Physiology in Perspective: Fulfilling the Promise of Tissue Engineering

Tissue engineering is an area of applied research that is based on principles of both engineering and life sciences. Today, research in tissue engineering is directed toward the eventual development of functional substitutes for biological tissue. While we have made great strides in developing biocompatible materials and applying developmental biology and cell culturing techniques in the biomaterial environment, we are only now beginning to achieve the ultimate functional substitute stage of tissue engineering. In this regard, physiology plays a central and key role, as we learn more about the complexity of cell-cell interactions, particularly in three-dimensional structures. In moving forward in this important area of research, we must solve the puzzle of physiological complexity, and, in this regard, we can learn from past and present discoveries. As Hippocrates proposed, it is important to “Declare the past, diagnose the present, foretell the future.” The future of tissue engineering is very promising but only if founded on central principles of physiology.

Adult cardiovascular disease accounts for 20% of global mortality, and congenital cardiac anomalies are the leading cause of death in the neonatal period. Current management of these conditions is limited by the poor performance of prosthetic implants and paucity of viable tissue for transplant or surgical reconstruction. Tissue engineering has emerged in response to these pressing challenges and seeks to develop constructs that are indistinguishable in form and function from their native counterparts. Successful translation of tissue-engineered blood vessels, valves, and myocardium to the bedside holds the promise of significantly improving patient outcomes by decreasing the complications caused by synthetic materials and reducing the re-operative procedures to which these patients are subjected. In their review (1), Best et al. discuss various challenges in the field of tissue engineering as it progresses toward the holy grail of achieving a tissue-engineered human heart. Among these challenges, we must solve complex signaling processes and develop methods for engineering a successful three-dimensional scaffold and finding the right cells to grow on it. Currently, preclinical research in both small and large animal models seeks to provide an understanding of the molecular, cellular, and physiological mechanisms of cardiovascular neo-tissue development. The marriage of these findings to advancements in biomaterial science, available cell sources, and initial clinical studies should inform the next generation of cardiovascular tissue engineering, with the ultimate goal of producing a fully functional tissue-engineered human heart.

Exosomes are endogenous nanovesicles that have been shown to carry biological information and modulate signaling pathways in target cells. Micro-RNAs (miRNAs) are small noncoding RNAs that regulate gene expression at the posttranscriptional level. Exosomal miRNAs could play a key role in intercellular communication, particularly in cardiovascular diseases. In their review (4), Iaconetti and colleagues address the role of exosomal miRNAs in the development and progression of cardiovascular diseases and their potential application as clinical biomarkers. Understanding how exosomes deliver different types of signal molecules to mediate intercellular communication may lead to applications for stem cell-based therapies and novel biomarkers for the diagnosis and prognosis of heart disease.

In adults, renin is synthesized and released by juxtaglomerular cells in the kidney, and maintains homeostasis by generating angiotensin II, a powerful vasoconstrictor and regulator of sodium reabsorption. Accordingly, during development, the acquisition and maintenance of renin release by juxtaglomerular cells is sufficient to maintain homeostasis under normal circumstances. However, when there is a more profound homeostatic challenge (such as dehydration, hemorrhage, hypoxemia) and more renin is needed to restore balance, additional cells along the kidney vasculature and glomeruli regain the ability to synthesize renin as they did in embryonic life. Yet, chronic persistent stimulation may result in concentric vascular hypertrophy of renal arterioles with severe focal renal hypoxia and fibrosis. In their review (3), Gomez and Lopez discuss the origin, fate, and novel roles of renin cell precursors. For example, renin cells, which are widely distributed throughout the body, regulate kidney development and are at the center of major defense mechanisms linking blood pressure control, fluid-electrolyte homeostasis, immune responses, hematopoiesis, and regeneration. The identification of mechanisms controlling the memory of the renin phenotype should lead to deeper understanding of its role in coordinating multiple homeostatic defense responses and may generate novel target therapies for life-threatening vascular, renal, and hematopoietic diseases such as leukemia.

Neuroendocrine systems regulate many of our most basic human physiological processes. A standard method of neuroendocrine monitoring has been to assay various hormone concentrations in the blood over time. Within these time-varying concentrations is information as to the system’s regulatory feedback and control mechanisms, with the loss of such control often being an early indicator of disease. A fundamental aspect of the time variance of these systems is the pulsatile release of hypothalamic neuropeptides—signaling dynamics that cannot be easily observed. In their review (5), Keenan and Veldhuis discuss five key challenges to understanding how pulsatility arises and is propagated in the patterns of downstream products. Phenomena such as amplification and desensitization, modulation by circadian rhythms, mutual interplay among various neuroendocrine axes, and time-varying pulse shape, pulse size, basal secretion, and, possibly, disappearance kinetics all contribute to inherent biological variation. This level of complexity underscores the need for innovative new biostatistical models that can identify age- or disease-related loss of control in the neuroendocrine system’s regulatory feedback and...
control mechanisms. Resolution of these challenges could lead to therapeutics that target and regain control of hormonal dynamics in systems such as those that govern reproduction, growth, bone mineralization, and physiological and psychological stress.

Torpor is a tightly regulated physiological state during which metabolic rate can be suppressed to 96% below basal metabolic rate. Torpid mammals can drop their body temperature close to ambient temperature and actively rewarm themselves in the absence of an external heat source. Deep torpor (hibernation) averages 15–20 torpor bouts lasting 8 days. Short-term torpor bouts maintain the circadian activity period by averaging 8 h/day and allow the animal to forage. In their review (2), Cubuk et al. discuss torpor regulation in the Siberian hamster, a mammal that uses spontaneous daily torpor to save energy during winter. In the torpid state, mammals are able to survive periods of low respiratory rate, blood flow, and body temperature, and consequent rewarming and reperfusion without any sign of organ damage. Artificial hypothermia is a common therapy to prevent severe damage in humans from trauma and stroke, and during open-heart surgery. The hypothalamus appears to be key in torpor induction, and knowledge derived from molecular and in vivo investigations of the hypothalamus could be used to develop therapeutics that suppress immune and inflammatory responses and prevent bone, muscle, and neuron loss.

Today, nearly all of life’s energy is derived from the sun. However, when life originated, photosynthesis was not yet an innate property. In the prebiotic Earth, hydrogen sulfide (H$_2$S) appears to have played a far greater role in the origin of life and primordial metabolism than previously thought. Remnants of these activities persist in modern animals, not as a primary energy source but as an important regulator or modulator of metabolism and signaling. In their review (6), Olson and Straub discuss the role of H$_2$S throughout evolution and its biochemical production and metabolism in modern-day animals. H$_2$S has many physiological functions: anti-inflammatory; tissue protection from hypoxia and re-oxygenation insults such as heart attacks and stroke; allowing cells to sense oxygen levels; and as a direct source of energy. Synthetic drugs that slowly release H$_2$S are showing considerable potential as anti-inflammatory and anti-cancer agents. Furthering the understanding of the mechanisms by which tissue H$_2$S is regulated or how H$_2$S interacts with physiological control systems may lead to new therapies for a wide variety of diseases.

No conflicts of interest, financial or otherwise, are declared by the author(s).

References