Persistent Immune Activation and Macrophage Accumulation in SARS–Coronavirus Infection.

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Damage to the lung in SARS–CoV infection has been attributed to the direct viral destruction of respiratory epithelium as well as excessive inflammatory responses triggered by the virus. However, the relative contribution of these mechanisms to SARS remains controversial. Furthermore, the phenotypic identification of immune cells involved in early SARS–CoV–mediated inflammation has not been elucidated, in part due to the lack of a useful animal model. Our recently developed nonhuman primate model is uniquely suited for systematic examination of the timing and extent of lung inflammation to improve our understanding of SARS–CoV immunopathogenesis. In African Green monkeys intranasally–infected with SARS–CoV, lung viral load levels peak early, between days 1 and 5 post infection (p.i.). Pathological changes consistent with interstitial pneumonia, follow the peak in viral replication and extend beyond active viral infection. Gross pulmonary lesions and histological evidence of interstitial pneumonia are not apparent until after day 10 p.i. Flow cytometric analysis of inflamed lung tissue reveals that monocytes/macrophages increase in frequency and in the level of activation as compared to the total leukocytes in the lung. Areas of activated monocyte/macrophage accumulation persist in SARS–CoV infected animals and can be detected out to day 28 p.i. In addition, inflammatory cytokines IL–15 and IL–18, which are predominantly produced by monocytes/macrophages remain elevated until day 21 in SARS–CoV infection. These findings suggest that SARS–CoV triggers prolonged immune activation in the lung and that monocytes/macrophages play a prominent role in the immunopathogenesis of SARS–CoV infection.

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