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Use of viral phage-therapy in periodontal disease: animminent future chance coming from the past

Abstract

Viral phage bacterial activity was first described by Hankin in 1896, but Felix D'Herelle (1917) supposed and conceived potential use of phages for therapeutic purposes. He also idealized the term "bacteriophage": bacteria + phage which derive from the Greek (eating or munching). In 1923 D'herelle and George Eliava founded the Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia, which is still active and researched the possibilities of phages in systemic diseases. The first case was described in 1937: Richard Bruyoghe and Joesph Maisin directly injected doses of selected phages in a patient following a cutaneous staphylococcal infection. In Eliava's research Institute the use of phages and their use in various epidemical diseases in the former Soviet Union has continued in various hospitals. It was done in Russian and poorly disclosed and studied in Western Europe. Only recently some of the works translated by the Polish have been published in English. On the contrary, the interest of Western Researchers has been limited to a small number of passionate analyst and academics, also due to the evolution of antibiotic use since the 40s. In recent years and in particular after the 2016 Paris Congress there is a strong interest in the potential of bacteriophages and their use. The role of viruses in human microbioma alterations obtained a progressive increased attention. Most of the viruses identified in these communities were bacteriophages that invade the cellular microbiota rather than the human host. Phages have the ability to eliminate host or giving them peculiar advantages performing a lisogenic-conversion. Conditions such as periodontitis are associated with an altered bacterial biota, it has been hypothesized that alterations of bacterial communities have a fundamental role in promoting periodontal disease. Even the communities of peoples differ between the periodontal biotypes and the diseases, but the genetic expression of the communities of the peoples has only recently been examined. The current research is to understand the microbial systems and the relationship that they share with hosts and the environment. Bacterial viruses, intracellular oligo-parasites are structurally simple with short life cycles of 20 to 60 minutes. Bacteriophages are natural antibacterial, able to regulate the tablets through the induction of bacterial lysis. They are active against most bacteria, including antibiotic resistant bacteria. Molecular biology research has renewed the original application of the phage as a therapy for the treatment of human and animal infections. This rematch of therapy has been triggered by the emergence of many antibiotic-resistant pathogens. This phenomenon could be a strike to the effective treatment of infectious diseases. To understand the mechanisms of resistance it is important to remember.1

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That antibiotics are classified according to their mechanism of action as follows

Agents that inhibit the synthesis of cell membrane (eg penicillin and cephalosporin); Agents that interfere with the cell membrane of the microorganism, influencing the permeability (for example some antimycotic agents); Agents that inhibit protein synthesis by influencing 30S or 50S sub-ribosomal units functions (e.g. tetracyclines, macrolides and clindamycin) Agents that block important metabolic phases of microorganisms (for example in sulfonamides). Agents that interfere with nucleic acid synthesis (eg. metronidazole and quinolones). Antimicrobial resistance can be classified into 3 groups: intrinsic, mutational and acquired resistance. Intrinsic resistance developed to a specific antibiotic is a peculiar natural feature of the microorganism. For example, some oral bacteria, such many streptococci, lack in nitroreductase needed for converting and processing metronidazole inactive metabolites in their active form and therefore are not affected by the drug. Mutational resistance occurs due to a spontaneous chromosomal mutation that produces a g en tically modiified bacterial popuplation that is resist ant to the drug. Finally, the acquired resistance is an acquisition from another microorganism of a genetic element that codes for antibiotic resistance. This process can take place by transduction, transformation or conjugation. Phages can play a key role in bacteria in oral dysbiosis even in the presence of resistant species. This previously ignored idea is becoming one of the most reliable hypotheses on the complex structures of oral biofilm. Bacteriophage therapy can be developed for most infections because bacteriophages are present in almost all species of bacteria. The oral cavity is one of the most densely populated habitats of microorganisms and includes about 6 billion bacteria.[2–4] These bacteria together with saliva are the main components of oral microbioma, they can be harmful, but they also play beneficial and necessary role in the immune system. These bacteria have evolved to survive on the surface of the tooth, on the gingival epithelium and in the oral cavity. Bacteria aggregate into complex communities called biofilms. Within the oral biofilm the

bacteria are able to be safer almost 1000 times compared to planktonic forms. They develop antibiotics protective shield-like mechanism, creating a sort of barrier that is unlikely to be altered by the standard use of antibiotics. Oral human phages are co-evolving with bacteria, limiting the possibility for other phages to enter the community. The oral mucosa offers a large surface area for gene transfers and phage adhesion. Sifoviruses have been found mainly in saliva, subgingival and supragingival plaques suggesting the lysogenic conversion of bacteria. Phage nucleic acids have been richly founded in the mucosa and also in the blood of some immunocompromised patients. The interest in the use of phages in periodontal therapy is given since they are able to bind bacterial receptors and modify them, leading to the inability of the oral bacteria to form the biofilm that protects them from the external environment and from antibiotics.[5]

Phages perform bacterial alterations with at least four known mechanisms

a. Bacteriophages replicate in their host cells, resulting in the release of infectious progeny in the biofilm and destruction of the infected bacteria.

b. Bacteriophages carry or express depolymerizing enzymes that destroy the extracellular polymeric substance of bacteria.

c. Bacteriophages can induce depolymerizing enzymes within the host genome that destroy EPS. (Extracellular polymeric substances)

d. Bacteria communities form sleep-resistant, antibiotic-resistant cells called Persisting cells. These cells are not mutants, but phenotypic variables of the wild type.

The bacteriophage can infect these cells. Current research aims to understand how to use them, indeed phages cannot spread through the membranes; therefore how the phage directly reaches the target bacteria is still to be defined. Some researchers have even proposed to use non-pathogenic species of bacteria to bring the phage to its destination. Recently, proposals have been put forward that phages can be included in nebulizers and sprays as respirable powders to treat various lung infections. Phages are more numerous than bacteria and grow together with their target and, together with these; they die making the host safe after killing the pathogen. Phages are available in almost every possible shape, simplifying their administration. Phages are more specific to the host than antibiotics, making them less toxic, therefore with little or no chance of collateral damage. Even the intestinal flora, after their administration, remains unchanged, reducing the possibility of secondary opportunistic infections by organisms such as Clostridium difficile, Candida albicans, etc. Phages can be the key to solving antibiotic resistance problems and helping people fight diseases faster. The isolation and identification of new bacteriophages able to eliminate oral bacteria, could lead to a decreased dental plaque formation. This procedure could be considered an innovative approach, free from side effects for the patient and could possibly conceive in dental medicine. Viral Phage Therapy strongly aims at oral symbiosis as a source of oral and systemic health. Phages represent a future for modern medical and pharmaceutical biotechnology that comes from the past.[6,7]

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Conflict of interest

None.

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