

Biobliography

Akopian, T.N., Kisselev, A.F., and Goldberg, A.L. (1997). Processive degradation of proteins and other catalytic properties of the proteasome from *Thermoplasma acidophilum*. *J. Biol. Chem.* 272, 1791–1798.

Alpi, A.F., Chaugule, V., and Walden, H. (2016). Mechanism and disease association of E2-conjugating enzymes: lessons from UBE2T and UBE2L3. *Biochem. J.* 473, 3401–3419.

Baehrecke, E.H. (2005). Autophagy: Dual roles in life and death? *Nat. Rev. Mol. Cell Biol.* 6, 505–510.

Bebington, C., Doherty, F.J., and Fleming, S.D. (2000). Ubiquitin and ubiquitin-protein conjugates are present in human cytotrophoblast throughout gestation. *Early Pregnancy* 4, 240–252.

Bedford, L., Lowe, J., Dick, L.R., Mayer, R.J., and Brownell, J.E. (2011). Ubiquitin-like protein conjugation and the ubiquitin–proteasome system as drug targets. *Nat. Rev. Drug Discov.* 10, 29–46.

Behrends, C., and Harper, J.W. (2011). Constructing and decoding unconventional ubiquitin chains. *Nat. Struct. Mol. Biol.* 18, 520–528.

Borden, K.L.B. (2000). RING Domains: Master Builders of Molecular Scaffolds? *J. Mol. Biol.* 295, 1103–1112.

Buchan, D.W.A., and Jones, D.T. (2019). The PSIPRED Protein Analysis Workbench: 20 years on. *Nucleic Acids Res.* 47, W402–W407.

Caspari, T. (2000). Checkpoints: How to activate p53. *Curr. Biol.* 10, 315–317.

Castañeda, C.A., Kashyap, T.R., Nakasone, M.A., Krueger, S., and Fushman, D. (2013). Unique structural, dynamical, and functional properties of K11-linked polyubiquitin chains. *Structure* 21, 1168–1181.

Chan, A.W.E., Hutchinson, E.G., Harris, D., and Thornton, J.M. (1993).

Identification, classification, and analysis of beta-bulges in proteins. *Protein Sci.* 2, 1574–1590.

Chen, B.P.C., and Hai, T. (1994). Expression vectors for affinity purification and radiolabeling of proteins using *Escherichia coli* as host. *Gene* 139, 73–75.

Ciechanover, A. (1998). The ubiquitin–proteasome pathway: on protein death and cell life. *EMBO J.* 17, 7151–7160.

Ciechanover, A. (2006). The ubiquitin proteolytic system. *Neurology* 66, S7 LP-19.

Ciechanover, A., Heller, H., Elias, S., Haast, A.L., and Hershko, A. (1980). ATP-dependent conjugation of reticulocyte proteins with the polypeptide required for protein degradation. *Proc. Natl. Acad. Sci. USA* 77, 1365–1368.

Ciechanover, A., Heller, H., Katz-Etzion, R., and Hershko, A. (1981). Activation of the heat-stable polypeptide of the ATP-dependent proteolytic system. *Proc. Natl. Acad. Sci. U. S. A.* 78, 761–765.

Ciechanover, A., Elias, S., Heller, H., and Hershko, A. (1982). “ Covalent Affinity ” Purification of Ubiquitin-activating Enzyme *. *J. Biol. Chem.* 257, 2537–2542.

Ciechanover, A., DiGiuseppe, J.A., Bercovich, B., Orian, A., Richter, J.D., Schwartz, A.L., and Brodeur, G.M. (1991). Degradation of nuclear oncoproteins by the ubiquitin system *in vitro*. *Proc. Natl. Acad. Sci.* 88, 139–143.

Ciechanover, A., Yaacov, H., and Hershko, A. (1978). A HEAT-STABLE POLYPEPTIDE COMPONENT OF AN ATP-DEPENDENT PROTEOLYTIC SYSTEM FROM RETICULOCYTES. *Biochem. Biophys. Res. Commun.* 81, 1100–1105.

Cook, B.W., and Shaw, G.S. (2012). Architecture of the catalytic HPN motif is conserved in all E2 conjugating enzymes. *Biochem J* 174, 167–174.

Cox, J.P.L., Evans, P.A., Packman, L.C., Williams, D.H., and Woolfson, D.N. (1993a). Dissecting the Structure of a Partially Folded Protein: Circular Dichroism and Nuclear Magnetic Resonance Studies of Peptides from Ubiquitin. *J. Mol. Biol.* 234, 483–492.

Cox, J.P.L., Evans, P.A., Packman, L.C., Williams, D.H., and Woolfson, D.N. (1993b). Dissecting the Structure of a Partially Folded Protein: Circular Dichroism and Nuclear Magnetic Resonance Studies of Peptides from Ubiquitin. *J. Mol. Biol.* 234, 483–492.

Craig, A.M., Jareb, M., and Banker, G. (1994). Neuronal polarity. *Annu. Rev. Neurosci.* 17, 267–310.

Craiu, A., Gaczynska, M., Akopian, T., Gramm, C.F., Fenteany, G., Goldberg, A.L., and Rock, K.L. (1997). Lactacystin and clasto-lactacystin β -lactone modify multiple proteasome β -subunits and inhibit intracellular protein degradation and major histocompatibility complex class I antigen presentation. *J. Biol. Chem.* 272, 13437–13445.

Cui, H., Matsui, K., Omura, S., Schauer, S.L., Matulka, R.A., Sonenshein, G.E., and Ju, S.-T. (1997). Proteasome regulation of activation-induced T cell death. *Proc. Natl. Acad. Sci.* 94, 7515–7520.

Delic, J., Morange, M., and Magdelenat, H. (1993). Ubiquitin pathway involvement in human lymphocyte gamma-irradiation-induced apoptosis. *Mol. Cell. Biol.* 13, 4875–4883.

Deshaies, R.J., and Joazeiro, C.A.P. (2009). RING Domain E3 Ubiquitin Ligases. *Annu. Rev. Biochem.* 78, 399–434.

Deveraux, Q., Ustrell, V., Pickart, C., and Rechsteiner, M. (1994). A 26 S protease subunit that binds ubiquitin conjugates. *J. Biol. Chem.* 269, 7059–7061.

Deveraux, Q., Jensen, C., and Rechsteiner, M. (1995). Molecular cloning and

expression of subunit Enriched in Dileucine repeats. *J. Biol. Chem.* *270*, 23726–23729.

Dikic, I., Wakatsuki, S., and Walters, K.J. (2009). Ubiquitin-binding domains — from structures to functions. *Nat. Rev. Mol. Cell Biol.* *10*, 659–671.

Drexler, H.C.A. (1997). Activation of the cell death program by inhibition of proteasome function. *Proc. Natl. Acad. Sci.* *94*, 855–860.

Driscoll, J., Brown, M.G., Finley, D., and Monaco, J.J. (1993). MHC-linked LMP gene products specifically alter peptidase activities of the proteasome. *Nature* *365*, 262–264.

Duda, D.M., Walden, H., Sfondouris, J., and Schulman, B.A. (2005). Structural analysis of *Escherichia coli* ThiF. *J. Mol. Biol.* *349*, 774–786.

Eletr, Z.M., Huang, D.T., and Duda, D.M. (2005). E2 conjugating enzymes must disengage from their E1 enzymes before E3-dependent Ubiquitin and Ubiquitin-like transfer E2 conjugating enzymes must disengage from their E1 enzymes before E3-dependent ubiquitin and ubiquitin-like transfer. *Nat. Struct. Mol. Biol.* *12*, 933–934.

Eustice, D.C., and Wilhelm, J.M. (1984). Mechanisms of action of aminoglycoside antibiotics in eucaryotic protein synthesis. *Antimicrob. Agents Chemother.* *26*, 53–60.

Finley, D., Ciechanover, A., and Varshavsky, A. (1984). Thermolability of ubiquitin-activating enzyme from the mammalian cell cycle mutant ts85. *Cell* *37*, 43–55.

Finley, D., Ozkaynak, E., and Varshavsky, A. (1987). The yeast polyubiquitin gene is essential for resistance to high temperatures, starvation, and other stresses. *Cell* *48*, 1035–1046.

Finley, D., Bartel, B., and Varshavsky, A. (1989). The tails of ubiquitin precursors are ribosomal proteins whose fusion to ubiquitin facilitates

ribosome biogenesis. *Nature* 338, 394–401.

Finley, D., Sadis, S., Monia, B.P., Boucher, P., Ecker, D.J., Crooke, S.T., and Chau, V. (1994). Inhibition of proteolysis and cell cycle progression in a multiubiquitination-deficient yeast mutant. *Mol. Cell. Biol.* 14, 5501–5509.

Fu, H., Lin, Y.L., and Fatimababy, A.S. (2010). Proteasomal recognition of ubiquitylated substrates. *Trends Plant Sci.* 15, 375–386.

Gerlach, B., Cordier, S.M., Schmukle, A.C., Emmerich, C.H., Rieser, E., Haas, T.L., Webb, A.I., Rickard, J.A., Anderton, H., Wong, W.W.L., et al. (2011). Linear ubiquitination prevents inflammation and regulates immune signalling. *Nature* 471, 591–596.

Ghosh, S., May, M.J., and Kopp, E.B. (1998). NF- κ B AND REL PROTEINS: Evolutionarily Conserved Mediators of Immune Responses. *Annu. Rev. Immunol.* 16, 225–260.

Gilbert, E.O., Lydie, L., Emma, L., Ronald, B., Christopher, O., and Deutsch (2016). Metrics for the Human Proteome Project 2016: Progress on Identifying and Characterizing the Human Proteome, Including Post-Translational Modifications. *J Proteome Res.* 15, 477–491.

Glickman, M.H., Rubin, D.M., Coux, O., Wefes, I., Pfeifer, G., Cjeka, Z., Baumeister, W., Fried, V.A., and Finley, D. (1998a). A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome and eIF3. *Cell* 94, 615–623.

Glickman, M.H., Rubin, D.M., Fried, V.A., and Finley, D. (1998b). The Regulatory Particle of the *Saccharomyces cerevisiae* Proteasome. *Mol. Cell. Biol.* 18, 3149–3162.

Goldstein, G., Scheid, M., Hammerling, U., Schlesinger, D.H., Niall, H.D., and Boyse, E.A. (1975). Isolation of a polypeptide that has lymphocyte-differentiating properties and is probably represented universally in living

cells. *Proc. Natl. Acad. Sci.* 72, 11–15.

Grenfell, S.J., Trausch-Azar, J.S., Handley-Gearhart, P.M., Ciechanover, A., and Schwartz, A.L. (1994). Nuclear localization of the ubiquitin-activating enzyme, E1, is cell-cycle-dependent. *Biochem. J.* 300 (Pt 3, 701–708.

Groettrup, M., Soza, A., Kuckelkorn, U., and Kloetzel, P.M. (1996). Peptide antigen production by the proteasome: Complexity provides efficiency. *Immunol. Today* 17, 429–435.

Groll, M., Ditzel, L., Lowe, J., Stock, D., Bochtler, M., Bartunik, H.D., and Huber, R. (1997). Structure of 20S proteasome from yeast at 2.4Å resolution. *Nature* 386, 463–471.

Grotenberg, G., and Ploegh, H. (2007). Dressed-up proteins. *Nature* 446, 469–471.

Gupta, R., Kus, B., Fladd, C., Wasmuth, J., Tonikian, R., Sidhu, S., Krogan, N.J., Parkinson, J., and Rotin, D. (2007). Ubiquitination screen using protein microarrays for comprehensive identification of Rsp5 substrates in yeast. *Mol. Syst. Biol.* 3, 1–12.

Gyorgy, B. (2006). Citrullination : A posttranslational modification in health and disease. *Int. J. Biochem. Cell Biol.* 38, 1662–1677.

Haast, A.L., Baboshina, O., Williams, B., and Schwartz, L.M. (1995). Coordinated Induction of the Ubiquitin Conjugation Pathway Accompanies the Developmentally Programmed Death of Insect Skeletal Muscle. *J. Biol. Chem.* 270, 9407–9412.

Harbers, K., Muller, U., Grams, A., Lid, E.N., Jaenisch, R., and Franzi, T. (1996). Provirus integration into a gene encoding a ubiquitin-conjugating enzyme results in a placental defect and embryonic lethality. *Proc. Natl. Acad. Sci. USA* 93, 12412–12417.

Harper, J.W., and King, R.W. (2011). Stuck in the middle: Drugging the

ubiquitin system at the E2 step. *Cell* 145, 1007–1009.

Hatakeyama, S., Yada, M., Matsumoto, M., Ishida, N., and Nakayama, K.I. (2001). U Box Proteins as a New Family of Ubiquitin-Protein Ligases. *J. Biol. Chem.* 276, 33111–33120.

Haupt, Y., Maya, R., Kazaz, A., and Oren, M. (1997). Mdm2 promotes the rapid degradation of p53. *Nature* 387, 296–299.

Hawe, A., Sutter, M., and Jiskoot, W. (2008). Extrinsic fluorescent dyes as tools for protein characterization. *Pharm. Res.* 25, 1487–1499.

Hefti, M.H., Van Vugt-Van der Toorn, C.J.G., Dixon, R., and Vervoort, J. (2001). A Novel Purification Method for Histidine-Tagged Proteins Containing a Thrombin Cleavage Site. *Anal. Biochem.* 295, 180–185.

Henry, P., Staub, O., Correa, J., Rotin, D., Ishikawa, T., Dho, S., and McGlade, J. (1996). WW domains of Nedd4 bind to the proline-rich PY motifs in the epithelial Na⁺ channel deleted in Liddle's syndrome. *EMBO J.* 15, 2371–2380.

Hershko, A., and Ciechanover, A. (1998). the Ubiquitin System. *Annu. Rev. Biochem* 67, 425–479.

Hershko, A., Ciechanover, A., Heller, H., Haas, A.L., and Rose, I.A. (1979). Proposed role of ATP in protein breakdown: Conjugation of proteins with multiple chains of the polypeptide of ATP-dependent proteolysis (protein/turnover/energy dependence/isopeptide linkage). *Biochemistry* 77, 1783–1786.

Hershko, A., Ciechanover, A., and Rose, I.A. (1981). Identification of the active amino acid residue of the polypeptide of ATP-dependent protein breakdown. *J. Biol. Chem.* 256, 1525–1528.

Hershko, A., Heller, H., Elias, S., and Ciechanover, A. (1983). Components of Ubiquitin-Protein Ligase System. Resolution, Affinity purification, and Role

in protein breakdown. *J. Biol. Chem.* 258, 8206–8214.

Hicke, L., Schubert, H.L., and Hill, C.P. (2005). Ubiquitin-binding domains. *Nat. Rev. Mol. Cell Biol.* 6, 610–621.

Hochstrasser, M. (1996). Ubiquitin-dependent protein degradation. *Annu. Rev. Genet.* 30, 405–439.

Hochuli, E., Döbeli, H., and Schacher, A. (1987). New metal chelate adsorbent selective for proteins and peptides containing neighbouring histidine residues. *J. Chromatogr. A* 411, 177–184.

Hough, R., Pratt, G., and Rechsteiner, M. (1986). Ubiquitin-lysozyme conjugates. Identification and characterization of an ATP-dependent protease from rabbit reticulocyte lysates. *J. Biol. Chem.* 261, 2400–2408.

Hu, M., LI, P., Li, M., Li, W., Yao, T., Wu, J.-W., Gu, W., Cohen, R., and Shi, Y.S. (2002). Crystal Structure of a UBP-Family Deubiquitinating Enzyme in Isolation and in Complex with Ubiquitin Aldehyde. *Cell* 111, 1041–1054.

Huang, Y., and Fischer-Vize, J.A. (1996). Undifferentiated cells in the developing *Drosophila* eye influence facet assembly and require the Fat facets ubiquitin-specific protease. *Development* 122, 3207–3216.

Huang, D.T., Paydar, A., Zhuang, M., Waddell, M.B., Holton, J.M., and Schulman, B.A. (2005). Structural basis for recruitment of Ubc12 by an E2 binding domain in NEDD8's E1. *Mol. Cell* 17, 341–350.

Huang, L., Klinnucan, E., Wang, G., Beaudenon, S., Hoeley, P.M., Huibregtse, J.M., and Pavletich, N.P. (1999). Structure of an EGAP-UbcH7 Complex: Insights into Ubiquitination by the E2-E3 Enzyme Cascade. *Science* (80-.). 286, 1321–1326.

Huang, Y., Baker, R.T., and Fischer-vize, J.A. (1995). Control of Cell Fate by a Deubiquitinating Enzyme Encoded by the fat facets Gene. *Science* (80-.). 270, 1828–1831.

Huibregtse, J.M., Yang, J.C., and Beaudenon, S.L. (1997). The large subunit of RNA polymerase II is a substrate of the Rsp5 ubiquitin-protein ligase. *Proc. Natl. Acad. Sci. U. S. A.* *94*, 3656–3661.

Hunt, Lois; Dayhoff, M. (1977). AMINO-TERMINAL SEQUENCE IDENTITY OF UBIQUITIN AND THE NONHISTONE COMPONENT OF NUCLEAR PROTEIN A24. *Biochem. Biophys. Res. Commun.* *74*, 650–655.

Ikeda, F., Deribe, Y., Skanland, S., Stieglits, B., Grabbe, C., Franz-Wachtel, M., Wijk, S., Goswami, P., Nagy, V., Terzic, J., et al. (2011). SHARPIN forms a linear ubiquitin ligase complex regulating NFκB activity and apoptosis. *Nature* *471*, 637–641.

Inn, K.S., Gack, M.U., Tokunaga, F., Shi, M., Wong, L.Y., Iwai, K., and Jung, J.U. (2011). Linear Ubiquitin Assembly Complex Negatively Regulates RIG-I- and TRIM25-Mediated Type I Interferon Induction. *Mol. Cell* *41*, 354–365.

Iyer, L.M., Burroughs, A.M., and Aravind, L. (2006). The prokaryotic antecedents of the ubiquitin-signaling system and the early evolution of ubiquitin-like β-grasp domains. *Genome Biol.* *7*, 1–23.

Jackson, P.K., Eldridge, A.G., Freed, E., Furstenthal, L., Hsu, J.Y., Kaiser, B.K., and Reimann, J.D.R. (2000). The lore of the RINGs: Substrate recognition and catalysis by ubiquitin ligases. *Trends Cell Biol.* *10*, 429–439.

Janknecht, R., and Nordheim, A. (1992). Affinity purification of histidine-tagged proteins transiently produced in HeLa cells. *Gene* *121*, 321–324.

Janknecht, R., De Martynoff, G., Lou, J., Hipkind, R.A., Nordheim, A., and Stunnenberg, H.G. (1991). Rapid and efficient purification of native histidine-tagged protein expressed by recombinant vaccinia virus. *Proc. Natl. Acad. Sci. U. S. A.* *88*, 8972–8976.

Jentsch, S. (1992). The ubiquitin-conjugation system. *Annu.Rev.Genet.* *26*, 179–207.

Jentsch, S., and Pyrowolakis, G. (2000). Ubiquitin and its kin: how close are the family ties? *Trends Cell Biol.* *10*, 335–342.

Jin, J., Li, X., Gygi, S.P., and Harper, J.W. (2007). Dual E1 activation systems for ubiquitin differentially regulate E2 enzyme charging. *Nature* *447*, 1135–1138.

Johnson, E., Ma, P., Ota, I., and Varshavsky, A. (1995). A proteolytic Pathway that recognizes ubiquitin as degradation signal. 17442–17456.

Johnson, E.S., Schwienhorst, I., Dohmen, R.J., and Blobel, G. (1997). The ubiquitin-like protein Smt3p is activated for conjugation to other proteins by an Aos1p/Uba2p heterodimer. *EMBO J.* *16*, 5509–5519.

Jones, D.T. (1999). Protein Secondary Structure Prediction Based on Position-specific Scoring Matrices. *J. Mol. Biol.* *292*, 195–202.

Joshi, R.G., Kulkarni, S., and Ratna Prabha, C. (2015). Engineering degrons of yeast ornithine decarboxylase as vehicles for efficient targeted protein degradation. *Biochim. Biophys. Acta - Gen. Subj.* *1850*, 2452–2463.

Kamadurai, H.B., Souphron, J., Scott, D.C., Duda, D.M., Miller, D.J., Stringer, D., Piper, R.C., and Schulman, B.A. (2009). Insights into Ubiquitin Transfer Cascades from a Structure of a UbcH5B~Ubiquitin-HECTNEDD4L Complex. *Mol. Cell* *36*, 1095–1102.

Kaslow, D.C., and Shiloach, J. (1994). Production, Purification and Immunogenicity of a Malaria Transmission-Blocking Vaccine Candidate: TBV25H Expressed in Yeast and Purified Using Nickel-NTA Agarose. *Bio/Technology* *12*, 494–499.

Kishino, T., Lalande, M., and Wagstaff, J. (1997). UBE3A/E6-AP mutations cause Angelman syndrome. *Nat. Genet.* *15*, 70–73.

Koepp, D.M., Harper, J.W., and Elledge, S.J. (1999). How the cyclin became a cyclin: Regulated proteolysis in the cell cycle. *Cell* *97*, 431–434.

- Komander, D., Reyes-Turcu, F., Licchesi, J.D.F., Odenwaelde, P., Wilkinson, K.D., and Barford, D. (2009). Molecular discrimination of structurally equivalent Lys 63-linked and linear polyubiquitin chains. *EMBO Rep.* *10*, 466–473.
- Kulka, R.G., Raboy, B., Schuster, R., Parag, H.A., Diamond, G., Ciechanover, A., and Marcus, M. (1988). A Chinese Hamster Cell Cycle Mutant Arrested at G2 Phase Has a Temperature-sensitive Ubiquitin-activating Enzyme, E1. *263*, 15726–15731.
- Kulkarni, M., and Smith, H.E. (2008). E1 ubiquitin-activating enzyme UBA-1 plays multiple roles throughout *C. elegans* development. *PLoS Genet.* *4*.
- Kuusinen, A., Arvola, M., Oker-Blom, C., and Keinänen, K. (1995). Purification of Recombinant GluR-D Glutamate Receptor Produced in Sf21 Insect Cells. *Eur. J. Biochem.* *233*, 720–726.
- Lahav-Baratz, S., Sudakin, V., Ruderman, J. V., and Hershko, A. (1995). Reversible phosphorylation controls the activity of cyclosome-associated cyclin-ubiquitin ligase. *Proc. Natl. Acad. Sci.* *92*, 9303–9307.
- Lake, M.W., Wuebbens, M.M., Rajagopalan, K. V, and Schindelin, H. (2001). Mechanism of ubiquitin activation revealed by the structure of a bacterial MoeB-MoaD complex. *Nature* *414*, 325–329.
- Lardeuxs, B.R., Mortimore, G.E., and Milton, T. (1987). Amino Acid and Hormonal Control of Macromolecular Turnover in Perfused Rat Liver. *J. Biol. Chem.* *262*, 14514–14519.
- Larsen, C.N., and Finley, D. (1997). Protein translocation channels in the proteasome and other proteases. *Cell* *91*, 431–434.
- Lauwers, E., Jacob, C., and Andre, B. (2009). K63-linked ubiquitin chains as a specific signal for protein sorting into the multivesicular body pathway. *J. Cell Biol.* *185*, 493–502.

Lee, I., and Schindelin, H. (2008). Structural Insights into E1-Catalyzed Ubiquitin Activation and Transfer to Conjugating Enzymes. *Cell* 134, 268–278.

Lee, T. V., Ding, T., Chen, Z., Rajendran, V., Scherr, H., Lackey, M., Bolduc, C., and Bergmann, A. (2008). The E1 ubiquitin-activating enzyme Uba1 in *Drosophila* controls apoptosis autonomously and tissue growth non-autonomously. *Development* 135, 43–52.

Lehmann, C., Begley, T.P., and Ealick, S.E. (2006). Structure of the *Escherichia coli* ThiS-ThiF complex, a key component of the sulfur transfer system in thiamin biosynthesis. *Biochemistry* 45, 11–19.

Leimkühler, S., Wuebbens, M.M., and Rajagopalan, K. V. (2001). Characterization of *Escherichia coli* MoeB and Its Involvement in the Activation of Molybdopterin Synthase for the Biosynthesis of the Molybdenum Cofactor. *J. Biol. Chem.* 276, 34695–34701.

Lipford, J.R., Smith, G.T., Chi, Y., and Deshaies, R.J. (2005). A putative stimulatory role for activator turnover in gene expression. *Nature* 438, 113–116.

Liu, H.Y., and Pfeleger, C.M. (2013). Mutation in E1, the Ubiquitin Activating Enzyme, Reduces *Drosophila* Lifespan and Results in Motor Impairment. *PLoS One* 8, 1–10.

Lois, L.M., and Lima, C.D. (2005). Structures of the SUMO E1 provide mechanistic insights into SUMO activation and E2 recruitment to E1. *EMBO J.* 24, 439–451.

Lopes, U.G., Erhardt, P., Yao, R., and Cooper, G.M. (1997). P53-Dependent Induction of Apoptosis By Proteasome Inhibitors. *J. Biol. Chem.* 272, 12893–12896.

Lupas, A., Koster, A.J., and Baumeister, W. (1993). Structural Features of 26S

and 20S Proteasomes. *Enzym. Protein* 47, 252–273.

Maki, C.G., Huibregtse, J.M., and Howley, P.M. (1996). *In Vivo* Ubiquitination and Proteasome-mediated Degradation of p53. *Cancer Res.* 56, 2649–2654.

Malik, B., Price, S.R., Mitch, W.E., Yue, Q., and Eaton, D.C. (2006). Regulation of epithelial sodium channels by the ubiquitin-proteasome proteolytic pathway. *Am. J. Physiol. Physiol.* 290, F1285–F1294.

Mansfield, E., Hersperger, E., Biggs, J., and Shearn, A. (1994). Genetic and molecular analysis of hyperplastic discs, a gene whose product is required for regulation of cell proliferation in *Drosophila melanogaster* imaginal discs and germ cells. *Dev. Biol.* 165, 507–526.

Matsuura, T., Sutcliffe, J.S., Fang, P., Galjaard, R.-J., Jiang, Y., Benton, C.S., Rommens, J.M., and Beaudet, A.L. (1997). De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat. Genet.* 15, 74–77.

Merkley, N., and Shaw, G.S. (2004). Solution Structure of the Flexible Class II Ubiquitin-conjugating Enzyme Ubc1 Provides Insights for Polyubiquitin Chain Assembly * □ . *J. Biol. Chem.* 279, 47139–47147.

Meusser, B., Hirsch, C., Jarosch, E., and Sommer, T. (2005). ERAD: The long road to destruction. *Nat. Cell Biol.* 7, 766–772.

Meyer, H.J., and Rape, M. (2014). Enhanced protein degradation by branched ubiquitin chains. *Cell* 157, 910–921.

Micsonai, A., Wien, F., Bulyáki, É., Kun, J., Moussong, É., Lee, Y.H., Goto, Y., Réfrégiers, M., and Kardos, J. (2018). BeStSel: A web server for accurate protein secondary structure prediction and fold recognition from the circular dichroism spectra. *Nucleic Acids Res.* 46, W315–W322.

Minguez, P., Parca, L., Diella, F., Mende, D.R., Kumar, R., Helmer-citterich,

- M., Noort, V. Van, and Bork, P. (2012). Deciphering a global network of functionally associated post-translational modifications. *Mol. Syst. Biol.* *8*, 1–14.
- Minguez, P., Letunic, I., Parca, L., and Bork, P. (2013). PTMcode: A database of known and predicted functional associations between post-translational modifications in proteins. *Nucleic Acids Res.* *41*, 306–311.
- Mishra, P., Volety, S., Rao, C.M., and Prabha, C.R. (2009). Glutamate64 to Glycine Substitution in G1 b -bulge of Ubiquitin Impairs Function and Stabilizes Structure of the Protein. *J. Biochem.* *146*, 563–569.
- Mishra, P., Ratna Prabha, C., Rao, C.M., and Volety, S. (2011). Q2N and S65D Substitutions of Ubiquitin Unravel Functional Significance of the Invariant Residues Gln2 and Ser65. *Cell Biochem. Biophys.* *61*, 619–628.
- Monera, O.D., Kay, C.M., and Hodges, R.S. (1994). Protein denaturation with guanidine hydrochloride or urea provides a different estimate of stability depending on the contributions of electrostatic interactions. *Protein Sci.* *3*, 1984–1991.
- Morrison, R.S., Kinoshita, Y., Johnson, M.D., Uo, T., Ho, J.T., McBee, J.K., Conrads, T.P., and Veenstra, T.D. (2002). Proteomic Analysis in the Neurosciences. *Mol. Cell. Proteomics* *1*, 553–560.
- Moudry, P., Lukas, C., Macurek, L., Hanzlikova, H., Hodny, Z., Lukas, J., and Bartek, J. (2012). Ubiquitin-activating enzyme UBA1 is required for cellular response to DNA damage. *Cell Cycle* *11*, 1573–1582.
- Muralidhar, M.G., and Thomas, J.B. (1993). The *Drosophila* bendless gene encodes a neural protein related to ubiquitin-conjugating enzymes. *Neuron* *11*, 253–266.
- Muratani, M., and Tansey, W.P. (2003). How the ubiquitin-proteasome system controls transcription. *Nat. Rev. Mol. Cell Biol.* *4*, 192–201.

Nalepa, G., Rolfe, M., and Harper, J.W. (2006). Drug discovery in the ubiquitin - Proteasome system. *Nat. Rev. Drug Discov.* 5, 596–613.

Nishikawa, H., Ooka, S., Sato, K., Arima, K., Okamoto, J., Klevit, R.E., Fukuda, M., and Ohta, T. (2004). Mass Spectrometric and Mutational Analyses Reveal Lys-6-linked Polyubiquitin Chains Catalyzed by BRCA1-BARD1 Ubiquitin Ligase. *J. Biol. Chem.* 279, 3916–3924.

Oh, C., McMahon, R., Benzer, S., and Tanouye, M. (1994). *bendless*, a *Drosophila* gene affecting neuronal connectivity, encodes a ubiquitin-conjugating enzyme homolog. *J. Neurosci.* 14, 3166–3179.

Ohi, M.D., Craig, V.K.W., Rosenberg, J.A., Chazin, W.J., and Gould, K.L. (2003). Structural insights into the U-box, a domain associated with multi-ubiquitination. *Nat. Struct. Biol.* 10, 250–255.

Ordureau, A., Heo, J.-M., Duda, D.M., Paulo, J.A., Olszewski, J.L., Yanishevski, D., Rinehart, J., Schulman, B.A., and Harper, J.W. (2015). Defining roles of PARKIN and ubiquitin phosphorylation by PINK1 in mitochondrial quality control using a ubiquitin replacement strategy. *Proc. Natl. Acad. Sci.* 112, 6637–6642.

Ozkan, E., Yu, H., and Deisenhofer, J. (2005). Mechanistic insight into the allosteric activation of a ubiquitin-conjugating enzyme by RING-type ubiquitin ligases. *Proc. Natl. Acad. Sci.* 102, 18890–18895.

Ozkaynak, E., Finley, D., and Varshavsky, A. (1984). The yeast ubiquitin gene: head-to-tail repeats encoding a polyubiquitin precursor protein. *Nat. Publ. Gr.* 312, 663–666.

Ozkaynak, E., Finley, D., and Solomon, M.J. (1987). The yeast ubiquitin genes: a family of natural gene fusions. *EMBO J.* 6, 1429–1439.

Paul, I., and Ghosh, M.K. (2014). The E3 Ligase CHIP: Insights into Its Structure and Regulation. *Biomed Res. Int.* 2014, 1–12.

Peters, J.M., Franke, W.W., and Kleinschmidt, J.A. (1994). Distinct 19 S and 20 S subcomplexes of the 26 S proteasome and their distribution in the nucleus and the cytoplasm. *J. Biol. Chem.* *269*, 7709–7718.

Pfleger, C.M., Harvey, K.F., Yan, H., and Hariharan, I.K. (2007). Mutation of the gene encoding the ubiquitin activating enzyme uba1 causes tissue overgrowth in *Drosophila*. *Fly (Austin)*. *1*, 95–105.

Pickart, C. (2001). Mechanisms Underlying Ubiquitination. *Annu. Rev. Biochem* *70*, 503–533.

Pickart, C.M., and Eddins, M.J. (2004). Ubiquitin: structures, functions, mechanisms. *Biochim. Biophys. Acta - Mol. Cell Res.* *1695*, 55–72.

Pickart, C.M., and Fushman, D. (2004). Polyubiquitin chains: Polymeric protein signals. *Curr. Opin. Chem. Biol.* *8*, 610–616.

Pickart, C.M., and Rose, I.A. (1985). Functional heterogeneity of ubiquitin carrier proteins. *J. Biol. Chem.* *260*, 1573–1581.

PORATH, J., CARLSSON, J.A.N., OLSSON, I., and BELFRAGE, G. (1975). Metal chelate affinity chromatography, a new approach to protein fractionation. *Nature* *258*, 598–599.

Raasi, S., Varadan, R., Fushman, D., and Pickart, C.M. (2005). Diverse polyubiquitin interaction properties of ubiquitin-associated domains. *Nat. Struct. Mol. Biol.* *12*, 708–714.

Raimalani, V., Panchamia, B., and Prabha, C.R. (2019). Construction and Characterization of UBC4 Mutants with Single Residues Swapped from UBC5. *Cell Biochem. Biophys.*

Rajapurohitam, V., Wing, S.S., Lefrançois, S., Bedard, N., Morales, C.R., and El-Alfy, M. (1999). Activation of a UBC4-Dependent Pathway of Ubiquitin Conjugation during Postnatal Development of the Rat Testis. *Dev. Biol.* *212*, 217–228.

Ramser, J., Ahearn, M.E., Lenski, C., Yariz, K.O., Hellebrand, H., von Rhein, M., Clark, R.D., Schmutzler, R.K., Lichtner, P., Hoffman, E.P., et al. (2008). Rare Missense and Synonymous Variants in UBE1 Are Associated with X-Linked Infantile Spinal Muscular Atrophy. *Am. J. Hum. Genet.* 82, 188–193.

Rank, K.B., Mildner, A.M., Leone, J.W., Koeplinger, K.A., Chou, K.C., Tomasselli, A.G., Heinrikson, R.L., and Sharma, S.K. (2001). [W206R]-Procaspase 3: An Inactivatable Substrate for Caspase 8. *Protein Expr. Purif.* 22, 258–266.

Regni, C.A., Roush, R.F., Miller, D.J., Nourse, A., Walsh, C.T., and Schulman, B.A. (2009). How the MccB bacterial ancestor of ubiquitin E1 initiates biosynthesis of the microcin C7 antibiotic. *EMBO J.* 28, 1953–1964.

Reyes-Turcu, F.E., Horton, J.R., Mullally, J.E., Heroux, A., Cheng, X., and Wilkinson, K.D. (2006). The Ubiquitin Binding Domain ZnF UBP Recognizes the C-Terminal Diglycine Motif of Unanchored Ubiquitin. *Cell* 124, 1197–1208.

Rinetti, G. V., and Schweizer, F.E. (2010). Ubiquitination Acutely Regulates Presynaptic Neurotransmitter Release in Mammalian Neurons. *J. Neurosci.* 30, 3157–3166.

Rock, K.L., and Goldberg, A.L. (1999). Degradation of Cell Proteins and the Generation of Mhc Class I-Presented Peptides. *Annu. Rev. Immunol.* 17, 739–779.

Rock, K.L., Gramm, C., Rothstein, L., Clark, K., Stein, R., Dick, L., Hwang, D., and Goldberg, A.L. (1994). Inhibitors of the proteasome block the degradation of most cell proteins and the generation of peptides presented on MHC class I molecules. *Cell* 78, 761–771.

Rodrigo-brenni, M.C., and Morgan, D.O. (2007). Sequential E2s Drive Polyubiquitin Chain Assembly on APC Targets. *Cell* 130, 127–139.

Roest, H.P., Van Klaveren, J., De Wit, J., Van Gorp, C.G., Koken, M.H.M., Vermey, M., Van Roijen, J.H., Hoogerbrugge, J.W., Vreeburg, J.T.M., Baarends, W.M., et al. (1996). Inactivation of the HR6B ubiquitin-conjugating DNA repair enzyme in mice causes male sterility associated with chromatin modification. *Cell* 86, 799–810.

Rosenthal, G. (1977). The biological effects and mode of action of L-canavanine, a structural analogue of L-arginine. *Q Rev. Biol.* 52, 155–178.

Rotin, D., and Kumar, S. (2009). Physiological functions of the HECT family of ubiquitin ligases. *Nat. Rev. Mol. Cell Biol.* 10, 398–409.

Ruth Geiss-Friedlander and Frauke Melchior (2007). Concepts in sumoylation: a decade on. *Nat. Rev. | Mol. Cell Biol.* volume 8, 947–956.

Sadoul, R., Fernandez, P.A., Quiquerez, A.L., Martinou, I., Maki, M., Schröter, M., Becherer, J.D., Irmeler, M., Tschopp, J., and Martinou, J.C. (1996). Involvement of the proteasome in the programmed cell death of NGF-deprived sympathetic neurons. *EMBO J.* 15, 3845–3852.

Scf, L., Saha, A., and Deshaies, R.J. (2008). Multimodal Activation of the Ubiquitin Ligase SCF by Nedd8 Conjugation. *Mol. Cell* 32, 21–31.

Scheffner, M., Werness, B.A., and Huibregtse, J. (1990). The E6 oncoprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell* 63, 1129–1136.

Scheffner, M., Nuber, U., and Huibregtse, J.M. (1995). Protein ubiquitination involving an E1–E2–E3 enzyme ubiquitin thioester cascade. *Nature* 373, 81–83.

Schelpe, J., Sixma, T.K., and Rucktooa, P. (2016). Structure of UBE2Z Enzyme Provides Functional Insight into Specificity in the FAT10 Protein Conjugation Machinery *. *J. Biol. Chem.* 291, 630–639.

Schmidt, M., Tuominen, N., Johansson, T., Weiss, S.A., Keinänen, K., and

Oker-Blom, C. (1998). Baculovirus-Mediated Large-Scale Expression and Purification of a Polyhistidine-Tagged Rubella Virus Capsid Protein. *Protein Expr. Purif.* 12, 323–330.

Schneider-poetsch, T., Ju, J., Eyler, D.E., Dang, Y., Bhat, S., Merrick, W.C., Green, R., Shen, B., and Liu, J.O. (2010). Inhibition of eukaryotic translation elongation by cycloheximide. *Nat. Chem. Biol.* 6, 209–217.

Schulman, B. a, and Harper, J.W. (2009). Ubiquitin-like protein activation by E1 enzymes: the apex for downstream signalling pathways. *Mol. Cell* 10, 319–331.

Schwartz, L.M., Myer, A., Kosz, L., Engelstein, M., and Maier, C. (1990). Activation of polyubiquitin gene expression during developmentally programmed cell death. *Neuron* 5, 411–419.

Seufert, W., and Jentsch, S. (1990). Ubiquitin-conjugating enzymes UBC4 and UBC5 mediate selective degradation of short-lived and abnormal proteins. *EMBO J.* 9, 543–550.

Siepmann, T.J., Bohnsack, R.N., Tokgo, Z., Baboshina, O. V, and Haas, A.L. (2003). Protein Interactions within the N-end Rule Ubiquitin Ligation Pathway *. *J. Biol. Chem.* 278, 9448–9457.

Sloper-Mould, K.E., Jemc, J.C., Pickart, C.M., and Hicke, L. (2001). Distinct Functional Surface Regions on Ubiquitin. *J. Biol. Chem.* 276, 30483–30489.

Staub, O., and Rotin, D. (2006). Role of Ubiquitylation in Cellular Membrane Transport. *Physiol Rev* 86, 669–707.

Stewart, M.D., Ritterhoff, T., Klevit, R.E., and Brzovic, P.S. (2016). E2 enzymes : more than just middle men. *Cell Res.* 26, 423–440.

Stolz, A., Hilt, W., Buchberger, A., and Wolf, D.H. (2011). Cdc48: A power machine in protein degradation. *Trends Biochem. Sci.* 36, 515–523.

Sugaya, K., Ishihara, Y., Inoue, S., and Tsuji, H. (2014). Characterization of ubiquitin-activating enzyme Uba1 in the nucleus by its mammalian temperature-sensitive mutant. *PLoS One* 9, 1–12.

Swaminathan, S., Amerik, A.Y., and Hochstrasser, M. (1999). The Doa4 Deubiquitinating Enzyme Is Required for Ubiquitin Homeostasis in Yeast. *Mol. Biol. Cell* 10, 2583–2594.

Szczepanowski, R.H., Filipek, R., and Bochtler, M. (2005). Crystal structure of a fragment of mouse ubiquitin-activating enzyme. *J. Biol. Chem.* 280, 22006–22011.

Taylor, S. V., Kelleher, N.L., Kinsland, C., Chiu, H.J., Costello, C.A., Backstrom, A.D., McLafferty, F.W., and Begley, T.P. (1998). Thiamin biosynthesis in *Escherichia coli*. Identification of this thiocarboxylate as the immediate sulfur donor in the thiazole formation. *J. Biol. Chem.* 273, 16555–16560.

Thomas, M., Dadgar, N., Aphale, A., Harrell, J.M., Kunkel, R., Pratt, W.B., and Lieberman, A.P. (2004). Androgen Receptor Acetylation Site Mutations Cause Trafficking Defects, Misfolding, and Aggregation Similar to Expanded Glutamine Tracts. *J. Biol. Chem.* 279, 8389–8395.

Turcu Francisca E. Reyes, Ventii Karen H., W.K.D. (2009). Regulation and Cellular Roles of Ubiquitin-specific Deubiquitinating Enzymes. *Annu Rev Biochem* 78, 363–397.

VanDemark, A.P., and Hill, C.P. (2002). Structural basis of ubiquitylation. *Curr. Opin. Struct. Biol.* 12, 822–830.

Varadan, R., Assfalg, M., Haririnia, A., Raasi, S., Pickart, C., and Fushman, D. (2004). Solution Conformation of Lys63-linked Di-ubiquitin Chain Provides Clues to Functional Diversity of Polyubiquitin Signaling. *J. Biol. Chem.* 279, 7055–7063.

Varadan, R., Assfalg, M., Raasi, S., Pickart, C., and Fushman, D. (2005). Structural determinants for selective recognition of a Lys48-linked polyubiquitin chain by a UBA domain. *Mol. Cell* 18, 687–698.

Vijay-Kumar, S., Bugg, C.E., Wilkinson, K.D., Vierstra, R.D., Hatfield, P.M., and Cook, W.J. (1987a). Comparison of the three-dimensional structures of human, yeast, and oat ubiquitin. *J. Biol. Chem.* 262, 6396–6399.

Vijay-Kumar, S., Bugg, C., and Cook, W. (1987b). Structure of Ubiquitin Refined at 1.8 Å Resolution. *J. Mol. Biol. Mol. Biol.* 194, 531–544.

Vinitzky, A., Anton, L.C., Snyder, H.L., Orłowski, M., Bennink, J.R., and Yewdell, J.W. (1997). The generation of MHC class I-associated peptides is only partially inhibited by proteasome inhibitors: involvement of nonproteasomal cytosolic proteases in antigen processing? *J. Immunol.* 159, 554–564.

Voges, D., Zwickl, P., and Baumeister, W. (1999). The 26S proteasome: a molecular machine designed for controlled proteolysis. *Annu. Rev. Biochem.* 68, 1015–1068.

Wade, B.E., Wang, C.-E., Yan, S., Bhat, K., Huang, B., Li, S., and Li, X.-J. (2014). Ubiquitin-Activating Enzyme Activity Contributes to Differential Accumulation of Mutant Huntingtin in Brain and Peripheral Tissues. *J. Neurosci.* 34, 8411–8422.

Walden, H., Podgorski, M.S., and Schulman, B.A. (2003). Insights into the ubiquitin transfer cascade from the structure of the activating enzyme for NEDD8. *Nature* 422, 330–334.

Wang, C., Xi, J., Begley, T.P., and Nicholson, L.K. (2001). Solution structure of ThiS and implications for the evolutionary roots of ubiquitin. *Nat. Struct. Biol.* 8, 47–51.

Wefes, I., Mastrandrea, L.D., Haldeman, M., Koury, S.T., Tamburlin, J.,

Pickart, C.M., and Finley, D. (1995). Induction of ubiquitin-conjugating enzymes during terminal erythroid differentiation. *Proc. Natl. Acad. Sci. U. S. A.* 92, 4982–4986.

Wenzel, T., and Baumeister, W. (1995). Conformational constraints in protein degradation by the 20S proteasome. *Nat. Struct. Mol. Biol.* 2, 199–204.

Wenzel, T., Eckerskorn, C., Lottspeich, F., and Baumeister, W. (1994). Existence of a molecular ruler in proteasomes suggested by analysis of degradation products. *FEBS Lett.* 349, 205–209.

Weston, C.R., and Davis, R.J. (2007). The JNK signal transduction pathway. *Curr. Opin. Cell Biol.* 19, 142–149.

Wilk, S., and Orłowski, M. (1983). Evidence that Pituitary Cation-Sensitive Neutral Endopeptidase Is a Multicatalytic Protease Complex. *J. Neurochem.* 40, 842–849.

Wilkinson, K.D., Urban, M.K., and Haas, A.L. (1980). Ubiquitin Is the ATP-dependent Proteolysis Factor I of Rabbit Reticulocytes. *J. Biol. Chem.* 255, 7529–7532.

Wing, S.S. (2003). Deubiquitinating enzymes — the importance of driving in reverse along the ubiquitin – proteasome pathway. *Int. J. Biochem. Cell Biol.* 35, 590–605.

Wishart, T.M., Paterson, J.M., Short, D.M., Meredith, S., Robertson, K.A., Sutherland, C., Cousin, M.A., Dutia, M.B., and Gillingwater, T.H. (2007). Differential Proteomics Analysis of Synaptic Proteins Identifies Potential Cellular Targets and Protein Mediators of Synaptic Neuroprotection Conferred by the Slow Wallerian Degeneration (*Wld^s*) Gene. *Mol. Cell. Proteomics* 6, 1318–1330.

Wishart, T.M., Pemberton, H.N., James, S.R., McCabe, C.J., and Gillingwater, T.H. (2008). Modified cell cycle status in a mouse model of altered neuronal

- vulnerability (slow Wallerian degeneration; Wlds). *Genome Biol.* *9*.
- Wishart, T.M., Mutsaers, C.A., Riessland, M., Reimer, M.M., Hunter, G., Hannam, M.L., Eaton, S.L., Fuller, H.R., Roche, S.L., Somers, E., et al. (2014). Dysregulation of ubiquitin homeostasis and β -catenin signaling promote spinal muscular atrophy. *J. Clin. Invest.* *124*, 1821–1834.
- Wu, H., Pomeroy, S.L., Ferreira, M., Teider, N., Mariani, J., Nakayama, K.I., Hatakeyama, S., Tron, V.A., Saltibus, L.F., Spyrapoulos, L., et al. (2011). UBE4B promotes Hdm2-mediated degradation of the tumor suppressor p53. *Nat. Med.* *17*, 347–355.
- Wu, P., Hanlon, M., Eddins, M., Tsui, C., Rogers, R.S., Jensen, J.P., Matunis, M.J., Weissman, A.M., Wolberger, C.P., and Pickart, C.M. (2003). A conserved catalytic residue in the ubiquitin-conjugating enzyme family. *EMBO J.* *22*, 5241–5250.
- Xu, P., Duong, D.M., Seyfried, N.T., Cheng, D., Xie, Y., Robert, J., Rush, J., Hochstrasser, M., Finley, D., and Peng, J. (2009). Quantitative Proteomics Reveals the Function of Unconventional Ubiquitin Chains in Proteasomal Degradation. *Cell* *137*, 133–145.
- Yan, D., Guo, L., and Wang, Y. (2006). Requirement of dendritic Akt degradation by the ubiquitin-proteasome system for neuronal polarity. *J. Cell Biol.* *174*, 415–424.
- Yau, R., and Rape, M. (2016). The increasing complexity of the ubiquitin code. *Nat. Cell Biol.* *18*, 579–586.
- Ye, Y., and Rape, M. (2009). Building ubiquitin chains: E2 enzymes at work. *Nat. Rev. Mol. Cell Biol.* *10*, 755–764.
- Yi, Y.J., Zimmerman, S.W., Manandhar, G., Odhiambo, J.F., Kennedy, C., Jonáková, V., Maňásková-Postlerová, P., Sutovsky, M., Park, C.S., and Sutovsky, P. (2012). Ubiquitin-activating enzyme (UBA1) is required for

sperm capacitation, acrosomal exocytosis and sperm-egg coat penetration during porcine fertilization. *Int. J. Androl.* 35, 196–210.

Zheng, N., Wang, P., Jeffrey, P.D., and Pavletich, N.P. (2000). Structure of a c-Cbl-UbcH7 Complex: RING Domain Function in Ubiquitin-Protein Ligases. *Cell* 102, 533–539.