Almost 2,500 years ago, Hippocrates stated that “All disease begin in the gut.” Ivan Pavlov, the Russian physiologist and father of modern gastroenterology (GI) research, recognized that “The digestive canal represents a tube passing through the entire organism and communicating with the external world, i.e., as it were the external surface of the body, but turned inwards and thus hidden in the organism” (Nobel Lecture, 1904). His research emphasized the complexity of regulating gut motility and its importance in digestion. However, he also keenly understood that the GI tract communicated with the entire organism and that the GI tract’s interactions with the external world, i.e., as it were the external surface of the body, but turned inwards and thus hidden in the organism, was crucial. His research recognized that “The digestive canal represents a tube passing through the entire organism and communicating with the external world, i.e., as it were the external surface of the body, but turned inwards and thus hidden in the organism” (Nobel Lecture, 1904).

Obesity is a growing epidemic that brings with it many associated complications including cardiovascular disease and Type 2 diabetes mellitus, which place an ever increasing burden on healthcare. Obesity results from a complex interaction of genetic, environmental, cultural, behavioral, and microbial factors. The gut microbiome is a diverse array of microorganisms that colonize our GI tract. In recent years, we have increased our understanding of the delicate symbiosis that exists between the trillions of microbes that reside in the GI tract and humans as hosts. It has been suggested that disruption of this mutual tolerance may play a significant role in modulating host physiology during obesity. In their review (4), Nehra and colleagues explore environmental and lifestyle influences such as diet, exercise, and early life exposures that can significantly impact the composition of the gut microbiome. They emphasize that any resulting microbial imbalance or dysbiosis can lead to increased host adiposity via a number of different mechanisms. For example, it appears that microbiota have the ability to regulate host fat deposition, metabolism, and immune function. Thus characterization of the gut microbiome in health and disease should eventually lead toward early diagnosis, better prognostication, and intentional modulation of the composition of the microbiome in favor of disease prevention. Based on different microbial composition, there is potential for development of specific biomarkers to identify individuals at risk for development of specific disease states. If the passage of insulin out of the circulation contributes to whole-body insulin resistance, enhancement of this process may lead to a novel therapeutic approach for patients with Type 2 diabetes, a disease that afflicts hundreds of millions of people.

Cells in the body are exposed to irregular physiological forces, such as touch, movement, gravity, blood flow, blood pressure, and breathing. For example, blood pressure exerts a physiological force on the vascular wall that displays beat-to-beat variability. Similarly, changes in pressure across the thoracic wall and lungs move air into and out of the lung, with natural physiological variability of mechanical forces. The irregularity of mechanical stimuli significantly influences many basic cell functions, yet studies exploring mechanotransduction (mechanical force-induced cellular processes) invariably investigate only monotonous stretch. In their review (6), Suki and colleagues discuss how fluctuations in mechanical stimuli regulate mechanotransduction, called fluctuation-driven mechanotransduction (FDM). The two main FDM mechanisms are an increase in cellular ATP production as a result of mechanical fluctuations, and structural reorganization of the cytoskeleton with selective activation of signal transduction pathways. These processes have significant implications for human health. Hypertension is accompanied by increased blood pressure variability, an independent risk predictor of cardiovascular morbidity, with...
consequences on vascular smooth muscle contractility. Since FDM also regulates surfactant metabolism in the lung, artificial elimination of breath-to-breath tidal volume variability during mechanical ventilation may directly affect patient care. Finally, everyday physical activity likely generates blood pressure and breathing variabilities that are important for cellular metabolism in health, whereas therapeutic activity during rehabilitation may help restore normal cell function in diseases.

Fluid shear stress, the force that flowing blood exerts on the endothelial cells of vessel walls, is a major determinant of vascular development, physiology, and disease. Shear stresses, which vary in different types of vessels and in different regions of the same vessel, have a major influence on endothelial phenotype. For example, shear stress controls vasodilation vs. vasoconstriction, vessel stabilization vs. remodeling, and arterial vs. venous identity. In their review (2), Gerhold and Schwartz discuss ion channels and their fast kinetics, sensitivity, and modulation by multiple inputs that make them candidates for the detection of shear stress and its signaling integration with other pathways. Understanding how endothelial cells detect shear stresses, how they integrate that information to control cellular responses, and how those responses contribute to blood vessel biology and pathology may lead to the development of new treatments for diseases such as hypertension, atherosclerosis, and vascular malformations.

Recently identified molecular mechanisms for transport and sensing of Cl\(^-\) and HCO\(_3\)^- substantiate the importance of these anions for regulation of vascular wall structure and function. Cl\(^-\) and HCO\(_3\)^- accumulate in vascular smooth muscle and endothelial cells due to secondary active transport mechanisms. Cellular anion uptake contributes to intracellular pH regulation and establishes outwardly directed electrochemical gradients that permit anion conductances to modify membrane potential. Anion transport proteins and intracellular and extracellular sensors for Cl\(^-\) and HCO\(_3\)^- also modify vascular function and structure through control of cell proliferation, protein trafficking, and regulation of gene expression. In their review (1), Boedtkjer et al. discuss the importance of anion transport proteins and intracellular and extracellular sensors for Cl\(^-\) and HCO\(_3\)^-. By influencing arterial contractility and structure, Cl\(^-\) and HCO\(_3\)^- affect blood pressure and local perfusion. Specifically, regulated anion conductances and signals from Cl\(^-\) and HCO\(_3\)^- sensors ensure proper control of vascular tone in response to hormones and neurotransmitters, and contribute to adaptation of vascular tone during disturbed local metabolism and hemodynamics. These mechanisms come into play during disease conditions such as ischemia, hypertension, and cancer but are also prominent during physiological circumstances such as during exercise. Therefore, manipulating Cl\(^-\) and HCO\(_3\)^- transport and sensing in the vascular wall has considerable potential for therapeutic targeting and is especially relevant for patients with cardiovascular disease.

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