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COMMENTARY

Cutibacterium acnes: the Urgent Need To Identify Diagnosis Markers

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ABSTRACT *Cutibacterium acnes* role is well described during acne but remains a mystery regarding its implication in bone and prosthesis or cerebrospinal fluid shunt infections. The main issue is that these low-grade symptom infections are difficult to diagnose and lead to irreversible and grave sequelae for patients. Consequently, there is an urgent need to find new biomarkers to accelerate the diagnosis of disease, an issue addressed by Beaver et al. thanks to a promising proteomic approach.

KEYWORDS *Cutibacterium acnes*, diagnostics

In this issue of *Infection and Immunity*, Beaver et al. (1) describe the investigation of biomarkers for the *Cutibacterium acnes* cerebrospinal fluid (CSF) shunt infection diagnosis. They successfully distinguish *C. acnes* infection from sterile postoperative inflammation thanks to the alteration of the CSF proteome. Thus, these specifically identified proteins could be used for enhancing the diagnosis of these difficult to identify infections.

OPPORTUNISTIC PATHOGEN

C. acnes is a Gram-positive bacterium of the normal flora of the skin, oral cavity, large intestine, conjunctiva, and the external ear canal (2). Although primarily recognized for its role in acne, *C. acnes* may also cause a range of postoperative and medical device-related infections such as bone and prosthesis infections (BPI) (3), as well as cerebrospinal fluid (CSF) shunt infection. This commensal bacterium could become an opportunistic pathogen, but the underlying processes are unclear. *C. acnes* infections are often delayed (occurring 3 to 24 months or more after medical device setting) (4). Unfortunately, the diagnosis of *C. acnes* infections is long and difficult due to the challenges of *C. acnes* culturing and due to low-grade clinical symptoms, representing an additional issue for the patients. This delay in pathogen identification can lead to serious long-term consequence as the infection progresses during the time of diagnosis. In CSF shunt infections, *C. acnes* infections are associated with serious neurologic morbidity for patients. In implantable devices-related infections, a second surgery, removal of any foreign material and prolonged antibiotic treatment are required to manage *C. acnes* infection (3, 5–10). Such therapeutic approaches may have dramatic consequences: irreversible sequelae and emergence of antibiotic resistance.

C. ACNES FORMS BIOFILMS ON MEDICAL DEVICES

C. acnes infection is often associated with a peculiar bacterial ability to form biofilm, a social bacterial behavior leading to an increase of antibiotic tolerance. The first step of biofilm formation is bacterial adhesion to a substrate. This is favored in case of medical device as the latter is rapidly coated with host proteins (serum, extracellular matrix. . .) on which bacteria can easily adhere (2). Moreover, orthopedic implants are mostly made of a metallic (titanium, chromium, and cobalt. . .) surface, substrates that

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seem to favor *C. acnes* adhesion and so biofilm formation (11). Biofilms contain bacteria embedded in a complex matrix composed of extracellular DNA, protein, and polysaccharides. With such a protective coating, bacteria are less susceptible to antimicrobials than their planktonic counterparts. This peculiar bacterial growth makes such chronic infections difficult to treat and eradicate without bone or prosthesis extraction. This is one of the reasons underlying why BPI represent a severe threat for public health. *C. acnes* is estimated to account for 10% of BPI, but this proportion is probably underestimated (12). The establishment of biofilms explains the complex pathogenesis of *C. acnes*-related BPI.

LOW-GRADE SYMPTOMS AND NONSPECIFIC BIOMARKERS OF INFLAMMATION DURING *C. ACNES* INFECTION

Clinical manifestations of *C. acnes* low-grade infection are usually nonspecific with a chronic pain, a rarely described fever and a slight increase of systemic biological markers of inflammation (13). *C. acnes* infections do not induce a clear inflammatory response, meaning this microorganism is able to escape the immune system. Hudek et al. showed that *C. acnes* was detected immunohistochemically to persist intracellularly within stromal cells and macrophages of asymptomatic patients' joint shoulders (14).

Only a few studies have focused on inflammatory factors involved in *C. acnes* infection. Biomarkers that characterize *C. acnes* infection are not yet identified. Classical biomarkers of bacterial infection such as C-reactive protein, erythrocyte sedimentation rate, or procalcitonin have shown limited utility in diagnosing *C. acnes* infections such as CSF shunt infection or BPI (3, 7, 15, 16). Only a few studies have focused on other inflammatory mediators to consider as *C. acnes*-related inflammation biomarkers. Studies looking for modification in proteome serum or other biological markers (biochemical, genetic, or molecular substances) are necessary to characterize that kind of infection. A relevant diagnosis biomarker should detect or confirm the presence of the infection. The main issues in this context are the multiplicity of confusing biological targets due to surgery, aseptic inflammation, and infection (17).

In *C. acnes*-related intervertebral disc inflammation, Dudli et al. showed increased proinflammatory cytokines expression by local cells. Interleukin-6 (IL-6) and IL-8 mRNA expression was detected by PCR at 3 and 24 h of coculture (18). Such an activation of proinflammatory cytokine production depended on Toll-like receptor 2 (TLR2) and TLR4 activation (19) and, more specifically, in regard to acne, the activation of keratinocyte was mainly triggered by the TLR2 and NF-κB pathway (20). Other proinflammatory cytokines, such as tumor necrosis factor alpha, IL-1β, macrophage chemoattractant protein-1, and monocyte inflammatory protein, were overexpressed in intervertebral discs infected by *C. acnes in vivo*. An accumulation of neutrophils was also found in *C. acnes*-infected intervertebral discs (21), but their inflammatory activity is unknown. However, all of these potential biomarkers are *in situ* and failed to be detected in easily accessible biological fluids.

In this issue, Beaver et al. (1) examine CSF fluid for markers of CSF infection to discriminate inflammatory responses between sterile and infected catheters in a rat model with an increase of IL-1β, (C-C motif) ligand 2 (CCL2), and (C-C motif) ligand 3 (CCL3) coinciding with an increase in neutrophils. Moreover, mass spectrometry revealed an alteration of CSF proteome during infection providing hope for the identification of biomarkers for *C. acnes* infection diagnosis. Thus, these results highlight the potential interest for the use of similar approaches to study *C. acnes* BPI and other type of infections.

PERSPECTIVES

New diagnostic methods are needed as classical microbiological cultures lead to diagnosis delay. Delayed diagnosis represents a severe danger especially in CSF shunt infections that may lead to irreversible neurologic sequelae (Beaver et al. [1]). In such a clinical context, the challenge is to understand the rules that govern *C. acnes*, host cells and medical device interaction in tissue specific environments. Taking these together,

identification of biomarkers may make it possible for more rapid *C. acnes*-related infection diagnosis. Moreover, this will help to define therapeutic targets and thus innovative strategies, such as the association of antibiotics with immunomodulatory molecules to induce synergistic effects. Indeed, interfering with host-pathogen interactions will unlock the possibility of using immunomodulatory molecules as a means of fine-tuning the immune response, perhaps leading to synergy with antimicrobial treatments.

In conclusion, prolonged bacterial culture time and molecular biology have provided evidence for the involvement of *C. acnes* in BPI and CSF shunt infections. It is now necessary to decipher the interaction between bacteria and host cells to identify biomarkers, which must be reliably and precisely measured at a low cost.

As demonstrated by Beaver et al. for CSF shunt infection, the use of omics on biofluids or tissues offers promising approaches for the detection of biomarkers specific to an infected site as a means to refine diagnosis. This seminal paper will pave the way to fill the gap in other chronic pathologies such as *C. acnes*-related BPI to lighten patient burden.

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