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The emerging role of elasticity of intrinsically disordered proteins in force sensing and signal transduction

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Natively disordered segments and domains are prevalent in eukaryotic multidomain proteins. These intrinsically unstructured regions link folded domains and act as binding sites with proteins, RNA's and DNA and as sites of protein modifications such phosphorylation. They play major roles in signaling transduction, cell control, and transcriptional and translational regulation. Disordered regions are generally flexible and open, and posses some degree of orderness of secondary structures. These structural characteristics allow them to recognize and bind to a wide range of partners with high specificity yet low affinity, thus promoting the rapid exchange of partners, especially as hubs and nodes in signaling networks.

The most extended disordered regions are found in the PEVK segments of the giant muscle protein titin. Titin has a segmented domain structure consisting mainly of tandem repeats of immunoglobulin-like and fibronectin beta-barrels and a special PEVK segment. The extension of this unique segment accompanies the rise in passive tension when resting muscle is stretched moderately, while maintaining the overlap of the actin and myosin filaments. Its multifaceted function includes the assembly of the muscle sarcomere, the maintenance of sarcomere symmetry and integrity and the generation of passive tension.

The passive elasticity of muscle at a physiological range of stretch arises primarily from the extension of the PEVK segment, which is a polyampholyte with dense and alternating-charged clusters. Our NMR, CD, atomic force microscopy and computational studies reveal clearly that indicated that PEVK is a highly evolved, gel-like spring with its elasticity dominated by the sequence-specific charge interactions. A single polyampholyte chain may be fine-tuned to generate a broad range of molecular elasticity by varying charge pairing schemes and chain configurations. Our protein interaction studies indicated that titin PEVK also represents an extended open and flexible regions for protein recognition, especially with proteins in the SH3 signaling pathways. The stretch-sensitive protein interaction of titin PEVK with SH3 ligands strongly suggests that the elasticity of titin PEVK is functionally important in its ability to sense force and transduce force to biochemical signals. It is conceivable that elasticity and ligand binding of intrinsically disordered protein segments are biologically important attributes for these key players in signaling and stress pathways.

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Seminar Announcement

Artwork by Yong Ann Nee, DBS, NUS