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EDITORIAL

# Special Issue on Oxidative Stress in Health and Disease

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Recent advances in free-radical biology and natural product chemistry enhanced our understanding for the molecular pathophysiology of a number of human diseases and application of natural products as novel therapeutic means of intervention. Free radicals are interesting chemical entities with an unpaired electron that makes them highly reactive. They are known to play paradoxical roles in determining human health, sometimes being beneficial e.g., phagocytosis of bacteria, redox signaling and sometimes being toxic e.g., interacting with vital molecules such as DNA to form stable adducts thereby inducing mutagenicity. By virtue of nature, human health system is provided with certain "electron sinks" popularly known as antioxidants that can quench chain propagation induced by free radicals. Perturbation in the delicate balance between prooxidants and antioxidants might increase the susceptibility to several human disorders including inflammation, autoimmune diseases, cancer, diabetes, ischemia–reperfusion (IR) injury, lung injury, neurodegenerative diseases, and cardiovascular diseases. Recent development in the technologies for rapid detection of free radicals, tools to understand the molecular pathophysiology of multi-factorial disorders, ability to isolate and purify the ingredients of natural products, and availability of a multitude of cell lines to study different biological processes have contributed remarkably for efficient and effective utilization of natural products and nutraceuticals for treatment of many disorders.

Scientific community in India has contributed remarkably in the areas of oxidative stress and biomedicine. *Indian Academy of Biomedical Sciences* (IABS) and *Society for Free Radical Research-India* (SFRR-India) are pioneering bodies providing an academic platform for interaction between scientists and clinicians, thus disseminating the technological and scientific advancements to younger generation. Over the years, conferences held under the banner of IABS and SFRR-India covered a wide variety of topics including genomics and proteomics, free radical-mediated pathogenesis of disease, natural products, antioxidants, radioprotectors, etc., thus presenting new insights into biomedical research. In this series, we have compiled a focused issue of *Cell Biochemistry and Biophysics* (CBB) that covers an important topic of oxidative stress, which will help in the better understanding of cellular and molecular mechanisms underlying multi-factorial human disorders like cancer, cardiovascular diseases, inflammation, lung diseases, etc. This special issue encapsulates technological and scientific developments in the area of free-radical research, biological concepts of oxidative stress and its connotation in the pathogenesis of various disease processes. This focused issue on "Oxidative stress in health and disease" of CBB contains 24 peer-reviewed research contributions, including five reviews and 19 original articles of which four are related to technological advancements and six are dedicated to therapeutic advances, whereas nine papers contribute to molecular and cellular mechanisms underlying various diseases.

Two excellent reviews dealing with angiogenesis and tissue remodeling provide valuable updates in the field of cardiac repair and chronic respiratory diseases. *Alagappan et al.* state that vascular changes directly add to the airway

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narrowing and hyperresponsiveness by exudation and transudation of pro-inflammatory mediators, cytokines, and growth factors; facilitating trafficking of inflammatory cells; and causing edema of the airway wall and airway smooth muscle (ASM) accumulation. This research group has earlier shown that ASM in patients with COPD produce vascular endothelial growth factor (VEGF), the key regulator of angiogenesis that in concerted action with other endothelial mitogens play pivotal role in regulating bronchial angiogenesis and remodeling that contribute in the pathogenesis of chronic airway diseases. *Lu et al.* present about the fundamental factors that regulate the angiogenesis process and the use of stem cells as therapeutic regime for the treatment of ischemic diseases. Vasculogenesis and angiogenesis are the major forms of blood vessel formation. Angiogenesis is the process where new vessels grow from pre-existing blood vessels, and is very important in the functional recovery of pathological conditions, such as wound healing and ischemic heart diseases. Hypoxia turned out to be the important driving force for angiogenesis in various ischemic conditions. It stimulates expression of many growth factors like VEGF, platelet-derived growth factor, insulin-like growth factor, and fibroblast growth factor (FGF), which play critical role in induction of angiogenesis. In another study on the mechanisms of angiogenesis, *Sharma et al.* investigated the effects of interleukin-1β on the expression and secretion of VEGF and placenta growth factor (PlGF) in porcine ASM cells in relation to nitric oxide (NO) pathway. Data presented in this paper conclude that NO donors augment IL-1β-induced VEGF synthesis in ASM cells during inflammation contributing to bronchial angiogenesis and vascular leakage.

Adipose-derived stem cells (ADSC) are stromal mesenchymal stem cells which display a broad potential to differentiate toward different lineages. In their original research paper, *Pasini et al.* present data demonstrating the dynamic and flexible chromatin arrangement as characteristic of most lineage-specific and developmental genes-associated control at expression level such as in early cardiac regulatory genes *MEF-2C*, *GATA-4*, and *Nkx2.5* and such regulatory genes could be explored as an intervention to address the differentiation of human ADSCs toward the cardiac lineage. In another study on mesenchymal stem cells, *Paul et al.* assessed whether ADSC are also immune tolerant, such that they can be used as universal donor cells for myocardial regenerative therapy. The study also focuses on investigating the potential therapeutic effects of human ADSC for myocardial infarction in xenotransplant model, and compares its effects with that of human bone marrow-derived mesenchymal stem cells. Both in vitro- and in vivo-based experiments suggest that human ADSC are superior in terms of their proliferative, viability, and phenotypic adaptation potential and hence can serve as universal donor cells for xenogeneic or allogeneic cell therapy.

*Khan et al.* present on the possible involvement of pulmonary-generated reactive oxygen species (ROS) on cardiac dysfunction using a rat model of IR injury. They show that the lung IR generates an increased burst of ROS that results in significant cardiac dysfunction, including hypotension indicating that ROS produced due to acute IR lung injury may cause direct cardiac dysfunction independent of injury caused to the myocardium as a result of regional myocardial IR injury alone. On the similar topic of IR injury, *Adluri et al.* discuss the therapy for protection against IR injury. Circumstantial evidence points to involvement of oxygen-derived free radicals and oxidative stress as mediators of myocardial ischemia/reperfusion injury. Their work provides evidence that external supplementation of natural antioxidants, VitaePro, a novel antioxidant mix of astaxanthin, lutein, and zeaxanthin show substantial cardioprotection in a rat ex vivo model of IR injury by decreasing oxidative stress and apoptosis, which may be of therapeutic benefit in the treatment of cardiovascular complications.

*De et al.* evaluated cardioprotective effects of dendrodoine analog (DA), an aminothiazole compound derived from dendrodoine, present in a marine tunicate. Using an isoproterenol-induced myocardial tissue damage model in mice, they found that increased levels of creatine kinase-MB, lactate dehydrogenase, and aspartate aminotranferase in serum were restored by pretreatment of animals with DA. DA also gave significant protection against lipid peroxidation in the heart besides restoring histopathological changes showing significant reactivity toward superoxide radicals that can possibly be attributed to its antioxidant property. *Diwan et al.* investigated dietary supplementation with piperine, the active principle of widely used black pepper, to high-carbohydrate, high-fat (HCHF) diet-fed rats as a model of human metabolic syndrome. After 16 weeks, rats fed with HCHF diet developed hypertension, elevated oxidative stress, and inflammation-induced cardiac changes including fibrosis and increased ventricular stiffness and when these animals were given supplementation with piperine all the above parameters got normalized with attenuation of cardiac and hepatic inflammation as well as fibrosis.

Employing DNA Microarray and Quantitative Analysis, *Peters et al.* studied molecular phenotype of right ventricular failure in patients with congenital heart malformation. Their data suggest that right ventricular hypertrophy is associated with profound changes in gene profile for a number of genes of which VEGF/VEGF-R system contributes to enhance but stunted myocardial angiogenesis in patients with tetralogy of Fallot.

The diverse deleterious health effect upon exposure to toxic heavy metals in the environment is a matter of serious concern and a global issue. Much emphasis has been given to elucidate the mechanism of toxicity due to common environmental toxicants and to develop a safer chemotherapeutic approach to mitigate the toxic effects. Mercury, especially methylmercury (MeHg), is implicated in the etiology of cardiovascular diseases. In continuation of their earlier study, *Sherwani et al.* report that MeHg induces phospholipase D (PLD) activation through oxidative stress and thiol-redox alteration. The authors demonstrate that MeHg activates PLD in vascular ECs through the upstream action of $cPLA_2$ and the COX- and LOX-generated eicosanoids and conclude that mechanism(s) of the MeHg-mediated vascular endothelial cell lipid signaling is the underlying cause of mercury-induced cardiovascular diseases.

*Willems–Widyastuti et al.* investigated the role of FGF-1/-2 in VEGF production in ASM cells and assessed the influence of azithromycin and dexamethasone and their underlying signaling mechanisms. Authors demonstrated that FGF-1 and FGF-2 upregulate VEGF production via $ERK1/2^{MAPK}$ and $p38^{MAPK}$ pathways. Both azithromycin and dexamethasone elicited their anti-angiogenic effects via $p38^{MAPK}$ pathway in vitro, thereby suggesting a possible therapeutic approach to tackle VEGF-mediated vascular remodeling in patients with chronic airway diseases like COPD.

*Sipkens et al.* evaluated that ROS-producing signaling pathways contribute to homocysteine-induced apoptosis in endothelial cells via NADPH oxidases. Homocysteine induced caspase-3 activity and apoptosis which was accompanied by an increase in cellular NOX2, p47phox, and NOX4, but not NOX1. 3D digital imaging microscopy followed by image deconvolution analysis showed nuclear accumulation of NOX2 and $p47^{phox}$ in endothelial cells exposed to homocysteine. The data presented in this manuscript further revealed accumulation of nuclear NOX2 and peri-nuclear NOX4 as potential source of ROS production in homocysteine-induced apoptosis in endothelial cells.

*Lakshmi et al.* report on the risk associated with polymorphisms regulating the folate-uptake and transport such as the glutamate carboxypeptidase II (GCPII) C1561T, reduced folate carrier 1 (RFC1) G80A, and cytosolic serine hydroxymethyltransferase (cSHMT) C1420T. They observed that (GCPII) 1561T, MTRR 66A, and MTHFR 677T variants were found to be independent risk factors for coronary artery disease (CAD). Elevated oxidative stress was observed in subjects carrying these variant alleles and also found to influence homocysteine levels. Low oxidative stress was observed in the subjects carrying cSHMT 1420T, TYMS 5'-UTR 2R alleles and found to confer protection against CAD. Finally, the authors summarize that elevated oxidative stress is associated with the aberrations in one carbon metabolism which could probably influence the CAD risk.

*Ravi et al.* discuss the role of phosphatase-and-tensin homolog on chromosome 10 (PTEN), in pulmonary hypertension (PH). PTEN is associated in the progression of multiple cancers and is implicated in arterial remodeling. For this purpose, they induced PH in rat by monocrotaline administration (60 mg/kg) or continuous hypoxic exposure (10 % oxygen). They observed PTEN degradation via proteasomal degradation pathway and also observed a significant downregulation of cell-cycle regulatory proteins p53 and p27, and upregulation of cyclin D1 in the lungs of both models and concluded that PTEN plays a key role in the progression of pulmonary hypertension and depicting PTEN is a potential target for PH.

*Nagababu* and *Rifkind* review the routes of formation of *S*-nitrosothiols (RSNO). RSNO are involved in posttranslational modifications of many proteins analogous to protein phosphorylation and also possess physiological roles similar to NO, which are presumably involving the release of NO from the RSNO. However, the much longer lifespan in biological systems for RSNO than NO suggests a dominant role for RSNO in mediating NO bioactivity. The reactions of NO with oxygen, metalloproteins, and free radicals can lead to the formation of RSNO and the potential for each mechanism to provide a source for RSNO in vivo has been evaluated. *Premkumar et al.* describe the role reactive oxygen and nitrogen species (ROS/RNS), in the development and progression of diabetic peripheral neuropathy. Both type 1 and type 2 diabetes mellitus are characterized by chronic hyperglycemia, leading to the development of diabetic peripheral neuropathy and microvascular pathology. The mechanism(s) of development and progression of diabetic peripheral neuropathy is also discussed.

*Sliman et al.* report the role of adiponectin (Ad) in the protection against the hyperoxia-induced lung damage. Ad, an adipokine exclusively secreted by the adipose tissue, has emerged as a paracrine metabolic regulator as well as a protectant against oxidative stress. The authors show that exogenous Ad protect against the hyperoxia-induced oxidative stress, loss of glutathione (GSH), cytoskeletal reorganization, barrier dysfunction, and leak in the lung endothelial cells in vitro. Further, they demonstrate the attenuation of hyperoxia-induced lung injury, vascular leak, and lipid peroxidation AdTg mice in vivo. Also, AdTg mice exhibit elevated levels of total thiols and GSH in the lungs as compared to WT mice. Individuals working in the poultry farms have received considerable attention, as they are more prone for respiratory diseases that are presumably due to exposure of poultry particulate matter.

*Kotha et al.* describe the mechanism of poultry particulate matter (PM)-induced respiratory disorders. The authors demonstrate that poultry PM induced IL-8 secretion by human lung epithelial cells through the activation of cPLA2 through ERK-mediated serine phosphorylation.

*Ullah et al.* showed that dietary antioxidants can alternatively switch to a prooxidant action in the presence of transition metals such as copper. Such a prooxidant action leads to strand breaks in cellular DNA and growth inhibition in cancer cells, hence, such dietary antioxidants have implications for chemotherapeutic action against cancer. In another study, *Singh and Trigun* showed that treatment of Dalton's lymphoma (DL) by emodin is associated with modulations of hydrogen peroxide metabolizing enzymes resulting in activation of mitochondrial pathway of apoptosis in the DL cells in vivo.

Oxygen is a critical determinant in the prediction of the treatment outcome of several diseases and therapies. *Fischer et al.* demonstrate noninvasive monitoring of the partial pressure of oxygen ($pO_2$) in rat small intestine (SI) using a model of chronic mesenteric ischemia by electron paramagnetic resonance oximetry over a period of 9 days. The authors used a particulate oxygen-sensing probe named lithium octa-n-butoxynaphthalocyanine embedded into the oxygen permeable material polydimethyl siloxane by cast-molding and polymerization (Oxy-Chip) and implanted in outer wall of the SI. The superior mesenteric artery was banded to approximately 30 % blood flow for experimental rats. Tracking $pO_2$ in conditions that produce chronic mesenteric ischemia will contribute to the understanding of intestinal tissue oxygenation and how changes impact symptom evolution and the trajectory of chronic disease. Highlighting the importance of metal/metal oxide nanoparticles such as superparamagnetic iron oxide (SPION), *Murray et al.* present that UV radiation and SPIONs may be toxic to skin by inducing oxidative stress and redox-sensitive transcription factors affecting/leading to inflammation. The data indicate that co-exposure to UVB and SPIONs is associated with induction of oxidative stress and release of inflammatory mediators.

*Buettner et al.* in their comprehensive review, describe the new field of *Quantitative Redox Biology* to identify new targets for intervention to advance our efforts to achieve optimal human health. Free radicals, related oxidants, and antioxidants are central to the basic functioning of cells and tissues, and, therefore, are key to regulation of biochemical pathways and networks, thereby influencing organism health. To understand how short-lived, quasi-stable species, such as superoxide, hydrogen peroxide, and NO, connect to the metabolome, proteome, lipidome, and genome, one need absolute quantitative information on all redox-active compounds as well as thermodynamic and kinetic information on their reactions, i.e., knowledge of the complete redoxome. Quantitative information is essential to establish the dynamic mathematical models needed to reveal the temporal evolution of biochemical pathways and networks.

We gratefully acknowledge and thank all authors, the reviewers, the editors, and staff of Springer's editorial and production office for their invaluable work and help that made this special issue possible. We hope that this compilation of review and original articles contributed by the leading experts in the field will strengthen our understanding of oxidative stress in human health and disease and serve as an important source of information for the biomedical research community.