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

Litvinov R., Kononova O., Zhmurov A., Marx K., Barsegov V., Thirumalai D., Weisel J.
*Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia*

## Abstract

© 2018 National Academy of Sciences. All Rights Reserved. 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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