structures in the inward open and outward occluded conformations and two homology models of the inward occluded and outward open conformations [1]. Interestingly, the binding constants calculated by docking analyses depend on the conformation of the protein, indicating that the affinity (Km or Ki) measured by transport assays is mostly influences by the occluded conformations. Under specific conditions, LAT1 also mediates substrate uniport. It was previously demonstrated that the natural occurring mutation P375L reduces the coupling of antiport reaction causing a familiar form of ASD [2]. Furthermore, WT LAT1 mediates an ATP-dependent uniport of the substrate His in complex with Cu^{2+}. This apparently unphysiological function explains the efficacy of the Cu-$(His)_2$ administration in the treatment of Menkes Disease patients. In this respect, the ability of LAT1 to transport Cu-$(His)_2$ at high rate can be exploited as a novel intervention in human cancers characterized by LAT1 over-expression. To uncover the molecular basis of the antiport/uniport switch, the altered function of site directed mutants have been investigated.

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Th 5 L-4
The highlight of the unique structural fold of NhaA Na^+/H^+ antiporter

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In 1969, P. Mitchell and Moyle identified Na^+/H^+ antiporter activity in mitochondria. P. Mitchell suggested that Na^+/H^+ antiporter proteins have a primary role in the homeostasis of H^+ and Na^+ in all cells and organelles. Over the 40 years since P. Mitchell's discovery all his predictions have been realized: Na^+/H^+ antiporters are present in the cytoplasmic membrane of almost every cell and also in the organelle membranes of eukaryotes. Na^+/H^+ antiporters are critical to cell-homeostatic processes including bioenergetics. They regulate intracellular pH, Na^+ content and volume. Several antiporters are involved in heart failure and other pathological syndromes.

Up to now the antiporters have been mainly studied in the prokaryotic and eukaryotic cytoplasmic membrane. However, insight into their molecular, cellular and physiological diversity has increased greatly in the past few years with the advent of genome sequencing, genetic manipulation, techniques etc. providing novel alkali cation/protons exchangers that are present in endomembranes. A great example is the MRP antiporters that are homologous to complex I of the electron transport chain. I'll present NhaA, the Na/H antiporter of Escherichia coli and its unique structural fold dubbed the NhaA fold. Despite considerable sequence diversity, increasing numbers of secondary transporters and other membrane proteins were found to share the NhaA structural fold, both in prokaryotes and in eukaryotes.

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Th 5 L-5
Mitochondrial potassium channels: new properties and functions

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Mitochondria are recently implicated in phenomena such as cytoprotection, cellular senescence, tumor metabolism, and inflammation. The basis of these processes relies on biochemical functions of mitochondria such as the synthesis of reactive oxygen species or biophysical properties such as the integrity of the inner mitochondrial membrane. The transport of potassium cations plays an important role in all these events. The K^+ influx is mediated by potassium channels present in the inner mitochondrial membrane. In this article, we present an overview of our new findings on the properties of mitochondrial large-conductance calcium-activated and ATP-regulated potassium channels. This concerns the role of mitochondrial potassium channels in cellular senescence, and interactions with other mitochondrial proteins or small molecules such as quercetin, hemin, and hydrogen sulfide. We also discuss the prospects of research on potassium channels present in mitochondria.

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Fr 1 From quantum physics and quantum information chemistry to quantum biology of respiratory and photosynthetic electron transfer. 80 years after Erwin Schrödinger's *What is Life?*

Fr 1 L-2
What is a feeling? A bioenergetic explanation

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Feelings are by definition subjectively felt by organisms, but their molecular basis remains enigmatic. Assuming that feelings evolved, selection must act on some kind of biophysical patterning. Analogous processes seem to operate at a cellular level because anaesthetics work on single-celled protists, as well as animals such as Drosophila with relatively simple brains. Volatile anaesthetics suppress respiratory complex I, which we show induces reversal of the ATP synthase, increasing membrane potential and ROS flux. Recent work suggests that anaesthetics may disrupt the chirally induced spin polarization of respiratory electrons in complex I. Given that this spin polarization must be lost on quinone reduction, we argue that anaesthetics disrupt local magnetic fields generated by complex I alone. We calculate that oscillating fields from parallel cristae could be amplified up to hundreds of micro-Tesla, sufficient to influence the behaviour of voltage-gated channels in neuronal membranes over distances of 1-10 μm, potentially modulating neural firing and so conscious states. These oscillating fields depend on the specific orientation and morphology of cristae in synaptic or brainstem mitochondria, which we predict would be dynamic in real-time, influencing EEG traces directly. But why would mitochondrial electromagnetic fields become associated with sentience? Mitochondria derive from bacteria, whose plasma membrane interfaces between the outside world and metabolism within, acting as a Markov blanket. Metabolism dynamically generates electrical

membrane potential while at once being powered by it, making membrane potential uniquely sensitive to global changes in cell state relative to the environment. Cells detect multiple stimuli through automated feedback loops, but genetic responses typically take minutes or hours, when decisions must be immediate and binary (move or stay put). A feeling is an organism's best guess (inference) as to its state in the world, given incomplete information. We show that the shifting balance of electrostatic to electromagnetic fields from the plasma membrane can give an integrated real-time readout of state that guides action. Feelings are intrinsically subjective membrane-derived fields corresponding to physiological states, elaborated by selection in the brains of sentient animals.

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Fr 1 L-3

Low Magnetic Fields Stimulates Cardiac Mitochondrial Bioenergetics with a Bell-Shaped Response, Possibly Through the Radical Pair Mechanism

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Studies have shown that low magnetic fields (LMFs) of less than 1×10^{-3} Tesla (T) affect numerous biological events, including bacteria and plant growth, bird migration, and human brain activity. On a cellular level, LMFs affect mitochondrial reactive oxygen species generation (mROS), ion channel activities, and intracellular Ca^{2+} concentrations. However, the mechanisms that could account for these effects are poorly understood. Here, we show that a static LMF ranging from 3.38×10^{-4} to 1.45×10^{-3} T, when applied to mitochondria isolated from adult rat hearts, produced an asymmetric bell-shaped increase of maximal respiration (Vmax, state 3 respiration) of up to 40%. A similar LMF-induced increase was also observed in mitochondria isolated from rat hearts subjected to ischemia-reperfusion (I-R) injury. This LMF-mediated bell-shaped response was also observed in the activity of several enzymes involved in oxidative phosphorylation (OXPHOS), including complexes II (succinate dehydrogenase), III, and V, and citrate synthase. By contrast, even though Vmax increased using the NADH-generating substrates malate and glutamate, the enzymatic activity of complex I was not affected or declined linearly, as suggested by straight-line fitting. With increasing MF, the generation of mROS responded with an inverted bell-shaped decrease. We propose a theoretical mechanism encompassing radical pair formation and electron spin transition that may account for LMF-induced bell-shaped changes in OXPHOS enzymes and mROS. Our results indicate that a narrow range of LMFs can enhance mitochondrial bioenergetics and may decrease mROS toxicity, such as during I-R injury, providing a non-invasive approach to treating diseases where energy generation is compromised.

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Fr 1 L-4

A protet-based model for oxidative and photosynthetic phosphorylation

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Two-stage (e.g. light-dark) phosphorylation experiments showed that there is a 'high-energy' intermediate linking electron transport and phosphorylation. Large, artificial electrochemical proton gradients can also drive phosphorylation, a fact seen as strongly supportive of the chemiosmotic coupling hypothesis that a pmf is the 'high-energy' intermediate. However, in such experiments there is a threshold (pmf >170 mV, equivalent to ΔpH ~2.8) below which no phosphorylation is observed, and 220 mV are required to recreate in vivo rates. This leads to the **correct** question, which is then **whether those values of the pmf generated by electron transport are large enough**. Even the lower ones are below the threshold [1, 2], whether measured directly or via the use of membrane-permeant ions and/or acids/bases (which are always transporter substrates [3], so all such measurements are artefactual). The single case that seemed large enough (220 mV) is now admitted to be a diffusion potential artefact [4]. Many other observables (inadequate bulk H^+ in 'O_2-pulse'-type experiments, dual-inhibitor titrations, uncoupler-binding proteins, etc.) are consistent with the view that values of the pmf, and especially of Δψ, are very low. A protet-based charge separation model [2], a protonic version analogous to how energy may be stored in devices called electrets, provides a high-energy intermediate that can explain the entire literature, including the very striking demonstration [5] that close proximity is required between electron transport and ATP synthase complexes for phosphorylation to occur.

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Fr 2 Bioenergetics and biosynthesis involving bioblasts of photosynthetic organisms

Fr 2 L-1

The evolution of assembly complexity of earth's most important CO_2 fixing enzyme

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Rubisco is the central CO_2 fixing enzyme of the Calvin cycle and responsible for the vast majority of all CO_2 fixation on our planet today. In plants, Rubisco undergoes an elaborate set of steps