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DISCUSSIONS

Bartonellae: Stealthy Pathogens or Novel Drug Factories (Letter to the Editorial Board of *Biokhimiya/Biochemistry (Moscow)*)

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We read with great interest the very thorough review article by Kabanov and Prokhorenko that recently appeared in *Biochemistry (Moscow)* [1]. The paper addressed a previously unconsidered feature, that is the structure–activity relationship between core and O-polysaccharide of bacterial endotoxins. The very large number of lipopolysaccharides (LPS) included in the review makes it very important for the fields of infectious diseases, intensive care, and microbiology. An outstanding aspect of the work is the detailed description of atypical LPS found in saprophytic, commensal, and pathogenic microorganisms. In the paragraph dealing with the lipid A structure of several LPS the different type of fatty acids found in typical as well as in unusual lipid A were discussed. A paper of Matera et al. [2] has been quoted to correlate the presence of very long chain fatty acids in the lipid A of *Bartonella* with a poor release of TNF-α in human whole blood samples. In this paper the LPS used was from *Bartonella quintana* and not from *Bartonella henselae*, as reported in Kabanov et al. paper [1].

On the other hand, pentaacyl lipid A containing very long chain fatty acids has been reported by Zähringer et al. [3] in a very important paper on the structure of *B. henselae* LPS.

Bartonella is a genus that includes two dozen species of bacteria bearing an atypical LPS and whose structure has been addressed by Zähringer et al. [3] for *B. henselae*. They are transmitted by ectoparasites and cause a long-lasting, sometimes asymptomatic bacteremia. The most clinically relevant members are *B. bacilliformis*, *B. henselae*, and *B. quintana*. Humans are the most common reservoir, although *B. henselae* frequently uses a non-human host [4].

Only *B. bacilliformis* is associated with 40-90% lethality during the first acute hemolytic phase of the disease [5]. The second, chronic stage of this disease may present with verrucous skin lesions "verruga peruana" and a milder illness, or may be clinically asymptomatic. *Bartonella henselae* and *B. quintana* are sometime asymptomatic or associated to flu-like fever. Only in HIV patients or in otherwise immunosuppressed subjects can a culture-negative endocarditis, bacillary angiomatosis, and bacillary peliosis of liver and spleen be observed.

Archaeological evidence suggests that some pathogens including *Bartonella* spp. have afflicted humans for several millennia. Examination of anthropomorphic pottery jugs (huacos) and carvings made by pre-Columbian Indians can reveal the telltale angiomatous lesions of Oroya fever, a sequela of chronic infection by *B. bacilliformis*. *Bartonella henselae* has been demonstrated by DNA PCR in remains of living creatures that have been buried for long time (800 years) [6].

In ancient times, ectoparasitism was probably common, and infections with *B. quintana* (transmitted by human body louse) could exhibit high prevalence. DNA of *B. quintana* was found in pulp from 12 teeth collected from human remains in southeastern France, thus demonstrating that *B. quintana* has been infecting humans for ≥4000 years [7].

Bartonella quintana LPS has been demonstrated to be a deep rough LPS with a molecular weight of about 5000 [8].

Bartonella henselae is one of these bacteria bearing an atypical LPS with an approximate molecular weight of

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5000 and with a penta-acylated lipid A containing an acyloxyacyl residue 16:0[3-O(28:0(27-OH))] [3].

Lipopolysaccharide is vital to both the structural and functional integrity of the Gram-negative bacterial outer membrane. Ubiquitously expressed by all Gram-negative bacteria, and containing several well-conserved domains, LPS also serves as one of the primary targets of the innate branch of the mammalian immune system.

Bartonella spp. LPS have been found to behave in a way that is substantially different from other LPS from saprophytic, commensal, and pathogenic microorganisms. Besides being a very weak stimulus of cytokine/mediator release, the experimental evidences strongly suggested an antagonistic activity for such LPS at the level of Toll-like transmembrane receptor 4 (TLR4) [9].

The LPS of *B. henselae* is lacking an O-chain polysaccharide [3]. The absence of O side chain could conceivably decrease complement fixation and provide a degree of serum resistance on *Bartonella*, but this possibility has not been explored. The unusual fatty acid composition renders *Bartonella* endotoxin at least 1000-fold less potent at TLR4 activation (as measured by IL-8 production) as compared with LPS from *Salmonella* [3]. Remarkably, *Bartonella* LPS possesses antagonistic properties for TLR4 and does not activate TLR2 [3, 9]. These LPS attributes undoubtedly contribute to the establishment and maintenance of persistent infection, since the bacterium's major surface component is subinflammatory and antagonistic to the host's innate immune response. Interestingly, long-chain fatty acids are a conserved feature in the LPS of intracellular bacteria that establish long-term symbioses with their host, including *Legionella*, *Chlamydia*, and closely related rhizobia.

Bartonella quintana and its LPS showed a different effect on the activation of genes involved in inflammatory response as revealed by molecular analysis of host cells [10].

Bartonella quintana microorganisms stimulated cytokine production through TLR2-mediated signals, whereas no role for TLR4 in the recognition of this pathogen was observed. When a single water–phenol extraction was performed, *B. quintana* LPS stimulated cytokine production in a TLR2-dependent manner. However, when double extraction was performed to generate highly purified LPS, *B. quintana* LPS entirely lost its capacity to stimulate cytokines, demonstrating that non-LPS components of *B. quintana* are responsible for the recognition through TLR2. Moreover, *B. quintana* LPS was shown to be a potent antagonist of TLR4. In conclusion, *B. quintana* is an inducer of cytokines through TLR2- but not TLR4-dependent mechanisms. This stimulation is induced by bacterial components other than lipopolysaccharide. *Bartonella quintana* LPS is a naturally occurring antagonist of TLR4 [11].

LPS and/or TLR4 are involved in a number of chronic/inflammatory diseases such as atherosclerosis, allergic illnesses, diabetes, and other endocrine disorders and inflammatory bowel diseases [12-14].

Because TLR4 proinflammatory signals play a pivotal role in a variety of pathologic inflammatory reactions, the use of the TLR4 antagonistic properties of *B. quintana* LPS may work as a novel and valuable therapeutic weapon.

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