From Mycobacteria to Sarcoidosis – Is the Gate Still Open?

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Despite more than a century of searching, the aetiology of sarcoidosis is still hidden in the veils of mystery. Sarcoidosis most frequently involves the lung, so in the majority of patients, the lungs are the principal target organ. The pathogenetic hallmark of sarcoidosis is granulomatous inflammation with the formation of non-caseating epithelioid cell granulomas, which may be triggered by persistent presentation of poorly degradable antigen(s). It appears that clinical, overt disease is the result of an exposition to the unknown antigen(s) together with a genetic predisposition [1]. Sarcoidosis has many features in common with infectious diseases, and for decades, researchers have been looking for microorganisms which might be involved in the pathogenesis. Many known infectious agents can induce granuloma formation, including bacteria, fungi, protozoans and helminths. In contrast, the antigens involved in the pathogenesis of sarcoidosis, Crohn's disease, biliary cirrhosis and Wegener's granulomatosis are unknown.

For many years, sarcoidosis was thought to be tuberculosis, or a variant hereof. Even the 'fathers' of sarcoidosis, Boeck and Schaumann, held this view. Clearly, however, by virtue of its clinical presentation, the absence of a demonstrable infectious agent, spontaneous improvement and response to corticosteroid therapy, as well as the absence of a positive tuberculin skin test and response to antituberculous medications, sarcoidosis is not classic tuberculosis.

The histological similarity between sarcoidosis and tuberculosis (with epithelioid cell granulomas as the typical common finding) has stimulated the search for an asso-

ciation between mycobacteria and sarcoidosis, and it has been hypothesized that sarcoidosis could be a separate manifestation of infection with mycobacteria. Therefore, most studies of a possible causal microorganism have focused on mycobacteria. Mycobacteria are ubiquitous all over the world with reservoirs in humans, animals, water and soil. Besides the usual forms, mycobacteria may exist in other disguises, such as cell wall-defective L forms. However, there is still no definite evidence for a causal relationship between mycobacterial infection and sarcoidosis.

Acute/subacute pulmonary sarcoidosis has features in common with a disease caused by inhalation of a precipitating antigen. In the initial phase of the disease, pulmonary sarcoidosis probably spreads from the bronchiole/alveoli through the lymphatic vessels to the hilar and mediastinal lymph nodes. However, serum antibody profiles (IgG and IgA) against *Mycobacterium tuberculosis* in patients with sarcoidosis and healthy control subjects demonstrate no consistent differences [2], and prolonged culture for mycobacteria from mediastinal lymph nodes in patients with sarcoidosis has been negative and did not support the hypothesis that mycobacteria could be directly involved in the pathogenesis of sarcoidosis [3].

Novel biomolecular techniques using identification of mycobacterial DNA with PCR have reopened the gate for a mycobacterial pathogenesis. The paper by Fité et al. [4] in this issue of *Respiration* is the latest of more than 20 reports within the last 13 years on the prevalence of *M. tuberculosis* DNA in biopsy specimens from sarcoidosis patients. Most of these studies have been performed in

Western Europe and display large variation in prevalences ranging from 0–72% [4]. In part, the variation could be explained by methodological differences in sensitivity and specificity of the PCR, but the organ specificity of the biopsy specimens and the regional incidence of tuberculosis may also exert an impact on the prevalence. Three studies [4–6] stand out due to their high prevalence of mycobacterial DNA in sarcoid specimens. Grosser et al. [5] in Eastern Germany found a prevalence of mycobacterial DNA in lung biopsies of 64% (32/50 patients) and showed that BCG vaccination did not tend to yield false-positive results. In Greece, Gazouli et al. [6] demonstrated a prevalence of mycobacterial DNA in lung/lymph node biopsies of 72% (33/46 patients vs. 0/20 controls). In their case-control study in Catalonia, Fité et al. [4] report a prevalence in lung/skin/lymph node biopsies of 39% (9/23 patients vs. 1/23 controls). In comparison, in 2002, the incidence of tuberculosis per 100,000 popu-

lation in Germany, Greece and Spain was 10, 20 and 30, respectively [7]. Fité et al. [4] performed a follow-up on the *M. tuberculosis* DNA-positive sarcoidosis patients after 7–14 years, and interestingly, none had developed clinical tuberculosis despite the fact that most were receiving corticosteroid treatment. So far, it has not been substantiated that mycobacteria can be a direct cause of sarcoidosis. However, the results of Grosser et al. [5], Gazouli et al. [6] and Fité et al. [4] suggest that mycobacteria/mycobacterial antigens could play a modifying pathogenetic role in sarcoidosis.

The findings by Fité et al. [4] signal that the gate is still open for a pathogenetic link between mycobacteria and sarcoidosis, at least in a subset of patients [5]. Sarcoidosis and mycobacteria might be associated through an unorthodox interference between mycobacteria and man, combined with a genetically driven immunological response in predisposed individuals.

References

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