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Roles of Hinges and Linkers in Protein Extension DENNIS DISCHER, NISHANT BHASIN, VANESSA ORTIZ, MICHAEL F. KLEIN — In many multi-repeat proteins, linkers between repeats have little secondary structure and place few constraints on folding or unfolding. However, the large family of spectrin-like proteins – including α-actinin, spectrin, and dystrophin – share repeats of 3-helix bundles that appear in crystal structures to be linked by long helices. Some of these proteins also have praline-rich hinge regions. Regardless, these proteins are regularly subjected to mechanical stress, and recent single molecule AFM experiments show the simultaneous unfolding of tandem repeats at high frequency. This suggests the contiguous helix between spectrin repeats often propagates a cooperative helix-to-coil transition. Here we describe further experiments and all-atom steered molecular dynamics (SMD) simulations of tandem spectrin repeats in explicit water. The results reveal several rate-dependent pathways, with one pathway (in SMD) showing distinct unfolding of the linker between repeats. The forced unfolding mechanism begins with a splay distortion of proximal loops away from hydrophobic contacts with the linker. This is followed by linker destabilization via stretch-splay unwinding and increased hydration of the backbone. **The end result is an unfolded helix that mechanically decouples tandem repeats.**

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