FORUM Regeneration

Defining adult stem cells

Adult tissues must maintain themselves and 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, two scientists present evidence from both sides of the debate.

Dedicated to the job

PURA MUÑOZ-CÁNOVES

The term stem cell was coined at the end of the nineteenth 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 proved in the 1960s[3]. The discovery of HSCs led to the defining concept of a stem cell as a self-renewing cell positioned 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. Both reside in specialized, protective niches — HSCs in the bone marrow and satellite cells in bundles of muscle fibres (myofibres). The niche enables both cell types to exist in a dormant state until needed, dividing as little as possible to minimize the risk of accumulating harmful genetic mutations. And, like HSCs, satellite cells are activated and divide in response to damage, subsequently self-renewing and differentiating into newly regenerated myofibres along a unidirectional, hierarchical pathway[5] (Fig. 1a).

HSCs were first identified through experiments demonstrating that the bone marrow could repopulate the blood system of mice whose own marrow had been destroyed[3]. Likewise, cell-tracing studies and experiments in which satellite cells were grafted into damaged muscle have shown that myofibre repair involves the direct participation of 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 such rare, 'professional' stem cells 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[6,7].

The lack of obvious physical stem-cell populations in some tissues has prompted increasingly strident challenges to the definition of adult 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 to shift the focus away from professional stem cells risks negating the benefits of identifying and understanding these dedicated populations.

> ***"The ability to use professional stem cells for grafting experiments makes the cells easier to harness for therapies."***

The ability to use professional stem cells for grafting experiments makes the cells 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[8]. 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[9]. In the midst of calls to expand the definition of stem cells, we should remember

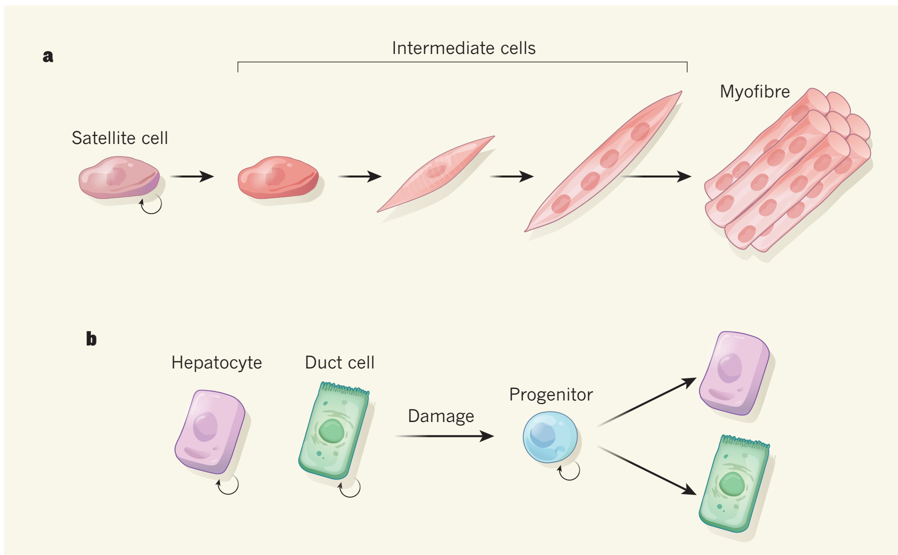

Figure 1 | Professional and facultative stem cells. **a**, Satellite cells are a dedicated (professional) population of muscle stem cells. Under normal conditions (in homeostasis), satellite cells are dormant (not shown). Following muscle damage, the stem cells begin both to self-renew (curved arrow) and to give rise to a series of intermediate progeny. The differentiation cascade terminates with the formation of fully differentiated, mature muscle cells called myofibres, which 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 also acquire a bi-potential progenitor state (here shown for the duct cell), from which they can self-renew and give rise to both hepatocytes and duct cells. Whether a bi-potent progenitor exists in homeostasis is yet to be confirmed (not shown).

that as-yet-unknown, dedicated stem-cell populations might still await discovery. Their identification could have major clinical implications. ■

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Regeneration on call

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Unlike blood and muscle stem cells, which 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 type 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 other systems[10] 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 does 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 are known as crypt-base columnar cells, and they self-renew and differentiate into several cell types[11]. 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[11]. 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 extensively investigated, and have provided further examples of facultative stem cells.

The lung, like the intestine, has a population of true 'HSC-like' stem cells that maintain the airway by means of homeostasis. Following injury, mature differentiated cells called club cells can dedifferentiate and behave as facultative stem cells[12,13]. By contrast, the existence of any dedicated stem cell in the liver has yet to be confirmed. 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[14] and mice[15], facultative stem cells arise from differentiated cells called cholangiocytes. In mice, cholangiocytes revert to a bi-potent stem-cell-like state that facilitates the regeneration of both hepatocytes and ductal cells[15] (Fig. 1b).

These three examples highlight ways in which different organs have solved similar problems. That brings to mind the natural-selection pressures that lead different groups of animals to achieve various solutions to common habitat challenges — developing different strategies to combat the extreme cold weather at the poles, for instance. 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. ■

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ASTRONOMY

A key piece in the exoplanet puzzle

The detection of a low-mass exoplanet on a relatively wide orbit has implications for models of planetary formation and evolution, and could open the door to a new era of exoplanet characterization. **SEE LETTER P.365**

RODRIGO F. DÍAZ

For decades, astronomers have looked for planets around a nearby star known as Barnard's star. On page 365, Ribas *et al.*[1] report evidence for such a planet, based on more than 20 years of data. Detailed information about the planet could be revealed by the next generation of astronomical instruments.

Planets around stars other than the Sun are known as exoplanets. They are extremely faint compared with their host stars, and their orbits are typically too small to be resolved — even using the largest telescopes available today. As a result, the latest high-resolution imaging techniques are limited to giant planets on wide orbits around nearby stars[2,3].

Most of what is currently known about the properties, formation and evolution of exoplanets therefore comes from indirect methods that measure variations in the light received on Earth from host stars. One of the most fruitful of these methods, used by Ribas and colleagues, is the radial-velocity technique. It involves measuring changes in the velocity of a host star along the line-of-sight of an observer,