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Direct evidence on the force-stabilized calcium binding of the gelsolin G6 domain YI CAO, CHUNMEI LV, XIANG GAO, MENG QIN, WEI WANG, Department of Physics, Nanjing University — Many proteins are subjected to forces in vivo. However, how force controls the structure, ligand binding and function has only been studied recently with the invention of single molecule force spectroscopy techniques. Generally, force will destabilize the native conformation of a protein and decrease its affinity to ligands. Here we show, for the first time, that force can also increase the ligand binding affinity. We used single molecule force spectroscopy by atomic force microscopy (AFM) to study the effect of calcium binding on the unfolding of the G6 domain of gelsolin. We found that at saturated calcium concentration, the unfolding forces of G6 are $\sim$ 40 pN, which are significantly higher than those of apo G6 of $\sim$ 20 pN. At intermediate calcium concentrations, the unfolding forces show a unimodal distribution, indicating fast inter-conversion rate between apo and holo G6. More strikingly, we found that if the binding constant of G6 is independent of force, the predicted unfolding forces based on the kinetic parameters obtained from apo and holo G6 are significantly lower than the experimentally obtained ones. To reconcile such discrepancy, we proposed a new model, in which we considered that the binding affinity of calcium to G6 is also force dependent. Fitting this model to experimental data clearly indicates that G6 has much higher calcium binding affinity at higher forces. We proposed that such a special force stabilized calcium binding may be important for the function of gelsolin in vivo.

Yi Cao
Department of Physics, Nanjing University

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