Design Principles for Life

Physiology often employs signaling pathways to effect communication within cells. A prime example of such a common signaling pathway is a transient elevation of intracellular Ca^{2+} through which a number of downstream physiological effectors are activated. The process of regulating intracellular Ca^{2+} is itself complex, involving a number of convergent pathways including Ca^{2+} influx across the cell membrane and Ca^{2+} release from intracellular stores. The sarco-/endoplasmic reticulum (SR/ER) network serves as a storage depot for Ca^{2+} within cells, and release of Ca^{2+} from the SR/ER is essential for a number of physiological functions.

Analysis of the crystallographic structure of the SR/ER has revealed important functional information about the channels that mediate Ca^{2+} release. The predominant Ca^{2+} release channels within the SR/ER are ryanodine receptor (RyR) and ionositol triphosphate receptor (IP_{3}R) channels. In their review (4), Stathopulos et al. summarize the present understanding of the structural bases for RyR and IP_{3}R function in the SR/ER and underscore the fundamental structural features of these proteins through evolutionary considerations. Understanding the structural mechanisms of RyR and IP_{3}R function at the atomic level provides an avenue to the rational design of agonists and antagonists with tissue specificity important for the maintenance of human health, treatment of disease, and development of new Ca^{2+} signaling research tools.

The proper synthesis and routing of contractile Ca^{2+}-handling proteins, as well as all other membrane proteins and secreted proteins, are essential elements of cardiac function. Proper regulation of the levels of cytosolic Ca^{2+}, which is responsible for cardiac myocyte contraction, is critical for normal heart function. Numerous proteins in the lumen and membrane of the sarcoplasmic reticulum (SR) are responsible for regulating the cycling of contractile Ca^{2+} between the SR and the cytosol. An imbalance in the levels of these proteins can impair contractility, leading to cardiac insufficiency and pathology. However, little is known about these processes. In his review (2), Glembotski summarizes studies that address the location and mechanism in cardiac myocytes of the synthesis of secreted and membrane proteins, a subset of which includes contractile Ca^{2+}-handling proteins. Moreover, the review explores the possibility that protein synthesis and cardiac contractile Ca^{2+} handling in the SR may be functionally integrated and that this integration may contribute to healthy heart function.

Cystic fibrosis (CF) is one of the most common chronic lung diseases in children and young adults and leads to multi-organ dysfunction and premature death. CF is a genetic disease that results from the malfunction of the CF transmembrane conductance regulator (CFTR), a chloride channel that plays a critical role in maintaining water and salt homeostasis across many epithelium-lining tissues. In their review (3), Jih and Hwang examine the gating defects that cause CF. Opening of the CFTR channel is associated with ATP-induced dimerization of its two nucleotide binding domains (NBD1 and NBD2), whereas gate closure is facilitated by ATP hydrolysis-triggered partial separation of the NBDs. This generally held theme of CFTR gating—a strict coupling between the ATP hydrolysis cycle and the gating cycle—is put to the test by recent reports that lead to a new model, featuring energetic coupling between CFTR’s NBDs and its two transmembrane domains (TMDs) that form the substrate translocation pathway. Since many pathogenic mutations of CFTR cause gating defects, understanding the molecular mechanism of gating conformational changes should help in the design of novel strategies for the treatment of patients with CF.

RNA editing is a process used by all true metazoans to systematically change genetic information. For example, codons within a mRNA can be recoded, resulting in novel protein isoforms. In their review (1), Garrett and Rosenthal suggest that RNA editing is used to help poikilotherms adapt to cold temperatures. Although much previous research has shown that RNA editing diversifies an organism’s transcriptome, the idea that it is used for a specific purpose like temperature adaptation is novel. Although homeotherms, humans, and other organisms that possess stable body temperatures do not use RNA editing as a mechanism for cold adaptation, it could have important implications if used as a directed mechanism for plasticity. For example, a small but growing body of data suggests that RNA editing can change in response to external inputs such as environmental and even social factors. Learning to control the editing process may lead to therapeutic potential by correcting genetic mutations and selectively tuning protein function.

References