Our lifespan is filled with physiological transitions that are too often ignored in our physiological and pathophysiological studies. In this issue of Physiology, we emphasize the importance of sex differences in the incidence and progression of disease. An important physiological transition that often unMASKs physiological sex differences is menopause and the removal of ovarian steroid influences. Yet menopause in humans is not abrupt and includes a progressive perimenopause transition into postmenopause. The first review in this issue of Physiology explores the use of a rodent model that includes a gradual perimenopause transition, similar to humans. Two examples of physiological transitions that I am personally experiencing are the impact of weight gain and advancing age, which affects almost every aspect of physiological performance. Weight gain and the progression toward obesity reflects transitions in cellular processes, among them autophagy, which is the normal degradation and repair process within cells. The link between obesity and other physiological dysfunctions, such as cardiovascular disease, may be related to the progressive dysregulation of autophagy-related genes. It is also possible that the progression toward obesity is associated with changes in our gut microbiota, with the production of lipopolysaccharide (LPS) and short-chain fatty acids (SCFA) by intestinal bacteria. As we age, a number of factors may increase the incidence of cellular damage, overwhelming the normal regenerative capacity of our cells. ExtrinsIC proteotoxicity is a prolonged pathophysiological process involving misfolded proteins that are released by one cell that exerts toxic effects on neighboring and remote cells. Proteotoxicity may underlie a number of chronic diseases, most notably neurodegenerative (Alzheimer’s, Parkinson’s disease), diabetic (hyperamylinemia), and cardiovascular (amyloid cardiomyopathy). These are all examples of the importance of integrative physiology at the cellular and molecular level. With the dramatic increase in our knowledge of basic cellular and molecular processes underlying regeneration and repair, this is an exciting time to be a physiologist piecing together the puzzle of human physiology.

The majority of women experience menopause over 5-10 years, with gradual reduction of ovarian function (perimenopause). Rodent models of menopause are based on the surgical removal of ovaries (ovariectomy), which has an immediate effect that negates the common perimenopausal transition. In their review (2), Brooks et al. discuss the use of a 4-vinlycyclohexene diepoxide (VCD) mouse model, which, by inducing gradual ovarian failure, preserves both the perimenopausal transition and the androgen-secreting capacity of residual ovarian tissue. Menopause has been associated with a variety of health risks in women, including cardiovascular disease, metabolic syndrome, osteoporosis, Alzheimer’s disease, and ovarian cancer. Studies have found that the risk factors for postmenopausal diseases begin during perimenopause. As life expectancy increases, the average woman could live 30% of her life in a postmenopausal state, making VCD-induced ovarian failure a valuable approach for menopause-related studies. For example, the model demonstrated that, while females are protected from angiotensin II-induced hypertension, obesity, and diabetes during perimenopause, disease onset accelerates after menopause.

Aromatase (estrogen synthetase) is known to supply steroidal selective estrogen receptor modulators (SERMs) to biological systems throughout the body. Since estrogen receptor-expressing cells are widespread, the effects of aromatase are not limited to the reproductive system and may have a variety of effects on the body’s biological systems. In their review (1), Blakemore and Naftolin discuss the implications and outcomes of aromatase action in health and disease. Topics include the role of aromatase in steroidogenesis as well as the potential leveraging of molecular potency by demethylation of androgens. The effect of functional mutations and the current clinical roles and effects of aromatase inhibitors are also discussed. A greater understanding of aromatase biology, including the mechanisms that block its actions, should lead to more effective treatments for a variety of conditions.

Autophagy is a normal, fundamental, house-keeping cellular process whereby the cell eliminates and recycles damaged or unneeded organelles and proteins to maintain homeostasis. Autophagy dysregulation is tied to the pathogenesis of a growing number of human diseases. The complex mechanisms that execute autophagy consist of several dozen autophagy-related genes (ATGs). In their review (4), Maixner et al., examine the unique case of dysregulation of ATGs in adipose tissue that occurs in obesity, particularly in obese subphenotypes characterized by increased cardiometabolic risk. In these individuals, ATGs are upregulated, and it is suggested that overactivated autophagy may constitute a signature of disease-promoting adipose tissue in obesity. Yet, the molecular mechanisms responsible are largely unknown. This research is important because it highlights novel mechanisms for the chronic dysregulation of autophagy in adipose tissue in obesity. Identification of molecular signatures of adipose tissue that contribute to obesity-related diseases may lead to better personalized care. Moreover, this research may help to unravel putative autophagy-regulating mechanisms in chronic disease and demonstrate how upregulated autophagy (and not only inhibition of the process) may contribute to pathogenesis.

Obesity and insulin resistance are the major predisposing factors to comorbidities, such as Type 2 diabetes, nonalcoholic fatty liver disease, cardiovascular and neurodegenerative diseases, and several types of cancer. Studies have shown that lean and overweight rodents and humans may present differences in the composition of their intestinal flora. In their review (5), Saad and colleagues look at the molecular connections between...
obesity and insulin resistance through mechanisms that are both independent and dependent on gut microbiota. These connections involve LPS and SCFA. The LPS from intestinal bacteria can induce a chronic subclinical inflammatory process and contribute to obesity, leading to insulin resistance through activation of the toll-like receptor 4 (TLR4). The reduction in circulating SCFA may also have an essential role in reduced insulin sensitivity of obesity. Understanding the physiological process of the development of obesity and insulin resistance, and their relationship to gut microbiota may lead to more effective treatment strategies for obesity/insulin resistance and its comorbidities by modulating the gut microbiota.

Extrinsic proteotoxicity occurs when misfolded proteins released by one cell exert a toxic effect on other local or distant cells, resulting in cellular dysfunction and/or death. Proteotoxicity has been implicated in many disease states such as Alzheimer’s disease, Parkinson’s disease, diabetic hyperamylinemia, and systemic amyloidosis. In their review (6), Sapp et al. discuss the current understanding of mechanisms underlying proteotoxicity and its contribution to the pathogenesis of amyloid cardiomyopathy. Amyloidogenic diseases serve as a model for understanding the impact of extrinsic proteotoxicity on the heart. Early forays into this area of science and biomedicine have altered our understanding of the pathobiology underlying amyloidoses and shed important biological insight into proteotoxic mechanisms. Future work will increase our knowledge of fundamental biology as well as uncover new diagnostic and therapeutic strategies for neurodegenerative, heart, and aging-related diseases.

The long-accepted cross-bridge and sliding filament models of muscle contraction and force production cannot fully explain the way muscles contract. In addition to the contractile filaments, actin and myosin, a third filament, titin, changes its stiffness and force by binding calcium at specific sites, and by attaching to actin upon muscle activation and force production. In their review (3), Herzog and colleagues discuss the contribution of titin in force production and muscle contraction via the actin-myosin-based sliding filament/cross-bridge model. A better understanding of how muscles contract stands to further optimize muscle performance in sport and leisure activities. The titin mechanism of muscle contraction also provides stability to the sarcomeres (basic contractile units of muscle) and prevents injuries associated with eccentric (lengthening) contractions. Understanding the molecular details of muscle contraction may improve our approach to muscle injury and disease.

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References