(i) Tim44, a coordinating platform, (ii) the subcomplex Tim14–Tim16, J and J-like proteins regulating the ATPase of mtHsp70, and (iii) Mge1 exchanging ADP vs. ATP on mtHsp70. Structure determination of the Tim14–Tim16 oligomer led to a working hypothesis for the import motor: the Tim14–Tim16 pair switches between two conformations, one in which the HPD motif of Tim14 is available for activating the ATPase domain of mtHsp70 and another one in which the activation is blocked. The switch of the TIM14–Tim16 pair is linked to changing interactions with Tim44 and mtHsp70. The reactions of the various components of the import motor are consistent with a Brownian ratchet type mechanism. In this model, spontaneous oscillations of the unfolded preprotein chain in the import channels of TOM and TIM23 complexes are converted into unidirectional movement by preventing retrograde sliding by regulated transient binding of mtHsp70.

doi:10.1016/j.bbabio.2008.05.163

(S5) Mitochondrial biogenesis symposium abstracts (poster and raised abstracts)

S5.4 Mitochondrial function in cancer cell line models

Hanne R. Hagland, Julie Nikolaisen, Linn I. Hodneland, Karl J. Tronstad
Department of Biomedicine, University of Bergen, Norway
E-mail: hanne.hagland@biomedisin.uib.no

Mitochondrial function and respiratory activity is regulated via complex mechanisms that respond to energy status, metabolic elements and stress insults. Elements of mitochondrial dysfunction have been connected to diseases such as metabolic syndromes, cancer and degenerative disorders. The search for biomedical modalities for improvement or stimulation of mitochondrial oxidative activity is therefore considered to be an attractive approach for finding new therapeutic procedures.

The objective of this study was to investigate effects in a selection of cancer cell lines exposed to agents expected to increase mitochondrial biogenesis and respiration. We used pharmacological modulators of glycolysis, respiration and energy status to selectively invoke and facilitate a metabolic shift in the cells towards increased mitochondrial oxidative phosphorylation. Parameters such as cellular content of mitochondria, mitochondrial membrane potential, respiratory rate and glycolytic activity were then analysed. The cell lines exposed different metabolic effects of the treatment, and some cell models were less tolerant than others since the viability was reduced. The metabolic flexibility of the cells seemed to be connected to their ability to thrive under these conditions. This demonstrates that metabolic modulation may have consequences for cell growth and survival, and such approaches may therefore be useful in cancer therapy. Tumours do normally have increased rates of glycolysis combined with reduced respiratory activities, and by targeting this feature it might be possible to develop more selective therapeutic approaches for tumours of different origins.

doi:10.1016/j.bbabio.2008.05.164

S5.5 The trehalose pathway regulates mitochondrial respiratory chain content through hexokinase2 and AMPc IN *Saccharomyces cerevisiae*

Michel Rigoulet[a], Abdelmajid Noubhani[b], Odile Bunoust[a], Beatriz M. Bonini[c], Johan Thevelein[c], Anne Devin[a]
[a]*IBGC du CNRS, UMR 5095, 1 rue Camille Saint Saëns, 33077 Bordeaux Cedex, France*
[b]*ESTBB, Université Bordeaux 2, 146 rue Léo Saignat, 33076 Bordeaux Cedex, France*
[c]*Laboratory of Molecular Cell Biology, Katholieke Universiteit Leuven, Kasteelpark Arenberg 31, B-3001 Leuven-Heverlee, Flanders, Belgium*
E-mail: michel.rigoulet@ibgc.u-bordeaux2.fr

TPS1 encodes for the trehalose-6-P synthase. The trehalose-6-phosphate phosphatase is encoded by TPS2. We studied the respiratory metabolism of both Δtps1 and Δtps2 strains. We show that mutants of the trehalose pathway exhibit modification in the respiratory chain content. In the Δtps1 there is a decrease in the amount of respiratory chains within the cells whereas in the Δtps2 there is an increase in this amount. Because the mitochondrial enzymatic content is modulated through the activity of the Ras/PKA/cAMP pathway, we assessed cAMP content in these strains. There is a good positive correlation between the cellular cytochrome $a+a_3$ content and the cellular cAMP amount. Thus, the effect of the mutations in the trehalose synthesis pathway on mitochondrial enzymatic content is mediated by cAMP level. Furthermore, we investigated the consequences of such mutations on hexokinase 2 deleted strains. In all three hexokinase deleted strains, the mitochondrial amount is comparable to the wild type. Thus, the influence of the tps1 and tps2 deletions on cAMP levels are likely to go through hexokinase.

doi:10.1016/j.bbabio.2008.05.165

S5.6 Reactive oxygen species mediated down-regulation of mitochondrial biogenesis

Cyrille Chevtzoff[a], Anne Galinier[b], Louis Casteilla[b], Bertrand Daignan-Fornier[a], Michel Rigoulet[a], Anne Devin[a]
[a]*IBGC du CNRS, UMR 5095, 1 rue Camille Saint Saëns, 33077 Bordeaux Cedex, France*
[b]*CNRS UMR 5241, CHU Rangueil, 31059 Toulouse Cedex 9, France*
E-mail: anne.devin@ibgc.u-bordeaux2.fr

Mitochondrial biogenesis necessitates the participation of both the nuclear and the mitochondrial genomes. It is highly regulated and mitochondrial content within a cell varies according to energy demand. In the yeast *Saccharomyces cerevisiae*, the cAMP pathway is involved in the regulation of mitochondrial biogenesis. An overactivation of this pathway leads to an increase in mitochondrial enzymatic content. Out of the three yeast cAMP protein kinases, we have shown that Tpk3p is the one involved in the regulation of mitochondrial biogenesis. Moreover, in the absence of Tpk3p, mitochondria produce large amounts of reactive oxygen species (ROS) that signal to the HAP2/3/4/5 nuclear transcription factors. These transcription factors are well-known to be involved in mitochondrial biogenesis. We clearly establish that an increase in mitochondrial ROS production down-regulates mitochondrial biogenesis. Furthermore, we identified the cysteine of the HAP4 transcription factor that serves the role of sensor of these ROS and is crucial for this signaling. It is the first time that a reactive oxygen specie sensitivity of the transcription factors involved in yeast mitochondrial biogenesis is shown. Such a process could be seen as a mitochondria quality-control process.

doi:10.1016/j.bbabio.2008.05.166

S5.7 Respiratory chain organization in *Neurospora crassa* upon disruption of mitochondrial bc_1 complex

Margarida Duarte, Arnaldo Videira