Local Dynamics in Protease Recognition

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Proteases catalyze cleavage of peptide bonds and are vitally important in a wide range of fundamental cellular processes. Far more than 500 proteases have been identified in the human genome, each individually tied to a unique cleavage pattern [1]. These patterns reach from specificity for a single peptide in case of proteases involved in signaling cascades to broad spectra of cleaved peptides for digestive enzymes.

To analyze the impact of local dynamics on protease specificity, a series of homologous proteases including highly specific as well as unspecific proteases was selected. Inspired by information theory, subpocket-wise substrate cleavage entropy values are presented based on cleavage data from the MEROPS database [2]. Calculated entropy scores, ranging from 0 for a conserved substrate to 1 for a random distribution of substrates [3], appear to be qualitatively linked to local flexibility of the binding site region. Consequently, temperature factors from X-ray structures as well as all-atom 100ns molecular dynamics trajectories using the AMBER package [4] are compared in respect to subpocket specificity.

Analysis of specificity and flexibility patterns reveal a consistent correlation of binding site rigidity and specificity. As conformational plasticity is paralleled by a broader conformational space, a mechanism of conformational selection [5] in the binding process of proteases is proposed. According to this model, the whole conformational ensemble contributes to the substrate specificity of proteases rather than single interactions derived from a static point of view. This finding implies the need for refined rules for substrate cleavage considering binding site flexibility in agreement with earlier findings for snake venom metallo proteases [6].

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