

Are Cattle a Surrogate Model for Pathogenic Mycobacterial Latent Infection?

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Editorial

Tuberculosis (TB) in humans is often produced as a consequence of infection with *Mycobacterium tuberculosis*, followed in number of cases by *Mycobacterium bovis*, that also causes bovine TB. *M. tuberculosis* is predominantly a human pathogen causing active TB in approximately eight million people every year, and on the other hand, *M. bovis* has the ability to infect a broader host range including domestic and wild animals. *M. bovis* can cause pathology in cattle and humans as well, yet rarely transmits between immuno-competent human hosts. Some reports have suggested an increase in the number cases of human TB caused by *M. bovis*, where probably inadequate disease control measures in animals and humans, a rise in the incidence of immunosuppressive diseases, and the close physical contact between humans and animals facilitate the transmission of *M. bovis* from animals to human hosts [1].

TB pathology as a consequence of TB infection induces comparable immune responses to those seen in humans. Heterogeneity in granuloma type is commonly found during human and bovine TB, and lesions are predominantly localized to the respiratory tract and associated lymphatic tissue, making a chronic disease that may take years to develop. Ten to thirty percent of the humans who are naturally exposed to *M. tuberculosis* get infected, where 10-40% of immuno-competent hosts develop an active TB. Disease manifestation is reached often within a year after infection, or later in life. In most immuno-competent infected people, the chronic form of TB will remain latent and will not progress.

In recent years, research has been made aiming to define the molecular basis that might, at least partially, explain how virulent mycobacteria are able to remain in a persistent or latent infection in its human host and how these bacteria could resuscitate and be able to promote an active phase of disease [2]. A number of studies have suggested that in *M. tuberculosis* the DosR regulon (48 genes induced by stresses such as hypoxia, nitric oxide, and during granuloma formation) plays a role in inducing a chronic infection and persistence in animal laboratory models that resemble human infection in some respects. Latency is the product of interaction between host and mycobacteria, and is defined as the persistence of a tuberculous lesion with viable mycobacteria in a host without symptoms and has been demonstrated because of reactivation of apparently healthy people and/or reactivity towards mycobacterial antigens. Cavitation is thought to be the condition that causes bacteria to go into the metabolically and morphologically distinct dormant state. It is relevant to note that caseous tubercles that lead to cavitation do form in cattle.

In bovines, most studies have focused on active disease and related immune responses, and only a few studies have suggested an existence of latent TB [3]. Human latent TB infection (LTBI) was first described because a tuberculin skin test (TST) positive was observed in clinically

healthy people. Nowadays, interferon-gamma release assays (IGRA) using mycobacterial specific antigens are considered a complementary test to TST by international guidelines, and even TST and IGRA tests have allowed to suggest that LTBI due to *M. bovis* could be present even in cattle. Even so, we propose that LTBI could be defined as the existence of a positive TST or IGRA test in cattle without visible lesions, a concept that will surely evolve as more biomarkers become available. In fact, cases of LTBI produced by *M. bovis* has been observed indirectly in healthy humans with overt active TB after anti-inflammatory treatment [4].

Veterinary scientists regularly perform research addressing bovine TB directly in the target species, and research addressing human TB is performed using mice, guinea pigs, rabbits, and monkeys as models. Unfortunately, bovine TB is not generally regarded as a model for human TB. In guinea pigs and in sensitive and resistant mouse models, there is less inter individual variation and all animals succumb from infection with *M. tuberculosis*. The same holds for sensitive and resistant rabbits experimentally infected with *M. bovis*. The advantages of rabbits and guinea pigs over mice are known to be their sensitivity to tuberculous bacteria, and the resemblance of their lung pathology to human lung pathology. All mice, rabbits, and guinea pigs show progressive lung pathology, independent from whether bacterial loads are stationary or increasing. Rabbits and guinea pigs form cavitations, but they show progressive disease in multiple tissues, and do not go through a period of clinical latency.

Results from our laboratory have led us to propose that, in analogy to human TB, it is possible that bovine TB indeed would have a latent phase of infection, and we hence have started to unravel this hypothesis directly in bovines based on the expression pattern of mycobacterial DosR genes in animal tissue of tuberculin test reactors [5]. In cattle, the outcomes of exposure to *M. bovis* shows inter individual differences, resembling the situation in humans exposed to *M. tuberculosis* [6]. Furthermore, similar to what is observed in humans, some infected cattle would clear the infection, however remnant immune responses and perhaps mycobacteria would be responsible of bovine immune responses turn TST positive and/or their blood cells release interferon-gamma upon stimulation with mycobacterial antigens, but they show no clinical signs of disease, no visible lesions are present when slaughtered, and *M. bovis* cultures are negative, therefore strongly suggesting they are subjects of a LTBI. Nowadays, a LTBI experimental model in cattle is missing. So, even though cattle may be the species in which latency resembles human latency optimally, we acknowledge that it is still a long road before we can categorically define that there is a latent stage in bovine TB, for example for testing post exposure vaccines against latency antigens.

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