CD8+ T Cells: Exacting a Toll in Viral Pneumonia

Over a 9-month period, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly spread across the globe, resulting in more than 170,000 deaths in the United States alone. Severely ill SARS-CoV-2–infected patients can develop a form of acute respiratory distress syndrome (ARDS) termed coronavirus disease (COVID-19) (1). Although there is hope (and some evidence) that antiviral drugs such as remdesivir may be beneficial early in infection, the only proven treatment for ARDS (irrespective of its etiology) is supportive ICU care (2); however, such care is resource intensive and often ineffective (3). Moreover, interventions such as O2 therapy and mechanical ventilation can themselves be injurious to the lung. New medical countermeasures to ameliorate the consequences of SARS CoV-2 infection for patients (including high mortality) are urgently needed.

In this issue of the Journal, Wali and colleagues (pp. 758–766) describe one such potential countermeasure (4). The authors tested the effects of early postinfection treatment with TLR (Toll-like receptor) agonists on lung injury severity in C57BL/6J mice infected with Sendai virus, which is a paramyxovirus with tropism for respiratory epithelial cells that causes tracheitis and bronchopneumonia (5). They treated mice with nebulized agonists of both the endosomal TLR2/6 heterodimer (Pam2 [Pam2CSK4]) and the TLR9 homodimer (ODN [oligodeoxynucleotide]) 1 day before infection and show diminished pneumonitis severity. Interestingly, they also show that this effect is associated with both reduced lung virus burden and attenuation of the CD8+ (cluster of differentiation 8–positive) antiviral T-cell response in the lungs. Furthermore, the authors found that this phenotype could be replicated in untreated mice by systemic CD8+ T-cell depletion late in the disease. Finally, Wali and colleagues elegantly demonstrate that the antiviral effect of Pam2–ODN treatment in Sendai virus infection occurred prior to viral entry into target cells. These experiments build on prior work by this group showing a similar protective effect of Pam2 and ODN cotreatment in mice infected with Gram–positive and –negative bacterial pathogens, pathogenic fungi, and influenza A virus (6, 7). They also recently reported that Pam2–ODN treatment reduced the long-term asthma-like sequelae of Sendai virus infection in mice (8). Taken together, work by this group suggests that immunomodulatory therapeutics that stimulate epithelial cell TLRs could be an important component of therapy for viral pneumonia and ARDS. Indeed, as the authors note in the current paper, two clinical trials investigating the efficacy of Pam2–ODN in patients with COVID-19 are ongoing. However, this study leaves several questions unanswered.

In previous work, this group has demonstrated the protective effect of using multiple TLR agonists to alter alveolar type II cell function. They showed that leukocyte ablation did not abrogate the protective effects of Pam2–ODN in mice infected with Pseudomonas aeruginosa or Streptococcus pneumoniae (9). However, TLR knockout in lung epithelial cells did block protection. Furthermore, they found that epithelial generation of reactive oxygen species was necessary for protection against influenza A virus–induced lung injury (10). Interestingly, this effect was IFN independent, yet the underlying mechanism remains undefined. The observation that Pam2–ODN treatment reduces viral replication could shed light on this, as it suggests the possibility that the reduced CD8+ T-cell response in Pam2-ODN–treated Sendai virus–infected mice is simply a reflection of reduced viral replication earlier in infection. Unfortunately, the authors did not measure the impact of CD8+ T-cell depletion (which improved survival after Sendai virus infection) on viral replication. Moreover, it is not apparent how viral inactivation occurs, and it would be interesting to determine whether the block in viral internalization is a consequence of reactive oxygen species–mediated damage to viral RNA.

In the mouse, infection with Sendai virus causes recruitment of neutrophils, macrophages, dendritic cells (DCs), and lymphocytes into the lungs beginning at Day 4 and a significant increase in CD8+ and CD4+ cells most notably at Day 8 postinfection (11). Macrophages play an important role in containing the viral infection via their production of type 1 IFN. In addition, Sendai virus infection also decreases nitric oxide (12) and proinflammatory cytokine release from macrophages, possibly by inhibiting inflammasome assembly (13). Interestingly, depletion of airway macrophages by clodronate-loaded liposomes enhanced Sendai virus replication and pathogenesis in vivo (14). However, in the current study, Pam2–ODN pretreatment did not alter either the kinetics or the magnitude of the macrophage response to infection, indicating that their role may not be essential.

Different subtypes of DCs play distinct roles in the immune response because of selective expression of pathogen recognition receptors. Previous work has demonstrated an important role for the maturation and migration of DCs to the lung in response to Sendai virus in coordinating the innate and adaptive immune responses (15). One limitation of the study by Wali and colleagues is that the CD8+ T-cell depletion method used will also deplete CD8+ DCs, which are important for cross-presentation of antigens. This effect could at least partially explain the decreased mortality observed in this group. Most importantly, the authors of the current work do not explain the mechanism by which preinfection stimulation of TLRs with Pam2–ODN results in reduced CD8+ T-cell infiltration of the lungs later in Sendai virus infection. It is essential that this mechanism be clarified in future studies.

A final important question from the current paper is whether Pam2–ODN treatment has protective effects when given in the face of established viral infection, especially when administered by aerosol to the inflamed, edematous lung; to date, this group has only reported the effects of Pam2–ODN treatment prior to...
infection. Clearly, postinfection efficacy is a prerequisite for an effective COVID-19 therapy. Nevertheless, the link between early TLR stimulation and modulation of antiviral T-cell responses is an intriguing, and somewhat counterintuitive, finding, which will have implications for both our understanding of the pathogenesis of viral lung injury and its treatment.

Author disclosures are available with the text of this article at www.atsjournals.org.

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