The 65th Symposium of the Society for General Physiologists: Energizing research in mitochondrial physiology and medicine

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The annual Society of General Physiologists (SGP) symposium has a six-decade legacy as the premier and innovative international meeting for physiologists, cell biologists, and biophysicists. During September 7–11th, 2011, more than 130 scientists participated in the 65th SGP symposium entitled "Mitochondrial Physiology and Medicine" at Woods Hole, MA. In a survey distributed at the end of the conference, participants ranked the overall science and quality of discussions very highly (average of 9.5 out of 10), with multiple respondents noting the highly collegial atmosphere, emphasis on unpublished research, and opportunity for younger scientists to interact with leaders in the field.

Recent groundbreaking discoveries demonstrating the pivotal role of mitochondria in human physiology and disease have repositioned mitochondria to the center stage of biomedical research. Mitochondria serve as gatekeepers between cell survival and death, as well as regulate proper cell signaling, energy metabolism, redox balance, and ion homeostasis. Mitochondrial dysfunction is associated with numerous acute and chronic human diseases, including heart failure, ischemia-reperfusion injury, atherosclerosis, cardiomyopathy, stroke, neurodegeneration, diabetes, obesity, cancer, rare diseases, and aging. Clearly, the SGP's selection of this year's topic on mitochondrial physiology and disease was timely and fitting.

The meeting was organized by **Shey-Shing Sheu** along with a committee consisting of recognized leaders in mitochondrial research, including Robert Balaban, Paolo Bernardi, Robert Dirksen, Roberta Gottlieb, Gyorgy Hajnóczky, and Brian O'Rourke. The program included two keynote speakers, both members of National Academy of Sciences: David Clapham, who spoke on "Mitochondrial Ca²⁺ Entry Pathways," and Douglas Wallace, whose talk was entitled "A Bioenergetic Etiology for Complex Diseases: Interaction between Mitochondrial Genetics and the Epigenome." The themes for the five sessions were: (1) mitochondrial morphology and dynamics; (2) system biology of mitochondria; (3) mitochondrial ion channels and transporters; (4) mitochondrial signaling, Ca²⁺, and reactive oxygen species (ROS); and (5) mitochondria in cell death and disease (for the complete program, see http://www.sgpweb.org/symposium2011 .html). These topics represent an integration of mitochondrial physiology and medicine from molecular to human levels, with a special emphasis on the role of mitochondria as therapeutic targets in human disease. Speakers included not only the established leaders in the mitochondrial research field, but also, several "rising stars" and junior investigators were invited to present short talks. Two special sessions on "controversies and breaking news" were added to the program by choosing presenters whose abstract contained controversial and exciting unpublished results. A total of 71 posters were presented in two poster sessions.

On the evening of September 7th, David Clapham delivered the first keynote address. Clapham's group made a major contribution to the mitochondrial Ca²⁴ transport field by recording the Ca2+ current of the mitochondrial inner membrane Ca²⁺ uniporter (MCU) with the patch-clamp technique applied to mitoplasts generated from COS-7 cells. The recording of singlechannel activity unequivocally established that MCU is an ion channel (MiCa). The results established that MiCa, which is responsible for 80% of the total inner membrane current, is a highly Ca2+-selective ion channel with extremely high Ca²⁺ affinity (2 nM), enabling high Ca²⁺ selectivity despite relatively low cytosolic Ca²⁺ concentrations (100 nM) (Kirichok et al., 2004). The MiCa is permeable to Sr²⁺ but not K⁺ and is not inactivated by internal Ca²⁺. The extremely high Ca²⁺ affinity seems at odds with the common belief that MCU has a relatively low Ca²⁺ affinity Ca²⁺ transporter. Clapham also presented his group's discovery of Letm1 (leucine zipper EF hand-containing transmembrane protein 1) through a genome-wide RNA interference screen as a mitochondrial Ca²⁺/H⁺ antiporter of the inner mitochondrial membrane (Jiang et al., 2009). Letm1 proteins are evolutionarily conserved homomeric inner membrane proteins, but their function was not previously established. Ca2+ uptake through Letm1 is more

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energetically conserving than other Ca²⁺ uptake mechanisms because one Ca²⁺ uptake is coupled with one H⁺ extrusion. Knockdown of Letm1 abolished the initial fast mitochondrial Ca²⁺ uptake by histamine. Letm1 was previously found to be related to Wolf-Hirshhorn syndrome, characterized by neurological disorders such as mental retardation and seizure. One controversial issue is that Letm1 has been characterized as a K⁺/H⁺ exchanger. Published results show that the K⁺/H⁺ exchanger nigericin reverses all mitochondrial defects caused by the absence of Letm1. This raised the debate of whether the Letm1-associated Ca²⁺ changes are secondary to the changes in K⁺.

Clapham's talk was followed by a roundtable discussion on the future of mitochondrial physiology and medicine. **Douglas Wallace** opened the discussion with a vision of complex diseases seen through the lens of mitochondria and their role in bioenergetics. The high rate of mitochondrial DNA (mtDNA) mutation (~1,000-fold higher than that of nuclear DNA [nDNA]) and its relatively high susceptibility to ROS generated by the respiratory chain place them at the epicenter of complex diseases. Wallace stated that this realization argues for a shift in focus from nDNA to mtDNA and the epigenome. He envisioned that a multidisciplinary approach to elucidate mtDNA genetic changes and epigenome fluctuations will be critical in our understanding of the etiology and search for cures of complex human diseases. Roberta Gottlieb agreed with Wallace that bioenergetics is an arbiter for cell life and death. She noted that cellular energy homeostasis in all tissues is critically dependent on mitochondrial quality control, which is regulated by a balance between ongoing biogenesis and autophagic destruction. In addition, mitochondrial quality control depends on a delicate, dynamic balance between mitochondrial fission and fusion. Thus, elucidation of molecular and cellular mechanisms of mitochondrial biogenesis and autophagy/mitophagy is a burning issue in mitochondrial research. Gyorgy Hajnóczky first drew attention to recent identification of major mitochondrial Ca²⁺ transport proteins, including Letm1, NCLX, MICU1, and MCU. He envisioned that these breakthrough discoveries will lead the field of mitochondrial Ca²⁺ signaling to explosive growth because molecular and structural manipulations are now readily accessible. Specifically, these manipulations will aid in the dissection of both the molecular mechanisms and physiological relevance of mitochondrial Ca²⁺ uptake. He then pointed out that the study of endoplasmic reticulum (ER)/sarcoplasmic reticulum (SR)-mitochondrial junctions that are central to Ca²⁺ delivery to the mitochondria has also been undergoing tremendous progress. The ER/SR-mitochondrial junctions are also the subject of immense interest because of their important roles in phospholipid synthesis and interorganellar protein transfer. Although the ER/SR-mitochondrial

junctions stabilize the position of some mitochondria, the mitochondrial population as a whole undergoes permanent remodeling that involves movements and fusion-fission. Mitochondrial dynamics is anticipated to attract growing attention because mutations of some of the key proteins are associated with and likely to contribute to a variety of human diseases. Finally, the integration of localized and global Ca2+ signaling in regulating cell function is a major topic in mitochondrial research. Brian O'Rourke indicated the necessity of the application of theoretical modeling for evaluating and assimilating experimental data in the field. He used an example that connects various ionic circuits (K+, Ca2+, Na+, and H+) in the plasma membrane, ER/SR, and mitochondria and predicts, on a beat-to-beat basis, how these parameters work together to orchestrate cellular energy, Ca2+, and ROS metabolism in cardiac muscle. This integration of knowledge will be extremely important in our understanding of cardiac protection, injury, apoptosis, and arrhythmias. Finally, because more and more signaling proteins have been identified in the mitochondria, the posttranslational modifications of mitochondrial proteins will become an increasingly hot topic. Robert Dirksen concurred with O'Rourke, emphasizing the need for integrative physiology in investigating normal mitochondrial function and disease affecting it, and how strongly future medicine will depend on the translation of basic mitochondrial biology to integrative human physiology. Robert Balaban echoed the views of O'Rourke and Dirksen, and emphasized the importance of a systems biology approach in mitochondrial research, noting that in his opinion, the mitochondrion affords one of the best opportunities in all of cell biology for developing a complete understanding of a how a complex, multimolecular organelle functions. Paolo Bernardi reminded us that all the new discoveries need to fit the basic principles of thermodynamics, such as Peter Mitchell's chemiosmotic theory, and urged the students and junior investigators to study the history of major mitochondrial research discoveries. Strong courses in mitochondrial biology are essential for the education of the next generation of mitochondriacs. Orian Shirihai passionately elaborated on this point.

The content of the roundtable discussion on the opening night of the symposium was both stimulating and remarkably prophetic as it served to foreshadow several central themes that were revisited throughout the remainder of the week. These themes included the molecular identification of mitochondrial ion channels and transporters, mechanisms controlling mitochondrial dynamics, the power of mitochondrial proteomics, quantitative modeling of mitochondrial function, and the central role mitochondria play in cell survival, death, and disease.

Molecular identities of mitochondrial channels and transporters

A major theme of the conference focused on recent advances in the molecular identification of mitochondrial transporters. After the biophysical characterization of the mitochondrial Ca²⁺ uniporter channel by Clapham and colleagues (Kirichok et al., 2004), two groups represented at the symposium identified the molecular mechanism. Building on their previous proteomic analysis (the "MitoCarta") (Pagliarini et al., 2008), Vamsi Mootha and colleagues used comparative genomics, RNAi screening, and measurement of mitochondrial calcium fluxes to identify the MCU (Baughman et al., 2011) and MICU1 (Perocchi et al., 2010), a novel protein with two EF hands that functions as the Ca²⁺ sensor for MCU. Independently, Rosario Rizzuto and colleagues used MitoCarta to identify MCU in silico, and used several physiological assays (including siRNA interference and overexpression in HeLa cells; single-channel recordings in lipid bilayers with mutagenesis) to validate the essential role of this protein in mediating mitochondrial Ca²⁺ uptake (De Stefani et al., 2011).

Other identifications reported in the meeting included **David Clapham**'s characterization of LETM1 as a mitochondrial Ca²⁺/H⁺ antiporter of the inner mitochondrial membrane (Jiang et al., 2009); **Brian O'Rourke**'s identification of Kir1.1 (ROMK) as "MitoK," the ATP-and glibenclamide-sensitive K channel involved in ischemic preconditioning and reperfusion protection; and **Yiuriy Kirichok**'s identification of the uncoupler protein UCP1 as a proton/fatty acid transporter.

A major unresolved issue in mitochondrial physiology is the elucidation of the complete molecular identity of the mitochondrial permeability transition pore (mPTP) (Di Lisa and Bernardi, 2006; Halestrap, 2006; Ricchelli et al., 2011). The mPTP is a voltage-dependent high conductance (\sim 1,200 pS) channel located in the inner mitochondrial membrane. When the channel is open, it allows passive movement of solutes with molecular masses of up to 1.5 kD. Paolo Bernardi gave an inspiring historical overview of mPTP research and the importance of this mechanism in physiology (e.g., as a rapid Ca²⁺ release channel), cell death (e.g., ischemia-reperfusion injury), and disease (e.g., congenital muscular dystrophy). In spite of the identification of mPTP function over 30 years ago (Hunter and Haworth, 1979a,b), the molecular identity of the mPTP remains enigmatic. It has been hypothesized that mPTP is a multiprotein complex, with ANT, cyclophilin-D, and phosphate carrier as the key components, and mitochondrial creatine kinase, hexokinase, voltage-dependent anion channel, and Bcl-2 family members serving important regulatory functions. However, Jeffrey Molkentin noted that results from knockout mice have so far supported a role for cyclophilin-D, but not VDAC or ANT, as an essential component of the mPTP. Clearly, one of the most exciting and challenging open questions in this field is to nail down the precise molecular identity of the mPTP. **Kathleen Kinnally** summarized evidence that Bax/Bak oligomerize in the outer mitochondrial membrane to form the mitochondrial apoptosis-induced channel (MAC), an alternate death channel through which cytochrome c can be released. Kinnally proposed that the MAC channel underlies the so-called "bystander effect," whereby cytochrome c released in one cell triggers apoptosis in neighboring cells (Peixoto et al., 2011).

Mitochondrial dynamics: Motility, fusion, and fission Another major theme of the symposium was mitochondrial dynamics, the molecular mechanisms that control mitochondrial motility, fission, and fusion as presented by Gyorgy Hajnoczky, Orian Shirihai, Yisang Yoon, and Roberta Gottlieb.

Published work has identified several protein fusion factors (Mfn1, Mfn2, Opa1) and fission factors (DLP1/ Drp1, Mff, Fis1). Drp1, for example, is a normally soluble dynamin-related protein proposed to act in concert with ER extensions to "cinch" mitochondria in preparation for fission (Friedman et al., 2011). Evidence was provided demonstrating that outer and interior membranes of adjacent mitochondria in many tissues including muscle are dynamically interconnected, allowing intermitochondrial transfer of proteins in both compartments, with full fusion at one end of this connectivity. As shown by Shirihai, often one of the daughter mitochondria of a fission event becomes depolarized and subsequently undergoes autophagy ("mitophagy"). This and observations by other speakers suggest the important hypothesis that mitophagy functions as a quality control system in which compromised mitochondrial proteins (e.g., oxidized by ROS) are first segregated by fission or by whole mitochondrion targeting, and then removed by mitophagy (Gustafsson and Gottlieb, 2009; Gottlieb and Carreira, 2010). Seen in the light of this hypothesis, many aspects of mitophagy are brought into sharper focus, such as the harmful reduction of mitophagy by high fat diets (Las et al., 2011), and the potential therapeutic utility of increased mitophagy in ischemic preconditioning (Huang et al., 2011).

Mitochondrial proteomics

Based on work presented at the symposium, mitochondrial proteomics clearly represents another important and rapidly emerging area in mitochondrial research. During the meeting, **Vamsi Mootha** discussed how new insights into mitochondrial function and disease can be mined using MitoCarta (http://www.broadinstitute.org/pubs/MitoCarta/index.html), a comprehensive inventory of more than 1,000 mouse and human genes encoding proteins revealed by mass spectrometry and found to be localized to mitochondrial across a wide range of tissues (Pagliarini et al., 2008). For example, MitoCarta was used

by both Mootha's group (Bashyam, 2008; Baughman et al., 2011) and Rosario Rizzuto and colleagues (De Stefani et al., 2011) to identify novel proteins involved in mitochondrial Ca²⁺ uptake (MICU1 and MCU). Brian O'Rourke discussed work that combined proteomic, bioinformatic, and functional analyses to demonstrate the presence and function of ROMK channels in the mitochondrial inner membrane, suggesting that these channels play an important role in controlling K⁺ ion transport into and out of the mitochondrial matrix, and are a candidate for the elusive mitochondrial KATP channel. Finally, Peipei Ping presented an impressive in scope analysis of the mouse cardiac mitochondrial phosphoproteome that she used to identify several potential regulatory pathways, protein kinases/ phosphatases, and phospho-targets that are likely to significantly impact mitochondrial function. Although these and other similar studies are already beginning to provide important new and unanticipated insights into mitochondrial biology, the current state of our understanding of the mitochondrial proteome is clearly only in its infancy.

Modeling mitochondrial function

A synthetic theme running through several of the talks, including those of Aon, Balaban, Bernardi, and O'Rourke, was the need for a systems biology approach, including formal modeling, to many aspects of mitochondrial function. Miguel Aon's presentation on the role of antioxidant defenses in determining mitochondrial redox balance ably illustrated this theme (Wei et al., 2011). Balaban exemplified the theme in an analysis of the large quantitative differences in the dynamic range (average metabolic rate vs. maximum rate) of different tissues (e.g., heart and liver mitochondria) and species. Variation in rates of key respiratory processes are only partially explicable in terms of the mitochondrial proteomes of the different tissues and species, and lead to consideration of posttranslation modifications, in particular, the phosphoproteomes. The future challenge lies on integration of massive, but incomplete, information regarding mitochondrial metabolic signaling networks with human physiology and pathology.

Mitochondrial role in cell survival, death, and disease

As described above, **Roberta Gottlieb** stressed that because mitochondria are key arbiters for numerous diseases, mitochondrial quality control provides a critical step in cell survival and disease prevention. Mitochondria achieved this quality control by establishing a delicate balance between eliminating damaged and dysfunctional mitochondria via autophagy (mitophagy) and generating new and healthy mitochondria via biogenesis, fusion, and fission. Just like mitochondria, cells also exhibit complex quality control mechanisms. For example, apoptosis is a crucial process for physiological

cell death required for proper embryonic development and tissue homoeostasis. Atan Gross presented his recent discovery of a 33-kD protein MTCH2/MIMP, a member of the mitochondrial carrier protein family, which forms a complex with activated tBID to cause permeabilization of the mitochondrial outer membrane that triggers cell death. He also showed that MTCH2/ MIMP deletion in the liver leads to a profound reduction in hepatic levels of fatty acids, consistent with MTCH2/MIMP regulating mitochondrial fatty acid metabolism. These findings raise the intriguing possibility of cross talk signaling between mitochondrial energy metabolism and tBID receptor-like protein during apoptosis. The crux of Kevin Foskett's presentation is the idea that mitochondrial Ca²⁺ uptake during constitutive InsP₃R Ca²⁺ release from the ER is a fundamental cellular process required for efficient mitochondrial respiration and maintenance of normal cellular bioenergetics. Any disturbances of this "privileged" inter-organelle Ca²⁺ transport would contribute to cellular energetic dysfunction, injury, and disease. As discussed above, another key player in dictating cell survival and death is the mPTP. Although transient openings of the mPTP is proposed to serve as a physiologically important rapid mitochondrial Ca2+ efflux mechanism, persistent mPTP activation results in mitochondrial membrane potential depolarization, cytochrome c release, and cell death. Indeed, mPTP activation is linked to cell damage/death in cardiac ischemia-reperfusion injury and muscle pathology observed in collagen VI diseases, and these effects are greatly diminished by inhibition of mPTP activity. The successful translation of these fundamental findings to the development of new and effective therapies in humans remains a major frontier in mitochondrial research.

Concluding session

The symposium culminated on the evening of September 10th with the second keynote address given by Douglas Wallace. The title of his lecture was "A Bioenergetic Etiology for Complex Diseases: Interaction between Mitochondrial Genetics and the Epigenome." Wallace, a pioneer in the field of human mitochondrial genetics for over 30 years, passionately advocated the importance of bioenergetic dysfunction in a wide range of both rare and common diseases. He described that traditional thinking in Western medicine is based on a predominately anatomical perspective of disease and a Mendelian perspective of genetics. However, the search for common disease variants in the nDNA has not been fruitful because the environment plays a major role in the etiology of common diseases. In his keynote lecture, Wallace provided a bioenergetic perspective on biology and medicine. Specifically, Wallace proposed that the availability and utilization of calories (energy) is the most important factor in the environment, which clearly brings mitochondria to the center stage of common disease etiology. For living species to adapt to regional and seasonal diversities in calorie availability, stable changes in cellular energetics over many years are needed, which is most readily achieved by the accumulation over time of functional variants in the mtDNA. The mtDNA has a high mutation rate, and the most injurious mtDNA mutations are eliminated before fertilization through a maternally inherited selective system. Moreover, cyclic seasonal changes in gene expression are achieved by alterations in the epigenome, which permits coordinate expression of the hundreds of nDNA-encoded bioenergetic genes. Therefore, Wallace concluded that genetic variants that predispose individuals to common diseases are predominantly a result of alterations in the mtDNA and the epigenome, not the nDNA. It can be envisioned that the central role of mitochondria in controlling this "flow of energy" will continue to drive new seminal discoveries and advances in physiology and medicine.

Upcoming JGP Perspectives on mitochondrial physiology and medicine

The success of the Mitochondrial Physiology and Medicine Symposium has inspired a future *JGP* Perspectives series that will broadly address many of the major themes of the 2011 SGP Symposium. For this upcoming Perspectives series, a subgroup of symposium speakers selected and recruited by representatives from the SGP council and the *JGP* editorial board will address several current controversies and breakthroughs in their respective fields.

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