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Surfactant in SARS-CoV-2 – a therapeutic option based on underlying lung cell damage?

Surfactante em SARS-CoV-2 – uma opção terapêutica baseada no dano celular subjacente aos pneumócitos?

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Abstract

Introduction*: the severe acute respiratory syndrome – coronavirus 2 (SARS Cov-2), leads to a diffuse alveolar deterioration due infection of type II pneumocytes. The type II pneumocytes are involved in synthesis and secretion of pulmonary surfactant in pulmonary alveoli.* ***Objective****: the purpose of this study is to discuss the indication of surfactant replacement as a potential adjunctive treatment modality for SARS CoV-2, similarly treatment to neonatal respiratory distress syndrome.* ***Methodology****: we argue that SARS can be triggered by surfactant deficiency secondary to production deficiency determined by type 2 pneumocyte injuries. In this sense, we carried out a bibliographic review.* ***Conclusion****: thus, the replacement of human surfactant could be a potential treatment modality for SARS CoV-2, in the same way that it is indicated for the treatment of neonatal respiratory distress syndrome.*

Keyword*: Severe acute respiratory syndrome. Coronavirus 2. Type II pneumocytes. Pulmonary surfactant.*

Resumo

Introdução: a síndrome respiratória aguda grave – coronavírus 2 (SARS Cov-2), leva a uma deterioração alveolar difusa devido à infecção do pneumócitos tipo II. Os pneumócitos tipo II estão envolvidos na síntese e secreção de surfactante pulmonar nos alvéolos pulmonares. **Objetivo**: o objetivo deste estudo é discutir a indicação de reposição de surfactante como uma potencial modalidade de tratamento adjuvante para SARS CoV-2, similarmente ao tratamento da síndrome do desconforto respiratório neonatal. **Metodologia**: argumentamos que a SARS pode ser desencadeada pela deficiência de surfactante, secundária à deficiência da sua produção determinada por lesões de pneumócitos tipo 2. Nesse sentido, realizamos uma revisão bibliográfica. **Conclusão**: o uso de surfactante humana pode ser uma potencial modalidade de tratamento para a SARS CoV-2, da mesma forma que é indicada para o tratamento da síndrome do desconforto respiratório neonatal.

Palavras-chave: Síndrome respiratória aguda grave. Coronavírus 2. Pneumócitos tipo II. Surfactante pulmonar.

INTRODUCTION

The severe acute respiratory syndrome – coronavirus 2 (SARS Cov-2), leads to a diffuse alveolar deterioration due to infection of type II pneumocytes[1]. Pulmonary surfactant is a lipid-protein complex mixture that wraps pulmonary alveoli, reducing the tension in air-alveolar interface pulmonary, being fundamental to preserve alveolar stability. The type II pneumocytes are involved in synthesis and secretion of pulmonary surfactant in pulmonary alveoli[2].

The coronavirus disease-19 (COVID-19) can vary from asymptomatic infection to SARS in neonates, children and adult1. Similarly, neonatal respiratory distress syndrome, where micro atelectasis observed had the appearance of ground glass[2], chest radiography in cases of SARS-CoV-2 shows patchy or diffuse asymmetric airspace opacities, and computed tomography often shows patchy areas of ground glass opacity and consolidation, similar radiological appearance in both children and adults[3]. Unlike other forms of SARS, autopsy findings performed on patients died of novel coronavirus pneumonia describe damages in the alveolar structure, with minor serous exudation and fibrin exudation. Hyaline membrane formation was observed in some alveoli. These findings suggest that micro atelectasis secondary to surfactant deficiency are probably the basic lesion of severe acute respiratory syndrome associated with infection by CoV-2 because type II pneumocytes injury leads to deficiency in surfactant production triggering alveolar atelectasis[4].

Thus, the replacement of human surfactant protein could be a potential treatment modality for SARS CoV-2, similarly treatment to neonatal respiratory distress syndrome.

The purpose of this study is to discuss the indication of surfactant replacement as a potential adjunctive

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treatment modality for SARS CoV-2, similarly treatment to neonatal respiratory distress syndrome. We argue that SARS can be triggered by surfactant deficiency secondary to production deficiency determined by type II pneumocyte injury.

The virus

Viruses are molecular parasites that cannot replicate outside a host cell and must invade and dominate the host cell and force it to produce countless copies of them. Once inside the cell, a virus hijacks cell structures, forcing it to produce more viruses[5].

Outside the host cell, a virus is bundled into individual infectious particles called virions. A virion usually contains a genome composed of one or more single or double-stranded DNA or RNA segments. A layer of structural viral proteins, called capsid, surrounds this genome. The capsid itself is surrounded by an envelope derived from the host cell membrane, in some viruses[5,6].

Structure, origin and transmission of SARS-CoV-2

The etiologic agent of the COVID-19 pandemic, SARS-CoV-2, is a zoonotic enveloped virus with a positive, single-stranded RNA genome, termed coronavirus based on his morphology as spherical virions with a core shell and surface projections resembling a solar corona[7]. The replication gene occupies two thirds of the ~ 30 kb long genome and encodes non-structural proteins. The remaining third encodes structural proteins, namely "spike" (S), membrane (M), nucleocapsid (N) and envelope (E) 14 proteins. The binding and entry of the virus into the cell is related to protein S[6].

There are four subfamilies, namely alpha-, beta-, gamma- and delta-coronaviruses, but only seven subtypes can infect humans. The beta-coronaviruses may cause severe disease and fatalities, whereas alpha-coronaviruses cause asymptomatic or mildly symptomatic infections. SARSCoV-2 belongs to the B lineage of the beta-coronaviruses and is closely related to the SARS-CoV virus[7].

Until the SARS-CoV outbreak in 2002-03, CoVs were known to cause mild respiratory disease in humans[6]. RNA viruses are capable of adapt to new hosts and environments due to their higher mutation rates[8,9]. The ability of a virus to be transmitted from human to human determines its power to cause a major epidemic. Transmission efficiency is measured as the basic reproduction number of the virus, R 0, which indicates the average number of secondary infections caused by an infected individual in an immunologically susceptible population. Usually a virus can cause an epidemic if R0 > 1[6,10]. SARS-CoV-2 is transmitted mainly through droplets, respiratory secretions and direct contact. The presence of the virus in fees and blood suggests other potential modes of transmission. The incubation period for SARS-CoV-2 is 1 to 14 days and asymptomatic individuals can transmit the virus during this period[1,11].

CoV-2 life cycle

Although the replicative life cycle of viruses varies greatly depending on the species and category of the virus, it consists of six basic stages, receptor binding, entry, shedding, replication, maturation and release[6,12].

The cell receptor for SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2). Virus S protein interacts and binds to ACE2 in the first stage of virus replication.10 Therefore, all cells expressing ACE2, including lung type II (AT2) alveolar cells, upper and stratified esophageal epithelial cells, absorbent enterocytes, myocardial cells, cholangiocytes, proximal kidney tubular cells, and bladder urothelial cells are potentially susceptible SARS-CoV-2 Infection[11,12].

The second stage called 'entry' leads to the insertion of the viral replication complex in the host cell's cytoplasm. In the case of SARS-CoV, protein S is cleaved by the cellular transmembrane serine protease 2, which exposes a fusion peptide, which then inserts itself into the cell membrane, starting the fusion of the cell membrane and virus. Finally, the viral genome enters the cytoplasm[13].

Direct positive translation of the viral RNA genome leads to the synthesis of structural and non-structural viral proteins (NSPs), in the next stage. NSPs, encoded by the viral replicase gene, are responsible for replicating the viral genome. This step is followed by the assembly; or "maturation" stage in which recently synthesized viral structural proteins, E, M and S are inserted in the intermediate compartment of the Golgi trans-rectoplasmic reticulum. Viral genomes coated with protein N enter the ERGIC by budding, forming mature virions[8].

Mature virions travel to the cell surface inside the vesicles and leave the cells by exocytosis[5]. Recently was discovered a new furin-like cleavage site in the spike protein SARS-CoV-2. This cleavage site, absent in SARS-CoV, may be involved in viral output and provide an efficient spread of the virus in the human population[5,8].

Pneumocyte type II and surfactant production

The alveolar epithelium has two types of cells, type I pneumocytes that covers/ line 95% of the alveolar area, and type II pneumocytes that are the source of pulmonary surfactant and act as progenitor cells for both cell lineages[14].

Pulmonary surfactant is a mixture of lipids and surfactant-specific proteins that is synthesized, packaged, and secreted from type II pneumocytes towards the alveolar surface, where the surfactant is quickly adsorbed to form a highly cohesive and multilayer phospholipid film at the air-liquid interface[15].

Pulmonary surfactant is composed of 90% lipids and 10% specific proteins, including SP-A, SP-B, SP-C and SP-D[16]. In the alveolar space, surfactant sits at the air-liquid interface over the residue and protective layer overlying the epithelium and decrease the surface tension generated by the lung liquid. Hydrophobic proteins SP-B and SP-C

are necessary for interfacing adsorption, stability and surfactant propagation activities during inspiration-expiration cycles[17].

The respiratory surface is stabilized by the pulmonary surfactant, which reduces the surface tension at the air-water interface, minimizing respiratory work and preventing alveolar collapse. The lack, deficiency or dysfunction of the pulmonary surfactant contributes to atelectasis, shunts, poor gas exchange and increased rates of ventilator associated pneumonia[15,18]. Severe respiratory disorders, such neonatal respiratory distress syndrome in premature babies or pulmonary dysfunction associated with acute respiratory distress syndrome, where inflammatory processes in the lung lead to surfactant inactivation, are related to deficiency or dysfunction of the pulmonary surfactant[15].

The immunological properties of surfactant have drawn attention /currently nowadays. Some proteins appear to have specific immune properties such as Apoproteins SP-A and SP-D. These proteins bind to bacteria; SP-A enhances the phagocytosis of bacteria and viruses and promotes the chemotaxis of phagocytic cells. Inhibiting the pulmonary edema formation and enhancing fluid dispersal and ciliary transport in the small airways, are other properties of surfactant[17].

Lung injury in SARS-CoV-2

The COVID-19 has a mean incubation period is five days and a median incubation period is three days, range from 0–24 days. The clinical manifestations of the disease usually start after less than a week, consisting of fever, cough, nasal congestion, fatigue and other signs of upper respiratory tract infections. Approximately 75% of patients can progress to severe disease with dyspnea and severe chest symptoms corresponding to pneumonia, which mostly occurs in the second or third week of a symptomatic infection[19].

Damages in the alveolar structure, with minor serous exudation and fibrin exudation were described in minimally invasive autopsies performed on patients died of novel coronavirus pneumonia in Chongqing, China[4]. Hyaline membrane formation was observed in some alveoli. Other findings have also been described, such as significant proliferation of type II alveolar cells, focal desquamation of alveolar epithelia, congestion of blood vessels in the alveolar septum with infiltration of monocytes and lymphocytes, presence of hyaline thrombi in the microcirculation, focal hemorrhage in the pulmonary tissue, organization of pulmonary tissue exudates in some alveolar cavities and interstitial pulmonary fibrosis[4].

SARS-CoV and SARS-CoV-2 connect to target cells upon to angiotensin-converting enzyme 2 (ACE2). Virus S protein interacts and binds to ACE2 in the first stage of virus replication. All cells that express ACE2, including lung type II (AT2) cells in the lung are potentially susceptible to CoV-2 infection.12 The type II pneumocytes are the source of pulmonary surfactant and act as progenitor cells for both cell lineages[16]. The respiratory surface is stabilized by the pulmonary surfactant, which reduces the surface tension at the air-water interface, minimizing respiratory work and preventing alveolar collapse. The lack, deficiency or dysfunction of the pulmonary surfactant contributes to atelectasis, shunts, poor gas exchange and increased rates of ventilator associated pneumonia[15].

Unlike SARS from other etiologies, SARS-CoV-2 installs in later stages of the disease, about half of the patients had dyspnea and the median from onset to dyspnea was 8 days[9], what supports the hypothesis that a week is enough time to cause a sufficiently extensive lesion of the pneumocytes and surfactant deficiency with consequent atelectasis. Similarly, to neonatal respiratory distress syndrome, the lungs of novel coronavirus pneumonia patients manifest significant pathological lesions, including the alveolar exudative inflammation and interstitial inflammation, alveolar epithelium proliferation and hyaline membrane formation[4], like neonatal respiratory distress syndrome.

SARS CoV-2 chest radiography shows patchy or diffuse asymmetric airspace opacities, and computed tomography often shows patchy areas of ground glass opacity and consolidation3, in the same aspect of neonatal respiratory distress syndrome, where the micro atelectasis observed had the appearance of ground glass[2,18].

We argue that the initial lung injury of SARs-Cov-2 is atelectasis determined by the surfactant deficiency secondary to injury of type II pneumocytes by CoV-2, and we propose the replacement of human surfactant as a potential treatment modality for SARS-Cov-2, in the same way to neonatal respiratory distress syndrome.

Replacement surfactant therapy has potential benefits, such as improved gas exchange reducing invasive ventilation time and reducing complications such as pneumothorax and interstitial emphysema, in addition to antimicrobial or anti-inflammatory activities[16].

CONCLUSION

Thus, the replacement of human surfactant protein could be a potential treatment modality for SARS CoV-2, in the same way that it is indicated for the treatment of neonatal respiratory distress syndrome.

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