RNAging: An exercise-regulated noncoding RNA counteracts muscle aging

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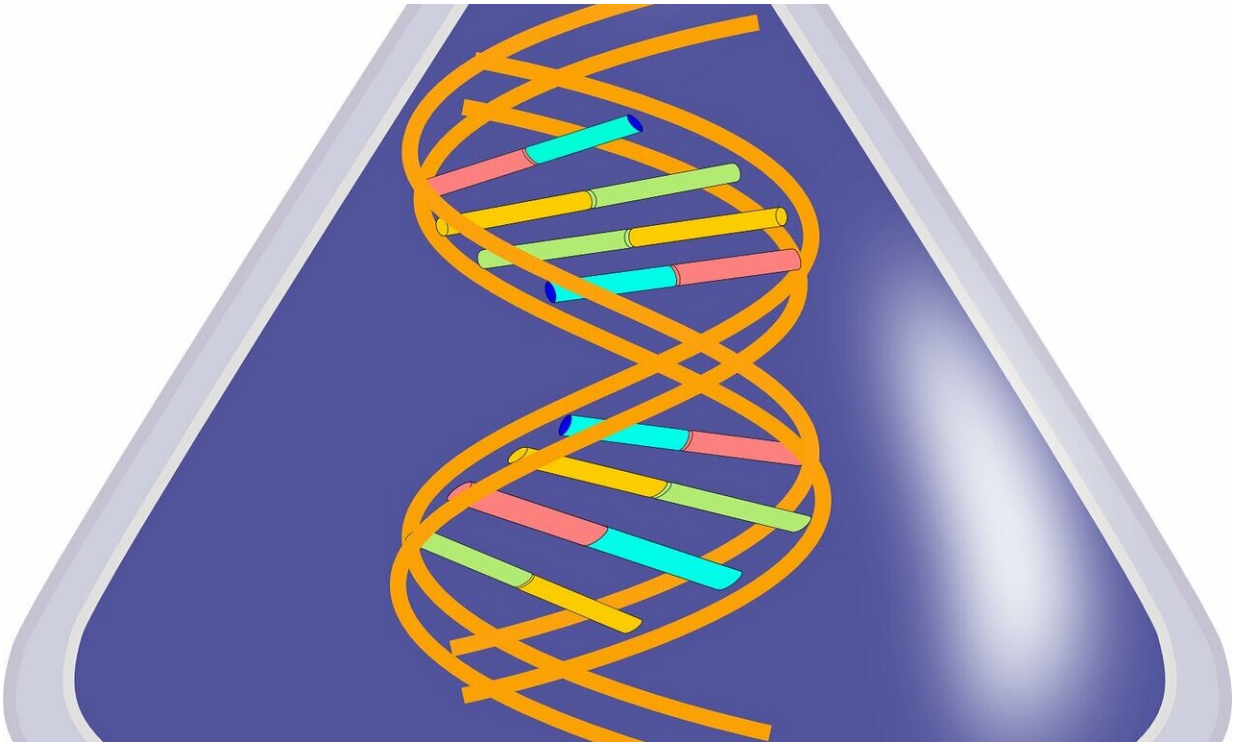

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In a joint, collaborative effort between laboratories at EPFL, NTNU Norway and CBMR Denmark, researchers examined the molecular effect of exercise upon noncoding RNA genes in skeletal muscle in *Science Translational Medicine*. In this study, they discovered the long noncoding RNA "CYTOR" and investigated its role in skeletal muscles

of rodents, worms and human cells.

Skeletal muscle displays remarkable plasticity upon exercise, but is at the same time one of our organs that is most affected by aging. Skeletal muscle aging is characterized by estimated yearly losses of ~1 percent muscle mass and ~3 percent muscle strength in the elderly, resulting in an accumulated net loss of >30 percent muscle mass during aging. This process is further exacerbated by sarcopenia, a degenerative disease syndrome whose prevalence is projected to increase tremendously in our aging societies.

The research team found that expression of the long, noncoding RNA CYTOR is induced by exercise but declines during rodent and human skeletal muscle aging. Using various genetic tools to inhibit or re-express the long noncoding RNA CYTOR in aged muscle revealed that CYTOR enhanced myogenic differentiation, notably favoring the fast-twitch myogenic fate.

"This finding was of particular interest to us, as fast-twitch myofibers are well known to deteriorate upon aging. We therefore, hypothesized that noncoding RNA gene therapy could deliver benefits to aged muscle," notes Martin Wohlwend, the first author of the study. Indeed, CRISPR-mediated re-establishment of Cytor expression in skeletal muscle of aged mice improved muscle morphology and muscle function.

To study the genetic effect of human CYTOR, the researchers identified and characterized an expression quantitative trait locus (eQTL) located within a skeletal muscle enhancer element nearby the CYTOR genomic locus. Individuals carrying a specific allelic configuration at the genetic marker rs74360724 locus displayed higher CYTOR levels in skeletal muscle, and genetic association studies revealed improved 6-minute walking performance in these elderly individuals. Benefits of CYTOR in aging was further demonstrated by forced expression of human CYTOR

in aged muscle of C. elegans, which improved several phenotypic parameters constituting worm healthspan.

To elucidate mechanisms of the long noncoding RNA CYTOR, the laboratory of Professor Johan Auwerx then turned to examine CYTOR's effects on epigenetics—the study of how environment can cause changes in gene expression without alterations in the DNA sequences. They found that Cytor re-configures chromatin accessibility at binding sites of other genes and transcription factors known to determine muscle fiber type.

By studying a noncoding RNA gene, the study sheds light on an interesting genomic entity, for which recent advances in RNA delivery provide therapeutic perspectives.

"Pharmaceutical incentives targeting fast-twitch muscle fibers in aging/sarcopenia have thus-far been elusive. Our current RNA-based approach hence provides an intriguing strategy to target age-related muscle disorders, such as sarcopenia," says Johan Auwerx.

More information: The exercise-induced long noncoding RNA CYTOR promotes fast-twitch myogenesis in aging, *Science Translational Medicine* (2021). www.science.org/doi/10.1126/scitranslmed.abc7367

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