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Bacteriophage Phi 6 as Surrogate and Human-Harmless Viruses to Study Anti-SARS-CoV-2 Approaches

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Abstract

Given safety challenges in conducting laboratory work with highly infectious human coronaviruses (pathogenicity, genetic mutations rate, biosafety level 3 and 4 requirements), many researchers have valued the potential of bacteriophages as appropriate viral surrogate to measure humans enveloped virus' survival, transfer and removal. The use of phage Φ6 seems to be useful as coronavirus surrogate to assess the effectiveness of anti-SARS-CoV-2 approaches, providing important insights concerning COVID-19 pandemic and human public health.

Keywords: SARS-CoV-2; COVID-19; bacteriophage Φ6

Review

The 2019 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has emerged as a new respiratory pathogen and is responsible for large-scale morbidities and mortalities around the globe [1]. It is caused by a single positive-stranded RNA virus from the coronavirus (CoV) family of Coronaviridae, composed of four genera out of which α- and β-CoV can infect mammals including humans. SARS-CoV-2 is identified as β-CoV and is responsible for coronavirus disease 2019 (COVID-19) [1,2]. These viruses are wrapped in host cells derived lipid membranes where viral surface proteins are embedded. One of these surface proteins known as spike [S] protein protrudes out of membranes and gives a characteristic crown/halo-like appearance to the virus when observed under electron microscope, hence named coronavirus [1]. Once the virus gains entry into the respiratory tract, SARS-CoV-2 causes damage to epithelial cells of the airways making lungs unable to clear dirt and mucus which can lead to pneumonia [1,2]. In extreme cases, patients experience a dramatic increase in the levels of pro-inflammatory chemokines and cytokines including IL-6 and TNF-α, a condition known as "cytokine storm". This leads to the development of Acute Respiratory Distress Syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and even death [1,2].

Given safety challenges in conducting laboratory work with highly infectious human coronaviruses (pathogenicity, genetic mutations rate, biosafety level 3/4 (BSL-3 and BSL-4)), many researchers have valued the potential of bacteriophages (phages) as an appropriate viral surrogate to measure humans enveloped virus' survival, transfer and removal [3,4]. Phages seem to be good alternatives once they are relatively easy to produce in large quantities, and several purification procedures are laboratory available [3,5–8]. Bacterial viruses of biosafety

level 1 (BSL-1), pose no risk to humans, being safe for laboratory workers, and their study does not require specialized biocontainment precautions. Moreover, their similarity with eukaryote viruses allow cross-study comparisons, making them interesting models for aerovirology research [6,7,9,10]. In 2020, several studies have shown the potential of phage Φ6, non-pathogenic viruses that infect specifically bacterium *Pseudomonas syringae*, as a surrogate virus to study infections caused by enveloped human viruses [6,7,9,10]. For instance, Turgeon et al. compared the effects of the aerosolization and sampling on the infectivity of 5 phages and 2 pathogenic viruses: MS2 (a single-stranded RNA [ssRNA] phage of the *Leviviridae* family), Φ6 (a segmented double-stranded RNA [dsRNA] phage of the *Cystoviridae* family), ΦX174 (a single-stranded DNA [ssDNA] phage of the *Microviridae* family), PM2 (a double-stranded DNA [dsDNA] phage of the *Corticoviridae* family), PR772 (a dsDNA phage of the Tectiviridae family), human influenza A virus H1N1 (an ssRNA virus of the *Orthomyxoviridae* family), and the poultry virus Newcastle disease virus (NDV; an ssRNA virus of the *Paramyxoviridae* family)[11]. These authors showed that the behaviour of the influenza virus resembled that of phages PR772 and Φ6, providing critical information for the selection of appropriate phages models to mimic the behaviour of specific human and animal viruses in aerosols [11].

Phage Φ6 is a segmented RNA virus involved by a phospholipid envelope (fatty) with spike proteins at its surface, with ~80–100 nm size, structural features similar to several human viruses, namely Influenza (belongs to Orthomyxoviridae family), SARS-CoV-1, SARS-CoV-2 and Middle East Respiratory Syndrome-associated coronavirus (MERS-CoV) (belong to *Coronaviridae* family) [3,5–9]. Thus, phage Φ6 has been used as surrogate virus model to understand the relationship between environmental conditions and virus infectivity in order to improve strategies for predicting and controlling disease transmission, namely COVID-19 [3,5–9]. For instance, Casanova et al. showed that recovery of phage Φ6 and Influenza virus from hands were comparable, with approx. 2–3 log10 loss after using protein and non-ionic detergent-based eluent solutions [3]. These authors concluded that viruses' inactivation was probably due those solutions with capability to destabilize the fatty envelope structure, a primary target for virus inactivation [3]. Dubuis et al. showed that ozone at low concentration combined with high relative humidity was able to kill airborne viruses, such as phage Φ6 and murine norovirus MNV-1[12]. Rockey et al. used phage Φ6 as surrogate model to evaluate the effectivity of heat and humidity treatments for N95 respirator de-contamination [9]. Buhr et al. proved that phage Φ6 could be a useful indicator model to evaluate the inactivation and survival of an enveloped RNA virus on contaminated aircraft materials after exposure to hot, humid air [13]. Fedorenko et al. showed that phage Φ6 presented a high survival rate in dry saliva deposited on glass surfaces, even when submitted to a wide range of relative humidity levels [6]. Phage Φ6 was considered a good model for virus respiratory pathogens, including SARS-CoV-2 [6].

Conclusion

Overall, the use of phage Φ6 may be useful as coronavirus surrogate to assess the effectiveness of anti-SARS-CoV-2 approaches, providing important insights concerning COVID-19 pandemic and human public health.

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