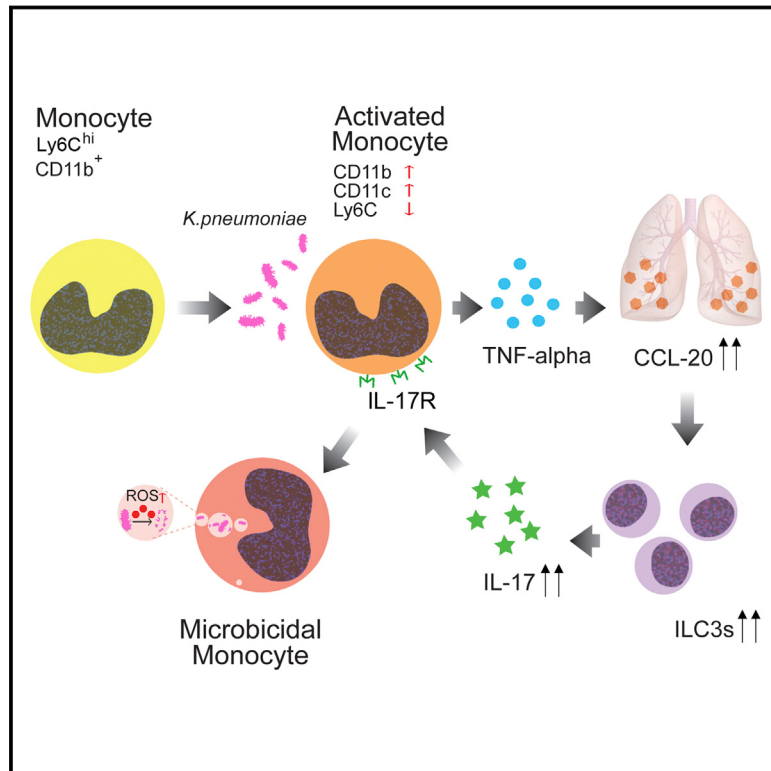


Innate Lymphocyte/Ly6C^{hi} Monocyte Crosstalk Promotes *Klebsiella Pneumoniae* Clearance

Graphical Abstract



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In Brief

Type 3 innate lymphoid cells engage in a positive-feedback loop with monocytes that promotes clearance of antibiotic-resistant *Klebsiella pneumoniae* pulmonary infections.

Highlights

- Inflammatory monocytes are required to clear *K. pneumoniae* from the lung
- TNF produced by activated monocytes enhances IL-17A production
- IL-17A produced by innate lymphocytes protects against *K. pneumoniae* infection
- IL-17A enhances the antimicrobial activities of inflammatory monocytes



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SUMMARY

Increasing antibiotic resistance among bacterial pathogens has rendered some infections untreatable with available antibiotics. *Klebsiella pneumoniae*, a bacterial pathogen that has acquired high-level antibiotic resistance, is a common cause of pulmonary infections. Optimal clearance of *K. pneumoniae* from the host lung requires TNF and IL-17A. Herein, we demonstrate that inflammatory monocytes are rapidly recruited to the lungs of *K. pneumoniae*-infected mice and produce TNF, which markedly increases the frequency of IL-17-producing innate lymphoid cells. While pulmonary clearance of *K. pneumoniae* is preserved in neutrophil-depleted mice, monocyte depletion or TNF deficiency impairs IL-17A-dependent resolution of pneumonia. Monocyte-mediated bacterial uptake and killing is enhanced by ILC production of IL-17A, indicating that innate lymphocytes engage in a positive-feedback loop with monocytes that promotes clearance of pneumonia. Innate immune defense against a highly antibiotic-resistant bacterial pathogen depends on crosstalk between inflammatory monocytes and innate lymphocytes that is mediated by TNF and IL-17A.

INTRODUCTION

Klebsiella pneumoniae is a Gram-negative bacterium that normally resides in the lower gastrointestinal tract. In patients with compromised immune defenses or impaired pulmonary clearance mechanisms, *K. pneumoniae* can cause severe infections of the lower respiratory tract. The emergence of high-level antibiotic resistance in some strains of *K. pneumoniae* limits treatment options and, in some cases, renders infections untreatable with available antibiotics. In the absence of effective antibiotics, optimizing or enhancing host immune defenses against *K. pneumoniae* represents a potential therapeutic option that might improve clinical outcomes.

As a bacterial species, *Klebsiella pneumoniae* is diverse and composed of a wide array of strains that differ in capsule composition, antibiotic resistance, mucoid phenotype, and virulence. Extensive studies with the rodent-adapted, antibiotic-sensitive strain 43816 of *K. pneumoniae* have demonstrated that TNF, neutrophils, IL17A, MyD88, and C-type lectins contribute to bacterial clearance from the mouse lung (Cai et al., 2009; Laichalk et al., 1996; Moore et al., 2005; Sharma et al., 2014; Steichen et al., 2013; Ye et al., 2001). However, which cell types produce defense-associated cytokines and which mediate bacterial clearance is incompletely defined. Further complicating the picture is the recent discovery that antibiotic-resistant strains of *K. pneumoniae* isolated from patients differ in their dependence on neutrophils or inflammatory monocytes for pulmonary clearance from infected mice (Xiong et al., 2015). While the clearance of five distinct strains of *K. pneumoniae* was consistently dependent on inflammatory monocytes, the contribution of neutrophils to clearance was more variable.

Inflammatory monocytes (IMs) are bone marrow-residing leukocytes that, in the setting of infection, rapidly traffic into the bloodstream and circulate to inflamed or infected tissues. IMs are pluripotent and, depending on the inflammatory environment they infiltrate, can acquire phenotypes that extend from pro-inflammatory TNF and iNOS production to immunosuppressive IL10-production (Biswas and Mantovani, 2010; Gordon and Taylor, 2005; Serbina et al., 2003). Although IMs enhance clearance of a wide range of pathogens, the exact mechanisms by which they promote microbial clearance remain unclear. Because TNF is essential for defense against intracellular pathogens, such as *Listeria monocytogenes*, and IMs can be prodigious producers of TNF, it has seemed likely that activated IMs mediate at least some level of bacterial clearance by producing TNF. However, the mechanism by which TNF enhances bacterial clearance remains largely undefined.

Pulmonary infection of mice with *K. pneumoniae* was one of the first infectious disease models to demonstrate the importance of IL-17A for host defense against extracellular bacterial infections (Ye et al., 2001). Indeed, IL-17A-deficient mice rapidly succumbed to infection with *K. pneumoniae* strain 43816 and neutrophils were essential for bacterial clearance. While Th17 CD4 T lymphocytes and $\gamma\delta$ T cells produce IL-17A (Harrington et al., 2005; Ivanov et al., 2009; Liang et al., 2006; Sutton et al., 2009), innate lymphocytes, at least in the gut, appear to be

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