“Anatomy is to physiology as geography is to history; it describes the theatre of events.” This quote is from Jean François Fernel, the 16th-century French physician who introduced the term physiology to describe the study of the body’s function. In emphasizing the close relationship between anatomy and physiology, Fernel followed in the tradition of the ancient 3rd-century BCE Greek physicians Herophilus and Erasistratus, who worked at the Museum of Alexandria. They recognized the importance of structure in the function of the human body and made many discoveries that were lost until the Scientific Renaissance of the 15th and 16th centuries. In our modern reductionist approach to biomedical research, we often forget the lessons learned from Fernel and Herophilus and Erasistratus that by exploring the integral relationship between structure and function, we gain a more thorough understanding of physiology. In the review articles in this issue of Physiology, we explore the insights provided by examining the link between structure and function.

Cell culture models are frequently used to advance our physiological understanding. Although flat, two-dimensional (2D) cell cultures have dominated past biomedical research, recent experiments have shifted toward use of three-dimensional (3D) cell culture models that more closely mimic the structural reality of the cellular microenvironment and thus provide a better underlyng of physiology. In their review (3), Duval et al. discuss the challenges of creating 3D cell culture models that elucidate differences in proliferation, motion, apoptosis, mechanical responses, and extracellular matrix. They provide a critical assessment of the pros and cons of both 3D and 2D cell culture approaches. With further development, 3D cell culture models are likely to provide an increasingly attractive platform for basic physiological research. In the meantime, a thorough understanding of each culture method should help scientists choose the optimal cell culture method for their particular experiment, increasing the likelihood of advancing research in cancer therapeutics, stem cell differentiation, wound healing, regenerative medicine, and many other applications.

The structure/function relationships of our tissues and organs are maintained through a delicate balance of proliferation and differentiation of tissue-resident adult stem cells. By incorporating both local and humoral biological signals, adult stem cells can respond to internal and external changes affecting the tissue in which they reside. Studying the molecular and cellular mechanisms of adult stem cell behavior provides novel insights in how our body maintains organ and tissue function; perturbation of these signals can cause—or contribute to—pathologies such as inflammatory bowel disease and cancer. Due to the harsh luminal environment of the gastrointestinal (GI) tract, tissue-specific adult stem cells are critical to restoring homeostasis by providing a continuous source of regenerated epithelial tissue. In their review (4), Andersson-Rolf and colleagues discuss how adult stem cells govern tissue homeostasis in normal tissue turnover, as well as in the presence of local and chronic damage. By incorporating both local and humoral biological signals, adult stem cells can respond to internal and external changes affecting the tissue in which they reside. They introduce the use of an adult stem cell-based 3D organoid system for applications in drug screening, tissue banking, disease modeling, and potential cell therapy. The recently acquired insights into adult stem cell biology and the consequent development of organoid technology have significantly expanded the experimental possibilities to study human disease and offer hope for the development of novel therapeutic strategies for regenerative medicine.

A wonderfully complex example of structure and function relationships is evidenced by endothelial cells that line the lumen of blood vessels where they mediate homeostatic regulation of vascular smooth muscle tone to affect blood flow to match tissue metabolic demands for nutrients and oxygen. After adolescence, most healthy endothelial cells lie dormant until needed to aid in the repair of wounded tissue by increasing vascularization. Endothelial cell dysfunction results in tissue ischemia and is often seen in aging and age-related ailments such as diabetes, muscle atrophy, and osteoporosis. Clinical efforts at promoting angiogenesis have largely focused on growth factor pathways with mixed results. In their review (5), Sawada and Arany discuss a recently discovered repertoire of endothelial intracellular molecules that are critical to endothelial metabolism and play an important role in regulating angiogenesis. The discovery that endothelial cells are highly glycolytic has revealed glycolysis as a potential therapeutic target affecting angiogenesis. This therapeutic focus could lead to significant advances in the treatment of ischemia in cardiovascular disease and age-related ailments, as well as for diseases characterized by metabolic perturbations, such as impaired glucose tolerance and excess lipid accumulation.

In adult humans, the brain constitutes ~2% of the total body weight but consumes nearly 20% of the total oxygen supply. The oxygen consumed is used by mitochondria to produce ATP through oxidative phosphorylation in a series of cellular processes known collectively as mitochondrial bioenergetics. At the same time, mitochondrial biogenesis takes place on a regular basis in healthy cells to maintain an adequate population of performing mitochondria. In addition to reduced ATP production, dysfunction of bioenergetics can result in increased generation of reactive oxygen species, leading to mitochondrial oxidative stress that in turn retards mitochondrial biogenesis. In their review (2), Chan and Chan specifically explore the role of defective mitochondrial bioenergetics and biogenesis in the pathophysiology of brain oxidative stress-associated hypertension.
generally, they discuss the genetic regulators of key molecules engaged in the multitude of cellular mechanisms that govern mitochondrial bioenergetics and biogenesis. Mitochondrial dysfunction affects overall cellular functions, especially in organs with high-energy demands such as the brain. Further understanding of the pathophysiology of defective mitochondrial bioenergetics and biogenesis could lead to novel therapeutics to treat diseases of high energy-demanding organs, including brain oxidative stress-associated hypertension.

Airway hyperresponsiveness in asthmatic patients is defined as an increased airway constriction in response to a given stimulus level. In addition, constriction of a hyperresponsive airway often persists without displaying the normal dilatory effect of a deep inspiration (DI). Airway constriction depends on the force generated by stimulated airway smooth muscle (ASM), which also reflects a complex signaling cascade. In their review (4), Lutchen and colleagues examine the pathophysiology that underlies airway hyperresponsiveness. They discuss how the contractile apparatus of the ASM depends on its dynamic length history, but in a way that is very difficult to translate directly to the intact airway response. They explore how remodeling of the airway wall can amplify the tendency to overconstrict while simultaneously making it less responsive to a DI via an increase in its stiffness. Furthermore, heterogeneous remodeling among asthmatic airways can serve to further amplify the decrease in whole lung function while making a DI even less effective. Add to this the confounding influence of inflammation and altered mechanical forces in the airway remodeling of asthma. Ultimately, treatment will need to appreciate that the pathophysiology of asthma is an emergent consequence of the ensemble behavior of all the airways and the constituent parts of the wall throughout the lung.

ORAI channels are ubiquitous, calcium-conducting channels that are of critical importance to a large number of physiological functions, including but not limited to immune function, skeletal muscle development, cardiovascular function, bone, sperm, and enamel development, and sweat, tear, and milk production, among others. In their review (6), Trebak and Putney explore these and other crucial roles of ORAI ion channels, which are highlighted by the fact that ORAI1-deficient patients are immunodeficient and suffer from muscle hypotonia, hypohidrosis, and ectodermal dysplasia, and do not survive long without bone marrow transplants. Mutations in ORAI1 or altered expression of these channels underlie a large collection of diseases, including immunodeficiency, autoimmunity, muscular dystrophy, hypertension, vascular remodeling, asthma, cardiac hypertrophy, sterility, and several types of cancers to cite a few. Therefore, research into the mechanisms of ORAI transcriptional and translational control, the molecular makeup of ORAI proteins at the plasma membrane, and their molecular mechanisms of regulation by second messengers and signaling proteins is crucial in understanding human physiology and in the development of therapeutic strategies targeting disease states where ORAI channel disruption is involved.

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References


