

LECTURE #2: REGULATION OF PROTEIN SYNTHESIS

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

•General Background (in your Reader):

(1) Richter JD, Sonenberg N (2005) Regulation of cap-dependent translation by eIF4E inhibitory proteins. Nature 433: 477-480.

(2) Proud CG (2007) Signalling to translation: how signal transduction pathways control the protein synthetic machinery. Biochem J. 403: 217-234.

(3) Fraser CS, Doudna JA (2007) Structural and mechanistic insights into hepatitis C viral translation initiation. Nature Rev. Microbiol. 5: 29-38.

•Paper for Friday Discussion Session (Nov. 16th) (handed out in class):

(4) LaRonde-LeBlanc N, Santhanam AN, Baker AR, Wlodawer A, Colburn NH (2007) Structural basis for inhibition of translation by the tumor suppressor PDCD4. Mol. Cell. Biol. 27: 147-156.

Regulation of Translation in Eukaryotes - General References:

Gebauer F, Hentze MW (2004) Molecular mechanisms of translational control. Nature Rev. Mol. Cell Biol. 5: 827-835.

Abbott CM, Proud CG (2004) Translation factors: in sickness and in health. Trends Biochem. Sci. 29: 25-31.

Ramakrishnan V (2002) Ribosome structure and the mechanism of translation. Cell 108: 557-572.

Macdonald P (2001) Diversity in translational regulation. Curr. Opin. Cell Biol. 13: 326-331.

Proud CG (2001) Regulation of mRNA translation. Essays Biochem. 37: 97-108.

Sonenberg N, Hershey JWB, Matthews MB (eds.) (2000) Translational Control of Gene Expression, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.

Preiss T, Hentze MW (1999) From factors to mechanisms: translation and translational control in eukaryotes. Curr Opin Genet Dev 9: 515-521.

Ribosome biogenesis, ribosomal RNA maturation and modification:

Lafontaine DL, Tollervey D (2001) The function and synthesis of ribosomes. Nature Rev Mol Cell Biol. 2: 514-520.

Lewis JD, Tollervey D (2000) Like attracts like: getting RNA processing together in the nucleus. Science 288: 1385-1389.

Eliceiri GL (1999) Small nucleolar RNAs. Cell Mol Life Sci. 56: 22-31.

Scheer U, Hock R (1999) Structure and function of the nucleolus. Curr Opin Cell Biol. 11: 385-390.

Nomura M (1999) Regulation of ribosome biosynthesis in *Escherichia coli* and *Saccharomyces cerevisiae*: diversity and common principles. J. Bacteriol. 181: 6857-6864.

Ribosome structure:

Berk V, Cate JH (2007) Insights into protein biosynthesis from structures of bacterial ribosomes. Curr Opin Struct Biol. 17: 302-309.

- Korostelev A, Trakhanov S, Laurberg M, Noller HF. (2006) Crystal structure of a 70S ribosome-tRNA complex reveals functional interactions and rearrangements. *Cell* 126: 1065-1077.
- Schuwirth BS, Borovinskaya MA, Hau CW, Zhang W, Vila-Sanjurjo A, Holton JM, Cate JH. (2005) Structures of the bacterial ribosome at 3.5 Å resolution. *Science* 310: 827-834.
- Moore PB, Steitz TA (2005) The ribosome revealed. *Trends Biochem. Sci.* 30: 281-283.
- Moore PB, Steitz TA (2003) The structural basis of large ribosomal subunit function. *Annu. Rev. Biochem.* 72: 813-850.
- Moore PB, Steitz TA (2002) The involvement of RNA in ribosome function. *Nature* 418: 229-235.
- Frank J (2001) Cryo-electron microscopy as an investigative tool: the ribosome as an example. *Bioessays* 23: 725-732.
- Maguire BA, Zimmermann RA (2001) The ribosome in focus. *Cell* 104: 813-816.
- Nissen P, Ippolito JA, Ban N, Moore PB, Steitz TA (2001) RNA tertiary interactions in the large ribosomal subunit: the A-minor motif. *Proc Natl Acad Sci USA* 98: 4899-4903.
- Yusupova GZ, Yusupov MM, Cate JH, Noller HF (2001) The path of messenger RNA through the ribosome. *Cell* 106: 233-241.

tRNA maturation, aminoacylation, and function:

- Frank J, Sengupta J, Gao H, Li W, Valle M, Zavialov A, Ehrenberg M (2005) The role of tRNA as a molecular spring in decoding, accommodation, and peptidyl transfer. *FEBS Lett.* 579: 959-962.
- Noller HF, Yusupov MM, Yusupova GZ, Baucom A, Cate JH (2002) Translocation of tRNA during protein synthesis. *FEBS Lett.* 514: 11-16.
- Schurer H, Schiffer S, Marchfelder A, Morl M (2001) This is the end: processing, editing and repair at the tRNA 3'-terminus. *Biol Chem* 382: 1147-1156.
- Rodnina MV, Wintermeyer W (2001) Ribosome fidelity: tRNA discrimination, proofreading and induced fit. *Trends Biochem Sci.* 26: 124-130.
- Ibba M, Soll D (2000) Aminoacyl-tRNA synthesis. *Annu Rev Biochem.* 69: 617-650.
- Woese CR, Olsen GJ, Ibba M, Soll D. (2000) Aminoacyl-tRNA synthetases, the genetic code, and the evolutionary process. *Microbiol. Mol. Biol. Rev.* 64: 202-236.
- Simos G, Hurt E (1999) Transfer RNA biogenesis: A visa to leave the nucleus. *Curr Biol.* 9: R238-R241.

Regulation of mRNA export by RNA-binding proteins:

- Huang Y, Steitz JA (2005) SRprises along a messenger's journey. *Mol. Cell* 17: 613-615.
- Dreyfuss G, Kim VN, Kataoka N (2002) Messenger-RNA-binding proteins and the messages they carry. *Nature Rev Mol Cell Biol.* 3: 195-205.
- Lei EP, Silver PA (2002) Intron status and 3'-end formation control cotranscriptional export of mRNA. *Genes Dev.* 16: 2761-2766.
- Keene JD, Tenenbaum SA (2002) Eukaryotic mRNPs may represent posttranscriptional operons. *Mol Cell.* 9: 1161-1167.

Protein synthesis— initiation:

Oberer M, Marintchev A, Wagner G (2005) Structural basis for the enhancement of eIF4A helicase activity by eIF4G. *Genes Dev.* 19: 2212-2223.

Sonenberg N, Dever TE (2003) Eukaryotic translation initiation factors and regulators. *Curr. Opin. Struct. Biol.* 13: 56-63.

Pestova TV, Kolupaeva VG, Lomakin IB, Pilipenko EV, Shatsky IN, Agol VI, Hellen CU (2001) Molecular mechanisms of translation initiation in eukaryotes *Proc Natl Acad Sci USA* 98: 7029-7036.

Schneider R, Agol VI, Andino R, Bayard F, Cavener DR, Chappell SA, Chen JJ, Darlix JL, Dasgupta A, Donze O, et. al. (2001) New ways of initiating translation in eukaryotes? *Mol. Cell. Biol.* 21: 8238-8246.

Sachs AB, Varani G (2000) Eukaryotic translation initiation: there are (at least) two sides to every story. *Nature Struct. Biol.* 7: 356-361.

Shatkin AJ, Manley JL (2000) The ends of the affair: capping and polyadenylation. *Nature Struct Biol.* 7: 838-842.

Kozak M (2000) Do the 5'-untranslated domains of human cDNAs challenge the rules for initiation of translation (or is it vice versa)? *Genomics* 70: 396-406.

Gallie DR. (1998) A tale of two termini: a functional interaction between the termini of an mRNA is a prerequisite for efficient translation initiation. *Gene* 216: 1-11.

Sachs, A.B., P. Sarnow and M.W. Hentze (1997) Starting at the beginning, middle, and end: translation initiation in eukaryotes. *Cell* 89: 831-838.

Gallie DR. (1991) The cap and poly(A) tail function synergistically to regulate mRNA translational efficiency. *Genes Dev.* 5: 2108-2116.

Protein synthesis— internal ribosome entry sites:

Sarnow P, Cevallos RC, Jan E (2005) Takeover of host ribosomes by divergent IRES elements. *Biochem. Soc. Trans.* 33: 1479-1482.

Hundsdoerfer P, Thoma C, Hentze MW (2005) Eukaryotic translation initiation factor 4GI and p97 promote cellular internal ribosome entry sequence-driven translation. *Proc. Natl. Acad. Sci. USA* 102: 13421-13426.

Pisarev AV, Shriokikh NE, Hekken CU (2005) Translation initiation by factor-independent binding of eukaryotic ribosomes to internal ribosomal entry sites. *C.R. Biol.* 328: 589-605.

Stoneley M, Willis AE (2004) Cellular internal ribosome entry segments: structures, trans-acting factors and regulation of gene expression. *Oncogene* 23: 3200-3207.

Sarnow P (2003) Viral internal ribosome entry site elements: novel ribosome-RNA complexes and roles in viral pathogenesis. *J. Virol.* 77: 2801-2806.

Prats AC, Prats H (2002) Translational control of gene expression: role of IRESs and consequences for cell transformation and angiogenesis. *Prog. Nucleic Acid Res. Mol. Biol.* 72: 367-413.

Hellen CU, Sarnow P (2001) Internal ribosome entry sites in eukaryotic mRNA molecules. *Genes Dev.* 15: 1593-1612.

Martinez-Salas E, Ramos R, Lafuente E, Lopez de Quinto S (2001) Functional interactions in internal translation initiation directed by viral and cellular IRES elements. *J. Gen. Virol.* 82:

973-984.

Vagner S, Galy B, Pyronnet S (2001) Irresistible IRES. Attracting the translation machinery to internal ribosome entry sites. *EMBO Rep.* 2: 893-898.

Sachs AB (2000) Cell cycle-dependent translation initiation: IRES elements prevail. *101*: 243-245.

Protein synthesis— elongation:

Green R (2000) Ribosomal translocation: EF-G turns the crank. *Curr Biol* 10: R369-R373.

Farabaugh PJ (2000) Translational frameshifting: implications for the mechanism of translational frame maintenance. *Prog Nucleic Acid Res Mol Biol.* 64: 131-170.

Rodnina MV, Savelsbergh A, Wintermeyer W (1999) Dynamics of translation on the ribosome: molecular mechanics of translocation. *FEMS Microbiol Rev.* 23: 317-333. Review.

Wilson KS, Noller HF (1998) Molecular movement inside the translational engine. *Cell* 92: 337-349.

Protein synthesis— termination:

Uchida N, Hoshino S, Imataka H, Sonenberg N, Katada T (2002) A novel role of the mammalian GSPT/eRF3 associating with poly(A)-binding protein in Cap/Poly(A)-dependent translation. *J Biol Chem.* 277: 50286-50292.

Cosson B, Berkova N, Couturier A, Chabelskaya S, Philippe M, Zhouravleva G (2002) Poly(A)-binding protein and eRF3 are associated in vivo in human and *Xenopus* cells. *Biol Cell.* 94: 205-216.

Kisselev LL, Buckingham RH (2000) Translational termination comes of age. *Trends Biochem Sci.* 25: 561-566.

Karzai AW, Roche ED, Sauer RT (2000) The SsrA-SmpB system for protein tagging, directed degradation and ribosome rescue. *Nature Struct Biol.* 7: 449-455.

Antibiotic action and other aspects of translation regulation in bacteria:

Brodersen DE, Carter AP, Clemons WM Jr, Morgan-Warren RJ, Murphy FV 4th, Ogle JM, Tarry MJ, Wimberly BT, Ramakrishnan V (2001) Atomic structures of the 30S subunit and its complexes with ligands and antibiotics. *Cold Spring Harb Symp Quant Biol.* 66: 17-32.

Leviton I (1999) Inhibitors of protein synthesis. *Cancer Invest.* 17: 87-92.

Spahn, C.M. and C.D. Prescott (1996) Throwing a spanner in the works: antibiotics and the translation apparatus. *J. Mol. Med.* 74: 423-439.

Nutrient sensing and control of protein synthesis (TOR):

Mamane Y, Petroulakis E, LeBacquer O, Sonenberg N (2006) mTOR, translation initiation and cancer. *Oncogene* 25: 6416-6422.

Hay N, Sonenberg N (2004) Upstream and downstream of mTOR. *Genes Dev.* 18: 1926-1945.

Fingar DC, Blenis J (2004) Target of rapamycin (TOR): an integrator of nutrient and growth factor signals and coordinator of cell growth and cell cycle progression. *Oncogene* 23: 3151-3171.

Beugnet A, Wang X, Proud CG (2003) Target of rapamycin (TOR)-signaling and RAIP motifs play distinct roles in the mammalian TOR-dependent phosphorylation of initiation factor 4E-

binding protein 1. *J. Biol. Chem.* 278: 40717-40722.

Jacinto E, Hall MN (2003) Tor signalling in bugs, brain and brawn. *Nature Rev. Mol. Cell Biol.* 4: 117-126.

Regulation of translation in eukaryotes (at the level of eIF-2alpha):

Proud CG (2005) eIF2 and the control of cell physiology. *Semin. Cell Dev. Biol.* 16: 3-12.

Deng J, Harding H, Raught B, Gingras A, Berlanga J, Scheuner D, Kaufman R, Ron D, Sonenberg N (2002) Activation of GCN2 in UV-irradiated cells inhibits translation. *Curr. Biol* 12: 1279-1286.

Dever TE (1998) Analysis of eIF-2 alpha kinases in yeast. *Methods Mol Biol.* 77: 167-178.

Hinnebusch, A.G. (1997) Translational regulation of yeast GCN4. A window on factors that control initiator-tRNA binding to the ribosome. *J. Biol. Chem.* 272: 21661-21664.

Regulation of translation in eukaryotes (at the level of eIF-4E):

Gingras AC, Raught B, Gygi SP, Niedzwiecka A, Miron M, Burley SK, Polakiewicz RD, Wyslouch-Cieszyńska A, Aebersold R, Sonenberg N (2001) Hierarchical phosphorylation of the translation inhibitor 4E-BP1. *Genes Dev.* 15: 2852-2864.

Raught B, Gingras AC, Sonenberg N (2001) Control of translation by the target of rapamycin (TOR) proteins. *Proc. Natl. Acad. Sci. USA* 98: 7037-7044.

Wakiyama, M., H. Imataka N. Sonenberg (2000) Interaction of eIF4G with poly(A)-binding protein stimulates translation and is critical for *Xenopus* oocyte maturation. *Curr. Biol.* 10: 1147-1150.

Zimmer SG, DeBenedetti A, Graff JR (2000) Translational control of malignancy: the mRNA cap-binding protein, eIF-4E, as a central regulator of tumor formation, growth, invasion and metastasis. *Anticancer Res.* 20: 1343-1351.

Rhoads, R.E. (1999) Signal transduction pathways that regulate eukaryotic protein synthesis. *J. Biol. Chem.* 274: 30337-30340.

Gingras, A.C., B. Raught and N. Sonenberg (1999) eIF4 initiation factors: effectors of mRNA recruitment to ribosomes and regulators of translation. *Annu. Rev. Biochem.* 68: 913-963.

Regulation of translation in eukaryotes (at the level of ribosomal protein S6):

Dorrello NV, Peschiaroli A, Guardavaccaro D, Colburn NH, Sherman NE, Pagano M (2006) S6K1- and betaTRCP-mediated degradation of PDCD4 promotes protein translation and cell growth. *Science* 314: 467-471.

Martin KA, Blenis J (2002) Coordinate regulation of translation by the PI 3-kinase and mTOR pathways. *Adv. Cancer Res.* 86: 1-39.

Volarevic S, Thomas G (2001) Role of S6 phosphorylation and S6 kinase in cell growth. *Prog Nucleic Acid Res Mol Biol.* 65: 101-127.

Gingras AC, Raught B, Sonenberg N (2001) Regulation of translation initiation by FRAP / mTOR. *Genes Dev.* 15: 807-826.

Meyuhas O (2000) Synthesis of the translational apparatus is regulated at the translational level. *Eur J Biochem.* 267: 6321-6330.

General Background (translational repressor proteins and mRNA localization in eukaryotes):

Cho PF, Gamberi C, Cho-Park YA, Cho-Park IB, Lasko P, Sonenberg N. (2006) Cap-dependent translational inhibition establishes two opposing morphogen gradients in *Drosophila* embryos. *Curr. Biol.* 16: 2035-2041.

Wilhelm JE, Smibert CA (2005) Mechanisms of translational regulation in *Drosophila*. *Biol. Cell* 97: 235-252.

Juschke C, Ferring D, Jansen RP, Seedorf M. (2004) A novel transport pathway for a yeast plasma membrane protein encoded by a localized mRNA. *Curr. Biol.* 14: 406-411.

Dean KA, Aggarwal AK, Wharton RP (2002) Translational repressors in *Drosophila*. *Trends Genet.* 18: 572-577.

Kloc M, Zearfoss NR, Etkin LD (2002) Mechanisms of subcellular mRNA localization. *Cell* 108: 533-544.

Irie K, Tadauchi T, Takizawa PA, Vale RD, Matsumoto K, Herskowitz I (2002) The Khd1 protein, which has three KH RNA-binding motifs, is required for proper localization of ASH1 mRNA in yeast. *EMBO J.* 21: 1158-1167.

Stebbing H (2001) Cytoskeleton-dependent transport and localization of mRNA. *Int Rev Cytol.* ;211: 1-31.

Kwon S, Schnapp BJ (2001) RNA localization: SHEDding light on the RNA-motor linkage. *Curr Biol.* 11: R166-R168.

Lipshitz HD, Smibert CA (2000) Mechanisms of RNA localization and translational regulation. *Curr. Opin. Genet. Dev.* 10: 476-488.

Bloom K, Beach DL. (1999) mRNA localization: motile RNA, asymmetric anchors. *Curr Opin Microbiol.* 2: 604-609.

Thomson AM, Rogers JT, Leedman PJ (1999) Iron-regulatory proteins, iron-responsive elements and ferritin mRNA translation. *Int J Biochem Cell Biol.* 31: 1139-1152.

Gavis, E.R. (1997) Expeditions to the pole: RNA localization in *Xenopus* and *Drosophila*. *Trends Cell Biol.* 7: 485-492.

Regulated polyadenylation in the cytosol:

Hall TM (2002) Poly(A) tail synthesis and regulation: recent structural insights. *Curr Opin Struct Biol.* 12: 82-88.

Eichenlaub-Ritter U, Peschke M (2002) Expression in in-vivo and in-vitro growing and maturing oocytes: focus on regulation of expression at the translational level. *Hum Reprod Update* 8: 21-41.

Mendez R, Richter JD (2001) Translational control by CPEB: a means to the end. *Nature Rev Mol Cell* 2: 521-529.

Control of mRNA stability by AU-rich elements (AREs) in the 3'-UTR:

Dean JL, Sully G, Clark AR, Saklatvala J (2004) The involvement of AU-rich element-binding proteins in p38 mitogen-activated protein kinase pathway-mediated mRNA stabilisation. *Cell Signal* 16: 1113-1121.

Gingerich TJ, Feige JJ, LaMarre J (2004) AU-rich elements and the control of gene expression through regulated mRNA stability. *Anim Health Res Rev.* 5: 49-63.

Bevilacqua A, Ceriani MC, Capaccioli S, Nicolin A (2003) Post-transcriptional regulation of

gene expression by degradation of messenger RNAs. *J. Cell Physiol.* 195: 356-372.

Rousseau S, Morrice N, Peggie M, Campbell DG, Gaestel M, Cohen P (2002) Inhibition of SAPK2 α /p38 prevents hnRNP A0 phosphorylation by MAPKAP-K2 and its interaction with cytokine mRNAs. *EMBO J.* 21: 6505-6514.

General Background (translational silencing by siRNAs, translational repression by microRNAs, and riboswitches):

Wang B, Love TM, Call ME, Doench JG, Novina CD. (2006) Recapitulation of short RNA-directed translational gene silencing in vitro. *Mol. Cell* 22: 553-560.

Nelson P, Kiriakidou M, Sharma A, Maniatakis E, Mourelatos Z (2003) The microRNA world: small is mighty. *Trends Biochem Sci.* 28: 534-540.

Denli AM, Hannon GJ (2003) RNAi: an ever-growing puzzle. *Trends Biochem Sci.* 28: 196-201.

Winkler WC, Breaker RR (2003) Genetic control by metabolite-binding riboswitches. *ChemBiochem.* 4: 1024-1032.

Lai EC (2003) RNA sensors and riboswitches: self-regulating messages. *Curr Biol.* 13: R285-R291.

Masse E, Majdalani N, Gottesman S (2003) Regulatory roles for small RNAs in bacteria. *Curr Opin Microbiol.* 6: 120-124.

Sudarsan N, Wickiser JK, Nakamura S, Ebert MS, Breaker RR (2003) An mRNA structure in bacteria that controls gene expression by binding lysine. *Genes Dev.* 17: 2688-2697.

Winkler WC, Nahvi A, Sudarsan N, Barrick JE, Breaker RR (2003) An mRNA structure that controls gene expression by binding S-adenosylmethionine. *Nature Struct Biol.* 10: 701-707.

Carrington JC, Ambros V (2003) Role of microRNAs in plant and animal development. *Science* 301: 336-338.

Zeng Y, Wagner EJ, Cullen BR (2002) Both natural and designed micro RNAs can inhibit the expression of cognate mRNAs when expressed in human cells. *Mol Cell.* 9: 1327-1333.

Lai EC (2002) Micro RNAs are complementary to 3' UTR sequence motifs that mediate negative post-transcriptional regulation. *Nature Genet.* 30: 363-364.

Dennis C (2002) The brave new world of RNA. *Nature* 418: 122-124.

Baulcombe D (2002) DNA events. An RNA microcosm. *Science* 297: 2002-2003.

Moss EG (2002) MicroRNAs: hidden in the genome. *Curr. Biol* 12: R138-R140.

Gottesman S, Storz G, Rosenow C, Majdalani N, Repoila F, Wassarman KM (2001) Small RNA regulators of translation: mechanisms of action and approaches for identifying new small RNAs. *Cold Spring Harb Symp Quant Biol.* 66: 353-362.

In vitro translation (practical aspects):

Asano K, Phan L, Krishnamoorthy T, Pavitt GD, Gomez E, Hannig EM, Nika J, Donahue TF, Huang HK, Hinnebusch AG. (2002) Analysis and reconstitution of translation initiation in vitro. *Methods Enzymol.* 351: 221-247.

Iizuka, N. and P. Sarnow (1997) Translation-competent extracts from *Saccharomyces cerevisiae*: effects of L-A RNA, 5' cap, and 3' poly(A) tail on translational efficiency of mRNAs. *Methods* 11: 353-360.

Hartley, A.D., M.A. Santos, D.R. Colthurst and M.F. Tuite (1996) Preparation and use of yeast cell-free translation lysate. *Methods Molec. Biol.* 53: 249-257.

Kim DM, Kigawa T, Choi CY, Yokoyama S (1996) A highly efficient cell-free protein synthesis system from *Escherichia coli*. *Eur J Biochem.* 239: 881-886.

In vitro translation (biotechnology / protein engineering applications):

Wang L, Schultz PG (2002) Expanding the genetic code. *Chem. Commun (Camb)* 7: 1-11.

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

Kigawa T, Yabuki T, Yoshida Y, Tsutsui M, Ito Y, Shibata T, Yokoyama S (1999) Cell-free production and stable-isotope labeling of milligram quantities of proteins. *FEBS Lett.* 442: 15-19.

Liu DR, Magliery TJ, Pastrnak M, Schultz PG (1997) Engineering a tRNA and aminoacyl-tRNA synthetase for the site-specific incorporation of unnatural amino acids into proteins in vivo. *Proc Natl Acad Sci USA* 94: 10092-10097.

Ibba, M. (1996) Strategies for in vitro and in vivo translation with non-natural amino acids. *Biotechnology and Genetic Engineering Reviews* 13: 197-216.

Benner, S.A. (1994) Expanding the genetic lexicon: incorporating non-standard amino acids into proteins by ribosome-based synthesis. *Trends Biotechnol.* 12: 158-163.

Translation in the nucleus?

Dahlberg JE, Lund E, Goodwin EB (2003) Nuclear translation: what is the evidence? *RNA* 9: 1-8.

Iborra FJ, Jackson DA, Cook PR (2001) Coupled transcription and translation within nuclei of mammalian cells. *Science* 293: 1139-1142.