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Phages as Promising Biomedical Tools

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Abstract

Bateriophages, natural killers of bacteria, are nowadays interesting tools in biomedical fields. Indeed, phages can be used in prevention, diagnosis, and as treatment against bacterial diseases. Interestingly, new phage technology allow them to be used against other pathogens like fungi and other viruses. Going beyond, bacteriophages can be even modified to specifically treat tumour cells. The large potential of phages as biomedical tools is increasing, thanks to their easy manipulation, high specificify, and low production cost. Nevertheless, ethical concerns and regulatory protocols should be revised in order to give trust to these applications and increase the general acceptance.

Introduction

Bacteriophages, also known as phages, are natural predators of bacteria. Phages were discovered one century ago by Frederick Twort [1] and Félix d'Hérelle [2] independently. After their discovery, phages were commonly used as therapeutic tools and successfully used to treat bacterial diseases, as dysenthery and cholera. Unfortunately, antibiotics were rapidly spread as main treatment and phage therapy was restricted to Eastern countries, were antibiotics were not allowed [3]. Phages present an enormous diversity compared with other organisms. Their particles contain nucleic acid (RNA or DNA), single o double stranded, circular or linear, segmented or unsegmented, and large number of morphologies have been observed. In addition, phages can be divided following their biological cycle, mainly as lytic or temperate phages (alternatives of cycles have been also reported) [4]. Phages have been extensively used to understand fundamental biological processes such as replication, transcription, and translation. Noteworthy, a large amount of phage products are commonly used as reagents in research, like ligases and polymerases. Phage technology is also increasing rapidly. The recently awarded with the Nobel prize George P. Smith, developed a method using phages as vectors for gene cloning or expression, known as phage display [5]. This technique is of special interest since allows to link genotype to phenotype physically in a single particle. This technology has many applications including drug discovery, antibody engineering, or antiviral research. For all these reasons, phages are recently increasing their interest due to their potential applications in medical fields. In addition, lack of immunogenicity of phages makes them safe for clinical uses, although phage antigens can be potentially able to trigger humoral and cell-mediated immune responses [6]. However, this can be a double edged sword, since highly immunogenic phages could be potentially used as vaccine candidates [7]. Here, I am going to summarize some interesting applications of phages in clinics, including prevention, diagnosis, and treatment (Figure 1).

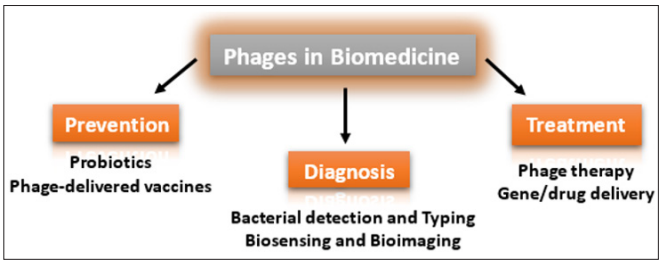

Figure 1: Phages as biomedical tools.

Phages in Prevention

In mammals, phages are commonly distributed in the body. Skin, mucous surfaces and digestive tract are examples of compartments were bacteria, viruses and other microorganisms are living forming the microbiome [8]. In addition, it is known that phages are also co-habitating with bacteria forming the phageome [9]. This suggest that phages and bacteria are co-evolving in the same environments, creating a microbiome equilibrium [10]. On this topic, phages can be used as "probiotics" in order to control bacterial communities

and prevent diseases associated to bacterial growth. Recent studies of microbiome are based in the interactions among its elements, and bacteria-phage system is the basis [11]. Phages are highly specific of bacterial strains, and this feature will be an important point to control specific bacterial strains, remaining unaltered the non-targeted strains. Phages can be then used to modulate microbiota population, as safety tools due to their natural environment forming the microbiome [12].

Another use of phages in prevention of diseases are phage-derived vaccines. In addition, specific phage products can be used as delivered vaccines. Phage engineering can be also used to produce specific vaccines against other pathogens like fungi or even viruses. Phage display allows to produce large amount of product in filamentous phages, which will help in the development of vaccines or drugs [13]. Phage display can be used to generate large libraries to generate recombinant antibodies. This library can be naive antibody libraries, immunized antibody libraries, synthetic antibody libraries, and in vivo recombined antibody libraries [14]. In this case, antibodies obtained can be used in prevention as prophylactic agents, but they can also have interest as diagnostic or therapeutic tools [15,16].

Phages can be also used as active anti-biofilm weapons in medical devices or prothesis. This has an special interest to prevent human diseases caused by nosocomial bacteria that are growing in hospitals. Bacteria are able to produce biofilms in inert surfaces, which are difficult to remove with common reagents. Phages can destroy actively these biofilms, since they can penetrate and kill the entire biofilm. For this reason, phages can be used to pre-treat medical devices prior to its use in clinics. Phage-derived enzymes like lysins or holins can be also a great tool to improve bacterial lysis and can be used in prevention to treat medical devices [17].

Phages in Diagnosis

Phages can be also interesting in bacterial detection and typing. Diagnosis of specific bacteria can be fastly done infecting them with phages. As previously commented, phages are highly specific of strains, so we can use phages to ultimate determine the strain. Sometimes, bacterial typing remains laborious and difficult, but phages are a fast solution. If it is possible to have a library of specific phages, bacterial detection or typing can be done easier. In this aim, bioimaging and biosensing are also potential uses of phages [18]. It is possible to link specific markers into phage genomes to detect by imaging where phages are spreading, and this can help in diagnosis [19]. In addition, phages are highly sensitive, and can detect bacteria in very low amounts. Thanks to viral replication, we can also determine bacterial concentration.

Phages as Treatment

Indiscriminate use of antibiotics has lead to the emergence of multi-drug-resistant bacteria. Nowadays, some bacterial strains are not able to be treated with any of the available antibiotics. This problem claim for alternative treatment to treat these superbugs, and phages are a real alternative. As previously mentioned, phages were used as therapeutic agents since their discovery. Many bacterial infections were treated with phages, mainly in Eastern countries, where are still under use. In contrast, Western countries are not allowed to use phages in clinics, although recent clinical trials are under essay in Europe [3]. Interestingly, for some superbugs without antibiotic treatment, distress calls in social and scientific networks have been used to find phages as a ultimate solution. Fortunately, some patients have been treated with phage cocktails and have been complete recovered. In contrast to the broad spectrum of antibiotics, phages are highly specific. This is of special interest in order to reduce side effects, because microbiome will remain in equilibrium, and only the targeted bacteria will be destroyed. In case of phage therapy, lytic phages are used to rapidly remove bacteria, avoiding latency.

In addition, phage display can be used to help in gene or drug delivery. Although phages are highly specific, it is possible to engineer phages to display sequences enabling their targeting of mammalian cells [20]. We can modify phages linking specific ligands to targeted cells, with the aim of produce binding capacity to specific receptors through receptor-mediated endocytosis. In this case, phages can be used as vehicles to deliver genes or drugs to the desired cells. This potential use of phages has special interest in oncology. Tumor-specific promoters can be targeted to enable specific transgene expression in tumorous cells. In addition, transductional targeting can be an alternative [21, 22].

Discussion

Phages are great and interesting tools from many points of view. Their limited cost of production favors their potential use in non-developing countries, allowing to arrive to many patients and diminishing the emergence of bacterial resistant (even to erradicate multi-drug-resistant strains). Although the potential of phages is huge, one main problem is the general acceptance of phages in clinics. Phages are viruses, and their use can be blocked by the acceptance by the general public and ethical concerns. For these reasons, regulatory protocols are needed to provide security to the population. Clinical trials and testing are necessary to demonstrate the safety of phages in human beings. In this regards, it is important remark that phages are not able to infect eukaryotic cells, making phages as biologically safe in mammalian organisms. In addition, the enormous diversity of phages is of special interest because is a great source of potential therapeutic tools and can open to novel applications. New technology linked to phages will help in the future to create better tools in clinics.

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