Lung epithelium and myeloid cells cooperate to clear acute pneumococcal infection.

The Gram-positive bacterium Streptococcus pneumoniae causes life-threatening infections, especially among immunocompromised patients. The host’s immune system senses S. pneumoniae via different families of pattern recognition receptors, in particular the Toll-like receptor (TLR) family that promotes immune cell activation. Yet, while single TLRs are dispensable for initiating inflammatory responses against S. pneumoniae, the central TLR adapter protein myeloid differentiation factor 88 (MyD88) is of vital importance, as MyD88-deficient mice succumb rapidly to infection. Since MyD88 is ubiquitously expressed in hematopoietic and non-hematopoietic cells, the extent to which MyD88 signaling is required in different cell types to control S. pneumoniae is unknown. Therefore, we used novel conditional knockin mice to investigate the necessity of MyD88 signaling in distinct lung-resident myeloid and epithelial cells for the initiation of a protective immune response against S. pneumoniae. Here, we show that MyD88 signaling in lysozyme M (LysM)- and CD11c-expressing myeloid cells, as well as in pulmonary epithelial cells, is critical to restore inflammatory cytokine and antimicrobial peptide production, leading to efficient neutrophil recruitment and enhanced bacterial clearance. Overall, we show a novel synergistic requirement of
compartment-specific MyD88 signaling in S. pneumoniae immunity.