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An exit strategy for the tubercle bacillus?

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Most studies on the host–pathogen interactions that occur between the residing infecting agent and its niche cell focus on the pathogenic manipulation of host cell entrance and intracellular propagation, but the timely and in-depth review by Kevin Hybiske and Richard S. Stephens (Exit strategies of intracellular pathogens. *Nature Rev. Microbiol.* **6**, 99–110 (2008))[1] focuses on exit of the pathogen from its host cell. The timing and mode of action of the cellular egress by the bacteria may, as the authors denote, determine the efficacy of secondary infection and the immune response. In addition, it may affect the dissemination of the disease within the host and also the transmission between hosts. We understand that it was impossible for the reviewers to cover all intracellular infections that depend on extracellular egress. However, we also think it should be noted that cytolysis-dependent cellular egress has recently been described for the causative agent of tuberculosis, *Mycobacterium tuberculosis*, which remains the leading cause of bacterial mortality worldwide.

Indeed, the key mechanism involved in host cell egress by the tubercle bacilli forms the basis of the primary attenuating mutation (region of difference 1; RD1) of the vaccine strain *Mycobacterium bovis* bacille Calmette–Guérin (BCG). Mycobacterial RD1 mutants exhibit a host cell lysis defect and exhibit reduced egress from host macrophages[2–4]. In the murine model of infection, RD1 was necessary to gain access to the deeper interstitial tissue of the lung and an *M. tuberculosis* RD1 mutant displayed both reduced disease progression and virulence[4,5]. Thus, in tuberculosis, RD1-mediated host cell exit is crucial both to cellular egress and to virulence. Interestingly, RD1 has recently been found to encode a novel type of secretion system and is responsible for both the production and secretion of a highly immunodominant virulence factor called early secreted antigenic target 6 (ESAT6)[4,6–8]. We found that ESAT6 is itself capable of lysing an artificial membrane[4], and it has since been reported that RD1-mediated whole-cell lysis is induced through the depletion of intracellular ATP owing to lysis of the mitochondrial membrane[3].

To conclude, we note that *M. tuberculosis* elicits cellular egress though RD1-mediated cytolysis, in a similar manner to many of the pathogens noted in the review, and that this is a requisite for disease progression and virulence. The mycobacterial mediators of cellular egress could be potential drug targets with which to halt dissemination and transmission of this global health threat. In addition, the benefits of understanding this potentially fundamental mechanism of disease progression include the development of much-needed improved strategies for the treatment and prevention of tuberculosis.

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