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INFECTIOUS DISEASE: REVIEW ARTICLE

Innate Resistance to Tuberculosis in Man, Cattle and Laboratory Animal Models: Nipping Disease in the Bud?

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Summary

Tuberculosis (TB) does not always develop in people or cattle exposed to the disease and some exposed individuals may not exhibit evidence of infection. Such variability in susceptibility may be mediated through host innate immunity, non-specific inflammatory responses that may successfully eliminate infection or at least reduce the infectious load, thus modulating and easing the burden on the subsequent acquired immune response. Assessing evidence from research in man, cattle and laboratory animal models, this review appraises the role of innate immunity in TB including the role of particular leucocytes (i.e. macrophages, neutrophils, γδ-T lymphocytes and natural killer cells), endogenous host defence compounds (i.e. cathelicidin, human neutrophil peptide, lipocalin and natural resistance-associated membrane protein-1) and, in particular, vitamin D. Innate responses may be particularly important in neonatal animals and people where adaptive responses have not yet established and their success in preventing the establishment of infection may be predicated on dose and/or route of infection as well as on characteristics of the infecting isolate. Innate defences could potentially be exploited in novel vaccination and immunotherapeutic approaches to disease control, modulating their effectiveness through the use of defined mycobacterial peptides as adjuvants or therapeutics. Such novel immunomodulatory compounds may be particularly relevant in countering emerging multi- and extremely drug-resistant strains of *Mycobacterium tuberculosis* (*Mtb*).

Keywords: bovine; human; innate immunity; tuberculosis

Contents

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Introduction

The global burden of tuberculosis (TB) in man is enormous and although *Mycobacterium tuberculosis* (*Mtb*) infection can result in primary disease, particularly in children, its most common manifestation is 'reactivation pulmonary disease' in adults of pre-existing, latent infection. It has been estimated that approximately one-third of the global human population harbours latent infection, 10–20% of which develop reactivation disease during their lifetime (Dye *et al.*, 1999; Horsburgh, 2004). TB in cattle has substantial economic significance globally and is a threat to public health through the human consumption of infected unpasteurized dairy products and exposure to aerosols containing *Mycobacterium bovis* (*Mb*) (Cosivi *et al.*, 1998; Anonymous, 2005; Amanfu, 2006; Bilal *et al.*, 2010).

It has long been recognized that many people and cattle, exposed to *Mtb* and *Mb*, respectively, do not subsequently show any evidence of infection (Gordon and Cashman, 1930; Israel *et al.*, 1941; Grzybowski *et al.*, 1975; Comstock, 1982; Rieder, 1999; Morrison *et al.*, 2000; Liebana *et al.*, 2008; Good and Duignan, 2011). Studies of people living in overcrowded conditions suggest at least one in every two close contacts of diseased individuals do not become infected with *Mtb* (Comstock, 1982) and some at apparent high risk of infection develop sensitivity to tuberculin skin tests over a much longer timespan than others (Gordon and Cashman, 1930; Israel *et al.*, 1941). Given it is not uncommon that only one or two tuberculin test-positive 'reactor' animals are identified in cattle herds (Morrison *et al.*, 2000), a similar situation would appear to exist for this species.

In such settings it is hypothesized that innate, non-specific inflammatory responses eliminate infection in people and animals exposed to infection or, if not entirely effective, at least reduce the infecting dose, thus modulating the subsequent acquired host response (Reiling *et al.*, 2002; Heldwein *et al.*, 2003; Elass *et al.*, 2005; Korbel *et al.*, 2008). The potential significance of such innate responses is also highlighted by the fact that mycobacteria interfere with host cell signalling via toll-like receptors (TLRs) and other mediators of innate immunity, as well as retarding the maturation of phagosomes in infected macrophages (Russell *et al.*, 1997; Netea *et al.*, 2004; Newton *et al.*, 2006). Innate host responses have also been implicated in the phenomenon of 'transient acute *Mtb* infection', reported in people in contact with active cases of TB (Ewer *et al.*, 2006; Nardell and Wallis, 2006). In such circumstances, variation in the capacity of TB-naïve individuals to initially control infection could have significant repercussions on intradermal skin test responsiveness and risk of disease development (Janulionis *et al.*, 2005).

Failure of appropriate innate responses may thus be critical to the establishment of infection and its progression to clinical disease. Prior to the onset of acquired immunity, the lungs of experimentally-infected susceptible rabbits contained 20- to 30-fold more *Mtb* organisms than those of resistant rabbits (Dannenberg and Rook, 1994) and a more recent study in rabbits suggested that the ultimate outcome of pulmonary *Mtb* infection is significantly influenced by the differential regulation of the innate immune response and associated gene expression as early as 3 h post infection (Subbian *et al.*, 2013). Variation in these innate responses may reflect the antibacterial effectiveness of myriad components within the host immune armoury such as pathogen recognition by cell receptors, phagocytosis and the production of intra- and extracellular immunomodulatory compounds including cytokines.

The reported genetic polymorphisms associated with increased susceptibility to, and severity of, TB may relate to components of innate immunity, although the complexities of such processes have proven difficult to elucidate (Casanova and Abel, 2002; Bellamy, 2003). Polymorphisms in genes encoding TLRs, vitamin D receptors (VDRs) and other innate immune effector molecules such as tumour necrosis factor (TNF) are associated with increased susceptibility to acquiring infection (Cobat *et al.*, 2009, 2013; Azad *et al.*, 2012). There is significant genetic variability in the susceptibility of Holstein dairy cattle to *Mb* infection (Bermingham *et al.*, 2009, 2014; Allen *et al.*, 2010; Brotherstone *et al.*, 2010; Tsairidou *et al.*, 2014) and Ameni *et al.* (2007) demonstrated that *Bos indicus* cattle are more resistant to *Mb* infection than *Bos taurus* animals. Allen *et al.* (2010) speculated that polymorphisms in genes coding for the dendritic cell (DC)-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) receptor may be associated with resistance of cattle to TB. A more recent study by Bermingham *et al.* (2014) found that variation in resistance to TB in Holstein–Friesian cattle was polygenic, but identified two genomic regions (encoding tyrosine phosphatase receptor T and myosin IIIB, respectively), that were particularly associated with disease resistance. Furthermore, Tsairidou *et al.* (2014) demonstrated that genomic selection for resistance to TB in dairy cattle is potentially feasible even in populations where pedigree data are unavailable.

Drawing on research in man, cattle and laboratory animal models, this review assesses the role of innate immunity to mycobacterial infection. It is likely that