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Helping stem cells to replicate over and over again could hold back the signs of ageing.

STEM CELLS

Repeat to fade

Stem cells rejuvenate our tissues but are not resistant to ageing themselves. How can they retain their effectiveness?

BY PETER WEHRWEIN

Stem cells are the cells that keep on giving. They resupply the body with new cells as the old ones wear out from DNA damage, the accumulation of malformed proteins, or shortening of the telomeres (DNA caps on the tips of the chromosomes). They also make copies of themselves, replenishing their own ranks in the process.

Little wonder that harnessing stem cells is seen as a possible way to fix or maintain failing organs and tissues, and maybe slow the general physical decline of old age. With a ready supply of active stem cells, older muscles might be made stronger, failing brains could become less prone to cognitive lapses, and aged bone marrow could be better able to produce the infection-fighting T and B cells.

If only it were that simple. As with so much else, stem cells in an older person are not the same as those in someone younger. They tend to be less productive and less reliable, and become slower and less predictable when it comes to replenishing cells affected by injury, illness or senescence — and the tissues they serve become less healthy and vital. In other words, stem cells are prominent in the fundamental biology of ageing. If stem cells in older people could be made to retain their effectiveness, perhaps broken bones and skin wounds could be made to heal faster and, with time, we might be able to treat the conditions of old age, such as dementia and heart disease.

Thomas Rando, a stem-cell researcher at Stanford University in California, points out that we already transplant bone marrow and perform skin grafts. Stem-cell transplantation of certain types of cells — those that mature into pancreatic cells, for example, to treat diabetes — could become a reality in five years, he says. "It's not so futuristic."

STEM-CELL HIERARCHY

There are different categories of stem cells with varying degrees of potency — the potential to differentiate into other cell types. Totipotent stem cells — found only in embryos — can become any type of cell in the body. As these stem cells differentiate, they become more specific to certain tissue types. Examples of these multipotent stem cells include neural stem cells, which develop only into neurons, astrocytes and oligodendrocytes. Muscle stem cells are even more specialized — these unipotent cells produce only muscle cells.

Ageing affects various stem-cell types in different ways. Blood-forming (haematopoietic) stem cells in the bone marrow, for example, shift towards making more myeloid cells and fewer of the lymphoid cells that generate T and B cells. This change might help explain why older people are more likely to develop myeloid-related cancers and are more vulnerable to infections. Similarly, according to a study[1] by Mark

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LaBarge, a cell biologist at Lawrence Berkeley National Laboratory in California, older stem cells in human breast tissue tend to produce fewer tumour-suppressing myoepithelial cells than younger stem cells in the breast. In both cases, the number of stem cells may remain the same, or even increase, with age.

With the brain and hair, it seems to be a different story. The pool of available stem cells starts to deplete. Indeed, the cognitive and sensory decline of old age has been associated with a reduction in the number of neural stem cells and hence the production of new brain cells. And fewer melanin-producing melanocyte stem cells leads to greying hair, one of the most obvious signs of senior status.

NICHE EFFECTS

Stem cells don't live in splendid isolation. Their behaviour is heavily influenced by their surroundings, and it has become apparent that the ageing stem cell is as much a product of its environment as of its intrinsic make-up.

In 2005, Rando and Irina Conboy, a bioengineer who was then working in Rando's Stanford lab, conducted a landmark experiment[2] showing the dramatic effect that external factors can have on stem cells. Working from what Rando says was a hunch, the researchers surgically attached the circulatory systems of pairs of mice — one young, one old — so that the two shared the same blood. They found that a minor muscle injury inflicted on the older mouse healed much better when the animal was attached to a younger mouse. Furthermore, tests showed that this improved healing was the result of the activity of the older mouse's stem cells, not those of its younger, conjoined companion. Clearly, something in the blood of the younger animal was rejuvenating the stem cells in the older one. This finding opened up the possibility of arresting, or even reversing, the decline of older stem cells by manipulating their environment. Or, as Rando puts it, "enhancing the niche may be just as important as finding the best stem cells".

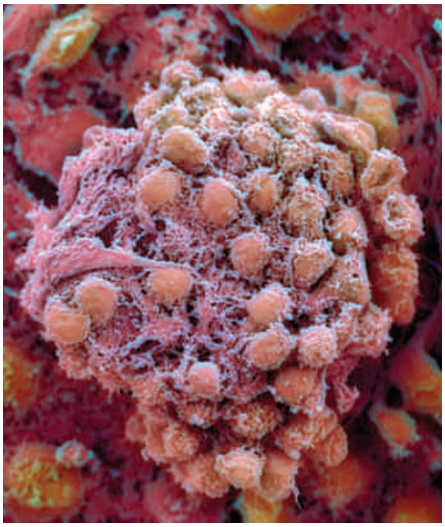
Using similar studies, other researchers have extended Rando and Conboy's findings to different types of stem cell. Conboy, now at the University of California, Berkeley, offers a hypothesis to explain this effect. She notes that stem cells are typically quiescent. "They have a talent for sitting quietly and waiting," she says. In old tissue, signals to stem cells might not get through "so they continue to sit quietly and do nothing". But enliven their environment and the signal can carry.

Now comes the hard work: working out precisely what it is that affects the stem-cell niche. As Conboy points out, it's likely to involve many factors, including some that reduce stem-cell activity as well as those that rev it up. As an example of a debilitating factor, Rando's team reported[3] that eotaxin — a chemokine, or immune-system chemical messenger — seems to contribute to age-related cognitive impairment by inhibiting adult neural stem cells.

Another aspect of the stem-cell environment is the ageing of normal cells. Senescent cells secrete a variety of signalling molecules such as cytokines and chemokines; proteins such as growth factors; and enzymes such as proteases. According to Judith Campisi, who studies senescence at the Buck Institute for Research on Aging in Novato, California, cytokines can act directly on stem cells to restrict proliferation and versatility, and proteases can degrade the extracellular environment. Transplanting young stem cells into a neighbourhood full of older cells, some of which are senescent, is probably not going to work very well, she says. "There's mounting evidence that senescent cells in the niche are going to be an important part of the stem-cell transplant story."

"Stem cells have a talent for sitting quietly and waiting."

How does a change in the niche alter a stem cell's behaviour? The cell's genes don't change, but epigenetic factors might cause them to be expressed in different quantities. So, both genes and environment play a role. "A cell's behaviour is always dictated by the microenvironment it is in," says LaBarge. "But the array of potential responses within those contexts is probably dictated by the genetic state of the cell."



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Embryonic stem cells can replenish any type of cell, but that potency is lost during ageing.

One way stem cells are connected to their niches is through signalling pathways, whose complexities are slowly coming into focus. Research has shown[4,5], for example, that an active Notch signalling pathway turns on the regenerative power of muscle stem cells, whereas firing up the Wnt signalling pathway leads to fibrosis. These pathways aren't isolated from one another. The strength of the Notch pathway depends in part on another pathway, known as MAP/ERK6. The Wnt pathway has a role in regulating telomerase, an enzyme that restores the chromosomal DNA caps, or telomeres, that otherwise shorten each time the chromosome is copied.

THE FLIP-SIDE OF THE COIN

Researchers studying stem-cell rejuvenation see an array of potential clinical applications. Bioengineered polymers could deliver drug packages that ramp up signalling pathways such as Notch. Agents that tweak DNA-reading RNA could alter which genes are expressed in an effort to return youthful vigour to decrepit stem cells. Investigation of agents already known to have anti-ageing effects, such as rapamycin (see 'Live long and prosper', page S18), might reveal pathways that alter older stem cells or their niches, or both.

However, says Rando, any treatment needs to be targeted, both in duration and specific location, to avoid the potential harm of systemically and chronically stimulating stem-cell function. The most worrying of the potential side effects is cancer. Many of the factors and mechanisms that reduce the efficacy of stem cells also keep cancer in check.

For example, when dividing cells are damaged or stressed, cell senescence keeps them from becoming cancerous. But once cells are senescent, they secrete cytokines and other molecules that might tip their neighbours — and possibly more distal cells — into a proliferative, cancerous state. Campisi says that some adult stem cells — for example, mesenchymal stem cells in connective tissue, and blood-forming haematopoietic stem cells — also undergo senescence. These cells are particularly disruptive and can activate nearby dormant cancer stem cells.

The p16 tumour-suppressor gene is another good example of the ageing–cancer trade-off[7]. Increased expression of p16 has been observed in a number of older tissues — so much so that active p16 seems to be an overall marker for ageing. But p16 is a tumour-suppressor gene that might limit age-related diseases, so targeting it is a high-risk strategy. "Tumour suppression and ageing are two sides of the same coin," notes Rando.

So, as enthusiastic as researchers are about making old stem cells young again, they are well aware that this is new territory where the best of intentions could easily have unintended consequences. ■

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