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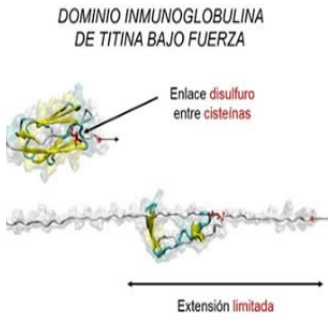
New mechanism regulates key protein for heart function



The discovery of a new mechanism regulating the elasticity of titin, a protein with important roles in the function of skeletal muscle and the heart, is described in a study published in Nature Communications. The study was a collaboration between scientists at Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) and Columbia University in New York.

Titin is a key protein in the functioning of striated muscles throughout the body, particularly in the heart. As such, mutations in the titin gene are a common cause of diseases affecting the muscles of the body and the heart, according to CNIC researcher Dr. Jorge Alegre-Cebollada.

Also, being the largest protein in the human body, titin has a multitude of functions. As Dr. Alegre-Cebollada explains, “in simple terms we can think of titin as a ‘molecular spring’ that allows muscle cells to contract in synchrony.” However, it is not a simple spring, and the many mechanisms that determine titin elasticity include the unfolding of specific regions in its structure called "immunoglobulin domains". In all, titin elasticity is determined by the concerted action of more than 100 immunoglobulin domains within the protein.

Bioinformatic and structural biology techniques enabled the research team to determine that immunoglobulin domains have a high cysteine content. When two cysteines in a protein come close to one another, they can form a chemical link between different parts of the polypeptide chain called a disulfide bond, says Dr. Alegre-Cebollada. In addition, many of the immunoglobulin domains in titin form disulfide links and that the cysteines participating in them can change dynamically, a process called isomerisation.

“The most interesting finding was that the formation and isomerization of disulfide bonds causes major changes in the elastic properties of titin,” Dr. Alegre-Cebollada points out.

The formation of disulfide bonds is an example of a broader class of biochemical transformations known as reduction-oxidation (redox). It has long been known that many disease processes affecting the heart, including myocardial infarction, involve sudden and drastic changes in the redox state of the heart muscle.

Dr. Alegre-Cebollada’s group is currently investigating how our cells modify the titin redox state as a mechanism to modulate skeletal and heart muscle activity and how different diseases can interfere with the mechanical action of the protein, resulting in loss of functionality.

Columbia University's collaborators for this study were led by Professor Julio Fernández, a pioneer in the development of single-molecule biophysical techniques for investigating the mechanical properties of proteins.

Source: CNIC
Image Credit: CNIC

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