The stuff of life: an integrated inflammatory response

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THE PAPER BY MARTIN ET AL. (6) in this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology presents important new information concerning the time-dependent effects of two cytokines, tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), on rat lung airway resistance. There is a large literature on cytokine and chemokine release and their actions during the inflammatory response relative to endothelial barrier function, but little is known about the effects of these important messengers on airway smooth muscle. The study by Martin et al. contains three very important findings: 1) after airway constriction with methacholine, IL-1β and IL-1β plus TNF-α but not TNF-α alone dilated the airways; 2) when either TNF-α or IL-1β was given to lungs in which the airways were not constricted, neither cytokine altered airway resistance; and 3) after 40 min of challenge with both cytokines, airway resistance began to increase and was associated with an upregulation of cyclooxygenase-2 (COX-2) mRNA expression and a “thromboxane-dependent” bronchoconstriction. In addition to this perfused lung study, another study from this group (5) adopted the technique of Krumdieck et al. (4) of using precision-cut lung slices to evaluate the effects of cytokines on airway smooth muscle tone. A combination of TNF-α, IL-1β, and interferon-γ (IFN-γ) contracted airways in thin lung slices by increasing COX-2 activity and thromboxane release; yet, these cytokines individually failed to cause airway constriction. These two studies clearly showed that although cytokines such as TNF-α, IL-1β, and IFN-γ individually produce little or no effect on airway resistance, the combined treatment with and IL-1β and TNF-α produced bronchial constriction by upregulating COX-2 and the subsequent release of thromboxane. Surprisingly, this challenge with cytokines can produce either dilation or constriction depending on the state of airway tone and the time expired after introduction of the cytokines.

Interestingly, Khimenko et al. (3) have found that TNF-α is required to produce ischemia-reperfusion (I/R) endothelial injury in isolated rat lungs because a specific antibody to TNF-α blocked I/R injury. However, when TNF-α was placed into the circulation of a normal lung, no damage occurred to the endothelial barrier over the same time frame. But, when TNF-α was given to lungs challenged with I/R, endothelial damage was significantly elevated (3). This was at first a puzzling finding. But as we studied the inflammatory response in more depth, we realized that blocking a particular cytokine may prevent the inflammatory response if it is a component of a series interaction with other cytokines, chemokines, leukocytes, and/or endothelial factors, whereas the cytokine given alone may produce no endothelial damage in normal lungs in the absence of other required factors.

A recent workshop summary by Crapo et al. (2) clearly indicates that we must understand the total time frame of the immune response of the lung relative to the actions of alveolar macrophages, T lymphocytes, B lymphocytes, neutrophils, eosinophils, mast cells, basophils, oxidative stress, prostaglandins, interleukin-10, transforming growth factor-β, IL-1, and various receptor agonists and antagonists before we can determine the mechanisms underlying the development of acute respiratory distress syndrome, asthma, bronchopulmonary dysplasia, emphysema, lung injury, interstitial lung disease, and pulmonary hypertension. I would add to this list that we also must understand the response of helper and nonhelper T cells, endothelial-neutrophil rolling and adherence factors, and the subsequent production of IL-1, IFN-γ, and TNF-α during the inflammatory responses that result in the endothelial junction openings that promote fulminating pulmonary edema.

Other questions also come to mind when considering the inflammatory responses in lungs: how does the inflammatory response affect other lung functions such as alveolar epithelial transport systems, airway and vascular smooth muscle, cilia mucus clearance, airway epithelial cell activity, and airway mucous gland activity? There is absolutely no doubt that we can now critically study the response of the lung to inflammation associated with infections, lung I/R conditions, and the injury associated with remote inflammation such as seen in the intestinal I/R model of lung endothelial...
The ability of the endothelial and epithelial cells of the lung to communicate with blood lymphocytes, tissue macrophages, and basophils influences not only the initial degree of lung damage but also alters the healing process. This system constitutes the most important and fascinating system in the body, yet it is perhaps the least understood of all control systems! The ability of the inflammatory system to operate correctly when challenged is the “thing life is made of” because it allows all living creatures, including humans, to live a long and productive life in a constantly changing internal and external environment. The immune response is a wondrous and complicated system that will keep us busy in our laboratories for years to come as we begin to sort out how these “pheromones” protect our bodies in both health and disease.

The paper by Martin et al. (6) emphasizes the complexity of this system using a simple research tool, isolated rat lungs, which clearly show that we need not only evaluate endothelial function during the inflammatory response but also study the associated changes in airway and vascular resistances. From their data, it is clear that many airway diseases may likely result when the inflammatory response goes “helter-skelter.” It is not sufficient to measure the actions of one or two chemokines or cytokines and from that information characterize the inflammatory system as it reacts to various lung insults. Several cells, cytokines, chemokines, and systems obviously work in concert to produce an effect that the paper of Martin et al. shows is also a function of time and the subsequent release of different components that comprise the inflammatory response. During the ensuing years, the techniques used in this paper and in other laboratories will provide the necessary information to build a better understanding of the inflammatory process, and then we will be able to alter the inflammatory response toward better healing and prevention outcomes.

REFERENCES