Investigations of the role of neutrophils and macrophages in immunophage synergy during experimental pulmonary phage therapy

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Résumé

In an era of unprecedented emergence of antibiotic resistant bacteria, alternative therapeutics are being urgently sought. There is a renewed interest in bacteriophages - viruses that replicate within and lyse bacteria cells - therapy to combat bacterial infections. However, the mechanisms underlying phage-medicated bacterial clearance in an animal host remain unclear. In previous work, we showed using a murine model and infection by *Pseudomonas aeruginosa* that synergy between bacteriophages and the immune system was necessary to clear bacterial infection. Specifically, severe neutropenia by injection of an anti-GR1 antibody leads to treatment failure, pointing to a primary role for neutrophilic polynuclei (NPCs)(Roach et al., 2017). In this work we aimed to determine the threshold of neutrophils required for an efficient synergy with bacteriophages and to investigate the role of alveolar macrophages during the treatment. Neutrophil depletion resulted in a rapid progression of infection relative to the non-depleted control. Furthermore, the level of neutropenia correlated with the severity of infection (R=0.8): the lower the level of neutrophils was at infection the higher the bacterial load was at the end of the infection. Bacteriophage treatment of neutropenic mice lowered the bacterial load but did not clear the infection within the time frame of our experiments. There was no correlation between the level of neutrophils at infection in the depleted mice and the efficacy of phage treatment. Infection of the macrophage depleted mice appeared to be more severe than the control mice (as derived from recording of bacterial luminescence in the lungs during infection), however, we did not find statistical evidence that macrophage depletion had an effect on the CFU levels of *Pseudomonas aeruginosa* at sacrifice. Phage treatment of the macrophage depleted mice was successful at clearing infection (no CFUs detected at sacrifice). Surprisingly, phage treatment was more effective in macrophage depleted mice than in the control. This indicates that the macrophages somehow interfere with phage mediated bacterial clearance by a mechanism that remains unclear for now.

Roach, D.R., Leung, C.Y., Henry, M., Morello, E., Singh, D., Di Santo, J.P., Weitz, J.S., Debarbieux, L., 2017. Synergy between the Host Immune System and Bacteriophage Is Essential for Successful Phage Therapy against an Acute Respiratory Pathogen. Cell Host Microbe 22, 38-47.e4. https://doi.org/10.1016/j.chom.2017.06.018

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