Biochimica et Biophysica Acta 1797 (2010) 106–110

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbabio

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.

Supported by NIH grant RO1 CA-22762.

doi:10.1016/j.bbabio.2010.04.319

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.

doi:10.1016/j.bbabio.2010.04.320

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