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Intrinsically Disordered Titin PEVK as a Molecular Velcro: Salt-Bridge Dynamics and Elasticity JEFFREY FORBES, WANXIA TSAI, NIAMS/NIH, RICHARD WITTEBORT, Univ. of Louisville, KUAN WANG, NIAMS/NIH — Titin is a giant modular protein (3-4 MDa) found in the muscle sarcomere, where the intrinsically disordered and elastic PEVK segment plays a major role in the passive tension of skeletal and heart tissues. We have proposed that salt-bridges play a central role in the elasticity of PEVK. The 50 kDa engineered PEVK polyprotein shows well-resolved NMR spectra at all concentrations. From long-range NOE's, we observed stable K to E salt-bridges. Simulated annealing with NMR restraints yielded a manifold of structures for an exon 172 trimer. Steered molecular dynamics simulations were done to study how the manifold of salt-bridges evolves during the stretching experiment. Repeated SMD simulations at slow velocity (0.0005 nm/ps) showed force spectra consistent with experimental AFM force spectra of the polyprotein. SMD shows that salt-bridges occur even at high degrees of stretch and that these short range interactions are in integral part of the mechanical properties of PEVK. We propose that the long-range, non-stereospecific nature of electrostatic interactions provide a facile mechanism to tether and untether the flexible chains, which in turn affect elasticity as well as control the accessibility of protein-protein interaction to these nanogel-like proteins.

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