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PHAGE-RESISTANT BACTERIA: CURSE OR BLESSING?

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Bibliographic review

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INTRODUCTION

New therapies such as bacteriophage therapy are needed to fight life-threatening infections as antibiotic therapy is progressively more limited due to resistance emergence. Phages and bacteria have co-evolved for ages so even though we know bacteria naturally develop resistance against phage infection, so do phages through counteradaptation mechanisms. Therefore, phage-resistance does not always imply a dead-end, as a growing body of literature shows that developing these resistance mechanisms to successfully avoid infection usually comes at a cost to bacterial fitness, which could be exploited in our favor.

OBJECTIVES

To determine:
-what specific phage-resistance mechanisms bacteria may develop against phages as antimicrobial agents
-Whether they really imply a fitness cost
-Which ones entail a higher fitness cost
-How science can take advantage of these trade-offs

METHODOLOGY

Extensive search of scientific literature related to the chosen topic was conducted in reliable and well-established documentation sources such as the Pubmed and Google Scholar databases.
Word search: "phage therapy", "phage resistance", "antibiotic AND phage resistance", "bacterial fitness trade-offs", "phage-resistance cost".
All of the selected information was thoroughly read and deeply analyzed once the objectives were established in order to draft the main body of work and draw pertinent conclusions.

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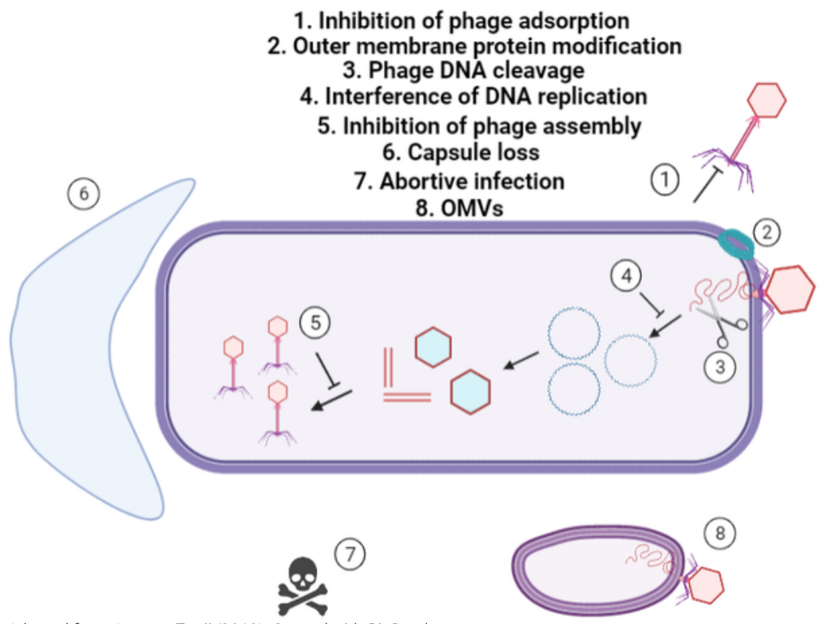
DISCUSSION

Bacteria can develop a wide range of defense mechanisms targeting almost all steps of a phage life cycle, as seen in Fig. 1. The most damaging mechanisms fitness-wise have been shown to be inhibition of adsorption through cell wall modifications, capsule loss -both of which are constitutive defenses-, or activation of inducible defenses like CRISPR-Cas. Other mechanisms might be costly as well but the addition of new pathways may be less likely to generate trade-offs than de novo mutations of existing genes related to phage receptors. Phages counteradapt but, in any case, the "arms-race" becomes progressively weaker due to widely generalist adaptations on both sides.

Fig. 1. Main bacterial resistance mechanisms against phages



Adapted from Azam et Tanji (2019). Created with BioRender.com

Table 1. Reviewed experimental studies on the relationship between phage resistance/ impact on bacterial fitness

Bacterium	Phage	Experimental model	Resistance emergence	Impact on fitness and virulence	Receptor	Ref.
Acinetobacter baumanii	ΦFG02 and ΦCO01	In vivo	Yes	Capsule loss, resensitation to human complement, beta-lactam antibiotics and alternative phages	Capsule polysaccharides	(1)
Escherichia coli	vB_EcoM-P10	In vitro	Yes	~65% decrease in overall growth	OmpA	(2)
Escherichia coli	T4	In vivo	Yes, after 92 days	ND	ND	(3)
Enterococcus faecalis	ϕ VPE25 and ϕ VFW	In vivo	Yes, phage resistant variant replaced WT	ND	Membrane protein PIP_{EF}	(4)
Klebsiella pneumoniae	P1 and P2	In vitro	Yes	ND	P1: capsule P2: LPS/ompC	(5)
Klebsiella pneumoniae	ϕNK5	In vivo	Yes	Reduced virulence, increased susceptibility to immune clearance	ND	(6)
Listeria monocytogenes	LP-048, LP-125	In vitro	Yes	ND	ND	(7)
Listeria monocytogenes	A511 and A500ΔLCR	In vitro	Yes	Attenuated virulence	Surface-associated Internalin B (InlB) in wall teichoic acids	(8)
Pseudomonas aeruginosa	PP1131 cocktail	In vitro/In vivo	In vitro: yes In vivo: no Phage monotherapy: yes In combination with antibiotics: no	Reduced virulence, diminished bacterial densities	LPS and pili	(9)
Pseudomonas aeruginosa	OMKO1	In vitro	Yes	Antibiotic resensitation	OprM and MexAB and MexXY	(10)
Salmonella enterica Paratyphi B	ϕ1	In vivo	Yes	Avirulence and short lifespan	O-Antigen (LPS)	(11)
Salmonella rissen	ϕ1	In vitro	Yes	Resistant strains elicit a weaker immune response	O-Antigen (LPS	(12)
Vibrio cholerae	ICP1, ICP2, and ICP3	In vivo	Yes, to each individually; not to the cocktail	ND	O-Antigen (LPS)	(13)

Graph 1. Resistance emergence and fitness cost proportion regarding Table 1

As portrayed in Graph 1, the majority of the experimental studies reviewed show that in most cases resistance is achieved at the cost of impairing fitness.
Fitnes trade-offs observed throughout this review, also displayed in Table 1, turn out to be advantageous for multiple purposes, but they are especially relevant regarding antibiotic resensitation (thus reenabling antibiotic therapy) and vaccine production, as avirulent bacteria provide protection against the virulent parent strains but lack infective capacity. Knowing specific bacteria-phage interactions also helps design better and more effective phage cocktails.

CONCLUSIONS

It is difficult to predict how relevant phage-resistance will be in vivo, as many factors are expected to play a role. What is sure is the fact that we need to anticipate the emergence of resistance as it will likely happen. Still, it could also provide us with unexpected advantages.
Future studies should focus on characterizing phage combinations that minimize resistance and rule out those that favor it. Some resistance mechanisms are stil understudied so future research should focus on what they could bring to the table. This also opens a way for phage genetic engineering to delay resistance. Further research focusing on exploiting fitness reduction to design new therapies is also adviced.
There is ground to think that phages hold more potential that is yet to be discovered.