Regeneration

Defining adult stem cells

Definitions for adult stem cells debated

Adult tissues must be able to maintain themselves and to regenerate after damage. But are these crucial functions mediated by dedicated populations of stem cells, or do differentiated cells adopt stem-cell-like properties according to an organ's needs? Here, scientists present evidence for both strategies.

Dedicated to the job

Pura Muñoz-Cánoves

The term stem cell was coined at the end of the 19th century to propose the notion of a common progenitor cell for distinct blood lineages[1,2]. The existence of this progenitor, called a haematopoietic stem cell (HSC), was finally proven in the 1960s[3]. The discovery of HSCs led to the defining concept of a stem cell as a self-renewing cell sat at the top of a hierarchy, giving rise to a range of fully differentiated, specialized cell types at the end of the hierarchy's branches. This type of dedicated adult stem cell has since been identified in several tissues.

A second clear example of a dedicated stem-cell population is the satellite cells of skeletal muscle[4]. There are many parallels between these cells and HSCs. For instance, both reside in specialized, protective niches — HSCs in the bone marrow, and satellite cells in muscle fibres called myofibres. The niche enables both cell types to exist in a dormant state until needed, dividing as little as possible to minimise the risk of accumulating harmful genetic mutations (Fig. 1a). And like HSCs, satellite cells activate and divide in response to damage, subsequently self-renewing and differentiating into newly regenerated myofibres along a unidirectional, hierarchical pathway (reviewed in ref. 5).

HSCs were first identified through experiments demonstrating that the bone marrow could repopulate the blood system of mice whose own marrow had been irradiated[3]. Likewise, grafting experiments and cell-tracing studies have shown that myofibre repair involves the direct participation of endogenous satellite cells. Furthermore, mice genetically depleted of

satellite cells lack the capacity to form new myofibres, confirming satellite cells as genuine adult stem cells (reviewed in ref. 5).

But although attempts to find rare, professional stem cells that can be identified as a discrete physical entity have been successful in some tissues, in others, stem-cell-like processes can be more varied. Indeed, it is becoming clear that, in some cases, repair can involve regression of differentiated cells into a less-differentiated state from which they repopulate the tissue. This is in stark contrast to the situation in blood and skeletal muscle; dedifferentiation of other niche cell types cannot compensate for HSC or satellite-cell loss.

The lack of obvious physical stem-cell populations in some tissues has prompted increasingly strident challenges to the definition of stem cells as discrete entities that follow unidirectional hierarchies, and has led to calls for an emphasis on the more diverse, plastic properties of stem cells. But this does not negate the benefits of identifying and understanding dedicated stem cells.

The ability to use professional stem cells for grafting-type experiments makes them easier to harness for therapies and experiments than more-plastic stem-cell-like populations. Indeed, HSC transplantation is increasingly used to treat a range of diseases, including blood, metabolic and immunological disorders and some cancers. Satellite-cell transplants are a promising tool for the treatment of muscle diseases, particularly those associated with reduced numbers of satellite cells and impaired regenerative capacity, such as ageing-associated and inherited muscle disorders. In the midst of calls to expand the definition of stem cells, we should remember that as-yet-unknown, dedicated stem-cell populations may way still await discovery. Their identification could have major clinical implications.

Pura Muñoz-Cánoves *is in the Department of Experimental and Health Sciences, Pompeu Fabra University and ICREA, 08003 Barcelona; and Spanish National Centre for Cardiovascular Research, 28029 Madrid, Spain.*

e-mail: pura.munoz@upf.edu

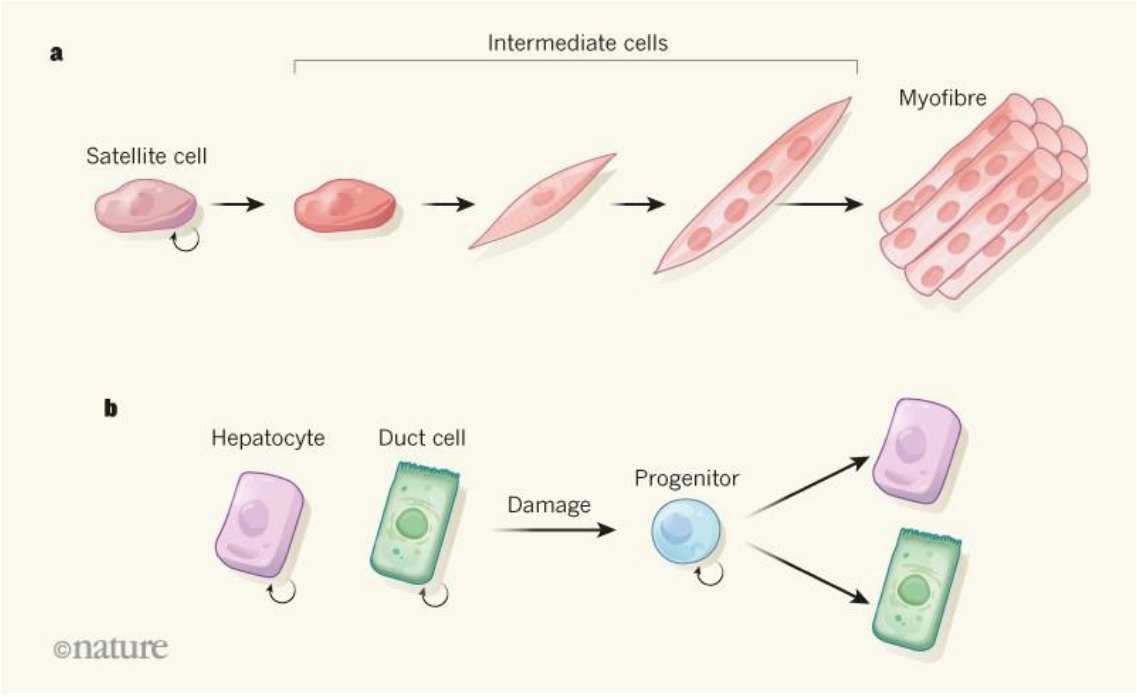

Figure 1 | Professional and facultative stem cells. a, Satellite cells are a dedicated physical population of muscle stem cells. Under normal conditions (in homeostasis), satellite cells are dormant. Following muscle damage, the stem cells begin to both self-renew (curved arrow) and to give rise to a series of intermediate progeny — early progeny proliferate (curved arrow), and later cells do not. The differentiation cascade terminates with the formation of fully differentiated mature muscle cells called myofibres that contain multiple nuclei. **b**, By contrast, the liver contains no known professional stem cells. Under homeostasis, progenitor cells for both the liver's main cell type (hepatocytes) and bile-duct cells maintain their own populations by proliferating . Following damage, these unipotent progenitors can acquire acquire a bi-potential progenitor state, from which they give rise to both hepatocytes and ductal cells. Whether a bi-potent progenitor exists in homeostasis is yet to be confirmed.

Regeneration on call

Meritxell Huch

Unlike blood and muscle, where stem cells reside in protected niches, epithelial tissues that line or bud off from the body's tubes are often exposed to external or internal stressors. An HSC-like branching hierarchy in which a single progenitor sits atop a direct line of descendants seems a very unsafe evolutionary solution for this type of tissue — dependence on a single 'master' cell would put the tissue at risk of disintegration should that cell die. An alternative approach involving overlapping hierarchies with two or more entry points seems a more-secure means of solving the problem. This idea suggests that facultative stem cells, which can act as stem cells if needed, but do not always do so, must exist.

The debate about whether the hierarchical HSC-like model fits to other systems[6] has been influenced by the tendency of researchers to consider normal organ maintenance (homeostasis) as equivalent to regeneration and repair, despite the highly divergent intrinsic cellular responses involved in the two phenomena. Repair often requires a higher level of proliferation than homeostasis — therefore bone fide stem cells that can mediate homeostasis cannot always repopulate a damaged tissue. This is where facultative stem cells come in.

One example of this phenomenon can be found in the intestinal epithelium, which is highly proliferative both in homeostasis and following injury. A population of dedicated stem cells maintains this tissue under normal conditions — these crypt-base columnar cells self-renew and differentiate into several cell types[7]. However, if the tissue is injured or the stem-cell population depleted, non-proliferative cells that have begun to differentiate or have even fully matured can revert to a stem-cell-like state to help repopulate the tissue[7]. Thus, cellular plasticity is key to gut maintenance in different conditions.

Unlike the intestine, most tissues undergo cellular turnover only slowly in everyday life, and show an increased proliferative capacity that enables them to repair some (but not

all) structures following injury. However, a few tissues that typically have low turnover, including the liver and lung, can completely regenerate following injury. The cells that enable this remarkable response have been the subject of extensive investigation, and have provided more examples of facultative stem cells.

The lung, like the intestine, has a population of true 'HSC-like' stem cells that maintain the airway under homeostasis. Following injury, mature differentiated cells called club cells can dedifferentiate and behave as facultative stem cells[8,9]. By contrast, the existence of any dedicated stem cell in the liver has yet to be proven. During homeostasis, two liver-cell types, hepatocytes and ductal cells, seem to maintain their respective cell types through proliferation. But following damage, at least in zebrafish[10] and mice[11], facultative stem cells arise from differentiated cells called cholangiocytes. In mice, cholangiocytes revert to a bi-potent stem-cell state that enables the regeneration of both hepatocytes and ductal cells[11] (Fig. 1b).

These three examples highlight ways in which different organs have solved similar problems. This brings to mind the natural-selection pressures that lead different groups of animals to achieve similar solutions to common habitat challenges — developing different strategies to combat the cold at the two poles, for instance ***[OK?]***. It is tempting to speculate that the battle to maintain tissues in a demanding environment that involves constant turnover and exposure to damage has resulted in the existence of a range of back-up strategies through which facultative stem cells help to ensure tissue integrity. A definition of stem cells that encompasses the existence of the full range of these plastic cell types is essential, if we are to truly understand the nature of regeneration.

Meritxell Huch *is at the Gurdon Institute, University of Cambridge, Cambridge CB2 1QN, UK, and at the Wellcome Trust – Medical Research Council Stem Cell Institute, Cambridge.*

e-mail: m.huch@gurdon.cam.ac.uk

1. Pappenheim, A. (in German) Ueber Entwickelung und Ausbildung der Erythroblasten. Virchows Arch. Pathol. Anat. Physiol. Klin. Med. 145, 587–643, 2986, 1896

2. Ramalho-Santos, M. & Willenbring, H. On the origin of the term “stem cell”. Cell Stem Cell 1, 35–38, 2007

3. Becker, A. J., McCulloch, E. A. & Till, J. E. Cytological demonstration of the clonal nature of spleen colonies derived from transplanted mouse. Nature 197, 452–454, 1963

4. Mauro A. Satellite cell of skeletal muscle fibers. J. Biophys. Biochem. Cytol. 9:493–495, 1961

5. Relaix F, Zammit PS. Satellite cells are essential for skeletal muscle regeneration: the cell on the edge returns centre stage. Development. 139:2845-56, 2012

6. Defining Adult Stem Cells by Function, not by Phenotype.
Clevers H, Watt FM.
Annu Rev Biochem. 2018 Jun 20;87:1015-1027. doi: 10.1146/annurev-biochem-062917-012341.

7. Plasticity within stem cell hierarchies in mammalian epithelia.
Tetteh PW, Farin HF, Clevers H.
Trends Cell Biol. 2015 Feb;25(2):100-8. doi: 10.1016/j.tcb.2014.09.003.

8. Dedifferentiation of committed epithelial cells into stem cells in vivo.
Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, Vinarsky V, Cho JL, Breton S, Sahay A, Medoff BD, Rajagopal J.
Nature. 2013 Nov 14;503(7475):218-23. doi: 10.1038/nature12777. Epub 2013 Nov 6.

9. The role of Scgb1a1+ Clara cells in the long-term maintenance and repair of lung airway, but not alveolar, epithelium.
Rawlins EL, Okubo T, Xue Y, Brass DM, Auten RL, Hasegawa H, Wang F, Hogan BL.
Cell Stem Cell. 2009 Jun 5;4(6):525-34. doi: 10.1016/j.stem.2009.04.002.

10. Extensive conversion of hepatic biliary epithelial cells to hepatocytes after near total loss of hepatocytes in zebrafish.
Choi TY, Ninov N, Stainier DY, Shin D.
Gastroenterology. 2014 Mar;146(3):776-88. doi: 10.1053/j.gastro.2013.10.019.

11. Cholangiocytes act as facultative liver stem cells during impaired hepatocyte regeneration.
Raven A, Lu WY, Man TY, Ferreira-Gonzalez S, O'Duibhir E, Dwyer BJ, Thomson JP, Meehan RR, Bogorad R, Koteliansky V, Kotelevtsev Y, Ffrench-Constant C, Boulter L, Forbes SJ.
Nature. 2017 Jul 20;547(7663):350-354.