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REVIEW ARTICLE

The Role of Oxygen in Health and Disease - A Series of Reviews

This is the third article in the series of reviews focusing on the role that oxygen plays in health and disease. In this article, Drs. Wright and Dennery discuss appropriate clinical indications of oxygen therapy and how oxygen affects gene-transcription signaling pathways, leading to interventions that prevent hyperoxic injury.

Sherin U. Devaskar, M.D.
Editor in Chief

Manipulation of Gene Expression by Oxygen: A Primer From Bedside to Bench

CLYDE J. WRIGHT AND PHYLLIS A. DENNERY

Division of Neonatology [C.J.W., P.A.D.], Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104; Department of Pediatrics [P.A.D.], University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania 19104

ABSTRACT: For nearly 100 y, pediatricians have regularly used oxygen to treat neonatal and childhood diseases. During this time, it has become clear that oxygen is toxic and that overzealous use can lead to significant morbidity. As we have learned more about the appropriate clinical indications for oxygen therapy, studies at the bench have begun to elucidate the molecular mechanisms by which cells respond to hyperoxia. In this review, we discuss transcription factors whose activity is regulated by oxygen, including nuclear factor, erythroid 2-related factor 2 (Nrf2), activator protein 1 (AP-1), p53, nuclear factor κB (NF-κB), signal transducers and activators of transcription protein (STAT), and ccat/enhancer binding protein (CEBP). Special attention is paid to the mechanisms by which hyperoxia affects these transcription factors in the lung. Finally, we identify downstream targets of these transcription factors, with a focus on heme oxygenase-1. A better understanding of how oxygen affects various signaling pathways could lead to interventions aimed at preventing hyperoxic injury. **(*Pediatr Res* 66: 3–10, 2009)**

Oxygen therapy has a long and tortuous history in Neonatology. The pendulum has swung from a liberal use of supplemental oxygen in the early 20th century, to limited application in the 1950s based on the association with retinopathy of prematurity. Today, clinical studies are focused on addressing which neonatal pathologic states require treatment with oxygen, and what level of oxygen administration is safe. In concert with these clinical studies, much work has been done at the bench to ascertain how oxygen affects gene expression. This is of particular relevance in neonates because changes in gene expression at critical times in development can have long-lasting effects and subsequent consequences on lung structure and function. This review will address lessons learned and new insights as to the effects of hyperoxia on pulmonary gene expression.

EVOLUTIONARY PERSPECTIVE

Responses to atmospheric oxygen have evolved in eukaryotes during the last 1.5 billion years (1). The ability of organisms to reduce oxygen to water critically altered cellular metabolism and energy production, but also resulted in the formation of toxic reactive oxygen species (ROS) *via* the mitochondrial respiratory chain. These radicals are electron donors, which can damage DNA, RNA, protein, and lipids. They can also propagate deleterious reactions throughout cells and tissues resulting in death and apoptosis. In addition, these ROS can alter gene expression by modulating transcription factor activation, which then impact downstream targets. In oxygen breathing animals, only three tissues—the cornea, the skin, and the respiratory tract epithelium—are exposed to 21%

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Correspondence: Phyllis A. Dennery, M.D., Division of Neonatology, Children's Hospital of Philadelphia, 34th and Civic Center Blvd., Philadelphia, PA 19104; e-mail: dennery@email.chop.edu
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Abbreviations: AP-1, activator protein 1; **ARE,** antioxidant response elements; **Bach1,** basic leucine zipper transcription factor 1; **BPD,** bronchopulmonary dysplasia; **C/EBP,** ccat/enhancer binding protein; **ENaC,** epithelium sodium channel; **HO-1,** heme oxygenase-1; **IκB,** inhibitor of κB; **Keap 1,** Kelch-like ECH-associated protein 1; **NF-κB,** nuclear factor κB; **Nrf2,** nuclear factor, erythroid 2 related factor 2; **ROS,** reactive oxygen species; **STAT,** signal transducers and activators of transcription protein

oxygen, equivalent to a partial pressure of about 160 mm Hg at sea level. The remaining tissues are exposed to much lower oxygen tensions. The affinity of Hb for oxygen maintains the P_{O_2} in the mitochondria below 0.5 mm Hg, limiting the production of ROS and effectively protecting the body from oxygen toxicity (2). Before the advent of the medical use of oxygen, humans were rarely exposed to oxygen tensions that were greater than those in their ambient environment. Thus, it stands to reason that evolution may not have dictated a well-developed response to acute increases in oxygen tension. The notable exception is the transition at birth from the womb to the outside world where we were rapidly shifted from a relative hypoxic environment to relative hyperoxia. Additionally, the lung epithelium is constantly exposed to "relative hyperoxia" compared with other tissues and is further stressed by oxygen therapy.

HISTORICAL PERSPECTIVE

From the time of its discovery in the 1770s, oxygen has held promise as an elixir for multiple human ailments. Within 10 y of its discovery, Anton Lavoisier applied oxygen to newborn infants requiring resuscitation (3). By the early 1900s, physicians were administering oxygen to treat cyanosis in premature infants (4). Shortly thereafter, oxygen therapy became widespread in neonatal units, with therapeutic indications ranging from respiratory distress to periodic breathing. However, by the early 1950s, published reports linking oxygen to the pathogenesis of retinopathy of prematurity began to appear, and the use of oxygen was quickly curtailed (5). Nevertheless, physicians were reminded that oxygen was a powerful and life-saving therapy when increased mortality from hyaline membrane disease (6) and the resurgence of cerebral palsy (7) were observed. This demonstrated that both too much and too little oxygen were problematic. Vigorous debates about the appropriate use of oxygen during newborn resuscitation (8) and the proper pulse oximetry saturation goals for premature infants (9) currently rage on. At this time, six multicenter randomized controlled trials are attempting to define optimal oxygen therapy goals for preterm babies (9).

Studies at the bench pair nicely with these clinical trials. Investigators have used multiple *in vivo* and *in vitro* models to determine how oxygen affects gene expression and subsequent lung structure and function. Hyperoxia results in alveolar and endothelial cell destruction, fluid leak into the air space, respiratory failure, and mortality (10). The lungs of animals exposed to hyperoxia show increased mean linear intercepts, influx of macrophages, extracellular matrix turnover, and fibrin deposition (11). During hyperoxia, ROS are produced both by the electron transport chain in the mitochondria and by the membrane-bound NADPH oxidase (12–15). ROS cause DNA strand breaks and other chromosomal aberrations (16,17), which stimulate the expression of genes involved in inhibiting cell cycle progression (18). There is clear evidence in animal models that exposure to hyperoxia results in lung morphology similar to that of bronchopulmonary dysplasia (BPD) (11,19). These studies serve as important correlates to the ongoing trials involving oxygen therapy for premature infants.

HYPEROXIC GENE REGULATION

Organs, tissues, and cells have evolved systems to rapidly respond to changes in their microenvironment. A stimulus, which causes a perturbation, must be detected and translated into a response, which then facilitates a return to the steady state (Fig. 1). Receptors, signaling pathways, transcription factors, and downstream changes in proteins and metabolic function have evolved for this purpose. Only a few transcription factors that specifically alter gene expression in response to increased oxygen tension have been identified, as well as some direct downstream targets (Table 1). These will be discussed later.

TRANSCRIPTION FACTORS RESPONSIVE TO HYPEROXIA

Nrf2. The detoxification of ROS and electrophiles is important to prevent cellular injury (Fig. 2). The transcription factor nuclear factor, erythroid 2-related factor 2 (Nrf2) regulates the inducible expression of a group of detoxification enzymes, such as glutathione S-transferase and NAD(P)H:quinone oxidoreductase, *via* antioxidant response elements

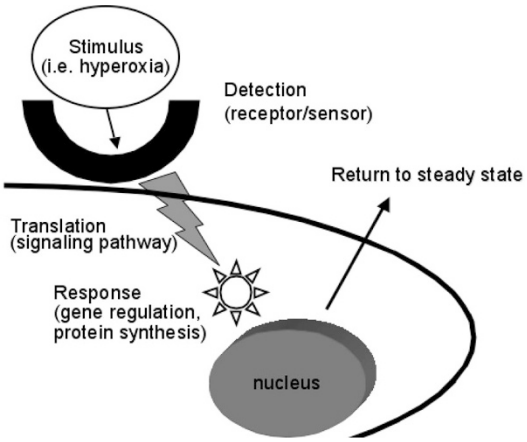

Figure 1. How a stimulus is perceived and how cells respond to return to the steady state. Cellular receptors or sensors detect stimuli such as hyperoxia. This leads to the translation of this signal *via* signal transduction pathways, which result in transcription factor activation. This then generates a response such as gene regulation and subsequent protein synthesis and a return to the steady state.

Table 1. *Summary of transcription factors regulated by hyperoxia*

Transcription factor	Regulated gene products	Protective effect against hyperoxia	References
Nrf2	ARE-mediated phase 2 detoxifying and antioxidant enzymes (i.e., HO-1)	Yes	(26–30)
AP-1	IL-8	Yes	(34–40)
NF-κB	IGFBP2 ICAM-1 IL-6 ENaC p21	Yes/no	(56,61–67,71,76, 78–87,94,103,106, 107,110,112–116, 118–125)
STAT	IL-6	Yes	(89,90)
CEBP proteins	CCSP	Yes	(38,92,93)

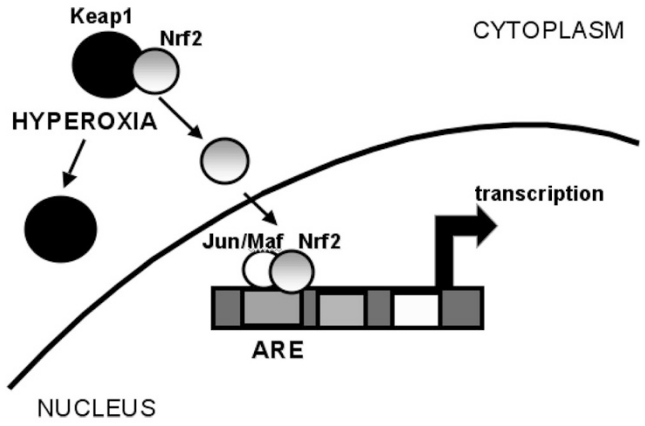

Figure 2. Nrf-2-mediated gene expression. The transcription factor Nrf-2 is sequestered in the cytoplasm bound to Keap1. Upon hyperoxic exposure, it dissociates from Keap1 and can migrate to the nucleus where it forms a complex with Jun or Maf proteins and results in gene activation.

(ARE). Under normal circumstances, Nrf2 is retained in the cytoplasm by a repressor protein Kelch-like ECH-associated protein 1 (Keap1). Exposure to xenobiotics and oxidants leads to the dissociation of Nrf2 from Keap1, which allows the free Nrf2 to translocate to the nucleus where it heterodimerizes with c-Jun, an activator protein 1 (AP-1) family protein (20). The consensus binding sequence of Nrf2 shows high similarity to the ARE/electrophile-responsive element sequence previously identified (21–23). Nrf2 can also heterodimerize with small Maf proteins to regulate ARE-mediated gene expression (24). These Maf proteins are so named because of their structural similarity to the founding member, the oncoprotein v-Maf. They include a characteristic basic region linked to a leucine zipper (b-Zip) domain, which mediate DNA binding and subunit dimerization, respectively (25).

Lung Nrf2 responds to hyperoxia (26). Linkage analysis identified Nrf2 as an important mediator of protection against lung hyperoxic injury (27) and mice deficient in Nrf2 exhibit aggravated lung injury and a lack of upregulation of ARE-mediated phase 2 detoxifying and antioxidant enzymes (28). Further gene array analysis of wild type *vs.* Nrf2-deficient mice revealed discordance in multiple genes, thus identifying potential downstream targets of this important transcription factor (29). In fact, a single nucleotide polymorphism found in the Nrf2 promoter increases the risk of acute lung injury in human subjects (30). This evidence provides an important translational correlate and may lead to the development of therapeutic strategies.

AP-1. AP-1 was first identified as a transcriptional factor that binds to an essential *cis*-element of the human metallothionein II gene (31). It is composed of fos and jun protein dimers that bind *via* hydrophobic interactions of their leucine-zipper regions (32). The jun/jun and jun/fos dimers form the AP-1 complex. This transcription factor controls genes involved in cellular proliferation and death in response to various stimuli including hyperoxia. The consensus AP-1-binding site is embedded in the ARE where fos and jun proteins may heterodimerize to Nrf2 in the presence of electrophiles and oxidants as discussed earlier (33). Blocking AP-1 activation enhances hyperoxia-induced cell death in murine lung epithelial cells (34,35). One specific target of hyperoxia-induced JNK1/AP-1 activation in A549 cells is the IL-8 promoter (36). This could modulate inflammatory responses with hyperoxic exposure. It is interesting to note that neonatal mice exposed to hyperoxia show no increase in lung AP-1 consensus sequence binding (37) in contrast to their adult counterparts (37,38). However, in the brain, increased AP-1 consensus sequence binding occurs in the forebrain and hippocampus of both adult and younger rats exposed to hyperoxia (39,40). These data suggest both maturational differences and tissue specificity of AP-1 activation.

p53. The transcription factor p53 regulates the expression of a large number of target genes including those related to cell cycle arrest, cell death, and DNA repair (41). Since its discovery in 1979, p53 has been identified as a tumor suppressor and its role in human cancer has become clearer (42). Under basal conditions, p53 resides in the cytoplasm and is subjected to ubiquitin-mediated proteolysis. However, in response to stimuli such as DNA damage, p53 is phosphorylated, stabilized, and enters the nucleus (41). Under conditions of cellular stress, activated p53 initiates growth arrest and induces pro-apoptotic gene expression (42). Hyperoxia increases p53 gene transcription, protein levels, and activity (16,43–45). In preterm baboons, exposure to hyperoxia results in increased p53 protein levels in airway epithelium (46,47). However, in $p53^{-/-}$ mice exposed to hyperoxia, lung injury and lethality did not differ from similarly exposed wild-type animals (16,48). These data indicate that the exact role of p53 in modulating the cellular response to hyperoxia remains to be elucidated.

NF-κB. The nuclear factor kappa B (NF-κB) family is composed of highly conserved dimeric proteins, which activate genes that regulate apoptosis, inflammation, and oxidative stress (49–51) (Fig. 3). This factor regulates gene expression and was first described by Baltimore and Sen (52). In quiescent cells, NF-κB dimers remain sequestered in the

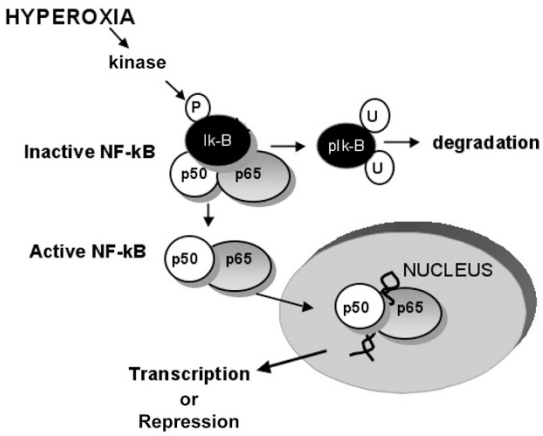

Figure 3. NF-κB-mediated gene expression. With hyperoxia, there is phosphorylation (p) of the inhibitory protein IκBα on tyrosine 42. This results in the ubiquination (u) and subsequent degradation of IκBα. This allows for dissociation and nuclear translocation of the active NF-κB complex (p65 and p50 are represented here), binding to consensus sequences on various genes and transcriptional activation or repression of gene expression.

cytoplasm bound to a member of the κB (IκB) family of inhibitory proteins (50). IκBα is the prototypical member of this family and the most well studied. With inflammatory or oxidant stress, IκBα is phosphorylated, resulting in dissociation and unmasking of the nuclear localization sequence of NF-κB (51). After inflammatory stimuli, such as TNF-α activation, IκBα is phosphorylated on serine 32/36 and degraded through the proteosomal pathway (51). In addition to this canonical pathway, an atypical pathway of NF-κB activation results from specific phosphorylation of IκBα on tyrosine 42 (53). This occurs after stimulation with pervanadate, nerve growth factor (NGF), hydrogen peroxide, and ischemia-reperfusion (53–55) and, as most recently demonstrated, with hyperoxia (56). This latter pathway represents an intriguing molecular target for modulating the pulmonary response to hyperoxia.

It is important to note that NF-κB nuclear translocation and DNA binding can either enhance or suppress target gene expression. The subunit composition of the NF-κB dimer likely confers specificity to the expression of target genes after activation (57). The most abundant NF-κB protein is the p65-p50 dimer (58). The p65 subunit contains a transactivation domain that interacts with other transcription proteins to increase gene expression (59). The p50 subunit lacks this transactivation domain, and can repress transcription when bound to DNA as a p50-p50 homodimer (59,60). Furthermore, the ability of NF-κB to alter gene expression is affected by posttranslational modifications including phosphorylation and acetylation (59).

Hyperoxia-induced NF-κB activation appears to be stimulus and cell type specific. Nuclear translocation of NF-κB was shown in A549 lung adenocarcinoma cells exposed to hyperoxia-induced but this activation did not protect against cell death (61). Also, in adult mice exposed to hyperoxia, NF-κB activated proinflammatory markers in pulmonary lymphocytes (62). Furthermore, in fetal mouse lung explants, hyperoxia-induced NF-κB activation was associated with increased apoptosis which was reversed by blocking NF-κB activation (63). In contrast, inhibition of hyperoxia-induced NF-κB activation accelerated nonapoptotic cell death in primary and transformed lung epithelial cells, resulting in decreased levels of MnSOD (64). Additionally, A549 cells pretreated with hyperoxia showed less apoptosis after exposure to hydrogen peroxide, an effect reversed by inhibiting NF-κB activation (65). In other examples, NF-κB was not activated in response to hyperoxic exposure (66,67), suggesting that this signaling pathway is cell specific. The lung contains over 40 different cell types (68), and the response to hyperoxia is cell type specific. Endothelial cells are very sensitive to oxygen toxicity, whereas type II epithelial cells are resistant and proliferate in the recovery phase (69). Furthermore, in the developing lung, exposure to hyperoxia prevents the normal differentiation of type II cells to type I cells in the developing lung (70). Further studies are necessary to fully dissect the specificity and complexity of hyperoxia-induced NF-κB activation. Nevertheless, these findings suggest that interventions to either inhibit or enhance NF-κB activation in hyperoxia could be of therapeutic benefit.

Various clinical interventions, such as glucocorticoids, can inhibit NF-κB activation (71–74). Adrenalectomized adult mice exposed to hyperoxia had less lung injury and had improved survival due to increased NF-κB activation (75). Thus, hyperoxia-induced NF-κB activation, when not limited by endogenous glucocorticoids, protects the adult lung from oxygen toxicity (71). Interestingly, after glucocorticoid therapy for BPD, cells obtained from tracheobronchial lavage fluid of premature neonates showed inhibition of NF-κB activation (76). Nitric oxide, which may prevent BPD in some infants (77), also inhibits NF-κB activity (78). The clinical implications of these findings remain to be explored in humans.

Of particular interest to pediatricians are the maturational differences found in NF-κB activation. Multiple models have shown increased NF-κB activation in neonates compared with adults after exposure to inflammatory and oxidant stimuli (79–81). In rat fetal alveolar type II cells, NF-κB translocates to the nucleus and binds DNA after hyperoxic exposure (82). This binding peaks soon after birth and gradually decreases postnatally, suggesting that NF-κB regulates genes involved in the transition from the relative hypoxic environment seen *in utero* (82). This activation may have important downstream effects as shown in hyperoxia exposed fetal lung fibroblasts where NF-κB activation prevented apoptosis through the suppression of proapoptotic genes (56). In contrast, this hyperoxic activation of NF-κB was not seen in adult lung fibroblasts (57). In the only published study evaluating hyperoxia-induced NF-κB activation in a neonatal *in vivo* model, Yang *et al*. showed that hyperoxia-induced NF-κB occurred in the lungs of neonatal but not in adult mice (81). This activation was associated with the relative tolerance to hyperoxic injury in the neonatal animals when compared with adults, and this tolerance was reversed when hyperoxia-induced NF-κB activation was inhibited (81). In contrast, clinical studies show that enhanced NF-κB activation is linked to respiratory distress syndrome and an increased risk of developing BPD in preterm infants (83–85). Thus, it is not yet clear whether inhibition of lung NF-κB is beneficial or harmful in human neonates.

The hyperoxic activation of NF-κB has also been investigated in tissues other than the lung. Using a bioluminescent NF-κB reporter mouse line, Dohlen *et al*. showed increased NF-κB activity in the brain after resuscitation with 100% O_2 (86). In other studies, hyperoxia without preceding ischemia decreased NF-κB activation in the basal forebrain, with a more pronounced effect in aged *vs.* young mice (87).

It is clear that the NF-κB–mediated response to oxygen is influenced by maturation. Whether these changes are beneficial or detrimental remain to be seen. Understanding the maturational differences in hyperoxia-induced NF-κB activation could help guide interventions aimed to modulate this response in neonates.

STAT. Another important transcription factor involved in hyperoxic gene regulation is the signal transducers and activators of transcription protein (STAT). This family of proteins is activated by various cell surface receptors in response to ligands, including cytokines, growth factors, and peptides

(88). Hyperoxic lung injury is attenuated in mice constitutively expressing Stat3 in respiratory epithelial cells (89). Conversely, mice with disruption of Stat3 in respiratory epithelial cells demonstrate exaggerated hyperoxic lung injury and increased expression of proinflammatory cytokines including IL-6 (90).

CEBP. The ccat/enhancer binding protein (C/EBP) family of proteins are basic leucine zipper transcription factors that respond to extracellular signals to regulate cell proliferation, differentiation, and tissue development (91). C/EBPβ and C/EBPδ consensus sequence binding was increased in the lungs of young and aged mice exposed to hyperoxia (38). In the mouse exposed to hyperoxia, there is downregulation of the protective Clara cell secretory protein (CCSP) due to enhanced C/EBPβ nuclear translocation and binding to the CCSP promoter (92). These studies are particularly relevant because C/EBPα is required for lung maturation (93).

Other transcription factors regulated by hyperoxia. Acute and chronic exposure to hyperoxia may result in activation of a variety of other transcription factors including cmyc, fos-related antigen (Fra)-1, junB, c-fos as well as NGF1-A and -B (94). Furthermore, in the neonatal lung, hyperoxia can cause downregulation of sox-7 and sox-18 (94). The relevance of these signaling events is not fully clear.

SPECIFIC DOWNSTREAM GENE TARGETS OF HYPEROXIA

Because transcription factors that are regulated in hyperoxia control a multitude of genes, it would be difficult to list all of these genes (Table 1). For example, the activation of NF-κB can regulate the expression of over 100 genes. Nevertheless, only a small fraction of NF-κB responsive genes are activated in hyperoxia. Some of the genes regulated by Nrf-2 and NF-κB will be highlighted below.

Nrf-2-regulated genes. Nrf2 binds to the ARE, driving the expression of genes including antioxidants such as glutathione peroxidase, catalase, superoxide dismutase, thiol metabolism-associated detoxifying enzymes such as glutathione-s-transferase and stress-response genes such as heme oxygenase-1 (HO-1), among others (25–28). These genes are all highly responsive to hyperoxia. We will focus on HO-1 as an example of an Nrf-2 regulated gene regulated in hyperoxia.

The HO-1 gene encodes for the rate-limiting enzyme in the degradation of heme and the formation of biliverdin, which is subsequently reduced to bilirubin by biliverdin reductase. In recent years, many roles have been identified for this protein and it has been clearly demonstrated that HO-1 is a generalized response to oxidative stress (95). The mouse HO-1 gene is 6.8 kb in length and organized into four introns and five exons. A promoter sequence is located 28 base pairs (bps) upstream of the transcription initiation site. There is a proximal enhancer (PE) directly upstream of the promoter and there are two more distal enhancers located at 4 kb (DE1) and 10 kb (DE2) upstream of the transcription initiation site. Each enhancer region contains multiple transcription factor binding sites including composite AP-1 and NF-E2 or CREB/ATF sites (Fig. 4) (96–98). Induction of HO-1 in oxidative stress is

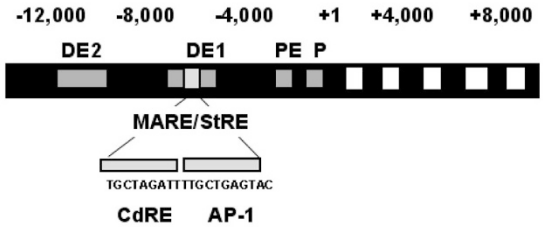

Figure 4. Diagram of the HO-1 gene. Numbers indicate base pairs. There are two DE. These contain a multiple antioxidant response element/stress response element (MARE/StRE), which has consensus sequence for a cadmium response element as well as an AP-1 binding site. The gene also contains a PE and a promoter (P).

via Nrf2 and small Maf proteins binding to the ARE (99). Competitive binding between Nrf2 and BTB and CNC homology 1, basic leucine zipper transcription factor 1 (Bach1), at the ARE is important in heme-mediated regulation of HO-1 (100). Several investigators have documented hyperoxic induction of HO-1 in adult mice. However, in the neonatal rodent HO-1 induction is limited. In the neonatal mouse and rat, hyperoxic exposure did not result in a significant increase in HO-1 mRNA as it did in similarly exposed adult (101,102). In another study, lung HO-1 mRNA only increased after 10 d of hyperoxic exposure in neonatal mice (94) whereas this occurred within 24 h in adult mice (103). There may be some teleological wisdom in not further elevating the levels of HO-1 when they are already quite high at birth and in the neonatal period, especially if this could lead to deleteriously high levels thus aggravating hyperoxic injury (104). We have also observed increased protein levels and DNA binding for Bach1, an inhibitor of HO-1 transcriptional activation, in neonates at baseline and after exposure to hyperoxia compared with adults (102). Typically, Bach1 is degraded in the presence of ROS (105). Enhanced Bach1 expression could ensure that there are sufficient levels for HO-1 gene inhibition in the neonate.

NF-κB regulated genes. The IGF-binding protein (IGFBP)2 promoter has NF-κB consensus sequence binding sites, and both NF-κB consensus sequence binding and IGFBP2-promoter reporter activity increase in response to hyperoxia (106). This binding protein inhibits DNA synthesis and cellular entry into the S-phase, indicating a role for hyperoxia-induced NF-κB activation in modulating oxygen toxicity in the lung. Methylprednisolone treatment inhibits hyperoxia-induced NF-κB activation and down-regulates ICAM-1 expression in human pulmonary artery endothelial cells (107), resulting in less neutrophil adhesion to the endothelium. As discussed earlier, adrenalectomized mice show attenuation of hyperoxic lung injury, and this is associated with preservation of NF-κB activation and induction of IL-6 (71). This cytokine is under the exclusive regulation of NF-κB with inflammation (108,109). Whether IL-6 is exclusively regulated by NF-κB in response to hyperoxia is not known. Nevertheless, IL-6 is enhanced in the lungs of neonatal and adult mice in response to hyperoxia (110), although this phenomenon is not consistently observed in adult mice (62,103). The amiloride-

sensitive sodium channel, epithelium sodium channel (ENac), responsible for sodium and fluid absorption from the alveolar space (111), has an NF-κB binding site (112), and both NF-κB activation and ENaC gene expression increase with relative hyperoxia (113,114). Furthermore, hyperoxia-induced ENaC expression is prevented with NF-κB blockade (114) in some reports but not others (115,116).

Cell cycle genes. Another important effect of hyperoxia is the modulation of genes involved in cell cycle regulation. Both acute and chronic exposures to hyperoxia result in upregulation of p21 (94). Of note, NF-κB is known to regulate the expression of p21 in some cells (117). This key inhibitor of cell cycle regulation and cellular proliferation is increased in both the neonatal (118) and adult (119) lung after exposure to hyperoxia. Expression of this protein in response to hyperoxia relies on either TGF-β signaling (120) or p53 activation (121,122). Upregulation of p21 is protective against hyperoxic injury in both neonatal (123) and adult (124) mice. It is hypothesized that inhibition of cellular proliferation during periods of oxidative stress allows for additional time to repair damaged DNA (125) thus providing cytoprotection.

CONCLUSION

Hyperoxia regulates multiple transcription factors in the lung. These, in turn, regulate a variety of downstream targets including ARE-regulated genes such as HO-1, antioxidant enzymes that are important in the detoxification of electrophiles, as well as genes involved in cell cycle regulation and the inflammatory response. The overall effect of hyperoxia in the lung depends on the maturational stage of the organism. The net effect of hyperoxic lung gene regulation may be both enhanced cytoprotection and worsened lung function. In the neonate where postnatal lung development is crucial to proper alveolar formation, hyperoxic gene regulation may have long-lasting effect on lung structure and function. A further understanding of how hyperoxia affects specific signaling pathways and subsequent gene expression could lead to interventions aimed at preventing hyperoxic injury.

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