Science at the Edge Seminar Series

Quantitative Biology Graduate Program/ Gene Expression in Development and Disease

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Solid-state NMR studies of amyloid formation by polyglutamine and huntingtin fragments.

Many neurodegenerative diseases are accompanied by protein misfolding and amyloid formation. In Huntington's Disease and a number of other human diseases, expansion of a polyglutamine element in different proteins leads to protein misfolding, loss of native function and gain of cellular toxicity. Through the use of solid-state NMR spectroscopy and other experimental tools, we are elucidating the structural features of the misfolded proteins within the aggregates and in particular amyloid-like fibrils. Our use of solid-state NMR allows for the determination of structure and dynamics with site-specific resolution, even for the non-crystalline fibrillar aggregates. We correlate observed structural features to mutational, mechanistic and toxicity studies. By studying both designed polyQ-based peptides and mutant huntingtin fragments we have gained new insights into the molecular and mechanistic features of the misfolding and aggregation of huntingtin and other polyQ-containing proteins. Our studies reveal that polyQ-expanded huntingtin shares structural features with generic polyQ peptides, but also displays important differences in its aggregation behavior.

(1) Sivanandam, V. N.; Jayaraman, M.; Hoop, C. L.; Kodali, R.; Wetzel, R.; van der Wel, P. C. A. J Am Chem Soc 2011, 133, 4558.

(2) Mishra, R.; Hoop, C. L.; Kodali, R.; Sahoo, B.; van der Wel, P. C. A.; Wetzel, R. J Mol Biol 2012, 424, 1.

(3) Kar, K.; Hoop, C. L.; Drombosky, K. W.; Baker, M. A.; Kodali, R.; Arduini, I.; van der Wel, P. C. A.; Horne, W. S.; Wetzel, R. J Mol Biol 2013, 425, 1183.

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Room 1400 BPS

Refreshments at 11:15