The Proteoliposome as a New Potential Therapeutic Approach for Coronaviruses

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Abstract: *In this paper we propose the use of pulmonary-proteoliposome as a new therapeutic approach for Coronaviruses. The designed strategy represents a potential treatment to reduce the overall viral load in lungs and to help the immune system to successfully stave off the infection.*

Keywords: Coronavirus. Liposome. SARS-COV-2

1. Introduction

The most recent virus to appear, belonging to the family of coronaviridae. The nCoV-2019 virus (today COVID-19) was identified in China last December 2019 and subsequently spread to Japan, South Korea and then all over the world. The virus caused 76,288 confirmed cases and 2345 deaths in China [1]. The SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) which causes the syndrome COVID-19 (Coronavirus Disease-2019). From the name itself, we can deduce that this virus, as shown also from the other elements of the same family, could induce severe problems leading to respiratory failure [2].

The main goal of all researchers is to develop new therapies in order to block the infection. 30 products have been identified (traditional and natural drugs) potentially useful in the treatment of COVID-19. The clinical data obtained with these drugs have demonstrated a preliminary positive effect [3].

Currently, the guidelines to be used for diagnosis, prevention and treatment of COVID-19-induced respiratory syndrome (issued by the NHC National Health Commission), include the use of antivirus agents like Interferon-gamma, lopinavir/ritonavir, chlorine china phosphate, ribavirin and arbidol [4].

2. Human Coronavirus Infection

The COVID-19 virus belongs to the Coronaviridae family, it is a positive-sense RNA virus with a 31Kb long genome, which makes it the largest RNA virus known [5,6].

In details, the Coronavirus have the ability to infect different animal species including humans. These viruses are pathogens capable to affect the respiratory tract determining mild or serious respiratory tract infection in both animals and humans [7,8]. The degree of pathogenicity allows to classifying coronaviruses into: Low pathogenicity hCoVs family (HCoV-229E, HCoVOC43HCoV-NL63 and HCoV-HKU) and High Pathogenicity CoVs family like SARSCoV (COVID-19) responsible fot the Severe Respiratory Syndrome and MERSCoV Syndrome Middle Eastern Respiratory [9,10]. The high rate of Coronaviruses pathogenicity, represent a major risk to public health. The epidemic induced by the SARS-CoV virus in 2002/2003 affected around 8400 people with a mortality rate of 9.6% [11,12,13]. In 2012, the MERS-CoV virus affected around 2,500 people with a mortality rate of 36% [14,15]. Therefore, coronaviruses can induce several clinical manifestations all affecting the respiratory system. In details, a large number of patients show mild or moderate symptoms for a short period; while fewer individuals have severe symptoms characterized by ALI and ARDS [16, 17-19].

Although coronaviruses have been studied for over 10 years, the processes that allow them to induce high mortality rates has not been clarified. The capability of coronaviruses to evade the control of the immune response, play a key role in the mechanism of action. Furthermore, recent research has shown that a deregulation of the immune response could induce hyper-activation of the inflammatory response with excessive production of cytokines (in particular Interleukin-6) and this mechanism would be the basis of respiratory distress syndrome [20,21].

3. Proposal

3.1 Proteoliposome Structure

The SARS-CoV-2 is a virus that invades the alveolar epithelial cells, resulting in acute respiratory distress syndrome that can lead to death of infected patients [2]. Unfortunately, there are not yet any antiviral drugs of undoubted effectiveness and developing a vaccine would likely require a very long time. The difficulty of developing specific antiviral therapies is due to the virus biology. A virus is a small parasite that cannot reproduce itself without hijacking the biochemical machinery of host cells to produce more viruses. Therefore, almost any drug developed to inactivate a molecular component necessary for the reproduction of the virus also risks damaging healthy cells of the infected organism. To overcome this problem, here we are proposing a different strategy aimed to reduce the spread of infections by offering a synthetic target tissue-like

competitor to the infectious virus. The competitor works as bait for the virus. Viruses, like coronaviruses, infect cells through specific proteins that stick out from their viral surfaces and hook to a specific receptor on the host cell membrane. Pulmonary receptor interacting with SARS-COV-2 is ACE2 protein, which is highly expressed in the lungs. SARS-CoV-2 infection is triggered by the binding of "spike" protein of the virus to ACE2, allowing the viral genetic material (RNA) entry into the human cells [22].

3.2 Use of Specific Proteoliposome in the control of COVID-19 proliferation

In our strategy, viruses will be distracted by using protocells as competitors, such as "pulmonary-proteoliposome". This is a complex formed by the fusion of membrane proteins of pulmonary cell origin (like ACE2) and liposomes [23]. Liposomes are in vitro self-assembled small size (from 30 nm to several micrometers) spherical vesicles created from cholesterol and natural non-toxic phospholipids, thus forming a cell membrane-like bilayer [24]. Liposome vesicles can entrap therapeutic molecules and are well known for their potential use as drug carriers which are released to the targeted tissue [25]. The use of liposomes has been shown to increase the therapeutic beneficial effect and to reduce the potential of systemic adverse effects of drugs [26,27]. Furthermore, many studies have also demonstrated the safety of liposomes for pulmonary administration of different molecules by inhalation [28].

In our strategy, we propose to create proteoliposomes from phospholipids and glycoproteins highly similar to human pulmonary cell membrane to be used as baits of coronaviruses particles. When the virus interacts with proteoliposome it should be stimulated to release its genomic content into the lumen of such prepared proteoliposomes that can be empty or carry a drug like RNase enzyme. The neo-proteoliposome should have limited endocytosis capability as it is expected because usually, under physiological conditions, liposome-cell membrane fusion efficiency is very low [29]. Furthermore, the choice of the type and density of electric charge on the surface of the proposed pulmonary-proteoliposome should take into account the effects of the cells–liposomes and virus-liposomes interactions. In that regard, anionic liposomes seem to be the best choice in respect to cationic ones, because in case of they are taken up into the cell by endocytosis, their content will follow the endosome-lysosome system for degradation, while cationic liposomes could transfer their contents directly into the cytosol [29, 30].

The pulmonary system seems to be a preferred target of the coronaviruses, most probably because of the lungs' large surface area. The idea we are proposing is to offer an even larger pulmonary-like surface area to the infectious viruses in order to facilitate virus-liposome interactions and hence virus titration, thus preserving the lung tissue from the infection. Thusly designed approach should in theory reduce the overall viral load of the pulmonary tissue while helping the immune system to successfully stave off the infection.

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