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Review

Oxidative stress, redox regulation and diseases of cellular differentiation ☆

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ABSTRACT

Background: Within cells, there is a narrow concentration threshold that governs whether reactive oxygen species (ROS) induce toxicity or act as second messengers.
Scope of review: We discuss current understanding of how ROS arise, facilitate cell signaling, cause toxicities and disease related to abnormal cell differentiation and those (primarily) sulfur based pathways that provide nucleophilicity to offset these effects.
Primary conclusions: Cellular redox homeostasis mediates a plethora of cellular pathways that determine life and death events. For example, ROS intersect with GSH based enzyme pathways to influence cell differentiation, a process integral to normal hematopoiesis, but also affecting a number of diverse cell differentiation related human diseases. Recent attempts to manage such pathologies have focused on intervening in some of these pathways, with the consequence that differentiation therapy targeting redox homeostasis has provided a platform for drug discovery and development.
General Significance: The balance between electrophilic oxidative stress and protective biomolecular nucleophiles predisposes the evolution of modern life forms. Imbalances of the two can produce aberrant redox homeostasis with resultant pathologies. Understanding the pathways involved provides opportunities to consider interventional strategies. This article is part of a Special Issue entitled Redox regulation of differentiation and de-differentiation.

1. Oxygen

Earth's atmosphere presently contains 78% nitrogen and 21% oxygen. Life has evolved within this biosphere such that higher eukaryotes derive much of their energy requirements through oxidative metabolism, to date the most efficient means of generating ATP and sustaining life. During the Precambrian epoch, oxygen was present at trace levels, but at given points in an evolving geology, increased and decreased, reaching a maximum of 35% during the Carboniferous period. Obviously, life has adapted (and presumably continues) to such significant changes in oxygen availability. Indeed, giant insects of the Carboniferous could only exist because of proportionally higher oxygen ratios allowing for greater diffusion rates in a spiracle dominated breathing physiology. Given that oxygen is now an obligate requirement in mammals, paradoxically, it also carries considerable toxicities. Chemical, and for our purposes biological, conversion of oxygen or nitrogen can lead to the production of reactive oxygen species (ROS) or reactive nitrogen species (RNS), families of chemically active molecules that contain free radicals and key contributors to cellular redox state [1]. In general, the fate of a mammalian cell is almost entirely contingent upon intracellular and extracellular levels of ROS/RNS. Co-opted during the evolutionary process, relatively low levels of ROS/RNS may function as signals to promote such activities as cell proliferation and

Abbreviations: AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; ATRA, all-trans retinoic acid; BHA, butylated hydroxyanisole; C/EBP, CCAAT/enhancer binding proteins; CREB, cyclic AMP response element-binding proteins; CSF, cerebrospinal fluid; DUOX, dual oxidase; ER, endoplasmic reticulum; Ero1, ER oxidoreductin 1; ETC, electron transport chain; FoxO, forkhead box-O; GPx, glutathione peroxidases; GR, glutathione reductase; Grx, glutaredoxins; GSH, glutathione; GST, glutathione S-transferase; GSTP, glutathione *S*-transferase pi; HDAC, histone deacetylases; HIF, hypoxia-inducible factors; HPC, hematopoietic progenitor cell; HSC, hematopoetic stem cells; IGF-1, insulin-like growth factor-1; JNK, c-Jun NH2-terminal kinase; MDS, myelodysplastic syndromes; MKP-1, mitogen-activated protein kinase phosphatase-1; MSC, mesenchymal stem cells; mtROS, mitochondrial ROS; NAC, N-acetylcysteine; NOS, nitric oxide synthases; NOX, NADPH oxidases; NSC, neural stem cells; PDI, protein disulfide isomerase; PPARγ, proliferator-activated receptor gamma; Prx, peroxiredoxins; RNS, reactive nitrogen species; ROS, reactive oxygen species; SeCys, selenocysteine; SOD, superoxide dismutase; TBI, traumatic brain injury; TG2, tissue transglutaminase; TGFβ, transforming growth factor beta; TrkA, tyrosine kinase receptor-A; Trx, thioredoxins; TrxR, thioredoxin reductase; UPR, unfolded protein response

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Table 1
Examples of free radicals and their biological relevance.

Radical	Reaction	Biology/function	Refs.
Superoxide $O_2^{\bullet-}$	$O_2 + e^- \rightarrow O_2^{\bullet-}$	Mainly produced by the reaction of O_2 with an escaped electron from mitochondria; also produced by xanthine oxidase, lipoxygenase, cyclooxygenase and NADPH dependent oxygenase.	[3,6,7]
Hydrogen peroxide H_2O_2	$2O_2^{\bullet-} + 2H^+ \rightarrow 2H_2O_2 + O_2$	An intermediate detoxification of $O_2^{\bullet-}$ by SOD; comparatively low intrinsic toxicity and biological half-life make H_2O_2 well suited to act as an intracellular signaling molecule; involved in remodeling the structure of cells and activation of transcription factors.	[8–12]
Hypochlorous acid HOCl	$H^+ + Cl^- + H_2O_2 \rightarrow HOCl + H_2O$	Formed by myeloperoxidase reaction of H^+, Cl^-, and H_2O_2; can terminate bacterial DNA replication by destroying DNA anchoring at the membrane.	[13]
Hydroxyl radical HO•	$HOCl + O_2^{\bullet-} \rightarrow HO^{\bullet} + O_2 + Cl^-$ $HOCl + Fe^{2+} \rightarrow HO^{\bullet} + Fe^{3+} + Cl^-$ $HOCl + Cu^{+} \rightarrow HO^{\bullet} + Cu^{2+} + Cl^-$ $H_2O_2 + Fe^{2+} \rightarrow HO^{\bullet} + Fe^{3+} + OH^-$ $H_2O_2 + Cu^{+} \rightarrow HO^{\bullet} + Cu^{2+} + OH^-$ $H_2O_2 + O_2^{\bullet-} \rightarrow HO^{\bullet} + O_2 + Cl^-$	Produced spontaneously by HOCl with $O_2^{\bullet-}$ or metal ions; also produced from H_2O_2 through Fenton reactions. Because of its high reactivity, short half-life and irreversible modification of macromolecules, HO• has high biological toxicity.	[3,14]
Nitric oxide NO	L-arginine + O_2 + NADPH → L-citrulline + NO + $NADP^+ + e^-$	Synthesized enzymatically by NOS; can function as a free radical scavenger as it has a long half-life compared with $O_2^{\bullet-}$ and HO•. At normal physiological concentrations, NO is an intracellular messenger for guanylate cyclase and protein kinases. NO conjugates with GSH.	[2,15–17]
Peroxynitrite $ONOO^-$	$NO + O_2^{\bullet-} \rightarrow ONOO^-$	In cells with high NO cells (e.g. stimulated leukocytes), reaction can be faster than the dismutation of $O_2^{\bullet-}$ by SOD, then $ONOO^-$ can undergo hemolysis to form HO• .	[2]
Nitrogen dioxide NO_2	$ONOO^- + H^+ \rightarrow HO^{\bullet} + NO_2$ $2NO + O_2 \rightarrow 2NO_2$	Increased formation of $ONOO^-$ can lead to autohomolysis into HO• and NO_2; NO_2 can also be produced by direct oxidation of NO by O_2.	[2,18]

differentiation, whereas high levels more likely lead to apoptosis and cell death. As such, redox pathways are essential in maintaining cellular homeostasis and as a consequence, within these pathways, a great deal of functional redundancy has evolved. An adequate balance between formation and elimination of ROS/RNS is maintained in cells via pro- and anti-oxidant enzymatic pathways. A variety of endogenous factors regulate generation of ROS/RNS and in turn, these contribute to cell physiology by influencing such events as proliferation, differentiation, apoptosis, autophagy and senescence. In virtually every case, subtle threshold effects determine the biological consequences of redox homeostatic pathways. The difference between too much and too little ROS will be subtle and yet determine the fate of many pathways critical to cell survival and proliferation. Such events will be of considerable influence on natural selection and it is apparent that many of the complex pathways that underlie redox homeostasis are evolutionarily well conserved. Therein lies the teleological beauty of sulfur biochemistry, for the variable valence and nucleophilic nature of the element provides much needed biological flexibility. In this review, we explore this dual nature of ROS/RNS and how sulfur and selenium can provide maintenance of a balanced oxidative: reductive environment conducive to an oxygen dependent lifestyle. Partly as a consequence of human adaptations to oxygen, we introduce concepts as to how ROS might influence human pathologies, particularly those linked with differentiation pathways.

2. Sources of ROS/free radicals

Although molecular oxygen has two unpaired electrons in different orbitals, it is not *per se* a free radical, which by definition contain a single unpaired electron. The term ROS refers to a number of chemically reactive molecules derived from O_2, while RNS are derivative of nitrogen and oxygen, particularly nitric oxide (NO). In general the half-lives of RNS are longer than ROS [2,3]. Three of the most common and biologically important ROS are $O_2^{\bullet-}$ (superoxide anions), H_2O_2 (hydrogen peroxide) and OH• (hydroxyl radicals) [4]. Of these, the hydroxyl radical is invariably toxic, superoxide is a byproduct of mitochondrial oxidation reactions and hydrogen peroxide has evolved into an important intermediary signaling molecule. A summary of how ROS/RNS might be formed, their associated pathways and cellular effects are shown in Table 1.

Both exogenous (e.g. pollutants, tobacco, smoke, drugs, xenobiotics or radiation [5]) and endogenous sources contribute to intracellular ROS/RNS levels. As illustrated in Fig. 1, primary sites of intracellular ROS include the mitochondrial electron transport chain (ETC.), endoplasmic reticulum (ER) and NADPH oxidase (NOX) complex. Significantly, a number of human pathologies are associated with dysfunction within mitochondria or ER. Because approximately 1% to 2% of electrons flow through the ETC. (generally within complexes I and III) in mitochondria [19], this organelle is a primary site of superoxide production [20]. ROS is produced in complex I during reverse electron transport, where electrons enter complex I through coenzyme Q binding [21]. Mitochondrial complex III catalyzes the electron transfer from ubiquinol to ferricytochrome c, which is coupled to proton translocation for ATP synthesis [22]. Mitochondrial membrane potentials and enhanced proton-motive forces increase ROS formation [7,21]. In addition, oxygen concentrations, whether hyperoxic or hypoxic may increase ROS levels [23].

Secondarily, ROS can be produced from ER during oxidative stress. The ER is a well-orchestrated protein-folding machine containing various chaperones and sensors that detect the presence of mis-folded or unfolded proteins. ROS may be generated as byproducts of the protein folding machinery in the ER [24]. Protein disulfide isomerase (PDI) and ER oxidoreductin 1 (Ero1) are two enzymes responsible for regulating oxidative protein folding in the ER. Disulfide bond formation is driven by a protein relay involving Ero1, a conserved FAD-dependent enzyme, which can be oxidized by molecular oxygen and in turn can