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The role of surfactant proteins SP-A and SP-D in viral infection: a focus on COVID-19

Kharlamova O.S.[1, 2], Nikolaev K.Yu.[1, 3], Ragino Yu.I.[1]

[1]*Research Institute of Internal and Preventive Medicine – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences*

[2]*City Clinical Hospital No. 25*
1a, A. Nevskogo Str., Novosibirsk, 630075, Russian Federation

[3]*Novosibirsk State University*
2, Pirogova Str., Novosibirsk, 630090, Russian Federation

ABSTRACT

An immune response to invasion of viral pathogens is an integral part of maintaining the physiological functioning of the bronchopulmonary system and effective gas exchange. Collagen-containing C-type lectins (lung collectins) are some of the key proteins in the identification of viral particles. They have image-recognizing receptors that identify pathogen-associated molecular patterns, particularly viral glycoproteins. The surfactant proteins SP-A and SP-D, which are composed of trimerized units, belong to pulmonary collectins and oligomerize into higher-order structures. These proteins play an essential role in recognition and elimination of microbial pathogens (viruses, bacteria, fungi, parasites, nanoparticles, allergens) through a variety of mechanisms.

Taking into account the burden of the novel coronavirus infection caused by the SARS-CoV-2 virus, it is important to consider the role of the surfactant proteins SP-A and SP-D in the pathogenesis of the immune response to viral invasion. Currently, there are data on the direct relationship between surfactant proteins and viruses belonging to the Coronaviridae family. The SP-A and SP-D proteins modulate inflammatory responses and cytokine synthesis, but prevent an excessive inflammatory response (cytokine storm). There is also an assumption that SARS-CoV-2 directly suppresses and alters the production of surfactant proteins. Thus, the key pathogenetic role of the surfactant proteins SP-A and SP-D in the response to the viral pathogen SARS-CoV-2 is evident. Today, this is a promising area of translational medicine, which will contribute to a profound understanding of the pathogenesis of coronavirus infection for assessing the diagnostic and prognostic potentials of the surfactant proteins SP-A and SP-D in COVID-19. Additionally, it will help evaluate the therapeutic potential of recombinant fragments of human SP-A and SP-D.

Keywords: surfactant, surfactant protein A, surfactant protein D, biomarker, viral infection, coronavirus infection, COVID-19, SARS-CoV-2

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✉ *Kharlamova Olga S.,* olga.kharlamova2016@yandex.ru

Роль белков сурфактанта SP-A и SP-D при вирусной инфекции, фокус на COVID-19

Харламова О.С.[1, 2], Николаев К.Ю.[1, 3], Рагино Ю.И.[1]

[1]Научно-исследовательский институт терапии и профилактической медицины – филиал Федерального исследовательского центра «Институт цитологии и генетики» Сибирского отделения Российской академии наук (НИИТиПМ – ИЦиГ СО РАН)
Россия, 630089, г. Новосибирск, ул. Б. Богаткова, 175/1

[2]Городская клиническая больница № 25 (ГКБ № 25)
Россия, 630075, г. Новосибирск, ул. А. Невского, 1а

[3]Новосибирский государственный университет (НГУ)
Россия, 630090, г. Новосибирск, ул. Пирогова, 2

РЕЗЮМЕ

Неотъемлемой частью поддержания физиологического функционирования бронхолегочной системы и эффективного газообмена является иммунологический ответ на инвазию вирусных патогенов. Одними из ключевых белков, участвующих в идентификации вирусных частиц, являются представители семейства коллагенсодержащих лектинов типа С (легочные коллектины). Они обладают образ-распознающими рецепторами, которые идентифицируют ассоциированные с патогенами молекулярные паттерны, в частности, вирусные гликопротеины. К легочным коллектинам относятся белки сурфактанта SP-A и SP-D, которые состоят из тримеризованных единиц и олигомеризуются в структуры более высокого порядка. Эти белки играют ключевую роль в распознавании и элиминации микробных патогенов (вирусов, бактерий, грибов, паразитов, наночастиц, аллергенов) посредством разнообразных механизмов.

С учетом бремени пандемии новой коронавирусной инфекции, вызванной SARS-CoV-2, крайне важно обратить внимание на роль белков сурфактанта SP-A и SP-D в патогенезе ответа на данную вирусную инвазию. В настоящее время известны указания на непосредственное взаимодействие белков сурфактанта и вирусов, принадлежащих к семейству Coronaviridae. Белки SP-A и SP-D модулируют воспалительные реакции и синтез цитокинов, при этом предотвращая чрезмерную воспалительную реакцию (цитокиновый шторм). Также существует предположение, что непосредственно SARS-CoV-2 подавляет и изменяет выработку белков сурфактанта. Таким образом, очевидна патогенетическая ключевая роль белков сурфактанта SP-A и SP-D в ответе на вирусный патоген SARS-CoV-2. Это на сегодняшний день является перспективным направлением трансляционной медицины как с точки зрения детального понимания патогенеза коронавирусной инфекции для оценки диагностических и прогностических потенциалов белков сурфактанта SP-A и SP-D при COVID-19, так и с точки зрения терапевтического потенциала рекомбинантных фрагментов человеческих SP-A и SP-D.

Ключевые слова: сурфактант, сурфактантный белок А, сурфактантный белок D, биомаркер, вирусная инфекция, коронавирусная инфекция, COVID19, SARS-CoV-2

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INTRODUCTION

An immune response to invasion of viral pathogens is an integral part of maintaining the physiological functioning of the bronchopulmonary system and effective gas exchange. Collagen-containing C-type lectins, also known as lung collectins, are among the key proteins involved in identification of viral particles. They have image-recognizing receptors that identify pathogen-associated molecular patterns, in particular,

viral glycoproteins [1]. Lung collectins include surfactant proteins SP-A and SP-D, which consist of trimerized units and oligomerize into higher-order structures [2]. These proteins play a key role in recognition and elimination of microbial pathogens (viruses, bacteria, fungi, parasites, nanoparticles, allergens) through a variety of mechanisms [2, 3]. Given the burden of the novel coronavirus infection pandemic caused by SARS-CoV-2, it is extremely important to draw attention to the role of SP-A and SP-D in the pathogenesis of the immune response to this viral invasion. Firstly, in viral diffuse alveolar damage with microangiopathy, SP-A and SP-D modulate inflammatory responses and cytokine synthesis (acting as a proactive link between innate and adaptive immunities), while preventing an excessive inflammatory response (cytokine storm) [4]. Secondly, there are indications of direct interactions between surfactant proteins and viruses belonging to the Coronaviridae family according to the classical pattern [5]. Thirdly, there is an assumption that it is SARS-CoV-2 that not only suppresses the production of surfactant proteins [6], but also causes the production of an altered surfactant [7]. This is determined by binding of the crystal-like structure of the receptor-binding domain (RBD) of SARS-CoV-2 spike protein to angiotensin-converting enzyme 2 (ACE-2) of alveolar epithelial type II cells [8], which directly produce SP-A and SP-D [1].

Therefore, despite few studies on the role of surfactant proteins SP-A and SP-D in the novel coronavirus infection, their crucial pathogenetic role in the immune response to the viral pathogen SARS-CoV-2 is obvious. Currently, it is a promising area in terms of a detailed understanding of the pathogenesis of coronavirus infection and the resulting prognostic potentials of surfactant proteins SP-A and SP-D in COVID-19, as well as in terms of the therapeutic potential of recombinant molecules SP-A and SP-D.

MOLECULAR STRUCTURE AND FUNCTIONS OF SP-A AND SP-D SURFACTANT PROTEINS

Lung surfactant is a lipoprotein complex of the respiratory mucosa consisting of 90% lipids (mainly phospholipids) and 10% proteins: SP-A, SP-B, SP-C, and SP-D [3, 4]. As mentioned above, the surfactant is predominantly produced by cube-shaped alveolar type II cells synthesizing surface active substances from typical organelles called lamellar bodies [9]. Surfactant proteins SP-B and SP-C are small hydrophobic peptides involved in packaging and processing of the surface active substance and contributing to its biophysical properties [10].

On the contrary, surfactant proteins SP-A and SP-D are large, soluble, hydrophilic proteins that are expressed on most mucosal surfaces and play the key multifunctional role in the immune response to pathogen invasion and in pulmonary immune homeostasis [1]. As stated above, SP-A and SP-D are calcium-dependent (C-type) lectins with collagen areas belonging to the group of proteins called collectins. Collectins are oligomerized proteins consisting of trimerized units with 3 polypeptide chains [11]. Each chain has a collagen triple helix domain consisting of repeating Gly-X-Y triplets, α-helical neck, and C-terminal end containing a C-type lectin or a CRD (Fig. 1) [2].

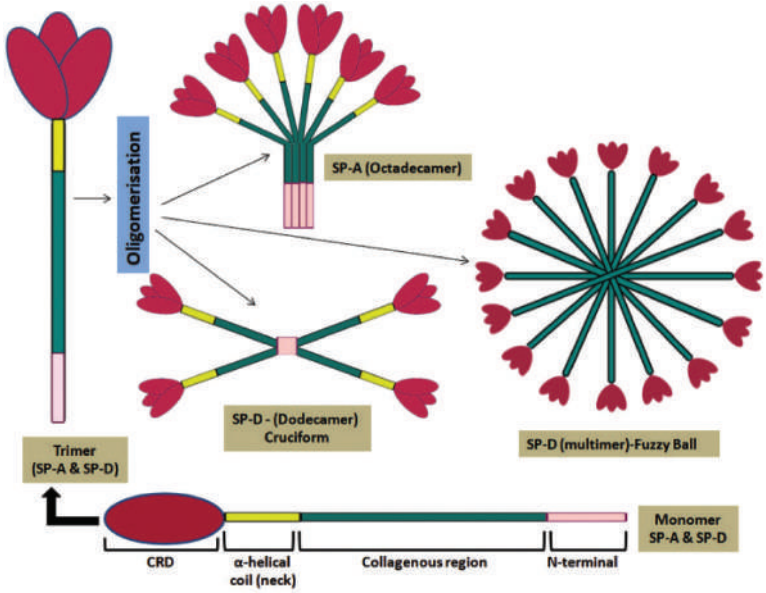

Fig. 1. Structure of SP-A and SP-D surfactant proteins (extracted from: Yasmin H., Kishore U. Biological Activities of SP-A and SP-D Against Extracellular and Intracellular Pathogens. *The Collectin Protein Family and Its Multiple Biological Activities*. 2021;103–133. DOI: 10.1007/978-3-030-67048-1_5)

Through interaction of N-terminal domains, these trimerized units oligomerize into an octodecameric structure for SP-A, forming a 630 kDa molecule consisting of 18 chains, and a dodecametric structure for SP-D forming a 520 kDa molecule, which may further amass composing "fuzzy balls" and (or) "astral bodies" [12]. This multimerization enhances the overall binding avidity to carbohydrate targets and increases the ability to agglutinate pathogens. While the SP-D trimer is a monogenic unit, SP-A is formed from two genetic products, SP-A1 and SP-A2, which have some functional differences [13].

The surfactant proteins SP-A and SP-D perform numerous functions of innate and adaptive immunity during pathogen invasion into the bronchopulmonary system (Fig. 2) [1].

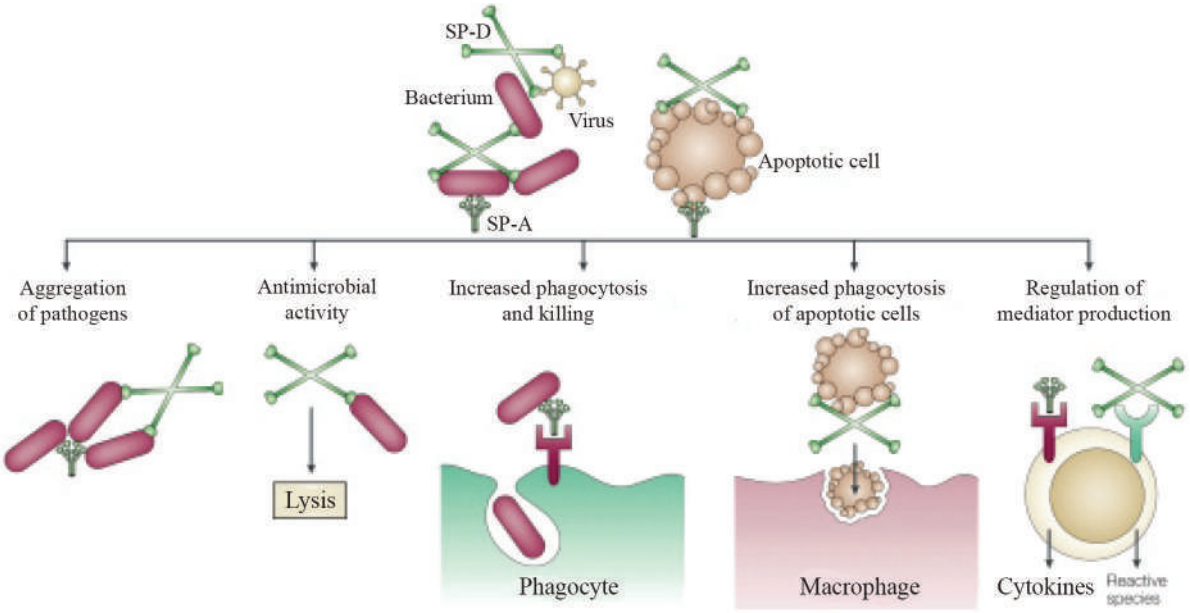

Fig. 2. Immune functions of surfactant proteins SP-A and SP-D (extracted from: Wright J.R. Immunoregulatory functions of surfactant proteins. *Nat. Rev. Immunol*. 2005;5(1):5868. DOI: 10.1038/nri1528.)

The surfactant proteins SP-A and SP-D bind and opsonize viruses, bacteria, worms, and allergens (including pollen and nanoparticles) [14]. SP-A and SP-D enhance microbial phagocytosis by such innate immune cells as macrophages and neutrophils by opsonising and aggregating bacteria and viruses, acting as a ligand for activation, and regulating the expression of surface receptors of immune cells responsible for pathogen recognition [1]. Both proteins have direct bactericidal effects against bacteria and fungi [15]. In addition, SP-A and SP-D also facilitate phagocytosis of apoptotic cells by innate immune cells and provide context-dependent regulation of cytokine and free radical production. For example, SP-A inhibits lipopolysaccharide-stimulated nitric oxide (NO) production by alveolar macrophages collected from healthy lungs, but promotes production of NO in macrophages activated by IFN-γ [14, 15].

SP-A and SP-D connect innate and adaptive immunities for regulation of protection against the background of pathogen invasion into the bronchopulmonary system. Despite the fact that both SP-A and SP-D can bind directly to T-cells and inhibit proliferation, SP-A can also inhibit proliferation of T-cells indirectly through suppressing maturation of dendritic cells (DCs) [15]. SP-D has been shown to enhance absorption and presentation of the antigen [1, 14]. *In vitro* results show that the combined role of SP-A and SP-D consists in modulation of the pulmonary immune environment in order to protect the body while preventing an excessive inflammatory response that could potentially damage the alveolar – capillary membrane and impair gas exchange, as in the case of hyper-induction of proinflammatory cytokines in development of cytokine storm as a response to SARS-CoV-2 invasion [16].

INTERACTION BETWEEN SURFACTANT PROTEINS SP-A AND SP-D AND VIRUSES

Further, the ways of specific interaction between surfactant proteins SP-A and SP-D and various viral particles will be considered, with a more detailed

description of the interaction between proteins and coronaviruses. Currently, the association between surfactant proteins and trimerized and glycosylated proteins on the surface of such viral capsids as SARS-CoV, SARS-CoV-2, respiratory syncytial virus (RSV), human immunodeficiency virus (HIV), and influenza A virus (IAV) is being actively studied. There is an assumption that surfactant proteins SP-A and SP-D have undergone coevolution with these viruses for their neutralisation through binding to glycosylated proteins for viral attachment, making their binding to the host cell impossible [14].

This interaction also enhances their aggregation, opsonisation, and clearance by phagocytes. Many enveloped viruses express class I fusion proteins, in particular, SARS-CoV-2 has spike protein (S) or S protein [17], paramyxoviruses have homotrimeric F protein, and influenza, Ebola virus, HIV, etc. – other class I fusion proteins [1, 14]. Fusion proteins of IAV and RSV are represented by a trimer with three copies of the same protein [18]. The HIV fusion envelope protein consists of two non-covalently associated glycoproteins (120 kDa and 41 kDa) – gp120 and gp41, respectively [19]. The discussed fusogenic proteins have a trimeric configuration similar to that of SP-A and SP-D, which makes it possible to suggest their coevolution for provision of selective binding to these viral surface molecules [14]. This configuration of surfactant proteins SP-A and SP-D provides direct binding with fusion proteins of the aforementioned viruses for their neutralisation, as well as for further aggregation and elimination of the virus using several fusion sites per molecule.

Annually, influenza A viruses lead to high prevalence of respiratory infection with excessive mortality in a number of cases [20]. The interaction between surfactant proteins SP-A and SP-D and influenza viruses has been investigated quite extensively. The SP-D protein binds to high-mannose oligosaccharides in immediate proximity to sialic acid binding sites to influenza hemagglutinin, which neutralizes it spatially via inhibiting its attachment to host cells [21]. On the contrary, influenza A virus demonstrates calcium-independent binding to the sialylated asparagine 187 residue of SP-A protein, making the binding of the virus to sialylated receptors impossible [22, 23]. It was also confirmed that SP-A protein is involved in the phagocytosis of influenza A virus by alveolar macrophages by using sialic acid residues as opsonin [23]. Influenza A virus may impair development of the respiratory burst of neutrophils in response to the viral infection, which leads to degranulation and intracellular destruction of bacteria by phagocytes, thus increasing the susceptibility of the human to bacterial superinfections, which is an important factor in mortality during the seasonal influenza pandemics [2]. Surfactant protein SP-D significantly potentiates the respiratory burst of neutrophils in response to influenza A virus *in vitro*, thus demonstrating a proinflammatory response [24].

Respiratory syncytial viruses (RSV) are the main causes of lower respiratory tract infection in newborns and children [25]. RSV is the leading cause of bronchiolitis and infant hospitalization in developed countries [26]. It has been shown that genetic polymorphisms in SP-A and SP-D genes are associated with susceptibility to severe RSV infection, which emphasizes their importance in the immune response to RSV [27]. It has been experimentally demonstrated that SP-A$^{-/-}$ and SP-D$^{-/-}$ mice have both a reduced capacity for RSV clearance and an increased inflammatory response in the lungs [28]. Currently, the mechanism of interaction between SP-A and SP-D surfactant proteins and RSV has not been fully studied. RSV has two main surface glycoproteins: protein G, important for attachment of the virus to the host cell, and protein F, a trimeric class I fusion protein important for fusion between the virus and the host cell membrane.

In one study, SP-A was shown to bind *in vitro* to RSV F protein, but not to G protein [29]. However, another study has shown that SP-A demonstrates calcium-independent binding to RSV using G protein, neutralizing the virus and increasing the clearance *in vivo* [30]. It has been experimentally demonstrated that a recombinant trimeric fragment of a closely-related molecule (surfactant protein SP-D) retains many functions of the native protein, while the importance of the oligomeric structure of SP-A in its interaction with RSV has not been determined [26]. Therefore, the mechanism through which SP-A and SP-D bind to RSV remains unclear and requires further investigation. However, considering the experimental efficacy of both rfhSP-A and rfhSP-D in RSV neutralization, it seems likely that virus neutralization occurs via binding of SP-A and SP-D proteins to the RSV fusion protein, which is also a trimeric protein with a helical conformation [31].

Human immunodeficiency virus (HIV) is one of the most severe public health problems around the globe [32]. HIV glycoprotein (gp)120 is required for infiltration of the virus into the cells and is the main target for HIV binding to various type-C lectins [33].

At present, the ability of surfactant proteins SP-A and SP-D to bind trimerized gp120 has been shown [34, 35]. SP-A binding inhibits the binding of CD4 using gp120, emphasizing the potential role of SP-A in HIV neutralization through blocking CD4-mediated fusion [35]. SP-D binding to gp120 prevents DC-SIGN interaction (membrane protein, C-type lectin receptor of macrophages and dendritic cells), which has also been demonstrated, to some extent, for SP-A [34, 36]. However, surfactant proteins SP-A and SP-D did not prevent binding of cyanovirin to gp120 in the experiment, which possibly confirms the DC-SIGN – gp120-type binding of SP-A and SP-D to gp120, during which none of the high-mannose N-linked glycosylation sites is responsible for DC-SIGN binding [34]. This is in contrast with cyanovirin, which is neutralized through targeting of a certain set of N-linked glycosylations [34, 35]. It is also important that SP-D binds gp41, which is required for formation of thee gp120 trimer and facilitates fusion between the viral and cell membranes [37].

Since both SP-A and SP-D have been identified in the female urogenital system, binding of these proteins to gp120 may be important in HIV infection (as a primary infection site) and in the lungs (as a common reservoir of HIV infection) [38, 39]. This binding has been shown to neutralize HIV and prevent direct infection of CD4+ of PM1 cells. However, SP-A and SP-D promote infection of immature monocyte-derived DCs and their transmission to the CD4+ T-cells in case of their co-cultivation [34, 35]. Currently, the mechanism by which collectins enhance this transmission is unclear. Further effort related to investigation of the interaction between SP-A and SP-D and HIV is of great importance in elucidating the role of these proteins in HIV infection. A number of studies have suggested that functional recombinant fragments of surfactant proteins SP-A and SP-D may have therapeutic potential for preventing infection and spread of HIV [37, 40].

THE ROLE OF SURFACTANT PROTEINS SP-A AND SP-D IN CORONAVIRUS INFECTION

Before the emergence of severe acute respiratory syndrome, SARS (SARS-CoV), in 2003, approximately ten coronaviruses in humans and animals were known. Then, the discovery of the civet cat and bat SARS-CoV viruses, as well as human coronaviruses NL63 and HKU1, followed. Currently, around 40 representatives of this family of diseases are known [41]. The sudden first pandemic of atypical pneumonia (Middle East respiratory syndrome coronavirus, MERS (MERS-CoV), 2012), its high mortality, a quick repeated outbreak after one year, and economic losses, as well as a subsequent outbreak of MERS led to extensive research on epidemiological, clinical, pathological, immunological, virological, and other fundamental scientific aspects of the group of coronaviruses. Following the outbreak of SARS and MERS, a global pandemic of another viral disease called COVID-19, induced by betacoronavirus SARS-CoV-2, is now observed [42]. Based on data available to date, COVID-19 is not much different from SARS in its clinical features. However, its mortality rate is 2.3%, which is lower than that of SARS (9.5%) and much lower than that of MERS (34.4%). However, COVID-19 can spread much more easily in the community than MERS and SARS [43].

MERS-CoV, SARS-CoV-2, and SARS-CoV are RNA viruses, the latter two containing the largest genomes among all RNA viruses [44, 45]. Genomic RNA of SARS-CoV-2 is 26.4–31.7 kb in size [44], being possibly the largest among all known RNA viruses [46]. The SARS-CoV-2 genome is similar to that of the SARS-like virus ZC45 (bat-SL-CoVZC45, MG772933.1) by over 85%. Together, these types of viruses form the unique Orthocoronavirinae subfamily with another SARS-like virus ZXC21 in the *Sarbecovirus* subgenus.

SARS-CoV-2 has a genomic structure similar to that of other betacoronaviruses. Like other coronaviruses, its genome contains 14 open reading frames (ORF) encoding 27 proteins. ORF1 and ORF2 at the 5’ end encode 15 non-structural proteins important for replication of the virus [47, 48]. The 3’ end of the genome encodes structural proteins, namely, the spike protein (S), the envelope protein (E), the membrane protein (M), and the nucleocapsid (N), as well as eight auxiliary proteins [48]. The viruses SARS-CoV and SARS-CoV-2 have differences in the spike protein (S) – the presence of the furin-like cleavage site in SARS-CoV-2 facilitates priming of the spike protein (S) and may increase the effectiveness of SARS-CoV-2 transmission in comparison with other betacoronaviruses [49]. The spike protein (S) is a class I fusion protein and is trimerized.

The conducted research showed that the majority of proteins in SARS-CoV-2 are highly homologous (95–100%) with proteins of SARS-CoV virus, which indicates their evolutionary similarity. However, two proteins (orf8 and orf10) in SARS-CoV-2 do not have homologous proteins in SARS-CoV [50]. The protein

orf8 in SARS-CoV-2 does not contain a known functional domain that activates intracellular stress signaling pathways and NOD-like receptors of NLRP3 inflammasomes [51]. This makes the analysis of the biological function of these two specific proteins (orf8 and orf10) clinically relevant.

Pathogenic coronaviruses SARS-CoV, MERS-CoV, and SARS-CoV-2 use the ACE2 receptor for access, infestation, and destruction of the alveolar lining layer and type II pneumocytes producing surfactant proteins [8]. In general, pathological features of COVID-19 resemble those observed in SARS and MERS in many aspects [52]. Biopsy and post-mortem samples in COVID-19 reveal diffuse alveolar damage, protein leakage, inflammation in alveolar walls, and desquamation of type II pneumocytes, which is typical of acute respiratory distress syndrome (ARDS) [53]. ARDS manifests through a decline in activity of proteins of the pulmonary surfactant and a change in its content [54].

In COVID-19, depletion of the pulmonary surfactant may also occur through virus-induced lysis of type II pneumocytes with associated formation of the hyaline membrane [53]. Pathophysiological data of such severely ill adult patients resemble primary surfactant deficiency in preterm infants with ARDS, successful therapy of which involves application of exogenous surfactant preparations [55]. Regarding the aforementioned, a number of studies related to the use of exogenous pulmonary surfactant in SARS-CoV-2-associated ARDS have been published [56]. These studies confirm the active role of surfactant proteins in the pathogenesis of COVID-associated severe lung damage and make it possible to consider therapeutic application of recombinant surfactant protein molecules.

However, currently, the studies devoted to specific mechanisms of interaction between SP-A and SP-D surfactant proteins and SARS-CoV-2 are few. Further, we will provide a more detailed description of the spike protein (S) participating in fusion between SARS-CoV and SARS-CoV-2 for analysis of its possible interactions with surfactant proteins (SP-A and SP-D), since it is this trimerized protein that is involved in virus neutralization and its further aggregation and elimination. It is worth noting that, despite not structurally identical fusion of SARS-CoV and SARS-CoV-2, the fusion of subunits eventually results into trimeric structures with three C-terminal ends being outside the central N-terminal trimeric core [57].

The spike protein (S) of SARS-CoV-2 has two functional subunits that mediate the infiltration of coronavirus [58]. The subunit S1 is responsible for binding to host cell receptors via the receptor-binding domain [59]. Binding to the receptor provides conformational changes in the subunit S2, which allows the fusion peptide to penetrate into the membrane of the host cell [57]. HR1 or the heptad region 1 located in the subunit S2 forms a homotrimeric orientation exposing three highly conserved hydrophobic grooves on the external surface that make it possible to bind to the heptad repeat 2 (HR2). Further, in the fusion process, a six-helix bundle (6 HB) is formed, which facilitates the approach of viral and cell membranes for viral fusion and penetration into target cells using the ACE2 receptor [8].

It is the trimeric structure of 6 HB that characterizes class I fusion proteins, which the surfactant protein SP-D is known to interact with. SP-D demonstrated this binding to recombinant trimerized proteins of SARS-CoV. The binding is calcium-dependent and inhibited by maltose, showing the properties of classical lectin – carbohydrate interaction [5]. In the meantime, a serum collectin, mannan-binding lectin (MBL), did not show the revealed binding to the purified S-protein of SARS-CoV in the experiment. It is worth noting that there are ligand differences between the collectins, and this interaction is particularly specific for SP-D [14].

Y.P. Wu et al. (2009) demonstrated that monitoring the SP-D systemic level is informative for monitoring alveolar integrity in SARS pneumonia, as well as revealed a significant correlation between plasma SP-D levels and specific antibodies to SARS-CoV, which once again confirms the role of SP-D in the relationship between innate and adaptive immunity in the pathogen invasion in the bronchopulmonary system [60]. Considering high homology of the spike protein (S) of SARS-CoV with that of SARS-CoV-2 (76.42%, according to J. Xu et al., 2020), it is possible to assume a similar classical lectin – carbohydrate binding mechanism involving calcium and multimerization of the full-length protein for facilitation of virus elimination [17].

In this context, the study by M.H. Hsieh et al. (2021) aimed at investigating a probable defensive role of the recombinant fragment of human SP-D (rfhSP-D) against SARS-CoV-2 infection is relevant. Dose-dependent binding of rfhSP-D to the spike protein S1 of SARS-CoV-2 and its RBD was demonstrated [61].

It is important to outline that the study showed that rfhSP-D inhibited the interaction between the S1

protein and the cell culture overexpressing the human ACE2 receptor. The defensive role of rfhSP-D against SARS-CoV-2 infection as an inhibitor of penetration was additionally confirmed via application of pseudotyped lentiviral particles expressing S1 protein of SARS-CoV-2 [61]. It is obvious that surfactant protein SP-D plays one of the key roles in the response to pathogen invasion of coronavirus. Considering the stated above, single studies on the potential role of SP-D as a marker for predicting the outcome and the possibility of treating COVID-19 have already emerged [62].

As for the surfactant protein SP-A, it is believed that its virus-neutralizing activity is lower than that of SP-D. However, as already mentioned, the protein plays an important role in the innate immune response to different viruses [63]. Currently, there are only a few studies devoted to the type of interaction between SP-A and the group of coronaviruses. For example, C.J. Funk et al. (2012) demonstrated that both SP-A and SP-D bind to the HCoV-229E strain and inhibit viral infection of human bronchial epithelial cells (16HBE) [64]. It can be assumed that the interaction between the surfactant protein SP-A and SARS-CoV-2 occurs through the direct interaction between the lectin domain and the molecule of glycosylated protein on the surface of the virus. Multiple direct interactions of SP-A protein with trimerized proteins, including class I fusion proteins, have been demonstrated. For example, SP-A has been noted to bind to herpes simplex virus [65], which also has trimerized surface proteins similar to those of influenza and RSV discussed earlier. The interaction between SP-A and SARS-CoV-2 has not been studied, but it probably depends both on the glycosylation status of SP-A protein itself and on the functional variants of SP-A1 and SP-A2 in humans.

A considerable amount of available data suggests that innate immune proteins SP-A1 and SP-A2 play at least an indirect role in COVID-19 infection. Thus, the functional features of SP-A1 and SP-A2 impact susceptibility to coinfections against the background of COVID-19 and the presence or absence of severe complications resulting from COVID-19 in patients with one or more non-SARS-CoV-2 pathogens [66]. Approximately 26% of COVID-19 patients have been noted to be infected with other pathogens, with RSV being one of the most frequent ones. It has been shown that it is SP-A that increases RSV clearance and that the functional trimeric fragment of SP-A is highly efficient in reducing RSV infection specifically [26]. It is also extremely important that the association between genetic variants of SP-A and ARDS development has been demonstrated [27].

SP-A variants are known to exert differentiated effects on regulation and functioning of macrophages, which is extremely important against the background of a hyperergic immune response in COVID-19 patients, indicating macrophage activation. Thus, M. Roschewski et al. (2020) put forward a hypothesis that innate immunity is involved in activation of inflammatory processes in macrophages in the pathogenesis of COVID-19 due to hyperergic inflammation, which shares common characteristics with the macrophage activation syndrome [16]. It is quite possible that the magnitude of the inflammatory response will vary depending on the SP-A genotype, which has been shown to have differentiated effects on a number of processes in the alveoli, alveolar macrophages, and epithelial cells [66].

Therefore, trimerized surfactant proteins SP-A and SP-D achieve high binding affinity to the ligand with repetitive surface structure, which is an advantage in binding to viral proteins. Additionally, these proteins have broad selectivity, allowing them to recognize a large number of rapidly changing pathogens, structurally similar trimerized fusion proteins in particular, including the spike protein (S) of coronaviruses. This prevents their attachment to the host cell, neutralizing the virus and increasing its clearance from the body, simultaneously modulating adaptive immunity. Currently, the leading role of surfactant proteins SP-A and SP-D is obvious not only in the immune response of the bronchopulmonary system, but also in the overall response of the body to the pathogen (in particular, viral) invasion.

Therefore, it is obvious that surfactant proteins SP-A and SP-D play one of the key roles in the pathogenesis of coronavirus infection. This, considering the burden of the COVID-19 pandemic, provides prerequisites for the detailed analysis of the interaction between these proteins and SARS-CoV-2, as well as for the analysis of the systemic role of SP-A and SP-D.

PROSPECTS IN APPLICATION OF SURFACTANT PROTEINS SP-A AND SP-D IN COVID-19

In conclusion, we would like to draw attention to a number of key points that justify a more in-depth and detailed analysis of the role of surfactant proteins SP-A and SP-D in the pathogenesis of COVID-19. First, surfactant proteins SP-A and

SP-D, having high binding affinity to the ligand, interact with the spike protein (S) of coronaviruses during the initial contact with the pathogen. Second, infection and destruction of type II pneumocytes producing surfactant proteins take place specifically against the background of SARS-CoV-2 invasion through the ACE2 receptor, which affects synthesis, secretion, and function of SP-A and SP-D. Third, the unique combined role of SP-A and SP-D in modulation of a cascade of the immune response consists in preventing an excessive inflammatory response that could potentially damage the alveolar – capillary membrane and impair gas exchange, as in the case of hyper-induction of proinflammatory cytokines in the novel coronavirus infection. The role of SP-A and SP-D in keeping the lungs in the hyporeactive state is essential because aberrant inflammation may rapidly affect vitally important gas exchange in the lungs through a thin alveolar – capillary membrane. Fourth, SP-A and SP-D participate in the development of severe life-threatening complications, which are accompanied by impairment of the alveolar – capillary membrane permeability.

It is important to assess the diagnostic and prognostic potential of SP-A and SP-D in coronavirus infection. Currently, surfactant proteins SP-A and SP-D are used as diagnostic and prognostic markers in many acute diseases of the bronchopulmonary system, such as community-acquired pneumonia [4, 9, 11, 14], ARDS [9, 54–56], cystic fibrosis [4, 36], interstitial lung disease [1, 4, 36], and lung cancer [1, 9]. In addition, they play an important role in modulation of chronic lung diseases and (or) bronchopulmonary dysplasia [1, 4, 9]. Over the past decade, the extrapulmonary systemic function of these proteins has been actively studied.

CONCLUSION

One of the most promising areas is evaluating the therapeutic potential of recombinant SP-A and SP-D molecules in anti-inflammatory therapy of different diseases, especially those of an infectious nature [14]. It is promising to develop forms of recombinant SP-D with alteration of the neck domain and CRD with increased binding affinity to SARS-CoV-2, as it was carried out for the molecule of mutant trimeric SP-D with increased binding affinity to influenza A virus [67]. Therefore, there is a potential for developing different forms of recombinant molecules of surfactant proteins SP-A and SP-D for treatment of COVID-19.

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Authors information

Kharlamova Olga S. – Junior Researcher, Laboratory of Emergency Therapy, Research Institute of Therapy and Preventive Medicine, Branch of the Institute of Cytology and Genetics of SB RAS; Head of the Therapeutic Department, City Clinical Hospital No. 25, Novosibirsk, Russian Federation, olga.kharlamova2016@yandex.ru, https://orcid.org/0000-0001-8788-685X

Nikolaev Konstantin Yu. – Dr. Sci. (Med.), Professor, Principal Researcher with duties of the Head of the Laboratory of Emergency Therapy, Research Institute of Therapy and Preventive Medicine, Branch of the Institute of Cytology and Genetics of SB RAS; Novosibirsk State University, Novosibirsk, Russian Federation, nikolaevky@yandex.ru, https://orcid.org/0000-0003-4601-6203

Ragino Julia I. – Dr. Sci. (Med.), Professor, Corresponding Member of RAS, Head of the Research Institute of Therapy and Preventive Medicine, Branch of the Institute of Cytology and Genetics of SB RAS, Novosibirsk, Russian Federation, ragino@mail.ru, https://orcid.org/0000-0002-4936-8362

(✉) **Kharlamova Olga S.,** olga.kharlamova2016@yandex.ru

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