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Immune Dysfunction in Silicosis: A Hypothesis

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Silicosis is a fibrosing lung disease induced by silica particle inhalation. In addition to its effects on pulmonary physiology, the disease is also associated with clinically important immune dysfunction, detectable both systemically and in the lung. An important local pulmonary manifestation of silicosis-associated immune dysfunction is impaired host defense against mycobacteria. Normal host defense against mycobacteria is accomplished through cell-mediated responses by T cells and macrophages. The mechanism underlying impaired antimycobacterial defense and silicotuberculosis in silicotics is unknown. Despite impaired host defense against mycobacteria, silicosis appears to be associated with increased and dysregulated antibody production, as evidenced by the presence of hypergammaglobulinemia, circulating immune complexes, and autoantibodies in many patients with silicosis. The apparent paradox of excess antibody production, but impaired cell-mediated immunity, is not unique to silicosis. In a variety of strong immune responses, antibody production and delayed-type hypersensitivity responses are mutually exclusive. In these settings, the underlying mechanism for up-regulation of one type of response and down-regulation of the other type has been regulation and cross-regulation by helper T (T_H)-cell subsets. Based on cytokine secretion patterns, two types of CD4+ T-cell subsets have recently been identified—T_H1 and T_H2. T_H2-cell-like responses are associated with strong antibody production, while T_H1-cell-like responses are associated with delayed-type hypersensitivity. Each T_H cell type is capable of down-regulating the other. We hypothesize that dysregulated T_H cell interactions occur in silicosis, resulting in augmentation of antibody responses, and suppression of cell-mediated immunity. WEISSMAN, D.N.; MA, J.K.H.; ROJANASAKUL, Y.; HUBBS, A.F.: IMMUNE DYSFUNCTION IN SILICOSIS: A HYPOTHESIS. APPL. OCCUP. ENVIRON. HYG. 11(7):962–965; 1996.

Silicosis is a crippling lung disease induced by silica particle inhalation. Although several silicates induce silicosis, alpha quartz is the major cause of silicosis worldwide.[1] Miners working in the metal and coal-mining industries (including surface coal miners), as well as any miners involved in tunneling through sandstone or granite, are at increased risk for inhalation of dusts high in silica content with subsequent development of silicosis.[2,3] Chronic silicosis develops over a period of years, as retained intrapulmonary dust induces a sequence of events including inflammation, fibrogenesis, and, ultimately, end-stage pulmonary fibrosis.[4,5] Stimulation of macrophages by silica and subsequent cytokine networking between macrophages, lymphocytes, neutrophils, fibroblasts, and potentially other cell types is an important mechanism for fibroblast stimulation and the development of pulmonary fibrosis.[6–9] This short review will examine the hypothesis that, in addition to induction of fibrosis, cytokine networking between macrophages and lymphocytes leads to dysregulated T_H cell interactions in silicosis, resulting in augmentation of antibody responses, and suppression of cell-mediated immunity.

Silicosis-Associated Immune Dysfunction: Clinical Manifestations

Silicosis is associated with clinically important immune dysfunction, both systemically and in the lung.[8] An important feature of this immune dysfunction is dysregulated and increased immunoglobulin production.[10–14] Increased serum gamma-G globulin (IgG) and gamma-M globulin (IgM) concentrations have been reported in sandblasters;[10] increased serum IgG and gamma-A globulin (IgA) concentrations in silicotic stone masons;[11] increased serum IgG, IgM, and IgA concentrations in slate-pencil workers;[12] increased IgG in quartz crushers;[13] and increased IgG, IgA, and IgE in silicotic miners.[14] Silicosis is also associated with increased prevalence of serum autoantibodies, such as antinuclear antibody and rheumatoid factor, as well as with increased prevalence of circulating immune complexes.[1,8,10,11,13,14] Taken together, these findings are consistent with polyclonal B-cell activation leading to increased antibody production.

Despite activation of humoral immunity, it has long been appreciated that silicosis is associated with impaired host defence against mycobacteria.[15] The association between silicosis and tuberculosis continues to be confirmed. A recent Danish study of 5579 male foundry workers over a 19-year period showed increased incidence of pulmonary tuberculosis in silicotics and in nonsilicotics with long work histories and, presumably, large cumulative silica exposures.[16] Studies in Hong Kong have documented the difficulty of treatment[17] and prophylaxis[18] of tuberculosis in the setting of silicosis. It is currently unclear what mechanisms lead to impaired antimycobacterial defence in silicosis. However, since normal host defence against mycobacteria is accomplished through cell-mediated delayed-type hypersensitivity responses by T lymphocytes and macrophages,[19,20] it is likely that silicosis is associated with *in vivo* functional impairment of one, or both, of these cell types.

Silicosis-Associated Immune Dysfunction: Potential Role of Helper T (T_H) Cells

The apparent paradox of excess antibody production, but impaired cell-mediated immunity, is not unique to silicosis.[21] In a variety of strong immune responses, antibody production

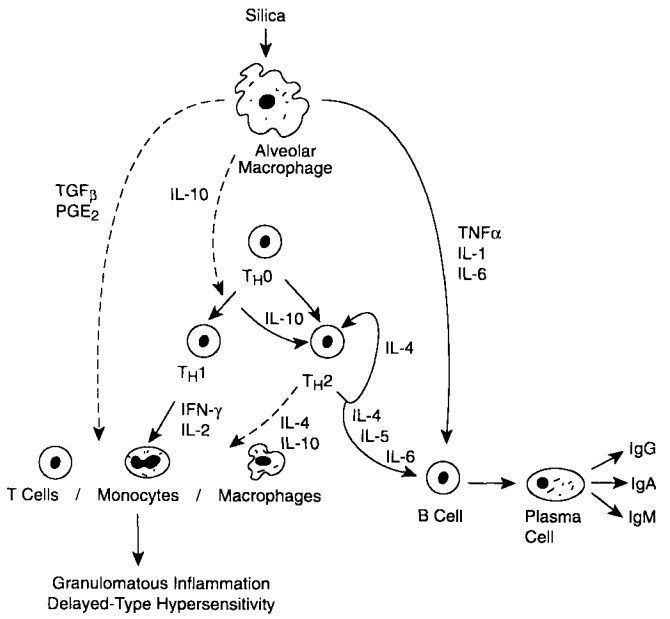

FIGURE 1. Potential cytokine networking between alveolar macrophages (AM) and lung lymphocyte subsets leading to suppression of cellular immunity and augmentation of antibody production in silicosis. Stimulation is represented by solid lines and suppression by interrupted lines. Silica-stimulated AM secrete mediators capable of both direct and indirect modulation of cellular immunity and antibody production. Examples of direct modulation include secretion of TGF_β and PGE_2 which suppress cellular responses such as delayed-type hypersensitivity (DTH) and secretion of TNFα, IL-1, and IL-6 which promote B cell differentiation and immunoglobulin production. Indirect modulation is achieved by effects of secreted products on T-helper (T_H) cell differentiation. For example, secretion of IL-10 inhibits differentiation of T_H0 cells to T_H1 cells and leads to conditions favoring differentiation to T_H2 cells. Resultant increased secretion of T_H2-derived cytokines leads to augmentation of antibody production and suppression of cellular immunity. T_H2 cells further inhibit T_H1 differentiation by secretion of IL-10 and autostimulate their own expansion through secretion of IL-4 (see text for details and for discussion of potential counterregulatory signals).

and delayed-type hypersensitivity responses are mutually exclusive. In these settings, an important underlying mechanism for up-regulation of one type of response, and down-regulation of the other type, has been regulation, and cross-regulation, by helper T (T_H)-cell subsets. Based on cytokine secretion patterns, two types of CD4+ T-cell subsets have recently been identified—T_H1 and T_H2 (Figure 1).[22] The T_H1, but not T_H2, cells produce interleukin 2 (IL-2), gamma-interferon (IFN-γ), and lymphotoxin, whereas T_H2, but not T_H1, cells express IL-4, IL-5, IL-6, and IL-10. *In vitro* studies have demonstrated that T_H2 clones are much more efficient providers of B-cell help than T_H1 clones. This is also the case *in vivo*, where T_H2-cell-like responses are associated with strong antibody production, while T_H1-cell-like responses are associated with delayed-type hypersensitivity (Figure 1). Important crossregulation occurs between T_H1 and T_H2 cells.[21] The T_H1 cells inhibit growth of T_H2 cells by secreting IFN-γ, while T_H2 cells autostimulate their own growth by secreting IL-4, and inhibit production of cytokines by T_H1 cells by secreting IL-10. IL-10 appears to act by impairing antigen presentation to T_H1 cells (but not B cells).[21]

In addition to mutual cross-regulation, and regulation of B-cell function, secreted T_H1 and T_H2 cell-derived cytokines exert contradictory regulatory effects on macrophages (Figure 1).[23] The T_H1 cell product, IFN-γ, is a potent activator of macrophages for effector functions such as antigen presentation, cytotoxicity, and secretion of cytokines.[23–25] In contrast, T_H2 cell-derived cytokines such as IL-4 and IL-10 suppress macrophage effector functions such as secretion of proinflammatory cytokines and nitric oxide[23,26,27] in part by antagonizing the effects of IFN-γ.[23] Thus, T_H1 cell-derived cytokines support both lymphocyte and macrophage participation in delayed-type hypersensitivity and poorly support antibody responses, while T_H2 cell-derived cytokines exert the converse effects of supporting antibody responses and depressing delayed-type hypersensitivity.

T lymphocytes are appropriately situated to orchestrate immune dysfunction in silicosis. Inflammation elicited by intrapulmonary silica particles leads to an influx of T lymphocytes into the lung.[5,7–9,28,29] Lymphocytes and macrophages are prominent constituents at the periphery of silicotic nodules.[1,8] Parenchymal T lymphocytes in experimental silicosis are activated, demonstrating increased proliferation and increased expression of IL-2 receptors.[28] Although it is not currently known whether such lymphocytes have T_H1, T_H2, or T_H0 (undifferentiated) cytokine-producing phenotypes, cytokine networking by T lymphocytes recruited to the lung in silicosis has the potential to induce the dysfunctional immunity seen in silicosis.

Silicosis-Associated Immune Dysfunction: Potential Role of Macrophages

Macrophages play a pivotal role in the pathogenesis of pulmonary fibrosis associated with silicosis.[6–8,30–32] In addition to their effects on fibroblasts, macrophages challenged *in vivo* or *in vitro* with silica secrete a number of immunomodulatory products. This is perhaps mediated by calcium, as exposure to silica increases cytosolic free calcium in alveolar macrophages.[30,31] TNF-α is a prominent secretory product of pulmonary macrophages in silicosis, and antagonism of TNF-α effect by anti-TNF-α antibodies or soluble TNF receptors ameliorates silica-induced pulmonary fibrosis.[32–34] Other cytokine products, such as IL-1, IL-6, and TGF-β_1, are also secreted by pulmonary macrophages in silicosis.[32,35,36] Alveolar macrophages harvested from rats with established experimental silicosis demonstrate altered arachidonic acid metabolite secretion, with increased PGE_2 secretion and decreased secretion of the leukotrienes LTB_4 and LTC_4.[37,38] The secreted macrophage products noted above have the potential to directly modulate several features of silicosis-associated immune dysfunction (Figure 1). For example, TNF-α, IL-1, and IL-6 are capable of promoting B cell proliferation and differentiation into IgG-secreting plasma cells.[39,40] TGF-β_1 and PGE_2 have the ability to suppress features of cell mediated immunity.[23,37]

In addition to direct modulation of immunity by secretion of immunomodulatory products, macrophages also potentially regulate immune function by influencing T_H lymphocyte differentiation into T_H1 or T_H2 cytokine-producing phenotypes (Figure 1). IL-10, discussed earlier as a T_H2 cytokine, can also

be produced by macrophages.[41] Secreted IL-10 possesses the ability to inhibit differentiation of T_H1 cells by blocking synthesis of IFN-γ, an important inducer of T_H1 differentiation.[41] Macrophages also possess the ability to secrete the recently described cytokine IL-12.[42] A growing body of evidence suggests that IL-12 plays a critical role in T_H cell differentiation by inducing differentiation to the T_H1 phenotype. Counterregulation is by IL-4, which induces differentiation to the T_H2 phenotype,[42] and possibly by IL-10, through suppression of IL-12 production.[43] Thus, macrophages likely participate in the genesis of immune dysfunction in silicosis both by the secretion of directly immunomodulating cell products and by cytokine networking with, and influencing the differentiation of, T_H cells.

Conclusion

Silica is pathogenic not only in its induction of pulmonary fibrosis, but also in its induction of immune dysfunction. Immunological abnormalities readily apparent in clinical silicosis include upregulated polyclonal antibody, including autoantibody, production; and impaired host defence against mycobacteria, a process normally accomplished by delayed-type hypersensitivity. In many situations, *in vivo* conditions associated with augmentation of antibody immunity and impairment of cellular immunity reflect underlying immunoregulation by T_H cell subsets, with the balance of regulation tilted toward T_H2 and away from T_H1 modulation. In silicosis, macrophages may also play a role in dysregulated immunity both directly, and via cytokine networking with T_H cells. As normal immune responses to tuberculosis are mediated by T_H1 cells,[44] and neutralization of IL-10 (a T_H2 cytokine) enhances antimycobacterial immunity,[45,46] dysfunctional antimycobacterial defence in silicosis is consistent with a tilt toward T_H2 immunity. Augmentation of antibody production in silicosis has similar implications. Thus, the abnormalities in immune function associated with silicosis are consistent with the hypothesis that, in silicosis, cytokine networking between macrophages and lymphocytes leads to dysregulated T_H cell interactions, resulting in augmentation of antibody responses and suppression of cell-mediated immunity.

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