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DEVELOPMENTAL DIFFERENCES IN THE ROLE OF INTERLEUKINS IN HYPEROXIC LUNG INJURY IN ANIMAL MODELS

Vineet Bhandari

Division of Perinatal Medicine, Department of Pediatrics, Yale University School of Medicine, New Haven, CT.

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1. ABSTRACT

Interleukins (IL) are part of the group of immune mediators known as cytokines. IL are produced by many different cells and possess a wide spectrum of biological activities. This review will be focused on the role of IL-1 to 6, 8, 10-13 as it pertains to the effects of hyperoxia on the adult and newborn lung in animal models. Hyperoxic exposure to the adult and newborn lung had variable effects on the expression of IL-1α and IL-1β. Increased IL-6 levels were seen in adult lungs by day 3 and in the newborn lungs by day 10 of exposure to hyperoxia. IL-8 also peaked around day 10 in the newborn lung but there were no significant changes in IL-10. Pretreatment with IL-1, endotoxin, rhSOD, lidocaine, lisofylline, pentoxifylline and overexpression of IL-6, 11, and 13 seemed to attenuate hyperoxic lung injury in the adult. This protection was accompanied by increased pulmonary MnSOD, VEGF expression and decreased apoptosis.

It is clear that IL have a significant role to play in hyperoxic lung injury. Increased IL expression and release has a cascade effect and appears to predate the influx of inflammatory cells. There are significant differences in the type and timing of IL expression and release in the adult and newborn lung in response to hyperoxia. Designing a therapeutic approach to counteract oxygen toxicity in the immature lung first needs understanding of the unique responses in the newborn.

2. INTRODUCTION

Cytokines are regulatory peptides that can be produced by virtually every nucleated cell type in the body and they have pleiotropic regulatory effects on hematopoietic and many other cell types that participate in host defense and repair processes (1). Cytokines often possess overlapping biological activities, exert different effects at different concentrations, can either synergize or antagonize the effects of other cytokines, are regulated in a complex manner, and function via cytokine cascades (2).

Interleukins (IL) are part of this group of immune mediators. Based on the pattern of cytokine production, Mossman *et al* classified the CD4+ helper T (Th) cells into 2 major groups (3). Murine Th1 cells produce interferon gamma, IL-2, tumor necrosis factor (TNF) and are responsible for macrophage activation, CD4+ T-cell mediated cytotoxicity, and B-cell help for synthesis of IgG2a, all of which are classic responses associated with cell-mediated immunity (4). By contrast, murine Th2 cells produce IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13 and facilitate humoral immune responses (4). These are summarized in Table 1. IL are produced by many different cells (probably all cell types) and possess a wide spectrum of biological activities. IL are involved in processes of cell activation, cell differentiation, proliferation and cell to cell interactions. Each IL acts on a specific group of cells that express the correct receptor for the IL. The same IL can be produced by different cell types and an individual IL may act on different cell types, eliciting variable biological responses depending on the particular cell and its environment.

Acute pulmonary injury secondary to hyperoxia is complex and multifactorial (5). The acute lung injury

Table 1. Characteristics of Th1 and Th2 responses[1]

	Th1 cell characteristics	Th2 cell characteristics
IFN-gamma, IL-2, TNF production	+ + +	-
IL-3 production	+ +	+ +
IL-4, IL-5, IL-13 production	-	+ + +
IL-10 production	±	+ +
Macrophage activation	+ + +	-
Antibody isotypes stimulated (mouse)	IgG2a	IgE, IgG1 (IgE, IgG4 in humans)
Biologic actions	• Cell mediated immunity • Stimulates microbicidal acivities of phagocytes • Production of opsonizing and complement fixing IgG antibodies • Proliferation and differentiation of CD8+ cytolytic T lymphocytes	• Humoral immunity • Defense against helminth and arthropod infections • Allergic reactions • IL-4, 10, 13 antagonize actions of IFN-γ and inhibit macrophage activation

Th: T helper cells; IL: interleukin; TNF: tumor necrosis factor; [1] Adapted from reference 72.

caused by hyperoxia is characterized by severe endothelial damage, alveolar epithelial injury and increased pulmonary permeability (6,7). Furthermore, there is an influx of inflammatory cells that increases lung damage (5). This inflammatory cell influx is orchestrated and amplified by chemotactic factors, including IL (8). The severe edema and hypercellularity occurring within a few days and the accompanying initial pulmonary inflammatory processes decrease despite continued exposure to hyperoxia (9). Despite the initial apparent histological improvement, chronic pulmonary inflammation ensues in the subsequent few weeks (9). The extent of the chronic process may depend on the lung's acute response to hyperoxia (9).

The response of the newborn animal is significantly different from that of the adult animal (10-15). Newborn animals of several species survive twice as long as adults in hyperoxia and have a significantly later onset of inflammation (10,11,13-15). Neonatal responses are unique, probably because injury occurs during the period of alveolar development (5). Studies of hyperoxic injury in newborn animals have shown morphologic changes similar to those seen in human bronchopulmonary dysplasia (BPD) (16,17).

The use of animal models with immature lungs to study hyperoxic lung injury is well established (5). A better understanding of the role of inflammation in the immature animal exposed to hyperoxia, especially the type and timing of the release of IL, will be useful in the elucidation of the possible sequence of events in the development of BPD in the human preterm neonate.

IL-1 to 25 have been described thus far. Only a handful (IL-1 to 6, 8, 10-13) have been studied in hyperoxic lung injury. The characteristics of the IL described to play a role in hyperoxic lung injury have been highlighted in Table 2. This review will be limited to the role of IL-1 to 6, 8, 10-13 as it pertains to the effects of hyperoxia on the lung in animal models/cell cultures. The focus will be on highlighting the developmental differences of hyperoxic lung injury vis-à-vis IL expression and release.

The following format will be used for each IL: (i) characteristics of the IL, (ii) details of studies in adult cell culture models of hyperoxic lung injury, (iii) details of studies in adult models, (iv) details of studies in newborn/fetal cell culture systems, (v) details of studies in newborn/fetal models, and (vi) summary.

3. INTERLEUKIN-1

The 3 known constituents of the IL-1 family, IL-1α, IL-1β and IL-1receptor antagonist (IL-1RA), are structurally related to one another and bind with similar affinities to IL-1 receptors (IL-1R) on cells (18). IL-1α and IL-1β are potent agonists that elicit broad-ranging biological responses in various cells, which are blocked by IL-1RA (19). Nearly all of the cell types that produce IL-1α and IL-1β also produce IL-1RA (18). Both isoforms of IL-1 recruit cells to sites of inflammation and stimulate the production of proinflammatory mediators (19). IL-1RA is the only known example of a naturally occurring protein that acts as a specific receptor antagonist of a cytokine or hormone-like molecule (18). Once expressed, the members of the IL-1 gene family appear to work in concert to control crucial inflammatory and host defense responses, thus the balance between agonists and antagonists in the IL-1 system is likely to have profound effects on the pathogenesis of inflammatory diseases (18-20). The levels of IL-1RA detected at sites of inflammation do not appear to be high enough to completely block IL-1R signaling; thus physiologically, IL-1RA may serve to downregulate the response to IL-1 rather than inhibit it (19).

Hyperoxic (95% O_2) exposure of alveolar macrophages obtained from adult monkeys via bronchoalveolar lavage (BAL) for 24 hours (h), resulted in significantly increased release of IL-1β (21).

Adult mice exposed to hyperoxia for 3 days had increased lung IL-1 mRNA compared to mice in room air (22). No increase of IL-1β expression was seen in murine lungs after 12 h of hyperoxia (23). Welty *et al* reported no increase in IL-1β mRNA in adult mice through 72 h of hyperoxia (24). In contrast, in adult mice exposed to hyperoxia, a 5-fold increase of IL-1α and a 7-fold increase in IL-1β mRNA (after correcting for CuZn superoxide dismutase (SOD), which is relatively unchanged in hyperoxic lungs) were observed by 4 days of exposure (25). IL-1β expression increased in polynuclear leukocytes with the length of oxygen exposure; in contrast, mononuclear leukocytes expressing IL-1β, decreased significantly (25). While IL-1α and IL-1β protein levels could not be detected in the BAL fluid, a large increase in IL-1β protein was detected by day 3 of hyperoxia by immunohistochemistry (25). The study by Welty *et al* (24) used FVB mice while the study by Piedbouf *et al* (25) used C3H/HeJ mice; this

Table 2. Characteristics of IL involved in hyperoxic lung injury [1]

Name	Size	Structure	Major cellular sources	Major cellular targets	Major biologic actions
IL-1 (α, β)	17 kD mature form; 33 kD precursor	β- barrel	• Monocytes • Macrophages • Neutrophils • Eosinophils • Mast cells • Platelets • Lymphocytes • Endothelial cells	• CD4+ Th2 cells • CD8+ T cells • B cells	Neutrophil and macrophage emigration Production of cytokines Cytotoxic activity
IL-2	14-17 kD	Short-chain 4-α helical bundle	• Mature T cells	• Monocytes • Macrophages • T cells • B cells • NK cells	Differentiation of monocytes to macrophages IL-1 secretion T, B, and NK cell proliferation and activity Cytotoxic activity
IL-3	20-26 kD	Short-chain 4-α helical bundle	• T cells • NK cells • Mast cells	• Monocytes • Macrophages • Eosinophils • Mast cells • Hemopoietic stem cells	Proliferation and differentiation of target cells
IL-4	18 kD	Short-chain 4-α helical bundle	• Thymocytes • Mature T cells • Mast cells • Basophils • CD4+ Th2 cells	• Monocytes • Macrophages • Neutrophils • Eosinophils • Endothelial cells • Fibroblasts • B cells • Th1 cells • Th2 cells • CD8+ cells • NK cells	Growth and activation of B cells Inhibition of differentiation of Th1 cells and production of IFN-γ Differentiation of Th2 cells Differentiation of CD8+ T cells Production of IL-5 Inhibition of proliferation of NK cells Anti-inflammatory action on T cells; monocytes
IL-5	45-50 kD; homodimer of 20 kD sub units	Antiparallel dimer	• Eosinophils • Mast cells • CD4+ T cells • CD8+ T cells	• Eosinophils • Basophils • B cells • T cells	Regulates eosinophil migration and activation Induction of IL-2R expression Differentiation of B cells Proliferation of basophils; histamine release
IL-6	19-26 kD	Long-chain 4-α helix	• Monocytes Macrophages • Fibroblasts • Endothelial cells • B cells	• Monocytes • Macrophages • Epithelial cells • B cells • T cells	Acute phase proteins production T cell differentiation and growth Maturation of B cells to plasma cells Inhibition of lipopolysaccharide Production of IL-1 and TNF-α Anti-inflammatory mediator
IL-8	8-12 kD	C-X-C chemokine containing the ELR amino acid motif	• Monocytes • Macrophages • Neutrophils • Endothelial cells • Epithelial cells • Fibroblasts • T cells	• Monocytes • Macrophages • Neutrophils • Endothelial cells • Basophils • T cells	Neutrophil, monocyte and T cell migration Neutrophil adherence to endothelial cells Histamine release from basophils Stimulates angiogenesis
IL-10	Homodimer of 34-40 kD; 18 kD sub units	Long-chain 4-α helix	• Monocytes • Macrophages • Mast cells • B cells • T cells [CD4+ Th0, Th1, Th2, CD8+]	• Monocytes • Macrophages • Mast cells • NK cells • B cells • T cells	Inhibition of IFN-γ, TNF, IL-4 Promotes T cell differentiation from Th1 to Th2 cells Inhibits NK cell function Stimulates mast cell proliferation and function B cell activation and differentiation
IL-11	19-23 kD	4-α helical bundle	• Fibroblasts • Epithelial cells • Endothelial cells	• Megakaryocytes • Plasma cells • B Cells	Hematopoiesis Enhances antibody responses Acute phase protein production
IL-13	15 kD	Short-chain 4-α helical bundle	• CD4+ Th2 cells	• Monocytes Macrophages • Endothelial cells • B cells	Inhibition of production of IL-1 and TNF Upregulation of VCAM-1 and C-C chemokine expression on endothelial cells B cell activation and differentiation

IL: interleukin; kD: kilodalton; NK: natural killer; Th: T-helper; IFN-γ: interferon-gamma; IL-2R: interleukin-2 receptor; TNF-α: tumor necrosis factor-alpha; VCAM-1: vascular cell adhesion molecule-1.[1] Adapted from references 18,45,46,50,52,53,64-66,70,72-74.

could account for the different results. However, Johnston *et al* (26) who evaluated the response to hyperoxia in 3 different strains of mice (C57B1/6J, 129/J and C3H/HeJ), stated that while there were differences in acute sensitivity to hyperoxia, once initiated, acute epithelial cell injury, abundance of cytokines (including IL-1β and *vide infra*) and associated inflammatory changes followed the same pattern in all strains. After 72 h of hyperoxia, there was a 2-fold increase in mRNA for IL-1β in adult mice lungs (10). At this point, the mice are at or near lethality (10). IL-1α was unaltered in all strains at all times of the hyperoxia exposure (10,26).

Adult rats pretreated with recombinant tumor necrosis factor/cachetin (TNF/C) and IL-1 and exposed to hyperoxia for 52 h had decreased lung injury and enhanced survival (27). No differences were found in the activities of various antioxidants [SOD, glutathione peroxidase, glutathione reductase, glucose-6-phosphate dehydrogenase or catalase] between the TNF/C IL-1 pretreated animals and saline–treated controls; however, the ratio of reduced to oxidized glutathione was increased (27). The same group of investigators, in a subsequent report, noted that if exposure to hyperoxia was increased to 72 h, this was accompanied by increased levels of the antioxidants (as mentioned above) in the TNF/C and IL-1 pretreated animals (28). This raised the possibility that the pretreatment can increase lung antioxidant activities and enhance survival in hyperoxia (28). White and Ghezzi could replicate the above results with pretreatment with TNF and IL-1, prior to exposure to hyperoxia; they suggested that IL-1 alone in ample doses could provide protection against lethal oxygen toxicity (29). Pretreatment with recombinant human (rh) TNF, followed by hyperoxic exposure, lead to improved survival compared to vehicle-treated or IL-1 treated animals (22). This survival advantage was accompanied by decreased lung inflammation and edema and increased MnSOD levels in the TNF pretreated mice (22). Tracheal insufflation with IL-1, prior to exposure to hyperoxia, protected rats in a dose dependent manner (29). This protection against oxygen toxicity was accompanied by increased activities of MnSOD, CuZnSOD, catalase and glutathione peroxidase (30). Pretreatment with IL-1α selectively enhanced pulmonary MnSOD and protected against oxygen toxicity (31,32). When pretreated with IL-1RA, an adult rabbit model exposed to hyperoxia/hyperventilation for 8 h had decreased evidence of pulmonary leak and inflammation (33).

In an adult rat model, treatment with serum from endotoxin-treated rats (which, *per se*, have some protection from hyperoxic lung injury), also protected "recipient" rats from hyperoxic lung injury (34). Unlike the "donor" protected rats, which have increased lung antioxidant enzyme activity, the "recipients" did not have increased SOD or catalase activities in the lung (34). Interestingly, levels of IL-1 (and TNF) were increased in the "protective" sera (34). Red blood cell (RBC) insufflation (but not RBC lysate) protected rats against oxygen toxicity (35). The former resulted in the production of IL-1 (and TNF), which was recoverable from the BAL (35). In another study on adult rats, parenteral injections of IL-1 (and TNF) or endotoxin was protective of pulmonary oxygen toxicity (36). The investigators concluded that early and sustained increases in endogenous MnSOD, but not CuZnSOD or other antioxidant enzymes, are associated with protection of rat lungs against hyperoxic damage by IL-1 (and TNF) or endotoxin pretreatment (36).

In an adult rabbit model, which was ventilated with 100% O_2 for 36 h, there was significantly increased lung wet/dry ratio, influx of neutrophils, BAL concentrations of IL-1β (among others, as mentioned later); pretreatment with rhSOD and continued treatment during the hyperoxic exposure attenuated these effects (37). They concluded that this prophylactic effect of rhSOD may be due, in part, to decreased chemical mediators such activated complements, cytokines, and arachidonic acid metabolites (37). In the same model, the same investigators also reported an attenuated inflammatory response with the use of lidocaine (which has been shown to inhibit neutrophil function) (38). In an adult murine hyperoxia model, lisofylline significantly decreased IL-1β expression in the lungs over the first 48 h of hyperoxic exposure as compared to control animals (39).

Clara cell secretory protein (CCSP) deficient (-/-) adult mice, exposed to hyperoxia, had decreased survival compared to wild type mice (93±13.6 h vs. 114±18.6 h; p=0.01) (40). There was a 3-fold increase in lung IL-1β mRNA compared to wild type mice at 68 h of hyperoxic exposure (maximal response); IL-1β was localized principally in the lung parenchyma (40). IL-1α mRNA was not detected at this or earlier time points. However, at the time of death, the mRNA for IL-1β was increased to similar levels in the hyperoxia-exposed CCSP (-/-) and wild type mice (40). The authors concluded that CCSP deficiency resulted in increased sensitivity to hyperoxic lung injury as evidenced by increased mortality, early onset of lung edema and induction of proinflammatory cytokines (40). In a study evaluating oxygen toxicity in tumor necrosis factor receptor I (TNFR-I) (-/-) adult mice, increase in IL-1α and IL-1β was highly variable, appearing to be animal specific and independent of the function of TNFR-I (-/-); no correlation was seen between severity of oxygen toxicity and level of cytokine mRNA (41). The authors concluded that global blockade of TNFR-I signal transduction would not protect against hyperoxia-induced pulmonary inflammation and toxicity (41).

Adult transgenic mice that overexpress IL-11 in lungs were found to have significantly better survival in hyperoxia and decreased IL-1β protein levels in the BAL fluid after 2 days of hyperoxia when compared to transgene negative litter mate controls (7).

Besides the cell types mentioned above, isolated rat fetal Type II pneumocytes in culture have also been shown to release IL-1β (42,43); there was, however, no significant difference between hyperoxia exposure and room air controls (43). No modulation of IL-1β release (in

response to 24 h of hyperoxia) was seen with the use of dexamethasone or pentoxifylline (43).

In neonatal mice exposed to >95% O_2, there was no change in lung mRNA for IL-1α over a period of 10 days (10). In contrast, IL-1α mRNA was increased in the lungs of newborn mice after 3 days of hyperoxia (85% O_2) and maintained an increase of 50-80% over 5-14 days of exposure in comparison to room air-exposed animals (5). Increased expression of IL-1α preceded the neutrophil influx (demonstrated in the histological sections and BAL after 2 weeks of oxygen exposure) and thus may have a role in the inflammatory response (5). Possible reasons for this discrepancy could lie with the different strains of mice used and exposure to different O_2 concentrations.

On the other hand, there was a 5-fold increase in lung mRNA for IL-1β at 7 days of exposure (10). This is in sharp contrast to the adult mice showing increased levels after 72 h of hyperoxia, as mentioned above (10). Acute alveolitis and slight edema were detected, but lethality was not observed till day 10 (10). In situ hybridization suggested accumulation of IL-1β transcripts in pulmonary interstitial macrophages and in a subset of neutrophils after 7 days of exposure (10). It was suggested that a rapid cytokine response to hyperoxic injury may significantly contribute to the adaptation of neonatal lungs to oxygen toxicity (10). In newborn rabbits exposed to hyperoxia, IL-1β was detected by in situ hybridization (in alveolar epithelial and interstitial cells as well as macrophages) by 2-4 days of hyperoxia, being maximal at 6-10 days and decreasing thereafter (44). This pattern of changes in IL-1β was paralleled by the evidence of a rise and then fall, of histologic inflammation (44).

In the immature baboon model of BPD, there were no significant differences of IL-1β levels in the tracheal aspirates at any of the study times (17).

To summarize, when hyperoxia exposure resulted in an increase in IL-1, it occurred by 3 days in the adult and by 10 days in the newborn animal. Pretreatment with IL-1 (and/or TNF), endotoxin, rhSOD, lidocaine, lisofylline, and pentoxifylline attenuated hyperoxic lung injury in the adult. CCSP appeared to have a protective role while TNFR blockade was shown not to be protectective against oxygen toxicity in the adult.

4. INTERLEUKIN-2

IL-2 is produced and secreted primarily by mature T-cells (45). It is considered the primary growth factor of T cells, a potent modulator of T-cell and natural killer (NK)-cell function, and plays a major role in the immune response (45). Its actions include proliferation of T (including NK-cells) and B lymphocytes, differentiation of monocytes to macrophages as well as stimulation of IL-1 secretion (45).

IL-2 mRNA was not detected in the lung at any time point in hyperoxia-exposed CCSP (-/-) and wild type adult mice (40). No alterations in lung mRNA levels for IL-2 were detected in adult or neonatal mice exposed to hyperoxia for 10 days at any time point (10).

5. INTERLEUKIN-3

The predominant source of IL-3 appears to be activated T cells, though other cell types have also been reported to produce it (46). IL-3 stimulates the formation of mixed colonies of neutrophilic granulocytes, macrophages, megakaryocytes, and erythrocytes (46). In combination with erythropoietin, IL-3 promotes early erythroid progenitors (47). IL-3 synergizes with Granulocyte-Colony Stimulating Factor (G-CSF), IL-1 and IL-6 to stimulate primitive cells (48,49).

In different strains of adult mice exposed to hyperoxia, death was accompanied by increase in IL-3 mRNA above controls (26). In CCSP (-/-) adult mice exposed to hyperoxia for 68 h, there was a 2.5-fold increase in IL-3 mRNA compared to wild type (40). No alterations in lung mRNA levels for IL-3 were detected in adult or neonatal mice exposed to hyperoxia for 10 days at any time point (10).

6. INTERLEUKIN-4

IL-4 production has been found to occur in thymocytes, mature T cells, certain malignant T cells, mast cells and basophils and occasionally, in transformed B cells (50). IL-4 has effects on B cells, T cells, monocytes, mast cells, endothelial cells, and fibroblasts (51). IL-2 has a prominent role indirectly and directly in the regulation of IL-4 producing cells (50).

IL-4 was unaltered in 3 different strains of mice at all times of the hyperoxia exposure (26). IL-4 mRNA was not detected in the lung at any time point in hyperoxia-exposed CCSP (-/-) and wild type adult mice (40). No alterations in lung mRNA levels for IL-4 were detected in adult or neonatal mice exposed to hyperoxia for 10 days at any time point (10).

7. INTERLEUKIN-5

Activated T-helper cell populations are the main source of IL-5, but secretion from other cell types have been reported (52). IL-5 induces marked proliferation of eosinophil precursors and eosinophil activation and survival (52). The functional overlap of IL-5 with IL-3 and Granulocyte Macrophage-Colony Stimulating Factor can be explained on the basis of a common receptor molecule and intracellular portions of the receptors resulting in the activation of similar, if not identical, intracellular events after receptor–ligand binding (52). Abnormally high levels of IL-5 are associated with infections with tissue-dwelling parasites and a diverse group of hypereosinophilic conditions of no known etiology (52).

IL-5 mRNA was not detected in the lung at any time point in hyperoxia-exposed CCSP (-/-) and wild type adult mice (40). No alterations in lung mRNA levels for IL-5 were detected in adult or neonatal mice exposed to hyperoxia for 10 days at any time point (10).

8. INTERLEUKIN-6

Most, if not all, nucleated cells have been shown to express and synthesize IL-6 *in vitro*. The most

prominent source appears to be stimulated monocyte/macrophages, fibroblasts, epithelial and endothelial cells (53). IL-6 has B-cell and T-cell functions and has a role as a hematopoietic growth factor. There is evidence that IL-6 acts as an autocrine, paracrine, and exocrine inflammatory hormone (53). The characteristic cytokine cascade response is well illustrated by the fact that mice treated with IL-1 showed a subsequent IL-6 response (54). The complexity of the multiple effects is also well illustrated by IL-6. Since IL-6 can induce cortisol and the latter is required for the hepatic acute phase response, IL-6 plays an inductive role in providing a second signal to the liver (55,56). On the other hand, inhibition of IL-6 production occurs with corticosteroid treatment (57,58). Interestingly, IL-6 also been shown to have anti-inflammatory effects by inhibiting neutrophil influx in a model of acute lung inflammation (59) and by inducing IL-1RA (and soluble TNF-receptor) (60); the latter 2 mediators would diminish macrophage-mediated inflammatory responses (53). It is obvious that the timing and intensity of the effects of IL-6 are carefully controlled to elicit the appropriate effect needed in the inflammatory response (53).

When alveolar macrophages (from adult monkey lungs via BAL) were exposed to hyperoxia (95% O_2) for 24 h, there was significantly increased release of IL-6 (21).

Adult mice exposed to hyperoxia for 3 days had increased lung mRNA for IL-6 compared to lungs of mice in room air (22). After 72 h of hyperoxia, there was a 2-fold increase in mRNA for IL-6 in adult mice lungs (10). In different strains of adult mice exposed to hyperoxia, death was accompanied by increase in IL-6 mRNA above controls (26). In adult rats exposed to hyperoxia for 52 h, pretreatment with pentoxifylline resulted in decreased supernatant lactate dehydrogenase, protein content, pleural fluid accumulation and IL-6 levels in the BAL fluid (61). In an adult rabbit model, ventilated with 100% O_2 for 36 h, there was significantly increased BAL concentrations of IL-6; pretreatment with rhSOD and continued treatment during the hyperoxic exposure attenuated these effects (37). In an adult murine hyperoxia model, lisofylline significantly decreased IL-6 expression in the lungs over the first 48 h of hyperoxic exposure as compared to control animals (39). In a study evaluating oxygen toxicity, IL-6 mRNA was comparably induced in the lungs of TNFR-I (-/-) and wild type adult mice (41). The decreased survival of CCSP (-/-) adult mice, on exposure to hyperoxia, compared to wild type was accompanied by a 14-fold increase in lung IL-6 mRNA at the 68 h time point; however, at the time of death, IL-6 levels were similarly increased in both groups of mice (40). Transgenic adult mice overexpressing IL-6 in the lung had significantly increased survival in hyperoxia (62). The protective effects were not associated with significant alterations in CuZn or Mn SOD, but with a marked diminution in apoptotic cell death (62).

Isolated rat fetal Type II pneumocytes in culture release IL-6 (42,43); there was, however, no significant difference between hyperoxia exposure (24 h) and room air controls (43).

In the premature baboon model of BPD, tracheal aspirate IL-6 levels on days 9-10 and 16-44 were significantly increased when compared with those at 48-72 h (17). Neonatal mice exposed to hyperoxia had an 8-fold increase in lung mRNA for IL-6 after 7 days of exposure; in contrast to the adult mice showing an increase after only 3 days in hyperoxia (10). Newborn rats exposed to 100% O_2 (for 9 days) had significant pulmonary edema and increased cellularity on days 1 and 3, which resolved by days 6 and 9 (9). IL-6, primarily of non-macrophage origin, was detected in the BAL on days 6 and 9, but not earlier (9). Placement of these animals in room air 4 days after hyperoxia (day 13) resulted in non-detectable (control) levels of IL-6 (9). Newborn rats exposed to 48 h of hyperoxia (95% O_2) had increased levels of IL-6 mRNA; dexamethasone treatment reduced these levels (63).

To summarize, IL-6 increased in the adult lung exposed to hyperoxia by day 3; it was by day 10 for the newborn lung. In the case of mice, this was near or at the time of lethality. Increased expression of IL-6 was protective in the adult lung exposed to hyperoxia; this was associated with decreased apoptosis. Dexamethasone decreased IL-6 expression in the newborn lung exposed to hyperoxia.

9. INTERLEUKIN-8

IL-8 belongs to the C-X-C chemokine family and is produced by an array of different immune and non-immune cells (64). Thus, monocytes/macrophages and lymphocytes are not the only source of these chemotactic agents, as stromal cells, epithelial and endothelial cells can generate significant chemokine levels (64). This raises the issue of the role of normal resident cells in a tissue in the initiation and maintenance of an inflammatory response (64). In such a scenario in the lung, alveolar or interstitial macrophages can respond to an initial insult (for example, exposure to hyperoxia) with the expression of the early-response cytokines (IL-1 and TNF). These cytokines can then activate resident lung endothelial cells, epithelial cells, and fibroblasts, resulting in the production of chemokines (64). This, in turn, would attract inflammatory cells like neutrophils to the lung.

In an adult rabbit model, ventilated with 100% O_2 for 36 h, there was significantly increased BAL concentrations of IL-8; pretreatment with rhSOD and continued treatment during the hyperoxic exposure attenuated these effects (37).

Elevated lung mRNA IL-8 were detected from hyperoxia-exposed newborn rabbits at 4 days of hyperoxia and significantly elevated by 10 days, compared to age-matched air-exposed controls (44). No expression of IL-8 mRNA above control levels was detectable at 14, 22, or 36 days of hyperoxia (44). BAL fluid levels of IL-8 protein became detectable by 4 days and was significantly increased at 6 and 10 days of hyperoxia. IL-8 protein levels in the BAL were highly correlated with the neutrophil presence in the BAL (44). In situ hybridization located IL-8 mRNA in macrophages, neutrophils, alveolar

epithelial and interstitial cells at 4-10 days of hyperoxia exposure IL-8 (44). In the premature baboon model of BPD, tracheal aspirate IL-8 levels on days 6-8 and 9-10 were significantly increased when compared with those at 24 h, 48-72 h, and 16-44 days (17). Increased IL-8 levels in tracheal aspirates obtained during the clinical course appeared to correlate when lung infection was suspected clinically in several of these animals (17). In the young piglet model, exposure to hyperoxia for 5 days revealed increased IL-8mRNA levels, compared to room air controls (8).

The above data are consistent with a role for IL-8 in the influx of neutrophils in response to hyperoxia (8,44), though the influence of infection cannot be excluded (17).

To summarize, hyperoxia results in increases in IL-8; in the newborn animal, it correlates well with the influx of neutrophils.

10. INTERLEUKIN-10

In murine systems, IL-10 production often correlates with production of other Th2 cytokines (such as IL-4); but, in humans, IL-10 is produced by both Th1 and Th2 type T-cell clones (65). IL-10 suppresses activation of macrophages and dendritic cells, inhibiting their abilities to secrete cytokines and function as accessory cells for T-cell and NK-cell stimulation (65). IL-10 also participates in stimulating proliferation and differentiation of B cells, mast cells, and mature and immature T cells (65). Consistent with its inhibitory effects on a number of *in vitro* assays of cell-mediated immunity, IL-10 has been shown to be a potent inhibitor of inflammatory responses *in vivo* (65).

No significant change in IL-10 expression was noted in the lungs of adult mice exposed to hyperoxia for 12 h (10, 23).

Isolated fetal rat Type II cells have been shown to release IL-10 (42,43). While no change was observed on exposure to 24 h of hyperoxia, addition of dexamethasone caused a significant elevation in IL-10 levels (43).

Neonatal mice exposed to hyperoxia did not demonstrate any changes in the lung mRNA of IL-10 at any time point (10). No significant differences were observed in the IL-10 levels from the tracheal aspirate specimens obtained from the baboon model of BPD (17).

To summarize, no changes were noted in IL-10 following exposure to hyperoxia. Interestingly, dexamethasone increased IL-10 levels in a fetal cell culture system exposed to hyperoxia.

11. INTERLEUKIN-11

In vitro studies have shown that IL-11 gene is expressed in a variety of cells of mesenchymal origin (66). Furthermore, IL-11 gene expression can be induced and/or upregulated by several inflammatory cytokines and agonists as well as hormones (for example, IL-1α, TGF-β, parathyroid hormone and parathyroid hormone-related protein) (66). It has biological activity in all aspects of hematopoiesis as well as non-hematopoietic effects (66). In respiratory epithelial and fibroblast cells, stimulation of IL-11 gene expression by IL-1α, transforming growth factor β1 (TGF-β1), and TGF-β2 is probably transcriptionally regulated (67,68). It is of interest that IL-11 and IL-6 can trigger the same primary response gene expression in all cell lines tested, supporting the fact that they may share common signal transduction pathways (69).

Adult transgenic mice that overexpress IL-11 in lungs were found to have significantly better survival in hyperoxia (7). BAL fluid in the transgene (+) mice had significantly less neutrophils and lymphocytes on days 1 and 3 of hyperoxic exposure (7). This protection was associated with similar levels of CuZn SOD and catalase; <2-fold (but statistically significant) increases in glutathione reductase, glutathione peroxidase, and MnSOD in the transgene (+) mice as compared to the wild type (7). As in the IL-6 overexpressing transgenic mice (62), IL-11 overexpressing mice in hyperoxia had significantly decreased apoptosis in the lungs (7).

To summarize, IL-11 overexpression in adult mice provided significant protection from hyperoxia.

12. INTERLEUKIN-13

IL-13 is produced by activated T lympocytes, B lymphocytes and mast cells (70). In the mouse, IL-13 is expressed almost exclusively by Th2 clones; however, in humans it can be expressed in both Th1 and Th2 lymphocyte clones (70). It shares receptor components and biological activities with IL-4 on most cell type, an exception being activated T lymphocytes, which apparently lack IL-13 receptors (70). It has a variety of pro- as well as anti-inflammatory effects (6). The latter effects include the ability to inhibit (among others) TNF, IL-1β, and IL-8 and also to induce the production of IL-1RA (6).

Transgenic adult mice that overexpress IL-13 had significantly increased survival in hyperoxia as compared to the wild type mice (6). The investigators also showed that IL-13 alone, and in combination with hyperoxia, stimulated pulmonary vascular endothelial growth factor (VEGF) accumulation and the protective effects of IL-13 are, in part, mediated by VEGF (6).

13. CONCLUSIONS

It is clear that IL (among a host of other factors) have a significant role to play in hyperoxic lung injury. Increased IL expression and release has a cascade effect and appears to predate the influx of inflammatory cells. It is possible that resident cells in the lung initiate the inflammatory response to hyperoxia by the release of various cytokines, which, in turn, attract inflammatory cells to the alveolar space and amplify the damage.

The concept of certain cytokines being “pro-inflammatory” while others are “anti-inflammatory” is

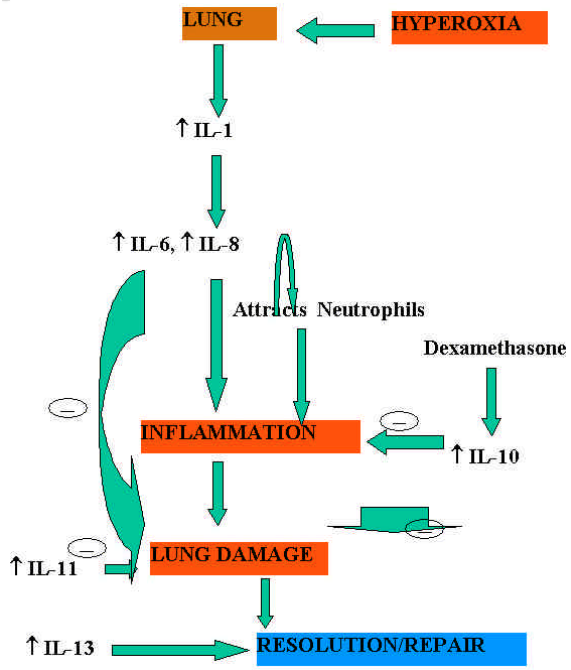

Figure 1. Proposed schema of events highlighting the role of IL in hyperoxia-induced lung injury. Note that IL-6 can both enhance and suppress inflammation.

overly simplistic. This is quite obvious from the fact that while increases in IL-1 ("pro-inflammatory") correlates with hyperoxia-induced lung injury (10,22,25), pre-treatment with the same offers protection (27-29, 31-33). Another IL, traditionally considered "pro-inflammatory", IL-6, is protective in a hyperoxia model (62). It is likely that the timing of the release of the cytokine in the presence or absence of other chemical mediators in the environment is what dictates whether it will be protective or destructive in a particular scenario. A proposed model for the sequence of events in hyperoxia-induced lung injury has been depicted in Figure 1. This is further complicated with the developmental stage of the lung. Not surprisingly, there are significant differences in the type and temporal sequence of IL expression and release in the adult and newborn lung in response to hyperoxia. The newborn lung is greatly resistant to hyperoxia as compared to the adult. The delayed increase in lung IL-1 and IL-6 in the newborn could induce protective factors which would help in the resolution of hyperoxia-induced injury. These protective factors include antioxidant enzymes (specifically, MnSOD) but there are others which have not been elucidated (71).

It is also important to remember that what provides protection to the hyperoxia-exposed adult lung may not be beneficial, perhaps, even be harmful, to the developing lung. Designing a therapeutic approach to counteract oxygen toxicity in the immature lung first needs understanding of the unique responses in the newborn.

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Send correspondence to: Vineet Bhandari, MD, DM, Yale University School of Medicine, Division of Perinatal Medicine, Department of Pediatrics, Children's Hospital WP493, P.O. Box 208064, New Haven, CT 06520-8064, Tel: 203-688-2320, Fax: 203-688-5426, E-mail: vineet.bhandari@yale.edu