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STEM CELLS

Differentiated cells in a back-up role

Two independent studies show that, if push comes to shove, differentiated cells of the stomach and lung can act as adult stem cells, generating various cell types of the tissues, including a pool of stem cells.

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When functional cells die, they are soon replaced. In most cases, the replacement cells arise either from the division of surviving mature cells of the same class or from the division and differentiation of tissue stem cells. But what happens when resident stem cells are selectively depleted? Two papers, one by Tata *et al.*[1] published on *Nature*'s website today and the other by Stange *et al.*[2] published in *Cell*, find that following depletion of stem cells in the stomach or lung, stem-cell function can be recovered through a surprising back-up function provided by specific differentiated cells in each tissue.

The stomach and lung are lined by a single layer of cells of various types that are continually replaced throughout life as they become damaged or die. In the central part of the stomach, the cells lining periodic evaginations called crypts are found in a specific distribution, organized by class (Fig. 1a). It is thought that cells in individual crypts are maintained by rapidly dividing tissue stem cells that reside just above the crypt's midpoint and whose daughter cells spread in both directions, differentiating into cells of various classes[3].

Stange and colleagues, working in mice, find that the base of the crypts contains cells that express Troy, a marker of intestinal stem cells. Using genetic techniques to 'pulse-label' these cells in a permanent and heritable manner at a low frequency, they occasionally find crypts in which all cells are derived from a Troy-expressing cell whose progeny slowly spread up from the base. When the authors destroyed the tissue stem cells, however, Troy-expressing cells executed this stem-cell function much more rapidly and in many more crypts. Remarkably, the Troy-expressing cells are a type of fully mature secretory cell called a chief cell, which maintains its differentiated identity even while performing its stem-cell function. Because their regenerative function is activated following depletion of the tissue stem-cell population, chief cells can be considered reserve stem cells.

Tata *et al.* independently demonstrate that differentiated airway secretory cells known as Clara cells can contribute to regeneration in the lung. Previous work showed[4,5] that undifferentiated basal cells in the mouse trachea replenish the stock of secretory and multiciliated cells, which produce and clear airway mucus, respectively. In the present paper[1], the investigators pulse-labelled mature secretory cells en masse before specifically killing basal cells. Surprisingly, they later found the lineage mark they had introduced before basal-cell destruction in newly arising basal cells. But Tata and co-workers' bulk-labelling strategy is a potential caveat, because it may have inadvertently marked some original basal cells that escaped destruction. It would be valuable to conduct studies using a sparse-labelling strategy, to trace the behaviour of individual secretory cells.

These authors go on to show that the marked basal cells, presumably descendants of labelled mature secretory cells, function as stem cells, renewing both multi-ciliated and secretory cell types (Fig. 1b). Because their progenitor activity is elicited only after elimination of basal stem cells, tracheal Clara cells can also be considered reserve stem cells.

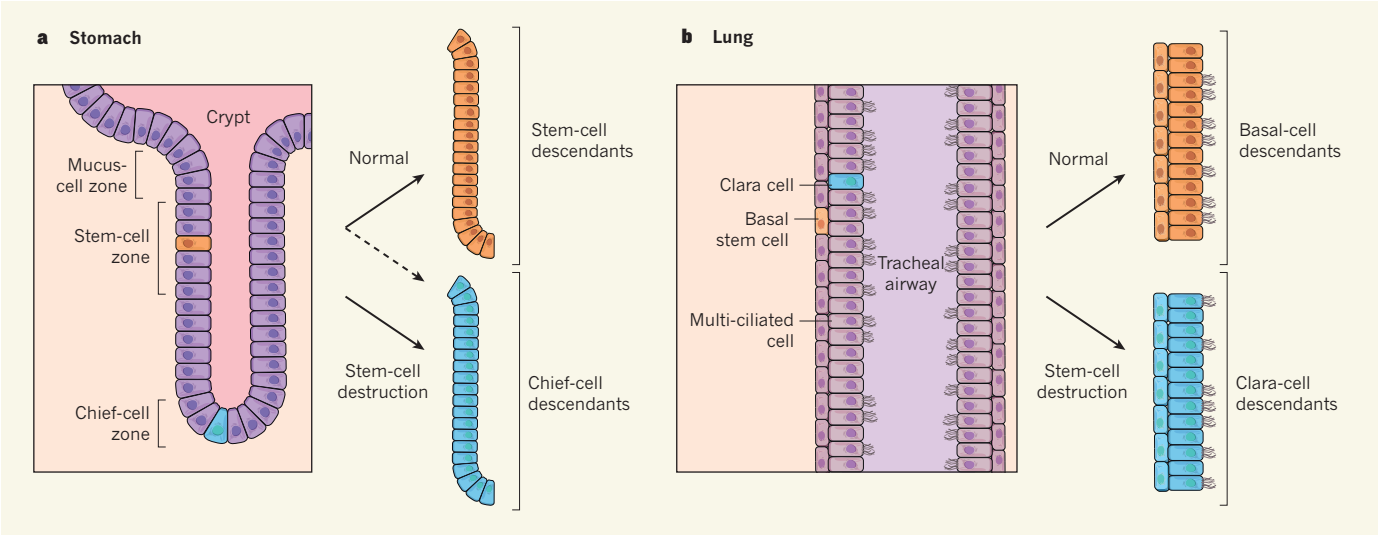

Figure 1 | When mature cells function as reserve stem cells. **a**, In the crypts of the stomach, undifferentiated adult stem cells (such as the orange cell) occupy the stem-cell zone, whereas functional, enzyme-secreting chief cells (blue) reside at the base. During cellular turnover, stem cells generate all cell types of the crypt (orange). But Stange *et al.*[2] find that if stem cells are destroyed, mature chief cells assume a stem-cell role, renewing even the depleted stem cells. Chief cells infrequently renew crypts in the absence of obvious injury (dotted arrow). **b**, The adult tracheal stem cells called basal cells (orange) replenish the complement of secretory Clara cells and multi-ciliated cells under normal physiological conditions and after injury. When Tata *et al.*[1] destroyed these stem cells, Clara cells became activated to regenerate basal cells, which resumed the task of maintaining tracheal cell types.

Although the differentiated Clara cells of the lung and chief cells of the stomach each give rise to multiple cell types, the routes they take are different. Clara cells generate replacement stem cells, whereas chief cells apparently bypass this requirement and are themselves stem cells. However, lower down in the airway tract, Clara cells seem to be stem cells, renewing themselves and multi-ciliated cells without first becoming basal cells[6]. Conversely, chief cells also seem to generate stem cells, albeit indirectly, because their descendants eventually replace all crypt cells, including the resident stem-cell populations. Thus, despite taking different routes, these mature cells share the potential to generate both differentiated cells and stem cells.

The two papers challenge the primacy of undifferentiated, resident stem cells, given that mature cells can substitute for their function and even make new ones. In other tissues, differentiated cells may similarly provide a reserve stem-cell function when the primary renewal mechanisms are inadequate[7,8]. The new studies also raise questions, such as what reprogramming factors regulate stem-cell behaviour in mature cells, and whether reversion to an undifferentiated state is an obligate step. Also, which cells generate the primary stem-cell population in a tissue? And how is an appropriate balance between mature cells and different types of stem cells within a tissue maintained? Tata *et al.* provide evidence that, in the trachea, contact between Clara cells and basal cells or short-range inhibition of Clara-cell dedifferentiation by basal cells may play a part.

The pursuit of these questions may have implications for regenerative medicine, given that there is an intrinsic appeal to the shorter path in redirecting differentiation of a mature cell instead of starting from scratch with an undifferentiated stem cell. Equally important is the possibility that these 'reserve' programs can be activated in differentiated cells *in vivo* by extrinsic signals. This would eliminate the need to introduce cellular reprogramming factors, and thereby avoid the attendant risk of promoting cancer through this form of potential therapy. ■

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