Atomic model of tropomyosin bound to actin

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New research sheds light on the interaction between the semi-flexible protein tropomyosin and actin thin filaments. The study, published by Cell Press on February 15th in the *Biophysical Journal,* provides the first detailed atomic model of tropomyosin bound to actin and significantly advances the understanding of the dynamic relationship between these key cellular proteins.

Tropomyosin is a long protein that associates with actin, a highly conserved thin filament protein found in organisms from yeast to humans. Actin, a major part of the cell's cytoskeleton, drives shape changes and cellular locomotion in many types of cells, and is part of the contractile apparatus in muscle cells. Tropomyosin binds to actin ad acts as a molecular barrier, essentially covering up active sites that are required for actin to interact with other proteins. In turn cellular signals can trigger additional regulatory proteins to move tropomyosin, dislodging the barrier in order to allow actin to associate with remodeling and motor proteins.

"Previous studies examining tropomyosin in isolation suggested that it is a coiled coil that matches the shape of actin filaments and is arranged along their surface," explains senior study author, Dr. William Lehman from the Department of Physiology and Biophysics at Boston University School of Medicine. "However, a complete elucidation of tropomyosin-based regulatory mechanisms requires a complete representation of the atomic structure and mechanical properties of the tropomyosin molecule linked to its biological substrate."

Building on previous findings that the association between tropomyosin and actin is an electrostatic attraction between oppositely charged amino acids, Dr. Lehman and colleagues explored thousands of combinations of different rotations and positions of tropomyosin to find the most favorable interaction between tropomyosin and actin. The researchers then used electron microscopy as a second approach to also reconstruct the interaction. The two methods yielded virtually identical solutions, "which is very gratifying", says Dr. Lehman.

The authors discuss how the interaction between tropomyosin and actin is just weak enough that tropomyosin can be readily perturbed by regulatory proteins and act as a molecular switch to regulate actin interaction with other proteins. "The atomic model that we propose can serve as a reference location to characterize tropomyosin regulatory movements on actin thin filaments," concludes Dr. Lehman. "Moreover, the map of actin-tropomyosin provides a structural platform to assess mutations that influence actin-tropomyosin behavior and also to develop tropomyosin-mimicking peptide drugs designed to modulate actin-myosin or other interactions."

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