Eicosanoids, Prostaglandins, and the Progression of Tuberculosis

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(See the major article by Kaul et al, on pages 1816–25.)

Mycobacterium tuberculosis (*M. tuberculosis*) is a highly successful human pathogen. This success is because *M. tuberculosis* effectively modulates the immune response to infection at several stages, including subversion of phagosome development, modulation of cytokine expression and various important immune signaling pathways [1, 2]. *M. tuberculosis* also survives and replicates within susceptible hosts by actively modulating the T-helper (Th) cell response.

Th1 cells (which produce interferon [IFN]–γ) play a critical role in host resistance to tuberculosis, whereas Th2 cells (which produce interleukin [IL]–4) favor the progression of disease [3]. The role of the regulatory T cells (Tregs) in this process is controversial, but it is largely accepted that Tregs have the potential to weaken protective anti-*M. tuberculosis* responses [4]. Th1 responses are also augmented via the Th17 subset, which express IL-17 and IL-23 [5]. IL-12 produced by infected macrophages and dendritic cells (DCs) directs Th1 differentiation. Similarly, transforming growth factor beta (TGF-β) produced by infected macrophages directs differentiation of induced Tregs (iTregs). In contrast, differentiation of the Th2 subset requires IL-4, which is not produced by *M. tuberculosis*-infected macrophages.

Tuberculosis is often a prolonged and chronic infection. In order to successfully modulate the pro/anti-inflammatory pendulum to its benefit, *M. tuberculosis* must not only direct the differentiation of Th2 and iTregs, but also maintain them over long periods of time. Loss of effective protective immunity (eg, during human immunodeficiency virus–AIDS coinfection), can reactivate latent tuberculosis via the inability of lung granulomas to contain *M. tuberculosis* replication and spread.

Recent reports indicate that *M. tuberculosis* can also modulate the host eicosanoid metabolism as a survival strategy [6]. Eicosanoids and prostaglandins are lipid molecules that have long been of interest in metabolic biology. However, it is being increasingly recognized that these molecules have the potential to shape the immune response to important infectious pathogens. The relative levels of prostaglandin E2 (PGE2) and lipoxin A4 (LXA4) govern whether macrophages undergo apoptosis, a phenomenon that correlates with pathogen containment; or necrosis, whereby *M. tuberculosis* is released from the infected cell, correlating with the spread of infection [7]. Virulent strains of *M. tuberculosis* induce the production of LXA4, which inhibits the production of PGE2. In contrast, the BCG vaccine strain and avirulent strains of *M. tuberculosis* preferentially induce the expression of PGE2, which protects against plasma membrane damage, leading to efficient apoptosis. In the absence of PGE2, extensive plasma membrane damage occurs, causing necrosis in lieu of apoptosis [6, 7].

Although modulation of macrophage apoptosis directly affects innate immunity, the effects of this modulation are also observed on adaptive immunity. PGE2 expressed by antigen-presenting cells is critical in polarizing immune responses [8]. For example, it has recently been reported that PGE2 inhibits activation-induced cell death (AICD) in Th2 cells, thus polarizing adaptive immunity towards a Th1-type response [9]. PGE2 can interact with four different receptors, EP1, EP2, EP3, and EP4, with each interaction leading to varied immunological responses. PGE2-mediated inhibition of AICD occurs via EP2. In this issue of the *Journal of Infectious Diseases*, Kaul et al [10] studied the expression of all four PGE2 receptors during the progression of tuberculosis in a BL/6 mouse model and report that *M. tuberculosis* infection induces the expression of EP2 in spleen-derived $CD4^+$ T cells, especially during the late stages of infection.

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Thus, macrophages that express PGE2 can potentially interact with these lymphocytes.

EP2 has been associated with T-cell polarization [11]. It was, therefore, conceivable that the prostaglandin receptor EP2 would be involved in the pathogenesis of tuberculosis. Thus, it might have been predicted that EP2-deficient animals should have better host-resistance capacity toward *M. tuberculosis* and would be able to resist that challenge better than congenic wild-type mice. Kaul et al convincingly show that *M. tuberculosis* infection specifically regulates EP2 expression in DCs. Using a knock-out mouse model, these authors surprisingly demonstrate that BL/6:EP2$^{-/-}$ mice are significantly more susceptible to aerosol infection with *M. tuberculosis* relative to congenic BL/6 mice [10]. Four weeks postinfection, about 4-fold more bacilli were present in the lungs, as well as spleens, of EP2$^{-/-}$ rather than BL/6 mice. Similarly, the lungs of these EP2$^{-/-}$ mice exhibited significantly higher levels of granulomatous immunopathology.

It could have been postulated that the increased susceptibility of EP2$^{-/-}$mice was due to impaired protective T-cell responses. Splenocytes from these EP2$^{-/-}$ mice, however, proliferated at a higher rate in response to *M. tuberculosis*-specific antigens relative to splenocytes from parental BL/6 mice [10]. Furthermore, spleen cells from EP2$^{-/-}$ mice expressed higher levels of iTreg and Th17, but not Th2 cytokines in an antigen-specific manner. As predicted, these animals also produced a sufficient amount of IFN-γ. These results indicate that the increased susceptibility of EP2$^{-/-}$mice was not a result of impaired lymphocyte response or function, but rather was due to hyperactive iTreg and Th17-type responses.

Since TGF-β is the main effector molecule of iTregs, Kaul et al were able to demonstrate significantly higher expression of this molecule in the lungs of EP2$^{-/-}$mice relative to BL/6 mice, again showing that higher numbers of iTregs were potentially recruited to the lungs of EP2$^{-/-}$ mice following *M. tuberculosis* infection. A confirmation of these observations was provided by flow cytometry and immunohistochemistry-based enumeration of total cell populations during different experiments. Twice as many CD4^{+}CD25^{+}FoxP3^{+} (iTreg phenotype) cells, and significantly more Th17 (IL-17^{+}) cells were present in the lungs of EP2$^{-/-}$relative to BL/6 mice when assessed by flow cytometry [10]. Similarly, significantly more iTregs were detected in the granulomatous lesions of EP2$^{-/-}$ mice than in BL/6 mice when analyzed by immunohistochemistry. Hence, the authors were able to decipher the molecular mechanisms of such an unpredictable result and showed that EP2$^{-/-}$ animals produce a large amount of TGF-β, which drives differentiation of iTregs.

The results of Kaul et al clearly demonstrate an important role for EP2-mediated PGE2 signaling in the control of *M. tuberculosis* infections [10]. This observation is not an isolated one. In a pleural tuberculosis model using infection with *M. bovis* BCG, it was shown that infected macrophages express high amounts of PGE2 and TGF-β concomitantly [12]. Zebrafish mutants in the leukotriene A4 hydrolase locus, which enzymatically synthesizes proinflammatory leukotriene LXB4, confer hypersusceptibility to *M. marinum* infection [13]. If a proinflammatory response were all that was required for a better clearance of mycobacteria, a mutation in leukotriene A4 hydrolase would have facilitated sterilizing immunity, rather than hypervirulence. This observation implies that the balance between LXA4 and PGE2 is critical for the control of tuberculosis immunopathology. Thus, the progression of tuberculosis (and hence the replication of the pathogen) can occur as a result of both extreme pathology and extreme immune response.

It was previously reported that PGE2 signaling through EP2 aids in the survival of intracellular pathogens [14, 15]. On the other hand, the results of Kaul et al [10] indicate that PGE2 signaling via EP2 is a host-protective pathway for *M. tuberculosis* infections. Clearly, multiple outcomes can be generated from the same pathway as a result of the interplay of different infectious challenges. These results appear to indicate that during the course evolution, *M. tuberculosis* and the host's response to it are in a continuing tug of war. During this process, a molecule like EP2 can act like "Janus," the two-faced Roman god, with differential function depending on the local environment and timing. This article [10] is another illustration that this deadly and smart pathogen may be constantly trying to evolve the mechanisms of its survival based on the very molecules that the host continues to depend on to contain *M. tuberculosis*.

Notes

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