Conformational stability of the bacterial adhesin, FimH, with an inactivating mutation

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Abstract

Allostery governing two conformational states is one of the proposed mechanisms for catch-bond behavior in adhesion proteins. In FimH, a catch-bond protein expressed by pathogenic bacteria, separation of two domains disrupts inhibition by the pili domain. Thus, tensile force can induce a conformational change in the lectin domain, from an inactive state to an active state with high affinity. To better understand allosteric inhibition in two-domain FimH (H2 inactive), we use molecular dynamics simulations to study the lectin domain alone, which has high affinity (HL active), and also the lectin domain stabilized in the low-affinity conformation by an Arg-60-Pro mutation (HL mutant). Because ligand-binding induces an allostery-like conformational change in HL mutant, this more experimentally tractable version has been proposed as a "minimal model" for FimH. We find that HL mutant has larger backbone fluctuations than both H2 inactive and HL active, at the binding pocket and allosteric interdomain region. We use an internal coordinate system of dihedral angles to identify protein regions with differences in backbone and sidechain dynamics beyond the putative allosteric pathway sites. By characterizing HL mutant dynamics for the first time, we provide additional insight into the transmission of allosteric information across the lectin domain and build upon structural and thermodynamic data in the literature to further support the use of HL mutant as a "minimal model." Understanding how to alter protein dynamics to prevent the allosteric conformational change may guide drug development to prevent infection by blocking FimH adhesion.

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