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Abstracts

S13 Biogenesis

Lectures

13L.1 Role of hnRNPA2 and Akt1 in mitochondrial respiratory stress mediated transcription activation of nuclear genes

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Mitochondrial respiratory stress (also called mitochondrial retrograde signaling) activates a Ca^{2+}/calcineurin-mediated signal that culminates in transcription activation/repression for a large number of nuclear genes. This signal is propagated through activation of the regulatory proteins NFκB cRel/p50, C/EBPδ, CREB, and NFAT. Additionally, hnRNPA2 functions as a coactivator in upregulating the transcription of *Cathepsin L*, *RyR1*, and *Glut-4*, the target genes of stress signaling. Activation of IGF1R, which causes a metabolic switch to glycolysis, invasiveness, and resistance to apoptosis, is a phenotypic hallmark of C2C12 myoblasts subjected to mitochondrial stress. Here we report that mitochondrial stress leads to increased expression, activation, and nuclear localization of Akt1. Mitochondrial respiratory stress also activates Akt1-gene expression, which involves hnRNPA2 as a coactivator, indicating a complex interdependency of these two factors. Using $Akt1^{-/-}$ mouse embryonic fibroblasts and Akt1 mRNA-silenced C2C12 cells, we show that Akt1-mediated phosphorylation is crucial for the activation and recruitment of hnRNPA2 to the enhanceosome complex. Akt1 mRNA silencing in mtDNA-depleted cells resulted in reversal of the invasive phenotype, accompanied by sensitivity to apoptotic stimuli. Results will be presented to show how Akt1 mediated phosphorylation results in the activation and recruitment of hnRNPA2 to the enhanceosome and hnRNPA2 induces chromatin remodeling through recruitment of proteins with histone acetyl transferase activity. These results together show that Akt1 is an important regulator of the mitochondrial stress mediated change in the nuclear transcriptional program.

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13L.2 The organellar peptidasome, PreP: A journey from *Arabidopsis* to Alzheimer's disease

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The novel peptidasome, called Presequence Protease, PreP, was originally identified and characterized in *Arabidopsis thaliana* as a mitochondrial matrix and chloroplast stroma localized metalloprotease. PreP has a function as the organellar peptide clearing protease and is responsible for degrading free targeting peptides and also other unstructured peptides up to 65 amino acid residues that might be toxic to organellar functions. PreP contains an inverted Zn-binding motif and belongs to the pitrilysin protease family. The crystal structure of *At*PreP refined at 2.1 Å demonstrated a unique totally enclosed large cavity of 10,000 $Å^3$ that opens and closes in response to peptide binding, revealing a novel catalytic mechanism for proteolysis. Homologues of PreP have been found in yeast and human mitochondria. Interestingly, the human PreP, hPreP, is the protease that is responsible for clearing the human brain mitochondria from the toxic amyloid-β peptide (Aβ) associated with Alzheimer's disease (AD). Accumulation of Aβ has been shown in brain mitochondria from AD patients and mutant transgenic mice overexpressing Aβ. We were able to show that Aβ is transported into mitochondria via the Translocase of the Outer Membrane (TOM) machinery. Biochemical analysis of genetic variation in the gene encoding hPreP, *PITRM1*, single nucleotide polymorphisms (SNPs), revealed a decreased proteolytic activity of several hPreP-SNPs compared to wild type hPreP. Structural and functional characteristics of PreP and its Aβ-degrading activity in human brain mitochondria in relation to AD will be discussed.

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13L.3 Mitochondrial biogenesis in skeletal muscle: Effect of exercise and age

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Mitochondrial biogenesis in muscle can occur as a consequence of regularly performed exercise. The mechanisms underlying organelle biogenesis are now intensively studied because of the increasing recognition of the role of mitochondria in disease pathophysiology, apoptosis and cellular adaptation. Evidence suggests that the initial signals generated by exercising muscle which provoke the onset of gene expression leading to mitochondrial biogenesis are related to changes in intracellular calcium, reactive oxygen species, and AMP kinase activity. Activation of AMP kinase leads to the transcription of the gene encoding PGC-1α, an important regulator of the expression of multiple nuclear genes encoding mitochondrial proteins. Following transcription, mRNA stabilization as a result of exercise can enhance the level of cytosolic protein available for import into mitochondria. In addition, the import of newly synthesized proteins into the organelle is increased following a

period of regular exercise. This is a result of an exercise-induced augmentation in the expression of protein import machinery components. During the aging process, mitochondrial content in muscle declines, and this is reflected in a reduced endurance performance. The decrease in mitochondrial content does not appear to be due to altered post-translational import mechanisms, but may be transcriptionally-related, since PGC-1α levels are markedly reduced, particularly in slow-twitch muscle fibers. In addition, in response to a standardized acute contractile activity paradigm, signaling kinase activation is increased to a lesser degree than in muscle from young animals, which could lead to a reduced transcriptional activation with age. This likely contributes to the reduced adaptation of aged muscle to regular exercise, consisting of attenuated increases in the expression of biogenesis regulatory proteins of transcription and protein import, reduced increases in mitochondrial enzymes, and lesser improvements in endurance performance. These data suggest that the exercise-induced activation of mitochondrial biogenesis is down-regulated with age. Despite this, adaptive responses to exercise can still occur in aging muscle, leading to reduced fatiguability and improved quality of life.

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13L.4 ATP-dependent proteases in biogenesis and maintenance of *Arabidopsis* mitochondria

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It is now widely accepted that tissue- and time-specific control of the quantity and quality of mitochondrial proteins is essential to cope with the challenges of changing developmental and environmental conditions. Recent studies indicate that in plant mitochondria, like in the yeast and animal ones, ATP-dependent proteases are the key components of such control. One of the best characterized plant mitochondrial ATP-dependent protease is FtsH4 from *Arabidopsis*. I will present results which imply that AtFtsH4 is involved in maintaining mitochondrial homeostasis late in rosette development under short-day photoperiod and in plant thermo-tolerance after prolonged exposure to moderately elevated temperature. I will then present some new data on the role of ATP-dependent proteases including AtFtsH4 in coordination of nuclear and mitochondrial genome expression in *Arabidopsis* mutant with impaired mitochondrial translation due to silencing of ribosomal RPS10 gene expression.

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13L.5 RNA turnover in human mitochondria

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Perturbations in functioning of mitochondrial (mt) gene expression have been linked to many human conditions including cancer, aging and neurodegenerative diseases. Therefore research on mechanisms of mt gene expression is of great importance. RNA degradation plays a very important role as it controls three major aspects of RNA metabolism: it determines the half-life of a given RNA species, it destroys the aberrant RNAs that might interfere with replication, transcription or translation in mitochondria, and finally it degrades processing intermediates. In our laboratory we are studying the human nuclear-encoded proteins: SUV3 helicase, polynucleotide phosphorylase (PNPase) and poly(A) polymerase. A model will be presented which describes this interplay of the proteins in ensuring transcript stability and surveillance in mitochondria. In addition we shall discuss data on their participation in molecular events outside mitochondria: cell cycle control and nuclear chromatin maintenance.

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Posters

13P.1 Transfer of disulfide bonds in biogenesis of mitochondrial intermembrane space proteins

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Mitochondria play a critical role in cellular metabolism and are involved in apoptosis, ageing and a number of diseases. Biogenesis of mitochondrial proteins involves several steps including targeting to mitochondria, transport across the mitochondrial membranes, maturation and associations with partner proteins to form functional complexes ([3]). The novel MIA (Mitochondrial Intermembrane Space Assembly) pathway is essential for the biogenesis of intermembrane space proteins in the entire eukaryotic kingdom ([1,2]). A hallmark of this pathway is the regulated transfer of disulfide bonds, a process that had not been previously described in mitochondria ([1,4]). The MIA pathway represents a novel disulfide-transferring system to control the vectorial translocation of proteins into mitochondria ([7]). Mia40, one of the essential components of this pathway, acts in a receptor-like manner ([5]). It dictates precursor entry into the intermembrane space specifically selecting the proteins that possess a cysteine-containing signal MISS (Mitochondrial Intermembrane Space Signal) ([6]). Furthermore, a mode of the cooperation between Mia40 and the sulfhydryl oxidase Erv1 is unique. We propose that the simultaneous association of Mia40, Erv1 and a substrate protein in the ternary complex allows the efficient transfer of multiple disulfide bonds into substrate proteins ([8]). Our findings have important implications for the biogenesis of mitochondria, generation and transfer of disulfide bonds and their impact on protein compartmentalization and organelle functioning.

References

[1] Chacinska A *et al* (2004) *EMBO J.* **23:** 3735–3746.
[2] Chacinska A *et al* (2008) *J. Biol. Chem.* **283:** 29723–29729.
[3] Chacinska A *et al* (2009) *Cell* **138:** 628–644.
[4] Mesecke N *et al* (2005) *Cell* **121:** 1059–1069.
[5] Milenkovic D *et al* (2007) *J. Biol. Chem.* **282:** 22472–22480.
[6] Milenkovic D *et al* (2009) *Mol. Biol. Cell* **20:** 2530–2539.
[7] Müller JM *et al* (2008) *Mol. Biol. Cell* **19:** 226–236.
[8] Stojanovski D *et al* (2008) *J. Cell Biol.* **183:** 195–202.

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13P.2 Biogenesis of the bacterial cbb_3 oxidase of *Rubrivivax gelatinosus:* Evidence for an active core-complex, composed of the catalytic subunit CcoN and the monoheme cytochrome CcoO

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