Split decisions: oesophageal progenitor cell behaviour

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The maintenance and regeneration of continually shedding epithelial tissues that make up the linings and barriers of our bodies requires rapid and continual input of proliferative progenitor cells for tissue homeostasis. The mechanisms by which epithelial progenitor cells maintain tissues remain controversial. In a recent *Science* paper, Doupé *et al* (2012) demonstrate that a population of equivalent progenitor cells support tissue homeostasis of the oesophagus without the need for slow cycling cells as described in other rapidly dividing epithelia.

In tissues such as blood and skin in which differentiated cells constantly turnover, proliferative progenitor populations are required to continually produce lost differentiated cells. Several models have been proposed to explain mechanisms by which progenitor cells contribute to tissue maintenance (Figure 1). A hierarchical model has been suggested in which longer lived stem cells, which may also cycle slowly, produce highly proliferative cells with less self-renewal potential that differentiate into a restricted number of cells. Following proliferative cells in pulse-chase experiments and genetic lineage tracing has supported a hierarchical model in the blood, epidermis and intestine (Fuchs, 2009). Alternatively, an equivalency model has been proposed in which all proliferative progenitor cells are equally able to produce proliferative and differentiated progeny in a stochastic manner. Analysis of labelled clones has supported an equivalency model for progenitors in the interfollicular epidermis and intestine (Clayton *et al*, 2007; Doupé *et al*, 2010; Snippert *et al*, 2010).

An elevated interest in understanding the dynamics of oesophageal epithelium has resulted, in part, from the rapid increase in the incidence of oesophageal adenocarcinoma (Devesa *et al*, 1998). The oesophagus is a stratified epithelium that lacks any appendages or glands, and thus consists of a basal layer of proliferative keratinocytes and several suprabasal layers of differentiated cells, which are continually shed. Previously, labelling of proliferative cells with DNA analogues has demonstrated that proliferation is restricted to the basal cells, which all proliferate in 5 days seemingly stochastically, supporting an equivalency model (Marques-Periera and Leblond, 1965). In contrast, studies using chimeric mice have suggested that proliferation of labelled progenitor cells occurs in a hierarchical manner (Thomas *et al*, 1988; Croagh *et al*, 2008).

To address this controversy, a recent study in *Science* uses several genetic mouse models to define the contribution of proliferative basal cells to oesophageal homeostasis (Doupé *et al*, 2012). In one mouse model, the authors utilized a genetic pulse-chase system based on the tetracycline-regulated expression of the histone H2B-GFP (Tumbar *et al*, 2004). They find that the rapidly dividing epithelial cells of the oesophagus lose H2B-GFP expression after 4 weeks. These data suggest that either H2B-GFP is degraded (Waghmare *et al*, 2008) or oesophageal progenitor cells proliferate faster than their counterparts in skin epithelial appendages or blood lineages, which retain H2B-GFP after 4 weeks (Tumbar *et al*, 2004; Foudi *et al*, 2009).

To analyse the properties of oesophageal progenitor cells in more detail, the authors label single cells using an inducible cre-lox genetic system and followed clones for a year. Similar to their results with this system in the tail and ear epidermis

Figure 1 Two types of models have been put forward to describe the pattern of progenitor behaviour within mammalian tissues. In the hierarchical model, a stem cell can produce proliferative progenitors with less self-renewal potential that differentiate into lineage-specific cells. Alternatively, an equivalency model has been proposed that assumes equal behaviour of progenitor cells to maintain tissue homeostasis.

(Clayton *et al*, 2007; Doupé *et al*, 2010), the authors find that the size of the persistent clones is linear with time. Statistical analysis of the clone size data supports the ability of the cells to contribute to proliferative and non-proliferative (i.e., differentiated) progeny with equal probability. Thus, these data support a model in which all of the labelled cells are equivalent.

In addition to homeostasis, the authors explore how proliferative progenitors contribute to alterations in tissue homeostasis. After inflicting wounds by biopsy, marked clones span both proliferative and non-proliferative zones of the healing oesophageal epithelium, suggesting that they maintain a progenitor fate with distinct phenotypes. With atRA treatment, the authors show that suprabasal cell formation increases, which is consistent with the known effect of atRA on the oesophagus (Lasnitzki, 1963). Statistical analysis reveals that the probability of forming basal and suprabasal cells was not altered with atRA administration. However, since proliferative cells exist in suprabasal layers during epithelial hyperplasia, additional analyses of cell state are required to determine if atRA maintains stochastic fate

decisions of progenitor cells. Furthermore, the progenitor response to atRA treatment might be limited by niche space along the basement membrane like in intestinal crypt progenitor cells (Snippert *et al*, 2010).

In summary, this study together with the authors' previous work provides additional support for the existence of equivalent progenitor cells within stratified epithelium in several tissues. Additional studies revealing how epithelial progenitor cells behave when proliferation and differentiation are altered in the oesophagus could shed light on mechanisms for the pathogenesis of oesophageal tumours or diseases such as Barrett's oesophagus.

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Conflict of interest

The author declares that she has no conflict of interest.

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