Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Immunology 215 (2020) 108426

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Letter to the Editor

On the molecular determinants of the SARS-CoV-2 attack

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection is linked to a respiratory syndrome with altered pulmonary and alveolar function that can lead to acute respiratory insufficiency and even death [1]. The molecular determinants and the mechanism that link SARS coronavirus infection to the pulmonary pathology are unknown. The scientific-clinical picture is further complicated by the fact that, while human SARS CoVs presents heavy pathogenicity leading to death, other human CoVs, such as HCoV-OC43 and HCoV-229E, are less pathogenic and cause common colds and mild lower respiratory tract infections [2].

Here, we explore the issue based on the rationale that, following a pathogen infection, peptide commonalities between the pathogen and the human proteins might trigger cross-reactions and a pathologic autoimmune sequela that might contribute to explain the pathogen associated diseases. Accordingly, we started the present study by investigating the spike glycoproteins from both SARS-CoV-2 and HCoV-229E for peptide sharing with human surfactant and related proteins.

Pulmonary surfactant plays a fundamental role in the physiology of ventilation by lowering the surface tension at the respiratory air-liquid interface within the alveoli. Excessively high values of surface tension would lead to alveolar collapse thus making ventilation and gas exchange impossible. Surfactant is produced by alveolar type II cells, secreted into the alveolar space, and it consists of lipids and proteins. The phospholipid component (dipalmitoylphosphatidylcholine, DPPC) reduces the surface tension, and the protein component - surfactant protein A (SP-A), surfactant protein B (SP-B), and surfactant protein C (SP-C) - together with a network of additional proteins regulate surfactant homeostasis and metabolism and, importantly, contribute to maintain immunological homeostasis in the lung, attenuating both infection and inflammation [4].

For the present study, pentapeptides were used as sequence probes since a peptide grouping formed by five amino acid (aa) residues is an immune molecular determinant that 1) can induce highly specific antibodies, and 2) determines antigen-antibody specific interaction [5]. Peptide sharing between spike glycoproteins and human surfactant-related proteins was analyzed as extensively described in previous publications [3 and refs. therein]. In brief. Spike glycoprotein primary sequences were dissected into pentapeptides offset by one residue and each viral pentapeptide was analyzed for matches within human proteins that had been retrieved from UniProtKB database (http://www.uniprot.org/) [6] using 'surfactant' as keyword. Next, the shared pentaptides were analyzed for presence in spike glycoproteins-derived immunoreactive epitopes by using the IEDB Immune Epitope DataBase (IEDB) [7] to analyze the immunological potential of the peptide sharing. The final results are reported in Table 1 and Table S1 and show that.

- quantitatively the peptide sharing of the two coronaviruses is similar, and both HCoV-229E and SARS-CoV-2 share many pentapeptides (19 and 24, respectively) with surfactant and related proteins,
- the peptide sharing between coronaviruses and surfactant-related proteins appears to be specific since none of the 43 shared pentapeptides described in Table 1 was found in infectious pathogens that do not cause lung disease such as rabies virus, rubella virus, hepatitis C virus, and human parvovirus B19. A paradigmatic control is parvovirus B19 that is transmitted through exposure to infected respiratory droplets, exhibits mild cold-like symptoms that are never linked to the virus [8], and associates with a wide spectrum of diseases — from erythema infectiosum and arthropathy to encephalopathy and autoimmune hepatitis — that does not include lung disorders [9].
- the peptide sharing described in Table 1 is also coronavirus-specific since not a single pentapeptide shared with surfactant and related proteins is common to the two coronaviruses,
- immunologically, the human vs SARS-CoV-2 peptide sharing is of high relevance with 13 out of the 24 shared pentapeptides to be found in 52 SARS-CoV-derived immunoreactive epitopes (Table 1 and Table S1). Instead, only one HCoV-229E pentapeptide (RLAAL) shared with the analyzed surfactant proteins is hosted in only one HCoV-derived epitope (Table 1 and Table S1).

Additionally, *Pneumocystis carinii* (NCBI:txid1408658), the pathogenicity of which is characterized by rapid onset and fast progression of severe pneumonia symptoms resulting in high mortality rate [10], was analyzed as control. *P. carinii* was found to contain 17 of the 24 pentapeptides shared between SARS-CoV-2 and surfactant molecules, ie, it contains EDDSE, FIEDL, FSQIL, GIGVT, GKQGN, IYQTS, LDSKT, LIRAA, LPPLL, LVLLP, NESLI, RAAEI, SNNSI, SSVLH, VFLVL, VLLPL, and VLPPL peptides. In other words, a high phenetic similarity - possibly indicating a similar pneumonia pathogenicity – exists between SARS-CoV-2 and *P. carinii* but not between the two coronaviruses.

To conclude. This letter addresses the issue of why SARS-CoV-2 attacks the respiratory system and reports on a vast peptide sharing between SARS-CoV-2 spike glycoprotein and surfactant-related proteins. Analyses using the Immune Epitope DataBase (IEDB) resource also show that many of the shared peptides are endowed with immunological potential. Given the caveat that the positive correlation of the pentapeptide sharing shown in Table 1 needs to be controlled by serologic validation, results suggest that immune responses following SARS-CoV-2 infection might lead to crossreactions with pulmonary surfactant and related proteins, and might contribute to the SARS-CoV-2-associated lung diseases. The data warn against using vaccines based on entire SARS-CoV-2 antigens to fight SARS-CoV infections, and highlight peptide uniqueness as a molecular concept for effective anti-CoV immunotherapy [3].

Funding

The Authors received no funding for this study.

https://doi.org/10.1016/j.clim.2020.108426
Received 25 March 2020; Received in revised form 13 April 2020; Accepted 16 April 2020
Available online 18 April 2020

Table 1
Peptides shared between spike glycoproteins from HCoV-229E and SARS-CoV-2 and human surfactant-related proteins, and immunological potential.

Spike glycoprotein pentapeptides[a]:		Human Surfactant-Related Proteins[d] [4]
HCoV-229E[b]	SARS-CoV-2[c]	
–	**VLPPL**	AA2BR. Adenosine receptor A2b. Highly and uniquely expressed in type II alveolar epithelial cells. Potent anti-inflammatory role
	LPPLL	
GVPQP	VFLVL	ABCA3. ATP-binding cassette sub-family A member 3. Crucial role in the formation of the storage compartment for surfactant, the lamellar body, and the transport of phospholipids in it; can cause chronic interstitial lung diseases
SIVSL ITGVP VELLK ELLKQ	HVNNS	ABCAC. ATP-binding cassette sub-family A member 12. ABCAC deficiency causes alveolar collapse and reduction of surfactant protein B
	GIGVT	
	NESLI	
IPFSL PFSLA	–	ADA2A. Alpha-2A adrenergic receptor. Dysfunctions of adrenoceptor mediated effects contribute to hyaline membrane syndrome, wet lung, bronchial asthma
PFSLA	RRARS	ADA2C. Alpha-2C adrenergic receptor. Pathology: see above
SQALQ	**CSCLK**	AGRF5. G-protein coupled receptor 116.Regulates lung surfactant homeostasis
GPLCV		C1QR1. Receptor for pulmonary surfactant protein A (SP-A)
–	**IYQTS**	CREB1. Cyclic AMP-responsive element-binding protein 1. CREB activation mediates anti-inflammatory activity of DPPC, the major phospholipid in pulmonary surfactant
RLAAL YTEVR VEKIH	–	CKAP4. Cytoskeleton-associated protein 4. SP-A binding protein in alveolar type II cells
–	**FIEDL**	DJC10. DnaJ homolog subfamily C member 10 aka ERdj5. Necessary for degradation of misfolded surfactant protein C
AMTNI	LDSKT	EPAS1. Endothelial PAS domain-containing protein 1 aka endothelial hypoxia-inducible factor-2α. Required for the maintenance of airway microvasculature
–	SNNSI	GATA6. Transcription factor GATA-6. Activates transcription of surfactant protein A
—	SSVLH NATRF	MY18A. Unconventional myosin-XVIIIa aka Surfactant protein receptor SP-R210. Expressed on the surface of type II pneumocytes; acts as a receptor of the surfactant-associated protein A that reduces T lymphocytes proliferation and maintains a state of hyporesponsiveness to prevent flooding of the air spaces with inflammatory cells
	FSQIL	
	LIRAA IRAAE	
	RAAEI	
QPLLL	–	NAPSA. Napsin-A. Involved in the C– and N-terminal processing of surfactant protein
–	LVLLP VLLPL	NPT2A. Sodium-dependent phosphate transport protein 2A. Essential since alveolar epithelial type II cells need phosphate for surfactant synthesis
	LVLLP	NPT2B. Sodium-dependent phosphate transport protein 2B. Function: see above
SYGVV	–	P2RY2. P2Y purinoceptor 2. The P2Y2 purinergic signaling pathway ultimately triggers exocytosis of lamellar bodies by ATII cells
LDTIQ	–	PCAT1. Lysophosphatidylcholine acyltransferase 1. Involved in phosphatidylcholine metabolism in pulmonary surfactant
YTGSL	–	PEPA3. Pepsin A-3. Component of pulmonary surfactant
LACAQ	–	PSPB. Pulmonary surfactant-associated protein B. Increases the collapse pressure of palmitic acid to nearly 70 millinewtons per meter. Involved in the structural organization of lamellar bodies
DSVSA	**DQLTP**	RCN3. Reticulocalbin-3. RCN3 deficiency causes death at birth owing to failure of functional maturation of alveolar epithelial type II cells during alveogenesis. This immaturity of type II cells is associated with a dramatic reduction in surfactant protein A and D, a disruption in surfactant phospholipid homeostasis, and a disorder in lamellar body
–	GKQGN	SFTPD. Pulmonary surfactant-associated protein D. Regulates innate immunity of the lung
–	ALTGI **EDDSE**	TTF1. Transcription termination factor 1. Modulates surfactant protein-B and −C promoters in lung cells

[a] Pentapeptides present in coronavirus spike glycoprotein-derived immunoreactive epitopes are given bold.
[b] Spike glycoprotein (Uniprot Accession: P15423) from HCoV-229E (NCBI:txid11137).
[c] Spike glycoprotein (id = QHD43416.1) from SARS-CoV-2, isolate Wuhan-Hu-1 (GenBank: MN908947.3).
[d] Human surfactant-related proteins are given by Uniprot names. Function/pathology data from www.uniprot.org, [4], and Omim and PubMed databases.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2020.108426.

References

[1] Z. Wang, B. Yang, Q. Li, L. Wen, R. Zhang, Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China, Clin. Infect. Dis. (2020), https://doi.org/10.1093/cid/ciaa272 pii:ciaa272.
[2] N. Satija, S.K. Lal, The molecular biology of SARS coronavirus, Ann. N. Y. Acad. Sci. 1102 (2007) 26–38.
[3] D. Kanduc, Y. Shoenfeld, From anti-EBV immune responses to the EBV diseasome via cross-reactivity, Infect. Int. 7 (2019) 1–21.
[4] J. Perez-Gil, Structure of pulmonary surfactant membranes and films: the role of proteins and lipid-protein interactions, Biochim. Biophys. Acta 2008 (1778) 1676–1695.
[5] D. Kanduc, Homology, similarity, and identity in peptide epitope immunodefinition, J. Pept. Sci. 18 (2012) 487–494.
[6] UniProt Consortium, UniProt: a worldwide hub of protein knowledge, Nucleic Acids Res. 47 (2019) D506–D515.
[7] R. Vita, S. Mahajan, J.A. Overton, S.K. Dhanda, S. Martini, J.R. Cantrell, et al., The immune epitope database (IEDB): 2018update, Nucleic Acids Res. 47 (2019) D339–D343.
[8] E.D. Heegaard, K.E. Brown, Human parvovirus B19, Clin. Microbiol. Rev. 15 (2002) 485–505.
[9] K. Broliden, T. Tolfvenstam, O. Norbeck, Clinical aspects of parvovirus B19 infection, J. Intern. Med. 260 (2006) 285–304.
[10] K. Sokulska, M. Kicia, M. Wesołowska, A.B. Hendrich, Pneumocystis jirovecii–from a commensal to pathogen: clinical and diagnostic review, Parasitol. Res. 114 (2015) 3577–3585.

Darja Kanduc[a,*], Yehuda Shoenfeld[b,c]
[a] *Department of Biosciences, Biotechnologies, and Biopharmaceutics, University of Bari, Italy*
[b] *Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, affiliated to Tel-Aviv, University School of Medicine, Tel-Hashomer, Israel*
[c] *I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian, Federation, Sechenov University, Moscow, Russia*
E-mail address: dkanduc@gmail.com (D. Kanduc).

* Corresponding author.