

E3 ubiquitin ligase components in GtoPdb v.2021.3

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Abstract

Ubiquitination (a.k.a. ubiquitylation) is a protein post-translational modification that typically requires the sequential action of three enzymes: E1 (ubiquitin-activating enzymes), E2 (ubiquitin-conjugating enzymes), and E3 (ubiquitin ligases) [19]. Ubiquitination of proteins can target them for proteasomal degradation, or modulate cellular processes including cell cycle progression, transcriptional regulation, DNA repair and signal transduction.

E3 ubiquitin ligases, of which there are >600 in humans, are a family of highly heterogeneous proteins and protein complexes that recruit ubiquitin-loaded E2 enzymes to mediate transfer of the ubiquitin molecule from the E2 to protein substrates. Target substrate specificity is determined by a substrate recognition subunit within the E3 complex.

Contents

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Database links

[E3 ubiquitin ligase components](#)

<https://www.guidetopharmacology.org/GRAC/FamilyDisplayForward?familyId=1023>

Enzymes

[cereblon](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3086>

[MDM2 proto-oncogene](#)

<https://www.guidetopharmacology.org/GRAC/ObjectDisplayForward?objectId=3136>

References

1. Asatsuma-Okumura T, Ito T and Handa H. (2019) Molecular mechanisms of cereblon-based drugs. *Pharmacol Ther* **202**: 132-139 [PMID:31202702]
2. Buneman P, Christie G, Davies JA, Dimitrellou R, Harding SD, Pawson AJ, Sharman JL and Wu Y. (2020) Why data citation isn't working, and what to do about it *Database* **2020** [PMID:32367113]
3. Carvajal LA, Neriah DB, Senecal A, Benard L, Thiruthuvanathan V, Yatsenko T, Narayanagari SR, Wheat JC, Todorova TI and Mitchell K *et al.*. (2018) Dual inhibition of MDMX and MDM2 as

a therapeutic strategy in leukemia. *Sci Transl Med* **10** [PMID:29643228]

4. Chamberlain PP, Lopez-Girona A, Miller K, Carmel G, Pagarigan B, Chie-Leon B, Rychak E, Corral LG, Ren YJ and Wang M *et al.*. (2014) Structure of the human Cereblon-DDB1-lenalidomide complex reveals basis for responsiveness to thalidomide analogs. *Nat Struct Mol Biol* **21**: 803-9 [PMID:25108355]
5. Del Prete D, Rice RC, Rajadhyaksha AM and D'Adamio L. (2016) Amyloid Precursor Protein (APP) May Act as a Substrate and a Recognition Unit for CRL4CRBN and Stub1 E3 Ligases Facilitating Ubiquitination of Proteins Involved in Presynaptic Functions and Neurodegeneration. *J Biol Chem* **291**: 17209-27 [PMID:27325702]
6. Fischer ES, Böhm K, Lydeard JR, Yang H, Stadler MB, Cavadini S, Nagel J, Serluca F, Acker V and Lingaraju GM *et al.*. (2014) Structure of the DDB1-CRBN E3 ubiquitin ligase in complex with thalidomide. *Nature* **512**: 49-53 [PMID:25043012]
7. Gandhi A, Dimartino J and Chopra R. (2014) Methods for the treatment of locally advanced breast cancer Patent number: WO2014039960A1.
8. Gandhi AK, Kang J, Havens CG, Conklin T, Ning Y, Wu L, Ito T, Ando H, Waldman MF and Thakurta A *et al.*. (2014) Immunomodulatory agents lenalidomide and pomalidomide co-stimulate T cells by inducing degradation of T cell repressors Ikaros and Aiolos via modulation of the E3 ubiquitin ligase complex CRL4(CRBN.). *Br J Haematol* **164**: 811-21 [PMID:24328678]
9. Hagner PR, Man HW, Fontanillo C, Wang M, Couto S, Breider M, Bjorklund C, Havens CG, Lu G and Rychak E *et al.*. (2015) CC-122, a pleiotropic pathway modifier, mimics an interferon response and has antitumor activity in DLBCL. *Blood* **126**: 779-89 [PMID:26002965]
10. Hartmann MD, Boichenko I, Coles M, Zanini F, Lupas AN and Hernandez Alvarez B. (2014) Thalidomide mimics uridine binding to an aromatic cage in cereblon. *J Struct Biol* **188**: 225-32 [PMID:25448889]
11. Heim C, Pliatsika D, Mousavizadeh F, Bär K, Hernandez Alvarez B, Giannis A and Hartmann MD. (2019) De-Novo Design of Cereblon (CRBN) Effectors Guided by Natural Hydrolysis Products of Thalidomide Derivatives. *J Med Chem* **62**: 6615-6629 [PMID:31251063]
12. Higgins JJ, Hao J, Kosofsky BE and Rajadhyaksha AM. (2008) Dysregulation of large-conductance Ca²⁺-activated K⁺ channel expression in nonsyndromal mental retardation due to a cereblon p.R419X mutation. *Neurogenetics* **9**: 219-23 [PMID:18414909]
13. Higgins JJ, Pucilowska J, Lombardi RQ and Rooney JP. (2004) A mutation in a novel ATP-dependent Lon protease gene in a kindred with mild mental retardation. *Neurology* **63**: 1927-31 [PMID:15557513]
14. Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, Yamaguchi Y and Handa H. (2010) Identification of a primary target of thalidomide teratogenicity. *Science* **327**: 1345-50 [PMID:20223979]
15. Ito T and Handa H. (2016) Cereblon and its downstream substrates as molecular targets of immunomodulatory drugs. *Int J Hematol* **104**: 293-9 [PMID:27460676]
16. Lopez-Girona A, Mendy D, Ito T, Miller K, Gandhi AK, Kang J, Karasawa S, Carmel G, Jackson P and Abbasian M *et al.*. (2012) Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide. *Leukemia* **26**: 2326-35 [PMID:22552008]
17. Matyskiela ME, Zhang W, Man HW, Muller G, Khambatta G, Baculi F, Hickman M, LeBrun L, Pagarigan B and Carmel G *et al.*. (2018) A Cereblon Modulator (CC-220) with Improved Degradation of Ikaros and Aiolos. *J Med Chem* **61**: 535-542 [PMID:28425720]
18. Momand J, Zambetti GP, Olson DC, George D and Levine AJ. (1992) The mdm-2 oncogene product forms a complex with the p53 protein and inhibits p53-mediated transactivation. *Cell* **69**: 1237-45 [PMID:1535557]
19. Morreale FE and Walden H. (2016) Types of Ubiquitin Ligases. *Cell* **165**: 248-248.e1 [PMID:27015313]
20. Nabet B, Roberts JM, Buckley DL, Paulk J, Dastjerdi S, Yang A, Leggett AL, Erb MA, Lawlor MA and Souza A *et al.*. (2018) The dTAG system for immediate and target-specific protein degradation. *Nat Chem Biol* **14**: 431-441 [PMID:29581585]
21. Ng SY, Yoshida N, Christie AL, Ghandi M, Dharia NV, Dempster J, Murakami M, Shigemori K, Morrow SN and Van Scoyk A *et al.*. (2018) Targetable vulnerabilities in T- and NK-cell lymphomas identified through preclinical models. *Nat Commun* **9**: 2024 [PMID:29789628]
22. Nguyen TV, Lee JE, Sweredoski MJ, Yang SJ, Jeon SJ, Harrison JS, Yim JH, Lee SG, Handa H and Kuhlman B *et al.*. (2016) Glutamine Triggers Acetylation-Dependent Degradation of Glutamine Synthetase via the Thalidomide Receptor Cereblon. *Mol Cell* **61**: 809-20 [PMID:26990986]
23. Pairawan S, Zhao M, Yuca E, Annis A, Evans K, Sutton D, Carvajal L, Ren JG, Santiago S and Guerlavais V *et al.*. (2021) First in class dual MDM2/MDMX inhibitor ALRN-6924 enhances antitumor efficacy of chemotherapy in TP53 wild-type hormone receptor-positive breast cancer models. *Breast Cancer Res* **23**: 29 [PMID:33663585]
24. Remillard D, Buckley DL, Paulk J, Brien GL, Sonnett M, Seo HS, Dastjerdi S, Wühr M, Dhe-Paganon S and Armstrong SA *et al.*. (2017) Degradation of the BAF Complex Factor BRD9 by

- Heterobifunctional Ligands. *Angew Chem Int Ed Engl* **56**: 5738-5743 [PMID:28418626]
25. Ries S, Biederer C, Woods D, Shifman O, Shirasawa S, Sasazuki T, McMahon M, Oren M and McCormick F. (2000) Opposing effects of Ras on p53: transcriptional activation of mdm2 and induction of p19ARF. *Cell* **103**: 321-30 [PMID:11057904]
 26. Sasaki M, Kawahara K, Nishio M, Mimori K, Kogo R, Hamada K, Itoh B, Wang J, Komatsu Y and Yang YR *et al.*. (2011) Regulation of the MDM2-P53 pathway and tumor growth by PICT1 via nucleolar RPL11. *Nat Med* **17**: 944-51 [PMID:21804542]
 27. Sheereen A, Alaamery M, Bawazeer S, Al Yafee Y, Massadeh S and Eyaid W. (2017) A missense mutation in the *CRBN* gene that segregates with intellectual disability and self-mutilating behaviour in a consanguineous Saudi family. *J Med Genet* **54**: 236-240 [PMID:28143899]
 28. Sun D, Li Z, Rew Y, Gribble M, Bartberger MD, Beck HP, Canon J, Chen A, Chen X and Chow D *et al.*. (2014) Discovery of AMG 232, a potent, selective, and orally bioavailable MDM2-p53 inhibitor in clinical development. *J Med Chem* **57**: 1454-72 [PMID:24456472]
 29. Vu B, Wovkulich P, Pizzolato G, Lovey A, Ding Q, Jiang N, Liu JJ, Zhao C, Glenn K and Wen Y *et al.*. (2013) Discovery of RG7112: A Small-Molecule MDM2 Inhibitor in Clinical Development. *ACS Med Chem Lett* **4**: 466-9 [PMID:24900694]