Uncovering the genetics of skeletal muscle growth and regeneration

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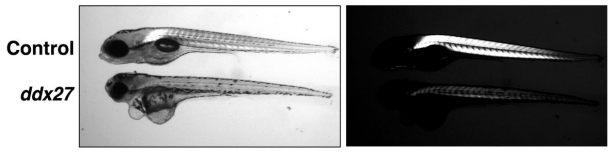

Zebrafish larvae with intact skeletal muscle structure and function (top) and impaired skeletal muscle structure (as seen with reduced birefringence, right panel) and function due to loss of Ddx27 (bottom). Credit: Vandana Gupta, Brigham and Women's Hospital

Skeletal muscle has a remarkable capacity to regenerate - a capacity that is diminished in many skeletal muscle diseases and aging. To investigate the mechanism behind skeletal muscle growth and regeneration, researchers from Brigham and Women's Hospital bombarded zebrafish with chemical mutagen and screened for larvae with defective skeletal muscle structure. Using genetic mapping, they found that zebrafish larvae with a mutation in DDX27 showed reduced muscle growth and impaired regeneration. Their results are published in *PLOS Genetics*.

"A major hindrance in the development of effective therapies for skeletal muscle diseases thus far has been a lack of understanding of the biological processes that promote muscle growth and repair," said corresponding author Vandana Gupta, PhD, of the Division of Genetics at BWH. "Our study is one of the first efforts to provide specificity to the processes controlling protein synthesis in muscles, which will hopefully allow for the development of effective targeted treatments for skeletal muscle diseases."

Loss of muscle mass is a debilitating feature that is a common manifestation of a wide array of diseases, and leads to reduced muscle function and increased morbidity and mortality. Maintenance of skeletal mass relies on a dynamic balance between protein synthesis and degradation. A number of conditions such as myopathies, sarcopenia, cancer cachexia, disuse atrophy, sepsis and chronic kidney diseases lead to a disruption of this balance in favor of reduced protein synthesis.

The researchers discovered that DDX27 is involved in ribosome biogenesis and protein synthesis in skeletal muscle. Loss of DDX27 affects the function of skeletal muscle by disrupting the regulation and production of proteins that are crucial for muscle function. Looking ahead the researchers hope to further explore the mechanism by which protein synthesis is changed in different disease conditions and develop approaches to target DDX27 regulated pathways to restore muscle growth and regeneration in skeletal muscle disorders.

"If we can promote muscle growth in patients with skeletal muscle disorders, we would be able to restore muscle strength and mobility in these patients, and reducing morbidity," said Gupta. "Our study is just the beginning of an effort to develop regenerative therapies for myopathies that could have a wide impact in a large patient population."

More information: Alexis H Bennett et al. "RNA helicase, DDX27 regulates skeletal muscle growth and regeneration by modulation of translational processes" *PLOS Genetics* DOI: doi.org/10.1101/125484

Provided by Brigham and Women's Hospital

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