Stem cell exhaustion and its role in healthy aging

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Scientist Sarallah Rezazadeh from the Icahn School of Medicine explores the molecular mechanisms behind adult stem cells as we age

What is stem cell exhaustion?

Stem cell exhaustion is the gradual decline in the function and regenerative potential of adult stem cells over time. In various tissues, the upkeep of homeostasis and the capacity to regenerate after injury depend on tissue-specific adult stem cells. These stem cells typically follow tissue-specific differentiation patterns. Their ability to alternate between states of rest (quiescence) and active proliferation is crucial for their survival and for preserving normal physiological function and regenerative capabilities. (1) Adult tissue-specific stem cells exhibit an extraordinary degree of plasticity as they transit through cellular states from a quiescent to an activated stem cell state and then revert to their original quiescent state. (2) To protect against infection and promote healing, the usual homeostatic signals that regulate transition through quiescent and active states – referred to as the 'milieu intérieur' by Claude Bernard in 1865 – must be bypassed in ways that are still not fully understood. (2)

Quiescence is not a passive condition; instead, like the differentiated state, it requires ongoing active regulation to be sustained. Such transitional capacity, however, is largely lost in aging, as stem cells fail to survive or properly regulate quiescence, self-renewal, and proliferation, a state called stem cell exhaustion. (3) These observations support the stem cell theory of aging, which suggests that aging results from the inability of tissue-specific stem cells to replenish tissues with functional differentiated cells that sustain tissue function. They also pave the way for a new era of research into the stem cell aging, which may offer therapeutic potential. (4) Key Features of stem cell exhaustion are reduced proliferation, impaired differentiation, accumulative DNA damage, senescence, and altered niche.

What do we know about the causes of stem cell exhaustion?

In many aging tissues, the stem cells reduced regenerative ability comes from both intrinsic changes within the stem cells themselves and extrinsic alterations in the stem cell niche microenvironment. Central to intrinsic factors, the transcriptional and epigenetic misregulation of gene pathways in aging stem cells leads to alterations in their proliferation and differentiation in vivo. For example, in muscle, quiescent stem cells possess a permissive chromatin state in which few genes are epigenetically repressed by repressive histone mark H3K27me3, and many genes encoding regulators that specify

non-myogenic lineages are demarcated by bivalent domains at their transcription start sites (TSSs). During aging, there is a global increase in H3K27me3 across the genome. [5]

As these epigenetic changes accumulate with age, they may contribute to a functional decline in quiescent muscle stem cells (MuSCs). Alterations of the chromatin landscape have also been seen in hair follicle stem cells (HF-SCs). Specifically, reduced open chromatin regions have been associated with differentiation, whereas enhanced open chromatin regions in HF-SCs have been associated with quiescence. [6] Surprisingly, during aging, HF-SC numbers decrease, but their epigenetic identity is retained. However, they show altered expression of extracellular matrix genes, which correlates with an age-related decline in hair regeneration after wounding. [7] This highlights the critical role of the dialogue between stem cells and their niche in monitoring stem cell turnover during aging.

A good example regarding the impact of extrinsic signals on stem cell turnover comes from MuSCc, in which components of the extracellular matrix (ECM), like fibronectin that anchor the stem cells, are diminished during aging. In response to injury, a sharp peak in fibronectin levels is needed to boost Pax7+ MuSCs and inhibit anchorage-dependent programmed cell death. Thus, failure to enhance fibronectin expression, as observed in aged muscle, can impede the regenerative capacity of MuSCs. In the case of neural stem cells (NSCs), the extrinsic factors are delivered through the bloodstream.

Various factors have been identified that have positive or negative effects on neurogenesis, many of which are immune-related. Delivered through blood, CCL11/Eotaxin, an inflammatory cytokine, and β2-microglobulin, a component of MHC class I, are both elevated in old blood and negatively affect neurogenesis and cognition in young animals. [8] Although considered extrinsic factors, it is still unclear whether these factors influence neurogenesis by acting directly on niche cells or indirectly by altering the niche environment to a less or more inflammatory state. In addition to systemic factors, local morphogens, including Notch, Wnt, and sonic hedgehog, are critical during embryonic development and regulate adult stem cells throughout life.

Considering solutions to slow down stem cell exhaustion

While there has been a recent surge in research on this topic, a major limitation remains the lack of human trials. It is well-established that lifestyle factors significantly impact tissue stem cell turnover. For example, exercise induces a state of quiescence in blood stem cells without reducing the number of oxygen-carrying red blood cells. Recent studies have also highlighted the role of sleep in blood stem cell regulation, with sleep fragmentation shown to have a lasting effect on the blood stem cell epigenome, favoring a myeloid lineage and priming stem cells for inflammation. [9] Diet is another crucial factor influencing adult stem cell turnover across various tissues. For instance, caloric restriction (CR) inhibits mTORC1 signaling in Paneth cells, shifting the intestinal stem cell balance toward self-renewal. In muscle, CR promotes a metabolic shift toward oxidative metabolism, which benefits quiescent stem cells. A deeper understanding of the

molecular mechanisms behind adult stem cell turnover in tissues like skeletal muscle, hematopoietic tissue, the brain, and skin could pave the way for new drug screenings and therapeutic strategies.

References

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