Organ Pathology in the Absence of Bacteria?

TO THE EDITOR—In the article by Reddy et al [1], a mutant of Mycobacterium tuberculosis is described that causes severe pathology in several organs of infected guinea pigs without any detectable bacteria. Here, we provide an alternative explanation for this observation without evoking homoeopathy.

Reddy et al constructed a mutant lacking one of the enzymes (MbtE) required for synthesis of siderophores in M. tuberculosis. The aim of this study was to examine whether siderophore-mediated iron acquisition is a virulence trait of M. tuberculosis, as it is for many other bacterial pathogens [2, 3]. Similar to other M. tuberculosis mycobactin synthesis mutants, the ΔmbtE mutant did not produce siderophores anymore and did not grow in medium with low iron [4]. Then, the authors infected guinea pigs with the ΔmbtE mutant and observed the same pathology as in guinea pigs infected with wild-type M. tuberculosis (Figure 5 [1]; see data from 4 weeks after infection). However, no bacteria were detected when lung or spleen homogenates were incubated on agar plates (Figure 5; p. 9 [1]). It is difficult to understand how apparently no mbtE mutant bacteria can cause the same severe organ pathology as approximately 100 000 or 10 000 wild-type M. tuberculosis bacteria in the lungs and spleens, respectively, of the infected guinea pigs. A simple explanation for this contradictory result is that the bacterial load of the ΔmbtE mutant is similar to that of wild-type M. tuberculosis, consequently causing similar pathology, but the ΔmbtE mutant did not grow on agar plates because it cannot use the iron salts in the medium without siderophores [4]. In fact, we experienced a similar problem when we examined an M. tuberculosis mutant deficient in siderophore secretion.

We overcame this problem by supplementing the agar plates with heme [5]. In addition, the pathogenicity defect of the ΔmbtE mutant, as reported by Reddy et al (see data from 10 weeks after infection), could result from a spontaneous loss of phthiocerol dimycocerosate (PDIM) [6, 7]. Unfortunately, the PDIM status of the ΔmbtE mutant was not examined. Further, genetic complementation of the ΔmbtE mutant would also reveal whether an apparent virulence defect is indeed due to the lack of the deleted gene or to an unknown secondary mutation. To this end, the complemented ΔmbtE mutant needs to be examined before the results of the infection experiments can be reliably interpreted.

Taken together, the experiments presented in this article do not support the conclusion of the authors that siderophores are important for virulence of M. tuberculosis [1]. They also do not “establish the enzymes of mycobactin biosynthesis as novel targets for the development of therapeutic interventions against tuberculosis” (abstract [1]). These critical issues need to be addressed to avoid confusion about the in vivo role of M. tuberculosis siderophores.

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References

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