Physiology in Perspective: Why Do We Continue to Ignore Sex Differences?

In 2001, the Institute of Medicine (IOM) of the National Academy of Sciences issued a report in which they highlighted the importance of exploring sex differences in biomedical research and medical practice. The IOM report recognized the obvious biological fact that sex, as defined by the presence of a specific (i.e., male or female) chromosome, is the major fundamental distinguishing feature of life from birth to death. On the other hand, “gender” is an individual’s assigned or perceived sex, and thus gender can also influence biological outcomes. Yet, sex (and gender) differences receive short shrift in basic and clinical research underlying “individualized” or “precision” medicine. Sex biologically defines the individual, whereas gender is an individual’s identity with sex, but we know very little about sex and gender differences across many aspects of physiology and medicine. It is hard to imagine how biomedical research can be precise while ignoring sex and gender differences. Our basic animal studies typically employ males only to obviate the complexity introduced by considering the potential biological impact of the estrous cycle in females. Our studies using cells do not consider the sex of these cells, while, at the same time, we characterize all types of other biological markers in defining cell type. In 2012, the American Physiological Society established a new policy that requires reporting the sex of humans, animals, or cells used in studies published in our journals. In 2014, the National Institutes of Health (NIH) finally enacted new policies to recognize the importance of sex differences in preclinical studies. However, these policies are difficult, if not impossible, to enforce without wide acceptance by the scientific community that sex matters and is biologically important. As Editor-in-Chief, I am embarrassed to say that in the reviews published by Physiology, sex differences are infrequently considered. Indeed, four of the five reviews published in this issue of Physiology did not consider sex differences. This will only change through a more consistent editorial review process and through more widespread recognition of the obvious biological importance of sex differences.

In their review (4), Fink and Klein discuss the implications of sex differences in the outcome of vaccines from a public health perspective. One could argue that the development of vaccines represents the major public health intervention in our fight to prevent, treat, and cure human disease. We now know that vaccine efficacy and adverse reactions are consistently higher in women than in men, but the underlying basis for this sex difference is poorly understood due to the lack of information. There are numerous social and biological differences between the sexes that could contribute to differences in the uptake, responses, and outcomes of vaccines. By considering sex as a variable in vaccine trials, vaccine efficacy and acceptance could be improved, and the socioeconomic burden of infectious diseases, especially in the elderly, could be dramatically reduced.

Adult skeletal muscle is highly vascularized, and numerous studies have explored the link between vessel organization and muscle plasticity, e.g., as occurs following intense exercise. In their review (5), Latroche et al. discuss the role of cells that compose the vessel wall (endothelial cells and periendothelial cells such as pericytes and smooth muscle cells) and explore how these cells, particularly those in the capillaries, establish specific interactions with muscle stem cells that sustain muscle repair. It is becoming increasingly clear that vessels are not just conduits that provide delivery of oxygen and nutrients to skeletal muscle. Vessels also play a significant role in skeletal muscle development and functional regeneration after injury. Therefore, an understanding of the cooperation between the cells comprising vessels and other skeletal muscle cell types may provide novel therapeutic targets to alleviate muscle diseases and improve muscle repair.

We have made important progress in our understanding of glucose signaling pathways involved in energy homeostasis. In particular, discovery of the transcription factor ChREBP (carbohydrate responsive element binding protein) has unraveled a critical molecular link between glucose metabolism and transcriptional reprogramming induced by glucose. In their review (2), Baraille and colleagues discuss the role of ChREBP in glucose signaling pathways in liver cells and in other key cells involved in energy homeostasis. Disruption of ChREBP-mediated glucose signaling may underlie the pathophysiology of obesity and metabolic syndrome. Furthermore, emerging evidence suggests that ChREBP could also play a role in diseases associated with abnormalities in cellular proliferation, including cancer. Thus a better understanding of intracellular glucose sensing through ChREBP will likely uncover new therapeutic opportunities, and not just for metabolic diseases such as obesity and Type 2 diabetes.

Plasma membrane repair involves active resealing of membrane disruptions to maintain cellular homeostasis and prevent cell death. In their review (3), Blazek et al. summarize the available literature concerning the roles played by several proteins known to contribute to the membrane repair process and blunt progression of multiple diseases associated with mechanical or chemical disruptions of cell integrity. Cell membrane repair repurposes proteins involved in various cellular functions, including vesicle trafficking, exocytosis, and endocytosis. Disruptions in plasma membrane repair contribute to pathophysiology in a number of different tissues and are linked to muscular dystrophy, heart failure, neurodegeneration, and other diseases that impact normal human physiology and functioning. Although it is likely that no single mechanism is at work under all injury conditions, a better understanding of the mechanisms responsible for membrane repair and the proteins involved is essential for the development of improved therapies.
Chronic musculoskeletal pain is debilitating and affects ~20% of the adult population across the globe, representing one of the leading causes for physician consultations. Tissue acidosis is a common feature present in various painful musculoskeletal conditions, including rheumatoid arthritis, myofascial pain, muscle fatigue, inflammation, and ischemia. Acid-sensing ion channels (ASICs) are widely distributed in the musculoskeletal system, being located on skeletal muscle and joint nociceptors as well as nonneuronal cells in the muscles and joints. ASICs are proton-gated sodium channels that are activated by fluctuations in extracellular pH and are implicated in the transmission of peripheral nociceptive signals from skeletal muscles to the spinal cord. In their review (1), Abdelhamid and Sluka discuss the properties of the different types of ASICs, the manner by which they are activated, the factors affecting their pH sensitivity, and their role in musculoskeletal hyperalgesia. Understanding the properties of ASICs and the role they play in musculoskeletal pain may facilitate the discovery of new, more effective pharmacological targets for the treatment of chronic pain.

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

References