Dissecting the geometric and hydrophobic constraints of stapled peptides

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Abstract

Stapled peptides are a promising class of molecules with potential as highly specific probes of protein-protein interactions and as therapeutics. Hydrocarbon stapling affects the peptide properties through the interplay of two factors: enhancing the overall hydrophobicity and constraining the conformational flexibility. By constructing a series of virtual peptides, we study the role of each factor in modulating the structural properties of a hydrocarbon stapled peptide PM2 which has been shown to enter cells, engage its target MDM2 and activate p53. Hamiltonian replica exchange molecular dynamics (HREMD) simulations suggest that hydrocarbon stapling favors helical populations of PM2 through a combination of the geometric constraints and the enhanced hydrophobicity of the peptide. To further understand the conformational landscape of the stapled peptides along the binding pathway, we performed HREMD simulations by restraining the peptide at different distances from MDM2. When the peptide approaches MDM2, the binding pocket undergoes dehydration which appears to be greater in the presence of the stapled peptide compared to the linear peptide. In the binding pocket, the helicity of the stapled peptide is increased due to the favorable interactions between the peptide residues as well as the staple and the micro-environment of the binding pocket, contributing to enhanced affinity. The dissection of the multi-facet mechanism of hydrocarbon stapling into individual factors not only deepens fundamental understanding of peptide stapling, but also provides guidelines in the design of new stapled peptides.

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