Abstract

The complex difficulty of protein misfolding and its consequences of neurodegeneration and cancer are prevented by protein quality control system comprising of ubiquitin proteasome system, autophagy and chaperones. In the ubiquitin proteasome system, E3 ubiquitin ligases are the chief players who individually mark and clear loads of the misfolded aberrant proteins from the cell and such E3 ligases are also designated as quality control E3 ubiquitin ligases. Leucine rich repeat sterile alpha motif containing 1 (LRSAM1) protein is a really interesting new gene (RING) finger domain containing E3 ubiquitin ligase, a mutation in which is linked to Charcot-Marie-Tooth Type 2P disease. LRSAM1 is also implicated in other neurodegenerative pathologies with cellular protective functions observed in Huntington's pathology. But the LRSAM1 associated molecular mechanism responsible for such diseases are not understood and is may be linked with loss in quality control function of LRSAM1. In the first section of this doctoral work, LRSAM1 novel quality control functions in various neurodegeneration linked misfolded protein aggregation conditions were explored. LRSAM1 follows the expression profile of established quality control protein like Hsp70 in several stresses. LRSAM1 is also observed to coordinate with protein quality control molecules like LC3 and ubiquitin to alleviate cells from cytotoxicity of aberrant protein inclusions. Furthermore, LRSAM1 was found to target misfolded protein for degradation and provide cytoprotection in various neurodegenerative protein aggregation stresses. It is still not understood, how cell control the basal level of essential quality control protein in different stresses. E6-associated protein (E6-AP) is a cellular protein quality control protein which is induced in different stresses. The second chapter in the thesis elucidates LRSAM1 role in modulating E6-AP by the proteasomal machinery. The study indicates overexpression of LRSAM1 degrades E6-AP by proteasome machinery and subsequently cause an upregulation of E6-AP cell cycle substrate proteins p53 and p27. However, LRSAM1 depletion causes accumulation of E6-AP and reduces the amount of its substrate protein. This finding will also provide inputs on LRSAM1 function in neurodevelopmental disorder, as E6-AP functions are lost in neurodevelopmental pathology of Angelman syndrome. Taken together, both these studies give information on mechanisms of LRSAM1 mediated control of neurodegeneration linked misfolded protein aggregation.

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