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EDITORIAL

Complement component 3: a new paradigm in tuberculosis vaccine

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ABSTRACT

Vaccines are critical for the control of tuberculosis (TB) affecting humans and animals worldwide. First-generation vaccines protect from active TB but new vaccines are required to protect against pulmonary disease and infection. Recent advances in post-genomics technologies have allowed the characterization of host–pathogen interactions to discover new protective antigens and mechanisms to develop more effective vaccines against TB. Studies in the wild boar model resulted in the identification of complement component 3 (C3) as a natural correlate of protection against TB. Oral immunization with heat-inactivated mycobacteria protected wild boar against TB and showed that C3 plays a central role in protection. These results point at C3 as a target to develop novel vaccine formulations for more effective protection against TB in humans and animals.

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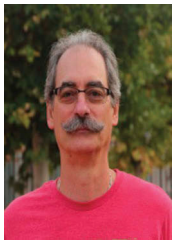

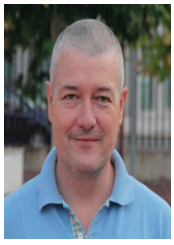

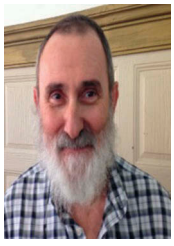

Tuberculosis (TB) is a pandemic caused by members of the *Mycobacterium tuberculosis* complex (MTBC) infecting 2.5 billion people worldwide with 1–13 million with TB.[1] Additionally, animal TB affects cattle industry and wildlife management and conservation; therefore, vaccines are required for TB control in reservoir host species involved in pathogen transmission cycle to cattle and wildlife.[2] The widely used *Mycobacterium bovis* Bacillus Calmette–Guérin (BCG) vaccine and other first-generation vaccines protect against some forms of TB but are not 100% efficacious in humans and new vaccines are required to protect against pulmonary disease and infection.[3,4] Additionally, although BCG may be effective against animal TB,[2] its use in animals may interfere with tuberculin skin test for TB diagnosis in eradication programs. Despite the fact that vaccines are among the best achievements in science, new strategies for vaccine development need to be conceived to increase possibilities for developing effective vaccines for TB control. These new strategies may benefit from latest post-genomics technologies to explore new possibilities for the discovery of new protective antigens and mechanisms to develop more effective vaccines for the control of TB in humans and animals.

Wild boar are natural reservoir hosts for MTBC in some regions and a model for mycobacterial infection and TB reproducing some of the clinical characteristics observed in human cases such as lung pathology and latent infection.[5] Recently, the characterization of the molecular interactions between wild boar and *M. bovis* showed that upregulation of genes encoding for complement component 3 (C3) and other innate and adaptive immune response proteins in lymph nodes and tonsils correlates with resistance to natural mycobacterial infection.[6,7] These results in the wild boar TB model were obtained using transcriptomics and proteomics approaches for the identification of natural correlates of protection against TB but resulted in the identification of a well-known component of the innate immune response such as C3. Consequently, these results prompted the question addressed here on how the C3-mediated protective mechanism could be used to develop more effective vaccines for TB control.

Bordet and Gengou recognized in 1901 the complement system as an important component of host

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protection against infection [8] and since then its role in infectious diseases has been well characterized.[9] C3 activation is required for both classical and alternative complement activation pathways, which have been shown to be involved in innate immune defense against several microorganisms including mycobacteria.[9–11] Additionally, the complement system links innate and adaptive immunity through C3 enhancement of antigen delivery to B cells.[12] Not surprisingly, certain bacterial inhibitors have evolved to act by blocking C3 activation and have been proposed as candidate protective antigens for vaccination against infectious diseases.[13] C3 opsonophagocytosis by macrophages results in the inhibition of bactericidal responses and survival of mycobacteria [14] while complement receptor CR3-mediated nonopsonic phagocytosis of mycobacteria may be essential for infection of macrophages after inhalation of mycobacteria.[15]

The connection between TB and C3 came from its role in innate immunity. Initial experiments using BCG demonstrated that infected mice develop an effective cell-mediated immune response that depends on sensitization with live organisms and require a secondary antigenic challenge that is antigen-specific and cannot be replaced by a nonspecific inflammatory stimulus.[16] In the wild boar model, immunization with BCG induces the increase in peripheral blood mononuclear cell (PBMC) C3 mRNA levels before infection with *M. bovis*.[2,17,18]

Recently, parenteral and oral immunization with heat-inactivated *M. bovis* protected wild boar against TB with special reduction in thoracic lesions,[2,10] suggesting that this approach might provide a novel vaccine for TB control with special impact on the prevention of pulmonary disease, which is one of the limitations of current vaccines.[4] Additionally, the immunotherapeutic use of heat killed *Mycobacterium vaccae* as an adjunct to anti-TB treatment in previously treated and untreated patients, multidrug-resistant TB patients and as a preventive agent for people at high risk for TB has provided evidence for its effectiveness through enhancement of cellular immune function by several mechanisms including regulation of complement system.[19] These experiments showed that C3 plays a central role in the protective mechanism elicited after oral immunization with heat-inactivated *M. bovis* in wild boar, resulting in C3 upregulation at both PBMC mRNA and serum protein levels.[10] Furthermore, a positive correlation was obtained between C3 mRNA and protein levels and the reduction in lesion and culture score after infection with *M. bovis*.[10] These results suggested a protective mechanism by which natural resistance to TB is enhanced in response to the oral immunization of wild boar with heat-inactivated *M. bovis*. The proposed protective mechanism in response to immunization of wild boar with heat-inactivated *M. bovis* in the absence of adjuvant includes the activation of dendritic cells (DCs) by pathogen-associated molecular patterns (PAMPs) present in the vaccine formulation through a surface Toll-like receptor (TLR), which triggers signaling cascades that lead to the transcription of genes encoding pro-inflammatory cytokines such as Interleukin-1 beta (IL-1b) that stimulates the production of C3 by DCs and other innate immune cells.[10]

The results of these experiments support the hypothesis that higher C3 levels may allow increased opsonophagocytosis and effective bacterial clearance, while interfering with complement receptors (CR3)-mediated opsonic and nonopsonic phagocytosis of mycobacteria, a process that could be enhanced by other mechanisms stimulating the production of C3, IL-1b and other cytokines by DC and other innate immune cells.[10] These mechanisms may include adaptive features of innate immune response related to C3 and IL-1b that could also contribute to increase vaccine efficacy against mycobacterial infection.[20]

In summary, these results suggest that C3 plays a central role in protection against TB after oral immunization with heat-inactivated *M. bovis* in the wild boar model and with heat-killed *M. vaccae* in humans. The upregulation of C3-coding gene expression in lymph nodes and tonsils correlates with resistance to TB in wild boar and this mechanism may be enhanced by immunization with heat-inactivated *M. bovis* to protect animals against mycobacterial infection and pulmonary disease. These results were obtained using the wild boar TB model reproducing some of the clinical characteristics observed in humans and may therefore be relevant for humans and probably other animal species. The C3-mediated mechanism challenges the standard assumptions on TB vaccination that for decades has ruled out both the use of inactivated bacteria and vaccine delivery by the oral route. Future research directions should include the development of novel vaccine formulations to increase the impact of immunization on the levels of C3, IL-1b and other cytokines for more effective protection against mycobacterial infection and TB. These results also point at a more relevant role of nonspecific innate immune responses in protection against TB for which C3 might be a readily available indicator to develop novel vaccine formulations against TB for humans and animals as well as a surrogate of protection when antigen-specific immune responses are not effective.

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