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Recent advances in sulfur biology and chemistry

This Special Issue in Redox Biology is dedicated to recent advances in the field of sulfur biology and chemistry that were discussed during the 6th *World Congress on Hydrogen Sulfide in Biology & Medicine*. The conference was held in Budapest, Hungary in May 2022. The meeting gathered a multi-disciplinary group of scientists from 5 continents to exchange break-through ideas and provide novel insights in the chemical biology and therapeutic applications of hydrogen-sulfide (H_2S) and related sulfur species. Review articles are committed to summarize methodological advances and challenges to detect Reactive Sulfur Species (RSS), their chemical properties and interaction partners, as well as to highlight their importance in different diseases. Original research topics cover molecular mechanisms, (patho)physiology, pharmacology and potential therapeutic exploitation of RSS in cardiovascular and neurodegenerative diseases, chronic kidney disease and cancer.

Detection of RSS in biological systems remains a major challenge of the field, which lead to the rise of a plethora of different methodological approaches. Sheih et al. critically discuss current RSS detection methods including cyanolysis, chemical derivatization followed by mass spectrometry measurements, proteomic analyses, fluorescent probes and resonance synchronous/Raman spectrometry highlighting their advantages and disadvantages [1]. Malaeb et al. developed a stable-isotope-dilution liquid chromatography mass spectrometry (LC-MS/MS) method for hydrogen sulfide measurement employing heavy sulfur-containing H_2S, which could facilitate robust quantification of total H_2S and other sulfur species in biological matrices [2].

RSS have widespread interactions with metalloproteins involved in transport and storage of oxygen, mitochondrial respiration and maintenance of redox homeostasis and therefore these interactions play fundamental roles in cellular functions. Domán et al. provide a comprehensive overview on these processes [3]. Sevalkar et al. extend the picture by showing that H_2S can regulate the heme-containing sensor kinase of *Mycobacterium tuberculosis*, a pathogen responsible for approximately 1.4 million deaths annually [4]. Alam et al. show that apart from their effects through interactions with metalloproteins, persulfides also stimulate mitochondrial respiration and ATP production via regulating Nrf2-mediated events [5].

Switzer and Fukuto highlight unique chemical properties of hydropersulfides and polysulfides, which, among others, are responsible for their unstable nature, for issues related to their detection and for their unique biochemical features including protective properties under oxidative and/or electrophilic stress [6]. Comas et al. demonstrate that gene knock-down of *cystathionine β synthase* (CBS) in immortalized human adipose-derived mesenchymal cells induce inflammation and oxidative stress, which promotes enhanced adipocyte differentiation with excessive lipid storage [7]. The cysteine persulfide donor cysteine trisulfide is shown by Griffiths et al. to reduce lipid peroxidation, protect against myocardial ischemia-reperfusion injury and restore post-ischemic cardiac function [8]. Exogenous administration of polysulfides increase intracellular sulfane sulfur, prevent neurodegeneration in spinal cord and rescue mice from delayed paraplegia after spinal cord ischemia in the study by Kanemaru et al. [9]. Pharoah et al. demonstrate that hydropersulfides effectively attenuate doxorubicin-induced cardiotoxicity by activating the mitochondrial master regulator *peroxisome proliferator-activated receptor gamma coactivator 1 alpha* (PGC1α) [10]. Wu et al. reveal that persulfidation of *dynamin-related protein 1* (Drp1), a critical regulator of cardiac function mediated by *Cystathionine γ lyase* (CSE), ameliorate heart dysfunction [11]. The H_2S donor AP123 is shown by Montanaro et al. to effectively restore vascular function in hyperglycemia induced endothelial dysfunction [12]. Moreover, Kolloru et al. demonstrate that metamphetamine usage-induced cardiovascular dysfunction is associated with decreased expression of CSE and lower levels of bioavailable H_2S, which could be counteracted by exogenous sulfide therapy or endothelial CSE overexpression [13]. Gáll et al. summarize the beneficial roles of H_2S in the progression of atherosclerosis via suppressing vascular calcification [14]. Combi et al. characterize calcified aortic valves to have lower levels of sulfide as a result of its enhanced catabolism by sulfide oxidation pathways. In addition, a mitochondria-targeting sulfide donor could rescue valvular interstitial cells from an osteoblastic switch in their study [15]. Higher levels of free sulfhydryl groups reflecting less oxidative stress in human serum are associated by Bourgonje et al. with decreased risk of developing chronic kidney disease [16].

Panagaki et al. provide evidence that overproduction of H_2S in down syndrome caused by the overexpression of the sulfide producing enzyme CBS, leads to the disruption of brain wave patterns and neurobehavioral dysfunction [17]. The same group demonstrate that CBS also promotes pseudohypoxia leading to a shift from oxidative phosphorylation to glycolysis and therefore to decreased mitochondrial ATP production in this disease, representing another example for the regulatory roles of sulfide in cellular bioenergetics [18]. In Parkinson's disease, increased activity of sulfide:quinone oxidoreductase, responsible for the oxidation of sulfide, diminish neurodegeneration in a murine model by Nagashima et al. [19]. In contrast, in Alzheimer's disease, Rao et al. show that stimulation of the H_2S-producing enzyme *3-mercaptopyruvate sulfurtransferase* (3MST) reduces oxidative stress and ameliorates disease pathology [20]. In Duchenne's muscular dystrophy, Panza et al. suggest that defects in the transsulfuration pathway might be involved in the disease process and demonstrate that by exogenous addition of H_2S the impaired locomotor activity in dystrophic mice can be recovered [21].

Because H_2S is produced in large quantities not only by colonocytes

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but also by intestinal microbes, it is not surprising that it plays a fundamental role in the occurrence, progression and treatment of colorectal cancer as shown by Lin et al. [22]. Thanki et al. conclude that in ulcerative colitis, an inflammatory disease which often leads to colitis associated cancer, CSE acts as a protective protein and its down-regulation accelerates the development and progression of colitis associated cancer [23]. *Cysteine-rich angiogenic inducer 61* (CYR61), which is connected to several cancer-associated processes including tumor growth, angiogenesis, migration and anticancer drug resistance, is shown by Ascencao et al. to be regulated by CBS and 3MST in colon cancer cells [24]. CBS is markedly increased in many forms of cancer (high-CBS-expressor cancers, e.g. colon cancer) and high CBS levels in these types are associated with lower survival rates, while in other types (e.g. liver cancers) low CBS expression predicts lower survival rates [25]. In pancreatic ductal adenocarcinoma, CBS levels are elevated in metastatic cancer cells and in ductal cells of human tumors compared to cells from/in non-metastatic primary tumors as shown by Czikora et al. The authors provide mechanistic insights how the sulfide/persulfide producing functions of this protein drive metastatic dissemination via inducing epithelial-to-mesenchymal transition through activation of Wnt signaling pathways [26]. To better understand the physiological roles of transsulfuration enzymes involved in the synthesis and catabolism of RSS, their *in vivo* activities were investigated in humans by Kozic et al. via sulfur metabolome analyses in patients with ultrarare genetic defects of these proteins [27].

Taken together, papers published in this special issue show the significance of RSS in several different clinical settings, which ensures that these biological molecules remain in the focus of redox biology research. Although several novel molecular insights are provided into the biological functions of RSS and current models are summarized in the included review articles, the underlying molecular mechanisms responsible for their versatile physiological roles need to be further elucidated in order to pave the way for developing RSS-based therapeutic interventions.

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