C. Wednesday July 26

Session 1: Molecular Perspectives

Fred Sachs (State University of New York, Buffalo) presented a talk entitled "A blocker for cationic SACs, from channels to animals." He discussed how a 4 kD peptide isolated from tarantula venom blocks cationic SACs with an affinity of about 500 nM. The peptide noted GsMTx-4 is specific for SACs. It doesn't affect steady state I/V curves of heart cells or of astrocytes. It does, however block stretch induced effects. It reduces volume activated currents in astrocytes and can block atrial fibrillation induced by dilatation in the rabbit heart with affecting the action potential.

Evan Evans (Boston University, University of British Columbia) presented a talk entitled "Exploring the Complex Relation between Force – Time – Chemistry in Single Biomolecular Bonds." He discussed how noncovalent-macromolecular bonds are the fundament of nanoscale chemistry in recognition, adhesion, signaling, activation, regulation, and a host of other processes from outside to inside cells. But not well-appreciated is that energy landscapes of these biomolecular bonds are rugged terrains with more than one prominent activation barrier. Near-equilibrium kinetics in conventional test tube assays only reveal a single-outer barrier, which is the classical paradigm of biological chemistry. However, when bonds are detached under a large range of loading rates (force/time), the measurements of single bond strength on a scale of Log(loading rate) provide a spectroscopic image of prominent energy barriers traversed along the force-driven reaction coordinate. In this way, dynamic force spectroscopy DFS exposes barriers – especially inner barriers – that are difficult or impossible to detect in solution assays. Because of the inherent logarithmic dependence of rupture force on speed of loading, the DFS method is most revealing when applied over many orders of magnitude in loading rate. Examining biomolecular bonds with dynamic force spectroscopy is leading to a new perspective of the important connection between force – time – chemistry in biology.

George Oster (University of California Berkeley) presented a talk entitled "How F1 ATPase uses nucleotide hydrolysis to generate a rotary torque." He discussed how the experimentally measured mechanical efficiency of the F1 ATPase under viscous loading is nearly 100%, far higher than any other hydrolysis driven molecular motor. A structural and bioenergetic analysis provides a molecular explanation for this remarkable property.

Session 2: Cellular Perspectives

These three talks [**Yale Goldman** (University of Pennsylvania), **Joyce Wang** (Boston University), and, **Charles Lindemann (**Oakland University)] and those by **Sheetz**, and **Elson** earlier in the meeting, have the common theme that the motor proteins and the cytoskeletal polymers exhibit bi-directional communication and energy transduction. The conventional energy transduction pathway is from metabolic energy into motion. Many cellular machines use energy liberated by splitting ATP or GTP to perform useful functions, such as motility, ion pumping, untwisting of tangled DNA or proof-reading of the genetic code during translation. It can easily be shown thermodynamically that this energy transduction implies an influence of the work output or mechanical properties of the load, such as its mass, stiffness or viscosity, on the rates of some of the accompanying biochemical reactions. In muscle, non-muscle myosin-based intracellular motility, locomoting cells and the flagellar axoneme the mechanical conditions, forces on the motors and properties of the substrate, strongly control the kinetics of the energy transduction process. Decoding the details of this 'reverse communication' and understanding the mechanisms at the molecular and atomic levels remain crucial tasks in most examples of cell motility.

Yale Goldman (University of Pennsylvania) showed several examples of the feedback of the loading conditions on actomyosin kinetics and some new methods for detecting the relevant mechanical and structural signals. This feedback is essential to minimize energy consumption. Non-muscle myosins participate in myriad cell biological roles, including development of the cell morphology, maintenance of native ultrastructure and signaling. Members of the myosin superfamily transduce force signals and move crucial cargoes to specific sub-cellular target. Wang used a new manipulatable substrate (cross-linked polyacrylamide) to detect traction forces of locomoting cells. He addressed the production of such forces, their magnitudes and mechanisms. The results are compatible with an engine-cargo model. How the cells detect and respond to mechanical properties of the substrate is just beginning to be understood. The functions of such detection may be probing the environment or long range signaling between cells or from the environment. **Lindemann** presented a model of the eukaryotic flagellum in which the transverse-force acting on the outer microtubule doublets regulates the dynein motors. A simulation based on this model replicates the behavior of cilia and flagella including mechanical sensitivity.

Force transduction by the force generators themselves controls their output and may also influence many other cellular processes. Another thread in these talks is that development

of new methods is essential to obtain discriminating experimental data. Using the widest possible armamentarium, including physical and engineering approaches, toward solving biological problems is the most fruitful avenue.

Session 3: Tissue/Organ Perspectives

The session on Biological Forces, Tissue-Organ Perspectives focused on the mechanisms of mechanotransduction in biological systems.

Shu Chien (University of California, San Diego) reported that the shear stress can activate integrins and a vascular endothelial growth factor receptor. The activation of these membrane proteins triggers intracellular signaling pathways to modulate gene expression and cellular functions. The temporal and spatial natures of the mechanochemical transduction in relation to flow dynamics may explain the preferential localization of atherosclerosis in branch points of the arterial tree.

Elisabeth Burger (Vrije University of Amsterdam) presented data showing that the flow of interstitial fluid in the canaliculi in strained bones induces significant shear stresses which are sensed by the osteocytes to induce bone remodeling. High bone strain and interstitial flow causes osteoblast recruitment and bone growth, whereas reduced bone strain and interstitial flow leads to osteoclast attack and bone loss. In addition to the modulation of cellular functions such as proliferation, motility, and secretion, mechanical forces also cause structural remodeling, e.g., the reorganization of cytoskeletal fibers and the alignment of endothelial cells and bone trabeculae and osteons with the direction of force application.

Stephan Levin (private practice) presented the tensegrity model of spine mechanics. In the tensegrity model, the bones act as compression elements enmeshed in soft tissues. In contrast to the traditional “stack of block” models, tensigrity structures are omni-directional, hierarchical, nonlinear, and independent of gravity, and local load distributing. The tensegrity model allows the synegistic linkage of structure and function for the creation of an integrated hierarchical system.