Age-resistant quiescent stem cells support muscle regeneration

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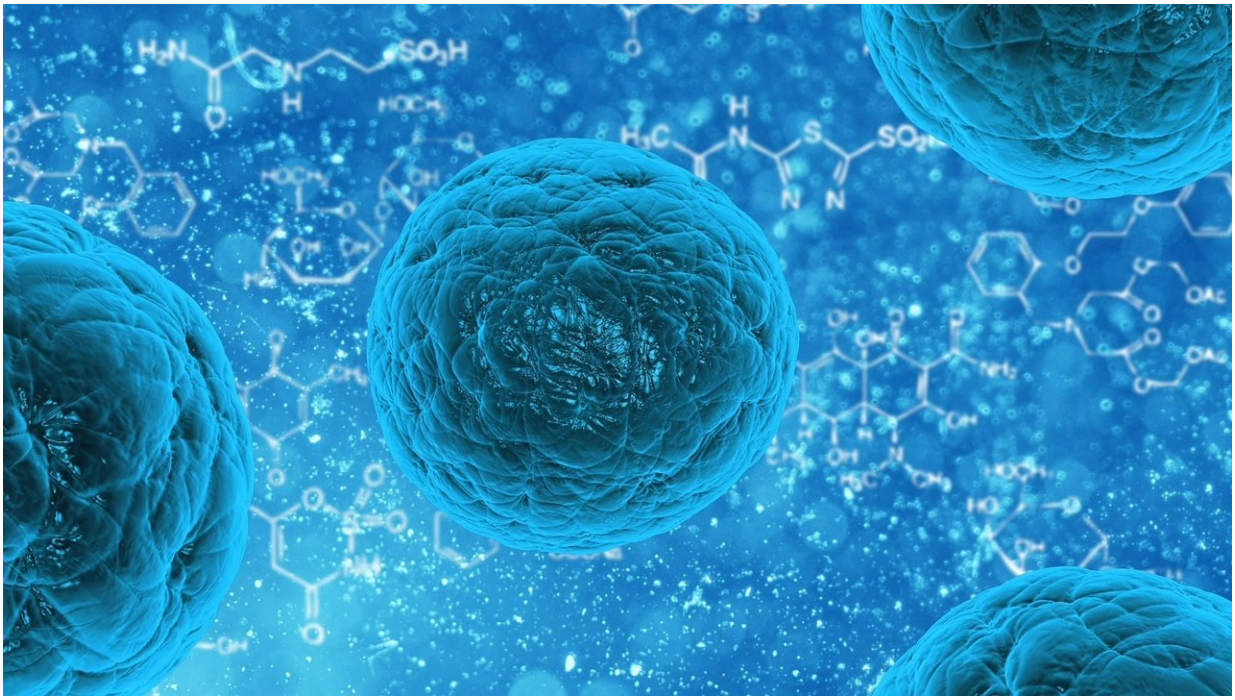

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Researchers from the Computational Biology group at the University of Luxembourg's Luxembourg Centre for Systems Biology (LCSB) participated in an international study focusing on adult stem cells in muscle tissue. The results of this collaboration highlighted the existence of two different types of quiescent stem-cell states with distinct properties. Thanks to the implementation of a new computational

method, the researchers were able to elucidate some of the molecular mechanisms involved in the observed stem-cell heterogeneity, and to restore stem cell regenerative function in old age. Their findings, recently published in *Nature Cell Biology*, showed that the diversity and regenerative properties of stem cells resist aging more than previously anticipated, ensuring prolonged survival and supporting tissue regeneration.

Adult stem cells are undifferentiated cells, found throughout the body, that have the the ability to self-renew and can differentiate into all cell types, helping regenerate damaged tissues. Stem cell aging is one of the causes of the decline observed in tissue regeneration over time, but the underlying mechanisms remain largely unknown. "The possibility of delaying or reversing stem-cell functional decline is one of the most fascinating challenges in regenerative medicine," explains Prof. Antonio Del Sol, head of the Computational Biology group at the LCSB.

Two stem cell states with different roles

Adult stem cells are quiescent for most of their life: they stay dormant for prolonged periods and only activate in response to injury. They then multiply and acquire distinct fates, some forming new muscles fibers while others replenish the stem-cell pool. Recent studies suggested that the quiescent stem cell population is heterogeneous, but the role of this heterogeneity in tissue repair and how it evolves throughout life remain unclear. Researchers from the LCSB and colleagues from Spain, Italy and U.S. collaborated to investigate these issues in mice, from early neonatal stages to geriatric age, and through innovative computational methods.

They identified two quiescent stem-cell states in undisturbed skeletal muscle that are distinguished by their relative expression of a specific gene called CD34. Quiescent stem cells expressing high CD34 levels are

set to self-renew upon injury, keeping the genuine hallmarks of stem cells (genuine state), whereas those expressing low levels are primed to differentiate into muscle cells (primed state).

Preservation of stem cell diversity through old age

The researchers further showed that the genuine stem cell state is preserved into old age: old genuine stem cells performed as well as young counterparts during muscle regeneration in vivo. Nonetheless, in extreme old age, these stem-cells undergo a steep functional decline and acquire traits characteristic of primed stem cells. If this final change likely explains the sharp deterioration in muscle regeneration in geriatric age, these results are also unexpected: diversity and regenerative properties of stem cells resist aging more than previously anticipated.

Understanding the underlying molecular mechanisms

To better understand how stem cell heterogeneity evolves over time, the researchers explored the mechanisms involved by using computational and mathematical modeling. They identified a molecular pathway that plays a role in maintaining the two quiescent stem cell states. First, the activity of a specific transcription factor—called FoxO—is required to preserve the genuine stem cell state. Conversely, FoxO inactivation deteriorates the genuine state,causing stem cells to acquire traits of the primed state, as seen in extreme old age. It suggests that long-lived quiescent stem cells primarily rely on FoxO signaling to preserve diversity and stemness.

Exploring further up the signaling pathway thanks to a new computational method, the researchers found that two molecules—Igf and Akt—impact FoxO transcription factors and regulate the stem cell states.

Countering age-dependent muscle atrophy

This study highlights loss of heterogeneity in long-lived stem cells as a driver of regenerative failure with aging.Understanding how to preserve the stem cell fraction endowed with the highest regenerative properties in old muscle will be critical to enhancing muscle regeneration, particularly at geriatric age.

"The identification of the IGF-1/Akt/FoxO signaling pathway and of its role in maintaining the heterogeneity of quiescent stem cells could help uncover ways to activate stem cells to repair muscle," emphasizes Prof. Del Sol. "Targeting these molecules could for example promote stemness and constitute a promising strategy to rejuvenate geriatric genuine stem cells, with beneficial consequences for regeneration after injury."

More information: Laura García-Prat et al. FoxO maintains a genuine muscle stem-cell quiescent state until geriatric age, *Nature Cell Biology* (2020). DOI: 10.1038/s41556-020-00593-7

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