The advantage of the lung is the abundance of available tissue for analysis of inflammatory reactions at the interface of the external and internal environments. Products of inflammatory reactions are thereby easily retrieved and provide an unusual opportunity for detailed studies of inflammatory responses. In addition, the lung offers the advantage of easy accessibility for therapeutic interventions. Therefore, in the past interest in evaluating the role of the airways in inflammatory processes has increased with regard to possible anti-inflammatory therapies.

The lung consists of two major anatomic compartments: the vascular and the airway compartment. Endothelial cells in the arteries, veins, and capillaries line the vascular system and are the cells most actively involved in an inflammatory response. Epithelial cells, on the other hand, may be regarded as the corresponding cells in the respiratory compartment. Distal airway epithelial cells, i.e., alveolar epithelial cells, are vital for maintenance of the pulmonary air-blood barrier. Type I alveolar epithelial cells, large thin cells that cover 95% of the alveolar surface, are essentially involved in gaseous diffusion. Type II cells, however, are cuboidal cells producing pulmonary surfactant. They are also progenitor cells capable of proliferating and differentiating into type I cells. Recent evidence suggests that airway epithelial cells might also act as immune effector cells in response to noxious exogenous stimuli. Several studies have shown that airway epithelial cells express and secrete various immune molecules such as adhesion molecules, cytokines, and chemokines (11, 20, 21). Through the expression and production of these inflammatory mediators, not only the vascular but also the airway epithelium is thought to play an important role in the initiation and exacerbation of an inflammatory response within the airways.

Lipopolysaccharide, a component of the cell walls of gram-negative bacteria, was recognized as a potentially important mediator in the pathogenesis of acute lung injury and acute respiratory distress syndrome from the early 1970s onward. Many investigators have reported that lipopolysaccharide given intravenously or intratracheally induces an acute non-cardiogenic pulmonary edema as well as neutrophil recruitment participating in the initiation and propagation of lung injury. Membrane CD14 as well as Toll-like receptors have been identified as lipopolysaccharide receptors. Binding of lipopolysaccharide induces a signaling pathway with activation of kinases and nuclear factors, resulting in transcription of inflammatory mediators such as tumor necrosis factor-α (TNF-α) or members of the interleukin family.

Leukocyte homing to sites of acute inflammation is a crucial step during an inflammatory response. Adhesion molecules play a major part in the inflammatory process by mediating adherence of leukocytes to the endothelium and initiating extravasation of these cells. Intercellular adhesion molecule-1 (ICAM-1), a member of the immunoglobulin superfamily, is a cell surface glycoprotein and a ligand for the β2-integrins CD11a/CD18 and CD11b/CD18 on leukocytes. It is upregulated by a variety of inflammatory stimuli such as endotoxin and different cytokines. Although endothelial ICAM-1 has been explored in detail, epithelial ICAM-1 has been characterized much less and its functional role might be different from endothelial ICAM-1.

This review will highlight recent progress in understanding the role of epithelial ICAM-1 in the respiratory compartment in the inflammatory process of endotoxin-induced lung injury. The past few years have witnessed an explosive growth concerning our knowledge about the basic mechanisms of cell adhesion. All of this information will provide clues to possible therapeutic approaches.

The vascular “chamber”

It has been a general belief for many years that endothelial cells of the vascular compartment are the main players in inflammatory reactions induced by exposure of the lung to an endotoxin such as lipopolysaccharide. Neutrophil emigration occurs in specialized regions of the vascular tree and can be divided into distinct phases: rolling, firm adhesion, and transmigration (Fig. 1). Neutrophil rolling represents the initial phase of endothelial cell-leukocyte adhesion cascade, and E-selectin is the key adhesion molecule involved in slowing down circulating neutrophils. At the same time, this last step is the prerequisite for the ensuing firm adherence of neutrophils to endothelial cells. Firm adhesion on the other hand is mediated through ICAM-1 on the endothelial cells and through CD11a/CD18 and CD11b/CD18 as counterreceptors on neutrophils. This process also changes the spherical configuration of the neutrophils to a flattened shape. The final step, characterized by transmigration of neutrophils through the endothelium, is triggered by platelet-endothelial cell adhesion molecule-1 and vascular cell adhesion molecule-1.
ways of neutrophil emigration. These two studies provide evidence for alternative path-
ways of neutrophil emigration compared with wild-type mice. Also, ICAM-1 mutant mice showed no
response of ICAM-1 expression in vivo. The striking lack of a response of ICAM-1 expression by
mice in acute pneumonia was not reduced (13). Also, ICAM-1 mutant mice showed no
inhibition of neutrophil emigration compared with wild-type mice in acute Pseudomonas aeruginosa lung inflammation (16). These two studies provide evidence for alternative path-
ways of neutrophil emigration.

The airway “chamber”

The main task of the airway chamber, defined as the upper respiratory tract with tracheobronchial epithelial cells and the lower one with alveolar epithelial cells, is gas exchange. In the early 1990s, for the first time experimental work from in vitro studies provided direct evidence that type I alveolar epithelial cells express ICAM-1 (4, 15). ICAM-1 was not detected imme-
diately after isolation of type II cells but appeared 48 h later, when cells had changed their phenotype toward type I cells. Therefore it was assumed that ICAM-1 expression was a dif-
ferentiation-related feature of the type I cell phenotype. On stimulation with TNF-α and interferon-γ (IFN-γ), ICAM-1 was not found to be upregulated on alveolar epithelial cells in vitro (1). The striking lack of a response of ICAM-1 expression by alveolar epithelial cells to inflammatory cytokines was in con-
trast to virtually all other epithelial cell studies. But Fakler et al. (6) demonstrated later a clear upregulation of ICAM-1 on a transformed human cell line of alveolar epithelial cells on lipopolysaccharide stimulation. In addition, Dentener et al. (5) described a human alveolar epithelial cell line producing binding-binding protein in response to interleukin-1β and TNF-α. The results of this group also implied that these cells were involved in inflammatory processes. On L2 cells, a line of rat alveolar epithelial cells, enhanced ICAM-1 expression

was seen as well after endotoxin exposure, underlining previous data (12). In a recent study, ICAM-1 expression was as-

sessed by stimulating primary culture of alveolar epithelial cells with TNF-α, IFN-γ, and lipopolysaccharide (2). All of
these experiments clearly showed upregulation of ICAM-1 mRNA and protein after stimulation with any of these three agonists, whereby lipopolysaccharide caused the strongest upregulation. Similar data for ICAM-1 upregulation were also found in alveolar epithelial cells in response to stimulation with Haemophilus influenzae (7). These newer data imply that epithelial ICAM-1 is involved in the inflammatory response in the endotoxin-induced lung injury.

To obtain more insight into the biological function of ICAM-
1 expression, several studies aimed at the localization of
ICAM-1 on alveolar epithelial cells. Guzman and et al. (8)

blocking studies with ICAM-1 antibody were performed as described above. Neutrophil adherence to stimulated cells increased by 100% in monolayers of LPS-stimulated alveolar epithelial cells. Blocking ICAM-1 protein on alve-
olar epithelial cells with ICAM-1 antibody resulted in a decreased adherence of neutrophils to alveolar epithelial cells (40% less on stimulated cells). Val-
dues are means ± SE. Statistical comparison was made between LPS-stimulated

A: neutrophil adhesion to alveolar epithelial cell monolayers pre-
inuously stimulated with Escherichia coli LPS (100 μg/ml) overnight. Alveolar
epithelial cells were blocked with monoclonal mouse anti-rat ICAM-1 anti-
body (1A29; 10 μg/ml) for 30 min or with a control antibody. At the same
time, neutrophils were preincubated with antibodies against FcγRII (CD16)
and FcγRII (CD32). Neutrophils were then added to alveolar epithelial cells.
Neutrophil adherence to stimulated cells increased by 100% in monolayers of LPS-stimulated alveolar epithelial cells. Blocking ICAM-1 protein on alve-
olar epithelial cells with ICAM-1 antibody resulted in a decreased adherence of neutrophils to alveolar epithelial cells (40% less on stimulated cells). Val-
dues are means ± SE. Statistical comparison was made between LPS-stimulated
group with control antibody and LPS-stimulated group with anti-ICAM-1 anti-
body (p < 0.001). Reproduced from Ref. 2, with permission. B: adherence of
alveolar macrophages to monolayers of alveolar epithelial cells. Confluent
alveolar epithelial cells were stimulated overnight with LPS (100 μg/ml). Alve-
olar macrophages were harvested from rat lungs and placed into the wells.
Blocking studies with ICAM-1 antibody were performed as described above.
Adherence of macrophages to LPS-stimulated alveolar epithelial cells
increased by 40% compared with adherence to nonstimulated alveolar epithe-
nal cells. Modest decrease in adherence of macrophages to stimulated alve-
olar epithelial cells (30% decrease) occurred in the presence of anti-ICAM-1
antibody. All values are expressed as means ± SE. Statistical comparison was
made between LPS-stimulated group with control antibody and LPS-stimu-
lated group with ICAM-1 antibody (p < 0.001). Reproduced from Ref. 2, with
permission.
Recent data from adherence assays with target cells (alveolar epithelial cells) and effector cells (neutrophils, alveolar macrophages) indicated that epithelial ICAM-1 is of great importance in target cell-effector cell interaction. The results of these adherence assays clearly demonstrated a functional importance in target cell-effector cell interaction. The results were supported by previous immunohistological examinations of mouse lungs, where ICAM-1 was only detected on the luminal surface of alveolar epithelial cells on stimulation with cytokines and lipopolysaccharide (3, 10). On endothelial cells, the apical expression of ICAM-1 is well known to be essential for emigration of white blood cells out of the blood stream in the direction of the site of inflammation. If these principal processes of inflammation were applied to the anatomy of the lung, one would rather expect a more basolateral expression of ICAM-1 on alveolar epithelial cells to enable white blood cells to immigrate from the pulmonary interstitium into the alveolar space.

During the past few years, it also became evident that soluble ICAM-1 plays an important role in the respiratory compartment during lung inflammation. The observation of soluble ICAM-1 enhancing alveolar macrophage production of macrophage inflammatory protein-1 and TNF-α is very interesting (17). It is apparent that adhesion pathways not only provide a mechanism for translocation of leukocytes from blood to inflammatory sites but also participate in intracellular signaling. In addition, recent reports have suggested that soluble ICAM-1 can interfere with leukocyte binding to counterreceptors (18), which might result in a self-limiting mechanism of the inflammatory response, also offering new therapeutic options.
Perspectives

Using cell and animal models, it has been demonstrated that epithelial ICAM-1 contributes substantially to the pathogenesis of endotoxin-induced lung injury. ICAM-1 confers this effect through its upregulated expression on alveolar epithelial cells, governing neutrophil retention. As shown for example in respiratory epithelial cells on stimulation with cytokines, keratinocyte growth factor seems to downregulate expression of ICAM-1 and VCAM-1, suggesting that keratinocyte growth factor may be involved in the resolution of the inflammatory reaction (9). All of these data imply that the lower airway compartment plays a pivotal role in endotoxin-induced inflammation through the expression of ICAM-1. The respiratory compartment offers the unique advantage of easy accessibility in case of therapeutic interventions (e.g., application of blocking antibodies) compared with other organs. Therefore, in view of promising results in attenuating lung injury by counteracting epithelial ICAM-1, detailed investigations should explore the potential for therapeutic interventions targeting the respiratory compartment of the lung. Further advances in our understanding of the mechanisms of cell adhesion will be extremely useful from both a scientific and a clinical perspective.

References


