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Editorials

Redox Signaling and Cardiovascular Disease: New Paradigms and discoveries

Discoveries of Nobel laureate Prof Albert Szent-Györgyi regarding vitamin C and catalysis of fumaric acid are perhaps some of the earliest foundations of redox signaling providing a clue to its critical role in biochemical and physiological processes. While his quote "Life is nothing but an electron looking for a place to rest" in 1937 may seem elegantly simplistic, the current truth of this statement is that it is incredibly complex. In this special issue entitled 'Redox Signaling and Cardiovascular Disease', compelling reviews of fundamental redox principles are discussed alongside new discoveries into redox regulation of tissue pathophysiology, molecular and cellular redox responses, and redox chemical biology reactions.

Overarching reviews regarding redox principals in cardiovascular disease elegantly integrate important concepts from mitochondrial function, cardiovascular thiol redox regulation, and aging associated atherosclerosis mechanisms. The graphical review by Nolfi-Donegan et al. vividly illustrates essential mitochondrial functions and redox principles along with important new considerations regarding translational bioenergetic profiles in the clinic that may be useful for delineating health versus disease [1]. The review by Rashdan et al. provides a detailed discussion regarding the importance of glutathione and its metabolism during cardiovascular disease with expanded consideration of post-translational S-glutathionylation of protein thiols regulating physiological versus pathological signaling responses [2]. Lastly, the review by Dominic et al. intricately discusses implications of disturbed flow premature aging versus replicative senescence in development of atherosclerosis with an understanding of how NAD^+ deficiency mediated mitochondrial ROS generation leads to DNA damage response activation [3]. Together, these reviews integrate previously established findings with new concepts and discoveries that provide the most up-to-date understanding of these research areas.

Redox dependent signaling is known to critically regulate cardiovascular pathophysiology and remains a highly investigated and cited research area across many fields. Several new discoveries are reported in this special issue that impact multiple facets of cardiac and vascular functions in a range of organ systems. The report by Zeng and colleagues reveals a unique role of NOX1 and NOX4 in governing NLRP3 inflammasome-mediated pyroptosis during experimental non-ischemic dilated cardiomyopathy [4]. Next, Saaoud et al. report that tristetraprolin (TTP), an mRNA binding and decaying protein, increases bone marrow derived macrophage mitochondrial ROS production influencing serum VLDL/LDL levels leading to inflammation and hepatic steatosis independent of atherosclerosis. This finding begins to unravel the metabolic complexities from high fat diet mediated atherosclerosis versus fatty liver disease [5]. The study by Zhang et al. supports a proposed novel multiple-hit model of disease progression for end stage renal disease (ESRD) versus chronic kidney disease (CKD) [6]. Interestingly, the authors find differential involvement of ROS-mediated proinflammatory secretomes of peripheral blood mononuclear cells. The next report by Shang and colleagues demonstrates a unique role of CircRNA_0001449 in modulating cerebral ischemia phosphatidylinositol homeostasis and AKT activity involving lipid membrane regulator Osbpl5 translation that impacts cellular antioxidant defense and cell survival [7]. This innovative study links plasma membrane regulation and AKT activation with circRNA sponge activity against miR-124–3p and miR-32–5p controlling Osbpl5 translation. Mitochondrial morphological changes are also equally important in cerebral ischemia-reperfusion as Lai et al. show that long optic atrophy-1 (L-OPA1) is important in restoring mitochondrial cristae and length during cerebral ischemia-reperfusion resulting in reduced mitochondrial bioenergetic defects, oxidative stress, and reduced apoptosis suggesting L-OPA1 could be a unique therapeutic target for stroke [8].

Vascular endothelial cells represent the first line of defense in regulating numerous pathophysiological processes in cardiovascular disease such as inflammation, vasodilation, and cell survival [9]. The report by McDonald and colleagues determines that hydrogen peroxide generated by Endoplasmic Reticulum Oxidoreductase 1α (ERO1α) modulates N-glycan modification of the cell adhesion molecule ICAM-1 that in turn differentially regulates leukocyte recruitment [10]. These findings show that mere upregulation of cell adhesion molecule expression is not fully responsible for increased leukocyte adhesion and inflammation during cytokine stimulation. The next study by Cheriyan and Alfaidi et al. provides insight into a novel regulatory pathway for eNOS function and activation [11]. The authors report that neurogranin (Ng) that typically regulates Ca^{+2}-calmodulin (CaM) signaling in the brain also modulates Ca^{+2} dependent calcineurin (CaN) activity in endothelial cells that suppresses Ca^{+2} independent AKT-dependent eNOS signaling and NO bioavailability. The report from Kopacz and colleagues reveals an important role for Keap1 in regulating age mediated protein aggregation in endothelial cells [12]. Specifically, the Keap1:Nrf2 protein ratio and Keap1 mediated protein S-nitroso thiol (SNO) formation influence Nrf2 transcriptional activity governing proteostasis. Lastly, the study by Liu et al. reveals a novel role of globular C1q/TNF-Related Protein 5 (gCTRP5) in modulating endothelial NOX-1 expression regulating endothelial apoptosis during diabetes [13]. These findings suggest that gCTRP5 might be a unique molecular target for attenuating redox dependent endothelial injury and death during diabetes.

It is well understood that redox signaling ultimate involves specific chemical alterations of small molecules. Rounding out the compendium of new research on cardiovascular redox signaling are a series of studies

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revealing important new redox molecular interactions that control key cellular functions necessary for health and disease. The study by Pardue et al. reveals hydrogen sulfide and its metabolites can uniquely switch xanthine oxidase to its reductase function converting nitrite (NO_2^-) to nitric oxide ($NO^\bullet$) while decreasing uric acid formation [14]. This unique H_2S molecular switch is active in vivo mediating both ischemic vasodilation responses and vascular remodeling. Work from Dei Zotti and colleagues show how erythrocyte ROS formation and metabolism modulate nitrosylated hemoglobin (HbNO) levels in that HbNO levels could be preserved by inhibition of NOX-1 or NOX-2 activity or by exogenous catalase treatment [15]. These findings may support HbNO as a unique marker of vascular oxidant stress or NO bioavailability. The study from Cap et al. uncovers a unique relationship of different amyloid-β concentrations on tau phosphorylation and ATP citrate lyase activation [16]. These results identify that p-Tyr42 Rho positively modulated NAD kinase (NADK) expression along with high superoxide production and reduced tau Ser422 phosphorylation. Lastly, Ma and colleagues show that peroxide mediated dimethyl H4R3 formation is associated with flap endonuclease 1 (FEN1) that enhances its activity and base excision repair efficiency, suggesting that symmetrical dimethylation of H4R3 serves as a bridge linking the DNA damage and repair (DDR) response in response to oxidative stress [17]. Together, these reports highlight critical molecular and signaling functions of redox reactions serve for different aspects of cellular functions. Supported by these many new findings, it is abundantly clear that redox dependent signaling regulation of cardiovascular health and disease continues to progress at a rapid pace and in various mechanistic pathways with many implications for future therapeutic targets.

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