Monoubiquitination-mediated intracellular trafficking: structural understanding

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Monoubiquitination refers to the covalent attachment of single ubiquitin molecule to a lysine residue of a target protein. It is widely accepted that monoubiquitination serves as a signal for intracellular trafficking for membrane proteins. The ubiquitin moiety on the target protein is recognized by proteins containing ubiquitin binding domains (UBDs). Here Iwill discuss structural and biochemical studies of two proteins harvesting three UBDs. GGAs (golgi-localized, gamma-ear-containing, ADP-ribosylation-factor-binding proteins) are clathrin adaptors that sort specific transmembrane proteins at the trans-Golgi network. GAT (GGAs and target of Myb (TOM)) domain of GGA proteins is responsible for recognizing the ubiquitin moeitry of the transmembrane proteins. The crystal structure of GAT domain of human GGA3 reveals that hydrophobic and acidic patch of the GAT binds ubiquitin on its canonical hydrophobic patch centered on Ile-44. The second ubiquitin binding site, which was suggested by NMR studies, is masked by crystal contact. Rabex-5 is an exchange factor for Rab5, a master regulator of endosomal trafficking.Rabex-5 binds monoubiquitin via two UBDs. The first UBD is A20 zinc finger which binds ubiquitin on its novel polar patch centered on Asp-58. The second UBD is motif interacting with ubiquitin (MIU) which binds ubiquitin on its canonical hydrophobic patch centered on Ille-44. The A20 zinc finger diaromatic patch mediates ubiquitin-ligase activity by directly recruiting a ubiquitin-loaded ubiquitin-conjugating enzyme.The two examples described above illustrate diversity of ubiquitin recognition by multiple UBDs.