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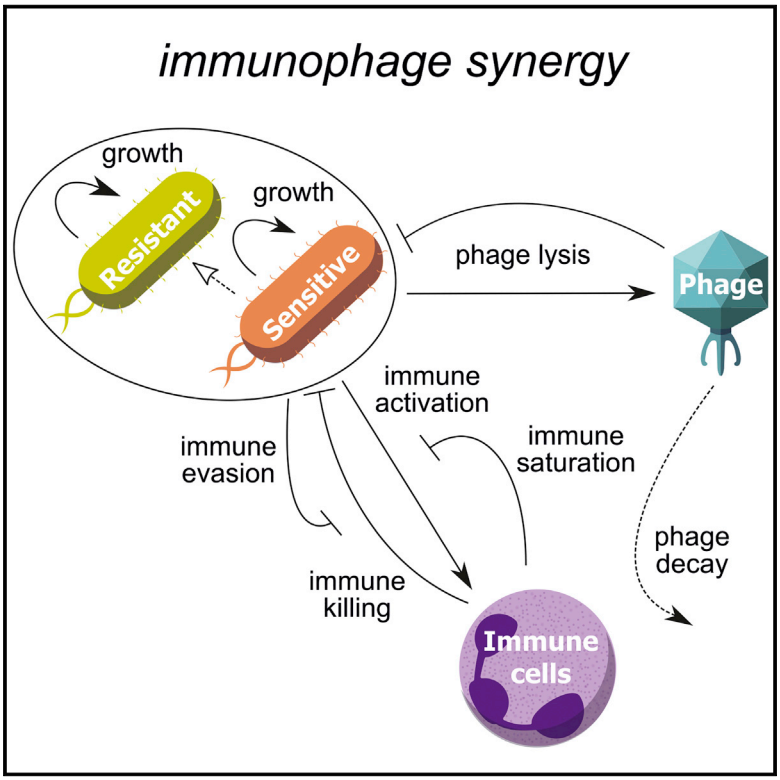
Synergy between the Host Immune System and Bacteriophage Is Essential for Successful Phage Therapy against an Acute Respiratory Pathogen

Graphical Abstract



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In Brief

The mechanisms underlying phage-mediated bacterial clearance in an animal host remain unclear. By coupling animal experiments and *in silico* modeling, Roach et al. show that host innate immunity is essential for the efficacy of phages in treating respiratory bacterial infections, defining the concept of "immunophage synergy."

Highlights

- Efficacious phage therapy to pulmonary *P. aeruginosa* requires innate immune components
- Neutrophils are required to control phage-sensitive and emergent phage-resistant bacteria
- Models predict "immunophage synergy" arises due to nonlinear feedback

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Synergy between the Host Immune System and Bacteriophage Is Essential for Successful Phage Therapy against an Acute Respiratory Pathogen

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SUMMARY

The rise of multi-drug-resistant (MDR) bacteria has spurred renewed interest in the use of bacteriophages in therapy. However, mechanisms contributing to phage-mediated bacterial clearance in an animal host remain unclear. We investigated the effects of host immunity on the efficacy of phage therapy for acute pneumonia caused by MDR *Pseudomonas aeruginosa* in a mouse model. Comparing efficacies of phage-curative and prophylactic treatments in healthy immunocompetent, MyD88-deficient, lymphocyte-deficient, and neutrophil-depleted murine hosts revealed that neutrophil-phage synergy is essential for the resolution of pneumonia. Population modeling of *in vivo* results further showed that neutrophils are required to control both phage-sensitive and emergent phage-resistant variants to clear infection. This "immunophage synergy" contrasts with the paradigm that phage therapy success is largely due to bacterial permissiveness to phage killing. Lastly, therapeutic phages were not cleared by pulmonary immune effector cells and were immunologically well tolerated by lung tissues.

INTRODUCTION

The global spread of antibiotic-resistant bacteria threatens all aspects of modern medicine, including advances in treatment of infectious disease, surgery, transplantation, and chemotherapy (Brogan and Mossialos, 2016). An acutely worrying trend is the spread of resistance to carbapenems—the "antibiotics of last resort"—predominantly among Gram-negative bacteria including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli* (Brogan and Mossialos, 2016; CDC (United States Centers for Disease Control and Prevention), 2013; Murray et al., 2015). Carbapenem resistance is almost always associated with resistance to several other classes of antibiotics, leading to the rise of multi-drug-resistant (MDR) bacteria (Brogan and Mossialos, 2016; Murray et al., 2015). Of the MDR bacteria, *P. aeruginosa* is a nosocomial opportunistic pathogen critical to the differential diagnosis of many Gram-negative infections, including pneumonia, bacteremia, and urinary tract infections (CDC (United States Centers for Disease Control and Prevention), 2013; Murray et al., 2015). Individuals with chronic pulmonary disorders, such as cystic fibrosis (CF), are also at considerable risk of *P. aeruginosa* respiratory infections (Salsgiver et al., 2016). With few, if any, replacements for β-lactam antibiotics in development, especially the carbapenems, physicians and scientists have renewed efforts to identify alternative antibacterial therapies (Czaplewski et al., 2016).

Phage therapy is an antibacterial approach that involves introducing bacterial viruses (phages) that infect and lyse bacteria to cure or prevent infectious disease (Knoll and Mylonakis, 2014; Roach and Debarbieux, 2017; Salmond and Fineran, 2015). In a growing era of precision medicine, phage therapy has the distinct advantage over broad-spectrum antibiotics of being highly specific toward target bacterial pathogens without adversely affecting the host or host commensal microbiota (Sarker et al., 2017). Pre-clinical animal studies have also shown success rates of phage therapy up to 100% for curing infections caused by MDR pathogens, including *P. aeruginosa* (Debarbieux et al., 2010; Pabary et al., 2015). Furthermore, a limited number of clinical trials evaluating phage therapy in humans have shown promising results (Abedon et al., 2011; Vandenheuvel et al., 2015). However, other clinical trials have produced conflicting results, e.g., demonstrating safety of phage but failing to provide evidence for improved clinical outcomes (Rhoads et al., 2009; Sarker et al., 2016). These data suggest the need to investigate the basis for therapeutic effectiveness, e.g., when and how is phage therapy effective, who should receive phage therapy, and how will phages be immunologically tolerated?

A mechanistic understanding of phage therapy and the inherent tension between clinical aims and the biological processes underlying phage-bacteria dynamics has yet to be