Breakthroughs and Views

Oxygen sensing and oxidant/redox-related pathways✩

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Abstract

What is the nature of the oxygen sensor(s) and how do organisms sense variations in oxygen? A progressive rise of oxidative stress due to the altered reduction–oxidation (redox) homeostasis appears to be one of the hallmarks of the processes that regulate gene transcription. Dynamic changes in oxygen homeostasis and its close association with redox equilibrium, therefore, constitute a signaling mechanism for the expression/activation of oxygenes. This variation subsequently regulates the compartmentalization and functioning of HIF-1α and NF-κB. In addition, oxygen-evoked regulation of HIF-1α and NF-κB is closely coupled with intracellular redox state, such that modulating redox equilibrium affects their responsiveness at the molecular level (expression/trans-activation). Interestingly, are these particular transcription factors potential oxygen sensors? The basic components of the intracellular oxidative/redox machinery and its crucial regulation of oxygen- and redox-sensitive transcription factors may help understand the network of oxygen sensing mechanisms and redox-related pathways.

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Keywords: Glutathione; HIF-1α; Hyperoxia; Hypoxia; NF-κB; Oxygen sensing; Transcription factor; Redox equilibrium

The major question of how cells sense oxygen (and respond to it) has physiological and pathophysiological implications [1–3]. Living aerobic organisms have developed elaborate sequences of adaptive mechanisms to maintain oxygen homeostasis and equilibrium. In mammals, the development of evolutionary complex systems allows the acquisition and appropriate distribution of oxygen as a substrate for oxidative phosphorylation, the major biochemical reaction for the derivation of ATP [2,4]. As the terminal electron acceptor for oxidative phosphorylation, molecular oxygen occupies an essential role in many of the metabolic processes associated with aerobic existence [1–5].

✩ Abbreviations: NAC, N-acetyl-γ-cysteine; ATP, adenosine triphosphate; SAM, S-adenosyl-L-methionine; ATII, alveolar type II/III; ARNT, aryl hydrocarbon nuclear translocator; ARI, AU-rich element; bHLH, basic helix-loop-helix; BCNU, 1,3-bis-(2-chloroethyl)-1-nitrosourea; BSO, l-buthionine-(S,R)-sulfoximine; CO, carbon monoxide; TAD, carboxy-terminal transactivation domain; CAT, catalase; ΔO2/ROS, chemioxyexitation; CAD, COOH-terminal transactivation domain; CBP, CREB-binding protein; DSF, 2,7-desferrioxamine; DCF, dichlorofluorescein; ENO, enolase; EPO, erythropoietin; GLUT, glucose transporter; GSH, glutathione (reduced); GSSG, glutathione oxidized disulfide; GSH-PX, glutathione peroxidase; GSSG-RD, glutathione reductase; γ-GCS, γ-glutamylcysteine synthetase; γ-GT, γ-glutamyl transpeptidase; GM-CSF, granulocyte–macrophage colony stimulating factor; Hsp, heat-shock protein; HO, heme oxygenase; H2O2, hydrogen peroxide; HIF-1α, hypoxia-inducible factor-1α; HBS, HIF-binding site; HIF-PE/PH, HIF-α prolyl-hydroxylase; HRE, hypoxia responsive element; iNOS, inducible nitric oxide synthase; IkB, inhibitory kB; IKK, IkB kinase; IL, interleukin; ICE, IL-1β-converting enzyme; LDH, lactate dehydrogenase; LPS, lipopolysaccharide endotoxin; MAPK, mitogen-activated protein kinase; MAPAP, MAPK activating kinase; MEKK, mitogen-activated protein kinase kinase kinase; MKK, mitogen-activated protein kinase kinase; ETS, mitochondrial electron transport chain system; NO, nitric oxide; NF-κB, nuclear factor-κB; NIK, NF-κB inducing kinase; ODDD, oxygen-dependent degradation domain; OTC, 2-oxothiazolidine-4-carboxylate; PDTC, pyrrolidine dithiocarbamate; ROS, reactive oxygen species; redox, reduction–oxidation; REF-1, redox factor-1; RD, respiratory distress; SOD, superoxide dismutase; O2−, superoxide anion; TGF, transforming growth factor; TNF-α, tumor necrosis factor-α; VEGF, vascular endothelial growth factor; pVHL, von Hippel–Lindau tumor suppressor protein.

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Molecular oxygen is an environmental and developmental signal that regulates cellular bioenergetics, growth, and differentiation [1,2,5–10]. Despite its central role in nearly all higher life processes, the molecular mechanisms for sensing oxygen levels and the pathways involved in transducing this information remain largely obscure or, at least, premature [11–17]. Oxygen plays univalent roles: while it is indispensable for the cell to obtain the essential chemical energy, it is often transformed into highly reactive forms, radical oxygen (ROS) and nitrogen (RNS) species, which are often biotoxic [1–5,18–24]. Defense mechanisms include reduction–oxidation (redox) enzymatic systems such as glutaredoxin and thioredoxin [6,8,9,11,15,25,26]. Studies having the nature of cell biology and molecular biochemistry have revealed that these molecules are also involved in cell signaling [1–5,18]. The term ‘oxidative regulation’ has thus been proposed to indicate the active role of oxide-reductive modifications of proteins in regulating their functions. Oxide-reductive reactions of bio-molecules, mostly proteins, used to be considered as ‘oxidative stress’ are now considered as ‘signals’ and contain biological information that is necessary for maintaining cellular homeostasis (Fig. 1). In this review, I emphasize on elaborating an overview of current understanding of oxygen sensing mechanisms and redox/oxidative-related pathways within the context of gene regulation and transcription.

Reduction–oxidation concepts: the paradigm of oxidative siege

The idea of free radicals gets a new dimension. Oxidative damage defines the consequences of a mismatch between the production of ROS/RNS and the ability to defend against them [2,3,5,7,10,12,18–20]. Biological systems are protected from the threat of oxidative assault by a diversity of mechanisms designed to suppress pernicious oxidative pathways. Raised against the challenges are an extensive and highly effective array of protective agents and defense antioxidant mechanisms. These comprise numerous small molecular weight antioxidants to forestall initiation of oxidative damage and/or limit its propagation, enzymes that convert and detoxify ROS/RNS, enzymes to repair oxidative damage when it occurs, and mechanisms to route damaged molecules for destruction and replacement [6,10,14]. Antioxidant processes usually work by direct scavenging of the initiating pro-oxidant species. Each tissue, for instance, has an antioxidative potential (AOP), which is determined by those exerting enzymatic and
non-enzymatic antioxidants to indicate a need for such protection. Reactive radical pathways and their enzymatic dismutation are schematized in Fig. 2.

Oxygen sensing mechanisms: oxygen-sensitive sensors and transcription factors

What is the identity of the oxygen sensor(s)? The proposed mechanism underlying oxygen sensing in mammalian cells involves a putative oxygen sensor that is a heme protein [1–5,29–31]. Studies on erythropoietin (EPO), a glycoprotein hormone required for the proliferation/differentiation of erythroid cells, demonstrate that its production is enhanced under hypoxia [12,18]. Furthermore, the induction of EPO expression by transition metals such as cobalt (Co\(^{2+}\)) and nickel (Ni\(^{2+}\)) supports the hypothesis that the oxygen sensor for the induction of this glycoprotein is a heme protein and that these metal atoms can substitute for the iron atom within the heme moiety [29–38]. Further evidence utilized carbon monoxide (CO); CO can non-covalently bind to ferrous (Fe\(^{2+}\)) heme groups in hemoglobin, myoglobin, cytochromes, and other heme proteins [23–26], where its ligation state is structurally identical to that of oxygen. It was suggested that the effect of CO on oxygen sensing might occur via locking the sensor in an oxy conformation, which could involve a multi-subunit mechanism [1–5,30–38] (Fig. 3).

Fandrey et al. [23] unequivocally suggested that the oxygen sensor might involve a microsomal mixed function oxidase. It was proposed that oxygen sensing for EPO involves an interaction between cytochrome P450 and cytochrome P450 reductase, thereby allowing the conversion of molecular oxygen to O\(_2^−\) and H\(_2\)O\(_2\) [39,40]. Acker [3,15] has provided support for the central role of an oxidase in oxygen sensing based on spectroscopic evidence. It was reported that cytochrome b functions as an NAD(P)H oxidase, converting oxygen to O\(_2^−\). The enzymatic complex in mammalian cells is membrane-bound and transduces the conversion of...
oxygen to ROS, according to the following: \( \text{CytFe}^{2+} + \text{O}_2 \rightarrow \text{CytFe}^{3+} + \text{O}_2^{-} \); \( \text{CytFe}^{3+} + \text{NAD(P)}H \rightarrow \text{CytFe}^{2+} + \text{NAD(P)}^{+} \). A resurgence of interest in mitochondrial physiology has developed as a result of new experimental data demonstrating that mitochondria function as important participants in a diverse collection of novel intracellular signaling pathways [24,25]. For instance, a spectroscopic photolysis with monochromatic light has identified a CO-binding heme protein falling within the spectrum of the mitochondrial cytochrome a\(_3\) [25]. This heme protein, presumably located on the plasma membrane, has a low affinity for oxygen and a relatively high affinity for CO (Fig. 3). The same model predicted that another heme protein in the mitochondria has a relatively higher affinity for oxygen and a lower affinity for CO.

These aforementioned observations pertaining to the mitochondrion as a possible oxygen sensor were supported by Duranteau et al. [26]. Compared with normoxia, graded increases in 2,7-dichlorofluorescein (DCF) fluorescence were seen during hypoxia. The antioxidants mercaptpropionyl glycine and phenanthroline attenuated these increases. Of note, azide produced graded increases in ROS signaling, demonstrating that mitochondria respond to hypoxia by increasing the generation of ROS and suggesting that cytochrome oxidase may contribute to this oxygen sensing mechanism [26,27]. It was also proposed that hypoxia activates transcription via a mitochondria-dependent signaling process involving increased ROS, whereas CoCl\(_2\) activates transcription by stimulating ROS generation via a mitochondria-independent mechanism [27–29].

A non-mitochondrial oxygen sensor has, however, been recently proposed as well. Ehleben et al. [30] applied biophysical methods like light absorption spectrophotometry of cytochromes, determination of NAD(P)H-dependent \( \text{O}_2^{-} \) formation, and localization of \( \cdot \text{OH} \) by three-dimensional (3D) confocal laser scanning microscopy to reveal putative members of the oxygen sensing signal pathway leading to enhanced gene expression under hypoxia.

Another hypothesis suggested that a K\(^{+}\) channel protein is an oxygen sensor and that the inhibition of this channel and the ensuing depolarization is the initial event in transduction mechanisms [1,24,25]. Several oxygen-sensitive K\(^{+}\) channels have been identified; however, their roles in the initiation of the transduction cascade and/or cell excitability remain unclear [1,31].

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**Abbreviations:** AA, arachidonic acid; ARNT, aryl receptor hydrocarbon nuclear translocator; CREB, cAMP-responsive element-binding protein; CBP, CREB-binding protein; DAG, diacyl glycerol; ECF, extracellular fluid; HIF-1, hypoxia-inducible factor-1; ICF, intracellular fluid; IP\(_3\), inositol triphosphate; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; ROS, reactive oxygen species; SAPK, stress-activated protein kinase.
In addition, recent studies indicated that molecular oxygen and a variety of neurotransmitters might also modulate Ca\(^{2+}\) channels [30,32].

**Oxygen responsiveness of regulatory transcription factors: molecular aspects**

The putative oxygen sensor responds to dynamic variations in pO\(_2\) and, upon ligand binding, this presumably membrane-bound receptor transduces intracellular chemical/redox signals that relay messages for the regulation of gene expression, a phenomenon mainly involving the activation of transcription factors [35].

**Oxygen homeostasis and HIF-1α regulation: is HIF the hypoxic sensor?**

HIF-1α is a mammalian transcription factor expressed uniquely in response to physiologically relevant hypoxic conditions [34,35]. Studies of the EPO gene led to the identification of a cis-acting hypoxia-response element (HRE) in the 3' flanking region [32–34,39,40]. HIF-1 was identified as a hypoxia-inducible HRE-binding activity (Fig. 3) [34].

Several major mechanisms have shed a thorough light on the role of this transcription factor in oxygen sensing [41–45]. The von Hippel–Lindau tumor suppressor protein (pVHL) has recently emerged as a key factor in cellular responses to oxygen availability, being required for the oxygen-dependent proteolytic cleavage of the α subunits of HIF [43–45]. Extracts from VHL-deficient cells have a defect in HIF-1α ubiquitination activity, which was complemented by exogenous pVHL [42–45]. Analysis of pVHL/HIF-1α interactions defined short sequences of conserved residues within the internal transactivation domains of HIF-1α molecules sufficient for recognition by pVHL. In oxygenated and iron replete cells, HIF-1α subunits were rapidly destroyed by a mechanism that involved ubiquitination by the pVHL E3 ligase complex [41–45].

**Oxygen homeostasis and NF-κB regulation: is NF-κB an oxygen sensor?**

NF-κB is a dimeric, oxygen-sensitive transcription factor that is involved in the regulation of a large number of genes that control various aspects of the immune and inflammatory response [46,47]. It is activated by a variety of stimuli ranging from cytokines, to various forms of radiation, to oxidative stress (such as exposure to H\(_{2}\)O\(_2\)). Recent studies have advanced our understanding of the signal transduction pathway leading to NF-κB activation by cytokines and will provide insights into the mechanism by which NF-κB is regulated by oxidative stress. An important question that is yet to be answered is whether ROS play a physiological role in NF-κB activation [48].

What are the signaling cofactors that trigger and mediate NF-κB signaling cascades? NF-κB is among the most crucial transcription factors shown to respond directly to oxidative stress [48,49]. Antioxidants, for instance, block NF-κB activation in certain cell types, leading to the hypothesis that the activation of this transcription factor is mediated by ROS [49,50]. The involvement of ROS is postulated to regulate the activity of the upstream kinases that converge onto the NF-κB signaling activation pathway. In this respect, wide arrays of antioxidants that can detoxify ROS/RNS have been purported to suppress the activation of NF-κB. For instance, hepatocarcinogen 2-acetylaminofluorene treatment led to the increase of intracellular ROS, which caused the activation of IKK kinases, the degradation of IκB-β, and the accumulation of NF-κB in the nuclear compartment [51–53]. Similarly, α-phenyl-tert-butylinonitrone, an effective spin-trapping agent that reacts with and stabilizes free radical species, has been shown to inhibit pancreatic β cell death and the development of insulin-dependent diabetes mellitus in an NF-κB-dependent pathway [54]. Superoxide dismutase (SOD) expression has negative effects on the activation of NF-κB in transient focal cerebral ischemia, indicating the involvement of specific ROS [54–57]. Of interest, treatment of mammalian cells with H\(_2\)O\(_2\) induced the nuclear translocation of NF-κB and its binding to κB DNA sequences present in the promoter region of numerous genes. In addition, an impaired pulmonary NF-κB activation has been observed in response to LPS in NADPH oxidase-deficient mice [58]. Of note, xanthine oxidase-derived ROS can activate NF-κB [58] and cellular enrichment with polyunsaturated fatty acids can induce the development of oxidative stress condition and the activity of activating protein-1 (AP-1) and NF-κB. Furthermore, hyperoxia has been reported to up-regulate the nitric oxide (NO)-sensitive pathway in vitro and similarly activate AP-1 and NF-κB, suggesting a role for RNS [59]. Because NF-κB can be rapidly induced in a variety of cell types by a diverse set of seemingly unrelated agents, it has been proposed that agents activating this transcription factor do so by increasing a minimum intracellular effective oxidative stress threshold (see Fig. 2).

However, the model of ROS/RNS (oxidative stress) as exclusive messengers in the regulation of the NF-κB signaling pathway cannot be universally accounted for. For instance, it was reported that ROS could act synergistically with TNF-α in causing cytotoxicity via the inhibition of a cytoprotective branch of TNF-α signaling pathways, which starts with NF-κB activation [60–62]. Furthermore, addition of glucosamine to chondrocytes treated with IL-1β or with ROS decreased the activation of NF-κB, but not that of AP-1.
Of note, it has been reported that irreversible inhibition of \( \gamma \)-glutamylcysteine synthetase (\( \gamma \)-GCS), the rate-limiting enzyme in the biosynthesis of glutathione (GSH), an antioxidant thiol, was associated with the augmentation of a pro-inflammatory signal in a ROS-sensitive manner despite the observation that the \( \kappa \)-B/\( \kappa \)-NF-\( \kappa \)-B signaling pathway was down-regulated \([5,6,63,64]\). It was reported that \( L \)-buthionine-\( (S\,;R) \)-sulfoximine (BSO), an inhibitor of \( \gamma \)-GCS, suppressed the oxyexcitation (\( \Delta P_{O2} \))-dependent nuclear localization of RelA (p65), the major transactivating member of the \( Rel \) family, and subsequently suppressed NF-\( \kappa \)-B activation \([5,6,65,66]\). However, in additional studies, BSO was also shown to be capable of inducing intracellular accumulation of ROS, particularly \( \cdot \)OH. Taken together, these data argue for ROS as potential second messengers for cytokine biosynthesis; however, ROS might not be favorably universal messengers in the activation of NF-\( \kappa \)-B \([65]\). In support of this view, further studies presented that the overall NF-\( \kappa \)-B signal transduction cascade begins with a parallel series of stimuli-specific pathways through which cytokines (such as TNF-\( \alpha \) and IL-1\( \beta \)), oxidants (such as \( H_2O_2 \) and mitomycin C), and phorbol ester (such as phorbol 12-myristate 13-acetate, PMA) individually and independently can initiate signaling. These initial pathways culminate in a common pathway through which all of the stimulating agents ultimately signal NF-\( \kappa \)-B activation \([67]\).

### Redox regulation of oxygen-sensitive transcription factors

The major determinant of the redox status in mammalian cells is glutathione (GSH; \( L \)-\( \gamma \)-glutamyl-\( L \)-cysteinyl-glycine), a tripeptide thiol (Fig. 4). This ubiquitous non-essential sulphhydryl amino acid plays a major role in maintaining intracellular redox equilibrium and in regulating cellular defenses augmented by oxidative stress. Synthesized by the action of the rate-limiting enzyme \( \gamma \)-glutamylcysteine synthetase (\( \gamma \)-GCS) \([5,6,65]\), GSH uniquely provides a functional cysteinyl moiety that is responsible for much of the diverse properties of glutathione.

#### Redox regulation of HIF-1\( \alpha \): a redox-sensitive, oxygen-responsive transcription factor

Antioxidant/pro-oxidant equilibrium regulates HIF-1\( \alpha \) redox sensitivity \([65]\). For instance, the cysteine residue in the carboxy-terminal transactivation domain (TAD-C) has been shown to be redox sensitive, thereby...
affecting its interaction with CREB-binding protein (CBP)/p300 co-activators, and that this interaction is directly regulated by redox factor-1 (REF-1) and thioredoxin [65–69]. HIF-1α ubiquitination and degradation by the proteasome system under normoxia is also regulated by redox modifications of the protein [69]. Furthermore, selective inhibition of γ-GCS (GSH depletion) in the alveolar perinatal epithelium has abrogated hypoxia-induced nuclear localization, stabilization, and activation of HIF-1α [5,6]. It appears, therefore, that maintaining GSH equilibrium and, by inference, the shuffling between reduction and oxidation states, are prerequisites for HIF-1α stabilization.

Redox regulation of NF-κB: a redox-sensitive, oxygen-responsive transcription factor

Redox regulation of NF-κB seems to be compartmentalized [5,6,65,69]. Whereas an oxidizing signal is required for the stabilization and translocation of NF-κB subunits, intriguingly, a reduced environment is critical for an optimum DNA-binding activity and transactivity [65]. The activation of NF-κB by a variety of agents can be blocked by NAC, suggesting that the production of ROS may act as a common pathway for a diverse range of stimuli [65,69]. In addition, the inhibitory effects of PDTC suggest post-translational instability and interference with the capacity of NF-κB to bind DNA [65]. This is further supported by the observation that phosphorylation of IkB at specific serine residues can be inhibited by dithiocarbamates, pointing to the possibility that NF-κB translocation and subsequent activation is mediated by ROS, which might induce a cytosolic kinase activity. There is another assumption that GSSG-mediated inhibition of NF-κB implicates the formation of an inactive NF-κB/disulfide complex, thereby inhibiting DNA-binding activity [69,70]. Therefore, although oxidizing conditions are necessary for the activation of NF-κB in the cytosol to allow optimum translocation and dissociation from inhibitory IkB, NF-κB must be maintained in a reduced state in the nucleus for activation to occur [71]. Comprehensive reviews recently discussed oxidant and redox aspects related to transcription factors such as NF-κB and HIF-1α [5,6,65] and cytokine-related pathways [66].

Summary, conclusion, and future prospects

One oxygen sensing theory holds that a heme-containing protein undergoes a conformational change when bound to oxygen, thereby ‘sensing’ oxygen. Two other related hypotheses center on ROS, which are highly unstable, highly reactive superoxides. One ROS theory holds that, as oxygen levels decrease, so do ROS levels. The second theory hypothesizes the opposite, counteracting that as oxygen levels decrease, ROS levels increase. Oxygen sensing and the molecular responses to oxidative stress are regulated, at least in part, by redox-sensitive transcription factors. The abrupt change in \( pO_2 \) constitutes a mechanism that allows a specific genetic regulation. Such transcription factors that form an integral part of redox/oxidative-related pathways are HIF-1α and NF-κB, both of which are sufficiently tuned to govern a specific response in hypoxia and a relative hyperoxic shift. The ability of cells to regulate a factor critical to the hypoxic/hyperoxic response depends on a specific post-transcriptional modification. Furthermore, modulating the antioxidant/pro-oxidant equilibrium by altering the GSH/GSSG redox potential evokes a genetic switch between HIF-1α and NF-κB, an effect uncoupled from the normal pattern followed with a prevailing \( pO_2 \). Thus, dynamic variations in oxidative stress and redox equilibrium regulate gene expression, thereby bearing consequences for screening emerging targets for therapeutic intervention under conditions of oxidative stress mimicking clinical oxygen therapy. Components of the intracellular oxidative machinery and its regulation of redox-sensitive transcription factors may, therefore, help unravel the oxygen sensing network and redox-related pathways in physiology and pathophysiology.

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