DANDRITE
Danish Research Institute of Translational Neuroscience
Nordic EMBL Partnership for Molecular Medicine

AARHUS UNIVERSITY

DANDRITE Topical Seminar

Tuesday 30 August 2022

15.00 – 16.00

Venue:

Department of Molecular Biology and Genetics, Universitetsbyen 81, 1870-816 (faculty club)

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Advanced Centre for Treatment, Research and Education in Cancer, Mumbai, India

Unraveling the conundrum of multitasking serine protease HtrA2

Mitochondrial high-temperature requirement protease A2 (HtrA2) is an integral member of the HtrA family of serine proteases that are evolutionarily conserved from prokaryotes to humans. Involvement in manifold intricate cellular networks and diverse pathophysiological functions make HtrA2 the most enigmatic moonlighting protease amongst the human HtrAs. Despite perpetuating the oligomeric architecture and overall structural fold of its homologs that comprise serine protease and regulatory PDZ domains, subtle conformational alterations, and dynamic enzymatic regulation through the distinct allosteric mode of action lead to its functional diversity. This mitochondrial protease upon maturation exposes its one-of-a-kind N-terminal tetrapeptide (AVPS) motif that binds and subsequently cleaves Inhibitor of Apoptosis Proteins (IAPs) thus promoting cell death and posing as an important molecule for therapeutic intervention. Interestingly, unlike its other human counterparts, HtrA2 has also been implicated in maintaining mitochondrial integrity through a bi-functional chaperone-protease activity, the on-off switch of which is yet to be identified. Furthermore, its ability to activate a wide repertoire of substrates through both its N- and C-terminal regions presumably has calibrated its association with several cellular pathways and hence diseases including neurodegenerative disorders and cancer. Therefore, the exclusive structural attributes of HtrA2 that involve multimodal activation, intermolecular PDZ-protease crosstalk, and an allosterically-modulated trimeric active-site ensemble have enabled the protease to evolve across species and partake functions that are fine-tuned for maintaining cellular homeostasis and mitochondrial proteome quality control in humans. These unique features along with its multitasking potential make HtrA2 a promising therapeutic target both in cancer and neurodegeneration.

Keywords: HtrA2, protease, cancer, PDZ domain, apoptosis, multitasking