Tuberculosis is, first and foremost, a disease of the human lung. For decades our model of tuberculosis pathogenesis has postulated that the posterior apical regions of the human lung in which cavitary pulmonary tuberculosis often develops are seeded by bacilli that disseminate from the site of primary infection. The early dissemination of bacilli is halted by adaptive immune responses. Some of this control involves the compartmentalization of infection within granulomas.

Beyond this point our ideas regarding pathogenesis become less certain. We know very little about the mechanisms involved in resolving granulomatous foci of lung infection heal or instead progress into active pulmonary tuberculosis.

A decade ago, 3 teams of researchers reported that SigH is a major regulator of the response of Mycobacterium tuberculosis to oxidative stress [1–3]. One team reported that their ΔsigH mutant induced less immunopathology in the lungs of mice than the parent M. tuberculosis strain [3]. The reduced lung pathology was not due to a difference in bacterial burden, which was comparable in both groups of mice. Instead, it seemed that the absence of sigH allowed the host to respond to lung infection in a manner that was inherently less destructive to lung tissue.

In this issue of the Journal, Mehra et al use a nonhuman primate (macaque) model to explore further the role of SigH in the pathogenesis of pulmonary tuberculosis [4]. Although small animal models commonly used to study tuberculosis have proven invaluable in understanding how granulomas develop, neither mice nor guinea pigs control inflammation in lesions infected with the parent strain. Recipients of the ΔsigH mutant achieved a lower bacillary burden in the lungs; and survived, rather than succumbed to, infection.

Macques were infected with the ΔsigH mutant or the parent M. tuberculosis strain. Compared with recipients of the parent strain, recipients of the ΔsigH mutant exhibited less fever, had lower levels of the inflammatory marker C-reactive protein, and gained, rather than lost, weight. They also developed less lung disease, as assessed by chest radiography and histopathology; had a lower bacillary burden in the lungs; and survived, rather than succumbed to, infection.

Tubercular lesions in the lungs of ΔsigH mutant–infected macaques shared many histopathologic features with lesions induced by the parent strain. However, differences were observed, including less acute inflammation in lesions caused by the ΔsigH mutant. Differences in host gene expression were also evident. Lesions infected with the parent strain exhibited 150-fold higher expression of matrix metalloproteinase 9, a protease associated with granulomatous lung remodeling. Conversely, lesions infected with the ΔsigH mutant expressed more SOCS3 and FOXJ1, genes associated with the dampening of inflammation. These lesions also contained a higher percentage of FoxP3- and CD25-expressing cells. Collectively, the findings suggested that the reduced inflammation in the ΔsigH mutant–infected macaques might involve the activation of host responses that control inflammation.

Because the ΔsigH mutant achieves a high lung burden in mice [3], its clearance...
from macaques demonstrates that macaques surpass mice in controlling the \(\Delta\text{sigH}\) mutant in vivo. The authors propose 2 mechanisms of control. First, because SigH regulates the bacterial response to oxidative stress, the phagocyte oxidative burst of macaques might be better at killing the \(\Delta\text{sigH}\) mutant than the immune system of mice in which nitric oxide is more prominent [5]. Second, there may be host-beneficial responses in macaques that are suppressed by the parent strain but that the \(\Delta\text{sigH}\) mutant is unable to suppress.

The authors acknowledge that their experimental design was inadequate to differentiate between these possibilities. They cite, however, additional work in macrophages in which the \(\Delta\text{sigH}\) mutant unmasks gene expression, including the \(\beta\)-chemokine and caspase/apoptosis networks. Furthermore, as noted above, their transcriptomic analysis hints that mechanisms involved in negatively regulating proinflammatory pathways are stronger in the lungs infected with the \(\Delta\text{sigH}\) mutant. These findings suggest that the low bacterial burden and minimal immunopathology associated with the \(\Delta\text{sigH}\) mutant in macaques were partly due to the unmasking of host-beneficial responses during infection.

Although the host-beneficial responses remain incompletely characterized, it is noteworthy that many of the observations made by Mehra et al are anticipated in the context of SigH’s role as the oxidative stress sigma factor. The inactivation of \(\text{sigH}\) cripples the ability of \(M.\ \text{tuberculosis}\) to produce many antioxidants; for example, 30 minutes after exposure to oxidative stress the \(\Delta\text{sigH}\) mutant expresses only 5% of the level of thioredoxin expressed by the parent strain [6]. In addition to their well-known antimicrobial activity against many pathogens, oxidants generated by immune cells benefit the infected host in other ways. First, oxidants participate in redox signaling, which activates phagocytes and other immune cells during early infection [7, 8]. Second, oxidants promote macrophage apoptosis, which restricts the growth of intracellular mycobacteria [9] and enhances antigen-specific CD8\(^+\) T-cell responses by cross-priming pathways of antigen presentation [10]. Third, the oxidant superoxide promotes cellular immunity by inactivating nitric oxide, a potent suppressor of T-cell proliferation [11]. Fourth, oxidants promote regulatory T-cell responses that limit tissue-damaging inflammation [12]. In summary, based on the role of SigH as the oxidative stress sigma factor, it is reasonable to assume that the \(\Delta\text{sigH}\) mutant is a poor scavenger of host-generated oxidants in vivo and that infection with this mutant might unmask oxidant-dependent host responses that restrict bacterial growth and limit lung immunopathology.

The hypothesis that mycobacterial SigH and antioxidants augment pulmonary tuberculosis is supported by other reports. In 2001, Edwards et al demonstrated that an \(M.\ \text{tuberculosis}\) mutant exhibiting 1% of the normal activity of iron-cofactoriated superoxide dismutase (SodA) induces greater recruitment and apoptosis of mononuclear cells in mice than the parent strain [13]. The SodA mutant and BCG Tice were comparably attenuated for bacterial burden in the lung; however, during prolonged infection, the SodA mutant induced less granulomatous pathology. This finding, along with evidence that the SodA mutant was more protective than BCG as a vaccine in mice [14] and the 2002 report of SigH’s role in lung immunopathology [3], led to the construction of a modified BCG vaccine with defects in both SodA and SigH [15]. Compared to the parent vaccine, the modified BCG vaccine induced greater antigen-specific CD8\(^+\) T-cell responses. It also conferred superior protection against challenge in a memory immune model. Two recent reports provide further evidence that SigH and SodA augment the pathogenesis of pulmonary tuberculosis. First, mice vaccinated with a Danish BCG mutant that overexpresses SodA developed more lung pathology after challenge with \(M.\ \text{tuberculosis}\) than mice vaccinated with the Danish BCG parent [16]. Second, some isolates of the W/Beijing family of \(M.\ \text{tuberculosis}\), including the hypervirulent HN878 strain, exhibited tandem duplication of a region of the chromosome that includes sigH and other virulence genes [17]. It is not yet known whether this genomic duplication explains the high rate of progression to active tuberculosis observed in persons infected with hypervirulent W/Beijing family isolates [18]. However, if it does, this finding would support the hypothesis that the risk of developing pulmonary tuberculosis is influenced by the balance between host-generated oxidants and microbial antioxidants that activate and suppress, respectively, the host responses that protect the lung [19].

Should we be surprised by the growing evidence that lung immunopathology in tuberculosis is augmented by mycobacterial antioxidants? Probably not, especially if we consider that granulomatous pathology is common not only in tuberculosis but also in chronic granulomatous disease (CGD). Indeed the prominence of granulomas in CGD, a genetic deficiency disease, and in granulomatous infections has been a long-standing mystery of medicine without an obvious explanation. To the casual eye these disorders appear unrelated; however, a model in which mycobacterial antioxidants augment granulomatous lung pathology suggests an underlying commonality. In effect, these diseases share a common phenotype, a deficiency of superoxide and other host-generated oxidants that are needed during early infection to activate host responses that limit immunopathology. In CGD, the deficiency of oxidants derives from defective production, whereas in tuberculosis it involves the inactivation of oxidants by mycobacterial antioxidants that are largely regulated by SigH. If this model is correct, then the struggle between host and tubercle bacillus to control the local redox environment
during early infection may be the key battleground that determines whether or not a host develops pulmonary tuberculosis. By focusing on this battleground it may be possible to construct tuberculosis vaccines that are not only antigenic but immunoregulatory, activating not only the host responses that control dissemination but also those that protect the lung.

**Notes**

**Potential conflicts of interest.** D. S. K. is listed as an inventor on patents for a technology to enhance the immunogenicity of bacterial vaccines by reducing the activity of anti-apoptotic enzymes including mycobacterial antioxidants. The technology has been assigned to Vanderbilt and the US government as represented by the US Department of Veterans Affairs.

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**References**


