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Preface

Biomaterials based on phages and other viruses



Phage is a unique type of virus nanoparticle in that it specifically infects bacteria. The recent years have witnessed enormous progress in the construction of biomaterials based on phages and other viruses. As biological entities, phages, like other viruses, display superior advantages over traditional chemical materials in producing an improved therapeutic outcome. Furthermore, by exploiting their potential power through genetic engineering or other technologies, phage-based biomaterials have enabled a paradigm shift in various medical areas such as antibacterial therapy, cancer therapy, drug delivery and novel vaccinations. The focus of this themed issue is on the use of phages for theranostic applications. Thus, this issue contains five reviews on phages and only three reviews on other viruses so as to highlight the fact that phages and other viruses collectively can advance virus-based theranostics. Considering the tremendous increase in therapeutic effects through the use of virus-based materials, this themed issue gives an overview of their advantages and disadvantages, and discusses the recent applications in advancing biomedicine in the context of disease prevention, diagnosis, and treatment (Fig. 1).

Bacteriophages, or more colloquially phages, are the natural predators of bacteria. Their infection and propagation are restricted in prokaryotic hosts, rendering human and other eukaryotic hosts safe from phage infection. During a long-standing evolutionary period, these viral entities have developed a constant relationship with mammalian hosts. In addition to the mammalian microbiome, phages were detected in many purely sterile compartments within the body, indicating that they possess an innate capability to traverse physiological barriers. As an increasing number of investigations have been conducted to explore phages as delivery vehicles in biological and medicinal applications, it is necessary to have a full understanding of the dynamic interactions between phages and mammalian tissues. In a comprehensive review by Slavcev et al., the accumulation of phages in various mammalian tissues has been summarized and the outstanding capacities of phages to go through relatively impermeable barriers in mammalian cells and tissues have been discussed [1]. In the circulatory system, phages with various morphologies and sizes could translocate across the endothelial and epithelial barriers to reach the sites of interest with sufficient phage titers for therapeutic activity. While phages are nearly omnipresent in mammalian species, extra administration of these viral particles could rapidly trigger the immune system and induce the clearance of phages. Additionally, pharmacokinetic studies of phages in gastrointestinal system, brain, respiratory system and skin have been elucidated in detail. Such studies support the future therapeutic applications of phage following various routes of administration. This review marks progress in filling the knowledge gap necessary for the future development of phage-based biomaterials.

Bacteriophages are excellent antibacterial agents, as they are highly specific against bacteria. The emergence and development of antibiotic-resistant bacterial species, called superbugs, have prompted a rise in the research of phage therapy. Due to their distinct characteristics, phages can efficaciously cure pathogenic bacterial infection with minimal disruption of normal flora bacteria. A review by Abedon et al. has given a new perspective on the subject of phage therapy [2]. It focuses on the applications of phage therapy in treating chronic or persistent infections that are difficult to be treated by traditional antibiotics. It elucidates the judging criteria of persistent or chronic infections, highlights the significance of biofilms in bacterial infections, and summarizes the successful applications of phages to cure chronic or persistent bacterial infections both in animals and in humans. This review also covers ways to deal with *Acinetobacter baumannii* infection and analyzes important factors, such as initial and late-stage phage dosing, patient conditions, phage resistance of two *A.baumannii* isolates, and phage therapy efficacy. Finally, it describes the correlations between persistence of bacterial infections, immune-deficiencies, and phage therapy efficacy. According to their unique advantages, phages offer new avenues for treating chronic or persistent infections and will bring brilliant scientific advance to the future of medicine.

New dimensions to the biomedical applications of viral agents have been inspired by ongoing breakthroughs in phage research, such as the introduction of phage display and the construction of phage library. Through biological or chemical strategies, antigenic epitopes can be displayed on the surface of phages. Yang et al. reviewed the status quo of engineered phages as vaccines [3]. These engineered phages can serve as novel vaccines to trigger both humoral and cellular immune responses against pathogenic infections. Compared with conventional vaccines, the phage-based vaccines display superior advantages in producing an improved immunogenic outcome. They are stable under harsh environment, present a high level of exposure of antigenic epitopes, can be produced in large scale by infecting bacteria, and bear a potent adjuvant capability. Due to these advantages, different types of phage-based vaccines have been designed to prevent diseases including viral, bacterial, fungal, and parasites infections as well as cancer. In this review, the recent progress in the development of phage-based vaccines as well as the related in-depth vaccination mechanisms have been summarized. Understanding the vaccination mechanisms of phages will promote and accelerate the future clinical applications of phage-based vaccines.

Among different types of phages, bacteriophage T4 provides an optimal platform for the design of phage-based vaccines. Due to their unique structural characteristics, phage T4 displays superior advantages over filamentous phages in producing an improved immune outcome. A

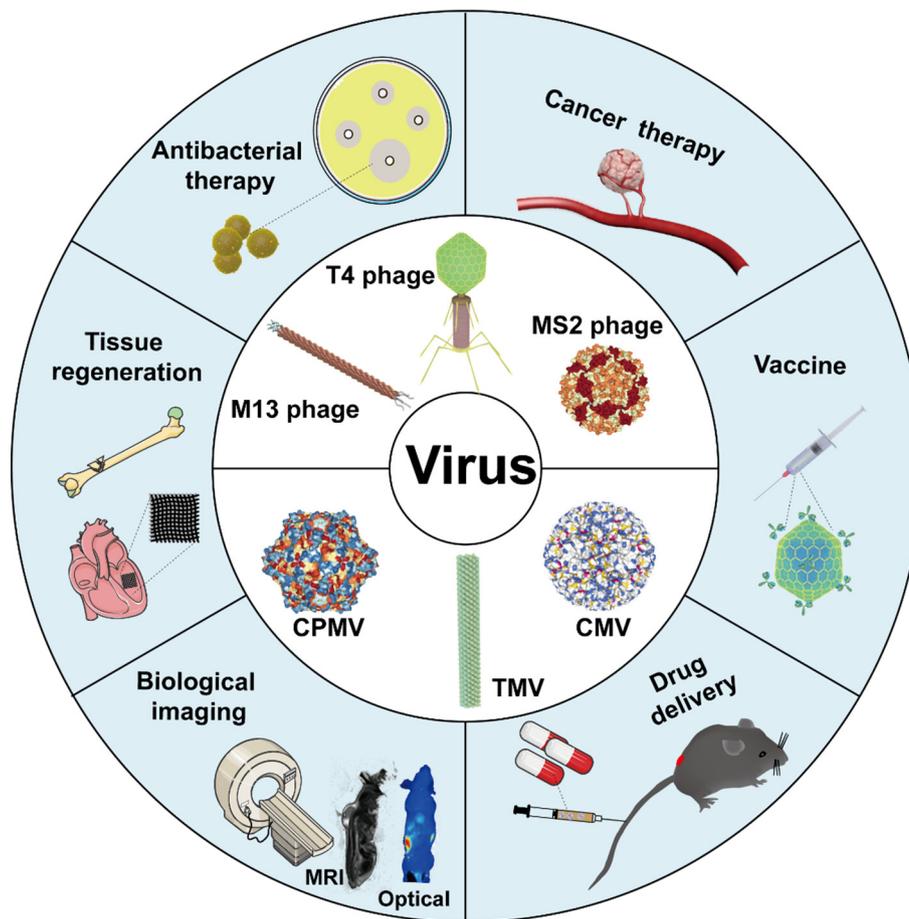


Fig. 1. The use of phages (such as M13 phage, T4 phage and MS2 phage) and other viruses (such as CPMV, TMV and CMV) as a biomaterial for disease prevention, diagnosis and treatment. The applications highlighted in this figure are covered in this themed issue, including vaccine, drug delivery, cancer therapy, antibacterial therapy, tissue regeneration, and bioimaging. CMV, cucumber mosaic virus; CPMV, cowpea mosaic virus; TMV, tobacco mosaic virus.

review by Rao et al. has provided comprehensive insight into phage T4-based vaccines, including immune activity and characteristics [4]. The capsid of phage T4 is an elongated icosahedron. Antigens can be fused on the surface of the capsid with a high exposure level. Comparing with filamentous phages, phage T4 systems can display proteins or peptides with large molecular weights. Furthermore, the phage nanoparticles allow the construction of multivalent vaccines for the integration of several antigens belonging to one or different pathogens within a single capsid platform. This comprehensive review also covers the characteristics of other bacteriophages used in vaccine applications. As phage-based materials are ideal candidates for novel vaccine and vaccine delivery, it is timely to drive this viral agent from the laboratory to practical applications.

Filamentous phages show great promise in tissue regeneration due to their unusual nanofiber-like structure and biological characteristics. In a review by Mao et al., the prominent advantages of filamentous phage-based materials in tissue regeneration applications have been discussed [5]. The rapid development of phage biopanning and display technologies have allowed for the possibility of identifying target-binding functional peptides or proteins and assembling bioactive molecules capable of promoting regeneration onto the surface of phages. Filamentous phages can be processed into ordered scaffolds through self-assembly, so as to bring about optimal materials for tissue regeneration. The ease of displaying peptides or proteins on the filamentous phages enables the scaffolds to bear the desired chemical cues in addition to the topographical cues from the phage assemblies, making it possible to use a single scaffold to direct stem cell differentiation and tissue regeneration through both chemical and topographical cues. Additionally,

the authors comprehensively summarized phage-derived peptide sequences that exhibit the capability of targeting and binding functional proteins to promote cell differentiation, guiding the future design of engineered phages for realizing various kinds of tissue restoration.

The next three review articles focus on the properties of plant viruses and construction of plant virus-based biomaterials. Similar with bacteriophages, plant viruses are also non-pathogenic to mammals and their multivalent protein surfaces are easy to be functionalized. Given the high yields, self-organized structure, biocompatibility and biodegradability, plant viruses are paving the way for new applications. Despite intensive research efforts and novel applications, a lot of nanomaterials and promising strategies have not been integrated with plant viruses so far. Wege and coworkers provide an overview of recent progress in the applications of biomaterials derived from plant viruses such as cucumber mosaic virus (CMV), cowpea mosaic virus (CPMV) and tobacco mosaic virus (TMV) [6]. Reliable and cost-efficient preparation routes have been established for plant virus-derived biomaterial processing. In this review, the applications of plant viruses discussed range from biomedical detection, replacement of cells and organs, therapeutics, to diagnostics. The potential risks and underestimated benefits of plant viruses are also discussed in detail.

Significant progress has been made in the preparation of plant virus-based vaccines after the development of genetic engineering techniques. TMV, in combination with epitopes display on the surface, is one of the first virus particle platforms in experimental vaccines. Zeltins et al. provide a critical review of strategies for using plant viruses and virus-like particles for generating vaccines [7]. This review focuses on the construction of vaccines and interprets the underlying mechanisms

in detail based on a large number of publicly available data. Representative studies of plant virus-based vaccine platforms and expression systems are included, which will promote the elaborate design of vaccines with high immunogenicity in the future. More importantly, this review provides an insight into the interplay between mammalian organisms and plant viruses, which is very important for plant virus-derived vaccine technologies from bench to bedside.

Cancer is one of the leading causes of death despite immense research efforts worldwide. Among numerous imaging platforms and drug delivery systems for cancer theranostics, viral nanoparticles including CPMVs are taking their place due to multifunctionality and structure stability. Lewis and coworkers summarize the advantageous features of CPMVs for their use in cancer imaging and therapy [8]. The native tropism to vimentin and abilities to be engineered with imaging moieties or drug cargos simultaneously make CPMVs an ideal system for cancer research. Lewis' review presents recent progress in utilizing CPMV nanoparticles as diagnostic, therapeutic and theranostic cancer tools. They also highlight some examples of shielding, imaging, targeting and therapeutic chemical groups conjugated to CPMV capsids, and describe the uses of engineered CPMV nanoparticles in intravital vascular imaging. The CPMVs are expected to open new prospects in the rational design of ideal platforms for cancer imaging and therapy in the future.

In summary, this themed issue includes biomaterials construction strategies and theranostic application examples, and showcases how viruses in general and phages in particular can be utilized in the biomedical field (Fig. 1). Preclinical or clinical trial of these materials are promising ways of improving their therapeutic outcome. It is our expectation that the topics discussed in this themed issue will push forward the research work of biomaterials based on phages and other viruses. Since all viruses are nanoparticles that can be chemically or genetically modified, phages and other viruses will continue to play an important role in advancing nanomedicine. Reproducibility in nanomedicine research is an emerging issue in the context of clinical applications [9]. Since phages, as well as other viruses, can be produced by biological methods with high reproducibility, the use of these biological nanoparticles in nanomedicine is an ideal approach to minimizing the irreproducibility in precision nanomedicine research [10].

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