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Editorial overview: Redox regulation of health and disease

Sruti Shiva and Miriam Cortese-Krott

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Sruti Shiva

Dr Sruti Shiva is an Associate Professor in the Department of Pharmacology and Chemical Biology and Principal Investigator in the Vascular Medicine Institute at the University of Pittsburgh. She is also Director of the Center for Metabolism and Mitochondrial Medicine. Dr Shiva's research focuses broadly on understanding the interactions between reactive oxygen/nitrogen species and mitochondria, and elucidating the mechanisms by which these interactions propagate signaling in cardiovascular health.

Miriam Cortese-Krott

Miriam Cortese-Krott is an Associate Professor at the University of Düsseldorf and Vice-Chair-Elect of the Nitric Oxide-Gordon-Research-Conference. She graduated (Laurea) with honors in Pharmaceutical Biotechnology at the University of Milan and obtained a PhD with honors in Pharmacology at the University of Düsseldorf. She won the Edens-Preis-2017 for scientific excellence.

Oxidation-reduction (Redox) reactions, broadly defined as reactions in which electrons are transferred between two species, encompass a wide spectrum of processes ranging from mitochondrial electron transfer for oxidative phosphorylation to post-translational modification of proteins and lipids by reactive oxygen (ROS), nitrogen (RNS), and sulfur (RSS) species. Though redox signaling is traditionally viewed as less specific in nature than classical receptor-ligand signaling, emerging technology has made it possible to elucidate molecular targets of redox modulators and define the characteristics that provide specificity in a physiological milieu. Thus, we can now more precisely define redox signaling mechanisms and determine their contribution to both tissue homeostasis and response as well as to disease pathogenesis. This review series aims to provide an overview of the major concepts and pathways of redox regulation that maintain health and propagate disease across different organ systems.

To gain a comprehensive understanding of the evolution, present state of the redox field, we encourage you to read Santolini *et al.*'s article entitled 'Redox Architecture of Physiology'. The authors take a systems biology approach to provide a conceptual framework of how processes from a subcellular level to higher physiological level are integrated for an organism to sense, adapt/respond to its surroundings. The review provides an insight into how redox reactions form the basis of life, carries this explanation through the evolution of the redox biology field to the modern day understanding of the reactions of ROS, RNS, RSS, their interplay with antioxidants, redox buffers. The review by Jacobson and Hannibal continues along this overview, discusses compartmentalization, speciation, concentration – central considerations for the understanding of redox biology – before focusing in on redox signaling in the mitochondrion, which contributes to systemic metabolism. The review then provides strong examples of how inborn errors of metabolism can utilized be as models to understand redox regulation (and the consequences of dysregulation) of metabolism.

An emerging theme in this series is that redox reactions and modulators are interconnected and essential for homeostatic cellular responses. Jennings *et al.* demonstrate this point in the context of inflammation. The review shows clearly how the production, reactions, and degradation of reactive species from different sources form an interactive network. Further, functionality of inflammatory cells is regulated by the spacio-temporal modulation of this network. For example, the crosstalk between nitric oxide (NO) production versus ROS production from mitochondria and NADPH oxidase regulates macrophage polarity and plasticity. Jennings *et al.* note that these processes are potentially further modulated by hydrogen sulfide (H_2S) which can regulate NO production from iNOS and antioxidant responses through NRF-2.

Motohashi and Akaike focus on H_2S and expand on its signaling role through KEAP-1/NRF-2 in their review ' Sulfur utilizing cytoprotection and energy metabolism'. Although H_2S has long been known to be generated endogenously and effect the function of a number of enzymes, only recently has its exact signaling properties and its ability to mediate physiological and therapeutic responses started to be elucidated. The review gives a concise overview of what is known about sulfur utilization and production of H_2S and persulfides, a new class of endogenously produced cytoprotective species, and discusses the emerging role of these species in aging, cytoprotection, and metabolism.

In our (Cortese-Krott and Shiva) review on the interactions between red blood cells and platelets, we expand the theme that redox regulators are interconnected to the concept of redox interactions between different cell types. This article provides an overview of ROS and NO signaling within the red blood cell and platelet, focusing on the role of endogenously produced NO, redox reactions of the heme moiety and thiol signaling in red blood cells to mediate physiological activation and aggregation in the platelet. Moreover, the article describes healthy interactions between the two cell types in physiology and discusses the pathological implications for red blood cell-platelet signaling when redox homeostasis in either cell is disrupted. Sickle cell disease (SCD) is a prominent example of a disease in which aberrant red blood cell redox control is central to pathology of the disease. Nolfi-Donegan *et al.* review the molecular events that are initiated by red blood cell hemolysis and lead to a pro-oxidant environment. The discuss antioxidant defenses, such as hemeoxygenase-1 and NRF-2 that may attenuate the oxidative environment and review current trial in antioxidant therapy for SCD.

Like in blood and inflammatory cells, solid tissues also rely on redox reactions to maintain homeostasis. Daneva *et al.* detail the mechanisms by which reactive species modulate endothelial and smooth muscle cell function in the pulmonary vasculature. They define sources of ROS in both cell types as well as molecular targets of these species. Dysregulation of these pathways contributes to oxidative stress and pathogenesis of disease such as pulmonary hypertension. Similarly, Milanese *et al.* review redox regulation in the brain. Specifically, they outline the evidence that low levels of oxidation are protective in the neurons of the substantia nigra. Interestingly, this oxidation is distinct from and in lower levels than the oxidation that is associated in these same neurons with the pathogenesis of Parkinson's disease.

The metabolic syndrome is a multi-factorial syndrome composed of disorders in a number of different organs. The review by Yeo and Lai focuses on skeletal muscle insulin resistance and non-alcoholic fatty liver disease—two characteristics of metabolic syndrome. They demonstrate that dysregulation of redox signaling, predominantly upregulation of pro-oxidant enzymes, mitochondrial dysfunction, endoplasmic reticulum, and altered iron metabolism play a central role in both skeletal muscle and liver dysfunction.

Perhaps the most studied redox signaling pathways are those mediated by NO. While the canonical NO signaling pathway involves activation of soluble guanylate cyclase to generate cGMP as a second messenger, it is now recognized that NO can mediate a number of other pathways depending on its concentration and localization. Aberrant production of high concentrations of NO are particularly relevant in cancer. Glynn reviews both the pro-tumorigenic and anti-tumorigenic signaling actions of NO. Specifically, the review provides a comprehensive summary of NO-dependent signaling pathways that lead to increased metastasis, tumor angiogenesis and proliferation. Additionally, the emerging role of NO in modulating cancer stem cells and the immunosuppressive effect of myeloid derived suppressor and stromal cells is reviewed. This is complemented by Palczewiski *et al.*'s review outlining a new paradigm of NO-dependent signaling. This review outlines the literature demonstrating that NO is a novel epigenetic regulator that mediates post-translational modification of histones. Mechanistically, these modifications are mediated through reactions of NO with cellular iron as well as *S*-nitrosation of cysteine residues on chromatin modifying enzymes. The implications and relevance of this pathway for cancer pathogenesis is discussed.

Beyond direct signaling, it is now known that metabolites of NO and nitrite can mediate the modification of fatty acids non-enzymatically, generating lipid signaling molecules called nitro-fatty acids. Khoo and Schopfer provide an overview of the mechanisms by which nitrolipids are formed, mediate signaling and are metabolized in their review entitled 'Nitrated fatty acid: from diet to disease'. These species, ubiquitous in the body, have electrophilic character and mediate anti-inflammatory signaling, potentially through the activation of NRF-2 and NFkB. Khoo and Schopfer discuss the protective effects of this class of signaling molecules in the context of organ fibrosis.

Collectively, the reviews in this series demonstrate the diverse mechanisms by which redox regulation of cellular processes contribute to the physiology and pathogenesis of disease in multiple organ systems. We would like to thank all the authors and reviewers who contributed to this series and acknowledge the valuable assistance of Editorial Manager Stacy King. We are sure that this compendium will serve as a solid reference and hope that it has increased enthusiasm for the mainstream study of redox biology and physiology.