Immunological Abnormalities in Sarcoidosis*

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Sarcoidosis is a systemic granulomatous disease of unknown aetiology. The diagnosis may be based on a classical clinical presentation, but is best established by histological evidence of noncaseating epithelioid cell granulomas when the existence of other granulomatous diseases has been excluded. Sarcoidosis is associated with a broad range of immunological abnormalities involving both the cell-mediated and humoral limbs of the immune response.

Cell-mediated immunity

Positive delayed hypersensitivity skin tests indicate an intact efferent cell-mediated response. Many patients with sarcoidosis are anergic upon delayed hypersensitivity skin testing with recall antigens. A "paradoxical" response, in which tuberculin anergy resolves when the patient is treated with systemic adrenal corticosteroids or when corticosteroids are injected into the skin along with the tuberculoprotein, is sometimes noted in such patients. It is not known whether this phenomenon occurs secondarily to corticosteroid inhibition of suppressor cell function.

Other in vivo changes include decreased numbers of circulating T lymphocytes and Fc mu receptor positive T cells (helper cell enriched), and increased numbers of Fc gamma positive T cells (suppressor cell enriched), and activated lymphocytes. The ratios of cells bearing OKT4 (helper cell) and OKT8 (suppressor cell) differentiation antigens have been reported to be normal, with the exception of decreased proportions of OKT8 cells in patients with concomitant erythema nodosum. However, studies of patients with "high-intensity" sarcoid alveolitis show significantly decreased ratios of OKT4 to OKT8 cells.

There are also numerous in vitro changes in the lymphocyte function of patients with sarcoidosis. Most studies show abnormally decreased lymphocyte reactivity in response to stimulation with T-cell mitogens. Stimulated lymphokine production may also be depressed. The decreased reactivity of the lymphocytes of patients with sarcoidosis can be attributed partly to the presence of prostaglandin-producing, glass-adherent suppressor monocytes. Some patients possess suppressor monocytes which inhibit mitogen-induced immunoglobulin secretion. The aforementioned in vitro studies indicate the presence of increased suppressor cell numbers and activity among circulating leucocytes.

In contrast to the changes in the peripheral blood, effector cell populations of the lungs are increased. There are increased numbers of activated macrophages and activated T-cells, with a marked increase in the T-cell/alveolar macrophage ratio. In addition, although there are decreased absolute numbers of circulating OKT4 lymphocytes, the number of such cells increases in the lungs and in the sarcoid granuloma.

The functional characteristics of the T-lymphocyte population in the lungs of patients with active pulmonary sarcoidosis include the spontaneous production of monococyte chemotactic and migration-inhibitory factors and B-cell helper factors which induced polyclonal immunoglobulin production. The spontaneous release of interleukin-2 (T-cell growth factor) by lung T helper lymphocytes may induce T-cell replication. These findings indicate an activated immune system with localisation of the activity at the sites of granulomatous inflammation.

The monocyte-macrophage is an essential component of the cell-mediated immune response. Its roles include antigen presentation and interleukin-1 production during the initiation of the immune response, regulatory functions such as those performed by prostaglandin-producing glass-adherent suppressor cells, and participation with T cells.

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in granuloma formation. In pulmonary sarcoidosis, activated macrophages release increased amounts of interleukin-1, fibronectin and fibroblast growth factor; antigen presentation is also enhanced. Macrophages are the precursors of the epithelioid cells of the granuloma. Granulomas are formed in order to enclose physically antigenic material when cellular cytotoxicity or humoral mechanisms are unable to eliminate such antigens.

In murine models, spontaneous "modulation" of granulomatous hypersensitivity entails decreased granuloma size and increased granuloma hydroxyproline content. Increased granuloma hydroxyproline is associated with increased fibrogenesis. This process is, in part, secondary to increased T suppressor cell activity.

Angiotensin-converting enzyme is present in human pulmonary alveolar macrophages and in the epithelioid cells of the sarcoid granuloma. The role of angiotensin-converting enzyme in granulomatous inflammation has been studied using murine models. Angiotensin-converting enzyme is present in isolated granulomas of mice infected with Schistosoma mansoni and in murine lung lavage fluids of Balb/c-Calmette-Guerin-induced chronic granulomatous pulmonary inflammation. Increased angiotensin-converting enzyme activity in serum and granulomas of schistosome-infected mice is associated with granuloma "modulation" and a diminished granulomatous response. Enhancement and diminution of T suppressor cell activity induce parallel changes in the converting enzyme activity of schistosome egg-induced granulomas.

Angiotensin-converting enzyme converts angiotensin I to angiotensin II and inactivates bradykinin. Murine schistosome granulomas contain angiotensins I, II and III; also, indirect evidence suggests the presence of angiotensinogenase. Angiotensin II, the product of the converting enzyme, inhibits murine macrophage migration and modulates both Fc receptor activity and phagocytosis. Bradykinin has been shown to inhibit murine lymphocyte reactivity and lymphokine production.

Because of the association of angiotensin-converting enzyme with sarcoid granulomatous inflammation, it appears likely that angiotensin II is generated in such human lesions. Human peripheral blood mononuclear cells possess binding sites for angiotensin II.

The effect of angiotensin II on human lymphocyte reactivity has been studied in our laboratory. We have found that phytohaemagglutinin-induced thymidine incorporation was inhibited by angiotensin II in leucocytes from most subjects (unpublished data). This finding is consistent with the findings of decreased murine macrophage migration after exposure to angiotensin II and with the association of high converting enzyme activity with a diminished murine granulomatous response. Paradoxically, in vivo captopril-induced inhibition of the converting enzyme results in decreased Bacille-Calmette-Guerin-induced chronic granulomatous pulmonary inflammation. Increased angiotensin-converting enzyme activity in serum and granulomas of schistosome-infected mice is associated with granuloma "modulation" and a diminished granulomatous response.

Humoral immunity

Sarcoidosis is also characterised by abnormalities of the humoral immune response (recently reviewed by R.P. Daniele). Although the systemic cellular immune response is diminished, antibody production is more active than normal. The concentration of the various immunoglobulin classes may be increased. Antibodies directed against mycoplasmal, viral and mycobacterial antigens have been found. Auto-antibodies in patients with sarcoidosis include antinuclear antibody, rheumatoid factor and lymphocytotoxins.

The in vitro concanavalin A-induced T-cell suppression of pokeweed mitogen-induced immunoglobulin G production is decreased in some patients with sarcoidosis. The inability of patients' monocytes to suppress pokeweed mitogen-induced immunoglobulin secretion is associated with active disease. The latter findings may be functionally related to humoral hyperreactivity.

Semenzato et al found that Fc receptor positive T cells from patients with sarcoidosis do not support immunoglobulin production as well as such cells from healthy subjects. Autologous mixed lymphocyte reactivity, which depends on the response of OKT4+ T helper cells to self-histocompatibility antigens, was found to be abnormally decreased in seven of 10 patients with active sarcoidosis. Such studies may indicate T helper cell dysfunction, which may contribute to a subtle abnormality in the formation of antibodies directed against the "sarcoid antigen.

The formation of immune complexes indicates the production of antibodies which can bind to their antigenic targets. Circulating immune complexes form when there is an antigen-to-antibody ratio of 3 to 2 or more. Most patients with acute sarcoidosis have circulating immune complexes, but those with the chronic disease do not. Erythema nodosum may be associated with circulating immune complexes in this disease. It is known that Fc gamma receptor positive (suppressor) T cells undergo a transition to Fc mu receptor positive (helper) T cells as a result of interaction with immune complexes. Immune complexes from sera of patients with sarcoidosis also have this effect on normal T cells. As noted earlier, many patients with sarcoidosis have increased numbers of Fc gamma positive and decreased numbers of Fc mu positive T cells, suggesting the absence of an immune complex-in-
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duced transition from T gamma to T mu.

Pathogenetic hypothesis

Many of these varied immunological abnormalities can be reconciled with the hypothesis that sarcoidosis is caused by an environmental agent which enters the body through the respiratory tract. One possibility regarding the pathogenesis of sarcoidosis is that the sarcoid agent is controlled by a normal antibody response in people who do not become ill. However, patients who develop sarcoidosis probably have a subtle defect in their T helper cell function. If the immunogen could not be contained by the humoral immune response, it would then become disseminated systemically. When the humoral response does not control the agent, as in the case of mycobacterial or fungal infection, the cell-mediated immune response physically contains the foreign substance by granuloma formation. When overwhelming amounts of antigen are present, however, there may be systemic energy and peripheral blood lymphocyte hyporeactivity secondary to T suppressor cells as seen with disseminated fungal infection.30 When the antigen is localized in one organ (e.g. the lungs), suppressor macrophages may be responsible for systemic hyporeactivity as is the case in anergic patients with tuberculous pleural effusions.31,32

Other possibilities are that the cell-mediated immune response is itself selectively defective, either in terms of containing the “sarcoid agent” or through the occurrence of an inappropriately massive response to a common or benign environmental antigen.

Summary

Sarcoidosis is characterised by diminution of systemic cell-mediated immunity associated with heightened activation of cellular immune function at the sites of granuloma-tous inflammation. Angiotensin-converting enzyme, which is associated with the sarcoid granuloma, may play an immunoregulatory role. Humoral immunity is also abnormal. Antibody production is enhanced and may be related to decreased suppressor cell activity. There is also evidence which suggests subtle defects in T helper lymphocyte function. Analogies to disseminated fungal and mycobacterial infections are noted.

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