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Hypoxia and the Lung: Beyond Hypoxic Vasoconstriction

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ABSTRACT

This article extends the influence and effects of hypoxia on the lung beyond vasoconstriction and regional blood flow control. Clearly, hypoxia, via the transcription factor hypoxia-inducible factor (HIF)-1α, induces a large number of genes encoding proteins, which control cellular metabolism and growth and also participate in inflammation. Hypoxia, likely via vascular endothelial growth factor (VEGF), recruits bone marrow precursor cells to the lung and affects the behavior of immune cells. How hypoxia shapes immune responses through VEGF and its receptors on mast cells, eosinophils, and dendritic cells and through lung endothelial cell/lymphocyte interactions will be a productive area for future research. *Antioxid. Redox Signal.* 9, 741–743.

Since the original description in the cat of the hypoxic pressure response by Von Euler and Liljestrand in 1946 (26), the mechanisms of hypoxic vasoconstriction and oxygen sensing in vascular cells have been of great interest to many investigators (11). However, hypoxia affects all the cells in the lung, and not unexpectedly, noncontractile cells may display a response to hypoxia that results in altered production and secretion of metabolites (6) or alterations of cell membrane receptor expression or function (23). Just one early example is the desensitization of adrenergic receptors in the heart and the pulmonary arteries after chronic hypoxia (25).

It has now been recognized that all cell types in the lung are affected by chronic hypoxia and that macrophages, fibroblasts, resident, and bone-marrow–derived precursor cells likely all cooperate toward the end product of chronic hypoxia-induced pulmonary vascular remodeling. For example, Satoh *et al.* (18) recently demonstrated that endothelial cell precursor cell recruitment from the bone marrow to the pulmonary endothelium was significantly impaired in hypoxic erythropoietin-receptor knockout mice, and this resulted in increased pulmonary vascular remodeling. These data indicate that endogenous erythropoietin receptors play a protective role during development of chronic hypoxic pulmonary hypertension (18). Davie *et al.* (2, 3) demonstrated, during chronic hypoxia, bone marrow–derived progenitor cells participating in pulmonary arterial adventitia remodeling. Thus, the role of progenitor cells in hypoxia-induced pulmonary vascular remodeling is still controversial and may be species dependent; Satoh *et al.* used mice, but Davie *et al*. used rats.

Thus, progenitor cells may have a key role in hypoxia-induced vascular remodeling. The cellular and molecular mechanisms of hypoxia-induced pulmonary vascular remodeling have recently been reviewed (19). David Stern showed in 1990 (15) that hypoxia disturbs endothelial cell function associated with suppression of thrombomodulin gene expression and later generation of cytokines such as interleukin (IL)-6 (17). More recently, this group demonstrated that hypoxia caused induction of early growth response-1 (Egr-1) transcripts in mouse lungs; this was paralleled by the enhanced expression of the downstream target gene tissue factor (28) in bronchial and vascular smooth muscle cells. Clearly, hypoxia has an impact on a number of lung signaling pathways.

One of the most prominent pathways implicated in hypoxia-mediated vascular remodeling centers on the molecule hypoxia-inducible factor (HIF)-1α. Antedating the discovery of the transcription factor HIF-1α by Gregg Semenza (27), Ono *et al*. (16) showed that a selective platelet-activating factor (PAF) antagonist inhibited chronic hypoxia-induced pulmonary hypertension and lung vascular remodeling,

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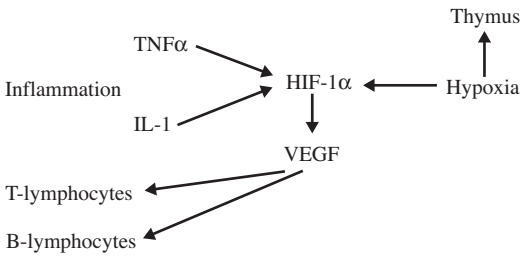

FIG. 1. A scheme depicting how hypoxia might modulate immune regulation.

without affecting pulmonary artery pressure when administered during a phase of acute hypoxic pulmonary vasoconstriction. Thus, an inhibitor of inflammation attenuated the development of chronic hypoxic pulmonary hypertension, suggesting that chronic hypoxia activates inflammatory pathways. It is now generally accepted that HIF-1α provides a pivotal molecular link between hypoxia and inflammation (4, 5, 9, 13). Prostaglandin E_2 can induce HIF-1α as can the immunomodulatory cytokines, tumor necrosis factor (TNF)-α and IL-1 (Fig. 1). HIF-1α, in turn, increases the transcription of many genes encoding proteins that control blood flow and cell growth, including vascular endothelial growth factor (VEGF) and nitric oxide synthase (NOS).

How does hypoxia affect lung endothelial cell form and function? Studies have been performed with cultured cells (20), but recent experiments (12) indicated that chronic hypoxia produces a "megalocytosis" of pulmonary arterial endothelial cells *in situ* and causes sequestration of eNOS in a cytoplasmic compartment away from its functional caveolar site, perhaps providing a mechanism for the reduction in pulmonary arterial nitric oxide (NO) levels in experimental hypoxia pulmonary hypertension, despite sustained eNOS protein levels.

HYPOXIA AND IMMUNE REGULATION

In the 1960s, it was recognized that chronic hypoxia affects the weight of the thymus in rodents (1, 22). Subsequently Kmets and Anthony (7) reported that hypoxia-induced thymic involution was associated with delayed skin graft rejection in mice, indicative of a suppressed immune response. Meehan (10) reviewed the effects of high altitude and chronic hypoxia exposure on the human immune system and concluded that B-cell function was unimpaired; in contrast, he concluded that T-lymphocyte function was impaired, in part because of endogenous glucocorticoid effects. Experiments in mice are consistent with this notion, demonstrating increased susceptibility to infections with a number of bacterial organisms. Recently, Nicolls *et al.* (14) reviewed the topic of severe pulmonary hypertension in immunocompromised patients. Clearly a very strong association exists of a variety of autoimmune disorders, as well as infection with human immunodeficiency virus (HIV), with the development of severe pulmonary hypertension. Based on our own data, which show that athymic rats, which lack functional T lymphocytes, develop severe, vasoobliterative pulmonary hypertension (21), we formulated the hypothesis that pulmonary vascular remodeling, including remodeling occurring during chronic hypoxia-induced pulmonary hypertension, is modulated by T lymphocytes. We postulate that one possible mechanism of hypoxia-induced immunosuppression manifests itself by activation of the HIF-1α/VEGF/VEGF receptor axis, because T lymphocytes as well as B cells produce VEGF and express VEGF receptors (see Fig. 1) (8).

CONCLUSION

We now are beginning to appreciate the complex relation between chronic hypoxia and lung tissue that leads to the so-called hypoxia-induced pulmonary vascular remodeling. Hypoxic vasoconstriction—although important—is only one component of this spectrum of molecular mechanisms. Gaps in our knowledge base and challenges for the future include the mechanisms behind cellular transdifferentiation (24), the participation of bone marrow–derived and pulmonary stem cells (3) and how the sympathetic nervous system and the individual components of the innate and adaptive immune system determine beneficial and pathologic responses of the lung circulation.

ABBREVIATIONS

Egr-1, early growth response-1; HIF, hypoxia-inducible factor; IL, interleukin; NO, nitric oxide; NOS, nitric oxide synthase; PAF, platelet-activating factor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

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