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Structural insights into mode of regulation of serine protease HtrA2

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High-temperature requirement protease A2 (HtrA2), a proapoptotic serine protease is involved in maintaining mitochondrial homeostasis. This multifaceted protein has been implicated in several diseases including cancer and neurodegeneration thus making it an important therapeutic target. HtrA2 comprises a short N-terminal region, a serine protease domain and regulatory PDZ (protein-protein interaction) domain. The complex trimeric structure, intricate PDZ-protease crosstalk, allosteric mechanism of activation that is mediated both through its N- as well as C-termini, and most importantly its involvement in both caspase-dependent as well as independent apoptotic mechanism has made this protease an important molecule for biomedical research. Unlike other members of the family, human HtrA2 has been found to be activated through its short N-terminal region in addition to the classical substrate/adapter binding pocket in the PDZ domain. Interaction with inhibitor of apoptosis proteins (such as XIAP) through its N-terminus, leads not only to subsequent cleavage of the molecule but also simultaneous activation of HtrA2, suggesting a 'positive feedback' mechanism. Similar mechanism is observed for PDZ-mediated substrate binding and activation as well. Therefore, understanding this complex mechanism and identifying the dual regulatory switch of its allosteric activation will help devise modulators with desired characteristics for therapeutic intervention against diseases it is associated with. It will also shed light on how point mutations lead to its inactivation as observed in diseases such as Alzheimer's and Parkinson's. Keeping these in mind, here we aim at understanding the structural correlates of mode of activation of HtrA2 and several pathogenic mutants (in complex with substrates) at atomic level using X-ray crystallography and biophysical probes.

Biography

Kakoli Bose is Principal Investigator and Assistant Professor at ACTREC which is a premier organization of the country dedicated to cancer research and patient care. She has completed her graduate studies at North Carolina State University, Raleigh and postdoctoral training at Tufts New England Medical Centre, Boston. Her research interest focuses on non-classical mechanisms of programmed cell death with emphasis on understanding structure-function relationship of proteins involved in novel adapter-independent extrinsic pathways and caspase-independent apoptosis with the aim of targeting them for disease intervention.

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