REGIONAL CENTRE FOR BIOTECHNOLOGY

Seminar series

Probing the mechanisms of chaperone mediated protein folding.

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Seminar Room

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Abstract

De novo synthesized and translocated unfolded polypeptides have the ability to spontaneously reach their native state without any assistance (1). Yet, the pathway to native folding is complex, stress-sensitive and prone to errors and leads to misfolded, non-native, functionally disabled proteins which are prone to aggregation (2). Misfolded and aggregated conformers are mostly toxic in nature and their accumulation in cells lead to ageing and neuro-degenerative diseases such as Alzheimer's, Parkinson's etc (3). Members of the canonical conserved families of molecular chaperones, Hsp100s, Hsp70/110/40s, Hsp60/CCTs, the small Hsps and Hsp90s, form a first line of cellular defenses against early misfolded species on the cytotoxic protein aggregation pathway. They can recognize and bind with high affinity, abnormally exposed hydrophobic surfaces on misfolded and aggregated polypeptides (4). We found that binding to Hsp70, Hsp110, Hsp40, Hsp60/CCTs and sHsps may cause partial unfolding of misfolded polypeptide substrates, further ATP hydrolysis can induce further unfolding and release from the chaperone, leading to spontaneous refolding into native proteins with low-affinity for the chaperones (5-7). Hence, specific chaperones act as catalytic polypeptide unfolding isomerases, rerouting cytotoxic misfolded and aggregated polypeptides back onto their physiological native refolding pathway, thus averting the onset of protein conformational diseases. It opens new directions to further investigate the functionality and mechanism of the stress-responsive molecular chaperones in regard to substrate shuttling between chaperone systems and the characterization of chaperone-substrate complexes.