

Mammalian cell responses to mitochondrial dysfunction: role in gene expression, mitochondrial biogenesis and sensitivity to apoptotic inducers.

***Prof. Thierry Arnould : Cell Biology Research Unit
University of Namur (FUNDP), Belgium***

Mitochondrial dysfunction is a central aspect of modern cell biology that impacts metabolism, mitochondrial disorders as well as cancers. We will present some data related to cell responses to mitochondrial dysfunction dealing with gene expression, biogenesis of mitochondria and cell death sensitivity.

We will first cover a new signalling pathway leading to the activation of cAMP-responsive element-binding protein (CREB) in several cell lines affected by mitochondrial dysfunction showing that CaMKIV is activated by a mitochondrial activity impairment as a result of high calcium concentration. Phosphorylated CREB was also found in a rho0 143B human osteosarcoma cell line and in a MERRF cybrid cell line mutated for tRNA(Lys) (A8344G) that might be involved in the proliferation defect induced by a mitochondrial dysfunction. This transcription factor might also explain why mitochondrial DNA (mtDNA)-depleted or rho0 cells still keep a mitochondrial membrane potential ($\Delta\psi$) in the absence of respiration through the control of mtCLIC expression (a mitochondrial chloride intracellular channel). Furthermore, CREB might play a role in the biogenesis of mitochondria by mechanisms that are still poorly understood. Our results suggest that mitochondrial biogenesis is stimulated in mtDNA-depleted cells and involves a calcium-CREB signalling pathway but is associated with a reduced mitochondrial import for matrix proteins that might affect the content of mitochondria. Finally, we also show that mtDNA-depleted 143B cells and MERRF cybrid cells are hypersensitive to staurosporine-induced cell death as evidenced by a more pronounced DNA fragmentation, a stronger activation of caspase-3, an enhanced PARP cleavage and a more dramatic cytosolic release of cytochrome c. We will briefly discuss the mechanisms leading to the hypersensitivity in terms of Bcl-2, Bcl-XL and Mcl-1 abundance, calpain activation and lysosomal proteases.

In conclusion, many cell responses such as cell proliferation, organelle biogenesis and cell death might be affected by mitochondrial dysfunction and could contribute to some mechanisms leading to mitochondrial diseases...