Study reveals starring role for shape-shifting mitochondria in stem cell function

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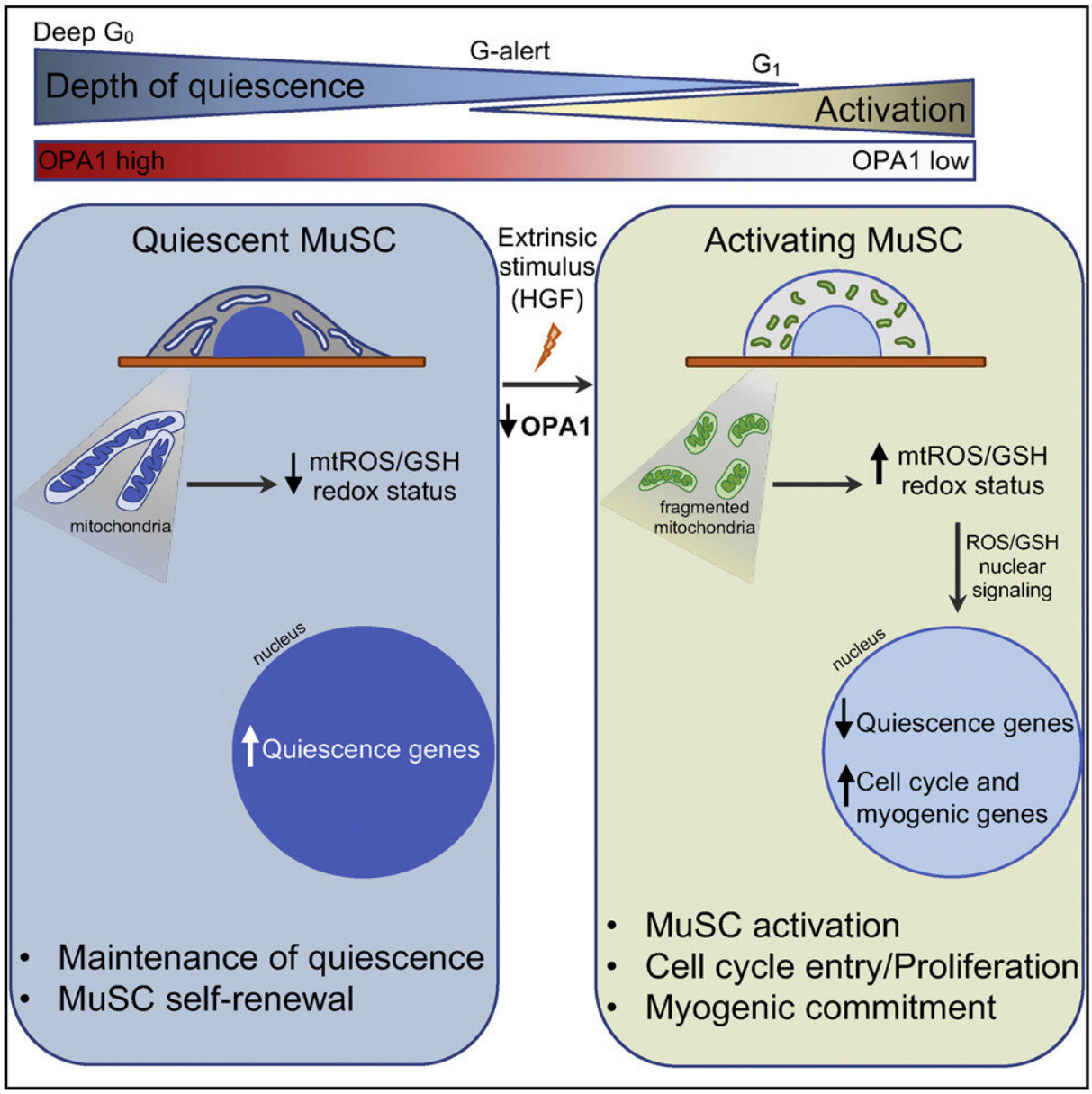

Graphical abstract. Credit: *Cell Stem Cell* (2022). DOI: 10.1016/j.stem.2022.07.010

Mitochondria are remarkable shape-shifting organelles that have long been understood as the powerhouses inside our cells. But relatively little is known about how the constant fission and fusion of these tiny energy generators impacts stem cell function and tissue regeneration.

Now, compelling new research from Dr. Mireille Khacho's lab at the University of Ottawa Faculty of Medicine reveals a starring role for mitochondrial dynamics within adult muscle stem cells—those unique and primitive cells that serve as the body's raw material for muscle renewal and repair.

Published today in *Cell Stem Cell*, the study found that mitochondria's shape transitions as they elongate and divide are in fact regulating the dormant state of adult muscle stem cells.

The new findings could be an important revelation because adult muscle stem cells ——which typically exist in a dormant state known as quiescence— are essential for tissue stability. Dormancy is crucial to these cells' longevity and they require a delicate balance. They get roused from their protective state when activated for renewal and when repairing tissue that suffers an injury or has been corroded by disease.

In essence, her lab suggests a wide-ranging repertoire for mitochondria. Not only do they act as internal sensors and communicators, but their fragmentation plays a big part in overall stem cell maintenance and functioning. Through a series of manipulations with a unique mouse model, the researchers showed that the essential mitochondrial shaping protein OPA1 regulates the dormant state of adult muscle stem cells.

And the chronic loss of this protein and persistent fragmentation leads to severe muscle stem cell defects.

Dr. Khacho's team says the findings show for the first time that the protein OPA1—one of the main regulators of mitochondrial fusion—is essential for muscle stem cell maintenance and function. They pieced together a connection between the depletion of stem cells and mitochondria becoming imbalanced and dysfunctional.

"This paper is a combination of uncovering physiological mechanisms and then using that to explain what could go wrong in diseases and aging," says Dr. Khacho, a uOttawa assistant professor in the Department of Biochemistry, Microbiology and Immunology who holds the Canada Research Chair in Mitochondrial Dynamics and Regenerative Medicine.

The tiny structure's role is somewhat counterintuitive. Generally, fragmentation of mitochondria is a destructive phenomenon for cells in tissues, Dr. Khacho explains. But in their experiments with adult muscle stem cells, her team found that their fragmentation also serves as a physiological mechanism that activates signaling to the nucleus. It does this by increasing levels of an antioxidant peptide called glutathione. Even more intriguing is that they uncovered a new function for this peptide: it acts as a signaling molecule that mediates the crosstalk between mitochondria and the nucleus.

"Disruption to mitochondria may be the reason why we lose our stem cells amid diseases and aging," Dr. Khacho says. "If you have a scenario where you have imbalanced mitochondrial dynamics, which could happen in diseases and in aging, what would ultimately happen is your stem cells would lose their protective dormancy and they would deplete over time."

The team's insights will certainly be of deep interest to scientists studying a range of muscle-related degenerative diseases, as well as muscle weakness and atrophy during aging. Further, it may eventually help pave the way for therapeutic strategies to modify mitochondrial dynamics and function in stems cells to restore the regenerative potential of tissues.

That's significant because muscle degeneration is a leading cause of disability worldwide. Findings that shed light on the contribution of mitochondrial disruptions to adult stem cell dysfunctions could be a step toward efforts at restoring the regenerative potential of muscle in degenerative disorders and aging.

More information: Nicole Baker et al, The mitochondrial protein OPA1 regulates the quiescent state of adult muscle stem cells, *Cell Stem Cell* (2022). DOI: 10.1016/j.stem.2022.07.010

Provided by University of Ottawa

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