at Cu_B in the O-state, or an additional hydroxyl group at Fe_{a3}. However, the electron densities of all high resolution structures are compatible best with a peroxo-bridge between Fe_{a3} and Cu_B. In addition, we find that the F-state generated in the traditional way by an excess of H_2O_2, can be converted into a P-state simply by addition of catalase. Finally we have discovered conditions under which the O-state spontaneously converts into a P-state with concomitant formation of a tyrosine radical. All these results can be understood best if the catalytic cycle starts with an O-state containing a bridging peroxide dianion and the F-state contains a superoxide bound to Cu_B.

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P/20 The proton translocation mechanism of cytochrome *c* oxidase

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The cytochrome *c* oxidases (CcO), which are responsible for most of the O_2 consumption in biology, are also redox-linked proton pumps that effectively convert the free energy of O_2 reduction to an electrochemical proton gradient across mitochondrial and bacterial membranes. Recently, time-resolved measurements have elucidated the sequence of events in proton translocation, and shed light on the underlying molecular mechanisms. One crucial property of the proton pump mechanism has received less attention, *viz*. how proton leaks are avoided. Here, we will analyse this topic and demonstrate how the key proton-carrying residue Glu-242 (numbering according to the sequence of subunit I of bovine heart CcO) functions as a valve that has the effect of minimising back-leakage of the pumped proton.

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P/21 The proton pumping heme-copper oxidases

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All known proton pumping respiratory oxidases are members of the heme-copper superfamily. This superfamily contains not only the oxygen reductases (respiratory oxidases) but also prokaryotic NO reductases that are used for denitrification and detoxification. Our work has focused on the largest group of respiratory oxidases, the A-family, with the aim being to understand how the chemistry of reducing oxygen to water is coupled to driving a unidirectional proton pump. Most studies have used the aa_3-type oxidase from *R. sphaeroides*. Mutations in one of the two proton input channels, the D channel, can decouple the proton pump from the redox chemistry. The properties of these mutants will be discussed. Recent studies have included respiratory oxidases that are not members of the major (canonical) family of heme-copper oxidases, but are in the B- and C-families. This includes work on the ba_3-type oxidase from *Thermus thermophilus*, in a collaboration with the group of Dr. James Fee (Scripps Institute). Results will be discussed.

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P/22 Cytochrome *c* binding to the cytochrome bc_1 complex: An interaction critical for electron transfer

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In cellular respiration, the mobile electron carrier cytochrome *c* shuttles electrons from cytochrome bc_1 complex to cytochrome *c* oxidase. The X-ray structure of the complex between cytochrome *c* and cytochrome bc_1 complex at 2.97-Å resolution gave the first structural insight for such a complex from the respiratory chain. The structure revealed the general features of the interface, which is well suited for transient interaction and fast turnover. Remarkably, cytochrome *c* binds to only one recognition site of the homodimeric complex. We now determined the structure of the electron transfer complex in the reduced state at 1.9-Å resolution. The high resolution allows an accurate description of the interface, especially of electrostatic and water-mediated interactions. The dimer structure is asymmetric. Monovalent cytochrome *c* binding is correlated with conformational changes of the Rieske head domain and subunit QCR6p and with a higher number of interfacial water molecules bound to cytochrome c_1. Comparison with a second structure obtained for isoform-2 cytochrome *c* bound to the cytochrome bc_1 complex led to the definition of a minimal interface, the so-called core interface, which is present in all of these structures. The importance of single core interface residues for formation of the reactive complex in solution was probed by site-directed mutagenesis and characterization of the variants.

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P/23 Toward a mitochondrial therapy of collagen VI muscular dystrophies

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Ullrich Congenital Muscular Dystrophy (UCMD) and Bethlem Myopathy (BM) are muscle diseases due to mutations in the genes encoding the extracellular matrix protein collagen VI. Generation of a dystrophic mouse model where collagen VI synthesis was prevented by genetic ablation of the *Col6a1* gene allowed an investigation of pathogenesis, which revealed the existence of a Ca^{2+}-mediated dysfunction of mitochondria and the sarcoplasmic reticulum. A key event appears to be inappropriate opening of the mitochondrial permeability transition pore, an inner membrane high-conductance channel. Consistently, the *Col6a1*$^{-/-}$ myopathic mice could be cured with cyclosporin A through inhibition of cyclophilin D, a matrix protein that sensitizes the pore to opening. Studies of myoblasts from UCMD and BM patients demonstrated the existence of a latent mitochondrial dysfunction irrespective of the genetic lesion responsible for the lack or the alteration of collagen VI. These studies suggest that PTP opening may represent the final common pathway for skeletal muscle fiber death; and provided a rationale for a pilot clinical trial with cyclosporin A in patients affected by UCMD and BM. Prior to treatment, all patients displayed mitochondrial dysfunction and increased frequency of apoptosis, as determined in muscle biopsies. Both these pathological signs were largely normalized after 1 month of oral cyclosporin A administration, which also increased muscle regeneration. These results indicate that mitochondrial dysfunction