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Redox Biology in Physiology and Disease

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Editorials

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The perception of reactive oxygen species (ROS) and free radicals as damaging and toxic byproducts of cellular function has undergone a rapid evolution in the last few decades, which has given rise to the era of redox biology. As new research emerges demonstrating the vital importance of these molecules to normal physiological processes, the concept of ROS acting in a purely detrimental nature is now antiquated. However, this new functional awareness does not mean these reactive species are harmless. To the contrary, dysregulation of the tight control of these volatile messengers may lead to irreversible cellular damage and pathology, which defines true oxidative stress. Yet, the line between physiological redox signaling and oxidative stress remains blurred, and a dearth of literature exists that attempts to firmly delineate these two biological phenomena. In this special issue entitled "Redox Biology in Physiology and Disease," we highlight the work from 11 different research groups investigating the role of redox biology in normal and pathological states. In addition to their contributions to this special issue, these investigators all participated in the inaugural research symposium entitled "Redox Biology in Physiology and Disease" held at the 2018 Experimental Biology Meeting in San Diego, California that was jointly sponsored by the Society for Redox Biology and Medicine (SfRBM) and the American Physiological Society (APS), and is planned to be held at future meetings on a biennial basis.

Given that redox biology is pervasive across virtually all cell types and biological systems, the research in this special issue covers many diverse topics such as inflammation, cardiovascular disease, renal function, airway disease, cancer, muscle biology, and neuroscience. For example, Dr. Adam Case and colleagues provided an original research manuscript examining the effects of uncontrolled mitochondrial superoxide ($O_2^{\bullet-}$) on normal T-lymphocyte physiology [1]. Using conditional and inducible manganese superoxide dismutase (MnSOD) knockout mice, they demonstrated that an increase in steady-state mitochondrial $O_2^{\bullet-}$ produced significant alterations in cellular metabolism, which ultimately affected T-lymphocyte activation and function. Moreover, they provide evidence that increased mitochondrial $O_2^{\bullet-}$ may also be disrupting nuclear epigenetic control via an alteration in cellular metabolite pools. This tight link between redox biology, metabolism, and genetic control illustrates the vital interconnections of biological systems, and reemphasizes the importance of moving the field to more systems based approaches when examining these pathways. In another original research manuscript examining the immune system, Dr. Gábor Csányi's laboratory outlines the role of the neurofibromatosis type 1 (NF1) gene in macrophage function [2]. They show that the loss of NF1 in macrophages led to increased NADPH oxidase 2 (NOX2) activity, which caused an increase in exosome uptake by micropinocytosis. This enhanced exosome absorption increased the pro-inflammatory phenotype of the macrophages, which may have significant relevance to patients with NF1 mutations who have a high risk of inflammatory conditions like cardiovascular disease.

Cardiovascular disease is the number one cause of death worldwide. While clinical trials using nonspecific antioxidants have not been successful in the amelioration of this disease, the appreciation and understanding of redox signaling, as opposed to oxidative stress, in the cardiovascular system has grown exponentially over the past decade, which gives hope for the potential of new redox-based therapeutic strategies for this immense public health concern. This special issue presents four excellent contributions in the area of redox biology in cardiovascular physiology and disease. First, Dr. Matthew Zimmerman and colleagues provide a mechanistic investigation into the redox signaling involved in neurogenic hypertension [3]. In this manuscript, they show that the pro-hypertensive peptide angiotensin II is able to initiate an intracellular signaling cascade in neurons via specific oxidation of the enzyme calcium/calmodulin-dependent protein kinase II alpha (CamKIIα). By using site-directed mutagenesis of CamKIIα, they elegantly demonstrate the necessity of redox signaling through this enzyme to potentiate angiotensin II-mediated hypertension. Another contribution examining redox signaling in cardiovascular disease is from Dr. Rajasekaran Soorappan, who provided an investigation into the role of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling during cardiac remodeling [4]. Using a mouse model of Nrf2 overexpression combined with isoproterenol-induced cardiac stress, the authors demonstrate significant protection from cardiac remodeling as a result of enhanced antioxidant signaling through Nrf2. The authors identify a possible new mechanism of Nrf2 contributing to this reduction in pro-oxidant stress, which suggests the potential for new therapeutic approaches for cardiac remodeling in regards to Nrf2 activation. In another manuscript examining cardiac remodeling, Dr. Shinn-Zong Lin and colleagues utilize adipose-derived stem cells in attempts to attenuate pathology to the heart during hypertension [5]. They demonstrate that stem cells pretreated with the antioxidant-promoting compound n-butylidenephthalide demonstrated better engraftment and decreased inflammation in the hearts of spontaneously hypertensive rats, which overall attenuated the hypertension-induced cardiac pathology. Last, moving away from the heart, Dr. Paul O'Connor provides an excellent examination into the mitochondrial redox environment in the kidney [6]. By exhaustively examining the role of voltage-gated hydrogen channel 1 (Hv1) using novel Hv1 knock-out rats, the authors report the new observation of Hv1 translocation to the mitochondria and modulation of the redox environment through complex I. Considering the important role of the kidney in numerous cardiovascular diseases, this study provides a potential new redox-modulating therapeutic target for future investigations. Together, these manuscripts offer a diverse view into the various research areas of redox biology in the cardiovascular system.

In other areas of physiology and disease, this special issue provides

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works relevant to pulmonary diseases, cancer, muscle physiology, and neurobiology. First, Drs. Joseph Sisson and Michael Price provide an excellent review article summarizing the redox regulation of cilia as it pertains to normal and pathological lung function [7]. They discuss the importance of redox balance in the maintenance of ciliary function, and examine how smoking, alcohol, and pulmonary diseases upset this balance leading to dysfunction. Next, two outstanding review articles are provided discussing redox modulation as a potential therapeutic target in cancer. Dr. Arnold Stern and colleagues provide the first of these reviews where he offers evidence as to the importance of nitric oxide and hydrogen sulfide signaling in various malignancies [8]. They propose that the use of nitric oxide and hydrogen sulfide donors that produce supraphysiological concentrations of these molecules may be effective strategies in the war on cancer. In the other review by Dr. Shazib Pervaiz, the role of protein phosphatase 2A (PP2A) is discussed with relevance to cancer [9]. The authors provide a convincing argument that redox regulation of PP2A is vital in various malignant states, thus suggesting implications for PP2A targeting in therapeutic management of cancer. Switching to muscle physiology, Dr. Jonathan Fisher and colleagues provide an original research manuscript elucidating a novel glucose-sensing mechanism of muscle cells [10]. The authors show that elevated extracellular glucose levels altered both the intracellular and extracellular redox environments leading to altered glucose uptake and metabolic states, which appeared to be dependent upon NOX activation. This work may have broad reaching implications ranging from normal muscle physiology to diabetes. Last, Dr. Jay Dean offers a wonderful review examining the neurological effects of hyperbaric oxygen [11]. Hyperbaric oxygen therapy is a double-edged sword as while it provides many beneficial effects for specific pathological conditions, it also may create unique pathology due to overt oxygen toxicity. This review provides an overview of hyperbaric oxygen and central nervous system function, and provides significant clinical relevance in regards to military personnel regularly performing deep sea missions.

In summary, this special issue devoted to redox biology in both physiological and pathophysiological conditions covers an array of topics. Yet, these 11 manuscripts only scratch the surface in regards to the universal nature of redox chemistry in the biology of life. A significant amount of work is still needed to delineate the normal and pathological roles of redox species, but this will not be successful in a vacuum. In order to make real progress in developing novel redox-based therapeutics for the improved treatment of human disease, investigations must focus more on modulating redox signaling and less on decreasing levels of oxidative stress biomarkers. It is the purpose of this special issue as well as the biennial Experimental Biology symposium to showcase the importance of cross-discipline research to advance the knowledge of redox biology. By bridging the divide between various fields of research, we hope to provide novel information regarding the crucial difference between redox biology and oxidative stress in the pathogenesis of human disease. In doing so, we speculate future investigations will continue to unveil how redox biology shapes life and how it may be targeted to minimize pathology.

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