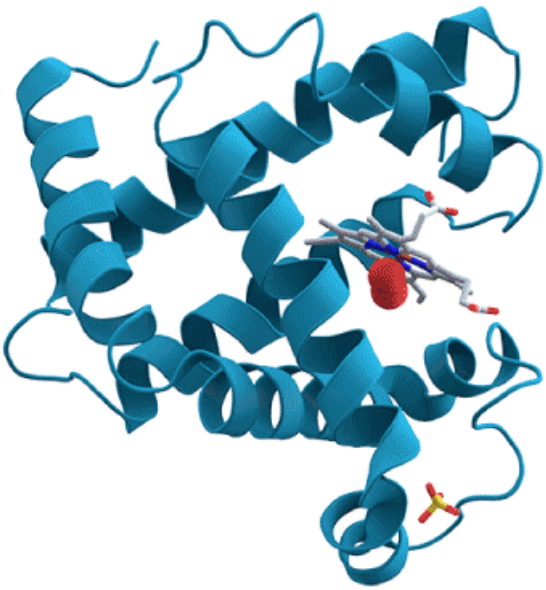
Study gets deeper insight on a protein of importance in Huntington disease

New Delhi, Sep 02: A major research focus of Dr Akash Ranjan's laboratory at the Department Of Biotechnology's Centre for DNA Fingerprinting and Diagnostics (DBT-CDFD) has been to understand the evolution and the function of HYPK proteins in the context of cellular proteostasis. These HYPK proteins were first identified as one of many human proteins that interact with huntingtin proteins that causes Huntington disease – a human neurodegenerative disorder. These HYPK proteins sequesters different aggregation-prone proteins of higher eukaryotic cells and are integral part of cellular proteostasis machinery.



Recently, Dr Ranjan's laboratory has shown that HYPK mRNA is differentially translated from an internal start/initiation codon to generate an amino terminal-truncated isoform (HSPC136) of HYPK protein. In this work, Dr Ranjan's team has provided a mechanistic detail of HYPK mRNA's translation initiation control that results in HYPC136/HYPK-ΔN which is a shorter isoform of full length HYPK protein. The HYPC136/HYPK-ΔN isoform lacks the nuclear localization and the functional ability to deal with aggregation of the mutant p53 (p53-R248Q) protein.

Dr Ranjan's research has shown that an IRES-dependent translation initiation of HYPK mRNA is responsible for the formation of the HSPC136/HYPK-ΔN isoform of HYPK protein. This IRES-driven translation product-HYPK-ΔN lacks the N-terminal tri-arginine

motif that acts as the nuclear localization signal (NLS) in the full-length HYPK protein. While the full-length HYPK protein translocate to the nucleus and prevents the aggregation of the mutant p53 (p53-R248Q) protein, the HYPK-ΔN lacks this activity.

Dr Ranjan's work has further shown that the NLS of HYPK is not evolutionarily conserved. NLS is exclusively present in the HYPK protein of higher eukaryotic organisms. Dr Ranjan's team argues that the recently acquired NLS offers an additional advantage to the HYPK proteins of higher animals in tackling both the cytosolic as well as the nuclear protein aggregates. Hence, the presence of the NLS in full-length HYPK allows this protein to manage the nuclear protein aggregates that intern affects the cell cycle.

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