Investigations on endogenous and synthetic modulators of prion amyloidogenesis

Thesis submitted by ANKIT SRIVASTAVA
KSBS, IIT DELHI

ABSTRACT

Transmissible spongiform encephalopathies (TSE) result from accumulation of cellular prion protein (PrPc) in an altered, aggregated, scrapie conformation (PrPcs). Cellular interacting partners causing this aggregated form are largely unknown. The present work includes identification of natural interacting proteins based on experimental and theoretical evidences. It is found that this functional protein-association network involves a cytoskeleton-modulating protein, gelsolin. Gelsolin is an actin-severing, nucleating, and capping protein that acquires an open and functionally active conformation in the presence of calcium or low pH. The interaction between prion and gelsolin was probed using spectroscopic and structural studies. This was further verified using ex vivo experiments where both the proteins were found to co-localize in the cytosol. Further, it was demonstrated that gelsolin sequesters monomeric prion molecules and halt their association into a polymeric amyloid structure.

Besides establishing a novel endogenous partner of human prion protein, this work is focussed on designing exogenous or synthetic molecules that could influence its amyloidogenic properties. The anti-prion properties of bispidine-based peptidomimetics (BPMs) was explored that conjugate evolutionary subdued residues in prion core sequence. Keeping the bispidine unit unaltered, a series of structurally diverse BPMs were synthesized and tested for their prion modulating properties. It was found that each BPM-induced prion protein to form unique oligomeric nanostructures differing in their biophysical properties, cellular toxicities and response to conformation-specific antibodies. In conclusion, the work canvasses the examination of endogenous as well as synthetic molecules on the amyloidogenic tendencies of human prion protein. Overall, the observations from the present work provide new and crucial information based on which new intervention strategies for pernicious prion diseases could be proposed without adversely effecting the normal cellular functioning.