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Single Molecule Force Spectroscopy of Stimulus-Responsive Polypeptides: What Can We Learn from Pulling on Single Biomacromolecules?

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Summary

Single molecule force spectroscopy (SMFS), performed with an atomic force microscope (AFM), allows for the direct study of inter- and intramolecular interactions in macromolecules and between macromolecules and surfaces. For example, SMFS has been used extensively over the past decade to better understand the conformational mechanics of biomacromolecules and the unbinding energetics of protein-ligand interactions. In SMFS, the deflection of a micro-cantilever is used to report the forces that are exerted upon stretching a molecule or ligand-receptor pair, tethered between the cantilever tip and a solid substrate. With the proliferation of AFMs over the last few years, SMFS has become available to a large number of researchers, and together with the growing ability to fabricate and manipulate nanoscale structures, SMFS has seen increasing use to answer technology and engineering driven questions.

To illustrate the power and limitations of the technique, I will draw on recent work from our group where we used SMFS to study 1) the prolyl cis-trans isomerization in elastin-like polypeptides (ELP), and 2) the details of hydrophobic hydration of stimulus-responsive polyproteins. We used SMFS to investigate force-induced peptidyl-prolyl cis-trans isomerization. This transition is often fundamental for the biological activity of proteins, protein stability and folding pathways. In most of the previously reported experiments, cis-trans isomerization was catalyzed in a chymotrypsin-coupled, proline isomerase assay. Certain proteins, however, cannot be catalyzed using enzymes, and we show that force may provide an alternate trigger in these cases. We present evidence for this mechanism by Monte Carlo simulations of the force-extension curves using an elastically coupled two-state system. These results suggest that SMFS could be used to assay proline cis-trans isomerization in proteins and may thus have significant diagnostic utility. I will also present an approach we have developed that allows us to infer effects of changes in solvent quality and minor changes in molecular architecture on the molecular-elasticity of individual biomacromolecules. Specifically we show how changes in the effective Kuhn segment length can be used to interpret the hydrophobic hydration behavior of elastin-like polypeptides. Our results are intriguing as they suggest that SMFS can be used to study the subtleties of polypeptide-water interactions on the single molecule level.