Covalent Magnetic Tweezers: A New Window to See Biology

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Magnetic tweezers have shaped much of our understanding of molecular mechanics, but classical approaches face inherent limitations—non-specific tethers, signal drift, and short experimental lifetimes often obscure the most interesting biology. Covalent Magnetic Tweezers (CMT) overcome these barriers by anchoring molecules through irreversible covalent linkages and integrating them with real-time microfluidics. This next-generation platform allows single proteins to be followed for hours to weeks with nanometre precision, while simultaneously quantifying elasticity, conformational transitions, unfolding energetics, and dynamic force responses.

With CMT, we uncovered a striking picture of how mechanical force rewires chaperone-assisted folding. Chaperones associated with translocation pathways—TF, DsbA, BiP and ERdj3—traditionally viewed as passive holdases, undergo a force-induced functional switch into active foldases. Under mechanical load, they accelerate folding and stabilize intermediates that would otherwise be short-lived. Notably, BiP and ERdj3 can harness up to 54 zJ of mechanical work inside the Sec61 channel, in sharp contrast to cytoplasmic DnaK–DnaJ systems, whose activity remains largely force-insensitive. Strain-energy analyses pinpoint substrate-specific stabilization of folded states as the molecular basis for this divergence.

By bridging molecular mechanics with chaperone biology, CMT reframes protein folding as an intrinsically force-regulated process. More than a technological advance, it opens a new observational window into mechanobiology—revealing how cells strategically use physical forces to lower the energetic cost of protein biogenesis and sustain proteostasis.