Poster Presentation

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Carbapenemase NDM-1, Structural Analysis of the Catalytic Mechanism

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The New Delhi Metallo β-lactamase (NDM-1), first identified in Klebsiella pneumoniae has been shown to hydrolyze nearly all clinical β-lactam antibiotics including carbapenems, considered "last resort" antibiotics. Its gene resides on mobile plasmids that move between different strains of bacteria posing a serious global threat to human health. There have also been reports of several variants, up to NDM-9, some with increased carbapenemase activity. As part of the NIGMS PSI:Biology effort, the Midwest Center for Structural Genomics (MCSG) together with the Structures of Mtb Proteins Conferring Susceptibility to Known Mtb Inhibitors partnership, made significant progress in investigating the enzyme atomic structure and catalytic mechanism. A large number of protein constructs as well as mutants were made and a number of high-resolution structures of NDM-1 (no Zn, one Zn, two Zn, two Mn or Cd, and complexed with antibiotics) and NDM-1 variants, NDM-2, NDM-3, NDM-4, NDM-5 and NDM-6 have been determined. We have determined the two structures of Michaelis complex: NDM-1 with two cadmium ions and a mixture of hydrolyzed and unhydrolyzed ampicillin (1.50 Å) and one with two cadmium ions and partly hydrolyzed faropenem (2.00 Å). The crystal structures revealed a ligand-binding pocket consisting of several flexible loops capable of accommodating many β-lactam substrates of different sizes and shapes. The structures with various metals suggest that the distance between the two metal atoms is closely correlated with substrate binding efficiency and hydrolysis and the pH-dependency of catalytic activity. For better understanding of catalytic mechanism of NDM-1, particularly the dynamics of substrate binding and the energy surfaces along the suggested reaction pathways, molecular dynamics calculations and hybrid classical/quantum (QM/MM) calculations were performed. This work was supported by NIH Grant GM094585 and by the U.S. DOE, OBER contract DE-AC02-06CH11357

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