figure 2. Current model of the stem cell hierarchies in the intestinal epithelium during homeostasis and regeneration. **(A)** The image shows a histological image of the mouse intestine [nuclei, blue hematoxylin, Goblet cells, red periodic acid–Schiff (PAS) staining], and the insert shows a schematic representation of a crypt unit and part of the villus. At the top of the hierarchy are highly proliferative crypt base columnar cells (CBCs) that are intermingled between Paneth cells at the crypt bottom. These divide to generate new CBC stem cells and daughter cells [transit amplifying (TA) cells] that are either absorptive progenitors, which proliferate and then differentiate into enterocytes that make up the bulk of the villus region, or progenitors of secretory cells. **(B)** The cell lineage relationships of diverse progenitor populations. The expression of markers, as discussed in the text, is indicated in the boxes. In homeostasis, proliferative *Lgr5*+ CBCs at the crypt base self-renew and spawn a heterogeneous population of daughter cells in the adjacent 'differentiation zone' at cell position +4/+5, where cell lineage decisions take place [see (A)]. This heterogeneous population includes transit amplifying cells (TA), and Dll1+ secretory progenitors with a limited proliferative capacity that give rise to Paneth cells (PC), enteroendocrine cells (EECs), goblet cells (GCs), and tuft cells (TC). Moreover, CBCs give rise to proliferative absorptive progenitors and quiescent label retaining cells (LRC, blue shaded region) that include *Lgr5*+ secretory precursors of PCs and EECs and an *Lgr5*- population that may represent the +4 stem cell. Proposed +4 markers such as *Bmi1*, *Lrig1*, and *mTert* have been shown to be ubiquitously expressed in all crypt cells as represented by the red line on the left. Upon damage-induced loss of CBCs, committed progenitors can dedifferentiate (broken blue arrows) to become CBCs and to restore homeostasis.