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Fast Force Loading Disrupts Molecular Bond Stability in Human and Mouse Cell Adhesions

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Abstract: Force-mediated molecular binding initiates numerous cellular activities such as cell adhesion, migration, and activation. Dynamic force spectroscopy (DFS) is widely used to examine molecular binding and cell mechano-signaling [1]. The rate of dissociation, off-rate, is an important attribute of molecular binding that reflects bond stability. Extensive DFS works have demonstrated that off-rates are a function of force magnitude, yielding signature bond behaviors like "catch bond" [2]. However, as a controversial topic of the field, different DFS assays, i.e., force-clamp and force-ramp assays, often yielded distinctive "off-rate vs. force" relations from the same molecular system [3]. Such discrepancies cast doubt on the existing theoretical models of force-regulated molecular binding, and suggest the existence of unknown factors, other than the force magnitude, that also affect bond dissociation.

We used a live-cell DFS technique, Biomembrane Force Probe, to measure the single-bond dissociation in three receptor–ligand systems which respectively play a critical role in vascular and immune systems: human platelet GPIbα–VWF A1, mouse T cell receptor–OVA peptide:MHC and mouse platelet integrin αIIbβ3–fibrinogen. Using force-clamp and force-ramp assays in parallel, we identified that the force loading disrupted the stability of molecular bonds in a rate-dependent manner. This disruptive effect was achieved by the transitioning of bonds between two dissociation states: faster force loading induces more bonds to adopt the fast-dissociating state (and less to adopt the slow-dissociating state). Based on this mechanism, a new biophysical model of bond dissociation was established which took into account the effects of both force magnitude and loading rate. Remarkably, this model reconciled the results from the two assays in all three molecular systems under study.

In conclusion, our discoveries provided a new paradigm for understanding how force regulates receptor-ligand interactions, and a guideline for the proper use of DFS technologies. Furthermore, our work highlighted the opportunity of using different DFS assays to answer specific biological questions in the field of cell adhesion and mechano-signaling.

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