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Correlated structural kinetics and retarded solvent dynamics at the metalloprotease active site

Source

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Abstract

Solvent dynamics can play a major role in enzyme activity, but obtaining an accurate, quantitative picture of solvent activity during catalysis is quite challenging. Here, we combine terahertz spectroscopy and X-ray absorption analyses to measure changes in the coupled water-protein motions during peptide hydrolysis by a zinc-dependent human metalloprotease. These changes were tightly correlated with rearrangements at the active site during the formation of productive enzyme-substrate intermediates and were different from those in an enzyme-inhibitor complex. Molecular dynamics simulations showed a steep gradient of fast-to-slow coupled protein-water motions around the protein, active site and substrate. Our results show that water retardation occurs before formation of the functional Michaelis complex. We propose that the observed gradient of coupled protein-water motions may assist enzyme-substrate interactions through water-polarizing mechanisms that are remotely mediated by the catalytic metal ion and the enzyme active site.