Biochimica et Biophysica Acta 1797 (2010) 1–7

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Abstracts
Plenary Lectures

PL. 1

Pathophysiology of the mitochondrial permeability transition

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The mitochondrial permeability transition (PT) is a Ca^{2+}-dependent increase of mitochondrial inner membrane permeability to solutes with molecular masses up to about 1500 Da [1]. Its occurrence is always accompanied by depolarization, while onset of matrix swelling, depletion of matrix pyridine nucleotides, outer membrane rupture and release of intermembrane proteins including cytochrome *c* depend on the open time. The PT is due to the reversible opening of a high-conductance, voltage-dependent channel in the inner mitochondrial membrane, the PT pore (PTP). In spite of many efforts, its molecular identity remains unknown (reviewed in [2]). In this lecture I shall cover the essential aspects of PTP pathophysiology, with specific emphasis on the role of matrix cyclophilin D [3]; the mechanism of action of cyclosporin A [4]; the modulation by the proton electrochemical gradient [5] and redox effectors [6]; and the consequences of PTP opening as a key to understanding its role in cell dysfunction and death. From this analysis the PTP emerges as a viable target for therapeutic intervention in cancer [7] and degenerative diseases [8].

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doi:10.1016/j.bbabio.2010.04.021

PL. 2

UCP1 and mitochondrial uncoupling

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Uncoupling protein 1 (UCP1) remains as the prototypic — and possibly only — physiologically relevant uncoupling protein (although several closely related proteins do exist). Despite its unchallenged uncoupling function, agreement has still not been reached as to how the uncoupling is accomplished, with hypotheses ranging from it actually being a proton translocator to it being a fatty acid anion transporter. In several respects, recent developments have changed the classical views concerning UCP1 gene expression and function. Whereas expression of the UCP1 gene was earlier considered to be fully under adrenergic control, it is now clear that also agents working through PPAR-gamma can in themselves induce UCP1 gene expression. Similarly, while it was earlier accepted that a cell expressing UCP1 was a brown adipocyte, it has become clear that UCP1 is expressed in adipocytes ("brite adipocytes") that do not possess all the properties of classical brown adipocytes. Although an absence of UCP1 has been accepted to lead to an absence of nonshivering thermogenesis, it was thought until recently that diet-induced thermogenesis was unaffected. It is now clear that also diet-induced thermogenesis is fully UCP1-dependent — and the absence of UCP1 causes or aggravates obesity. Finally, whereas it has been the accepted view that UCP1 and brown adipose tissue are only found and active in newborn humans, it is now evident that a significant fraction of adult humans also possess brown adipose tissue and that UCP1 activity thus may be of significance for metabolic efficiency in adult humans.

doi:10.1016/j.bbabio.2010.04.022

PL. 3

Mitochondrial stress signaling

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Mitochondria are crucial for a wide spectrum of cellular processes. Their involvement not only encompasses the energy metabolism, but also apoptosis, cell growth, differentiation, movement, signaling and proliferation. Thus, any malfunction of mitochondria can have profound consequences for cell physiology. Severe mitochondrial malfunctions, leading to changes in $\Delta\Psi$, are termed the mitochondrial stress and trigger magnitude of cellular stress responses. Cellular calcium metabolism and mitochondrial dynamics (balance of fusion/fission processes) are modified by the mitochondrial stress.

Signaling from the mitochondria under a stress condition to nucleus (also known as retrograde signaling) affects expression of nuclear genes allowing for cell adaptation to impairment of mitochondrial functions. These adaptive changes can lead to an enhancement of mitochondrial mass and expression of a number of mitochondrial and nuclear genes encoding for mitochondrial proteins. Mitochondria-to-nucleus signaling can be mediated by a number of molecules and one of them are reactive oxygen species (ROS). The mitochondrial stress affects production of ROS. On the other hand, increased ROS level has been shown to be a causative factor of diseases associated with mitochondrial dysfunction. In the lecture the current understanding of mitochondrial stress mechanism will be presented.

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doi:10.1016/j.bbabio.2010.04.023

PL. 4

The family of proton-pumping heme–copper respiratory oxidases

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The respiratory chains of nearly all aerobic organisms contain at least one member of the heme-copper superfamily of oxygen reductases to catalyze the 4-electron reduction of dioxygen to water. Genomic and metagenomic studies have revealed that there is a remarkable diversity to these enzymes, but that they have a single evolutionary origin. The superfamily includes not only the respiratory oxygen reductases, but also several families of NO reductases. The superfamily is defined by homology within a single transmembrane subunit which, in all cases, have three histidines which are the axial ligands to one low spin heme and to one high spin heme. In addition, there are three additional histidines which ligate to a copper ion located at the active site of the oxygen reductases, or to an iron in the case of the NO reductases. More than 99% of the respiratory oxidases can be grouped into three families (A-, B- and C-families). Members of each of these families have been examined and shown to pump protons across the membrane. The stoichiometry of proton pumping for the A-family enzymes, which includes the mitochondrial cytochrome *c* oxidase, is 1 proton per electron. However, the stoichiometry of proton pumping appears to be about half (0.5 proton per electron) for members of the B-family and the C-family. This might be the result of an adaptation to life at very low dissolved oxygen concentrations.

doi:10.1016/j.bbabio.2010.04.024

PL. 5

How plants regulate the photosynthetic activity: Linear versus cyclic electron flow and non-photochemical quenching

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Plants have developed different strategies to adapt photosynthetic activity to the highly variable light intensity in their environment. The ATP concentration within the chloroplast is one of the key parameters that control the rate of CO_2 assimilation *via* the Benson–Calvin cycle. It can be estimated by the measurement of the electrochemical proton gradient [1]. At the onset of illumination, the photosynthetic process mainly operates according to the cyclic process that induces a fast increase in the ATP concentration. Under weak illumination, a tight correlation is observed between an increase in the rate of linear electron flow, which reflects the activation of the Benson–Calvin cycle and the decrease in the rate of cyclic electron flow [2]. After a few-minute illumination sufficient to induce steady state conditions, ATP generated by the linear electron transfer chain is sufficient to sustain the ATP consumption through the Benson–Calvin cycle and the rate of the cyclic electron flow is negligible. The rate of the cyclic flow increases as a function of the light intensity while the ATP concentration in the chloroplast has reached its maximum value. Thus, under strong light excitation, the cyclic flow exclusively promotes a large proton gradient. The acidification of the lumen induces: 1) the formation of non photochemical quenchers (NPQ) in the vicinity of PS (photosystem) II reaction centers. NPQ protects PSII from the photodestruction induced by the excess of light; 2) a slowdown of the cytochrome *b*6/*f* turnover that leads to the partial oxidation of the PSI primary donor P_{700}. Oxidation of P_{700} protects PSI by preventing the occurrence of back reactions that would induce photodamages. The inhibition of NPQ formation and of P_{700} oxidation is observed in the presence of low nigericin concentration (0.4 μM) that partially collapses the proton gradient. In these conditions, the illumination (>1 h) induces partial photodestruction of both PSI and PSII reaction centers. Thus, the acidification of the lumen associated with the activation of the cyclic electron flow protects both photosystems against photodamages induced by an excess of light.

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doi:10.1016/j.bbabio.2010.04.025

PL. 6

Biogenesis of the membranes of mitochondria

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Mitochondria, unlike most cellular organelles, have an architecture that is quite unique, elaborate and highly variable between different organisms and tissues. The membranous elements of mitochondrial structure are the outer membrane and the inner membrane. The inner membrane is divided in a complex manner into subdomains: the inner boundary membrane (IBM) which together with the tightly linked outer membrane forms a kind of double