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Phage Cocktail Therapy: A Promising Approach to Combat Bacterial Plant Pathogens

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SUMMARY

The phage cocktail therapy is a multidimensional approach effectively employed for the biocontrol of diverse resistant bacterial infections without affecting the fauna and flora. Phages engage a diverse set of counter defense strategies to undermine wide-ranging anti-phage defense mechanisms of bacterial pathogens.

INTRODUCTION

Bacteriophages or phages are viruses with an ability to infect and in many cases, kill bacterial cells. As with most viruses, these infections begin with virion binding to specific cell-surface receptors, which is then followed by intracellular replication. Phage therapy have been proposed as an alternative to pesticides to kill bacterial pathogens of crops. Frederick Twort and Felix d'Herelle independently discovered bacteriophages in 1915 and 1917, respectively, after 20 years of virus discovery. The antimicrobial characteristics of phages were immediately recognized by Felix d'Herelle in 1919, demonstrating the phage preparation aptitude to treat dysentery patients in the Paris Hospital [Letarov, 2020]. Phages are tadpole-shaped consisting a polyhedral head, a short neck with collar and a straight tail are the hallmarks of their morphology (Fig. 1). The benign nature of phages to eukaryotic cells, host specificity, self-replication, capability to overcome resistance and ease of biosynthesis are all factors that have sparked interest in them as biocontrol agents. Their omnipresence and abundance in the biosphere enable their isolation from their surroundings [Vu and Oh, 2020].

Fig. 1: Bacteriophage Structure

How they are distinct from antibiotics?

The phages are very specific to their host bacteria. Some phages are so specific that they only infect one or few bacterial strains under one species. This feature is beneficial for maintaining the microbial ecosystem but requires the use of phage mixtures (cocktails) as biocontrol agents due to the genetic diversity of phytopathogens.

What are the different ways of using phage cocktails?

First, phages are used to target different pathogens (either different species causing a similar disease or different strains under one species). Phages often exhibit host specificity and limits the application of a single phage when targeting different phytopathogens in the field. As a result, multiple phages of different hosts can be formulated into a cocktail that expands the host range. It is therefore important that prior to the preparation of a phage cocktail, the required phage host range should be determined (Chan *et al*., 2013). Second, phage cocktails are used to prevent the development of phage-resistant bacteria. The constant arms race between phages and bacteria has led to the evolution of multiple phage-resistance mechanisms in bacteria such as inhibition of phage adsorption and DNA entry, abortive infection, CRISPR/Cas immune system and restriction-modification systems. By using more than one type of phage, the targeted bacteria would not develop resistance to all the phages at once (Van Houte *et al*., 2016).

Different mechanisms involved in suppressing pathogenicity:

Wang *et al*. (2019) revealed at least three ways that phage cocktails function to suppress the pathogenicity of the plant bacterial pathogens (Fig. 1). First, each type of phage infects and kills a group of bacterial pathogens. Collectively, these phages result in a significant reduction of the pathogen population directly. Second, due to the selection of phage-resistant but slow-growing pathogen strains, the competitiveness fitness of the pathogen is diminished, which will result in further reduction of pathogen population. Third, in the presence of phage cock-tails, microbiome diversity will be higher due to a lack of dominancy of the pathogens in the soil.

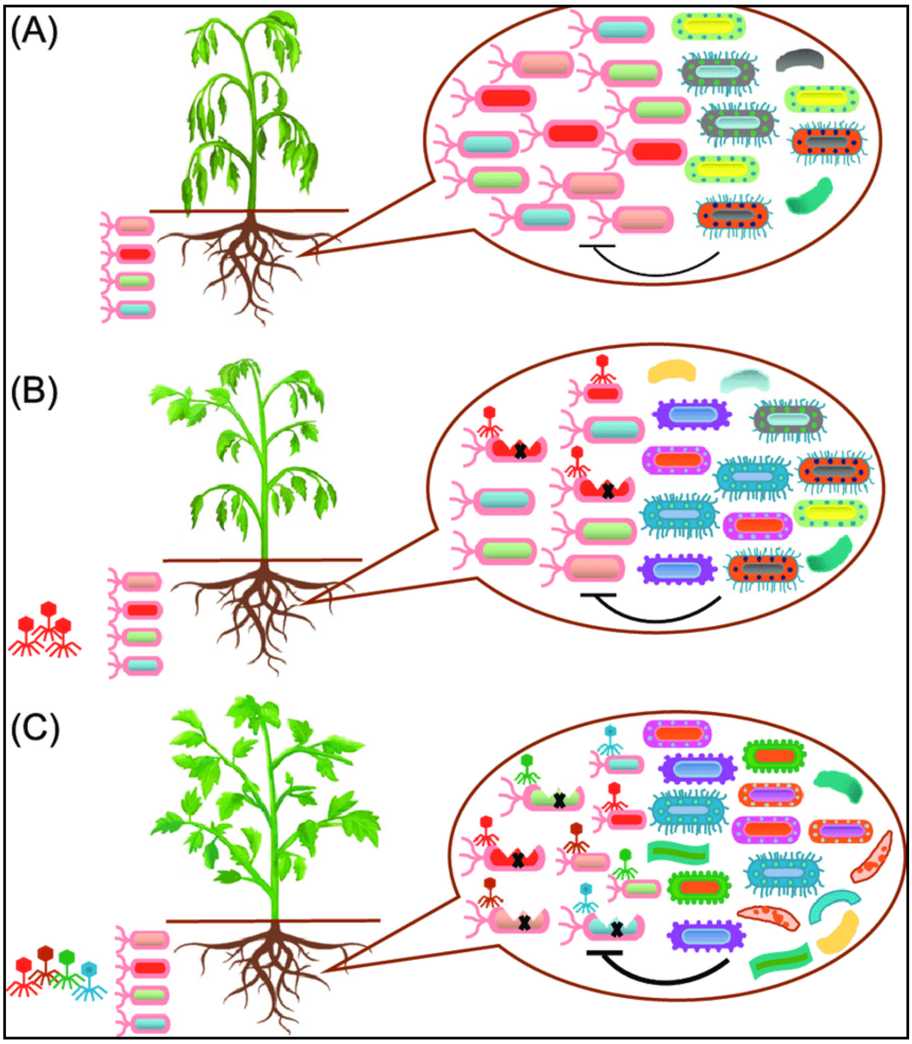

Fig. 2: A Schematic Model of the Control of Bacterial Wilt Disease by Phage Cocktails

Consequently, there is an enrichment of bacterial species that are antagonistic to the bacterial pathogen, which will cause the pathogen density to decrease further. Together, these three mechanisms contribute to a dramatic reduction in the pathogen population both directly and indirectly. Therefore, the pathogen population cannot reach the threshold necessary to turn on quorum sensing-dependent virulence mechanisms to cause severe disease.

CONCLUSION

Phage cocktail therapy has heralded a revolutionary track in the management of various plant bacterial diseases, resulting in increased agricultural productions to sustain the food supply chain. Biotechnological platforms have provided new insights into the development of multifaceted phage cocktails, capable of targeting resistant plant pathogenic bacteria with extremely high efficiency. Although agrochemicals, including antibiotics and copper-based microbial compounds, are still applied in the field to combat bacterial plant diseases, phage cocktail application has the potential to reduce the number of agrochemicals employed or to replace these agrochemicals for the management of bacterial plant diseases.

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