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"Innate and trained immune responses to methicillin-resistant *Staphylococcus aureus* respiratory infection."

by
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Infection, Immunity and Inflammation Program

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Tuesday, January 17th, 2023
11:00 AM
Cancer Center, G-1196

Join Zoom presentation
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Meeting ID: 941 3746 9256
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ABSTRACT

Staphylococcus aureus is a versatile bacterium responsible for conditions ranging from mild skin and soft-tissue infections to serious disorders such as pneumonia and sepsis. Due to its high propensity to develop antibiotic resistance, treatment options against this pathogen have become scarce and, as a result, Methicillin-Resistant *Staphylococcus aureus* (MRSA) was associated with 748,000 deaths, globally in 2019 and over $1.7 billion in healthcare costs in the United States in 2017. To this day, no vaccine against *S. aureus* is available. A better understanding of the immune responses to this pathogen, could allow the design of more efficacious treatments that rely on the immune system and could by-pass the need for antibiotics.

Our studies aimed to characterize the role of monocytes in antimicrobial defense against acute *S. aureus* airway infection and to investigate the innate immune memory responses generated by such infection.

In our first study, using CCR2-DTR transgenic mice, we showed that mice lacking monocytes exhibit a defect in bacterial clearance of *S. aureus* from the airway. Monocyte depletion was accompanied with significant decreases in IFN-γ and IFN-γ-related cytokines: interleukin-12 (IL-12), IP-10, MIG and RANTES. Interrogation of gene expression by RNA-sequencing revealed the existence of an IL-12 signature in lung monocytes from *S. aureus* infected mice, which was confirmed by ELISA. This indicates that IL-12 can be directly produced by monocytes in response to *S. aureus* infection. Administration of IL-12 during infection restored the pulmonary bacterial burdens of CCR2-depleted mice to the level of wild-type mice. Similar results were observed when IFN-γ neutralizing antibodies were administered simultaneously to IL-12. These results suggest that production of IL-12 by monocytes mediates the control *S. aureus* bacterial burden in the lung in an IFN-γ-independent manner.

In our second study, we found that wild-type mice inoculated intranasally with *S. aureus* exhibited enhanced pulmonary bacterial clearance upon secondary challenge with related and unrelated pathogens compared to naïve mice. This protection was observed to last for at least one month and to be independent of the adaptive immune system. Loss of function experiments relying on bone marrow chimera, transgenic mice model and antibody depletion showed that tissue-resident cells, but not alveolar macrophages or $CD11c^+$ cells were responsible for this protection phenotype. ATAC-seq, RNA-seq and metabolomic analyses revealed that *S. aureus* respiratory infection resulted in persistent epigenetic, metabolic and transcriptional changes in airway epithelial cells. These results indicate that *S. aureus* infection could induce trained immunity in airway epithelial cells.