REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

"What is on your backside?" Unique 'backside' interactions between an ubiquitin-conjugating enzyme and ubiquitin-ligase regulate ubiquitylation

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The post-translational modification of proteins by chains of ubiquitin molecules has long been known to play several functions in the inducible and reversible control of signaling pathways. Since several cellular functions regulated by ubiquitin are often deregulated in human cancers along with the reported genetic alterations, abnormal expression or dysfunction of various ubiquitin components, the ubiquitin system offers highly attractive drug targets for the development of anti-cancer treatments. A comprehensive understanding of the ubiquitin-modification or ubiquitylation is the key to effective drug design. Ubiquitylation is a multistep process where several classes of enzymes function in a sequential regulated manner. First, ubiquitin is activated by an activating enzyme (E1). The activated ubiquitin is then conjugated to the conjugating enzymes (E2s). The E2s interacts with another class of proteins known as ubiquitin ligase (E3s), which function to transfer ubiquitin to the targeted protein. A majority of E3s have an internal domain, known as a RING finger, which binds weakly to E2s and allows ubiquitylation to proceed. However, some RING finger E3s like gp78 has a supplementary region called G2BR that strongly binds to its E2, Ube2g2. The structural and functional implication of this new binding site was investigated in this study. A combination of structural, biophysical and biochemical studies reveal that each of the two E2-interacting domains in gp78, RING finger and G2BR has diverse effects on Ube2g2. G2BR recruits and modulates Ube2g2 for enhanced interaction with RING finger, resulting in increased ubiquitylation. The RING finger modulates Ube2g2 to discharge ubiquitin and dissociate rapidly from G2BR (and gp78) for the next round of ubiquitylation. These two gp78-domains work in tandem to ensure efficient ubiquitylation of its substrates. The functional dynamics of gp78 is intensively studied by Nuclear Magnetic Resonance (NMR) spectroscopy and correlates well with the biochemical data. This unique mode of action introduces the possibility of entirely new therapeutic avenues in cancer and other diseases.