REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Structural Basis of Ubiquitin C-terminal Hydrolases' Function

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Covalent conjugation of ubiquitin to protein plays a crucial role in different biological processes. Ubiquitin is covalently linked to proteins via formation of an amide bond between the C-terminal carboxyl group of ubiquitin and the amino group of a lysine residue on the acceptor protein. The ubiquitin is recycled by proteolytic removal from its conjugating protein by deubiquitinating enzymes (DUB). Ubiquitin C-terminal hydrolase-1 (UCHL1) is a small acidic protein of UCH family of deubiquitinating enzyme. The function of UCHL1 is not clear and it has been implicated both in Parkinson's disease (PD) and in lung cancer. It is highly abundant in brain, constituting up to 2% of total protein in brain. It is normally expressed exclusively in neurons and testis, however, abnormal expression of UCHL1 is found in many disease conditions including cardiovascular diseases. The crystal structure of apo UCHL1 showed that the active-site residues are not aligned in a canonical form, with the nucleophilic cysteine being 7.7 Å from the general base histidine, an arrangement consistent with an inactive form of the enzyme. We have solved the crystal structures of the wild type and two Parkinson's disease-associated variants of the enzyme, S18Y and I93M, bound to a ubiquitin-based suicide substrate, ubiquitin vinyl methyl ester (UbVMe). My talk will focus on the structural basis of UCHL1 function. In context of UCHL1 structure, I will also discuss about the other members of UCHs.