plays a critical role in human muscle diseases *in vivo*; and they represent an important proof of principle that hereditary muscle diseases can be cured with proper drugs downstream of the genetic lesion if the pathogenetic mechanisms are understood. This is a useful example of how translational medicine can rapidly move from animal models to treatment of human diseases; and of how mitochondrial medicine may be useful beyond the cure of primary mitochondrial diseases.

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P/24 Distance metrics for heme protein electron tunneling

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Distance is the principal parameter that sets the order of magnitude for electron-tunneling rates; however, there continue to be varying ways to measure electron-tunneling distances in proteins. This distance uncertainty blurs the issue of whether the intervening protein medium has been naturally selected to speed or slow any particular electron-tunneling reaction. For redox cofactors lacking metals, or for chlorophylls, distances can be defined from conjugated cofactor edge atoms, approximating the space that includes most of the tunneling electron wavefunction. However, for the iron-containing heme, an appropriate cofactor edge is ambiguous. Electron-tunneling distances may be measured from the conjugated heme macrocycle edge or from the metal, which can be up to a significant 4.8 Å longer. To address this ambiguity, we consider both natural heme protein electron transfer and light-activated electron transfer in ruthenated heme proteins. We find that the edge of the conjugated heme macrocycle provides a reliable and useful tunneling distance definition consistent with other biological electron-tunneling reactions. Furthermore, with this distance metric, heme axially- and edge-oriented electron transfers appear similar and are equally well described by a simple square barrier tunneling model. This is in contrast to recent reports for metal-to-metal metrics that require exceptionally poor donor/acceptor couplings to explain heme axially-oriented electron transfers.

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P/25 Is the modified Q-cycle sufficient as a model to describe the mechanism of the bc_1 complex without invoking electron transfer across the dimer interface?

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Recent progress in understanding the Q-cycle mechanism of the bc_1 complex is reviewed. The data strongly support a mechanism in which the Q_o-site operates through a reaction in which the first electron transfer from ubiquinol to the oxidized iron–sulfur protein is the rate determining step for the overall process. The reaction involves a proton-coupled electron transfer down a hydrogen bond between the ubiquinol and a histidine ligand of the [sFe-2S] cluster, in which the unfavorable protonic configuration contributes a substantial part of the activation barrier. The reaction is endergonic, and the products are an unstable ubisemiquinone bound at the Q_o-site, and the reduced iron–sulfur protein, the extrinsic mobile domain of which is now moves away to deliver an electron to cyt c_1 and liberate the H^+. When oxidation of the semiquinone is prevented, it participates in bypass reactions, including superoxide generation if O_2 is available, which are minimized by the above characteristics, and through coulombic gating. The mechanism discussed is monomeric, but the literature suggests that the dimeric structure participates in a more complicated mechanism. We show from myxothiazol titrations and mutational analysis of cyt *b* Tyr-199, that no inter-monomer electron transfer occurs at the level of the b_L hemes. Analysis of strains with mutations at Asn-221 shows that there are coulombic interactions between the b-hemes in a monomer, and likely also across the dimer interface.

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P/26 The systems biology of the mammalian mitochondria

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The mitochondrion is a self contained biochemical machine involved numerous functions of the cell. A quantitative mathematical model of mitochondria function reveals deficits in our understanding of this process including the enzyme catalyzed reaction pathways and kinetics, post-translational modifications and chemical activity of reaction intermediates. To begin to fill these gaps, the tissue specific mitochondrial biochemical pathways have been characterized using quantitative proteomics by several groups. Using this data, the nuclear "protein program" for a mitochondrial function was evaluated. An example of "reprogramming" associated with Type I diabetes will be discussed. With this metabolic roadmap, the acute regulation of enzymatic function was evaluated by screening matrix phosphoproteome using fluorescent probes, isoelectric focusing and ^{32}P labeling. These studies reveal an extensive and dynamic matrix phosphoproteome. The functional significance, specific interaction sites and nature of the matrix kinase/phosphatase system, including autophosphorylation, are being investigated. All of these approaches, along with those from many other laboratories, begin to fill in the gaps in a quantitative consensus model of mitochondrial function. Clearly this type of systematic approach will need to be continued to establish the entire mitochondria metabolic reaction network and its regulation.

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(S1) ATP synthase/ATPase symposium lecture abstracts

S1/1 Mode of ion binding in the ATP synthase family

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ATP synthases operating in tandem with a respiration or light-driven proton pump use protons and those operating in tandem with a