The synergistic effect of host immunity with phage and probiotic therapy against bacterial pathogens

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***Short Abstract*— The rise of antibiotic resistance in bacterial pathogens is a major public health concern. Existing alternatives to antibiotics include the use of phage (bacterial viruses) and probiotic bacteria. However, these therapies have not demonstrated consistent efficacy comparable to antibiotics, possibly due to heterogeneity in the host immune response against the pathogen. Through analysis of a combination of population models and data from animal experiments, we show that host immunity works synergistically with phage to cure an acute respiratory infection. We extend our modeling framework to show that the same principle of immunological synergy may also be applicable to probiotic therapy.**

***Keywords*— Bacteriophage, Phage therapy, Probiotics, Commensal bacteria, Antibiotic resistance, Mathematical model**

I. INTRODUCTION

The spread of antibiotic-resistant pathogens has become a major public health crisis. Without urgent intervention in antibiotic stewardship and development, the world may be approaching a post-antibiotic era where common infections can become fatal [1]. The plight of antibiotic resistance has stimulated interest in developing alternative or adjunct antimicrobial therapies to antibiotics, including the use of phage (viruses that exclusively infect bacteria) [2] and competitive exclusion by commensal or probiotic bacteria [3]. Unfortunately, these alternatives have yet to achieve the level of robust efficacy on par with antibiotics.

To understand the variations in clinical outcomes of these antimicrobial therapies, it is essential to consider contributions from the host immune system, which is a critical driver of the *in vivo* dynamics of pathogens. The *in vivo* host-pathogen interactions as well as *in vitro* pathogen-antimicrobial interactions have been relatively well studied. However, research into the tripartite interactions between pathogenic bacteria, antimicrobials and host immunity has remained scarce. Recent advances in mathematical modeling have suggested that host immunity can have a significant effect on the pharmacodynamics of antibiotics [4]. Here, we explore the role of host immunity in the effectiveness of novel antimicrobial therapies including phage therapy and probiotics therapy.

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II. RESULTS

We propose a nonlinear population model of phage therapy that considers the interactions between pathogenic bacteria, phage and host immune response [5]. Our model accounts for bacterial growth, phage predation, and immune killing of pathogenic bacteria. Crucially, we include the key immunological features of saturation of the immune response and immune evasion by bacteria. The model predicts a synergistic effect between host immunity and phage that eliminates bacterial pathogens, even when neither of which can do so when acting alone. This synergism is validated in animal experiments of acute pneumonia under different immunological backgrounds, and adaptation of the model to the *in vivo* conditions show that host immunity can prevent the emergence of phage resistance during therapy [6].

We extend our theoretical framework to incorporate competition between bacterial pathogen and commensal or probiotic bacteria. Our results indicate that host immunity may also act synergistically with probiotic therapy to prevent and cure bacterial infections. We systematically explore the effects of different competition strengths between the pathogenic and probiotic bacteria, and find that host immune killing promotes competitive exclusion of the pathogen by stabilizing the pathogen-free state of the system.

III. CONCLUSION

We demonstrate that synergy with host immune response can be a general mechanism of antimicrobial therapy applicable to phage and probiotic therapies. Our results highlight the need to characterize the host immune status when evaluating the effectiveness of novel antimicrobial therapies.

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