strain shows a number of interesting properties which may reflect the role of Nnt in a wildtype mouse, i.e., a glucose intolerance reflecting an insufficient insulin secretion, a several-fold higher sensitivity to MPTP, an agent that introduces a Parkinson's disease-like condition, and a low frequency of spontaneous as well as chemically induced tumors. In addition, knockout of the mitochondrial superoxide dismutase (SOD2) in the C57BL/6J background produces mice with serious cardiac disease. Most of the above observations in the C57BL/6J mice can be explained by a decreased capacity for inactivating free radicals and preventing oxidative stress by GSH-linked reactions. The reason for the lowered cancer frequency is less obvious. It is proposed that Nnt, by being linked to the Δp, in addition to maintaining a high GSH, constitutes a sensing device for estimating the quality of the mitochondria and thus the host cell. A lowered Δp leads to a lower Nnt activity, a lower NADPH/$NADP^+$ ratio, a higher steady-state concentration of H_2O_2, and a higher rate of apoptosis. A lack of Nnt, as in the C57BL/6J mouse, thus favours an even higher level of H_2O_2, apoptosis and counteracts tumours. The mechanisms involved will be discussed.

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PL.13

The mechanism and regulation of F-ATPases

John E Walker
Medical Research Council Mitochondrial Biology Unit, Cambridge, UK
E-mail: walker@mrcbu.cam.ac.uk

More than 25 high-resolution structures of mitochondrial F_1-ATPase have been determined to date. Comparison of all of the structures with each other, and examination of lattice contacts in the crystals used to solve each structure show that neither the conformations adopted by the catalytic subunits nor the occupancy of those subunits by nucleotides is influenced by lattice contacts. Therefore, the structures interpreted as representing ground and transition states depict the structures of intermediates in the catalytic cycle. In the ground state two of the catalytic sites are attached by nucleotides and the third site is unoccupied, whereas in the transition state, nucleotides occupy all three catalytic sites. Two recent structures, one of yeast F_1-ATPase inhibited with yeast inhibitor protein, IF_1, the other of the enzyme crystallized in the presence of phosphonate, appear to represent post-hydrolysis pre-product release intermediates. The current structures occupy about 20° of each of the three 120° steps in a complete 360° catalytic cycle. The lecture will discuss strategies for accessing structures that represent the "missing" part of the catalytic cycle. It will also discuss the different regulatory mechanisms of F-ATPases from mitochondria, chloroplasts and bacteria, by the inhibitor protein, by a redox switch, and possibly by the binding of ATP to the ε-subunit, respectively.

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SEL.1

The fateful encounter of mitochondria with calcium: How did it happen?

Ernesto Carafoli
Venetiuan Institute of Molecular Medicine, University of Padova, Italy
E-mail: ernesto.carafoli@unipd.it

Indirect findings in the 1950s had indicated that mitochondria could accumulate Ca^{2+}. In 1961, the phenomenon was directly demonstrated using isolated mitochondria: the uptake process was found to be driven by respiratory chain activity or by the hydrolysis of added ATP. It could be accompanied by the simultaneous uptake of inorganic phosphate, in which case precipitates of hydroxyapatite were formed in the matrix, buffering its free Ca^{2+} concentration. In conditions of cytoplasmic Ca^{2+} overload mitochondria could thus store large amounts of precipitated Ca^{2+}-phosphate, permitting cells to overcome situations of Ca^{2+} emergency. Work in the 1960s established that the uptake of Ca^{2+} occurred electrophoretically on an unidentified carrier, and was released *via* a Na^+/Ca^{2+} antiporter (a H^+/Ca^{2+} release exchanger was also identified, and a permeability transition pore was later also found to mediate the efflux of Ca^{2+} from mitochondria). In the mitochondrial matrix two dehydrogenases, pyruvate dehydrogenase and phosphate phosphatase, were found to be regulated by Ca^{2+} The uptake process had very low affinity for Ca^{2+}: since the bulk concentration of cytosolic Ca^{2+} is in the low to mid-nM range, it was difficult to postulate a role of mitochondria in the regulation of cell Ca^{2+}. Nevertheless, energy linked Ca^{2+} transport did occur efficiently in mitochondria of various tissues in situ. The paradox was only solved in the 1990s, when it was found that the concentration of Ca^{2+} in the cytoplasm is not uniform: as perimitochondrial micropools of high Ca^{2+} concentration, sufficient to activate the low affinity uniporter, are created by the agonist-promoted discharge of Ca^{2+} from vicinal stores. Mitochondria thus regained center stage as important regulators of cytoplasmic Ca^{2+} (not only of their own internal Ca^{2+}). Their Ca^{2+} transport systems react very rapidly, even in the 150–200 ms time scale of processes like the contraction and relaxation of heart. An important recent development in the area of mitochondrial Ca^{2+} transport is the involvement in the disease process. Ca^{2+} signaling defects are now gaining increasing importance in the pathogenesis of diseases, particularly in neurodegenerative diseases.

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SEL.2

Wanderings in bioenergetics and biomembranes

Martin Klingenberg
Institute for Physiological Chemistry, University of Munich, Schillerstr. 44, D-80336 München, Germany
E-mail: Klingenberg@meduenchen.de

Having worked for 55 years in the center and at the fringe of bioenergetics, the major research stations are reviewed in my wanderings from microsomes to mitochondria, from NAD to CoQ, from reversed electron transport to reversed oxidative phosphorylation, from mitochondrial hydrogen transfer to phosphate transfer pathways, from endogenous nucleotides to mitochondrial compartmentation, from transport to mechanism, from carrier to structure, from coupling by AAC to uncoupling by UCP, and from specific to general transport laws. These wanderings are recalled with varying emphasis paid to the covered science stations. Major attention will be