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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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.

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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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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

layered envelope, the cristae and the crista junctions that link the cristae to the IBM. Correct architecture is prerequisite for mitochondrial function, in particular for OXPHOS and inheritance of the mitochondrial DNA. Whereas there is a plethora of information on the mitochondrial OXPHOS complexes only little is known about the molecules that determine mitochondrial architecture. We have studied several aspects of the complexity of mitochondrial architecture. One aspect relates to the structure and function of the various molecular machines that mediate the topogenesis of newly synthesized, nuclear-encoded proteins that are imported into the mitochondria. For instance, the TOM translocase in the outer membrane and the TIM23 translocase in the inner membrane work in physical conjunction to transport proteins, at the same time, across both membranes. Thus, import of these proteins is confined to the IBM. This raises the important question as to whether there is a permanent or dynamic subcompartmentation of proteins in the various parts of the inner membrane. A largely open question in this context relates to the kinds of interactions of OM and IBM in various other transport processes, one of the most important being the translocation of lipids into the mitochondria. Another aspect regards the nature, function and molecular structure of the crista junctions and crista tips and rims. In particular the proteins that are shaping these structures are largely unknown. A number of experiments and results will be presented that provide some answers to some of these questions.

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PL. 7

Proton circuits and mitochondrial dysfunction

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The terms mitochondrial 'function and dysfunction' are used widely in the cell biology field, generally without a precise definition of their meaning. Mitchell's chemiosmotic proton circuit, first published in 1966, provides a precise quantitative framework within which to quantify these critical parameters for the life and death of the cell. The proton circuit has units of potential (the protonmotive force, Δp) and flux (the proton current, JH^+), and these additionally allow calculation of inner membrane leak conductance, C_mH^+ (JH^+ per unit Δp) and power ($JH^+ \times \Delta p$). The analogy with an equivalent electrical circuit has considerable utility for visualizing and manipulating the proton circuit, and is equally applicable to isolated mitochondria and intact cells. An early application of this quantitative approach was the elucidation of the regulatable proton conductance pathway in brown adipose tissue, leading to the identification of UCP1. One observation that emerged from these studies is that 'uncoupling' is not an all-or-nothing process. Thus while a large excess of a protonophore can almost totally collapse Δp, at the critical concentration at which respiratory control is just lost Δp may be only 10–20% below its maximal State 4 value, and thermodynamically competent to maintain ATP synthesis. Until this threshold is reached Δp changes modestly as C_mH^+ is increased. In intact cells titration to this threshold can help to define a critical parameter of mitochondrial 'function' — the spare respiratory capacity, defined as the capacity over basal of the electron transport chain in concert with the inputting metabolic pathways to support an increase in flux in response to this imposed increase in proton conductance. With the proviso that this proton current could all be utilized by the ATP synthase in the absence of protonophore, the spare respiratory capacity provides a safety margin preventing an 'ATP crisis' during periods of maximal ATP demand, for example in neurons during potentially excitotoxic stimulation. Mitochondrial 'dysfunction' defined as a decrease in this spare respiratory capacity has been shown in various neural preparations to greatly potentiate cell death under conditions of high energy demand.

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PL. 8

Redox-optimized mitochondrial ROS balance

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While it is generally accepted that mitochondrial reactive oxygen species (ROS) balance depends on the both rate of single electron reduction of O_2 to superoxide ($O_2^{\bullet -}$) by the electron transport chain and the rate of scavenging by intracellular antioxidant pathways, considerable controversy exists regarding the conditions leading to oxidative stress in intact cells versus isolated mitochondria. Here, we postulate that mitochondria have been evolutionarily optimized to maximize energy output while keeping ROS overflow to a minimum by operating in an intermediate redox state. We show that at the extremes of reduction or oxidation of the redox couples involved in electron transport ($NADH/NAD^+$) or ROS scavenging ($NADPH/NADP^+$, GSH/GSSG), respectively, ROS balance is lost. This results in a net overflow of ROS that increases as one moves farther away from the optimal redox potential. At more reduced mitochondrial redox potentials, ROS production exceeds scavenging, while under more oxidizing conditions (e.g., at higher workloads) antioxidant defense can be compromised and eventually overwhelmed. Experimental support for this hypothesis is provided in both cardiomyocytes and in isolated mitochondria from guinea pig hearts. The model reconciles, within a single framework, observations that isolated mitochondria tend to display increased oxidative stress at high reduction potentials (and high mitochondrial membrane potential), whereas intact cardiac cells can display oxidative stress either when mitochondria become more uncoupled (i.e., low mitochondrial membrane potential) or when mitochondria are maximally reduced (as in ischemia or hypoxia). The continuum described by the model has the potential to account for many disparate experimental observations and also provides a rationale for graded physiological ROS signaling at redox potentials near the minimum.

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PL. 9

The pivotal roles of mitochondria in cancer: Warburg and beyond and encouraging prospects for effective therapies

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Tumors usurp established metabolic steps used by normal tissues for glucose utilization and ATP production that rely heavily on mitochondria and employ a route that, although involving mitochondria, includes a much greater dependency on glycolysis. First described by Otto Warburg, this aberrant phenotype becomes more pronounced with increased tumor malignancy. Thus, while maintaining their capacity for respiration, tumors "turn more parasitic" by enhancing their ability to scavenge glucose. Relying significantly on