LECTURE #3: CHAPERONE FUNCTION AND PROTEIN FOLDING *IN VIVO*

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

•General Background (in your Reader):

(1) Young JC, Agashe VR, Siegers K, Hartl FU (2004) Pathways of chaperone-mediated protein folding in the cytosol. Nature Rev. Mol. Cell Biol. 5: 781-791.

(2) Richter K, Reinstein J, Buchner J (2007) A Grp on the Hsp90 mechanism. Mol. Cell 28: 177-179.

(3) Horwich AL, Farr GW, Fenton WA (2006) GroEL-GroES-mediated protein folding. Chem. Rev. 106: 1917-1930.

•Paper for Friday Discussion Session (11/16):

(4) Vogel M, Mayer MP, Bukau B (2006) Allosteric regulation of Hsp70 chaperones involves a conserved interdomain linker. J. Biol. Chem. 281: 38705-38711.

Protein folding (general considerations):

Bukau B, Weissman J, Horwich A (2006) Molecular chaperones and protein quality control. Cell 125: 443-451.

Young JC, Agashe VR, Siegers K, Hartl FU (2004) Pathways of chaperone-mediated protein folding in the cytosol. Nature Rev. Mol. Cell. Biol. 5: 781-791.

Walter S, Buchner J (2002) Molecular chaperones--cellular machines for protein folding. Angew. Chem. Int. Ed. Engl. 41: 1098-1113.

Hartl FU, Hayer-Hartl M (2002) Molecular chaperones in the cytosol: from nascent chain to folded protein. Science 295: 1852-1858.

Zhang X, Beuron F, Freemont PS (2002) Machinery of protein folding and unfolding. Curr. Opin. Struct. Biol. 12: 231-238.

Nollen EA, Morimoto RI (2002) Chaperoning signaling pathways: molecular chaperones as stress-sensing 'heat shock' proteins. J Cell Sci. 115: 2809-2816.

Dougan DA, Mogk A, Bukau B (2002) Protein folding and degradation in bacteria: to degrade or not to degrade? That is the question. Cell Mol Life Sci. 59: 1607-1616.

Schlieker C, Bukau B, Mogk A (2002) Prevention and reversion of protein aggregation by molecular chaperones in the *E. coli* cytosol: implications for their applicability in biotechnology. J. Biotechnol. 96: 13-21.

Frydman J (2001) Folding of newly translated proteins in vivo: the role of molecular chaperones. Annu. Rev. Biochem. 70: 603-647.

Grantcharova V, Alm EJ, Baker D, Horwich AL (2001) Mechanisms of protein folding. Curr. Opin. Struct. Biol. 11: 70-82.

Ellis RJ. (2001) Macromolecular crowding: an important but neglected aspect of the intracellular environment. Curr Opin Struct Biol. 11: 114-119.

Glover JR, Tkach JM (2001) Crowbars and ratchets: hsp100 chaperones as tools in reversing protein aggregation. Biochem Cell Biol. 79: 557-568.

Ben-Zvi AP, Goloubinoff P (2001) Review: mechanisms of disaggregation and refolding of stable protein aggregates by molecular chaperones. J Struct Biol. 135: 84-93.

Hohfeld J, Cyr DM, Patterson C (2001) From the cradle to the grave: molecular chaperones that may choose between folding and degradation. EMBO Rep 2: 885-890.

Bukau B, Deuerling E, Pfund C, Craig EA. (2000) Getting newly synthesized proteins into shape. Cell 101: 119-122.

Agashe, V.R. and F.U. Hartl (2000) Roles of molecular chaperones in cytoplasmic protein folding. Semin. Cell Dev. Biol. 11: 15-25.

Dinner AR, Sali A, Smith LJ, Dobson CM, Karplus M (2000) Understanding protein folding via free-energy surfaces from theory and experiment. Trends Biochem Sci. 25: 331-339.
Jaenicke R (2000) Stability and stabilization of globular proteins in solution. J. Biotechnol. 79: 193-203.

Wickner S, Maurizi MR, Gottesman S (1999) Posttranslational quality control: folding, refolding, and degrading proteins. Science 286: 1888-1893.

Nascent chain recognition on the ribosome:

Kaiser CM, Chang HC, Agashe VR, Lakshmipathy SK, Etchells SA, Hayer-Hartl M, Hartl FU, Barral JM (2006) Real-time observation of trigger factor function on translating ribosomes. Nature [E-pub ahead of print; 15 Oct 06]

<u>Hsp70/DnaK</u>:

Hennessy F, Nicoll WS, Zimmermann R, Cheetham ME, Blatch GL (2005) Not all J domains are created equal: implications for the specificity of Hsp40-Hsp70 interactions. Protein Sci. 14: 1697-1709.

Erbse A, Mayer MP, Bukau B (2004) Mechanism of substrate recognition by Hsp70 chaperones. Biochem. Soc. Trans. 32: 617-621.

Slepenkov SV, Witt SN (2002) The unfolding story of the Escherichia coli Hsp70 DnaK: is DnaK a holdase or an unfoldase? Mol Microbiol 45: 1197-1206.

Mayer MP, Brehmer D, Gassler CS, Bukau B (2001) Hsp70 chaperone machines. Adv. Protein Chem. 59: 1-44.

Zylicz M, Wawrzynow A (2001) Insights into the function of Hsp70 chaperones. IUBMB Life. 51: 283-287.

Song J, Takeda M, Morimoto RI (2001) BAG1-Hsp70 mediates a physiological stress signalling pathway that regulates Raf-1/ERK and cell growth. Nature Cell Biol. 3: 276-282.

<u>Hsp40/DnaJ</u>:

Ohtsuka K, Hata M (2000) Molecular chaperone function of mammalian Hsp70 and Hsp40--a review. Int J Hyperthermia 16: 231-245.

Kelley WL (1999) Molecular chaperones: How J domains turn on Hsp70s. Curr Biol. 9: R305-R308.

Cheetham ME, Caplan AJ. (1998) Structure, function and evolution of DnaJ: conservation and adaptation of chaperone function. Cell Stress Chaperones. 3: 28-36. R

Nagata H, Hansen WJ, Freeman B, Welch WJ (1998) Mammalian cytosolic DnaJ homologues affect the Hsp70 chaperone-substrate reaction cycle, but do not interact directly with nascent or newly synthesized proteins. Biochemistry 37: 6924-6938.

<u>Hip and Hop and other cofactors</u>:

Kimmins S, MacRae TH (2000) Maturation of steroid receptors: an example of functional cooperation among molecular chaperones and their associated proteins. Cell Stress Chaperones 5: 76-86.

Frydman, J. and J. Hohfeld (1997) Chaperones get in touch: the Hip-Hop connection. Trends Biochem. Sci. 22: 87-92.

Harrison, C.J., M. Hayer-Hartl, M. Di Liberto, F.U. Hartl and J. Kuriyan (1997) Crystal structure of the nucleotide exchange factor GrpE bound to the ATPase domain of the molecular chaperone DnaK. Science 276: 431-435.

Hsp90:

Pearl LH (2005) Hsp90 and Cdc37 -- a chaperone cancer conspiracy. Curr. Opin. Genet. Dev. 15: 55-61.

Whitesell L, Lindquist SL (2005) Hsp90 and the chaperoning of cancer. Nature Rev. Cancer 5: 761-772.

Prodromou C, Pearl LH (2003) Structure and functional relationships of Hsp90. Curr. Cancer Drug Targets 3: 301-323.

Rosenhagen MC, Soti C, Schmidt U, Wochnik GM, Hartl FU, Holsboer F, Young JC, Rein T (2003) The heat shock protein 90-targeting drug cisplatin selectively inhibits steroid receptor activation. Mol. Endocrinol. 17: 1991-2001.

Neckers L (2002) Hsp90 inhibitors as novel cancer chemotherapeutic agents. Trends Mol Med. 8 Suppl.: S55-S61.

Pearl LH, Prodromou C (2001) Structure, function, and mechanism of the Hsp90 molecular chaperone. Adv Protein Chem. 59: 157-186.

Young JC, Moarefi I, Hartl FU (2001) Hsp90: a specialized but essential protein-folding tool. J. Cell Biol. 154: 267-273.

Piper PW (2001) The Hsp90 chaperone as a promising drug target. Curr Opin Investig Drugs 2: 1606-1610.

Mayer MP, Bukau B. (1999) Molecular chaperones: the busy life of Hsp90. Curr Biol. 9(: R322-R325.

Hsp60/GroEL and Hsp10/GroES:

Horst R, Bertelsen EB, Fiaux J, Wider G, Horwich AL, Wuthrich K (2005) Direct NMR observation of a substrate protein bound to the chaperonin GroEL. Proc. Natl. Acad. Sci. USA 102: 12748-12753.

Saibil HR, Horwich AL, Fenton WA (2001) Allostery and protein substrate conformational change during GroEL/GroES-mediated protein folding. Adv Protein Chem. 59: 45-72.

Feltham JL Gierasch LM (2000) GroEL-substrate interactions: molding the fold, or folding the mold? Cell 100: 193-196.

Horwich, A.L., E.U. Weber-Ban and D. Finley (1999) Chaperone rings in protein folding and degradation. Proc. Natl. Acad. Sci. USA 96: 11033-11040.

Martin, J. (1998) Protein folding assisted by the GroEL/GroES chaperonin system. Biochemistry 63: 374-381.

Richardson, A., S.J. Landry and C. Georgopoulos (1998) The ins and outs of a molecular chaperone machine. Trends Biochem. Sci. 23: 138-143.

TCP complexes:

Dunn AY, Melville MW, Frydman J (2001) Cellular substrates of the eukaryotic chaperonin, TRiC/CCT. J Struct Biol. 2001 Aug;135(2):176-84. Review.

Leroux MR, Hartl FU (2000) Protein folding: versatility of the cytosolic chaperonin TRiC/CCT. Curr Biol. 10: R260-R264.

Gutsche I, Essen LO, Baumeister W (1999) Group II chaperonins: new TRiC(k)s and turns of a protein folding machine. J. Mol. Biol. 293: 295-312.

Disulfide bond formation:

Sevier CS, Kaiser CA (2002) Formation and transfer of disulphide bonds in living cells.
Nat Rev Mol Cell Biol. 3: 836-847.

Collet JF, Bardwell JC (2002) Oxidative protein folding in bacteria. Mol Microbiol. 44: 1-8.

Ritz D, Beckwith J (2001) Roles of thiol-redox pathways in bacteria. Annu Rev Microbiol. 55: 21-48.

Tu BP, Ho-Schleyer SC, Travers KJ, Weissman JS (2000) Biochemical basis of oxidative protein folding in the endoplasmic reticulum. Science 290: 1571-1574.

Bader MW, Xie T, Yu CA, Bardwell JC. (2000) Disulfide bonds are generated by quinone reduction. J. Biol. Chem. 275: 26082-26088.

Debarbieux L, Beckwith J (1999) Electron avenue: pathways of disulfide bond formation and isomerization. Cell 99: 117-119.

Wang, C.C. (1998) Isomerase and chaperone activities of protein disulfide isomerase (PDI) are both required for its function as a foldase. Biochemistry 63: 407-412.

Proline isomerization:

Shaw PE (2002) Peptidyl-prolyl isomerases: a new twist to transcription. EMBO Rep. 3: 521-526.

Schmid FX (2001) Prolyl isomerases. Adv Protein Chem 59: 243-282.

Harrar Y, Bellini C, Faure JD (2001) FKBPs: at the crossroads of folding and transduction. Trends Plant Sci. 6: 426-431.

Gothel SF, Marahiel MA (1999) Peptidyl-prolyl cis-trans isomerases, a superfamily of ubiquitous folding catalysts. Cell Mol Life Sci. 55: 423-436.

Zhou XZ, Lu PJ, Wulf G, Lu KP (1999) Phosphorylation-dependent prolyl isomerization: a novel signaling regulatory mechanism. Cell Mol Life Sci. 56: 788-806.

Secretory pathway escort proteins:

Fewell SW, Travers KJ, Weissman JS, Brodsky JL (2001) The action of molecular chaperones in the early secretory pathway. Annu Rev Genet. 35: 149-191.

Sexton PM, Albiston A, Morfis M, Tilakaratne N (2001) Receptor activity modifying proteins.
Cell Signal. 13: 73-83.

Bu G (2001) The roles of receptor-associated protein (RAP) as a molecular chaperone for members of the LDL receptor family. Int Rev Cytol. 209: 79-116.

High S, Lecomte FJ, Russell SJ, Abell BM, Oliver JD. (2000) Glycoprotein folding in the endoplasmic reticulum: a tale of three chaperones? FEBS Lett. 476: 38-41.

Foord SM, Marshall FH (1999) RAMPs: accessory proteins for seven transmembrane domain receptors. Trends Pharmacol Sci. 20: 184-187.

Gething MJ (1999) Role and regulation of the ER chaperone BiP. Semin. Cell Dev. Biol. 10: 465-472.

Zimmermann, R. (1998) The role of molecular chaperones in protein transport into the mammalian endoplasmic reticulum. Biolog. Chem. 379: 275-282.

Hsp100/Clp's:

Hinnerwisch J, Fenton WA, Furtak KJ, Farr GW, Horwich AL (2005) Loops in the central channel of ClpA chaperone mediate protein binding, unfolding, and translocation. Cell 121: 1029-1041.

Hattendorf DA, Lindquist SL (2002) Cooperative kinetics of both Hsp104 ATPase domains and interdomain communication revealed by AAA sensor-1 mutants. EMBO J. 21: 12-21.

Wu WF, Zhou Y, Gottesman S (1999) Redundant in vivo proteolytic activities of Escherichia coli Lon and the ClpYQ (HslUV) protease. J Bacteriol 18: 3681-3687.

Porankiewicz J, Wang J, Clarke AK (1999) New insights into the ATP-dependent Clp protease: Escherichia coli and beyond. Mol Microbiol. 32: 449-458.

Small Hsp's:

Kato K, Ito H, Inaguma Y (2002) Expression and phosphorylation of mammalian small heat shock proteins. Prog Mol Subcell Biol 28: 129-150.

Michaud S, Morrow G, Marchand J, Tanguay RM (2002) Drosophila small heat shock proteins: cell and organelle-specific chaperones? Prog Mol Subcell Biol. 28: 79-101.

Candido EP (2002) The small heat shock proteins of the nematode *Caenorhabditis elegans*: structure, regulation and biology. Prog Mol Subcell Biol 28: 61-78.

Sun W, Van Montagu M, Verbruggen N (2002) mall heat shock proteins and stress tolerance in plants. Biochim Biophys Acta 1577: 1-9.

van Montfort RL, Basha E, Friedrich KL, Slingsby C, Vierling E (2001) Crystal structure and assembly of a eukaryotic small heat shock protein. Nat Struct Biol. 8: 1025-1030.

Cold shock response:

Phadtare S (2004) Recent developments in bacterial cold-shock response. Curr. Issues Mol. Biol. 6: 125-136.

Phadtare S, Alsina J, Inouye M (1999) Cold-shock response and cold-shock proteins. Curr. Opin. Microbiol. 2: 175-180.

Practical matters:

de Marco A, Deuerling E, Mogk A, Tomoyasu T, Bukau B (2007) Chaperone-based procedure to increase yields of soluble recombinant proteins produced in *E. coli*. BMC Biotechnol. 7: 32.1-32.9.

The prion problem:

Jones GW, Tuite MF (2005) Chaperoning prions: the cellular machinery for propagating an infectious protein? Bioessays 27: 823-832.

Wickner RB, Edskes HK, Roberts BT, Baxa U, Pierce MM, Ross ED, Brachmann A (2004) Prions: proteins as genes and infectious entities. Genes Dev. 18: 470-485.

Sakahira H, Breuer P, Hayer-Hartl MK, Hartl FU (2002) Molecular chaperones as modulators of polyglutamine protein aggregation and toxicity. Proc. Natl. Acad. Sci. USA 99 (Suppl 4): 16412-16418.

Horwich A (2002) Protein aggregation in disease: a role for folding intermediates forming specific multimeric interactions. J. Clin. Invest. 110: 1221-1232.

Kim S, Nollen EA, Kitagawa K, Bindokas VP, Morimoto RI (2002) Polyglutamine protein aggregates are dynamic. Nature Cell Biol 4: 826-831.

Uptain SM, Lindquist SL (2002) Prions as protein-based genetic elements. Annu. Rev. Microbiol. 56: 703-742.

Wickner RB, Edskes HK, Roberts BT, Pierce M, Baxa U (2002) Prions of yeast as epigenetic phenomena: high protein "copy number" inducing protein "silencing". Adv Genet. 46: 485-525.

Osherovich LZ, Weissman JS (2002) The utility of prions. Dev Cell. 2: 143-151.

Chernoff YO, Uptain SM, Lindquist SL (2002) Analysis of prion factors in yeast. Methods Enzymol. 351: 499-538.

Dobson CM (2001) The structural basis of protein folding and its links with human disease. Philos Trans R Soc Lond B Biol Sci. 356: 133-145.

Jackson GS, Clarke AR. (2000) Mammalian prion proteins. Curr. Opin. Struct. Biol. 10: 69-74.