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Title: A conformational switch autoregulates the scaffolding protein NHERF1

Abstract

Scaffolding proteins are molecular switches that control diverse signaling events. A particularly important example is the scaffolding protein NHERF1, which assembles and regulates the localization and intracellular trafficking of a number of important membrane proteins. At its N-terminus, NHERF1 begins with two modular protein-protein interaction domains-PDZ1 and PDZ2-and ends with a C-terminal (CT) domain. The CT domain binds to ezrin, which, in turn, interacts with cytosekeletal actin. Previously we have shown that ezrin binding to NHERF1 increases the binding capabilities of both PDZ domains. Our solution small angle neutron scattering and NMR experiments reveal the autoregulated intramolecular domain-domain interactions, as well as much longer range conformational changes in NHERF1 upon activation by ezrin binding. The results provide a structural explanation, at both mesoscopic scales and atomic resolution, of the allosteric control of NHERF1 by ezrin as it assembles protein complexes. We propose that this long-range allosteric regulation of NHERF1 by ezrin enables the membrane-cytoskeleton to assemble protein complexes that control cross-talk and regulate the strength and duration of signaling.