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New insights on mechanism that could help treat muscle-related diseases

Marcela Quintanilla-Dieck · 617-726-0954 · mquintanilladieck@mgh.harvard.edu

Key Takeaways

- Expression of the MyoD gene combined with exposure to three chemicals causes skin cells to become primitive muscle progenitors that can be maintained indefinitely in the lab and later coaxed into becoming mature muscle cells to treat muscle-related diseases.
- Skin-derived muscle progenitors are molecularly similar to muscle tissue stem cells, and muscle cells derived from these progenitors are more stable and mature than muscle cells directly converted from skin cells.
- Erasure of specific DNA modifications is key for acquiring a muscle progenitor state.

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Konrad Hochedlinger, PhD
Center for Regenerative Medicine, Massachusetts General Hospital

BOSTON – Investigators who previously developed a recipe for turning skin cells into primitive muscle-like cells that can be maintained indefinitely in the lab without losing the potential to become mature muscle have now uncovered how this recipe works and what molecular changes it triggers within cells. The research, which was led by scientists at Massachusetts General Hospital (MGH) and is published in *Genes & Development*, could allow clinicians to generate patient-matched muscle cells to help treat muscle injuries, aging-related muscle degeneration, or conditions such as muscular dystrophy.

It's known that expression of a muscle regulatory gene called *MyoD* is sufficient to directly convert skin cells into mature muscle cells; however, mature muscle cells do not divide and self-renew, and therefore they cannot be propagated for clinical purposes. "To address this shortcoming, we developed a system several years ago to convert skin cells into self-renewing muscle stem-like cells we coined induced myogenic progenitor cells, or iMPCs. Our system uses *MyoD* in combination with three chemicals we previously identified as facilitators of cell plasticity in other contexts," explains senior author Konrad Hochedlinger, PhD, a principal investigator at the Center for Regenerative Medicine at MGH and a professor of medicine at Harvard Medical School.

In this latest study, Hochedlinger and his colleagues uncovered the details behind how this combination converts skin cells into iMPCs. They found that while *MyoD* expression alone causes skin cells to take on the identity of mature muscle cells, adding the three

chemicals causes the skin cells to instead acquire a more primitive stem cell–like state. Importantly, iMPCs are molecularly highly similar to muscle tissue stem cells, and muscle cells derived from iMPCs are more stable and mature than muscle cells produced with MyoD expression alone. “Mechanistically, we showed that *MyoD* and the chemicals aid in the removal of certain marks on DNA called DNA methylation,” says lead author Masaki Yagi, PhD, a research fellow at MGH. “DNA methylation typically maintains the identity of specialized cells, and we showed that its removal is key for acquiring a muscle stem cell identity.”

Hochedlinger notes that the findings may be applicable to other tissue types besides muscle that involve different regulatory genes. Combining the expression of these genes with the three chemicals used in this study could help researchers generate different stem cell types that closely resemble a variety of tissues in the body.

Co-authors include Masaki Yagi, Fei Ji, Jocelyn Charlton, Simona Cristea, Kathleen Messemer, Naftali Horwitz, Bruno Di Stefano, Nikolaos Tsopoulidis, Michael S. Hoetker, Aaron J. Huebner, Ori Bar-Nur, Albert E. Almada, Masakazu Yamamoto, Anthony Patelunas, David J. Goldhamer, Amy J. Wagers, Franziska Michor, Alexander Meissner and Ruslan I. Sadreyev.

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About the Massachusetts General Hospital

Massachusetts General Hospital, founded in 1811, is the original and largest teaching hospital of Harvard Medical School. The Mass General Research Institute conducts the largest hospital-based research program in the nation, with annual research operations of more than $1 billion and comprises more than 9,500 researchers working across more than 30 institutes, centers and departments. In August 2021, Mass General was named #5 in the *U.S. News & World Report* list of "America’s Best Hospitals."

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