Hypersensitivity pneumonitis (HSP) is an immunologically mediated alveolar and interstitial lung disease caused by repeated inhalation of organic dusts and occupational agents. Although there are numerous inciting agents that may elicit HSP, the pathogenesis and the disease that ensues are similar. There are a number of unexplained features of HSP including (1) why do so few of the exposed individuals develop clinical HSP, (2) what triggers an acute episode after prolonged periods of previous sensitization, and (3) what leads to disease progression. It is known that, following exposure to inhaled environmental antigens, most individuals develop precipitating antibodies. However, only a few individuals will become symptomatic. The reason for this is not clear. It is likely that genetic susceptibility is important in determining the susceptibility of some individuals for the development of HSP. It has been shown, for example, that polymorphisms in the major histocompatibility complex, tumor necrosis factor (TNF) α, and tissue inhibitor of metalloproteinase 3 are associated with the development of or resistance to the disease.

As the disease may present acutely after antigenic challenge, it has been hypothesized that the inhaled antigen, when it enters the alveolar space, crosses the alveolar endothelium and binds to circulating antibody leading to immune complex deposition within the lung eliciting an inflammatory response. Although this is an attractive hypothesis, there are little clinical data that support it. The acute phase, which is mediated by neutrophils, is followed by a chronic phase mediated by lymphocytes and macrophages, which is thought to represent a delayed-type hypersensitivity response. This may eventually result in the formation of granuloma and in time progress to pulmonary fibrosis. Some experimental studies have shown that animals whose immune response is skewed toward a TH1 response over a TH2 response are more likely to develop HSP. Most current information about the pathogenesis of HSP has been obtained by studying the cells and inflammatory mediators present in bronchoalveolar lavage (BAL) fluid and by studying lung biopsies. Bronchoalveolar lavage fluid is thought to provide a fairly accurate representation of intrapulmonary events and be representative of the immunologic and inflammatory mechanisms that lead to the pulmonary manifestations of HSP.

Following antigen exposure, BAL fluid shows increased numbers of neutrophils, which peaks after 48 hours. This is then followed by increased numbers of macrophages and lymphocytes, which is seen between 48 and 72 hours. This is associated with increased levels of inflammatory mediators such as interferon (INF) γ, TNF-α, interleukin (IL) 1, IL-6, IL-2, IL-8, and macrophage inflammatory protein 1α. Monocyte chemoattractant protein 1 peaks at 48 hours and IL-12 at 48 to 72 hours. Macrophage inflammatory protein 1α peaks at 4 to 6 hours following antigen inhalation and induces lymphocyte chemotaxis. IL-4 is chemotactic for T cells, and the levels of IL-8 are correlated with the number of neutrophils. Following the neutrophil increase, there is an influx of activated T cells. The influx of CD4 cells precedes that of CD8 cells. Increased reactive oxygen species is...
seen in the BAL of patients with HSP. It is produced by macrophages and may have a role in mediating damage to alveoli.19

When BAL is performed in normal individuals, 90% of the recovered cells are macrophages20 with the remainder consisting of lymphocytes. Fewer than 1 \( \times 10^6 \) lymphocytes per mL are normally found. The lymphocytes are predominantly CD4RO memory T cells and their CD4/CD8 ratio reflects that of the peripheral blood. In patients with HSP, lymphocytes are increased more than 25-fold. There is also an increased number of macrophages and the relative proportion of lymphocytes is increased. Following the early influx of CD4 cells, CD8 cells are increased and the CD4/CD8 ratio is decreased. There is also a higher proportion of \( \delta \gamma \) T cells. Some cells express the cytotoxic T-cell–associated markers CD56 and CD57.21,22

LYMPHOCYTIC RESPONSE

As the pathology of HSP is that of delayed-type hypersensitivity response, it is useful to explore the development of this immune reaction. \( T_0 \) and \( T_1 \) cells develop from a common \( T_0 \) progenitor. These cells are directed to the \( T_1 \)1 and \( T_1 \)2 cell pools under the influence of cytokines.10 IL-12 exposure influences the development of \( T_0 \) cells to \( T_1 \)1 cells, and IL-4 influences the development of \( T_0 \) cells to \( T_1 \)2 cells. \( T_1 \)1 T cells are responsible for delayed-type hypersensitivity. The hallmark of this response is the presence of macrophages and granulomas and the development of cytotoxic T lymphocytes. \( T_1 \)2 cells are associated with humoral immunity, the immunoglobulin E response, and allergenic responses and regulate \( T_1 \)1 activity through the secretion of IL-10. \( T_1 \)1 cells secrete IL-2, IFN-\( \gamma \), and TNF-\( \alpha \) and TNF-\( \beta \), while \( T_1 \)2 cells secrete IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13. Of note, alveolar macrophages produce IL-12, which likely supports the \( T_1 \)1 response. It has been shown that mice with a strong \( T_1 \)1 response are susceptible to HSP,23 whereas animals with a strong \( T_1 \)2 response are resistant to HSP. It is possible that the influence of the \( T_1 \)1/\( T_1 \)2 balance may determine which individuals are susceptible to HSP. Moreover, HSP is more severe when the \( T_1 \)1/\( T_1 \)2 balance is skewed to the \( T_1 \)1 response.24,25

NATURAL KILLER T CELLS

Natural killer T cells also may influence the development of immune response. Natural killer T cells are a subset of \( \alpha \beta \) T cells that coexpress markers of classical T cells and natural killer cells.26 Natural killer T cells modulate the \( T_1 \)1/\( T_1 \)2 balance by secreting IL-4 and IFN-\( \delta \). In a mouse model of farmer’s lung induced by Saccharopolyspora rectivirula27 it has been shown that natural killer T cells secrete IL-4 and suppress IFN-\( \gamma \) production by neutrophils, which is essential for CD8 T-cell activation and proliferation. Neutrophils are the major source of IFN-\( \gamma \) in experimental HSP27 and may be necessary for the induction of the disease.

SUMMARY

The preceding data provide evidence suggesting that HSP is an immunologically mediated delayed-type hypersensitivity reaction occurring in susceptible individuals. What determines susceptibility is not entirely clear. There is, however, good evidence that individuals with a \( T_1 \)1 dominant response will develop clinical disease. There is also some evidence that genetic factors such as polymorphisms in the major histocompatibility complex, TNF-\( \alpha \), and tissue inhibitor of metalloproteinase-3 are associated with the development of or resistance to the disease.

References