

Structure Determination of Proteins that Regulate Ubiquitin-Dependent Proteolysis

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Ubiquitin-dependent proteolysis is involved in the regulation of diverse cellular processes, including cell cycle progression, signal transduction, apoptosis and DNA repair, and deregulated proteolysis of tumor suppressor and oncogene proteins is often associated with tumorigenesis. Ubiquitination involves a multi-enzyme system, but from a regulatory point of view, the ubiquitin-protein ligases (E3s) are the key components because they are responsible for the recognition of the substrate protein. E3s also bind a specific member of the ubiquitin-conjugating enzyme (E2) family and promote the ubiquitination of the substrate by the E2 in a process that is poorly understood.

F-box proteins are the substrate recognition components of SCF (Skp1-Cullin-F box protein) E3s. F-box proteins bind to the SCF constant catalytic core through their F-box motif interacting with the Skp1 adapter protein, and they bind substrates through their protein-protein interaction domains. The structure of the F-box protein Skp2 bound to Skp1 (submitted) reveals a general mechanism for F-box protein recruitment to SCF ligases, a second binding site that provides a basis for specificity among family members, and suggests that the F-box protein may also help position the substrate for the ubiquitination reaction.