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Review

Cullin 5-RING E3 ubiquitin ligases, new therapeutic targets?

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ABSTRACT

Ubiquitylation is a reversible post-translational modification of proteins that controls a myriad of functions and cellular processes. It occurs through the sequential action of three distinct enzymes. E3 ubiquitin ligases (E3s) play the role of conductors of the ubiquitylation pathway making them attractive therapeutic targets. This review is dedicated to the largest family of multimeric E3s, the Cullin-RING E3 (CRL) family and more specifically to cullin 5 based CRLs that remains poorly characterized.

Contents

Abbreviations: ASB, ankyrin repeat-containing proteins with a SOCS box; β-Trcp, β-transducin repeat−containing protein; BTB, bric-a-brac; CIS1, cytokine-inducible Src homology 2-containing protein; CRL, Cullin-RING E3 ubiquitin Ligase; CAND1, cullin-associated and neddylation-dissociated 1; CSN, COP9 signalosome complex; DCAF, DDB1- and CUL4-associated factor homolog; DCNL, defective in cullin neddylation protein 1-like proteins; DCN1, defective in cullin neddylation protein 1; DDB1, DNA damage-binding protein 1; DUB, deubiquitylating enzyme; Elo, Elongin B; EloC, Elongin C; E1, E1 ubiquitin-activating enzyme; E2, E2 ubiquitin-conjugating enzyme; E3, E3 ubiquitin ligase; FAK, Focal Adhesion Kinase; Fbw7, F-box WD40 repeat−containing protein 7; HECT, Homologous to E6-associated protein carboxyl terminus; HIV-1, human immunodeficiency virus-1; IRS, Insulin Receptor Substrate; JAK2, Janus Kinase 2; KSHV, Kaposi's sarcoma-associated herpes virus; LANA, latency-associated nuclear antigen; MAL, Myeloid differentiation primary-response gene 88 -Adaptor-Like protein; MLL, Mixed Lineage Leukemia; MuHV-4, murid herpes virus-4; NAE, NEDD8-activating enzyme; Mre11, meiotic recombination 11; NEDD8, Neural precursor cell expressed developmentally down-regulated protein 8; RING, really interesting new gene; RBX, RING box protein; ROC, regulator of cullins; SKP1, S-phase kinase-associated protein 1; Skp2, S-phase kinase-associated protein 2; SOCS, suppressors of cytokine signaling; SPSB, SPRY domain-containing proteins with a SOCS box; TNF-R2, tumor necrosis factor receptor 2; VHL, von Hippel-Lindau; WSB, WD40 repeat-containing protein with a SOCS box; Vif, viral infectivity factor.

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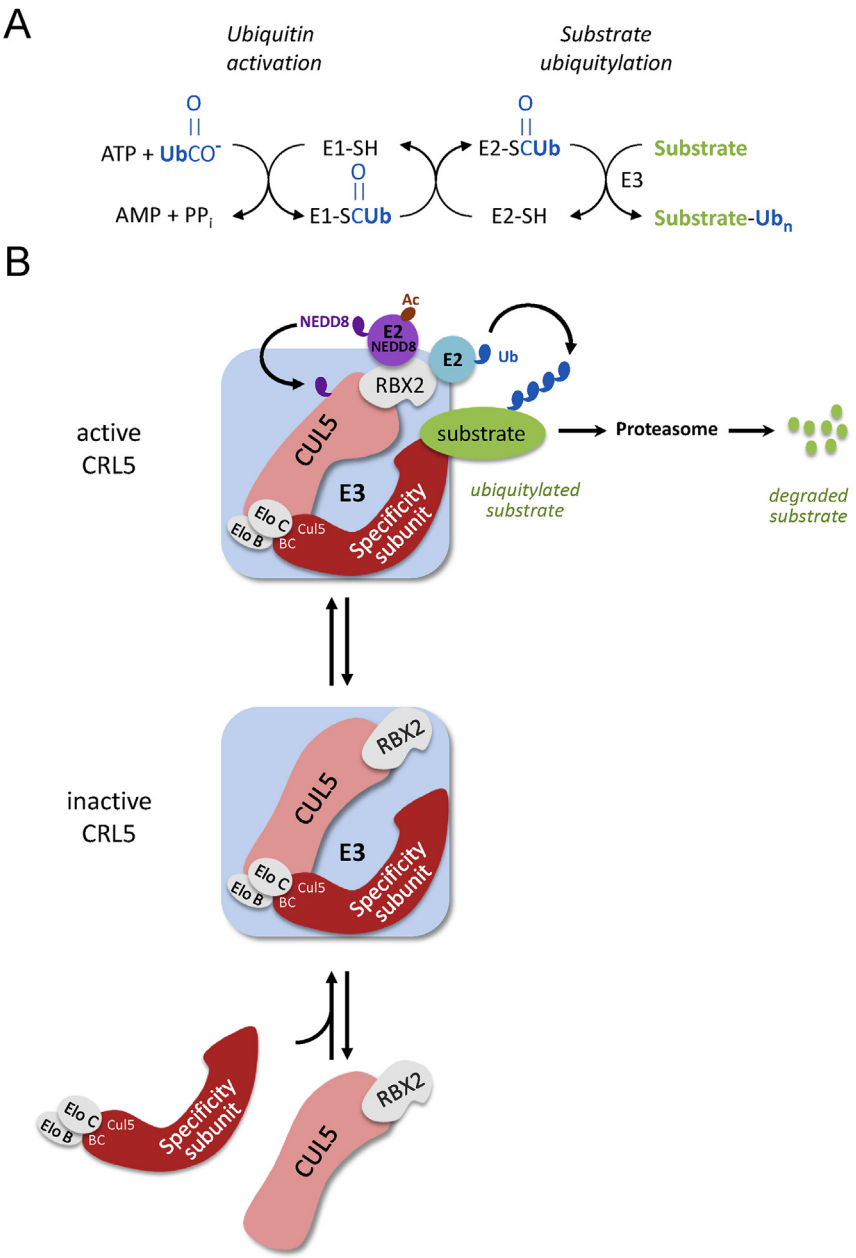

Fig. 1. CRL5 in ubiquitin-dependent protein degradation. (A) Ubiquitin (Ub) is first activated in an ATP-dependent reaction that leads to the formation of a thioester intermediate that involves the carboxy-terminal glycine residue of ubiquitin and the active site cysteine residue on the ubiquitin-activating enzyme E1. Ubiquitin is then transferred to the active site cysteine of a ubiquitin-conjugating enzyme E2. In the case of RING-finger E3s, activated ubiquitin is transferred directly from the E2 to the substrate. After multiple rounds, Lys48-linked ubiquitin chains are formed. These represent the canonical recognition motif for proteasomal degradation of the protein substrate. (B) In the CRL5 family, CUL5 can assemble with the RING subunit RBX2 and with numerous specificity subunits (also called substrate receptor, substrate recognition module or substrate targeting protein) involved in the recruitment of specific targets via adaptors (EloB and EloC). RBX2 is involved in the binding of the E2 enzyme that allows substrate ubiquitylation and is required for the covalent attachment of NEDD8 to a lysine residue of CUL5. NEDD8 ligation to CUL5 is enhanced following N-terminal acetylation (Ac) of the E2 NEDD8-conjugating enzyme. When CUL5 is post-translationally modified by NEDD8 (neddylation), activation of the CRL5 occurs. CUL5 inactivation occurs through NEDD8 removal by deneddylation by the CSN.

Protein ubiquitylation is a reversible post-translational modification that has proteolytic and non-proteolytic roles thereby regulating a wide spectrum of biological functions. As such, defects in the ubiquitin pathway can contribute to disease pathogenesis providing the rationale for drug discovery targeting this pathway.

1. The ubiquitylation cascade

The ubiquitin molecule is first activated through an ATP-dependent reaction by forming a high-energy thioester bond between the carboxy-terminal glycine residue of ubiquitin and the catalytic cysteine of an E1. Activated ubiquitin is then transferred

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