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ROLE OF BACTERIOPHAGE IN COVID 19

Microbiology

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ABSTRACT

The therapeutic role of bacteriophage in bacterial infection has promising results. Due to the emergence of multi drug resistant bacteria, the role of bacteriophage as an adjuvant with antimicrobial therapy or use as a single antibacterial agent against different infections also has been documented. The role of bacteriophage has surpassed its therapeutic range limited to bacterial infection and now it is seen as a potential antiviral and anti -fungal agent. In COVID 19 or SARS CoV 2 infection cytokine storm medicated by Nuclear Factor-kB(NF-kB) has lead to significant mortality worldwide. Bacteriophages are potential inhibitors of this transcription mediator directed over exaggerated immune response and could serve as an agent of therapeutic importance.

KEYWORDS

bacteriophage, covid-19, cytokine storm, NF kB

INTRODUCTION:

Bacteriophages are viruses which uses bacterial genome machinery to replicate and form progeny. In the lysogenic stage. bacteriophage gets incorporated with the bacterial genome but does not lyse the bacterial cell however, in lytic stage bacteriophage acquires full control of bacterial machinery and makes progeny while destroying the host cell[1,2]. The role of bacteriophage has been studied extensively from its invention back in 1910[3]. The dissemination of resistance to antibacterial agents has refocussed our interest in use of bacteriophages as a potential saviour therapeutic modality[4].

Apart from its capacity in combating bacterial infections, emerging evidence suggests role of bacteriophages in viral infections as well[5,6]. Generally speaking, many viral illness does not have specific treatment and same antiviral drugs have been used for different viral diseases[7,8].

Since the end of December 2019, the Chinese city of Wuhan has reported a novel pneumonia caused by coronavirus disease 2019 (COVID-19), which is spreading all over the world[9]. Patients with COVID-19 are at risk of developing fatal pneumonia and acute respiratory distress syndrome (ARDS) and unavailability of established treatment for this novel virus, compel us to refocus our understanding towards use of available resources. Though many of the patients of COVID 19 are asymptomatic[10], it has affected a significant proportion of world population and mortality is among one of the highest recorded in any disease affecting worldwide[11,12]. To combat this virus, many countries have used different strategies including use of Oseltamivir, Hydroxychloroquine or recently approved plasma therapy but still death rate remain high and efficacy of these agents remain controversial[13,14,15].

Bacteriophage role as anti-inflammatory and Immunomodulator

Immunomodulation is concerned with intervention which modify or regulate immune system. Bacteriophage control the microbial atmosphere in the intestine and provide local immunity via interacting with gut lymphoid tissue and also with other body tissue via translocation[16].The cytokine storm due to exaggerated immune response leading to septicaemia is mediated by IL-1β, IL-2, IL-4, IL-6, IL-8, TNF α, IFN γ. Among them, IL-6 and TNF α brings most potent pro inflammatory action, which are inhibited by bacteriophage [17].

The NF-kBis family of transcription factors, plays a central role in the induction of innate and adaptive immunity via classical and alternate way of activation. The classical pathway gets activated by degradation of IkBα through phosphorylation of IkB kinase complex, while alternate pathway is activated through p100 phosphorylation, a precursor of NF- kB2.[18,19] The activation of NF-kB serve as signalling pathway for pattern recognition receptors present on innate immunity cells to release various pro- inflammatory cytokines.[20] It also plays a significant role in the transcription of macrophages producing more inflammatory cytokines apart from indirectly promoting differentiation of T cells.[19,21] Its role is also seen in inflammasome regulation. Reports suggest that phage on preincubation with epithelial and endothelial cells significantly reduces NF-kBactivation[22,23] which is pivotal mechanism of cytokine storm in COVID 19, an essentially endotheliitis.[24] The IkB proteins inhibit the NF-kBactivation[19] and it is probably its dysregulation or polymorphism causing an exaggerated immune response leading to cytokine storm and subsequent acute respiratory distress syndrome and death.

The spike projections from the surface of Corona virus, glycoprotein S is considered to be attached with respiratory epithelium before starting its human journey[25]. The antibodies against surface glycoprotein is considered to be effective against Corona virus infection. In vivo induction studies with phage displayed peptides with specific antibody, was associated with significant protection against corona virus[26] indicating its possible role in COVID 19.

The mode of delivery of Bacteriophage is an important aspect of the therapy. Bacteriophage has been tried by inhalational route as well as intravenously in human to combat multidrug resistant bacteria [27-30]. T4 phase showed promising results in E-coli, one of the highly drug resistant bacteria listed by world health organisation(WHO)[31]. The same route of administration can also be used in the patients of Corona virus disease (COVID-19), as inhalational route would help to counteract the local inflammation and intravenous route would help in inhibition of the cytokine storm and its subsequent complications, as autopsy studies in COVID 19 patients revealed diffuse alveolar damage, pulmonary microthrombi in the background of marked local inflammatory changes[32].

Safety profile of any treatment has utmost importance. Studies have showed that bacteriophage has decent safety profile and can be used without any side effects. However, further human trials must be undertaken for considering it as therapeutic modality.

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