# Etiologic Link between Sarcoidosis and *Propionibacterium acnes*

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**SARCOIDOSIS IS ONE** of the best-known systemic granulomatous diseases. Despite intensive investigation, however, the etiology of sarcoidosis has remained unresolved for more than 100 years. 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 based on the clinical similarities to infectious granulomatous diseases.

Granulomas serve as 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 have been present within the sarcoid granuloma. Histopathologic studies are therefore essential to demonstrate suspected organisms or antigens within sarcoid granulomas to demonstrate an etiologic link between sarcoidosis and the organisms.

*Propionibacterium acnes* is the only microorganism that has been isolated from sarcoid lesions. We previously reported that many *P. acnes* have been detected in sarcoid lymph nodes using quantitative PCR (*Lancet* 354:120,1999) and in sarcoid granulomas by *in situ* hybridization (*J. Pathol* 198:541,2002) and that *P. acnes* trigger-factor protein causes a cellular immune response only in sarcoid patients and induces pulmonary granulomas in mice sensitized with the protein and adjuvant, but only those with latent *P. acnes* infection in their lungs (*Am J Pathol*163:631,2004).

Our recent study published in *Modern Pathology* (2012;25:1287-97) demonstrated *P. acnes* antigens within sarcoid granulomas using immunohistochemical methods with novel *P. acnes* specific monoclonal antibodies that react with cell-membrane-bound lipoteichoic acid (PAB antibody) and ribosome-bound trigger factor protein (TIG antibody). The PAB antibody reacted with small round bodies within sarcoid granulomas in 88% and 89% of lymph node biopsy samples from Japanese and German patients with sarcoidosis, respectively. Reactivity to the antibody was not observed in non-sarcoid granulomas, including those from patients with tuberculosis and so-called sarcoid reaction. The high frequency and specificity of *P. acnes* detected within sarcoid granulomas indicates that this indigenous bacterium is the cause of granuloma formation in many patients with sarcoidosis. Immuno-electron-microscopy revealed that the immunoreactive products of the PAB antibody and TIG antibody were differentially distributed in the outer and inner areas of the HW bodies that frequently appear in sarcoid lymph nodes (Fig. 1). Furthermore, conventional electron microscopy revealed that these bodies lack a cell-wall structure and occasionally exhibit protrusions from the body that appear to be yeast-like proliferating features (not mitotic, but sprouting or branching), characteristic of cell-wall-deficient (L-form) bacteria.

According to the results obtained by a series of our studies, we hypothesized the mechanism of sarcoid granuloma formation caused by *P. acnes* (Fig. 2). This indigenous low-virulence bacterium can cause latent infection in the lung and lymph nodes and persists in a cell-wall-deficient form. The dormant form is activated endogenously 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.

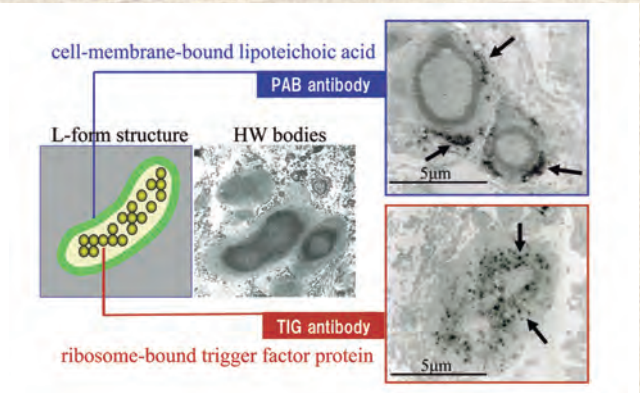


***Fig. 1:*** Cell-wall-deficient *P. acnes* in sarcoid lymph nodes demonstrated by immuno-electron-microscopy with the novel monoclonal antibodies

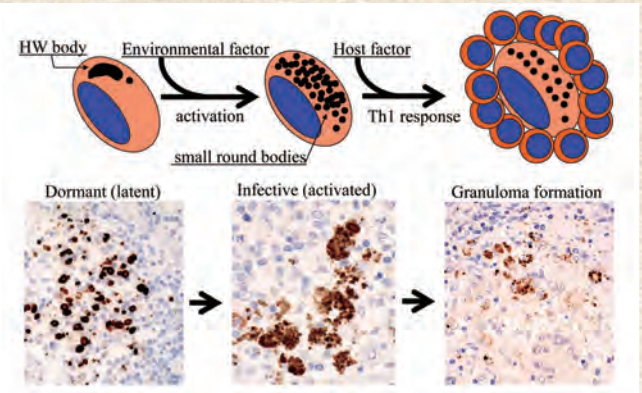


***Fig. 2:*** Hypothesized mechanism of sarcoid granuloma formation as an endogenous infection caused by hypersensitivity to *P. acnes*