

Membrane activation of a bacterial GEF investigated by Molecular Dynamics with Excited Normal Modes

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Arf GTPases are major regulators of most aspects of lipid and membrane traffic. They cycle between an inactive, cytosolic state bound to GDP, and an active, membrane-bound state bound to GTP. Guanine nucleotide exchange factors (GEFs) promote this intrinsically slow GDP to GTP exchange, resulting in an active membrane-bound conformation that interacts specifically with the downstream effectors. *Legionella pneumophila*, a bacterium that causes severe pneumonia (Legionnaire's disease), injects a large number of effectors that divert membrane traffic to establish a vacuole where it hides and replicates. One of these effector proteins is RalF, which diverts the host traffic by functioning as an illicit GEF to activate host Arf1 on the Legionella-containing vacuole. RalF is comprised of a Sec7 domain, which carries the GEF domain, and an autoinhibitory domain which is also responsible for the recruitment of RalF to the vacuole membrane. The structure of autoinhibited RalF has been determined, but the major conformational change needed to reach its active membrane-bound conformation has remained unknown. Using the method of Molecular Dynamics with Excited Normal Modes (MNeNM) here we present the mechanism of autoinhibition release and the membrane-bound open conformation of RalF.