Innate immune recognition and control of adaptive immune responses to respiratory syncytial virus infection

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Respiratory syncytial virus (RSV) is the leading cause of respiratory viral infection in infants and children, yet little is known about the natural antiviral response to RSV. We identified the signalling pathway activated by RSV that induces type I interferon production and T cell priming, and we spatiotemporally tracked the cellular source and major producer of interferon-β using interferon-β/YFP reporter mice. We then analysed the *in vitro* and *in vivo* patterns of interferon production by flow cytometry in RSV-stimulated bone marrow cells and RSV-infected lung cells. Results from *in vitro* analysis of RSV-stimulated bone marrow cells revealed that RSV induces interferon-β production in plasmacytoid dendritic cells, monocytes, and neutrophils. Spatial and kinetic analysis of interferon-β-producing cells in *in vivo* RSV-infected lung cells indicated that monocytes are rapidly recruited to the inflamed lung during the early phase of infection. These cells produced interferon-β via the MyD88-mediated, rather than the MAVS-mediated, pathway. In addition, monocyte-ablated mice exhibited decreased interferon-γ-producing $CD8^+$ T cell frequencies. Collectively, these data indicate that monocytes play pivotal roles in cytotoxic T cell responses and are the major type I interferon producers during RSV infection.

Alveolar macrophages (AMs) play a crucial role in combatting airborne pathogens, strongly express CD169, and are localized in the lung alveoli. Therefore, we used CD169-diphtheria toxin receptor (DTR) transgenic mice to explore the roles of $CD169^+$ cells in immune responses to mucosal RSV infection. The administration of diphtheria toxin to CD169-DTR mice induced specific AM depletion and reduced the recruitment of $Ly6C^{hi}$ monocytes. Notably, $CD169^+$ cell depletion reduced levels of innate cytokines, such as IFN-β, IL-6, and TNF-α, in bronchoalveolar lavage fluid during RSV infection without affecting the production of proinflammatory chemokines. Moreover, the depletion of $CD169^+$ cells increased the recruitment of inflammatory cells to the lung

during the early stage of RSV infection, although not during the later stages of RSV infection. Furthermore, the depletion of $CD169^+$ cells reduced the recruitment of effector $CD8^+$ T cells to the lungs after RSV mucosal infection. Our findings suggest that modulating the number of $CD169^+$ cells to enhance immune responses to RSV infection may be useful as a new therapeutic strategy.