**Press Releases**

### Etiologic Link between Sarcoidosis and Propionibacterium acnes

**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 mechanisms to sequester and degrade the invading agent. The pathological 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. Histopathological 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 granulomas. *P. acnes* trigger-factor protein (TIG antibody) reacts with cell-wall-bound lipoteichoic acid (PAB antibody) and ribosome-bound trigger factor protein (TGF antibody). The TGF antibody reacted with small rounded 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 reactions. 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 TGF 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 inducibly 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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### 3D MRI Analyses Clarify that Pathologic Myopia is Caused by Eye Globe Deformity

**THE PREVALENCE OF** myopia (short-sightedness or near-sightedness) has rapidly increased worldwide, especially in East Asia. In urban areas in Asian countries, 80-90% of children completing high school are now myopic, whereas 10-20% can have pathologic myopia. People with pathologic myopia are at a substantially increased risk of potentially blinding myopic pathologies, which are not prevented by optical correction. Thus, pathologic myopia is a major cause of legal blindness worldwide.

The visual impairment in pathologic myopia is caused by development of vision-threatening complications in the retina and optic nerve. Most of these lesions are difficult to treat and it has long been unclear why and how pathologic myopia develops such vision-threatening complications.

TMDU is the home of the High Myopia Clinic, which was established by Honorary Professor Takeshi Tokoro in 1974 as the world’s only clinic specific to high myopia. Through our clinical experience, we have considered that pathologic myopia is not a simple exaggeration of myopia, but pathologic myopia may accompany severe eye deformity especially in the posterior segment of the eye. And such deformity of the eye can mechanically damage the nervous tissue inside the eye, such as neural retina and the optic nerve.

To visualize the entire eye shape, we used 3-dimensional high-resolution magnetic resonance imaging (3D MRI). Volume renderings of the T2-weighted images were done on a computer workstation. The globe margins were then identified semiautomatically, and the tissue outside the globes were removed. To analyze the eye shape quantitatively and objectively, we developed a software in collaboration of Dai Nippon Printing Company (DNP). The software incorporates six views of each 3D MRI image and automatically analyzes several parameters, including symmetry and pointedness of the posterior segment of the eye.

Our results demonstrate that normal eyes (without myopia) showed a completely spherical eye globe (Fig. 1). A normal eye is symmetrical in all directions. In contrary, there are different ocular shapes in eyes with pathologic myopia, and the difference in the ocular shape is correlated with the development of vision-threatening conditions in eyes with pathologic myopia. The eye deformity in pathologic myopia was classified into four distinct patterns: nasally-distorted type, temporally-distorted type, cylinder type, and barrel type (Fig. 2). Among these four types of eye deformity, optic nerve damage was significantly more frequently observed in eyes with a temporally-distorted shape.

This study clarified that an important feature of pathologic myopia lies in eye deformity, especially in deformity of the posterior segment of the eye. The eye contains central nervous tissue (retina and optic nerve) just as the brain does. Unlike the hard skull bone which protects the brain, the eye wall is made of collagen fibers and is less rigid. Thus, an eye deformity can directly damage the retina and optic nerve, and this causes an impairment of vision. Pathologic myopia is probably the only disease which causes an acquired deformity of the eye.

Based on the findings obtained by 3D MRI analyses, our team is currently developing novel therapies to treat and prevent eye deformities. For this purpose, we are using a modified printing technique which we have long collaborated with DNP, and are transferring the collagen sheet with amniotic membrane into the deformed eye shell. We are also injecting stem cells into the space between the retina and sclera. We believe that this treatment will be a fundamental treatment against pathologic myopia and will rescue many patients worldwide who suffer from severe vision loss due to pathologic myopia.