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P7 Mitochondrial Physiology

P7.1

Mitochondrial stress signaling in disease and aging

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Mitochondria are multi-faceted organelles in eukaryotic cells that stand at the nexus of energy metabolism, oxidative stress, and apoptosis. Consequently, circumstances (genetics, environmental factors, aging) that result in mitochondrial dysfunction disrupt a multitude of cellular processes that can cause human disease pathology, ranging from heart, skeletal muscle and nerve dysfunction to diabetes, blindness, and deafness. Of course, a major function of mitochondria is to generate ATP through the process of oxidative phosphorylation (OXPHOS), which also produces reactive oxygen species (ROS). Oxidative stress due to increased production of mitochondria-derived ROS, declines in cellular energy metabolism, and disruptions of apoptotic responses are some of the major downstream cellular consequences leading to the observed pathology of mitochondrial-based diseases. In addition to causing molecular damage, ROS and other forms of mitochondrial stress participate in numerous signaling pathways that regulate diverse physiological processes, including stress resistance, cell differentiation, immune system function, and apoptosis. In my talk, I will highlight studies from my laboratory that link mitochondrial stress signaling pathways to pathology, the innate immune system and regulation of lifespan.

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P7.2

Mitochondrial dynamics and inheritance in yeast

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Mitochondria are essential organelles of eukaryotic cells. They are the major sites of energy production and play important roles in programmed cell death and ageing. In many cell types, mitochondria show an amazingly dynamic behaviour. They continuously move along cytoskeletal tracks, and their membranes frequently fuse and divide. These processes are important for maintenance of mitochondrial functions, for inheritance of the organelles upon cell division, for cellular differentiation, and for programmed cell death. Budding yeast *Saccharomyces cerevisiae* is a particularly useful model organism to study these processes. Systematic screening of comprehensive yeast mutant collections revealed novel molecular components and cellular pathways required for mitochondrial fusion, division, motility, mitochondrial DNA inheritance, and respiratory activity. These large scale genetic analyses are combined with functional characterization of newly identified proteins by biochemical and imaging techniques. Our current work focuses on the molecular mechanisms contributing to mitochondrial transport, distribution, inheritance, and turn-over in yeast. The class V myosin, Myo2, was identified as the motor directing anterograde mitochondrial transport [1]. The cell cortex-associated protein, Num1, is an important factor for retention of mitochondria in the mother cell [2]. The mitochondria-ER tethering complex ERMES is crucial for mitochondrial turn-over by mitophagy [3]. The ultimate goal of our ongoing work is to obtain a comprehensive picture of the molecular processes contributing to mitochondrial inheritance in a simple eukaryotic cell.

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P7.3

Mitochondria take center stage in Alzheimer's disease

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder that affects more than 35 million people worldwide. Despite considerable progress of AD research in recent years, we still lack the means to either arrest or prevent this devastating disorder. Accumulating evidence shows that mitochondrial abnormalities elicit a cascade of pathological events that underlies neuronal degeneration in AD pathology. Studies performed in our laboratory demonstrate prominent alterations in mitochondrial structure, function, and turnover in several experimental models of AD. It was also observed that mitochondrial dysfunction is a possible bridge between AD and type 2 diabetes, a major risk factor for AD. These findings corroborate the notion that mitochondria are a promising target for drug discovery and therapeutic interventions.

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P8 Membrane Channels, Pumps and Transporters

P8.1

A potassium "transporter" regulated by the ATP/ADP ratio

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The KtrAB potassium "transporter" plays an important role in adaptation to osmotic shock in bacteria. This membrane protein complex is composed by two polypeptides: KtrB is the membrane protein involved in potassium and sodium permeation and KtrA is the cytosolic protein involved in regulation of transporter activity. KtrA binds ATP and/or ADP. We have determined the structure of the KtrAB complex in the ATP bound state and have been performing biochemical and structural studies to unravel the mechanism of regulation of this complex by the ATP/ADP ratio.

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P8.2

Functional and structural dynamics of NhaA, a prototype for Na^+ and H^+ antiporters, which are responsible for Na^+ and H^+ homeostasis in cells

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The crystal structure of the down regulated NhaA crystallized at acidic pH 4 [1] has provided the first structural and functional insights into the antiport mechanism and pH regulation of an Na^+/H^+ antiporter (reviewed in [2]). NhaA is organized into two functional regions: (i) a cluster of amino acids responsible for pH regulation, and (ii) a catalytic region at the middle of the TM IV/XI assembly, containing unique antiparallel unfolded regions that cross each other, forming a delicate electrostatic balance in the middle of the membrane. This unique structure contributes to the cation-binding site and facilitates the rapid conformational changes expected for NhaA. Although extended chains interrupting helices have since emerged as a common feature for ion-binding in transporters, the NhaA fold, shared by ASBTNM [3] and NapA [4] is unique among the three structural folds that comprise the secondary transporters e.g., MFS, LeuT and NhaA [5]. Computational and electrophysiological methods (reviewed in [2]) have been used to develop intriguing models for the mechanism of NhaA. However, the dynamics of the conformational changes and how energy is transduced in this "nano-machine" are still unknown. Ultimately, interdisciplinary integrative results will shed light on the mechanism of activity and pH regulation of NhaA, a prototype of the CPA2 family of transporters.

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P8.3

Mitochondrial machinery for import and assembly of proteins

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Mitochondria contain more than 1000 different proteins, most of which are synthesized as precursor proteins on cytosolic ribosomes. Mitochondrial outer and inner membranes possess translocases that import the precursor proteins. The translocase of the outer mitochondrial membrane (TOM) initially recognizes and transports the large majority of precursor proteins across the outer membrane. Subsequently, at least four different pathways sort the precursor proteins to their intramitochondrial destinations [1]. Presequence-carrying preproteins are translocated by the presequence translocase of the inner membrane (TIM23) and the associated import motor PAM [2]. Metabolite carriers are transferred through the intermembrane space by the small TIM chaperones and are inserted into the inner membrane by the carrier translocase (TIM22) [3]. The mitochondrial intermembrane space import and assembly machinery (MIA) mediates the import of cysteine-rich proteins in a redox-regulated manner [4]. Beta-barrel proteins use small TIM chaperones and the sorting and assembly machinery (SAM) of the outer membrane. Additionally, some alpha-helical outer membrane proteins bypass the TOM channel and are inserted into the outer membrane by the MIM machinery. The mitochondrial contact site and cristae organizing system (MICOS), located at crista junctions between inner boundary membrane and cristae, plays a dual role. MICOS is required for maintaining the characteristic inner membrane morphology and interacts with TOM and SAM of the outer membrane, thus promoting protein biogenesis.

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P9 General Bioenergetics

P9.1

Toward the biogenesis of manmade oxidoreductases working in cells

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