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# Sexual dimorphisms in redox biology

Sex differences have been reported for all major diseases, including cardiovascular diseases [1,2] and cardiometabolic disorders [3], hypertension [4,5], obesity [6], diabetes and diabetic complications [7], neurodegenerative disorders [8,9], autoimmune diseases [10,11] and cancers [12]. They can arise from developmental processes, from reversible effects of gonadal hormones and from expression differences of genes located on sex chromosomes. However, the molecular mechanisms driving these sex differences are incompletely understood.

As we live in an oxygen-rich environment, all biological processes involved in human health and disease are either directly or indirectly under the control of redox-regulated mechanisms. In fact, it is has been proposed that this critical redox interface between an organism and its environment is what allows the genome to adapt to environmental resources and challenges during the course of life and thus controls (healthy) aging [13]. It is therefore not surprising that generators of ROS, RNS and RSS, antioxidants, mitochondria and bioenergetics as well as redox regulation and signaling are emerging as critical drivers of sex differences. The purpose of this series is to review our current knowledge and recent advances in sexual dimorphism in redox biology, to identify knowledge gaps in this field, and, perhaps more importantly, to provide new perspectives in our understanding of sex differences in human health and disease.

Our series of reviews opens with two articles looking at the effects gonadal hormones on cellular and tissue redox homeostasis. Cruz-Topetye and colleagues review pro- and antioxidant effects of testosterone signaling in the heart and discuss the potential for a combined antioxidant/testosterone replacement therapy to protect the aging heart [14]. Next, Dr. Klinge provides a comprehensive overview on the molecular mechanisms by which estrogens regulate mitochondrial morphology, metabolism and function, including bioenergetics, oxygen consumption rates and extracellular acidification [15]. The third review by Drs. Wang, Ahn and Asmis addresses sexual dimorphism in glutathione metabolism and glutathione-dependent responses and explores how these differences contribute to the sex-dependent development of human pathologies and diseases [16]. This article is followed by an in depth review by Tower et al. of sex differences in diseases that involve oxidative and proteolytic stress and the authors explore why female cells are generally more resistant to heat and oxidative stress [17].

Further, the role of sex hormones in regulating redox state and mitochondrial function in the brain is reviewed by Torrens-Mas et al. [18]. The authors focus on the role of sex hormones in the aging brain and their roles in the onset and progression of neurodegenerative diseases and other brain pathologies. This article is followed by an in-depth review by Mitchell et al. of sex differences in redox signaling in the kidney which highlights sexual dimorphism in redox signaling in renal disorders, including acute kidney injury, diabetic nephropathy, kidney stone disease and salt-sensitive hypertension [19]. Next, sex differences in the redox biology of autoimmune diseases are reviewed by Di Florio and colleagues, with a special focus on the male-dominated autoimmune disorder myocarditis [20]. The series concludes with an overview by Drs. Casin and Kohr on our current state of knowledge on sex differences in cardiac redox biology with a special focus on the regulation of nitric oxide and aldehyde signaling [21]. The authors advocate for a revised approach to research into sex differences in cardiovascular diseases.

We know all the contributors made every effort to provide the reader with state-of-the-art information and we hope their contributions will stimulate new ideas and discoveries. In closing, we would like to thank all the authors for their valuable contributions.

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Reto Asmis*
*Department of Internal Medicine, Wake Forest School of Medicine, USA*
*E-mail address:* rasmis@wakehealth.edu.

Samantha Giordano-Mooga
*Department of Clinical and Diagnostic Sciences, School of Health Professions, University of Alabama at Birmingham, USA*

* Corresponding author. Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, USA.