Design Principles for Life

Physiology is the science exploring the function of living tissue and is inextricably linked to the structural properties of cells and tissues down to the molecular level. Unraveling structure-function relationships epitomizes the science of physiology, and, with the development of new tools, we are discovering the design principles for life. The reviews in this issue address structure-function relationships of living tissues at various levels.

How do mechanical cues, such as the touch of a loved one, the vibration of a cell phone, or the painful stub of a toe, give rise to reproducible perceptions and behaviors? In their review, Eastwood and Goodman (2) probe the mysteries of touch by studying the molecular events that give rise to the sensation of touch and pain in *C. elegans* nematodes. Mechanotransduction channels translate mechanical energy into neuronal signals. Key insights are derived by combining information gained from touch-disrupting mutations in *C. elegans* DEG/ENaC channels with high-resolution crystal structures. This combined approach is leading to a better understanding of how mechanotransduction channel structure relates to function. More broadly, proposed design principles might govern not only the specializations that enable these channels to detect touch but also common activation principles across the functionally diverse superfamily of DEG/ENaC channels.

Epithelial ion transporters play an essential role in maintaining fluid and electrolyte balance in the body. The kidney regulates systemic fluid and electrolyte composition by the directional transport of ions with an associated osmotic transport of water through water channels. In their review, Park et al. (4) explore the role of the antagonist WNK/SPAK kinases and IRBIT/PP1 regulatory pathways that affect important ion transporters. WNK/SPAK kinases facilitate phosphorylation of ion transporters, whereas the IRBIT/PP1 pathway serves to dephosphorylate these transporters. Recent evidence suggests that the reciprocal effects of these pathways on fluid and electrolyte transport may form a common pathway that determines both resting and stimulated secretory states in epithelial cells. Thus an understanding of how WNK/SPAK kinases and IRBIT/PP1 regulatory pathways interact may allow the design of better therapeutic approaches to diseases that affect fluid balance and electrolyte composition such as hypertension.

The incidence of obesity and diabetes has increased to nearly epidemic proportions and, most unfortunately, it is affecting ever younger individuals. Thus the duration of this chronic disease is increasing with greater personal, health, and socio-economic impact. The pathophysiology underlying obesity and diabetes is complex and heterogeneous, potentially involving excessive glucose production, reduced glucose utilization, and/or impaired insulin secretion. This complexity and heterogeneity has limited the development of effective preventive or therapeutic strategies. It is now evident that diverse, non-genetic causes underlie the vast majority of these metabolic diseases and that concept of “metabolic diversity” and the need for a “personalized medicine” approach are required.

In his review, Remy Burcelin (1) explores the intestinal microbiota-to-host relationship. This complex interaction may trigger an immune response and tissue metabolic infection responsible for the low-grade inflammation that characterizes the onset of obesity and diabetes. If metabolic diseases are convincingly linked to a change in the intestinal microbiota, novel preventive and therapeutic strategies may be possible.

Rhythmic contraction and relaxation of the heart reflects the transient elevation and decline of Ca$^{2+}$ within cardiac muscle cells. The dynamic regulation of intracellular Ca$^{2+}$ during both the systolic and the diastolic phases of the heart cycle is essential for normal cardiac function. In their review, Louch et al. (3) focus on Ca$^{2+}$ regulation during the relaxation phase of the cardiac cycle, which is essential for proper refilling of the ventricles. They emphasize that Ca$^{2+}$ regulation during diastole is not simply a passive process but is highly regulated by different Ca$^{2+}$ fluxes, including uptake into the sarcoplasmic reticulum (SR) via the SR Ca$^{2+}$/ATPase (SERCA) and extrusion out of the cell via the Na$^+$/Ca$^{2+}$ exchanger and plasma membrane Ca$^{2+}$ ATPase. The importance of diastolic Ca$^{2+}$ regulation is reflected by the fact that approximately half of all heart failure patients exhibit myocardial dysfunction due to impaired diastolic relaxation.

References