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# Adaptation of the Group A *Streptococcus* bacteriophages to the human host

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## Résumé

*Streptococcus pyogenes*, or Group A *Streptococcus* (GAS), is responsible for mild (pharyngitis) to life-threatening (necrotizing fasciitis) infections. A resurgence in severe invasive infections and scarlet fever has been observed since the 1980s. Population genomic studies have highlighted the key role of bacteriophages, which carry virulence genes, and horizontal gene transfer in the emergence and expansion of epidemic lineages. Despite this, little is known about the biology of GAS phages. In addition, after a century of vaccine development, we still rely on antibiotics to treat GAS infection. Success of new strategies, like phagotherapy, also requires the understanding of the tripartite phage-pathogen-host interactions. To decipher phage-GAS interactions, we used RNAseq to explore the changes in transcriptome during infection by the virulent phage A25. We found a reprogramming of up to 33% of the transcriptome in a susceptible M25 strain. The most downregulated genes belong to the fatty acid synthesis (FASII) pathway. In presence of human serum, GAS is known to both downregulate this pathway and use fatty acids (FAs) bound to albumin (HSA). Moreover, GAS is able to shield from the human host immune system through the binding of serum proteins. At physiological concentration, we showed that the serum also protects GAS from phage A25 infection. In contrast, addition of HSA+FAs fasten the collapse of the bacterial population compared to HAS alone. We next quantified the FAs content of GAS and found a lack of C18:2 FAs, which can be provided by HSA+FAs and decrease by 21% during phage infection. Moreover, adding linoleic acid (C18:2) to HSA-FA restored the faster collapse of the bacterial population. The phage A25 originated from a temperate phage by loss of integrase and repressor genes. Therefore, the ancestor may have evolved to use F.As to compensate for the negative effect of serum on its infectivity. To determine if this applies to other prophages, we used the functional prophage  $\phi$ M1 integrated in a M1 strain. Interestingly, we found that the serum rather increases the lytic growth of  $\phi$ M1 during infection of a highly virulent M1T1 clone, ultimately leading to an increase in the proportion of potentially even more virulent lysogens. Altogether, these results highlight the need to study phage-pathogen interactions in a more physiological context. While the virulent phage A25 seems not a good candidate to treat GAS infection, turning virulent the phage  $\phi$ M1 could be a promising strategy.

**Mots-Clés:** *Streptococcus pyogenes*, Temperate & lytic phages, Transcriptomic, Human serum, Fatty acids

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