Oxidant signaling in lung cells

THIS ISSUE of the American Journal of Physiology-Lung Cellular and Molecular Physiology features five articles that provide new insights into the mechanisms and cellular pathways regulating oxidant signaling in lungs. Reactive oxygen species (ROS) from cellular sources have been regarded as toxic byproducts of metabolism with the potential to cause damage to lipids, proteins, and DNA (22). Oxidative stress has been implicated in a large number of human diseases and conditions, including atherosclerosis, pulmonary fibrosis, cancer, neurodegenerative diseases, and aging (13, 27). Yet the relationship between oxidative stress and the pathobiology of these diseases or normal processes, such as aging, is not clear, largely because of the lack of understanding of the mechanisms by which ROS function as “signals” in physiological states.

Recent evidence indicates that ROS are essential participants in cell signaling and regulation (20, 51). The apparent paradox in the roles of ROS as molecules in the regulation of cellular functions and as toxic byproducts of metabolism may be, at least in part, related to differences in the concentrations of ROS produced by different cell types (15, 61).

Because cytokines appear to generate ROS at or near the plasma membrane, activation of cytokine receptors is important for oxidant signaling. In this series of papers, Lesur and colleagues (38) showed that oxidant production induced by the lung fibrosis-promoting agent bleomycin was involved in the upregulation of membrane IL-2 receptor-chain expression in rat type II lung epithelial cells. They further showed that the combination of IL-2 and IFN induced epithelial cell repair. These findings suggest that oxidant signaling in alveolar epithelial cells may set into motion “protective pathways” that induce the expression of cytokine receptors and thus prevent epithelial injury.

Although a number of signaling pathways are regulated by ROS (2, 4, 8, 16, 21, 25, 29, 34, 36, 40, 45, 48, 59), the signaling molecules specifically targeted by ROS are less clear. There is evidence that redox regulation of signaling intermediates may occur at multiple levels (26, 30, 31, 35, 47, 56, 63). Olschewski and colleagues (46) showed that the effects of changes in oxygen tension on vascular tone are mediated by the redox status of the cell. They observed opposite regulation of K⁺ channel activity induced by the same redox changes in the cytosol of smooth muscle cells from the duc tus arteriosus (which constricts in response to oxygen) vs. the pulmonary artery (which dilates in response to oxygen). Thus redox control of the gating of K⁺ channels in a vascular smooth muscle cell-specific manner may be a key mechanism of differential oxygen signaling.

The intramitochondrial concentrations of superoxide are maintained at very low steady-state levels because of high concentrations of mitochondrial superoxide dismutase (58). Thus, unlike H₂O₂, which is capable of diffusing across the mitochondrial membrane into the cytoplasm (9), mitochondria-generated superoxide is unlikely to escape into the cytoplasm. The potential for mitochondrial ROS to mediate cell signaling has gained significant attention in recent years, particularly with regard to the regulation of apoptosis (11, 37, 39, 60). There is evidence to suggest that tumor necrosis factor-α and IL-1-induced apoptosis may involve mitochondria-derived ROS (54, 55, 62). It has also been suggested that the mitochondria function as “O₂ sensors” to mediate hypoxia-induced gene transcription (10, 17). Inhalation of high concentrations of O₂ in combination with inhaled nitric oxide (NO) has been promoted as a treatment for pulmonary hypertension and acute lung injury (3, 12, 43). Whereas several studies have shown the effects of NO on mitochondrial function, in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology, Lightfoot and colleagues (42) now show an effect of NO in reducing mitochondrial DNA (mtDNA) damage. Thus a benefit of NO signaling may be the rapid and efficient repair of injured mtDNA. The mechanism of this effect of NO is not clear but may be related to the NO-induced “annihilation” of O₂.

NF-κB, the transcription factor that regulates the expression of a number of genes involved in immune and inflammatory responses (including IL-8), has long been considered to be oxidant responsive (18, 44, 52, 57). However, the contribution of oxidant regulation in NF-κB activation is still the subject of intense debate (7, 28, 33). Several studies have reported that H₂O₂-induced NF-κB activation is highly cell type dependent (1, 6, 39, 41), indicating that NF-κB activation is not a universal response to oxidant signaling. In this issue, D’Angio and colleagues (14) investigated the differential roles for NF-κB in LPS- and oxygen-induced IL-8 expression in alveolar macrophages. Hypoxia-induced IL-8 secretion in the U-937 macrophage cell line required NF-κB binding to the IL-8 promoter but not the nuclear translocation of additional NF-κB. In contrast, LPS-stimulated IL-8 secretion required both NF-κB translocation and NF-κB binding. These observations raise the possibility that oxidant signaling may regulate the activation of the NF-κB bound to the IL-8 promoter.

Oxidant signaling in lung endothelium has an important role in pulmonary vascular permeability in vivo (5, 32) and in endothelial monolayers (19). Studies have shown that oxidant generation is involved in the signaling cascade mediating the TNF-α-induced activation of adhesion molecules, such as ICAM-1, in endothelial cells (49, 50, 53). It was also shown that NADPH oxidase subunits p47phox and gp91phox are required for TNF-α-induced oxidant production in lung endothelial cells (23). However, the role of NADPH oxidase-dependent generation of superoxide in the TNF-α-induced pulmonary endothelial barrier dysfunction is not clear. The paper by Gertzberg and colleagues (24) showed, in an interesting series of experiments, that TNF-α induced an increase in endothelial permeability that was dependent on NADPH oxidase-mediated generation of superoxide.

The Call for Papers articles in this issue provide further insights into the mechanisms of oxidant signaling and their...
consequences. The new information will undoubtedly stimulate further study of the importance of oxidants in signal transduction in lung cells.

Randall S. Frey
University of Illinois College of Medicine

Asrar B. Malik, Editor
American Journal of Physiology—Lung Cellular and Molecular Physiology and University of Illinois College of Medicine

REFERENCES


