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TNF-mediated alveolar macrophage necroptosis drives disease pathogenesis during respiratory syncytial virus infection

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RIPK1-, RIPK3- and MLKL-dependent alveolar macrophage necroptosis triggered by RSV infection is mediated by autocrine TNF and harmful to viral clearance. Alveolar macrophage necroptosis may drive RSV disease pathogenesis. https://bit.ly/3fS34uw

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ABSTRACT Respiratory syncytial virus (RSV) is the major cause of acute bronchiolitis in infants under 2 years old. Necroptosis has been implicated in the outcomes of respiratory virus infections. We report that RSV infection triggers necroptosis in primary mouse macrophages and human monocytes in a RIPK1-, RIPK3- and MLKL-dependent manner. Moreover, necroptosis pathways are harmful to RSV clearance from alveolar macrophages. Additionally, *Ripk3*$^{-/-}$ mice were protected from RSV-induced weight loss and presented with reduced viral loads in the lungs.

Alveolar macrophage depletion also protected mice from weight loss and decreased lung RSV virus load. Importantly, alveolar macrophage depletion abolished the upregulation of *Ripk3* and *Mlkl* gene expression induced by RSV infection in the lung tissue.

Autocrine tumor necrosis factor (TNF)-mediated RSV-triggered macrophage necroptosis and necroptosis pathways were also involved in TNF secretion even when macrophages were committed to cell death, which can worsen lung injury during RSV infection. In line, *Tnfr1*$^{-/-}$ mice had a marked decrease in *Ripk3* and *Mlkl* gene expression and a sharp reduction in the numbers of necrotic alveolar macrophages in the lungs. Finally, we provide evidence that elevated nasal levels of TNF are associated with disease severity in infants with RSV bronchiolitis.

We propose that targeting TNF and/or the necroptotic machinery may be valuable therapeutic approaches to reduce the respiratory morbidity caused by RSV infection in young children.