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Regulatory element in fibrin triggers tension-activated transition from catch to slip bonds

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Abstract

 Fibrin formation and mechanical stability are essential in thrombosis and hemostasis. To reveal how mechanical load impacts fibrin, we carried out optical trap-based single-molecule forced unbinding experiments. The strength of noncovalent A:a knob-hole bond stabilizing fibrin polymers first increases with tensile force (catch bonds) and then decreases with force when the force exceeds a critical value (slip bonds). To provide the structural basis of catch–slip-bond behavior, we analyzed crystal structures and performed molecular modeling of A:a knob-hole complex. The movable flap (residues γ295 to γ305) containing the weak calcium-binding site γ2 serves as a tension sensor. Flap dissociation from the B domain in the γ-nodule and translocation to knob 'A' triggers hole 'a' closure, resulting in the increase of binding affinity and prolonged bond lifetimes. The discovery of biphasic kinetics of knob-hole bond rupture is quantitatively explained by using a theory, formulated in terms of structural transitions in the binding pocket between the low-affinity (slip) and high-affinity (catch) states. We provide a general framework to understand the mechanical response of protein pairs capable of tension-induced remodeling of their association interface. Strengthening of the A:a knob-hole bonds at 30- to 40-pN forces might favor formation of nascent fibrin clots subject to hydrodynamic shear in vivo.

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Keywords

Catch-slip bond, Fibrin polymerization, Fluctuating bottleneck, GPU computing, Interface remodeling

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