In toxic lung injuries BAL assists in exclusion of any serious infection; recognition of the syndrome from characteristic findings; development of therapies for these agents; and toxins e.g. in diffuse alveolar haemorrhage, where neutrophil inflammation is occasionally observed in BAL fluid when there are no detectable neutrophils in the peripheral blood; this has led to trials of glucocorticoid therapy.

Various transplants place special stress on the lung. Distortion of the pleural space can lead to severe bleeding. Liver transplantation is associated with the development of right-sided pleural effusions and right upper lobe atelectasis, presumably due to subdiaphragmatic dissection. Most transplantation patients receive large volumes of intravenous fluids and medicines. All have some underlying disease which can affect the lung directly or indirectly. The ability of BAL to sample the lung is helpful in assessment of the pathophysiology of pulmonary complications following transplantation. Management of such complications is becoming increasingly important and BAL will play a major role.

References


Pulmonary toxicity induced by chemical agents

W.J. Martin

Pulmonary toxins include a spectrum of agents from clinically useful drugs to environmental pollutants. Many probably cause lung damage at a cellular level in a similar manner (table I). Better understanding of this mechanism improves the diagnostic and therapeutic approach to patients with serious pulmonary reactions to toxins.

Supplemental oxygen is a well-known therapeutic agent, associated with significant pulmonary toxicity when used in concentrations exceeding 50-60% for a long period. Although hyperoxia has been shown to be directly toxic to lung parenchymal cells [1] there is clear evidence to implicate the inflammatory response in the mediation of oxygen toxicity [2, 3]. There is increasing evidence for direct and indirect mechanisms operating in the development of pulmonary toxicity.

Oxygen is the ultimate electron acceptor in aerobic metabolism, with its eventual reduction to water. The cell must "handle" O₂ carefully using a divalent reductive process in the cytochrome system, since univalent reduction of O₂ results in generation of potentially lethal O₂-derived species such as superoxide, hydrogen peroxide and the hydroxyl radical. The cell has derived a variety of defences to prevent damage from inadvertent generation of toxic O₂-derived species. These include superoxide dismutase, catalase, glutathione etc., which detoxify these species and protect the cell. Normally the antioxidant defences are available in excess and generation of occasional O₂-derived radicals is no risk. In conditions where their generation is facilitated, i.e. hyperoxia, paraffin toxicity, blyoomycin toxicity etc., antioxidant defences are overwhelmed and oxidants induce a variety of biochemical insults to the cell such as lipid peroxidation (cell membrane damage), DNA damage (inhibited or altered replication) or attack of sulphydryl bonds (protein destruction). A large variety...
of agents (drugs, herbicides, asbestos) have been implicated in the mediation of lung parenchymal injury by direct toxic mechanisms (often generation of toxic \( \text{O}_2 \)-derived radical species).

Bronchoalveolar lavage (BAL) is useful in detection of a cytotoxic drug reaction in the lung, a common sequelae to the use of cancer chemotherapeutic agents. Cytotoxic drugs frequently cause cell injury or death by causing oxidant damage. Such injury may be manifest as an atypical morphological change; cellular atypia in alveolar macrophages and epithelial cells typically consists of nuclear hyperchromasia, cytomegaly and cytoplasmic cosinophilia.

**Table 1.** Examples of chemical agents or drugs associated with lung toxicity

<table>
<thead>
<tr>
<th>Direct toxicity</th>
<th>Indirect toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidant</td>
<td>Other</td>
</tr>
<tr>
<td>( \text{O}_2 )</td>
<td>NO</td>
</tr>
<tr>
<td>Paroxetin</td>
<td>Cyclophos</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Phamid</td>
</tr>
<tr>
<td>Bleomycin</td>
<td></td>
</tr>
<tr>
<td>Asbestos</td>
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</tbody>
</table>

Inflammatory or immune mechanisms are commonly involved in the development of toxic lung injury. In animal models, the development of \( \text{O}_2 \) toxicity has been associated with a potent inflammatory response, *i.e.* recruitment of neutrophils to the lung [2]. Subsidence of the neutrophil response by induction of neutropenia protects animals from \( \text{O}_2 \) toxicity [2]. *In vivo* animal studies suggest that the inflammatory response to \( \text{O}_2 \) toxicity contributes significantly to lung injury. Widespread species differences exist in susceptibility to \( \text{O}_2 \) toxicity. Do similar mechanisms occur in humans with \( \text{O}_2 \) toxicity? For example, neutrophils and neutrophil products have been detected in the lower respiratory tract of patients with adult respiratory distress syndrome [4] but they often have multiple factors, *e.g.* sepsis, \( \text{O}_2 \) toxicity and pneumonia, which complicate the interpretation of inflammatory mechanisms. In contrast, Davis *et al.* [5] examined the response of normal control subjects to high inspired \( \text{O}_2 \) concentrations and found that inflammatory mediators were detectable within several hours of exposure to hyperoxia. Thus, hyperoxia in human subjects is characterized by an associated inflammatory response which may be critical to the development of the toxicity.

In addition to those agents which cause direct lung damage by generating toxic oxidants, others appear to induce a hypersensitivity reaction in the lung. Organic antigens such as those associated with farmer’s lung or pigeon breeder’s disease induce a CD8 positive lymphocytosis in the lower respiratory tract [6, 7] and this altered immune response probably results in the poorly formed granulomatous reaction characteristic of these disorders. Similar reactions have been reported with drugs such as nitrofurantoin, gold and amiodarone which induce the identical CD8 profile in BAL [8, 9]. The role of CD8 lymphocytes in the pathogenesis of hypersensitivity reactions is unclear but they appear to possess both cytotoxic and suppressor functions [6]. BAL is the best method available to assess the immune response in these disorders and to characterize the lymphocyte subpopulations in the lung.

It is likely that agents associated with pulmonary toxicity mediate lung injury by direct and indirect pathways. Assessment of direct mechanisms of toxicity often requires use of *in vitro* approaches. BAL, together with standard histopathological studies, usually provide the best approach to assess evidence for activation of inflammatory and immune mechanisms. Recognition of these two different mechanisms and their possible interaction in the mediation of lung toxicity will improve our insight into the disease process and permit development of better therapeutic strategies.

**References**