News & views

Stem cells

Relocation keeps up the numbers

Stephanie J. Ellis & Elaine Fuchs

A dynamic mode of stem-cell regulation has been discovered. Intestinal stem cells use migration to maintain a large pool of multifunctional cells, perhaps endowing the organ with robust responses to injury. See p.548

Stem cells come in many guises, from the multifunctional cells of early embryos to the more restricted variety found in adult tissues. Their role is to provide a source of specialized cell types, while also maintaining a stock of stem cells. Adult stem cells are located in specific tissue regions called niches that support the cells' long-term survival and capacity for tissue regeneration. Although, by definition, any given stem cell in a population should be equally able to execute stem-cell functions, this is not completely true[1]. In fact, the physical position of a stem cell within its niche is key to its functional abilities[2,3]. On page 548, Azkanaz *et al.*[4] examine the positioning and movement of one type of adult stem cell, developing a strategy that allows repeated imaging of the intestinal lining of living mice.

The small and large intestines are lined with a single layer of epithelial cells, which allow the selective passage of food and other molecules from the intestine into the bloodstream, but limit the movement of harmful substances and pathogens. In the normal course of events, these cells eventually die or become damaged, so this wafer-thin epithelial lining must be continuously renewed – which is where stem cells come in.

"The authors have devised a strategy that allows repeated imaging of the same intestinal crypt in a live mouse over many weeks."

In the small intestine, these cells – characterized by expression of the surface marker protein Lgr5 – are housed in niches called crypts. Over short periods of a few days, Lgr5-expressing stem cells that are close to the physical border of the niche are more likely than those farther away to undergo differentiation into epithelial cells and exit the crypt[2]. This observation fuelled the prediction that, over the long lifetime of this tissue, most events that regenerate stem cells (rather than leading to differentiated cell types) would be driven by cells located at the crypt base. But this theory was hard to test, owing to technical limitations that prevented long-term imaging of the behaviour of single stem cells. Indeed, the broader question of how stem-cell position within a niche might change over long lifetimes has not been well addressed.

Now, Azkanaz and colleagues have devised a strategy that allows repeated imaging of the same crypt in a live mouse over many weeks. In combination with mathematical modelling, their imaging data reveal that the stem-cell 'potential' of any single Lgr5-expressing cell in a crypt depends on two behaviours. The first is cell division: cells that divide are more likely to be lost, because passive cell repositioning pushes emergent daughter cells farther up the crypt. The second, less expected behaviour is active cell relocation – stem cells in the crypt often migrate downwards, towards the crypt base (Fig. 1a). Such 'retrograde' migration increases the odds of any one stem cell being retained in the niche. So, contrary to initial predictions[2], the long-term survival of stem cells does not correlate with their initial position in the crypt.

Behaviours observed in stem cells in one niche are frequently conserved, and re-emerge in the regulation of others across species and tissue types. So, similar modes of active stem-cell migration are likely to be important regulatory mechanisms in other niches. Following this line of thinking, Azkanaz *et al.* investigated whether comparable

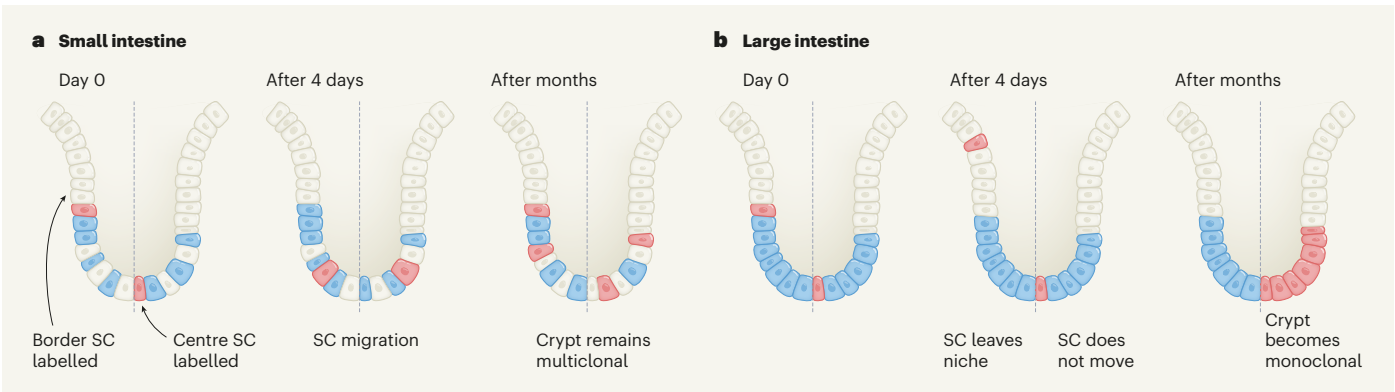

Figure 1 | Stem-cell migration in the intestines. a, Azkanaz *et al.*[4] labelled a stem cell (SC) in the border or centre of a crypt in the small intestine of mice (labelled stem cell is red, others are blue). After four days, the labelled cell had changed position through 'retrograde' migration. After months it had multiplied, but the crypt remained multiclonal (derived from multiple stem cells). **b**, In the large intestine, the same labelling approach gave rise to different clonal dynamics, with no retrograde motion and either loss of the stem cell from the crypt or monoclonality of the stem-cell population.

mechanisms of retrograde migration exist in the large intestine, whose architecture is very similar to that of the small intestine: the stem cells also reside in crypts and are identified by the surface marker Lgr5, and the number of Lgr5-positive cells is remarkably similar. Yet the authors almost never observed stem-cell rearrangements and retrograde migration in the crypts of the large intestine (Fig. 1b).

This finding has two major implications. First, in the large intestine, Lgr5-expressing cells that are farthest from the base of the crypt cannot act effectively as stem cells, because they cannot relocate towards the crypt base and so are lost from the niche relatively quickly. Therefore, the number of bona fide functional stem cells is lower in the large intestine than in the small. Second, crypts in the large intestine become dominated by the activity of a smaller number of spatially restricted stem cells, and so progress to monoclonality (that is, to being entirely derived from one stem cell) more rapidly than do crypts in the small intestine. This renders the tissue more vulnerable to random harmful mutations or other tissue damage. Reinforcing the physiological significance of these differences, the authors found that, when stem cells are removed, the cell pool regenerates more quickly in the small intestine than in the large.

This work raises fascinating questions about the developmental roots and physiological consequences of differences in stem-cell dynamics along the intestinal tract. In particular, in humans, cancers of the small intestine are much rarer than those of the large intestine. Could this be explained, at least in part, by the absence of retrograde migration in the large intestine's crypts? The existence of such migration in the small intestine could mean that potential tumour-initiating stem cells there would have more wild-type stem cells to compete against than exist in the large intestine before they could initiate an overgrowth. Azkanaz and colleagues also found that retrograde migration depends on secreted Wnt proteins, probably supplied by niche cells known as Paneth cells that are present only in the small intestine. Administration of Wnt proteins would not be a tenable prophylactic treatment for people at high risk of intestinal cancers. But studies that seek to better define the molecular and biophysical factors that endow small intestine stem cells with this migratory capacity might open up viable therapeutic avenues.

Also of interest will be to understand how other microenvironmental differences between the small and large intestines — apart from the presence of Paneth cells — affect stem-cell regulation. Differences in tissue biomechanics and the composition of the extracellular matrix between the two regions might be crucial, especially with respect to the migratory capacity of stem cells. The distinct composition of gut microorganisms, inflammatory signals and immune-cell populations associated with each anatomical region are also likely to have a substantial influence on the repertoire of stem-cell behaviours.

Perhaps the most burning question of all is this: do the active rearrangements of stem cells serve as a general controller of long-term self-renewal in other tissues and organisms? This question will be one to mobilize the entire stem-cell field.

Stephanie J. Ellis and **Elaine Fuchs** are at the Howard Hughes Medical Institute, Robin Neustein Laboratory of Mammalian Cell Biology and Development, Rockefeller University, New York, New York 10065, USA. **S.J.E.** is also at Max Perutz Labs Vienna, University of Vienna, Vienna, Austria.
e-mail: fuchs@rockefeller.edu

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Condensed-matter physics

Strain solves switch hitch for magnetic material

Kab-Jin Kim & Kyung-Jin Lee

Applying strain to a material that has a type of magnetism called antiferromagnetism allows its magnetization to be fully switched with an electric current — making it appealing for use in next-generation magnetic memory devices. **See p.474**

Conventional computers store much of their information using electric charge, but these memories are volatile, and miniaturizing components — to build laptops with high memory capacity, for example — increases their power consumption. Information can be more stably encoded magnetically, using the spin (intrinsic angular momentum) of electrons, in a form of electronics known as spintronics[1]. However, commercial spintronic devices are slower than conventional computers and are sensitive to stray magnetic fields. Attempts to overcome these problems using a type of magnetism called antiferromagnetism have yet to optimize switching between binary states in these devices. On page 474, Higo *et al.*[2] show that tensile strain can be used to achieve full electrical switching in an antiferromagnetic material.

"Switching with an electric current allows the components of the device to be densely packed into a tiny chip."

Spintronic devices are typically built from ferromagnetic materials, in which all of the spins point in the same direction. This results in a large net magnetic moment, making these materials sensitive to external magnetic fields that can interfere with device performance. Attention has therefore turned to antiferromagnetic materials, in which neighbouring spins point in opposite directions[3,4]. Antiferromagnetic memories are insensitive to stray fields and can operate hundreds of times faster than ferromagnetic memories[1,5], but most antiferromagnetic materials have multiple directions along which they can magnetize, instead of the two that would correspond to binary states 0 and 1.

Full switching refers to the magnetization of a material being rotated through 180°, so as to switch between these states. Such switching is crucial for rapid operating speeds, because it maximizes the signal that the device reads to determine the state of the material, and this, in turn, reduces the time required to do so. Moreover, switching with an electric current allows the components of the device to be densely packed into a tiny chip. Electrical switching has been achieved in several antiferromagnetic materials[6–11], but full switching has not yet been demonstrated, owing to the multiple directions along which these materials can magnetize.

Higo *et al.* achieved full electrical switching of the antiferromagnetic manganese–tin compound Mn_3Sn, a material in which two single layers of manganese atoms lie in a pattern of