Integrins, Macrophages, and Sarcoidosis

The article by Striz et al in this issue of Chest (see page 882) examines β₂ integrin and ICAM-1 expression on human alveolar macrophages in patients with sarcoidosis and in control subjects. To put this interesting article in context, a brief overview of the background leading to this work is necessary.

The cell population recovered by bronchoalveolar lavage (BAL) from normal lungs is predominantly (>90 percent) alveolar macrophages in various stages of maturation. Small numbers of lymphocytes are also found. Pulmonary alveolar macrophages normally ingest and contain inhaled particulates without inducing local inflammation. Moreover, specific immune responses to inhaled antigens appear to be downregulated under normal circumstances. For instance, alveolar macrophages facilitate lymphocyte proliferation to mitogen in vitro at low macrophage-lymphocyte ratios. However, at high macrophage-lymphocyte ratios, like those in the lung and in BAL fluid, this proliferation is suppressed. At least four mechanisms are thought to be involved in this down-regulation. Compared with blood monocytes or newly recruited lung monocytes, pulmonary alveolar macrophages demonstrate increased intracellular degradation (processing) and decreased cell surface display (presentation) of antigen, deficient production of the T-cell activator interleukin (IL)-1, active suppression of lymphocyte activation by the production of large quantities of prostaglandin E₂ (PGE₂), and decreased surface contact with T cells due to decreased expression of surface LFA-1, an alpha subunit of β₂ integrins.

Integrins are cell-surface glycoproteins, which facilitate cell adhesion to extracellular matrix proteins and ligands on other cells. More recently, they have been shown to play other roles, including involvement in cellular growth and differentiation. Integrins include at least 15 dipeptide transmembrane molecules, which have been divided into six subfamilies based on unique beta chains. Each of these associates noncovalently with an alpha chain of one or more types. Integrins are found on many cells, including endothelial cells, fibroblasts, and immunocompetent cells. Many of them have been characterized adequately enough to be given cluster designation (CD) nomenclature.

The β₂, or very late activation, integrins, are widely distributed and facilitate adhesion to extracellular matrix proteins such as fibronectin and collagen. They are believed to be important in embryogenesis and wound healing.

The β₂, or leukocyte, integrins are the best studied. The β₂ (CD18) subunit associates with one of three alpha subunits: LFA-1 (CD11a), CR3/Mac-1 (CD11b), or P150,95 (CD11c). This results in β₂ integrins CD11a/CD18, CD11b/CD18 and CD11c/CD18. CD11a/CD18 is found on B and T lymphocytes, blood monocytes, macrophages, granulocytes, and natural killer (NK) cells. The principal ligands for this integrin appear to be the intracellular adhesion molecules ICAM-1 (CD54) and ICAM-2. These adhesion molecules are found on leukocytes and endothelial cells. Epithelial cells appear to express ICAM-1, but not ICAM-2. CD11b/CD18 is found on monocytes, macrophages, granulocytes, and NK cells, and binds the complement component iC3b, as well as ICAM-1, factor X, fibrinogen, and polysaccharides. CD11c/CD18 is found on the same cells, and binds to iC3b. Leukocyte integrins are required for neutrophil and T-cell function. For instance, anti-CD11a/CD18 antibodies inhibit T-cell proliferation in response to cell adhesion in vitro, and prevent transplant rejection in vivo. Put simply, T-cell stimulation by antigen presentation requires binding between LFA-1 on antigen-presenting cells and its ligand, designated ICAM-1, on T cells, and/or the reciprocal case, LFA-1 on T cells binding to ICAM-1 on macrophages.

The β₃, or cytoadhesion, integrins, are found on platelets, endothelial cells, neutrophils, and monocytes. They bind to fibronectin, vitronectin, fibrinogen, and von Willebrand factor. The β₃ and β₂ integrins, found on epithelial cells, appear important in cell-matrix adhesion. The β₃ integrins, found on lymphocytes, are thought to mediate adhesion to Peyer's patches in lymphoid tissue.

Active sarcoidosis is associated with the accumulation of large numbers of activated helper T cells and newly recruited monocytes/macrophages in the lung. Compared with normal alveolar macrophages from healthy control subjects, alveolar macrophages from patients with sarcoidosis have decreased production of PGE₂, increased production of IL-1, and increased antigen-presenting capacity. These features of pulmonary alveolar macrophages in sarcoidosis could be explained either by increased numbers of monocytes newly recruited into the lung or the activation of mature macrophages already present by IL-2 from increased numbers of activated T cells present. Moreover, the increased levels of alveolar macrophage-derived IL-1 and decreased levels of PGE₂ could facilitate T-cell activation.

Increased CD11b (CR3) expression has previously been associated with the increased phagocytic capacity
of sarcoid macrophages. This finding is corroborated by Striz et al, who found increased CD11b on pulmonary alveolar macrophages of patients with active sarcoidosis compared with controls and patients with inactive disease. The finding by these authors that CD11a (LFA-1) is not increased on these cells is surprising, as increased CD11a expression would have been expected in the face of reports of increased antigen-presenting capacity of sarcoid macrophages. Further studies, especially those that clearly separate smoker and nonsmoker control groups, are required to confirm this observation. The increased antigen-presenting capacity of sarcoid macrophages may result from increased macrophage expression of ICAM-1, which can enhance antigen presentation by binding to LFA-1 on T cells. As the authors note, LFA-1 is also involved in giant cell formation. Increased expression of ICAM-1 could also be involved in macrophage-macrophage binding prior to giant cell formation.

What causes sarcoidosis? Does the cell-mediated immune response in the lung derive from an appropriate or aberrant response to an unknown antigen (eg, an infectious agent)? Does dysregulation of cytokine networks initiated by lung mononuclear cells trigger the granulomatous response? Regardless of the cause, activated macrophages appear central to the pathophysiology of sarcoidosis. An understanding of the cellular mechanisms by which activation of these cells occurs is a required element in understanding the pathophysiology of sarcoidosis. The work of Striz et al in this issue of Chest moves us further in that direction.

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REFERENCES
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