Nature Biomedical Engineering: A new method for studying mechanical proteins and their involvement in muscular disorders

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This new tool will advance the development of treatments for congenital muscle diseases and cardiomyopathies.

A team at the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC), led by Dr. Jorge Alegre-Cebollada, has developed an innovative method, called TEVs-TTN, for studying the specific mechanical functions of proteins through their controlled cleavage, a process that renders the proteins unable to sense and transmit mechanical force. The study results extend knowledge about the development of muscular diseases.

The study, published in *Nature Biomedical Engineering*, demonstrates that interrupting mechanical transmission by the protein titin precipitates muscular diseases. This finding opens new routes to understanding muscular dystrophies and other diseases associated with the protein **titin**.

Titin, named after the titans of Greek mythology, is the largest protein in animals and plays a critical role as the structural linchpin of sarcomeres, the contractile units of muscle cells. Mutations in the titin gene (*TTN*) are a leading cause of congenital muscular diseases and cardiomyopathies, explains first authorDr. Roberto Silva-Rojas: “Many of these mutations generate a prematurely truncated form of the protein, impeding its correct anchoring in the sarcomeres and disrupting muscle function.”

"In the absence of experimental animal models with titin-cleavage mutations, our approach allows a structured and targeted analysis of the impact of these types of alterations. This makes TEVs-TTN an ideal tool for testing therapies designed to mitigate the effects of impaired sarcomere integrity.”

One intriguing finding of the study is that titin cleavage caused complete disintegration of sarcomeres over the course of a few days, leaving muscle cells devoid of their basic functional unit. Nevertheless, these cells survived, suggesting that similar processes might operate in other situations, such as muscle tears, heart failure, or cardiotoxicity associated with chemotherapy.

The methodology developed at the CNIC marks a milestone in the study of how protein mechanics contribute to tissue and organ physiology. Just as titin is critical for force transmission in sarcomeres, other proteins, such as dystrophin, dystroglycan complexes, integrins, and lamins, play critical roles in extracellular matrix regulation and cell membrane integrity.

The new tool will enable the research team to confirm or refute hypotheses about the functioning of these proteins. These advances, in turn, could pave the way to the development of new therapeutic strategies for many diseases beyond those affecting muscle.

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- *Silva-Rojas R, Vicente N, Gavilán-Herrera M, Labrador-Cantarero V, Sicilia J, Giménez-Sáez O, Dumitru AC, Sánchez MI, Gato-Vilaseca M, Velázquez-Carreras D, López JA, Vázquez J, Herrero-Galán E, López-Unzu MA, Pricolo MR, Alegre-Cebollada J. Mechanically knocking out titin reveals protein tension loss as a trigger of muscle disease. **Nat Biomed Eng.** 2025 Jun 5. doi: 10.1038/s41551-025-01403-x. Epub ahead of print. PMID: 40473933.*