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Mechanical Unfolding of the NRR Domain from Human Notch 1[1] ASHIM DEY, KATARZYNA MALEK, NICOLETA PLOSCARIU, ROBERT SZOSZKIEWICZ, Kansas State University — Notch signalling in mammals is responsible for cellular processes related to embryonic development and tissue homeostasis. Problems in Notch signaling lead to many diseases, including T-cell acute lymphocytic leukemia and solid tumors in breast cancer. Exposure of the S2 site within an extracellular NRR domain of Notch is the key early event in Notch signaling. In this paper we use single molecule force-extension (FX) AFM force spectroscopy to investigate the role of mechanical force in unfolding the NRR domain from human Notch 1. We provide probability analysis of the NRR unfolding traces, which supports the sequential NRR unfolding model. Our FX AFM measurements provide us also with histogram of the N to C termini lengths related to conformational transitions within the NRR domain. By fitting multiple Gaussians to this histogram we detect four classes of events. Based on the related steered molecular dynamics (SMD) study, we associate the first two classes of events with the S2 site exposure. We obtain that their mean unfolding forces are 77.2 $\pm$ 60.4 pN and 82.2 $\pm$ 57.67 pN, respectively. These substantial molecular forces constitute a double protection barrier against any accidental S2 site exposure.

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