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Regulation of RING ubiquitin ligases by small protein molecules

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Post-translational modification by ubiquitin (Ub) regulates diverse cellular processes. Ubiquitin ligases (E3s) catalyze the final step of Ub transfer from E2 ubiquitin-conjugating enzyme thioesterified with Ub (E2~Ub) to a lysine side chain of substrate. RING-type E3s are the largest family of E3s with approximately 600 members in humans. RING E3s function by recruiting E2~Ub via the RING domain and promote direct transfer of Ub from E2 to the substrate lysine. The extent of substrate ubiquitination depends on the processivity of the RING E3-E2~Ub complex. RING domain activates E2~Ub by stabilizing E2~Ub in the closed conformation such that the thioester bond is optimally oriented for nucleophilic attack by the substrate lysine. Moreover, we showed that non-covalent Ub binding to the "backside" of E2 UbcH5B stimulates the catalytic efficiency of the RING E3-E2~Ub complex by enhancing RING E3's affinity for E2~Ub complex. Recently we have developed small protein molecules that modulate the activity of RING E3s. I will present these results in this meeting
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