Why doesn’t Mycobacterium tuberculosis spread in animals?

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In their recent Spotlight article, entitled ‘Why doesn’t the bovine tubercle bacillus spread in humans?’\(^1\), Berg and Smith discussed work by Gonzalo-Asensio and colleagues who investigated mutations specific to the bovine tubercle bacillus, *Mycobacterium bovis*\(^2\). It has been known for about a decade that, of the two major forms of the tubercle bacillus, *Mycobacterium tuberculosis* has the more ancestral genome structure, with the *M. bovis* genome marked by several mutations and deletions\(^3,4\). In their recent work, Gonzalo-Asensio *et al.* used elegant molecular studies to define functional consequences of these mutations in *M. bovis* by recapitulating evolutionary steps between *M. tuberculosis* and *M. bovis*\(^2\). Given that *M. tuberculosis* is pandemic in humans, while *M. bovis* causes sporadic disease that rarely transmits among humans, there is a natural urge to link these molecular differences to a loss-of-virulence phenotype. However, this putative link overlooks three natural features of *M. bovis* that argue, if anything, towards a greater pathogenicity.

First, setting aside humans, whose health is of the most interest to authors and readers of this journal, *M. bovis* is the more successful in nature, maintaining and transmitting successfully among cattle, goats, East-Asian water buffaloes, deer, bison, brush-tailed possums, and last, but not least, the badger. Second, while the mutations engineered by Gonzalo-Asensio and colleagues resulted in diminished virulence as assayed in experimental infections, it must be remembered that the intermediate forms of the *M. tuberculosis* complex that separate *M. tuberculosis* from *M. bovis* are successfully spreading from antelope to antelope (in the case of *Mycobacterium oryxis*\(^5\)) and from seal to seal (in the case of *Mycobacterium pinnipedi*), the latter causing zoonotic infections in New World humans before *M. tuberculosis* came to the Americas\(^6\). Third, when *M. tuberculosis* and *M. bovis* have been contrasted directly in a neutral host, such as mice, guinea pigs, and rabbits, it has been *M. bovis* that is the more virulent of the two\(^7\). Indeed, long before these pathogens could be distinguished based on the genomic deletions that brand their lineages, the first-generation assay for differentiation of human and bovine bacilli was lethality in rabbits, with *M. tuberculosis* producing the nonlethal disease\(^8\). These same data could be used to argue that *M. tuberculosis* is more transmissible, not because it is more virulent, but rather because it can induce a focus of chronic inflammatory pathology that does not immediately threaten the survival of its biological atomizer.

While we applaud the elegance of the molecular microbiologic investigations of Gonzalo-Asensio and others, we caution that host infection, disease, and transmission require more than an able bacterium, and that host factors might also contribute to the unique specificity of *M. tuberculosis* for humans and *M. bovis* for cattle. It has been suggested that the most plausible common ancestor of the *M. tuberculosis* complex resembles extant smooth tubercle bacilli, such as *Mycobacterium canetti*\(^9,10\). From this common starting point, each organism has been subject to prolonged coevolution with its respective host, resulting in closely related organisms that are now genetically and phenotypically distinct. This long cohabitation within mammalian hosts that have different social and biological attributes may have selected for several bacterial properties that are not obviously manifest as laboratory-defined virulence. If *M. bovis* were merely an attenuated version of *M. tuberculosis*, one would expect to see more pronounced disease following experimental infection of cattle with *M. tuberculosis*, but the converse is true\(^11\).

The *M. tuberculosis* complex is an ideal group of pathogens in which to explore host adaptation, a search initiated by the seminal work of Theobald Smith in first differentiating human and bovine tubercle bacilli in 1896\(^12\). Smith contended that such comparative studies would ‘lead eventually to more light on the whole subject of tuberculosis from the preventive as well as the therapeutic side’\(^12\). The interface between human and animal TB still holds this rich potential.

References

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