diseases associated with the only T>G mutation are primarily caused by a severe bioenergetic deficiency.

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S12/3 Recent progress in elucidating the molecular mechanism of the mitochondrial permeability transition pore

Andrew P. Halestrap
Department of Biochemistry and The Bristol Heart Institute, University of Bristol, UK
E-mail: A.Halestrap@Bristol.ac.uk

Opening of the mitochondrial permeability transition pore (MPTP) plays a key role in cell death, especially necrosis, and mediates the injury tissues such as the heart and brain experience following ischaemia and reperfusion. However, the molecular identity of the MPTP remains uncertain. Knockout studies have confirmed a role for cyclophilin-D (CyP-D), probably mediated by its peptidyl-prolyl *cis-trans* isomerase activity that facilitates a conformational change in an inner membrane protein. However, knockout studies have cast doubt on the central role of the adenine nucleotide translocase (ANT), previously implicated as the channel-forming component of the MPTP. The evidence for and against a role for the ANT in MPTP opening will be reviewed and data presented to suggest that it usually plays a regulatory role rather than provide the transmembrane pore component. Our recent data suggest that the protein fulfilling the latter role is the mitochondrial phosphate carrier (PiC) and recent evidence in support of this proposal will be summarised. Our data are consistent with a model for the MPTP in which a calcium-triggered conformational change of the PiC, facilitated by CyP-D, induces pore opening. We propose that this is enhanced by an association of the PiC with the "c" conformation of the ANT. Agents that modulate pore opening may act on either or both the PiC and the ANT.

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S12/4 Mitochondria as ATP consumers: the cell biology of the endogenous inhibitory protein, IF1

Michelangelo Campanella, Choon Tan, Andrey Abramov, Andrew Tinker, Michael Duchen
Departments of Physiology and Medicine, UCL, London WC1E6BT
E-mail: m.duchen@ucl.ac.uk

When the mitochondrial membrane potential ($\Delta\psi_m$) is compromised, the F_1F_oATP synthase runs in reverse, and mitochondria switch from ATP producers to consumers. In studies of the isolated enzyme, the protein IF_1 inhibits ATPase activity at an acidic pH. As its impact on mitochondrial function in intact cells is not established, we have explored the effect of overexpression or knockdown of IF_1 in cell lines (HeLa, C2C12). Upon inhibition of respiration, IF_1 conserves ATP (measured using luciferase transfected cells or measurements of $[Mg^{2+}]_c$) at the expense of mitochondrial depolarisation and reduces hypoxic cell death. Knocking down the protein promoted conservation of $\Delta\psi_m$ at the expense of ATP. Surprisingly, IF_1 also had a profound impact on mitochondrial structure and function: IF_1 overexpression increased both the number of mitochondrial cristae and ATP synthase activity, decreasing $\Delta\psi_m$ and favouring a dependence of ATP homeostasis on oxidative phosphorylation. Knocking down the protein had the opposite effect. Further, using immunofluorescence, we found that the relative expression of IF_1 to ATPase is considerably greater in primary neuronal cultures compared to adjacent astrocytes, showing that IF_1 expression level is not fixed in relation to the ATPase. These observations show that IF_1 has an influence on mitochondrial function at rest and that it is effective at preserving cellular ATP in hypoxic or ischaemic conditions.

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S12/5 Mitochondrial glutamate pathways and the control of metabolic homeostasis

Pierre Maechler
Department of Cell Physiology and Metabolism, Geneva University Medical Centre, 1 rue Michel-Servet, 1211 Geneva 4, Switzerland

Cellular glutamate pathways are essentially controlled by mitochondrial metabolism. Although enzymes of the mitochondrial matrix have been studied quite extensively, the regulation of mitochondrial membrane carriers is still rather mysterious. Moreover, recent advances show that it is inappropriate to extrapolate regulation models acquired from one cell model to another, as every tissue uses glutamate for specific functions. Very little is known about molecular mechanisms responsible for tissue specificities. For instance, expression of different isoforms of glutamate carriers might contribute to tissue specificity. Regarding glutamate dehydrogenase, flux direction depends on metabolic parameters such as substrate availability, redox and energy state of mitochondria. These parameters may be tissue specific. At the post-translational level, new modes of regulations have been described these recent years. Indeed, ADP-ribosylation of GDH mediated by SIRT4 offers another regulatory mechanism that might be tissue specific, pending different levels of *SIRT4* expression. This newly identified mode of regulation certainly deserves further investigations to better integrate molecular and cellular glutamate pathways into metabolic homeostasis at the organism level.

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S12/6 Activity of uncoupling protein-2 in pancreatic beta cells

Charles Affourtit, Martin D. Brand
MRC Dunn Human Nutrition Unit, Cambridge, UK
E-mail: ca@mrc-dunn.cam.ac.uk

Pancreatic beta cells secrete insulin when blood glucose levels are high. Dysfunction of this glucose-stimulated insulin secretion (GSIS) is partly responsible for the manifestation of type 2 diabetes, a metabolic disorder that is rapidly becoming a global pandemic. Mitochondria play a central role in GSIS by coupling glucose oxidation to production of ATP, a signal that triggers a series of events that ultimately leads to insulin release. Beta cells express a mitochondrial uncoupling protein, UCP2, which is rather surprising as activity of such a protein is anticipated to lower the efficiency of oxidative phosphorylation, and hence to impair GSIS. The mounting evidence demonstrating that insulin secretion is indeed blunted by UCP2 agrees with this prediction, and has provoked the idea that UCP2 activity contributes to beta cell pathogenesis and development of type 2 diabetes. Although this notion may be correct, the evolved function of UCP2 remains unclear. In this lecture, data will be presented that were obtained from our RNA interference studies to probe the effect of *Ucp2*