Medical Xpress

Researchers illustrate how muscle growth inhibitor is activated, could aid in treating ALS

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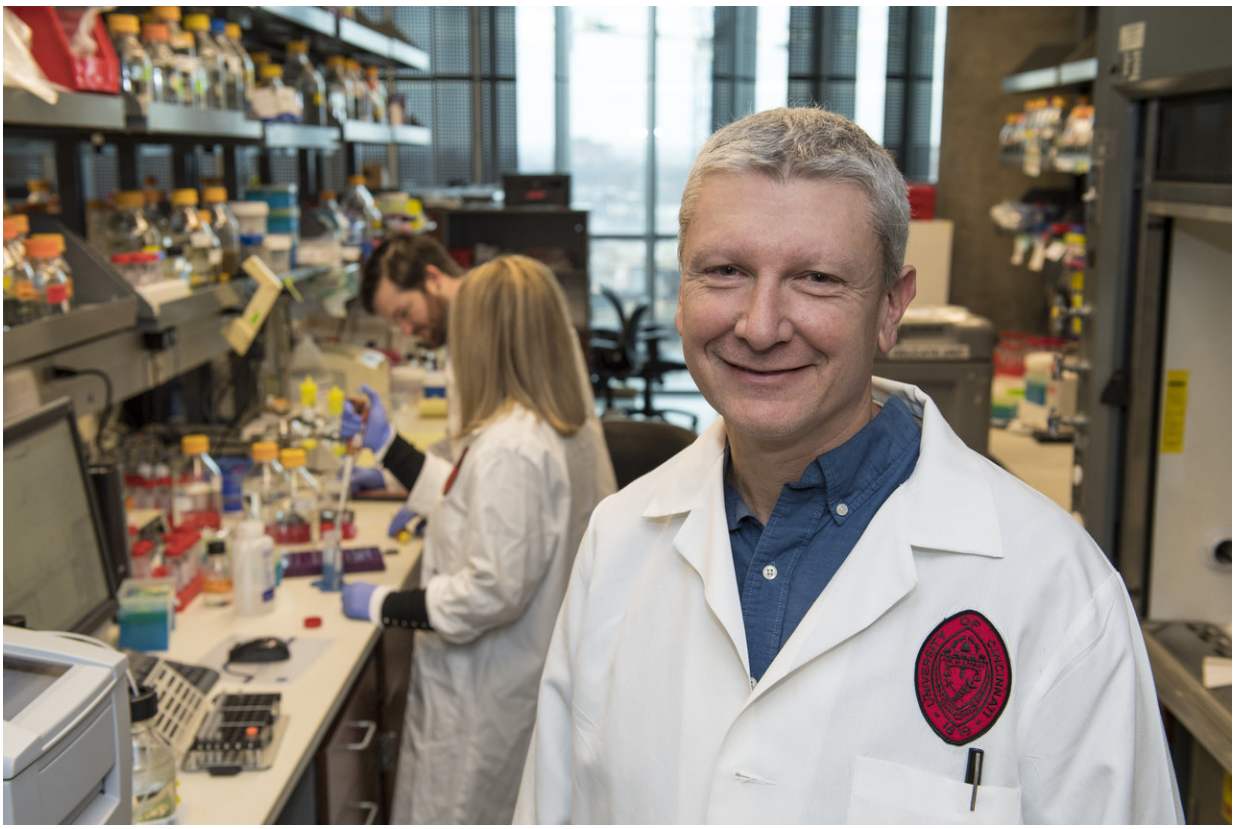

Thomas Thompson, PhD, is shown in his laboratory at the University of Cincinnati College of Medicine. Credit: University of Cincinnati College of Medicine

Researchers at the University of Cincinnati (UC) College of Medicine are part of an international team that has identified how the inactive or latent form of GDF8, a signaling protein also known as myostatin responsible for limiting muscle, is activated.

That knowledge could someday help in finding a better treatment to improve muscle function in diseases such as muscular dystrophy, amyotrophic lateral sclerosis (ALS) or Lou Gehrig's disease, and cancer cachexia, a muscle wasting condition, says Tom Thompson, PhD, professor in the UC Department of Molecular Genetics, Biochemistry and Microbiology. Muscular Dystrophy is a hereditary condition marked by weakness and progressive wasting of the muscles, while ALS impacts nerve cells that control voluntary muscle movement.

The research team's findings are detailed in a peer-reviewed article in the scholarly journal for the *Proceedings of the National Academy of Sciences* (*PNAS*). Thompson is the corresponding author for the journal article, "Molecular Characterization of Latent GDF8 Reveals Mechanisms of Activation," and its first author, Ryan Walker, is a postdoctoral fellow at Harvard University and a former UC doctoral student who once worked in Thompson's laboratory. Also from UC participating in the study are Jason McCoy, a doctoral student, and Magdalena Czepnik, a research assistant.

"All animals have the protein molecule myostatin which limits the size of our muscle," explains Thompson. "Myostatin is being targeted therapeutically to boost muscle production in patients with muscle disorders."

"Myostatin is one member in this very large family of molecules that includes 33 ligands. They play very important roles in many aspects of the human body and often are wrongly regulated in many human diseases such as cancer. Some are used to develop bone while others play

large roles during in human reproduction."

During synthesis, GDF8 or myostatin, is made as a precursor which remains in a dormant state with half of the molecule holding the section of GDF8 responsible for signaling inactive, says Thompson. Activation involves slicing a section of the molecule responsible for dormancy, thus allowing signaling to occur in myostatin and inhibition of muscle growth. Researchers were able to demonstrate that myostatin could be turned on with minor changes to the molecule's dormant mechanism.

"As researchers, our goal is to understand the details of how these molecules are locked," says Thompson, adding that they will be using animal models to conduct this research. "By tweaking the dormant state of the molecule, we can get myostatin to signal without the need for cutting, basically picking the lock without a key. Our study illustrates what parts of the dormant state are important for holding GDF8 inactive and can be helpful in understanding the mechanism for GDF8 signaling."

More information: Ryan G. Walker et al. Molecular characterization of latent GDF8 reveals mechanisms of activation, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1714622115

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