ABSTRACT #18

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The role of recruited CCR2+ monocytes during pulmonary Pseudomonas aeruginosa infections

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Background: P. aeruginosa (PA) infections and hyperinflammation drive bronchiectasis in patients with Cystic Fibrosis, which ultimately causes respiratory failure. We have previously shown that monocytes and monocyte-derived lung macrophages drive pathological lung neutrophil inflammation and cause non-resolving lung structural damage in CfrImtU/rd (CF) mice. Importantly, genetic ablation of C-C Motif Chemokine Receptor 2 (CCR2), the major chemokine receptor for recruiting circulating monocytes into inflamed tissues, lowered lung neutrophilia and tissue damage. Our data thus support the use of a CCR2 inhibitor as a potential therapeutic approach to preserve lung function in patients with CF. However, the role of recruited CCR2+ monocytes during PA infections remains unclear.

Aims: to assess whether inhibition of CCR2+ monocytes recruitment compromises the host defense against pulmonary PA infections in WT and CF mice.

Methods: WT and CCR2−/− mice were infected with 5x10⁶ colony-forming units (CFU) of the PA laboratory strain PAO1 and sacrificed at 3h, 6h, 24h and 48h post infection. To assess the role of CCR2+ immune cell recruitment in the CF background, we used CF, and CCR2−/− x CF double knockout (dKO) and sacrificed these mice at 24h post infection (n=6-10 mice per group/genotype). We assessed lung and blood immune cell populations, bacterial load in lungs and spleen, and measured cytokines in bronchoalveolar lavage fluids (BALF).

Results: CCR2 deficiency showed a clear lack of recruited monocyte and macrophage populations in lung tissues following PAO1 infection, while other immune cell populations were not affected throughout the timecourse when compared to WT mice. Lung and BALF CFUs of PAO1 were not altered between WT and CCR2−/− mice. Mice with a CF background (CF and dKO) had increased CFUs in lung and BALF at 24h post infection, but CCR2 deficiency itself did not affect CFU numbers. This indicates that the complete lack of CCR2 was not detrimental to bacterial clearance during acute PAO1-pneumonia. Cytokine levels were similar between WT and CCR2−/− as well as CF and dKO mice.

Conclusion: We show that inhibition of CCR2 might be a valuable target to prevent lung tissue remodeling in CF, without affecting the host-defense mechanisms against CF-relevant lung pathogens.

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