Potential Association of *Cutibacterium acnes* with Sarcoidosis

Subjects: Infectious Diseases

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The immunohistochemical detection of *Cutibacterium acnes* in sarcoid granulomas suggests its potential role in granuloma formation. *C. acnes* is the sole microorganism ever isolated from sarcoid lesions. Histopathologic analysis of some sarcoid lymph nodes reveals latent infection and intracellular proliferation of cell-wall-deficient *C. acnes* followed by insoluble immune-complex formation. Activation of T helper type 1 (Th1) immune responses by *C. acnes* is generally higher in sarcoidosis patients than in healthy individuals. Pulmonary granulomatosis caused by an experimental adjuvant-induced allergic immune response to *C. acnes* is preventable by antimicrobials, suggesting that the allergic reaction targets *C. acnes* commensal in the lungs. *C. acnes* is the most common bacterium detected intracellularly in human peripheral lungs and mediastinal lymph nodes. In predisposed individuals with hypersensitive Th1 immune responses to *C. acnes*, granulomas may form to confine the intracellular proliferation of latent *C. acnes* triggered by certain host-related or drug-induced conditions.

Cutibacterium acnes | Propionibacterium acnes | sarcoidosis

1. *C. acnes* in Sarcoid Granulomas

A search for the causative agent of sarcoidosis via immunohistochemistry was performed based on two premises: the presence of the causative agent in sarcoid lymph nodes based on the Kveim reaction and localization of the causative agent in sarcoid granulomas based on the pathologic principle of granuloma formation [1][2]. In early studies, the SG5 antibody, which reacts with an exogenous antigen located in sarcoid granulomas, was generated by immunizing mice with sarcoid lymph node tissue homogenate followed by immunohistochemical screening of antibody-producing hybridoma clones using formalin-fixed paraffin-embedded (FFPE) sarcoid lymph nodes [1]. The SG5 antibody reacted specifically with a *C. acnes* culture supernatant and not with other bacterial supernatants (including those of *M. tuberculosis*). Accordingly, an anti-*Propionibacterium acnes* monoclonal antibody (PAB antibody) that reacts with a species-specific lipoteichoic acid (LTA) of *C. acnes* in sarcoid granulomas was developed by immunizing mice with the whole bacterial lysate and conducting immunohistochemical screening of *C. acnes*-specific antibody-producing hybridoma clones using FFPE sarcoid lymph nodes [2].

Immunohistochemistry with the *C. acnes* LTA-specific PAB antibody revealed positive signals in sarcoid granulomas in 88% of sarcoid lymph nodes and 74% of sarcoid lungs; no positive signals were detected in non-sarcoid granulomas in cases with tuberculosis or sarcoid reaction [2]. Positive PAB antibody signals were also observed in sarcoid granulomas obtained from originally aseptic organs such as the heart [3] and eyeball [4][5]. Localization of the immunohistochemical signals to *C. acnes* in sarcoid granulomas is shown in **Figure 1**.

Numerous case reports have described *C. acnes* detection in the granulomas of patients with pulmonary sarcoidosis [6][7][8][9], cutaneous sarcoidosis [10][11][12][13][14][15], nasal sarcoidosis [16], and neurosarcoidosis [17][18]. The term "*C. acnes*-associated sarcoidosis" is applied to cases in which *C. acnes* is detected in granulomas via immunohistochemistry using the PAB antibody [19]. The detection sensitivity of *C. acnes* in sarcoid granulomas depends on the evaluation method [20][21]; an automated method of detection using a Leica system with a commercially available PAB antibody (MBL, D372-3) has been used for differential diagnosis of sarcoidosis from other granulomatous diseases.

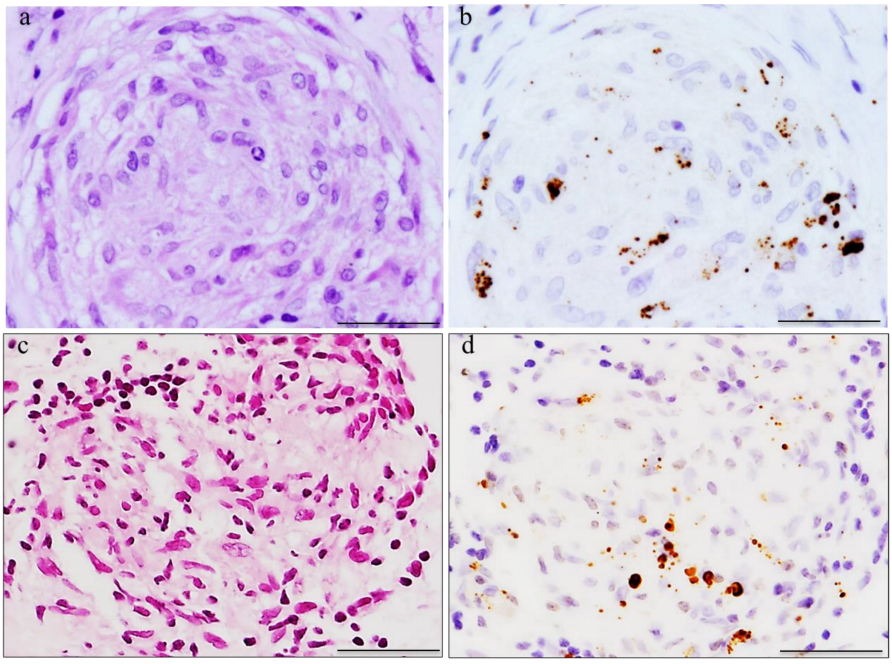

Figure 1. Immunohistochemical localization of *C. acnes* in sarcoid granulomas. Hematoxylin–eosin stain and immunohistochemistry with the *C. acnes*-specific PAB antibody are shown pairwise. Mainly small round and occasionally large ovoid PAB antibody-positive signals can be observed in non-caseating epithelioid cell granulomas of the lung (**a**,**b**) and ocular epiretinal membrane (**c**,**d**) from patients with sarcoidosis irrespective of the sites at which the granuloma formed. All photos are original and were previously published [19]. Scale bar: 50 µm.

2. Histopathologic Analysis of *C. acnes* in Sarcoid Lymph Nodes

PAB-antibody-positive structures in sarcoid granuloma cells are observed via electron microscopy as small round electron-dense bodies that cannot be identified as bacteria by their morphology alone because the cell wall structure is lacking (**Figure 2**) [22]. In the early stage of granuloma formation, macrophages are filled with PAB-antibody-positive small round bodies, and some are accompanied by PAB-antibody-positive Hamazaki-Wesenberg (HW) bodies with a large spindle shape. A report published in 1966 described HW bodies in association with sarcoidosis [23]. These HW bodies had ceroid characteristics [24] and were suspected to be cell-wall-deficient forms of *M. tuberculosis* [25][26].

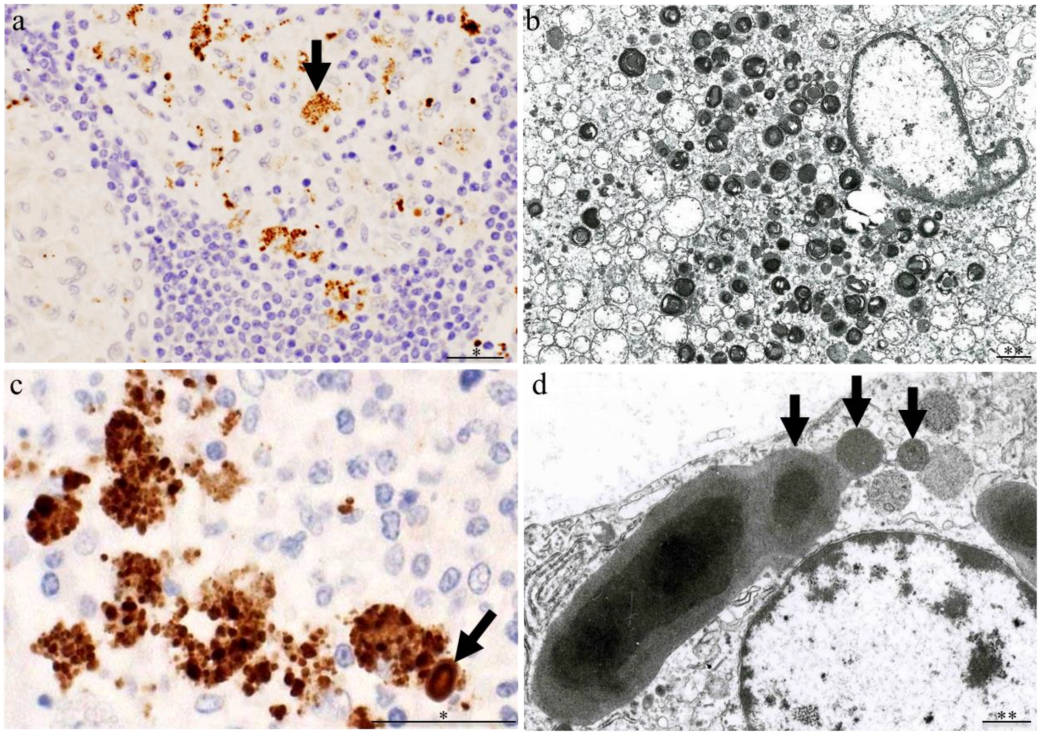

Figure 2. Features of intracellular *C. acnes* proliferation in sarcoid lymph nodes. Some granuloma cells (arrow) (**a**) are filled with PAB antibody-positive signals that are observed via electron microscopy as small round electron-dense bodies with a lamellar structure due to their partial deterioration (**b**). A cluster of swollen macrophages filled with many PAB-antibody-reactive small round bodies with a similar PAB antibody-reactive HW body (arrow) (**c**) can be observed at the paracortical area adjacent to granulomas. Small round bodies (arrows) (**d**) extruding from the large ovoid HW body can be observed in macrophages. All photos are original and were previously published [19]. Scale bar: * 50 µm, ** 1 µm.

Electron microscopy shows small round bodies extruding from the HW bodies in macrophages that are indicative of a dividing cell-wall-deficient bacterium [2]. Immunoelectron microscopic analysis of HW bodies using two *C. acnes*-specific antibodies (PAB-antibody-detecting cell-membrane-bound LTA and TIG-antibody-detecting ribosome-bound trigger factor protein) revealed that the PAB antibody signals distribute around the periphery of the HW bodies, whereas TIG antibody signals distribute in a dot-like pattern over the entire internal region of the body [2]. The distribution pattern of these bacterial components in the HW body structure is consistent with their localization in the basic structure of a bacterium despite the lack of a cell wall structure, which indicates that the HW bodies themselves are the bacterial bodies of cell-wall-deficient *C. acnes* (**Figure 3**). HW bodies detected by these *C. acnes*-specific antibodies are mainly located in sinus macrophages of the lymph nodes and, although not specific to sarcoidosis patients, are present at a significantly higher frequency in sarcoid than in non-sarcoid samples (50% of 119 cases vs. 15% of 165 cases, respectively) [2].

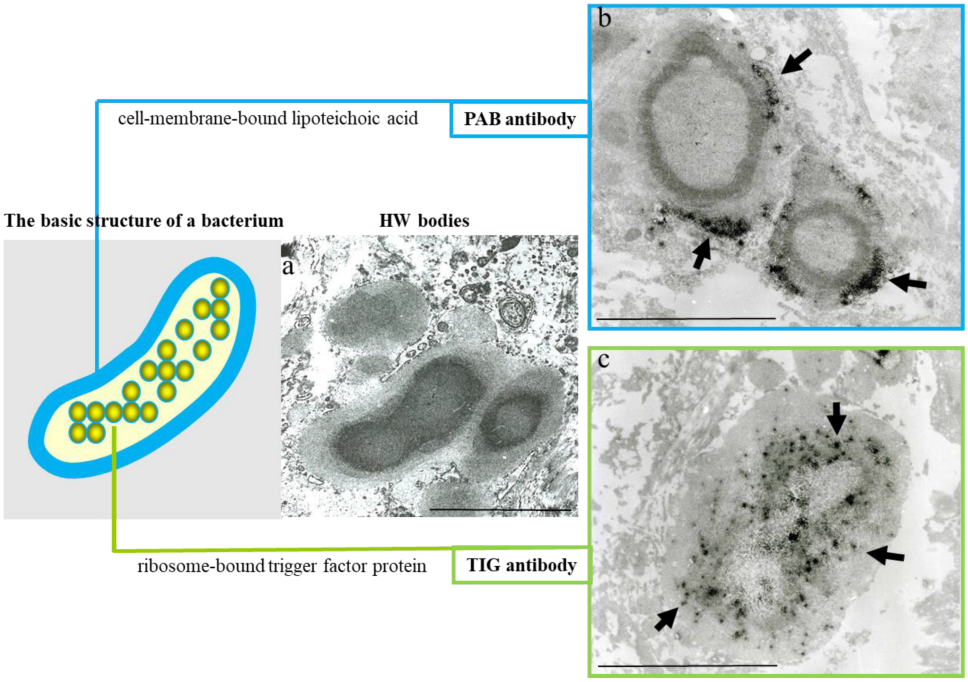

Figure 3. Evidence suggesting that HW bodies are cell-wall-deficient *C. acnes*. HW bodies lack a cell wall structure (**a**). Immunoelectron microscopic localization (black signals indicated by arrows) in HW bodies of two different *C. acnes*-specific bacterial components—cell-membrane-bound lipoteichoic acid detected by the PAB antibody (**b**) and ribosome-bound trigger factor protein detected by the TIG antibody (**c**)—was consistent with their localization in the basic structure of a bacterium despite their lacking a cell wall structure. All photos are original and were previously published [2]. Scale bar: 5 μm.

3. Latent Infection and Intracellular Proliferation of *C. acnes*

Based on histopathologic analysis, HW bodies are thought to represent latently infected *C. acnes*, while the small round bodies filling the cells are thought to represent intracellularly proliferating *C. acnes*. Unlike extracellular cell-walled *C. acnes* in the hair follicles of the skin, the intracellular *C. acnes* lack a cell wall. In culture medium containing a rich nutrient, these intracellular cell-wall-deficient *C. acnes* seem to revert to a conventional cell-walled form. Therefore, isolation of *C. acnes* from sarcoid lesions requires a longer incubation period than usual and a highly osmotic culture medium. In the early stages of culture, the organisms often appear round rather than coryneform.

A meta-analysis of 58 studies that included more than 6000 patients from several countries to investigate all types of infectious agents proposed to be associated with sarcoidosis revealed that *C. acnes* is most commonly linked to sarcoidosis [27]. Intracellular proliferation of *C. acnes* in sarcoid lesions was demonstrated via quantitative polymerase chain reaction (PCR) using FFPE lymph node specimens [28][29]. Although *C. acnes* DNA can also be detected in some control samples, sarcoid samples contain a larger number of *C. acnes* genomes—almost the same number of *M. tuberculosis* genomes detected in tuberculosis samples [28]. In situ hybridization using signal amplification with catalyzed reporter deposition also shows the localization of large numbers of *C. acnes* in sarcoid

granulomas [30]. Lymph node samples from European patients with sarcoidosis examined in an international collaboration study [31] also contained high amounts of *C. acnes* DNA, but *M. tuberculosis* DNA was almost undetected, which suggested the potential association of *C. acnes* with sarcoidosis even in European countries where *M. tuberculosis* has long been the suspected cause of sarcoidosis.

4. Humoral and Cellular Immune Responses to *C. acnes*

C. acnes is a commensal Gram-positive anaerobic bacterium that lives extracellularly on the skin and mucosal surfaces of the oral cavity and the gastrointestinal and genitourinary tracts [32]. The number of *C. acnes* detected via quantitative PCR in sebaceous materials aspirated from normal hair follicles begins to increase after the age of 10 years and reaches a maximum at the age of 15–19 years [33]. Serum antibody titers against *C. acnes* LTA (humoral immune response) are raised in all adults with no significant difference between healthy controls and sarcoidosis patients [34]. In contrast to the humoral immune response, PBMCs obtained from sarcoidosis patients that are stimulated by viable *C. acnes* exhibit increased production of a Th1-type cytokine interleukin-2 (cellular immune response) compared with PBMCs obtained from healthy controls [35]. Cellular immune responses are similarly increased when recombinant proteins of a *C. acnes* trigger factor [36] or catalase [37] are used as stimulating antigens. Bronchoalveolar lavage cells from sarcoidosis patients exhibit T-cell responses to even heat-killed *C. acnes* [38][39][40]. These observations suggest that sarcoidosis patients are predisposed to allergic cellular immune responses to this commensal bacterium.

5. Allergic Cellular Immune Response to Autoantigens

Granuloma formation may occur only in so-called “high responders” to *C. acnes*. The assumption of such a host factor is also based on the phenomenon of the Kveim reaction. Allergic cellular immune responses in sarcoidosis patients are assumed on the basis of experimental models of organ-specific autoimmune diseases such as experimental autoimmune encephalomyelitis [41] and experimental autoimmune thyroiditis [42]. For example, in an animal model of experimental autoimmune thyroiditis, the subcutaneous immunization of healthy animals with thyroglobulin using complete Freund’s adjuvant induces lymphocytic thyroiditis that simulates Hashimoto’s disease. In this animal model, DA strain rats are high responders and PVG strain rats are low responders; serum antibody titers to thyroglobulin are elevated in both DA and PVG rats, but lymphocytic thyroiditis occurs only in DA rats [43]. Such disease susceptibility of the host’s immune system [44] and dissociation of humoral and cellular immune responses to an identical antigen are also observed in sarcoidosis patients if *C. acnes* is assumed to be an intracellular antigen like the organ-specific autoantigen. Furthermore, experimental autoimmune thyroiditis is always self-limiting when induced in healthy animals, and DA rats that have undergone spontaneous remission are resistant to re-induction of experimental autoimmune thyroiditis [45]. These experimental observations are consistent with clinical observations that many sarcoidosis patients experience spontaneous remission.

6. Pathogenesis of Sarcoidosis Caused by *C. acnes*

The assumed pathogenesis of sarcoidosis caused by *C. acnes* is summarized in **Figure 4**. Commensal extracellular *C. acnes* causes asymptomatic intracellular infection via the respiratory tract. *C. acnes* is the most common bacterium detected intracellularly in the peripheral lungs and mediastinal lymph nodes in humans [2][20][46]. Susceptibility to latent *C. acnes* infection may be partly influenced by the NOD1 allele type of the host [47] or by catalase expression of the bacterium [48]. Latent *C. acnes* can be reactivated and proliferate intracellularly after certain triggering events, and this is not specific to sarcoidosis patients [2][20][49]. Autophagy is induced by an intracellular overload of *C. acnes* [50]; thus, intracellular *C. acnes* proliferation may induce the housekeeping function of autophagy, which plays a decisive role in determining the outcome of infection and immunologic balance [51]. It was recently proposed that dysfunction of mTOR, Rac1, and autophagy-related pathways not only hampers pathogen or nonorganic particle clearance, but also participates in T-cell and macrophage dysfunction, thereby driving granuloma formation [52]. The proposed mechanisms may contribute to the outcome of *C. acnes* infection and immunologic balance against intracellular *C. acnes* proliferation. Granuloma formation occurs only in individuals predisposed to a hypersensitive Th1 immune response against the intracellular proliferation of *C. acnes*. An allergic reaction to intracellular *C. acnes* proliferation seems to be caused by a different mechanism than the immunomodulatory effect of *C. acnes* itself [53]. Successful confinement of *C. acnes* that is proliferating intracellularly via granuloma formation prevents further spread of infective *C. acnes* to other cells, which resolves the granulomatous inflammation that leads to spontaneous remission in many sarcoidosis patients. Extracellular *C. acnes* that escapes granulomatous confinement or local phagocytosis has the potential to cause new latent infection in extrapulmonary organs (primarily in vascular endothelial cells) via dissemination through the lymphatic system and bloodstream, whereas local entry and subsequent latent infection of *C. acnes* through other than systemic spread may occur in some organs or patients. Latent infection in systemic organs can be simultaneously reactivated by additional triggering events, which leads to granuloma formation at all sites of latent infection in each organ of sarcoidosis patients.

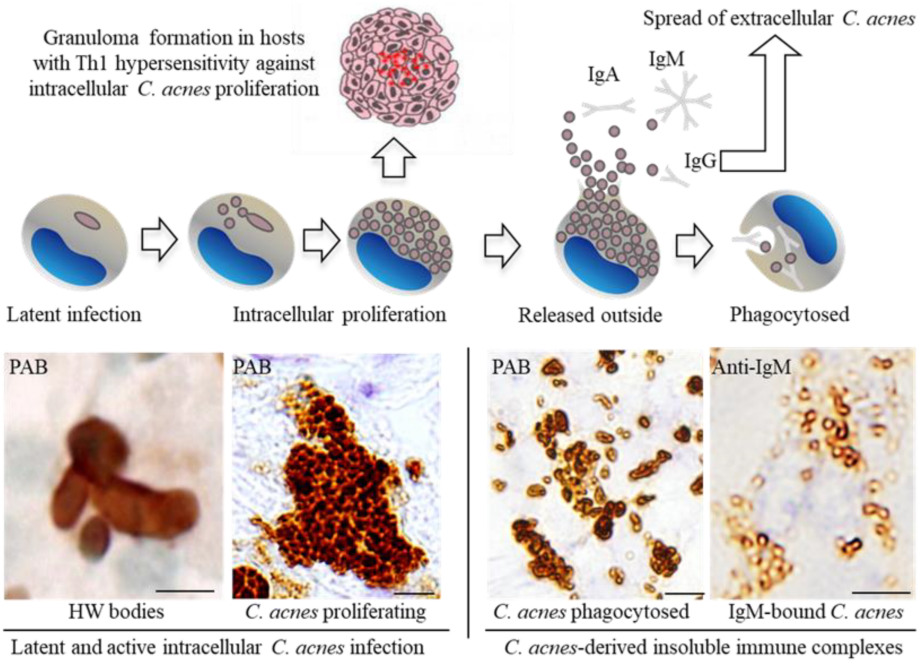

Figure 4. Assumed pathogenesis of sarcoidosis caused by *C. acnes*. Granuloma formation occurs only in some predisposed individuals with Th1 hypersensitivity against the intracellular proliferation of *C. acnes* reactivated at the sites of latent infection. Extracellular *C. acnes* after intracellular proliferation potentially causes new latent infection in the same or other organs. LNs, lymph nodes; CNS, central nervous system. * Local entry and subsequent latent infection of *C. acnes* other than the systemic spread may occur in some organs or patients. The figure is original and was previously published [19].

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