Stem cells

Yo-yoing stem cells defy differentiation dogma

Carlos Galvan & William E. Lowry

The observation that melanocyte stem cells migrate up and down the hair follicle, differentiating into melanocytes and then returning to a stem-cell identity, calls into question long-held assumptions about adult stem cells. **See p.774**

The baseball player Yogi Berra once said, "You can observe a lot by watching." Sun *et al.*[1] report a study on page 774 that takes this maxim to an extreme. The authors observed single melanocyte stem cells (McSCs) in individual hair follicles over two years. They discovered that McSCs have a unique lifestyle for an adult stem cell, yo-yoing up and down the hair follicle. Their work could explain why hair greying is one of the earliest signs of ageing.

Adult stem-cell populations across mammalian tissues have typically been described as stationary, residing in a set location called a niche, in which they give rise to progeny called 'transit-amplifying' cells[2,3]. These cells proliferate and migrate to the sites at which they're needed to replenish tissue[2]. So far, researchers have thought that McSCs follow this same pattern, remaining in a region composed of two structures – the bulge and the underlying hair germ – in the upper portion of the follicle, and giving rise to melanocytes that migrate to the base of the follicle during the active stage of hair growth (anagen) and provide the hair with pigment[3]. This perfectly reasonable model was based on observations of many follicles imaged at different time points.

In their work, Sun and colleagues tracked McSCs using a combination of lineage tracing (a cell-labelling approach in which a cell and its descendants are tracked over time) and intravital imaging (in this case, imaging the same spot of skin in a live mouse repeatedly). They observed that, as expected, mouse McSCs reside in the hair germ and the bulge in the resting phase (telogen) of the hair-growth cycle. However, during anagen, they move down towards the base of the growing follicle, before migrating back up to the bulge, then returning to their original niche in the hair germ (Fig. 1).

Sun *et al.* found that, as McSCs move to the follicle's base, they also begin a program of differentiation, adopting shapes that are indicative of differentiated melanocytes. Next, the group used single-cell RNA sequencing to analyse the gene-expression profiles of the migrating cells. This analysis revealed that McSCs begin to express markers of differentiation as they migrate to the follicle base and show some of the hallmarks of mature melanocytes (such as pigmentation). Remarkably, the cells then reverse that program, dedifferentiating back to stem cells in the bulge. The researchers found that McSCs could continue this cycle for at least two years – the approximate adult lifetime of mice.

These fascinating data suggest that McSCs behave differently from adult stem-cell populations described previously. There is little evidence that any other stem cells relocate physically from their niche to another site and back again. One study has reported similar behaviour in intestinal stem cells[4], but they did not migrate nearly as far and did not regress developmentally. There is also evidence that hair-follicle stem cells migrate out of the bulge during ageing[5] and wound healing[6], but in neither case do these cells return to their niche.

Indeed, the developmental flexibility of McSCs is perhaps even more surprising than their physical movement. There are examples of dedifferentiation of differentiated cells during regeneration of organs such as the liver and pancreas[7–9]. And in some experimental settings, deletion of adult stem cells leads to dedifferentiation of transit-amplifying cells to regenerate the stem-cell pool[10]. However, the idea that an adult stem cell could differentiate and then dedifferentiate in a physiological setting is unheard of. The finding calls into question a dogma in the field – that cells always adopt progressively more-differentiated states, unless the system is disrupted by injury or cancer[11,12].

Sun *et al.* next looked at the cell-signalling pathways that control the McSC cycle. The Wnt signalling pathway has been implicated in melanocyte production[13], so the authors tracked McSCs in a genetically engineered mouse strain in which this pathway was

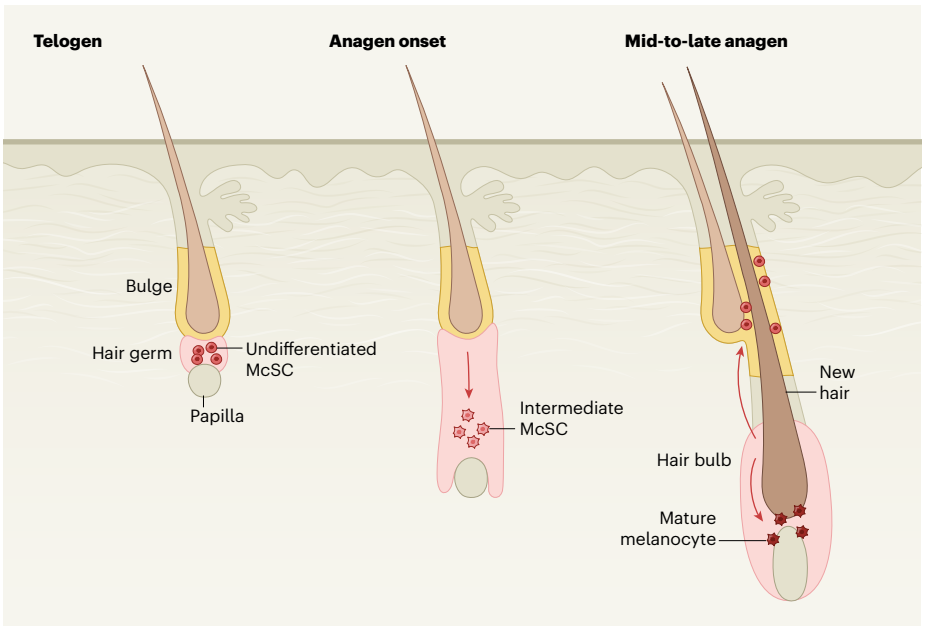

Figure 1 | A cycle to produce melanocytes from stem cells. Melanocyte stem cells (McSCs), which give rise to pigment-producing melanocyte cells, have been assumed to reside permanently in a region around the bulge and hair germ structures (which are located about a structure called the papilla in hair follicles). Sun *et al.*[1] found that the McSCs do indeed reside in this region during the resting phase of the hair-growth cycle, telogen. But when a phase of hair growth begins (anagen onset), the hair germ expands downwards. The authors found that McSCs migrate downwards, too, adopting a shape and gene-expression profile that indicate they are intermediate McSCs, on the road to becoming melanocytes. Towards mid-to-late anagen, after McSCs have divided (not shown), they can dedifferentiate and move back to the bulge of the hair follicle. From there, they can later re-enter the hair germ. Alternatively, they can differentiate into a mature melanocyte in the hair bulb, from where the new hair grows.

hyperactive. Increasing Wnt signals in McSCs induced their differentiation into melanocytes and prevented the cells from dedifferentiating in the bulge. The authors showed that the Wnt signals that activate McSCs come from surrounding cells in the hair germ and bulge — and genetically inhibiting this cell–cell signalling prevented McSCs from differentiating.

Melanocyte production is also stimulated by sunlight. Ito and colleagues found that irradiating mouse skin using ultraviolet light increased pigment production from melanocytes. But, again, the melanocytes retained the ability to yo-yo back to undifferentiated McSCs.

Finally, the authors asked how McSC behaviour was affected by ageing — a question pertinent to those of us with grey hair, which is caused by a lack of pigmentation. Analysis of follicles from aged mice revealed that McSC transit was diminished, meaning that fewer melanocytes were produced, thus leaving new hair shafts grey. This finding could open the door to new treatments to prevent greying by improving McSC activity.

It is worth noting that McSCs are thought to be key players in melanoma[14], a life-threatening cancer. Sun *et al.* suggest that the developmental plasticity they observed might explain why melanoma is so difficult to treat. It is also interesting to speculate that the reason hair greying is one of the first signs of ageing might be because the way in which McSCs produce progeny is more physically demanding than is the case for other stem cells. This would imply that the cells simply become worn out earlier. However, the premature ageing of McSCs could be an evolutionary strategy to prevent the formation of melanoma — if the cells stop replicating, they can't acquire the mutations that lead to cancer.

The unusual observations made in this study were possible only because the authors' innovative approach allowed them to monitor the same cells in their niche over time. Going forward, similar techniques should be applied where possible to take a fresh look at the behaviour of other populations of adult stem cells. Perhaps this yo-yoing behaviour will turn out not to be so unusual, after all.

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Engineering

Human–AI team halves cost of chip-design step

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Engineers and algorithms have competed in a virtual test to design a step in the process of manufacturing computer chips. Pairing human expertise with computational efficiency proves most cost-effective, but only when the timing is right. **See p.707**

Swift progress in semiconductor technology has lowered the cost of computer chips, but it has also introduced challenges for chip manufacturers. The operational dynamics associated with production processes have become increasingly complex, requiring that intelligent solutions be developed to maintain the quality of ever-smaller chips. On page 707, Kanarik *et al.*[1] explore how artificial intelligence (AI) can be used to decrease the cost of designing semiconductor processes without compromising quality. Their game-based approach shows that AI is best used during the late stages of process development, and that a hybrid strategy involving both humans and AI can markedly reduce costs compared with an AI-free production line.

The authors built a virtual game that tests how well humans and computers can design a single step in the chip-fabrication process. The step involves plasma etching[2], in which a gas of ions and electrons (a plasma) is used to etch features into the surface of a solid — in this case, a hole in a film of silicon dioxide. The team used existing data and a plasma-physics model to simulate a realistic etch output from a collection of input parameters, such as pressure and temperature, which were chosen by the player.

The goal of the game was to minimize the cost of producing an etched hole with a set of target characteristics, such as depth and diameter. Each player submitted batches of 'recipes' for the etch until they met the target. Recipes were each assigned a cost of US$1,000, with an extra $1,000 for the overheads associated with each batch — in other words, the typical costs incurred during process design.

Three senior engineers, three junior engineers and three players with no relevant experience participated in Kanarik and colleagues' experiment. The engineers all undertook a rapid initial phase of 'rough-tuning' before fine-tuning their designs, and the senior experts' strategies cost around half as much as those of their junior colleagues. The winning human player was a senior engineer, who spent just $105,000 to meet the target.

The authors then used a machine-learning method known as Bayesian optimization to design computer players that could compete with the humans without any previous training. These players were assigned a success rate on the basis of the percentage of their attempts that beat the winning engineer's low cost. Only 13 out of 300 attempts did so. Kanarik *et al.* concluded that the algorithms were no match for the winning human, and hypothesized that the computer players' lack of expert knowledge made them waste time exploring the full range of possible processes.

This hypothesis prompted the authors to test a 'human first–computer last' strategy, in which the expert undertook the rough-tuning and constrained the search, before handing over to the algorithms for fine-tuning. They found that this implementation reduced the cost of reaching the target, and that the amount by which the computer player's success rate improved depended on the point at which the human relinquished control of the game (Fig. 1). Specifically, as the algorithm gained access to more expert data, the cost decreased — but only up to a certain point. Beyond this point, further expert data increased the cost without aiding the algorithm. At the threshold, the most successful