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Physiology in Perspective: Cell-Cell Interactions: The Physiological Basis of Communication

"The truth is, the science of Nature has been already too long made only a work of the brain and the fancy: It is now high time that it should return to the plainness and soundness of observations on material and obvious things." In this statement from his book *Micrographia* published by the Royal Society in 1665, Robert Hooke (1635–1703) extolled the immense power of the microscope as a valuable tool for careful observation in advancing biology as a science. In his book, Hooke also first introduced the biological term "cell." Through careful observation and the introduction of other valuable scientific tools, we now know that cells are immensely complex structures that underlie function (physiology) and reflect life. We are multicellular organisms, only adding to the complexity of life, and our normal physiology depends on the interactions among cells. In this issue of *Physiology*, we explore just a few examples of cell-cell interactions. Typically, cell-cell interactions refer to the direct communication that occurs between cell surfaces mediated by protein structures such as gap junctions or myoendothelial junctions. Plasma membrane proteins can also couple to the extracellular matrix and affect other cells more remotely. Cell-cell interactions may also occur even more indirectly via release of hormones or neurotransmitters. Cell-cell interactions reflect the basic level of physiological communication, triggering responses to the internal or external environment that are essential for survival. The loss of cell-cell interactions can result in loss of essential communication, leading to various disease conditions.

Among his many accomplishments and discoveries, Robert Hooke is responsible for experiments that founded respiratory physiology. Together with Robert Boyle, he constructed the first air pump that allowed measurements on small animals at a reduced atmospheric pressure, clarifying the physiological effects of hypoxia and prompting the discipline of high-altitude physiology. He built the first human decompression chamber and studied the effects of rarified air and hypoxia on humans. He showed how the lung could function as a gas exchanger in the absence of its movement. As curator of the Royal Society for 40 years, he was involved in an enormous number of new findings. His own inventions include the balance spring in a pocket watch, the wheel barometer, and the universal joint. He was a mathematical and engineering genius and formulated the law of elasticity that states that strain is proportional to stress. He was a gifted architect who was heavily involved with rebuilding London after the Great Fire of 1666. His collection of microscopic observations, *Micrographia*, remains a classic. And yet few of us recognize Hooke's name. In his review (6), John West gives this polymath the credit he deserves for his many inventions and ideas.

Blood vessels carry oxygen and nutrients to all organs and tissues in the body. When the vessels do not form or function properly, disruptions that can contribute to a vast array of diseases occur in normal physiology. Thus understanding how the cells of the vasculature communicate with each other is fundamentally important in both health and disease. Formation and function of blood vessels relies on proper communication between the endothelial cells and smooth muscle cells. These interactions dictate how, when, and where blood vessels form and control their physiological responses to manage blood flow. In her review (3), Lilly highlights the pathways by which endothelial cells and smooth muscle cells communicate during blood vessel formation and discusses how disruptions in these pathways contribute to disease. The cells of the vasculature utilize multiple signaling pathways to communicate. They employ secreted molecules to regulate cell recruitment and proliferation, and engage in direct cell-cell contact to control vessel maturation. Understanding how endothelial cells and smooth muscle cells communicate with each other offers unique avenues to regulate blood vessels. Defining the signaling pathways that govern these important cell-cell interactions provides the opportunity to develop therapeutic strategies to cure or alleviate vascular-associated diseases.

Although myoendothelial junctions were described at the anatomical level over 40 years ago, only in the last 5–6 years have we started to elucidate the actual function of these unique anatomical structures, where the endothelium and smooth muscle make contact in resistance arteries. Myoendothelial junctions were originally thought to be simple conduits for information flow through the gap junctions. In their review (5), Straub and colleagues discuss recent insight provided by novel cell culture models that allow probing these polarized areas of endothelial cells with a vast array of proteomic approaches. Now it is known that myoendothelial junctions are much more than simple conduits–they are unique cellular signaling microdomains of endothelial cells that completely compartmentalize and regulate actions from other parts of the endothelial cell, in particular the action of nitric oxide on smooth muscle cells. Nitric oxide is a potent dilatory gas that compartmentalizes to myoendothelial junctions. The recent identification of hemoglobin alpha, a key scavenger of nitric oxide polarized to this unique junction, has exposed a new pharmacological target for diseases such as hypertension. In addition, the myoendothelial junction appears to have endoplasmic reticulum, which is important for calcium regulation at the unique cellular localization. Also, it has recently been shown that mRNA can be stabilized and locally translated in this distinct region. Thus the myoendothelial junction is now viewed as a complicated part of the resistance artery that holds potential as a drug target.

Endothelial dysfunction develops with age and increases the risk of age-associated vascular disorders. Nitric oxide insufficiency, oxidative stress, and chronic low-grade inflammation, induced by upregulation of adverse cellular signaling

processes and imbalances in stress resistance pathways, mediate endothelial dysfunction with aging. In their review (4), Seals and colleagues review the effects of healthy lifestyle behaviors (e.g., diet and exercise) that preserve endothelial function with aging by inhibiting these mechanisms, as well as pharmacological agents, including novel food supplements (nutraceuticals), that favorably modulate these pathways as a complementary approach for preserving endothelial health. Advancing age is the main risk factor for cardiovascular diseases, the leading cause of morbidity, disability, and death in modern societies. As the number of older adults is projected to double over the next few decades, delaying age-associated physiological impairments such as endothelial dysfunction becomes an important goal for biomedical research aimed at preventing disability and disease.

Protein quality control ensures that the panoply of cellular and extracellular proteins is maintained in their functionally and structurally competent conformation. This is a highly demanding task in light of the complexity and chemical instability of polypeptides in a highly hostile environment, the error-prone nature of their biosynthesis, and the unavoidable appearance of mutations. Accumulation of non-functional, potentially toxic plasma membrane proteins might compromise cellular and tissue physiology and eventually lead to cell death. Thus the quality control of plasma membrane proteins serves as a safeguard that can either repair/refold or eliminate defective plasma membrane polypeptides. In their review (1), Apaja and Luckacs provide an overview of emerging aspects of the underlying mechanisms of plasma membrane quality control. The regulation of plasma membrane quality control processes is even more pivotal in non-dividing cells (e.g., neurons) during their long lifespan. Although membrane protein quality control is fairly well mapped in multiple subcellular locations (e.g., ER, Golgi, cytoplasm, mitochondria, and nuclei), interrogation of the plasma membrane quality control is still in its infancy.

The SNARE (Soluble NSF Attachment protein REceptor) complex plays a key role in vesicle fusion, which releases many neurotransmitters and hormones in the body. In their review (2), Fang and Lindau discuss the hypothesis that, in neurosecretory cells, fusion pore formation is directly accomplished by a conformational change in the SNARE complex via movement of the transmembrane domains. Like a motorized door opener, this molecular machine opens a door to tiny storage compartments, the secretory vesicles, allowing release of transmitter molecules and forming a fusion pore between the membrane of a vesicle and the cell's plasma membrane. Similar fusion events mediate intracellular transport and viral infection. Due to the broad significance of fusion for release, intracellular transport, and virus entry, this research has the potential to lay the foundation for improved medical treatments from spasms and neurodegenerative diseases to cancer and infectious diseases. For example, in the treatment of Parkinson's disease, the drug levodopa increases dopamine release by increasing vesicle size, whereas, in BoTox treatment, the rate and speed of transmitter release events is reduced as a result of its affects on SNARE proteins.

Spermatocytes and spermatids are cells in the seminiferous epithelium lacking the cellular apparatus to elicit cell movement. Therefore, they must be "moved" from the base of the seminiferous epithelium to the edge of the tubule lumen for mature sperms to enter the epididymis. Without the timely transport of germ cells across the seminiferous epithelium, infertility results. In their review (7), Xiao and colleagues highlight the molecules that are crucial to regulate germ cell transport and provide a hypothetical model on the transport of development germ cells by somatic cells in the testis called Sertoli cells. Animal studies have provided new insights in *1*) developing potent and reversible male contraceptives, such as using inhibitors that block the function of crucial molecules necessary for germ cell transport (for example FAK, non-receptor protein kinases, phagocytosis); *2*) providing agonists or antagonists to reverse the inability of germ cell transport due to environmental toxicants in infertile men. A better understanding of this largely neglected area of research offers the potential of developing better male contraceptives and treating unexplained male infertility. ■

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