

LECTURE #4: PROTEIN TURNOVER AND PROTEIN PROCESSING

**Assigned (Required) Reading is (1) - (4):**

**•General Background (in your Reader):**

**(1) Kerscher O, Felberbaum R, Hochstrasser M (2006) Modification of proteins by ubiquitin and ubiquitin-like proteins. Annu. Rev. Cell Dev. Biol. 22: 159-180.**

**(2) Harper JW, Schulman BA (2006) Structural complexity in ubiquitin recognition. Cell 124: 1133-1136.**

**(3) Goldberg AL (2007) Functions of the proteasome: from protein degradation and immune surveillance to cancer therapy. Biochem. Soc. Trans. 35: 12-17.**

**•Paper for Friday Discussion Session (11/30):**

**(4) Schwartz DC, Felberbaum R, Hochstrasser M (2007) The Ulp2 SUMO protease is required for cell division following termination of the DNA damage checkpoint. Mol. Cell Biol. 27: 6948-6961.**

tmRNA in bacteria:

Moore SD, Sauer RT (2007) The tmRNA system for translational surveillance and ribosome rescue. Annu. Rev. Biochem. 76: 101-124.

Withey JH, Friedman DI (2003) A salvage pathway for protein synthesis: tmRNA and trans-translation. Annu Rev Microbiol. 57:101-123.

Moore SD, McGinness KE, Sauer RT (2003) Structural biology. A glimpse into tmRNA-mediated ribosome rescue. Science 300:72-73.

The ubiquitin system (general background):

Varshavsky A (2005) Regulated protein degradation. Trends Biochem. Sci. 30: 283-286.

Kaiser P, Huang L. (2005) Global approaches to understanding ubiquitination. Genome Biol. 6: 233.1-233.8.

Hicke L, Schubert HL, Hill CP. (2005) Ubiquitin-binding domains. Nature Rev. Mol. Cell Biol. 6: 610-621.

Pickart CM (2004) Back to the future with ubiquitin. Cell 116: 181-190.

Huang DT, Walden H, Duda D, Schulman BA (2004) Ubiquitin-like protein activation. Oncogene 23: 1958-1971.

Goldberg AL (2003) Protein degradation and protection against misfolded or damaged proteins. Nature 426: 895-899.

Glickman MH, Ciechanover A (2002) The ubiquitin-proteasome proteolytic pathway: destruction for the sake of construction. Physiol Rev. 82: 373-428.

Pickart CM (2001) Ubiquitin enters the new millennium. Mol. Cell. 8:499-504.

Varshavsky A (2001) Recent studies of the ubiquitin system and the N-end rule pathway. Harvey Lect. 96: 93-116.

Pickart CM (2001) Mechanisms underlying ubiquitination. Annu. Rev. Biochem. 70: 503-533.

Joazeiro CA, Hunter T. (2000) Ubiquitination--more than two to tango. Science 289: 2061-2062.

Wilkinson KD. (2000) Ubiquitination and deubiquitination: targeting of proteins for degradation by the proteasome. *Semin. Cell Dev. Biol.* 11: 141-148.

Hershko, A. and A. Ciechanover (1998) The ubiquitin system. *Annu. Rev. Biochem.* 67: 425-479.

Other ubiquitin-like modifications:

Hipp MS, Kalveram B, Raasi S, Groettrup M, Schmidtke G. (2005) FAT10, a ubiquitin-independent signal for proteasomal degradation. *Mol. Cell. Biol.* 25: 3483-3491.

Wilkinson CR, Dittmar GA, Ohi MD, Uetz P, Jones N, Finley D. (2004) Ubiquitin-like protein Hub1 is required for pre-mRNA splicing and localization of an essential splicing factor in fission yeast. *Curr. Biol.* 14: 2283-2288.

Schwartz DC, Hochstrasser M (2003) A superfamily of protein tags: ubiquitin, SUMO and related modifiers. *Trends Biochem Sci.* 28: 321-328.

Goehring AS, Rivers DM, Sprague GF Jr. (2003) Urmyletation: a ubiquitin-like pathway that functions during invasive growth and budding in yeast. *Mol. Biol. Cell* 14: 4329-4341.

Melchior F, Schergaut M, Pichler A. (2003) SUMO: ligases, isopeptidases and nuclear pores. *Trends Biochem Sci.* 2003 Nov;28(11):612-8.

Li SJ, Hochstrasser M (2003) The Ulp1 SUMO isopeptidase: distinct domains required for viability, nuclear envelope localization, and substrate specificity. *J. Cell Biol.* 160:1069-1081.

Hochstrasser M (2001) SP-RING for SUMO: new functions bloom for a ubiquitin-like protein. *Cell* 107: 5-8.

Stromhaug PE, Klionsky DJ (2001) Approaching the molecular mechanism of autophagy. *Traffic* 2: 524-531.

Lyapina S, Cope G, Shevchenko A, Serino G, Tsuge T, Zhou C, Wolf DA, Wei N, Shevchenko A,

Deshais RJ (2001) Promotion of NEDD-CUL1 conjugate cleavage by COP9 signalosome. *Science* 292: 1382-1385.

Melchior F (2000) SUMO--nonclassical ubiquitin. *Annu Rev Cell Dev Biol.* 16: 591-626.

Yeh ET, Gong L, Kamitani T (2000) Ubiquitin-like proteins: new wines in new bottles *Gene* 248: 1-14.

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

HECT domain E3's:

Tamai KK, Shimoda C (2002) The novel HECT-type ubiquitin-protein ligase Pub2p shares partially overlapping function with Pub1p in *Schizosaccharomyces pombe*. *J Cell Sci.* 115: 1847-1857.

Wang G, McCaffery JM, Wendland B, Dupre S, Haguenaer-Tsapis R, Huibregtse JM (2001) Localization of the Rsp5p ubiquitin-protein ligase at multiple sites within the endocytic pathway. *Mol Cell Biol* 21: 3564-3575.

Rotin D, Staub O, Haguenaer-Tsapis R (2000) Ubiquitination and endocytosis of plasma membrane proteins: role of Nedd4/Rsp5p family of ubiquitin-protein ligases. *J Membr Biol* 176: 1-17.

Huang L, Kinnucan E, Wang G, Beaudenon S, Howley PM, Huibregtse JM, Pavletich NP (1999) Structure of an E6AP-UbcH7 complex: insights into ubiquitination by the E2-E3 enzyme cascade. *Science* 286: 1321-1326.

RING-type E3's and SCF complexes:

Ang XL, Wade Harper J (2005) SCF-mediated protein degradation and cell cycle control. *Oncogene* 24: 2860-2870.

Jackson PK, Eldridge AG (2002) The SCF ubiquitin ligase: an extended look. *Mol Cell*. 9: 923-925.

Trockenbacher A, Suckow V, Foerster J, Winter J, Krauss S, Ropers HH, Schneider R, Schweiger S (2001) MID1, mutated in Opitz syndrome, encodes a RING-type ubiquitin ligase that targets phosphatase 2A for degradation. *Nature Genet*. 29: 287-294.

Jackson PK, Eldridge AG, Freed E, Furstenthal L, Hsu JY, Kaiser BK, Reimann JD (2000) The lore of the RINGS: substrate recognition and catalysis by ubiquitin ligases. *Trends Cell Biol*. 10: 429-439.

Joazeiro CA, Weissman AM (2000) RING finger proteins: mediators of ubiquitin ligase activity. *Cell*. 102: 549-552.

Tyers M, Jorgensen P (2000) Proteolysis and the cell cycle: with this RING I do thee destroy. *Curr Opin Genet Dev*. 10: 54-64.

Zheng N, Wang P, Jeffrey PD, Pavletich NP (2000) Structure of a c-Cbl-UbcH7 complex: RING domain function in ubiquitin-protein ligases. *Cell* 102: 533-539.

Deshaies RJ (1999) SCF and Cullin/Ring H2-based ubiquitin ligases. *Annu. Rev. Cell Dev. Biol*. 15: 435-467.

#### Variant RING Domain E3's:

Cadwell K, Coscoy L. (2005) Ubiquitination on nonlysine residues by a viral E3 ubiquitin ligase. *Science* 309: 127-130.

Lu Z, Xu S, Joazeiro C, Cobb MH, Hunter T (2002) The PHD domain of MEKK1 acts as an E3 ubiquitin ligase and mediates ubiquitination and degradation of ERK1/2. *Mol Cell*. 9: 945-956.

Capili AD, Schultz DC, Rauscher III FJ, Borden KL (2001) Solution structure of the PHD domain from the KAP-1 copressor: structural determinants for PHD, RING, LIM zinc-binding domains. *EMBO J*. 20: 165-177.

Coscoy L, Sanchez DJ, Ganem D (2001) A novel class of herpes virus-encoded membrane-bound E3 ubiquitin ligases regulates endocytosis of proteins involved in immune recognition. *J Cell Biol*. 155: 1265-1273.

#### U Box E3's:

Cyr DM, Höhfeld J, Patterson C (2002) Protein quality control: U-box-containing E3 ubiquitin ligases join the fold. *Trends Biochem Sci*. 2002 Jul; 27(7): 368-75.

Hatakeyama S, Yada M, Matsumoto M, Ishida N, Nakayama KI (2001) U box proteins as a new family of ubiquitin-protein ligases. *J. Biol. Chem*. 276:33111-33120.

#### Ubiquitinylation of transcription factors and histones:

Muratani M, Tansey WP (2003) How the ubiquitin-proteasome system controls transcription. *Nat Rev Mol Cell Biol*. 4: 192-201.

Oren M (2003) Decision making by p53: life, death and cancer. *Cell Death Differ*. 10: 431-442.

Bach I, Ostendorff HP (2003) Orchestrating nuclear functions: ubiquitin sets the rhythm. *Trends Biochem. Sci*. 28: 189-195.

Moore SC, Jason L, Ausio J (2002) The elusive structural role of ubiquitinated histones. *Biochem Cell Biol*. 80: 311-319.

Berger SL (2001) An embarrassment of niches: the many covalent modifications of histones in transcriptional regulation. *Oncogene* 20: 3007-3013.

Thomas D, Tyers M. (2000) Transcriptional regulation: Kamikaze activators. *Curr Biol.* 10: R341-R343.

Ubiquitylation in vesicular protein trafficking and endocytosis:

Riezman H (2002) Cell biology: the ubiquitin connection. *Nature* 416: 381-383.

Shih SC, Katzmann DJ, Schnell JD, Sutanto M, Emr SD, Hicke L (2002) Epsins and Vps27p/Hrs contain ubiquitin-binding domains that function in receptor endocytosis. *Nature Cell Biol.* 4: 389-393.

Hicke L (2001) Protein regulation by monoubiquitin. *Nature Rev Mol Cell Biol.* 2: 195-201.

Rotin D, Staub O, Haguenaer-Tsapis R. (2000) Ubiquitination and endocytosis of plasma membrane proteins: role of Nedd4/Rsp5 family of ubiquitin-protein ligases. *J Membr. Biol.* 176: 1-17.

Unfolded protein response and ERAD:

Ron D, Walter P (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nature Rev Mol Cell Biol.* 8: 519-529.

Hampton RY (2003) IRE1: a role in UPREgulation of ER degradation. *Dev. Cell.* 4: 144-146.

Kaufman RJ, Scheuner D, Schroder M, Shen X, Lee K, Liu CY, Arnold SM (2002) The unfolded protein response in nutrient sensing and differentiation. *Nature Rev Mol Cell Biol.* 3: 411-421.

Patil C, Walter P (2001) Intracellular signaling from the endoplasmic reticulum to the nucleus: the unfolded protein response in yeast and mammals. *Curr Opin Cell Biol.* 13: 349-355.

Hampton RY (2000) ER stress response: getting the UPR hand on misfolded proteins. *Curr Biol.* 10: R518-R521.

Lord JM, Davey J, Frigerio L, Roberts LM (2000) Endoplasmic reticulum-associated protein degradation. *Semin Cell Dev Biol.* 11: 159-164.

Plempner RK, Wolf DH. (1999) Retrograde protein translocation: ERADication of secretory proteins in health and disease. *Trends Biochem. Sci.* 24: 266-270.

Role of ubiquitylation in cell cycle control— APC and its targets:

Rape M, Reddy SK, Kirschner MW. (2006) The processivity of multiubiquitination by the APC determines the order of substrate degradation. *Cell* 124: 89-103.

Vodermaier HC (2004) APC/C and SCF: controlling each other and the cell cycle. *Curr. Biol.* 14: R787-R796.

Harper JW, Burton JL, Solomon MJ (2002) The anaphase-promoting complex: it's not just for mitosis any more. *Genes Dev.* 16: 2179-2206.

Levenson JD, Joazeiro CA, Page AM, Huang H.-K., Hieter P, Hunter T (2000) The APC11 RING-H2 finger mediates E2-dependent ubiquitination. *Mol. Biol. Cell* 11: 2315-2325.

Zachariae W, Nasmyth K. (1999) Whose end is destruction: cell division and the anaphase-promoting complex. *Genes Dev.* 13: 2039-2058.

Page AM, Hieter P (1999) The anaphase-promoting complex: new subunits and regulators. *Annu Rev Biochem.* 68: 583-609.

Morgan DO. (1999) Regulation of the APC and the exit from mitosis. *Nature Cell Biol.* 1: E47-E53.

Fang G, Yu H, Kirschner MW. (1999) Control of mitotic transitions by the anaphase-promoting complex. *Philos Trans R Soc Lond B Biol Sci.* 354: 1583-1590.

#### ClpP- and HslV-mediated protein degradation:

Sauer RT, Bolon DN, Burton BM, Burton RE, Flynn JM, Grant RA, Hersch GL, Joshi SA, Kenniston JA, Levchenko I, Neher SB, Oakes ES, Siddiqui SM, Wah DA, Baker TA (2004) Sculpting the proteome with AAA(+) proteases and disassembly machines. *Cell* 119: 9-18.

#### Proteosomes:

Elsasser S, Finley D (2005) Delivery of ubiquitinated substrates to protein-unfolding machines. *Nature Cell Biol.* 7: 742-749.

Dalton WS. (2004) The proteasome. *Semin. Oncol.* 31 (Suppl.) 3-9 & 33 (Discussion).

Groll M, Huber R (2003) Substrate access and processing by the 20S proteasome core particle. *Int. J. Biochem. Cell Biol.* 35: 606-616.

Zwickl P, Seemuller E, Kapelari B, Baumeister W (2001) The proteasome: a supramolecular assembly designed for controlled proteolysis. *Adv. Protein Chem.* 59: 187-222.

Kohler A, Bajorek M, Groll M, Moroder L, Rubin DM, Huber R, Glickman MH, Finley D (2001) The substrate translocation channel of the proteasome. *Biochimie* 83: 325-332.

Zwickl P, Baumeister W, Steven A. (2000) Dis-assembly lines: the proteasome and related ATPase-assisted proteases. *Curr Opin Struct Biol.* 10: 242-250.

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

Schmidt M, Lupas AN, Finley D. (1999) Structure and mechanism of ATP-dependent proteases. *Curr. Opin. Chem. Biol.* 3: 584-591.

#### Intein excision and protein splicing:

Gogarten JP, Senejani AG, Zhaxybayeva O, Olendzenski L, Hilario E (2002) Inteins: structure, function, and evolution. *Annu Rev Microbiol.* 56: 263-287.

Paulus H (2001) Inteins as enzymes. *Bioorg. Chem.* 29: 119-129.

Giriati I, Muir TW, Perler FB (2001) Protein splicing and its applications. *Genet Eng (NY)* 23: 171-199.

Gimble, F.S. (1998) Putting protein splicing to work. *Chem. Biol.* 5: R251-R256.

#### Other Practical Uses:

Thaminy S, Miller J, Stagljar I. (2004) The split-ubiquitin membrane-based yeast two-hybrid system. *Methods Mol. Biol.* 261: 297-312.

Varshavsky A. (2000) Ubiquitin fusion technique and its descendants. *Methods Enzymol.* 327: 578-593.

Blaschke UK, Silberstein J, Muir TW (2000) Protein engineering by expressed protein ligation. *Methods Enzymol.* 328: 478-496.

#### Ubiquitination and regulated proteolysis in metabolic and developmental signaling:

##### *Signaling complex assembly downstream of cytokine receptors—*

Kanayama A, Seth RB, Sun L, Ea CK, Hong M, Shaito A, Chiu YH, Deng L, Chen ZJ (2004) TAB2 and TAB3 activate the NF-kappaB pathway through binding to polyubiquitin chains. *Mol. Cell* 15: 535-548.

*Prohormone and other precursor processing—*

Thomas G (2002) Furin at the cutting edge: From protein traffic to embryogenesis and disease. *Nature Rev Mol Cell Biol.* 3: 753-766.

Khatib AM, Siegfried G, Chretien M, Metrakos P, Seidah NG (2002) Proprotein convertases in tumor progression and malignancy: novel targets in cancer therapy. *Am J Pathol.* 160: 1921-1935.

Rockwell NC, Fuller RS (2002) Specific modulation of Kex2/furin family proteases by potassium. *J Biol Chem.* 277: 17531-17537.

Castro MG, Morrison E (1997) Post-translational processing of proopiomelanocortin in the pituitary and in the brain. *Crit Rev Neurobiol.* 11: 35-57.

*Cubitus interruptus—*

Jiang J (2002) Degrading Ci: who is Cul-pable? *Genes Dev.* 16: 2315-2321.

Aza-Blanc P, Kornberg TB (1999) Ci: a complex transducer of the hedgehog signal. *Trends Genet.* 15: 458-462.

*Notch signaling—*

Justice NJ, Jan YN (2002) Variations on the Notch pathway in neural development. *Curr Opin Neurobiol* 12: 64-70.

Lai EC (2002) Notch cleavage: Nicastrin helps Presenilin make the final cut *Curr Biol* 12: R200-R202.

Lai EC (2002) Protein degradation: four E3s for the notch pathway *Curr Biol.* 12: R74-R78.

Chan YM, Jan YN. (1998) Roles for proteolysis and trafficking in notch maturation and signal transduction. *Cell.* 94: 423-426.

*Hedgehog signaling—*

Jeong J, McMahon AP (2002) Cholesterol modification of Hedgehog family proteins. *J Clin Invest.* 110: 591-596.

El-Husseini Ael-D, Brecht DS (2002) Protein palmitoylation: a regulator of neuronal development and function. *Nature Rev Neurosci.* 3: 791-802.

Ingham PW (2001) Hedgehog signaling: a tale of two lipids. *Science* 294: 1879-1881.

Chamoun Z, Mann RK, Nellen D, von Kessler DP, Bellotto M, Beachy PA, Basler K (2001) Skinny hedgehog, an acyltransferase required for palmitoylation and activity of the hedgehog signal. *Science* 293: 2080-2084.

Mann RK, Beachy PA (2000) Cholesterol modification of proteins. *Biochim Biophys Acta* 1529: 188-202.

*SREBP signaling—*

Horton JD, Goldstein JL, Brown MS (2002) SREBPs: activators of the complete program of cholesterol and fatty acid synthesis in the liver. *J Clin Invest* 109: 1125-1131.

Hampton RY (2002) Proteolysis and sterol regulation. *Annu Rev Cell Dev Biol* 18: 345-378.

*Easter processing of Spatzle—*

Chang AJ, Morisato D (2002) Regulation of Easter activity is required for shaping the Dorsal gradient in the Drosophila embryo. *Development* 129: 5635-5645.

Misra S, Hecht P, Maeda R, Anderson KV (1998) Positive and negative regulation of Easter, a member of the serine protease family that controls dorsal-ventral patterning in the *Drosophila* embryo. *Development* 125: 1261-1267.