11-Subg
Musings at MID-Career: What is so Special about omega-3 Fatty Acids?
Scott Feller.
Dept Chemistry, Wabash Col, Crawfordsville, IN, USA.
Receiving the Thomas E. Thompson award is a tremendous honor that provides an opportunity to reflect on a scientific journey that is inextricably linked to the Membrane Structure and Assembly subgroup of the Biophysical Society. Members of the subgroup have served as my closest collaborators, as sources of knowledge and wisdom, and as role models of a worthy scientific career. In this talk I will describe our efforts to use computational approaches to study highly polyunsaturated lipids, in particular those containing docosahexaenoic acid (DHA). By employing molecular dynamics simulations with enhanced sampling algorithms we have identified significant differences in lipid mediated protein-protein interactions. These results are analyzed in terms of the unique conformations available to omega-3 fatty acids and their subsequent effect on lipid packing at the lipid-protein interface.

Subgroup: Bioenergetics

12-Subg
Mitochondrial DNA Stress Primes the Antiviral Innate Immune Response
Phillip West.
Pathology, Yale School of Medicine, New Haven, CT, USA.
Mitochondria are central participants in a variety of cellular processes including ATP generation, programmed cell death, signal transduction, and innate immunity. Consequently, mitochondrial dysfunction is implicated in many human diseases through a wide array of pathogenic mechanisms. Mounting evidence suggests mitochondrial dysfunction engages stress-signaling cascades that can induce either beneficial or deleterious adaptive responses. Despite the biological importance of these responses, the signaling pathways involved and the mechanisms governing their activation remain poorly characterized. Here we describe an antiviral innate immune signaling pathway that is elicited by mitochondrial DNA (mtDNA) stress. Mechanistically, we have found that aberrant mtDNA packaging causes hyper-fusion of the mitochondrial network, which engages cGAS-STING-IRF3-dependent signaling to elevate interferon-stimulated gene (ISG) expression, potentiate type I interferon responses, and confer broad viral resistance. Furthermore, we demonstrate that Herpes viruses disrupt mtDNA packaging and organization, provoking mtDNA stress-dependent antiviral priming. Therefore, our results identify mtDNA stress as a trigger of innate immune signaling and suggest that viral disruption of mtDNA homeostasis may serve as a cell-intrinsic indicator of infection to enhance antiviral innate immunity.

13-Subg
High Resolution Crystal Structures of Translocator Protein 18 kDa (TSPO) Reveal Ligand Binding Sites and Effects of a Human Single Polymorphism
Shelagh Ferguson-Miller, Fei Li, Jian Liu, Yi Zheng, Lance Valls, R. Michael Garavito.
Biochemistry/Molecular Biology, Michigan State University, East Lansing, MI, USA.
Translocator protein 18kDa is a mitochondrial outer membrane protein that was first recognized in mammalian systems as the peripheral benzodiazepine receptor (PBR) and in Rhodobacter sphaeroides as the tryptophan-rich sensory protein (TspO). Although many aspects of its function in bacteria and mitochondria remain unclear and controversial, TSPO is ubiquitous and well conserved in bacteria through to mammals and is expressed at high levels in steroidogenic tissues and under conditions of inflammation, metastatic cancer, and neurological disease. A number of different ligands bind to TSPO including cholesterol, porphyrins and heme, as well as benzodiazepines and related compounds. Derivatives of TSPO ligands are widely used to image neurological injury by positron emission tomography. Recently, a human single nucleotide polymorphism was found to be associated with increased incidence of anxiety-related disease. We report high resolution crystal structures of Rhodobacter TSPO, along with ligand binding studies and mutational and evolutionary covariance analysis, which reveal new features of this enigmatic protein, including a dimer form and an altered structure induced by a mutant mimic of the human polymorphism. (NIH R01GM26916, MSU Center for Mitochondrial Science and Medicine, SF-M).

14-Subg
Translocator Protein in Mitochondrial Cholesterol Transport and the Pharmacology of Steroidogenesis
Vassilios Papadopoulos.
McGill University, Montreal, QC, Canada.
Steroidogenesis begins with the transfer of cholesterol from intracellular stores into mitochondria through a complex formed of cytosolic proteins, such as the steroidogenesis acute regulatory protein and 14-3-3 adaptor, and outer mitochondrial membrane proteins Translocator Protein (TSPO) and Voltage Dependent Anion Channel (VDAC). TSPO is an evolutionary conserved 18-kDa high affinity drug- and cholesterol- binding protein expressed in high levels in steroid synthesizing cells. Aberrant expression of TSPO has been linked to cancer, neurodegeneration, neuropsychiatric disorders and primary hypogonadism. TSPO drug ligands have been proposed as therapeutic and monitoring agents for these diseases. In the brain, steroids are local regulators of neural development and excitability. Changes in neurosteroid levels are linked to neuropsychiatric and neurological disorders such as depression, anxiety and neurodegeneration. Local administration of neurosteroids is unfeasible, and treatment of patients with large amounts of neuroactive steroids unsafe. In the testis, reduced serum testosterone (T) is common among subfertile and infertile young men as well as aging men and is often associated with depression, metabolic syndrome, and reduced sexual function. Although T-replacement therapy has been the treatment of choice, there are numerous side-effects. Thus, there is a clear need for developing repair therapies that restore the brain's and testis' abilities to make steroids. In vitro and in vivo studies, using animal models of disease, demonstrated that TSPO drug ligands increased neurosteroid production in neuropsychiatric disorders and T formation in hypogonadism. Moreover, peptides conjugated to 14-3-3ε site of interaction with VDAC1 blocked 14-3-3ε-VDAC1 and increased VDAC1-TSPO interactions in testis inducing T formation. In contrast, in constitutively steroid producing Leydig and adrenal cell tumors blocking TSPO function inhibits excessive steroid synthesis. TSPO and VDAC were identified as valid drug targets that control steroid formation both in vitro and in vivo.

15-Subg
Voltage Dependent Anion Channels (VDAC) and Regulation of Mitochondrial Metabolism
John J. Lemasters[1,2].
[1]Medical University of South Carolina, Charleston, SC, USA, [2]Institute of Theoretical and Experimental Biophysics, Pushchino, Russian Federation.
Voltage dependent anion channels (VDAC) are responsible for permeability of mitochondrial outer membranes to hydrophilic metabolites like ATP, ADP and respiratory substrates. Although previously assumed to remain open, VDAC closure is emerging as an important mechanism for regulation of global mitochondrial function. Acetaldehyde formation from hepatic ethanol metabolism leads to VDAC closure, which suppresses exchange of mitochondrial metabolites and inhibits ureagenesis. In vivo, VDAC closure after ethanol occurs coordinately with mitochondrial depolarization. Together, VDAC closure and uncoupling foster selective and more rapid mitochondrial oxidation of toxic acetaldehyde formed by ethanol metabolism. Glycolysis and suppression of mitochondrial metabolism are metabolic characteristics of cancer cells that promote cell proliferation (Warburg phenomenon). High free αβ-tubulin dimers in cancer cells block VDAC and suppress mitochondrial function, and reversal of tubulin inhibition of VDAC with erastin and erastin-like small molecules has an anti-Warburg effect that hyperpolarizes mitochondria, enhances oxidative phosphorylation and decreases glycolysis. Erastin-like compounds also enhance mitochondria formation of reactive oxygen species in cancer cells, leading eventually to mitochondrial dysfunction and cell death. Thus, VDAC is a key regulator of mitochondrial function (DK073336, DK037034 and 14.Z50.31.0028).

Subgroup: Molecular Biophysics

16-Subg
Bending, Twisting, Popping: Protein and Nucleic-Acid Remodeling by ATP-Dependent Machines and Switches
James Berger.
Department of Biophysics and Biochemistry, Johns Hopkins University, Baltimore, MD, USA.
RecA and AAA+ family ATPases play key roles in cellular events ranging from vesicle trafficking and proteolysis to chromatin remodeling and DNA replication/repair. A large subset of these enzymes form multimeric rings or