Redox Biology 8 (2016) 439–441

Contents lists available at ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Virtual issue by COST Action BM1203 (EU-ROS) "Emerging concepts in redox biology and oxidative stress"

Editorial summary

The article by Bacic et al. [1] (link to http://dx.doi.org/10.1016/j.redox.2015.10.007) provides an overview on the application of magnetic resonance imaging (MRI) and electron paramagnetic resonance (EPR) spectroscopy of stable nitroxide radicals to monitor metabolically induced changes in the redox status of organs. These techniques will not only contribute to the mechanistic understanding of oxidative stress-associated pathological states but also provide a basis for studying the effectiveness of interventions aimed to modulate oxidative stress (redox medicine approaches). The authors introduce the different MRI and EPR methods that are currently available and describe a broad spectrum of nitroxide-based spin traps and spin probes with emphasis on pharmacokinetic properties. In the second part of the review, the authors provide examples for the application of these techniques to study changes in the redox status in different tissues (e.g. skin, brain, tumors) upon induction of disease states (e.g. sepsis, ischemia/reperfusion, iron overload). With their conclusions, the authors provide an outlook on future technical needs and development of new probes with increased stability towards reduction, enhanced sensitivity to oxidative stress, or increased delivery into cells and through the blood–brain barrier as well as specificity towards certain ROS species or specificity towards certain pathologies such as tumors.

The review by Dunn et al. [2] (link to http://dx.doi.org/10.1016/j.redox.2015.09.005) discusses different pathways of bacterially-induced mtROS formation and its role for activation of the NLRP3 inflammasome via direct redox modifications of the NLRP3 components as well as redox-sensitive indirect pathways such as Nrf2/HO-1, NFκB/iNOS and TXNIP/mtDAMP interaction with the NLRP3 inflammasome leading to the formation of the pro-inflammatory cytokine IL-1β. Mitochondrial damage-associated molecular patterns (mtDAMPs) include the participation of mtDNA and/or cardiolipin that are released or surfaced by dysfunctional mitochondria. This also results in decreased activity of NAD^+-dependent deacetylases Sirt1 and Sirt2 that normally inhibit NFκB and NLRP3 activation. ROS in general also contribute to extracellular trap formation originating from nuclear or mitochondrial DNA.

The review by Espinosa-Diez et al. [3] (link to http://dx.doi.org/10.1016/j.redox.2015.07.008) highlights the adaptive cellular antioxidant responses to oxidative stress. In the first part, the role and function of classical thiol-based antioxidant proteins such as GCL, Grx, GPx, Prx, Trx, GST, GR and TrxR are discussed. In addition, the antioxidant gene response is discussed with the classical examples of Nrf2/Keap1, NFκB, AP-1 and the epigenetic pathway based on miRNA. A detailed list of miRNA targeting of specific antioxidant genes and the respective disease states in which the miRNA action was described is provided by the authors. In the last part, these antioxidant responses are discussed in the context of pathophysiological conditions (ER stress and ischemia reperfusion). The major key players in this redox regulatory network of antioxidant responses are finally presented (e.g. protein tyrosine phosphatases, protein kinases), the important role of mitochondrial ROS in this network is highlighted and therapeutic targeting of mtROS is discussed.

The review by Görlach et al. [4] (http://dx.doi.org/10.1016/j.redox.2015.08.010) provides insight into the impact of calcium levels on ROS sources such as mitochondria and NADPH oxidases. Vice versa, the role of oxidative stress on different types of calcium channels and pumps is discussed in full detail. In the second part of the review, the authors elaborate on the interaction (crosstalk) of calcium and ROS in the endoplasmic reticulum and mitochondria. In summary, the authors provide evidence that calcium can increase the production of ROS and these ROS can significantly affect calcium influx into the cell and intracellular calcium stores.

The second review by Görlach et al. [5] (http://dx.doi.org/10.1016/j.redox.2015.08.016) highlights the sources of ROS in different cellular compartments such as plasma membrane, cytosol, endoplasmic reticulum, mitochondria, peroxisomes and lysosomes (e.g. NADPH oxidases, xanthine oxidase, P450s, lipoxygenase, cyclooxygenase, lipid peroxidation, phospholipase, acyl-CoA oxidases, polyamine oxidase, Ero1 and liposomal redox chain) and provides an update on all NADPH oxidase isoforms (subcellular localization, cellular expression and cofactors). In addition, the authors emphasize on ROS-triggered signaling via redox-sensitive kinases (e.g. PKC, Akt and MAPK) and protein tyrosine phosphatases, transcription factors (e.g. NFκB, Nrf2 and HIF-1α). In the last part of the review, they discuss these concepts in the context of hypoxia, nutrition, energy metabolism and metabolic reprogramming.

The review by Jankovic et al. [6] (http://dx.doi.org/10.1016/j.redox.2015.08.018) provides detailed insights in the physiological function of adipocytes and the ratio and interconversion between white and brown adipose tissue, as well as the physiological consequences of this interconversion. Nutritional shifts in NAD^+/NADH ratio affect the redox balance in adipose tissue and overnutrition, oxidative stress and mitochondrial dysfunction contribute to adipocyte dysfunction, which is more concerning than fat accumulation per se. Dysfunctional adipocytes also

http://dx.doi.org/10.1016/j.redox.2015.12.007

support the recruitment of macrophages leading to adipose tissue inflammation with more pronounced ROS formation. Sources of ROS in dysfunctional adipocytes are highlighted, the interaction and co-stimulation of these ROS sources in a crosstalk fashion is detailed while the impact of mtROS in insulin resistant adipocytes and the important role of NO formation in functional adipocytes versus uncoupled eNOS in dysfunctional adipocytes is thoroughly discussed. Finally, the authors analyze the role of redox signaling in adipogenesis.

The review by Klotz et al. [7] (http://dx.doi.org/10.1016/j.redox.2015.06.019) delves into FoxO transcription factors by addressing their classical regulation (e.g. by insulin), the FoxO target genes (e.g. selenoprotein P, ceruloplasmin) conferring antioxidant protection and their regulation via phosphorylation by different kinase systems (Akt, ERK, JNK, MAPK, AMPK, most of them are redox-sensitive). The authors also emphasize the biological effects of FoxO activation. In the second part of the review, the different redox-regulatory pathways of FoxO transcription factors are recapitulated (FoxO gene induction, posttranscriptional regulation of FoxO expression levels, FoxO activity). In the last part, the authors highlight physiological and pathophysiological consequences of FoxO (dys)regulation (e.g. in obesity and diabetes) as well as dissect the interaction of FoxO and ROS in different organs and cell types.

The review by Manda et al. [8] (http://dx.doi.org/10.1016/j.redox.2015.06.014) provides an introduction on cancerogenesis with emphasis on the contribution of oxidative stress to this process, highlighting impaired DNA damage repair as one important constituent of cancer development. Redox signaling networks are unbalanced in cancer cells. As examples the activities of mitogen-activated protein kinases, FoxO transcription factors and Nrf2/Keap1 system are dysregulated in cancer cells, conferring higher oxidative stress resistance. In line with increased oxidative stress but also oxidative stress resistance of tumor cells, the hyperinflammation observed in tumor tissue (originating from infiltrated immune cells but also cytokines produced by specific cancer cells), contributes to tumor growth (e.g. increased cancer cell proliferation, angiogenesis). Therefore, oxidative stress-based therapies might include the suppression of antioxidant transcription factors (e.g. Nrf2 inhibitors). The authors also discuss the types of cell death induced by oxidative stress-based therapies. For an in-depth review of the dysregulation of the Keap1-Nrf2 pathway in cancer, the readers are also referred to an earlier graphical redox review by Kansanen et al. [9] (http://dx.doi.org/10.1016/j.redox.2012.10.001), which now forms part of this thematic virtual collection.

The review by Manea et al. [10] (http://dx.doi.org/10.1016/j.redox.2015.06.012) provides an overview on NADPH oxidase isoforms in different cell types and their pathophysiological actions in vascular inflammation and oxidative stress, vascular dysfunction and remodeling and finally progression to atherosclerosis. The authors highlight the milestones of the yet incompletely understood regulation of Nox enzyme expression by transcription factors and nuclear receptors (e.g. NF-kB, AP-1, STAT1/3, C/EBP and PPARs). In addition, epigenetic pathways are discussed accounting for Nox4 upregulation (e.g. miRNA-25, HATs and HDACs).

The review by McBean et al. [11] (http://dx.doi.org/10.1016/j.redox.2015.04.004) summarizes thiol-based cellular redox couples (e.g. sulfiredoxin, Trx, Prx, Grx) and links them to the respective reductases and cofactors (e.g. TrxR, GR, NADPH, GSH) as well as to the transcription factors accounting for their induction (e.g. Nrf2, AP1, FoxO). The L-cysteine metabolism is discussed in detail, starting at the level of the L-cystine x_c^- exchanger, the homocysteine cycle and the synthesis of GSH, H_2S and taurine, with special emphasis on neurodegenerative disease. In the second part, the authors discuss these thiol-based pathways in the context of glaucoma and neurodegeneration with focus on Grx, Trx and Prx as neuronal survival factors. The last part of the review highlights the role of impaired redox balance for neurodegeneration with particular reference to Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and glaucoma.

The review by Mikhed et al. [12] (http://dx.doi.org/10.1016/j.redox.2015.05.008) provides an overview on classical gene regulation, epigenetic pathways and components of the DNA repair machinery. In the second part the authors discuss in full detail examples of redox regulation of classical gene expression (e.g. by redox sensitive transcription factors such as NFκB, Nrf2 and HIF-1α or mRNA-binding proteins GAPDH or HuR) leading to activation of gene expression and/or modulation of mRNA stability, thereby affecting protein expression. In addition, the impact of ROS on DNA repair and epigenetic pathways (e.g. miRNA, DNA methylation and histone modifications) is highlighted, all of which will influence the genome stability. In the last part of the review the authors discuss clinical implications of these concepts and therapeutic strategies to target dysregulated DNA repair and classical gene regulation, but also expand on pharmacological modulation of epigenetic gene regulation (e.g. HDAC, HAT and DNMT inhibitors and modulators of miRNA function).

The original article by Mikhed et al. [13] (http://dx.doi.org/10.1016/j.redox.2015.11.008) highlights the special features of salicylaldehyde as a new probe for the detection of physiological formation rates of peroxynitrite in the nanomolar range. In contrast to previously described phenolic compounds such as phenol or L-tyrosine that yield mainly dimerization products when incubated in the free form with low fluxes of peroxynitrite, salicylaldehyde forms nitrated products (e.g. 2-nitrophenol) and only minor amounts of dimers with peroxynitrite donors such as Sin-1. This specific property together with the fact that nitric oxide alone or peroxidase/hydrogen peroxide/nitrite only generate trace amounts of nitrated products when present at physiological concentrations, provides salicylaldehyde with a unique capability for the detection of peroxynitrite in vivo.

The original article by Noichri et al. [14] (http://dx.doi.org/10.1016/j.redox.2015.08.011) addresses the mechanism of how peroxiredoxin function switches from peroxidase to chaperon. In the Prx peroxidase cycle, a homodimer reacts with hydrogen peroxide to yield a sulfenic acid modified thiol group in each subunit, leading to intermolecular disulfide bridge formation and dimerization of the loosely bound reduced homodimer. The “disulfide form” is reduced by Trx and oxidized Trx is reactivated by TrxR/NADPH. However, the “disulfenic acid form” can be further oxidized by hydrogen peroxide to a “disulfinic acid form”, which needs ATP-dependent reduction by sulfiredoxin. The loss of its peroxidase activity and inactivation of Prx by hyperoxidation provides the basis for its extra-antioxidant functions, and in particular its ability to operate as very efficient chaperone holdases. This process is initiated by formation of high molecular weight Prx structures formed by the stacking of Prx decamers up to filaments an event that correlates with enzyme hyperoxidation but is not fully understood. The authors used mutation approaches and size exclusion chromatography to elucidate the nature of the different high molecular weight forms of Prx and investigated the different binding modes within these structures and the correlation with hyperoxidation. With their results, the authors contribute to the molecular understanding of the Prx peroxidase to chaperone modes switch.

The review by O'Neill et al. [15] (http://dx.doi.org/10.1016/j.redox.2015.07.009) concentrates on the role of ROS for genetic disease such as Nox2 subunit-deficiencies in chronic granulomatous disease (CGD) and discuss the paradox of the absence of ROS and simultaneous hyperinflammation in CGD. Neuronal, cardiovascular and renal pathologies of CGD are presented in detail. Methods for clinical analysis of new genetic variants of Nox2 in CGD as well as

therapeutic strategies for its treatment are presented (e.g. induction of pluripotent stem cells). In the second part of the review, the authors highlight the aspects of inflammatory bowel disease, its association with reduced ROS formation and the role of Nox1 and Duox2 isoforms. Finally, the role of Duox2 and A2 isoforms for the development and progression of hypothyroidism, which is the most common congenital endocrine disorder, is elucidated on a mechanistic basis and a detailed list of gene variants of Duox2 and A2 is provided.

The review by Pajares et al. [16] (http://dx.doi.org/10.1016/j.redox.2015.07.003) provides an overview on the impact of oxidative stress and redox modifications on the proteasomal activity, highlighting classical examples such as hydroxylation-triggered HIF-1α degradation, oxidative Nrf2 stabilization and nuclear translocation, but also the canonical pathway of NFκB activation by ubiquitination and proteasomal degradation of its inhibitor (IκBα). Also described are more recent developments incorporating the role of direct redox modifications of proteasomal components, the interaction of oxidative stress with autophagy and proteasome activity and the impact of protein unfolding/misfolding on ROS formation and proteasome activity. In the last part of the review the authors discuss clinical implications of these concepts in neurodegenerative diseases (Prion, Alzheimer's and Parkinson's disease).

The original article of Semen et al. [17] (http://dx.doi.org/10.1016/j.redox.2015.11.009) investigates the effects of sildenafil (PDE-5 inhibitor) therapy on heart rate variability, fatty acid composition and 4-hydroxynonenal (as a read-out of oxidative stress) in patients with pulmonary arterial hypertension (PAH). PAH is characterized by a poor prognosis with a mortality rate of 10–15% per year and median survival of approximately 7 years upon first diagnosis. PAH is associated with increased oxidative stress, reduced NO and prostacyclin bioavailability, excessive formation of vasoconstrictors and an inflammatory phenotype of the vascular wall. Sildenafil partially compensates for impaired vasodilatory pathways and confers antioxidant and anti-inflammatory effects. Sildenafil therapy improved the pulmonary hemodynamic status, oxidative stress, normalized free fatty acid composition and partly also heart rate variability.

The review by Voskou et al. [18] (http://dx.doi.org/10.1016/j.redox.2015.07.018) highlights the role of oxidative stress in β-thalassemia and sickle cell disease. The phenotype of the diseases is described in full detail with focus on the sources of oxidative stress in red blood cells in this setting. ROS formation is mainly driven by autoxidation of hemoglobin and free iron leads to Fenton chemistry. To a minor extent NADPH oxidases account for ROS formation in red blood cells. The intracellular oxidative events in diseased red blood cells and the counter-regulatory mechanisms by antioxidant systems are presented. The authors provide mechanistic insights into ROS-driven hemolysis, impairment of erythropoiesis and oxidative stress-mediated erythroid expansion and accelerated differentiation. The extracellular oxidative stress in β-thalassemia and sickle cell disease leads to a vicious cycle of oxidative stress and inflammation as well as a hypercoagulability state. Reduced NO bioavailability is a direct consequence of increased superoxide formation but also increased break-down of NO by sequestered myeloperoxidase/hydrogen peroxide from neutrophils and increased consumption of NO by free oxyHb from hemolysis.

References

[1] G. Bacic, A. Pavicevic, F. Peyrot, In vivo evaluation of different alterations of redox status by studying pharmacokinetics of nitroxides using magnetic resonance techniques, Redox Biol. 8 (2016) 226–242.
[2] J. Dan Dunn, L.A. Alvarez, X. Zhang, T. Soldati, Reactive oxygen species and mitochondria: a nexus of cellular homeostasis, Redox Biol. 6 (2015) 472–485.
[3] C. Espinosa-Diez, Miguel V, D. Mennerich, T. Kietzmann, P. Sanchez-Perez, S. Cadenas, S. Lamas, Antioxidant responses and cellular adjustments to oxidative stress, Redox Biol. 6 (2015) 183–197.
[4] A. Gorlach, K. Bertram, S. Hudecova, O. Krizanova, Calcium and ROS: a mutual interplay, Redox Biol. 6 (2015) 260–271.
[5] A. Gorlach, E.Y. Dimova, A. Petry, A. Martinez-Ruiz, P. Hernansanz-Agustin, A. P. Rolo, C.M. Palmeira, T. Kietzmann, Reactive oxygen species, nutrition, hypoxia and diseases: problems solved? Redox Biol. 6 (2015) 372–385.
[6] A. Jankovic, A. Korac, B. Buzadzic, V. Otasevic, A. Stancic, A. Daiber, B. Korac, Redox implications in adipose tissue (dys)function—a new look at old acquaintances, Redox Biol. 6 (2015) 19–32.
[7] L.O. Klotz, C. Sanchez-Ramos, I. Prieto-Arroyo, P. Urbanek, H. Steinbrenner, M. Monsalve, Redox regulation of FoxO transcription factors, Redox Biol. 6 (2015) 51–72.
[8] G. Manda, G. Isvoranu, M.V. Comanescu, A. Manea, B. Debelec Butuner, K. S. Korkmaz, The redox biology network in cancer pathophysiology and therapeutics, Redox Biol. 5 (2015) 347–357.
[9] E. Kansanen, S.M. Kuosmanen, H. Leinonen, A.L. Levonen, The Keap1-Nrf2 pathway: mechanisms of activation and dysregulation in cancer, Redox Biol. 1 (2013) 45–49.
[10] S.A. Manea, A. Constantin, G. Manda, S. Sasson, A. Manea, Regulation of Nox enzymes expression in vascular pathophysiology: Focusing on transcription factors and epigenetic mechanisms, Redox Biol. 5 (2015) 358–366.
[11] G.J. McBean, M. Aslan, H.R. Griffiths, R.C. Torrao, Thiol redox homeostasis in neurodegenerative disease, Redox Biol. 5 (2015) 186–194.
[12] Y. Mikhed, A. Gorlach, U.G. Knaus, A. Daiber, Redox regulation of genome stability by effects on gene expression, epigenetic pathways and DNA damage/repair, Redox Biol. 5 (2015) 275–289.
[13] Y. Mikhed, K. Bruns, S. Schildknecht, M. Jorg, M. Dib, M. Oelze, K.J. Lackner, T. Munzel, V. Ullrich, A. Daiber, Formation of 2-nitrophenol from salicylaldehyde as a suitable test for low peroxynitrite fluxes, Redox Biol. 7 (2015) 39–47.
[14] Y. Noichri, G. Palais, V. Ruby, B. D'Autreaux, A. Delaunay-Moisan, T. Nystrom, M. Molin, M.B. Toledano, In vivo parameters influencing 2-Cys Prx oligomerization: the role of enzyme sulfinylation, Redox Biol. 6 (2015) 326–333.
[15] S. O'Neill, J. Brault, M.J. Stasia, U.G. Knaus, Genetic disorders coupled to ROS deficiency, Redox Biol. 6 (2015) 135–156.
[16] M. Pajares, N. Jimenez-Moreno, I.H. Dias, B. Debelec, M. Vucetic, K.E. Fladmark, H. Basaga, S. Ribaric, I. Milisav, A. Cuadrado, Redox control of protein degradation, Redox Biol. 6 (2015) 409–420.
[17] K. Semen, O. Yelisyeyeva, I. Jarocka-Karpowitz, D. Kaminskyy, L. Solovey, E. Skrzydlewska, O. Yavorskyi, Sildenafil reduces signs of oxidative stress in pulmonary arterial hypertension: evaluation by fatty acid composition, level of hydroxynonenal and heart rate variability, Redox Biol. 7 (2016) 48–57.
[18] S. Voskou, M. Aslan, P. Fanis, M. Phylactides, M. Kleanthous, Oxidative stress in beta-thalassaemia and sickle cell disease, Redox Biol. 6 (2015) 226–239.

Andreas Daiber
Universitätsmedizin der Johannes Gutenberg-Universität Mainz, II. Medizinische Klinik und Poliklinik – Labor für Molekulare Kardiologie, Geb. 605, Raum 3.262, Langenbeckstr. 1, 55131 Mainz, Germany
E-mail address: daiber@uni-mainz.de

Fabio Di Lisa
Department of Biomedical Sciences, University of Padova, Italy

Santiago Lamas
Department of Cell Biology and Immunology, Centro de Biología Molecular "Severo Ochoa" (CSIC-UAM), Nicolás Cabrera 1, 28049 Madrid, Spain
E-mail address: slamas@cbm.csic.es

Available online 21 December 2015