Controllable Activation of Nanoscale Dynamics in a Disordered Protein Alters Binding Kinetics.

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The phosphorylation of specific residues in a flexible disordered activation loop yields precise control of signal transduction. One paradigm is the phosphorylation of S339/S340 in the intrinsically disordered tail of the multi-domain scaffolding protein NHERF1, which affects the intracellular localization and trafficking of NHERF1 assembled signaling complexes. Using neutron spin echo spectroscopy (NSE), we show salt-concentration-dependent excitation of nanoscale motion at the tip of the C-terminal tail in the phosphomimic S339D/S340D mutant. The "tip of the whip" that is unleashed is near the S339/S340 phosphorylation site and flanks the hydrophobic Ezrin-binding motif. The kinetic association rate constant of the binding of the S339D/S340D mutant to the FERM domain of Ezrin is sensitive to buffer salt concentration, correlating with the excited nanoscale dynamics. The results suggest that electrostatics modulates the activation of nanoscale dynamics of an intrinsically disordered protein, controlling the binding kinetics of signaling partners. NSE can pinpoint the nanoscale dynamics changes in a highly specific manner.

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