Exploring How Cells Communicate

Communication within and among cells is fundamental physiology. Discovering and deciphering the basis of physiological communication is essential to understand life and disease. It is not surprising that modern molecular biology has adopted the physical term of transduction to describe the process of transferring genetic information. In physics and physiology, transduction is the process of converting one form of energy into another. Transduction is the essential basis of cellular communication, and the articles in this issue of *Physiology* explore various aspects of how cells communicate with their external environment, with other cells, or within the cell itself.

Hairy sensation provides animals with detailed and important information about objects and other animals encountered in their environment. Recent work has established that one or more of three types of mechanoreceptor endings innervate each hair of the skin. Each of these three mechanoreceptor types possesses unique molecular features that detect distinctive information about skin touch. In their review (5), Lechner and Lewin discuss the transcription factor c-Maf that controls the morphological development of peripheral endings associated with three rapidly adapting mechanoreceptor types, Aβ-fiber hair follicle receptors, Meissner’s corpuscle receptors, and Pacinian corpuscle receptors. c-Maf not only controls the morphological differentiation of such receptors but also controls the expression of ion channels like KCNQ4 that are essential for receptor tuning. The advent of tools such as optogenetics combined with the ability to genetically trace molecularly defined sensory populations should spur the development of new behavioral paradigms that can answer important questions, such as how information from different hairy skin mechanoreceptors is actually used in a realistic behavioral context.

Cell-cell communication is a hallmark of communication with the central nervous system (CNS) and is established early in life by the outgrowth of neuronal processes. In adults, the presence of growth-inhibitory factors underlies the severely restricted capacity of the CNS to regenerate nerve fibers following injury. Nogo-A is a major nerve fiber growth-inhibitory protein that interacts via different functional domains with a not yet fully characterized multi-subunit receptor complex. This interaction leads to a collapse of the cytoskeleton of growing nerve fibers, thereby suppressing growth. In the intact CNS, an induction of structural and synaptic plasticity occurs after neutralization of Nogo-A, pointing to an important physiological role of Nogo-A, perhaps acting as a tonic brake on CNS growth and plasticity, thereby stabilizing highly complex neuronal circuits. In their review (4), Kempf and Schwab present evidence that acute treatment with Nogo-A/Nogo receptor neutralizing agents increases regenerative fiber sprouting and growth after spinal cord injury or stroke in rats, mice, and monkeys. In addition, behavioral recovery of these animals suggests that growing axons form meaningful connections. Based on this exciting physiological evidence, clinical trials with anti-Nogo-A antibodies are ongoing in patients with acute spinal cord injury, amyotrophic lateral sclerosis, and multiple sclerosis.

Ligand-receptor interactions form the basis of transduction in cell-cell communication. Membrane-tethered ligands are recombinant bioactive peptides based on naturally occurring neurotoxins, hormones, or neuropeptides, which are anchored to the extracellular surface of the membrane and modulate the activity of cell surface receptors and ion channels both cell-autonomously and with pharmacological specificity. In their review (1), Choi and Nitabach discuss the use of membrane-tethered ligands as a unique transgenic tool due to their effective means of perturbing cellular circuits that can be examined for consequent changes in physiology and behavior. This toolset provides information regarding the identity of the cells and the signal/receptor molecules that comprise cellular circuits and how they integrate to control specific biological processes in model organisms. Such information provides not only insight to the basic circuit mechanisms of physiology and behavior but may also reveal novel strategies and drug targets in addressing human pathologies that can be ameliorated by restoring or adjusting relevant circuits.

Life is not possible without the many ion channel proteins that transport ions across cell membranes. Large-conductance Ca$^{2+}$- and voltage-gated K$^+$ (Slo1 BK) channels have numerous but specific functions in humans and are implicated in many diseases, including those affecting the nervous, cardiovascular, respiratory, and reproductive systems. In their review (3), Hoshi and colleagues summarize recent advances in the integration of biophysical and structural models of the Slo1 BK channel function. Opening of Slo1 BK channels, allosterically facilitated by an increase in intracellular Ca$^{2+}$ concentration and/or by membrane depolarization, generally acts to inhibit cellular excitability. Yet, we do not know the rate at which Slo1 BK channels transduce Ca$^{2+}$ and voltage signals, ultimately leading to opening of the ion conduction gate to allow movement of K$^+$ ions. Understanding these transduction mechanisms, as well as other characteristics of the Slo1 BK channel, could lead to pharmacological and genetic manipulations of specific aspects of channel function and may accelerate development of therapeutic strategies for many diseases. Additionally, because it represents an exemplar allosterically regulated protein, study of the Slo1 BK channel may reveal information applicable to many other proteins.

One or more members of the connexin family of gap junction proteins are found in nearly every cell type in the human body. Surprisingly, skin is one of the most complex connexin-rich organs with upward of 10 connexin family members that are temporally and spatially expressed in dermal fibroblasts or keratinocytes. Specific members of the connexin family are expressed and silenced as keratinocytes proceed to differentiate and ultimately enter programmed cell death as the skin becomes cornified. In wounded skin, the expression of connexins is reorganized as the epidermis begins to heal. In their review (2), Churko and Laird focus on mechanisms underlying connexin-linked skin diseases. Novel therapies have shown that
strategic and transient downregulation of the most prevalent connexin, Cx43, accelerates wound healing. However, patients who harbor germ-line mutations in any one of five genes that encode connexins can develop a plethora of skin diseases for which there is no cure or effective treatment. Further research may lead to therapies that can alleviate the suffering caused by these skin abnormalities.

Intracellular communication is also essential for life and is the target for many exciting new discoveries in physiology. Dysfunction of mitochondrial communication and function is implicated in numerous human diseases including cancer, diabetes, amyotrophic lateral sclerosis (ALS), cardiomyopathy, and Alzheimer’s, Parkinson’s, and Huntington’s diseases. Phosphorylation of mitochondrial proteins has emerged as a major regulatory mechanism for metabolic adaptation and a potential therapeutic target. In their review (6), Valsecchi and colleagues discuss the discovery of a compartmentalized source of cAMP in mitochondria generated by soluble adenylyl cyclase. The presence of mitochondrial cAMP has led to new ideas regarding how this ubiquitous signaling system is able to provide short-term metabolic regulation through protein phosphorylation. Increasing our knowledge of the downstream targets of cAMP signaling will shed new light on the mechanism of communication between mitochondria and other organelles that regulate fundamental processes, such as mitochondrial biogenesis and turnover.

References