Katedry biochémie a genetiky

Prírodovedeckej fakulty Univerzity Komenského

Vás pozývajú na **39**. prednášku v rámci Kuželových seminárov:

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New Insights into the Lon Protease and DnaJ-like Chaperone of Human Mitochondria: Roles in mtDNA metabolism and cell signaling

ktorá sa uskutoční

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http://www.fns.uniba.sk/~kbi/kuzela/

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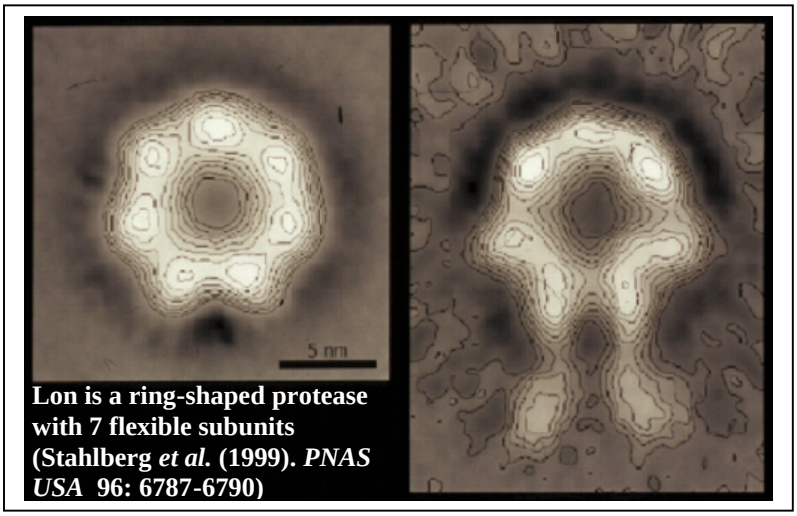
http://njms.umdnj.edu/biochemistry/fb_Suzuki_Carolyn_2002.htm

ATP-dependent proteases are highly conserved enzymes present in humans as well as in *Archaea* and *Eubacteria*. In eukaryotes, regulated degradation by the ubiquitin-proteasome system is understood in great detail. Far less is known however, about the regulatory function of ATP-dependent proteases localized to mitochondria. Recent work has shown that the human disease Hereditary Spastic Paraplegia is caused by mutations in a gene that has high sequence similarity to ATP-dependent proteases localized to the mitochondrial inner membrane of yeast. Studies performed in the budding yeast *Saccharomyces cerevisiae* have demonstrated the crucial role of mitochondrial proteases and chaperones in organelle biogenesis, respiration and mitochondrial DNA stability and gene expression.



Lon is a ring-shaped protease with 7 flexible subunits (Stahlberg *et al.* (1999). *PNAS USA* 96: 6787-6790)

Human Tid1-Long and -Short (hTid1-L and hTid1-S respectively), are mitochondrial matrix proteins that show a high degree of sequence similarity to the tumor suppressor Tid56 of *Drosophila melanogaster* and belong to the DnaJ family of molecular chaperones. The absence of Tid56 expression in *Drosophila* results in defective differentiation and morphogenesis giving rise to tumorous imaginal discs that proliferate to form lethal tumors, which maintain their neoplastic characteristics when transplanted into wild-type flies. hTid1-L and -S are produced by alternative splicing and are 98% identical, differing only at their carboxyl-terminal tails. Work by Karl Münger's lab strikingly showed that hTid1-L and a dominant negative mutant of the Short isoform augment cell death induced by an apoptotic signal, whereas hTid1-S and a dominant negative mutant of the Long isoform inhibit cell death. Although these proteins are principally localized to the mitochondrial matrix, recent data suggest that hTid1-L and -S also function within the cytosol or nucleus by interacting with the human papillomavirus oncoprotein- E7, the Ras GTPase activating protein- Ras-GAP and the Janus kinase- Jak2.

Recent publications:

Suzuki, C.K., K. Suda, N. Wang and G. Schatz (1994). Requirement of the yeast gene LON in intramitochondrial proteolysis and maintenance of respiration. *Science* **264**: 273-276 (1994).

Rep, M., J.M. van Dijl, K. Suda, G. Schatz, L.A. Grivell and C.K. Suzuki (1996). Promotion of mitochondrial membrane complex assembly by a proteolytically inactive yeast Lon. *Science* **274**: 103-106

Suzuki, C.K., M. Rep, J. M. van Dijl, K. Suda, L.A. Grivell and G. Schatz (1997). ATP-dependent proteases that also chaperone protein biogenesis. *Trends Biochem. Sci*. **22**: 118-123.

van Dijl, J.M., E. Kutejova, K. Suda, D. Perecko, G. Schatz and C.K. Suzuki (1998). The ATPase and protease domains of yeast mitochondrial Lon: Roles in proteolysis and respiration-dependent growth. *Proc. Natl. Acad. Sci. USA* **18**: 10584 – 10589.

Beilharz, T., C. K. Suzuki and T. Lithgow (1998). A toxic fusion protein accumulating between the mitochondrial membranes inhibits protein assembly *in vivo*. *J. Biol. Chem*. **273**: 35268-35272.

Stahlberg, H., E. Kutejova, K. Suda, B. Wolpensinger, A. Lustig, G. Schatz, A. Engel, and C.K. Suzuki (1999). Mitochondrial Lon of *Saccharomyces cerevisiae* is a ring-shaped protease with seven flexible subunits. *Proc. Natl. Acad. Sci. USA* **96**: 6787-6790.

Lu, B., T. Liu, J.A. Crosby, J. Thomas-Wohlever, J., I. Lee and C.K. Suzuki (2003). The ATP-dependent Lon Protease of *Mus musculus* is a DNA-binding Protein that is Functionally Conserved between Yeast and Mammals. *Gene* **306**: 45-55.