

Role of the surfactant in Severe Acute Respiratory Syndrome Coronavirus 2 infections

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ABSTRACT

This article reviews the role of the surfactant in the physiopathology and development of the pulmonary disease (COVID-19) caused by SARS-CoV-2 which is responsible for the ongoing pandemic that started in early 2020. This virus has capacity to modify the components of surfactant, and this increases its replication and dissemination. Given the important role surfactant has in antiviral host defenses and lung physiology, surfactant has been studied in the treatment of SARS-CoV-2 infections. However, much more research is needed to understand the role of the surfactant in the disease caused by SARS-CoV-2 and its potential use in treatment.

Keywords: Surfactant, COVID 19, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), pathogenesis, treatment

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic started in early 2020 and is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This virus belongs to Coronaviruses family and is considered a Beta coronavirus (subgenus Sarbecovirus) in the family Coronaviridae (subfamily Orthocoronavirinae), a family of single-stranded positive-sense RNA viruses.¹ The lungs are the primary organ involved during infection. The purpose of this review is to analyze the interaction between SAR-CoV-2 and pulmonary surfactant.

VIRAL CHARACTERISTICS

SARS-CoV-2 is single-stranded positive-sense RNA virus, containing a 26–32 kilobase genome; the viral envelope consists of a lipid bilayer on which the

viral membrane (M), envelope (E), and spike (S) structural proteins are anchored.² Although SARS-CoV-2 shares some similarities with the other members of the family, it has some unique characteristics. For example, SARS-CoV-2 does not use aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4) as a receptor.² This virus uses a novel metallopeptidase angiotensin converting enzyme 2 (ACE2) to enter human cells.^{3–4} The mode of ACE2 binding resembles almost exactly how the SARS-CoV receptor binding domain (RBD) binds to the ACE2 receptor, but it has characteristics that make SARS-CoV-2 unique. SARS-CoV-2 has several amino acid variations that occur in the middle of the binding domain of SARS-CoV-2, which are not seen in SARS-CoV, and these variations increase its affinity to ACE2, and this allows the SARS-CoV-2 to enter into cells more efficiently. The crystal structure of the receptor RBD of the spike protein of SARS-CoV-2 allows stronger binding than other viruses of the same family to the cell receptor ACE2.^{5–6}

SARS-CoV-2 infection requires not only binding to the ACE2 receptor, but also priming of the S protein by a transmembrane protease serine 2 (TMPRSS2) by

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cleavage of the S protein at S1/S2 sites. This results in fusion with the plasma membrane and then endosome formation. After release from intracellular endosomes, viral RNA is replicated. Viral assembly then occurs, and virions are released from the cell which in turn infect other cells. After pyroptosis of the infected host cells, Damage-Associated Molecular Patterns (DAMPs) are released, and these are recognized by antigen-presenting cell, such as macrophages and monocytes, that respond to viral infection by releasing cytokines.⁷⁻⁸

SURFACTANT

Pulmonary surfactant is an important component of the lungs and has an essential role in the pulmonary physiology. It is produced by alveolar type II cells and consists of lipids (phosphatidylcholine, phosphatidylglycerol) and proteins (surfactant protein A [SP-A], surfactant protein B [SP-B], surfactant protein C [SP-C], and surfactant protein D [SP-D]). Surfactant is essential for life by decreasing the surface tension in the alveoli and increasing lung compliance, and, therefore, preventing atelectasis during breathing. In addition, its composition has an important role in bacterial and viral lung infections.^{9,10} Its therapeutic use includes preterm infants with neonatal distress respiratory syndrome (NDRS), infants with meconium aspiration syndrome, and infants at risk for NDRS.¹¹ In adults therapeutic use has not reduced mortality or improved outcomes in patients with adult respiratory distress syndrome (ARDS).¹²

VIRAL AND BACTERIAL INTERACTION WITH SURFACTANT

The effect of surfactant and its role in different lung infections has been studied with several bacterial pathogens, including *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniae*, etc.^{10,13} Surfactant composition is essential to understand its role in host defenses against different pathogens. Surfactant proteins SP-C and SP-D are hydrophilic and are stored and secreted with surfactant; SP-A and SP-B are hydrophobic and form part of the innate immune proteins. These proteins opsonize

viruses and bacteria and help present them to the innate immune system, i.e., monocytes and macrophages.^{10,14} Surfactant has important roles in immune responses, and evidence suggests that it contributes to host defense responses against enveloped viruses.¹⁵ Therefore, each subcomponent has been widely studied; SP-D has direct interaction with a range of viruses, results in viral neutralization, and promotes phagocytosis *in vitro*.^{16,17}

COVID-19 AND HOST DEFENSES

Multiple hypotheses have been proposed about the interaction between SARS-CoV-2 and the immune system in the lungs and how the virus attaches to and infects human cells. Alveolar type II cells have an essential role in host defense mechanisms against both viral or bacterial infections. Furthermore, alveolar type II cells have ACE2 receptors on their surfaces.^{4,15,18}

One of the theories proposed by Takano is that the SARS-COV-2 can infect type II alveolar cells and suppress the production of surfactant. This would decrease host defense responses and increase of viral replication and survival in host tissue.¹⁵⁻¹⁹ Furthermore, Carcaterra et al. proposed the possible existence of a vicious cycle in which alveolar damage starts in cells with AEC2 receptors which then stimulates an inflammatory state supported by macrophage pro-inflammatory polarization (M1) with cytokine release and the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells pathway.²⁰ After the virus enters into the cellular network through ACE2 receptors and infects other cells, the inflammation persists. This leads to a cytokine storm, with an intense promotion of inflammation supported by the recruitment of neutrophils, monocytes and macrophages and by the activation of alveolar epithelial cells. The alveolar epithelium consists of 90% type I cells and 10% type II cells; both the cell types express ACE 2 receptors, especially type II cells. Injury of these cells by the virus or by inflammatory mediators contributes to development of ARDS.^{20,21,29,30}

COVID-19 AND LUNG INJURY

Tian et al. did post mortem core needle biopsies on different organs in four patients with COVID-19;

the main pathologic findings in the cases with pneumonia included diffuse alveolar type II cell hyperplasia suggesting reactive changes and/or cellular damage and surfactant depletion.²²

Recent studies have shown the SP-D and IL-6 are found in higher levels in patients with SARS-CoV-2. Kerge et al. measured the levels of SP-D and IL-6 in patients upon admission to investigate the course and prognosis of the disease. They tested 108 patients, and 88 had COVID-19. They found that patients who developed macrophage activation syndrome had significantly higher IL-6 and SP-D levels at the time of admission and on day 5 of treatment compared to the other patients (IL-6: $p = 0.001$ for both time periods; SP-D: $p = 0.02$, $p = 0.04$ for admission and day 5, respectively). Patients who developed acute respiratory distress syndrome had significantly higher IL-6 and SP-D levels at both time points compared to those who did not ($p = 0.001$ for all). Both parameters at the time of admission were also significantly higher in nonsurvivors than survivors (IL-6: $p = 0.001$, SP-D: $p = 0.03$).^{23,24}

SURFACTANT AND COVID 19 TREATMENT

Miao-His Hsieh et al. have studied the possible protective role of a recombinant fragment of human surfactant protein D (rfhSP-D) against SARS-CoV-2 infection.¹⁷ This fragment binds to the S1 spike protein of SARS-CoV-2 and its receptor binding domain with a dose response kinetics. Importantly, rfhSP-D inhibits the interaction of S1 protein with the HEK293T cells overexpressing human ACE2. The protective role of rfhSP-D against SARS-CoV-2 infection as an entry inhibitor was further validated by the use of pseudotyped lentiviral particles expressing SARS-CoV-2 S1 protein, and a 0.5 Relative Light Unit fold reduction in viral entry was seen following treatment with rfhSP-D (10 $\mu\text{g/ml}$). Therefore, this study demonstrates that rfhSP-D inhibits the entry of pseudotyped lentiviral particles expressing SARS-CoV-2 S1 protein in human ACE-2 overexpressing HEK293T cells mimicking the human SARS-CoV-2 infection. Surfactant protein D could have an important protective role in the pathogenesis of COVID-19 and contribute to innate immunity.

Additional studies have reported down regulation of the surfactant production and significant downregulation

of several cholesterol biosynthesis pathways in COVID-19 patient's lung cells. Islam and Khan found the viral protein NSP5 can recruit histone deacetylase 2 and downregulate the expression of transcription intermediary factor 1- γ which is needed for the expression of SP-B and SP-C. SP-A and SP-D can be targeted indirectly by several viral proteins, which might reduce the production of surfactant proteins in lungs, thus increasing the effect of infection on lung physiology.²⁵ The CSF2RA-CSF2RB complex modulates the surfactant recycling that maintains the overall balance of surfactant content. It was found that CSF2RA is dysregulated in SARS-CoV-2-infected lung, which could lead to abnormal surfactant recycling. As discussed above, the down regulation of the cholesterol biosynthesis could reduce the accumulation of phospholipids in lungs. Since phosphatidylcholine and phosphatidylglycerol are the principal phospholipids of surfactant proteins, disrupted production of lipids might make surfactant proteins non-functional.²⁵

Based on these results, studies have been conducted to understand the use of surfactant components as a treatment option to decrease mortality and severity of SARS-CoV-2. Surfactant was administered using different techniques. One study with ARDS patients treated them with liquid Curosurf® (Chiese USA, Inc.) (720 mg in 150 ml normal saline, divided into five 30 ml aliquots) delivered by bronchoscopy into second-generation bronchi. This study suggested that surfactant did not cause acute decompensation and could reduce mortality and mechanical ventilation duration in COVID-19 ARDS patients.²⁶ Another study administered surfactant by inhalation and found improvement in the PaO₂/FiO₂ ratio, a decrease in ICU admissions of patients and invasive mechanical ventilations, and a decrease in non-invasive ventilation and length of stay in the hospital.²⁷

CONCLUSIONS

Severe Acute Respiratory Syndrome Coronavirus 2 is a complex virus, and pulmonary surfactant has a central role in its pathogenesis and dissemination in the body. Furthermore, modification in the surfactant and its components during a viral infection contribute to disease progression and the severity of the disease.

These considerations suggest that surfactant could potentially be a treatment option or target in the near future.

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