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Review

Etiologic link between sarcoidosis and *Propionibacterium acnes*

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ABSTRACT

Propionibacterium acnes is the only microorganism isolated from sarcoid lesions by bacterial culture. Numerous *P. acnes* genomes are found in lymph node samples from Japanese and European patients with sarcoidosis, whereas a few genomes are found in some non-sarcoid samples. The high frequency and specificity of detecting *P. acnes* within sarcoid granulomas suggests that this indigenous bacterium causes granuloma formation in many patients with sarcoidosis. *P. acnes* is the most common commensal bacterium in the lungs and lymph nodes. Occasional detection of *P. acnes* in non-granulomatous areas of these organs from non-sarcoid patients suggests that host factors are more critical than agent factors in the etiology of sarcoidosis. A particular protein, i.e., trigger factor, from *P. acnes* causes a cellular immune response only in sarcoid patients. The *P. acnes* trigger-factor protein induces pulmonary granulomas in mice sensitized with the protein and adjuvant, but only in those with latent *P. acnes* infection in their lungs. Eradication of *P. acnes* by antibiotics prevents the development of granulomas in this experimental model. *P. acnes* can cause latent infection in the lung and lymph nodes and persists in a cell wall-deficient form. The dormant form is endogenously activated under certain conditions and proliferates at the site of latent infection. In patients with *P. acnes* hypersensitivity, granulomatous inflammation is triggered by intracellular proliferation of the bacterium. Proliferating bacteria may escape granulomatous isolation, spreading to other organs. Latent *P. acnes* infection in systemic organs can be reactivated by another triggering event, leading to systemic sarcoidosis.

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1. Introduction

Sarcoidosis is one of the best-studied systemic granulomatous diseases. Despite intensive investigation, however, the etiology of sarcoidosis has remained unresolved for more than 100 years [1]. Sarcoidosis seems to result from the exposure of a genetically susceptible subject to an environmental agent, and microbial etiologies of sarcoidosis have long been considered because of the clinical similarities to infectious granulomatous diseases [2]. Several epidemiologic mechanisms may underlie the association of an infective agent or agents with the etiology of sarcoidosis, including spatial, seasonal, and occupational clustering [3]. The results of A Case Control Etiologic Study of Sarcoidosis (ACCESS) study support an association between selected microbially rich environments and sarcoidosis [4].

Mycobacterial and propionibacterial organisms are the most commonly implicated etiologic agents based on studies indicating the detection, by polymerase chain reaction (PCR), of microbial DNA from these organisms in tissues from sarcoid patients around the world [5–7]. Different studies have produced considerably varying results, however, with microbial DNA detected in 0–80% of sarcoidosis tissues and in 0% to more than 30% of control tissues [8,9]. The failure to detect microbial DNA from these organisms in samples from some sarcoid patients suggests other causes of sarcoidosis in those patients, whereas detection of microbial DNA in some control samples suggests latent infection of the bacterium.

Immune responses against microbial antigens from these organisms, e.g., ESAT-6 and KatG peptides from *Mycobacterium tuberculosis* and a recombinant trigger-factor protein from *Propionibacterium acnes*, have been examined in sarcoid patients and control subjects [10,11]. Immune responses are frequently detected in sarcoid patients, as well as in some non-sarcoid patients and healthy subjects. Latent infection by these organisms complicates the interpretation of the results of these immunologic studies. Unless microbial antigens, which cause a specific immune response found only in sarcoid patients, can be used to stimulate an immune response, immunologic approaches will not be sufficient to unequivocally confirm that these organisms are causative.

Granuloma formation results from the persistence of a non-degradable product or a hypersensitivity response [12]. The two mechanisms overlap in most infectious diseases because microorganisms act as both foreign bodies and antigens to induce immunologic responses. Granulomas serve as a protective mechanism to sequester and degrade the invading agent. The pathologic hallmark of sarcoidosis is an epithelioid cell granuloma; thus, some etiologic agent of sarcoidosis must be present or has been present within the sarcoid granuloma. Histopathological studies are therefore essential to demonstrate mycobacterial or propionibacterial organisms or antigens within sarcoid granulomas to establish an etiologic link between sarcoidosis and these organisms.

P. acnes is so far the only microorganism isolated from sarcoid lesions by bacterial culture [13,14]. *P. acnes* is an anaerobic, non-spore-forming, gram-positive rod bacterium indigenous to the skin and mucosal surfaces. A series of Japanese studies has provided accumulating evidence for a role of *P. acnes* in sarcoidosis. In this review, we propose mechanisms of granuloma formation in response to this indigenous bacterium in subjects with sarcoidosis on the basis of our results obtained using histopathological and experimental approaches, and introduce a new concept of endogenous infection caused by hypersensitivity to indigenous bacteria.

2. Bacterial culture

The lung and its draining lymph nodes are the organs most commonly affected by sarcoidosis. As the lung constantly encounters airborne substances, including pathogens, many researchers have considered infection to trigger sarcoidosis and have, thus, tried to identify possible causative transmissible agents and their contribution to the mechanism of sarcoid granuloma formation [15,16].

In the late 1970s, a large Japanese research project, conducted by many clinicians and microbiologists with support by a grant from the Japanese Ministry of Health, was organized to seek the pathogens responsible for sarcoidosis. Extensive trials were performed to isolate microorganisms, including bacteria, viruses, and fungi, from tissue samples (in particular biopsied lymph nodes) affected by sarcoidosis. Only *P. acnes* and no other microorganism was isolated from the large number of samples [13]. *P. acnes* was isolated from cultures of biopsy samples of 31 (78%) of 40 lymph nodes from 40 patients with sarcoidosis [14], whereas this indigenous bacterium was also isolated from 20% of 141 control lymph nodes from patients with diseases other than sarcoidosis. The study was repeated twice to confirm that the initial samples had not been contaminated by cutaneous *P. acnes* during biopsy, and the results of both studies were identical.

Ishige et al. cultured peripheral lung tissue and various lymph nodes obtained from patients with diseases other than sarcoidosis [17]. *P. acnes* was isolated from 24 of 43 lungs and eight of 11 mediastinal lymph nodes, mostly in pure culture. *P. acnes* was isolated from 10 of 20 gastric and three of 12 intestinal lymph nodes; intestinal bacteria were also numerous. *P. acnes* was, in general, the only species isolated from these tissues. The number of *P. acnes* cells isolated was usually not more than 500 CFU/g in the lungs and lymph nodes. Of 43 lungs from