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Abstracts

EBEC 2008 Short Reports

(P) Plenary lecture abstracts

Peter Mitchell Medal Lecture:

P/1 Forty years of Mitchell's proton circuit: From little grey books to little grey cells

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It is more than 40 years since Peter Mitchell published his first 'little grey book' laying out his chemiosmotic hypothesis. Although ideas about the molecular mechanisms of the proton pumps have evolved considerably since then, his concept of 'coupling through proton circuits' remains remarkably prescient, and has provided the inspiration for the research careers of this mitochondriologist and many others. This review will be a personal account of how the proton circuit has been followed from the little grey book, via the brown fat uncoupling protein, the mitochondrial calcium transport 'set-point' and the bioenergetics of isolated nerve terminals to current investigations into the life and death of neurones, the 'little grey cells' of Agatha Christie's Hercule Poirot.

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P/2 Understanding the coupling mechanism of ATP synthase from its mosaic structure

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The current structure of the mitochondrial ATP synthase is a mosaic of accurate sub-structures determined by X-ray crystallography and solution NMR studies, assembled within the framework of a low resolution overall structure determined by cryo-electron microscopy. The lecture will discuss the depth of our understanding of the various component parts of the enzyme. Our knowledge and understanding are greatest in the catalytic F_1 domain, where highly accurate structures of both ground state and transition state have been determined. They describe six states of the catalytic site during the catalytic cycle. The mechanism of inhibition of ATP hydrolysis by the natural inhibitor protein IF_1 has also been described. The structure of the peripheral stalk is almost complete. In its role as stator, it appears to have rather rigid properties. Our knowledge of the membrane domain of the enzyme is the least complete. The structure of the c-ring in complex with the F_1 domain is known at modest resolution, and a more accurate structure of the mitochondrial c-ring has been provided by modelling, using data from the structure of the K-ring from a bacterial V-ATPase. The most important detail of the enzyme complex lacking at present is the structure of the a subunit, which, together with the c-ring, provides the transmembrane proton channel of the enzyme. The structures of the so-called "minor" subunits (e, f, g and A6L), and those of the more loosely associated proteins, DAPIT and 6.8 k proteolipid, are not known either. These proteins are unlikely to have a role directly in ATP synthesis, but they appear to influence variously the oligomeric state of the enzyme in the mitochondrial inner membrane, the formation of cristae and fusion and fission of mitochondria during the cell cycle.

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P/3 Mechanism and regulation of F_0F_1-motor

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Our knowledge on the mechanism of rotary motor F_oF_1-ATP synthase has been developed recently. In ATP hydrolysis-driven rotation, it appears that ATP-binding and ADP-release drive 80°-step rotation, and ATP-hydrolysis and Pi-release 40°-step rotation. All three β subunits participate with a 120°-phase difference like "*a trio singing-a-round*". The motor function is robust; rotation continues even when shaft portion of γ subunit is deleted, leaving only the rotor head sitting on top of the shaft housing of $\alpha_3\beta_3$. Regulation of F_oF_1 should be critical for living cells, particularly under starving conditions where F_oF_1 consumes ATP wastefully. At least four different regulatory mechanisms are known; inhibition by ε subunit, by disulfide formation of γ subunit, by trapping ADP at catalytic site, and by a specific inhibitor protein (IF1). The ε subunit can take two conformations and ATP hydrolysis, but apparently not ATP synthesis, is blocked when it takes an extended conformation. In some bacterial enzymes, folded conformation of ε subunit can bind ATP at physiological concentrations, thus enabling to respond to cellular ATP level.

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