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. SEE ARTICLE P.218

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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] on page 218 of this issue 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 multi-ciliated 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.

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

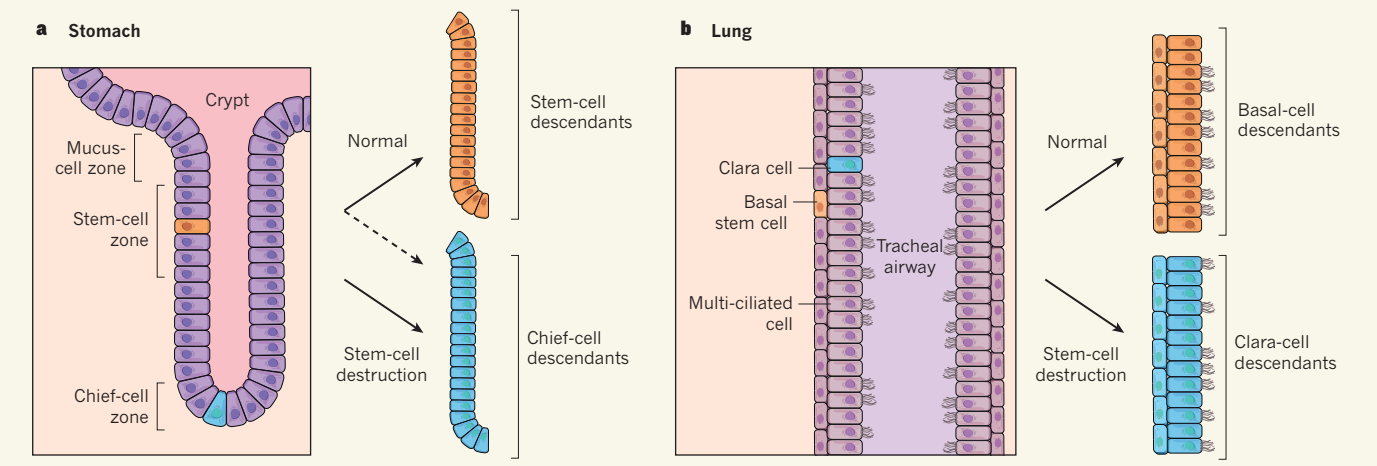

Figure 1 | When mature cells function as reserve stem cells. **a**, In the crypts of the stomach, undifferentiated adult stem cells (such as the orange cell) occupy the stem-cell zone, whereas functional, enzyme-secreting chief cells (blue) reside at the base. During cellular turnover, stem cells generate 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.

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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This article was published online on 6 November 2013.

QUANTUM PHYSICS

The right ambience for a single spin

Long-lived single electron spins are crucial for quantum computation and for understanding spin dynamics. A remarkably long lifetime — of the order of minutes — has now been obtained for a solid-state system. SEE LETTER P.242

MICHAEL E. FLATTÉ

Anyone who has had a pleasant dinner at a favourite restaurant ruined by noisy neighbours understands the disruption caused by too much interaction with one's environment. Most electronic spins in a solid are also buffeted by myriad naturally occurring 'noises', including nearby fluctuating electronic motion (spin–orbit interactions), interactions with other electronic or nuclear spins, and the mechanical motion of ions. The resilience of single-spin dynamics to these environmental effects is quantified by the spin coherence time or the closely related zero-field spin lifetime. Just as one might make modifications to soundproof a restaurant to improve the ambience for diners, so reducing the noises influencing a single spin by lowering the temperature, eliminating nuclear spins, and choosing solids made up of light atoms that have weak spin–orbit interactions, leads to long spin coherence times. Unfortunately, these methods also limit the materials in which long spin coherence times can be observed. But a deaf diner is impervious to noisy neighbours, and on page 242 of this issue, Miyamachi *et al.*[1] demonstrate an approach to making a single spin deaf to the dominant noises around it.

The system studied by Miyamachi and colleagues is a single holmium (Ho) atom adsorbed on the surface of platinum (Pt). The Ho atom has an electronic spin of 8, and its lowest-energy spin states correspond to the spin pointing towards the surface or away from the surface; these two spin states are degenerate (of equal energy). A dominant source of noise for the electronic spin of an atom adsorbed on the surface of a metal comes from a passing conduction electronic spin, which interacts with the adsorbed spin and changes its orientation, transferring one quantum of angular momentum. When this occurs, the spin orientation of the adsorbed spin also changes, so the rate of this process can limit the coherence time of the adsorbed spin.

Lengthening the spin lifetime by reducing the interaction with the environment has been demonstrated for single spins on metals, by building an insulating barrier between the adsorbed spin and the metal underneath[2]. In Miyamachi and colleagues' experiment, the Ho atom is adsorbed directly on a Pt surface (technically known as the (111) surface) chosen so that all the Pt surface atoms are arranged in regular, repeating equilateral triangles. The Ho atom sits in the centre of one of those triangles, and from its vantage point the surface would look the same if the entire surface were rotated 120° around it. Ordinarily, the presence of these neighbouring Pt atoms, combined with the spin–orbit interaction, would push the adsorbed spin into a quantum-mechanical state that is a superposition of the two low-energy (up and down) states, corresponding to a non-degenerate ground state for the Ho atom's electronic spin that has a vanishingly small spin orientation, and thus a short spin lifetime.

Here, however, it is this three-fold symmetry (so called because three rotations of 120° bring the surface back to its original configuration) that deafens the spin to its surroundings. The authors showed that for this geometric position of the Ho atom, and for the Ho atom's spin of 8, a transition from the Ho atom spin pointing away from the surface to it pointing towards the surface is not caused by the

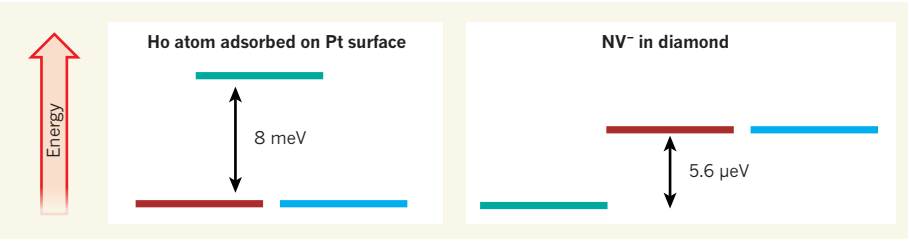

Figure 1 | Energy-level structure of spin systems. The energy splitting between the two degenerate (equal energy) spin states and a third spin state for a holmium (Ho) atom on a platinum (Pt) surface is three orders of magnitude larger than for a nitrogen vacancy (NV^-) centre in diamond. Furthermore, the two degenerate states are the ground states of the system, whereas the ground state of the NV^- centre is a single state. This energy-level structure and large energy splitting for Ho on Pt was shown by Miyamachi *et al.*[1], for temperatures corresponding to energies much less than the splitting, to eliminate spin processes that would reduce the lifetime of the electronic spin of the Ho atom.