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Investigating Cooperativity in the LC8 Protein Hub via Molecular Dynamics Simulations

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Keywords

Ebolavirus; Cooperative Behavior; Hemorrhagic Fever, Ebola; Molecular Dynamics Simulation; Peptides; Calorimetry; Thermodynamics; Signal Transduction; Apoptosis

Abstract

LC8 is a key molecular hub protein involved in a wide array of cellular processes (e.g., apoptosis, viral interactions, signal transduction). LC8 interacts with over 100 binding partners, some of which are intrinsically disordered (ID) regions of proteins. LC8, functioning as a homodimer, utilizes a two-step binding process essential for the structural organization of its client peptides. Isothermal titration calorimetry experiments indicate significant cooperativity occurs in the two binding steps, but the structural basis of the behavior remains unknown because there is negligible conformational change in binding. Using 1μs all-atom molecular dynamics (MD) simulations, this work explores the atomistic mechanisms of LC8's cooperative behavior and its effects on local and global dynamics for multiple client peptides. The peptides in this study include segments of several proteins exhibiting diverse binding thermodynamics: BIM, Swallow, IC, nNOS, as well as Ebola virus, which are considered at both their experimental lengths and at a standard length to carefully examine effects due to sequence alone. This work aims to generate a structural understanding of LC8's cooperative mechanisms and introduces a site-specific 'cooperativity index' for quantifying these interactions, advancing our knowledge of protein dynamics and interactions at the molecular level.