Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity

James Lyons-Weiler

The Institute for Pure and Applied Knowledge, USA

ARTICLE INFO

Keywords:
SARS-CoV-2
COVID-19
Autoimmunity
Pathogenic priming
Immunome Enhancement

ABSTRACT

Homology between human and viral proteins is an established factor in viral- or vaccine-induced autoimmunity. Failure of SARS and MERS vaccines in animal trials involved pathogenesis consistent with an immunological priming that could involve autoimmunity in lung tissues due to previous exposure to the SARS and MERS spike protein. Exposure pathogenesis to SARS-CoV-2 in COVID-19 likely will lead to similar outcomes. Immunogenic peptides in viruses or bacteria that match human proteins are good candidates for pathogenic priming peptides (similar to the more diffuse idea of “immune enhancement”). Here I provide an assessment of potential for human pathogenesis via autoimmunity via exposure, via infection or injection. SARS-CoV-2 spike proteins, and all other SARS-CoV-2 proteins, immunogenic epitopes in each SARS-CoV-2 protein were compared to human proteins in search of high local homologous matching. Only one immunogenic epitope in a SARS-CoV-2 had no homology to human proteins. If all of the parts of the epitopes that are homologous to human proteins are excluded from consideration due to risk of pathogenic priming, the remaining immunogenic parts of the epitopes may be still immunogenic and remain as potentially viable candidates for vaccine development. Mapping of the genes encoding human protein matches to pathways point to targets that could explain the observed presentation of symptoms in COVID-19 disease. It also strongly points to a large number of opportunities for expected disturbances in the immune system itself, targeting elements of MHC Class I and Class II antigen presentation, PD-1 signaling, cross-presentation of soluble exogenous antigens and the ER-Phagosome pathway. Translational consequences of these findings are explored.

1. Introduction

Autopsies of Chinese citizens who have died from COVID-19 following SARS-CoV-19 infection show evidence of interstitial changes, suggesting the development of pulmonary fibrosis [1]. This suggests, at least partly, an autoimmunology basis of the pathogenesis of COVID-19. A number of causal bases of autoimmunity from exposure to viral epitopes is well established, whether the route of administration be by exposure via infection or vaccination. Systemic respiratory viral infections can have numerous serious health effects, including dyspnea, hypoxemia, dysuria, meningitis, low blood pressure, shock and death. Sequelae of viral infections can include various short-term and sometimes permanent effects on the central nervous system, via direct injury to CNS tissue due to viral replication (viral neuropathology) or due to the host immune system learning to attack CNS tissue (viral neuroimmunopathology). The public health consequences from some viruses can include impaired immunity, encephalitis, and long-term neurological diseases such as demyelinating disorders and relapsing events such as those seen in multiple sclerosis (MS).

Both genetic and environmental factors are thought to contribute both to the severity of viral infections, and in determining who will develop autoimmune conditions. Various specific mechanisms (etiologies) of autoimmunity are recognized as plausible in viral induction of autoimmunity, including epitope spreading, molecular mimicry, cryptic antigen, and bystander activation, each a plausible etiological mechanism responsible for activating self-reactive (SR) immune cells.

Mortality in SARS-CoV-2 infection from COVID-19 is highly age-dependent, with older patient having the highest probability of death. The etiology of the age-specific mortality seen in COVID-19 is largely unknown. SARS-CoV and SARS-CoV-2 coronaviruses targets the epithelial cells of the respiratory tract, resulting in diffuse alveolar damage. Other tissues are obviously also potential targets for viral immunopathology, including mucosal cells of the intestine, epithelial cells of the kidneys, brain cells (neurons), and cellular components of the immune system. In severe cases of SARS, and likely in SARS-CoV-2, this viral targeting leads acutely to pneumonia. Exposure to other viral and
ambivalent antigens are known causal factors in chronic autoimmune diseases of the airways including asthma. The role of autoimmunity in enhancing the severity of secondary exposures following prior infection or vaccinations has been given little consideration.

Among coronaviruses, the spike surface glycoprotein is known to play a role in neuroinmunopathology. However, the SARS-CoV-2 virus has numerous other proteins and polyproteins, each which may serve as an antigen source during infection leading to autoimmunity, the immune system presents those proteins, like all human proteins, as “normal”. T-cells are trained to recognize a normal protein shape in the thymus. Biomimicry between or among proteins from pathogens (infection or injection) can conflate the signaling by creating a population of memory B-cells, especially if the reaction switches from a Th-1 toward a Th-2 response.

In SARS, a type of “priming” of the immune system was observed during animal studies of SARS spike protein-based vaccines leading to increased morbidity and mortality in vaccinated animals who were subsequently exposed to wild SARS virus. The problem, highlighted in two studies, became obvious following post-vaccination challenge with the SARS virus [2], found that recombinant SARS spike-protein-based vaccines not only failed to provide protection from SARS-CoV infection, but also that the mice experienced increased immunopathology with eosinophilic infiltrates in their lungs. Similarly [3], found that ferrets vaccinated against SARS-CoV also developed a strong inflammatory response in liver tissue (hepatitis). Both studies suspected a “cellular immune response”.

These types of unfortunate outcomes are sometimes referred to as “immune enhancement” ; however, this nearly euphemistic phrase fails to convey the increased risk of illness and death due to prior exposure to the SARS spike protein. For this reason, I refer to the concept as “pathogen priming”; the peptides with pathogenic potential therefore are referred to as “putative pathogenic priming peptides”.

In this study, I present the likely human epitopic targets of biomimicry-induced autoimmunological components of morbidity and mortality caused by SARS-CoV-2 infection. This is achieved via bioinformatics analysis of the homology between highly immunogenic SARS-CoV-2 epitopes and human proteins to promote comprehension of the etiologies of pathogenesis of SARS-CoV-2 in COVID-19. Thirty-seven identified proteins in SARS-CoV-2 were evaluated.

2. Methods

The investigative data analysis procedure included the following steps. First, for each ORF (open reading frame) reported as a canonical CDS (coding sequence) for the SARS-CoV-2 virus, flagged (significant) immunogenic SARS-CoV-2 epitopes were found using SVMTriP (http://sysbio.unl.edu/SVMTriP; [4]). These immunogenetic epitopes were then compared to human proteins using p-Blast (settings optimized for short sequences) against the Homo sapiens entries in the Protein Databank (https://blast.ncbi.nlm.nih.gov/). A list of human peptides with high local homology was compiled and their roles in the pathogenesis of COVID-19 from SARS-CoV-2 infection noted. The protein entries were mapped to nucleotide accession number, which were used to map as a gene set to pathways via Reactome (Reactome.org). Tissue distribution of the targeted proteins was explored using the Protein Atlas (ProteinAtlas.org).

3. Results

Thirty-seven SARS-CoV-2 proteins were downloaded from the NCBI SARS-CoV-2 NCBI resource. Of these, 8 proteins had no recognizably immunogenic peptides. The remaining proteins had between one and six immunogenic peptides (Table 1). The proteins with the largest number of immunogenic peptides were the Spike, or S protein (N = 6 in total), and the non-structural protein NS3 (also N = 6; Table 1). All of the proteins had at least one match to human proteins except one, specifically nucleocapsid phosphoprotein (epitope ’QQQQGQTVKKSAAEASKP’), however even nucleocapsid phosphoprotein has one other epitope (’RRGPEQTQGNFGDQELIRQG’) which has a localized match to the immunoglobulin heavy chain junction region (MOO20493; GNFGDQ).

Remarkably, over 1/3 (11/27) of the immunogenic proteins in SARS-CoV-2 have potentially problematic homology to proteins that are key to the human adaptive immune system (emboldened in Table 1). Mapping of the overall gene list to Pathways via Reactome.org revealed that many functions of the human adaptive immune system might be impacted via autoimmunity against these proteins and their interactors, including MCH Class I and Class II antigen presentation, PD-1 signaling, cross-presentation of soluble exogenous antigens and the ER-Phagosome pathway.

4. Discussion

These results could explain in part the high rates of serious illness associated with SARS-CoV-2. They could also explain the lengthy asymptomatic period prior to presentation of symptoms characteristic of COVID-19. SARS-CoV-2 could impair the immune response, at first, and then, over time, the immune system could begin to mount an attack on the myriad of proteins. Most of the identified human target proteins had low overall homology but high local homology over short segments of their epitopes. The Protein Atlas results indicated that numerous proteins are expressed in a variety of tissues as noted in Table 1.

Unintended consequences of pathogenesis from vaccines are not new, nor are they unexpected. They are unanticipated only if those who develop them do not include available knowledge in their formulation plan. For example, the H1N1 influenza vaccine used in Europe led to narcolepsy in some patients, resulting from homology between the human hypocretin (aka, orexin) receptor 2 molecule and proteins present in the vaccine. This was established via the detection of cross-reactive antibodies in the serum of patients who develop narcolepsy following H1N1 vaccination in Europe [5].

The fact that pathogenic priming may be occurring involving autoimmunity against multiple proteins following CoV vaccination is consistent with other observations observed during autoimmunity, including the release of proinflammatory cytokines and cytokine storm. Similar to the SARS-CoV animal studies [6], found that mice vaccinated against MERS-CoV (Middle East Respiratory Syndrome) development exaggerated pulmonary immunopathology when challenged with the MERS virus following vaccination. They reported that lung mononuclear infiltrates were observed in all groups after virus challenge, and that increased infiltrates that contained eosinophils and the eosinophil promoting IL-5 and IL-13 cytokines were observed only in the vaccinated animals.

Pathogenic priming may be more or less severe in vaccine or infection induced immune responses to some proteins than for others due to original antigenic sin; the immunologic reaction against self-antigens may be made less severe as fast-evolving viruses evolve away from the original vaccine type. Thus, the screening of immunogenic epitopes for pathogenic priming potential via homology may be augmented by studies of autoantibodies that cross-react with epitopes included in vaccines.

SARS-CoV-2 has some unexplained pathogenic features that might be related to the table of putative pathogenic priming peptides. Exposure to these specific peptides - via either infection or vaccination - might prime patients for increased risk of enhanced pathogenicity during future exposure due to either future pandemic or outbreaks or via universal vaccination programs. While the mechanisms pathogenesis of COVID-19 are still poorly understood, the morbidity and mortality of SARS has been extensively studied. Thus, the involvement of pathogenic priming in re-infection by COVID-19 is a theoretical possibility; of course no vaccine against SARS-CoV-2 has yet been tested in animals and therefore we do not yet know if pathogenic priming is in fact expected. Such studies should be undertaken before use of any vaccine against SARS-CoV-2 is
| Protein Accession | SARS-CoV-2 Protein Name | Immunogenetic epitope(s) | Accession | Human Protein Name | Putative pathogenic priming peptide (self-antigen) | Tissue RNA/Protein Expression |
|------------------|-------------------------|--------------------------|-----------|--------------------|----------------------------------------------------|-----------------------------|
| QHI73821        | ORF1ab polyprotein (partial) | RARTVAGVSCSTMTNRQFH       | CCO13833  | alternative protein TJP1 | TVICDTMLCPKVYFTNTRQF | nearly ubiquitous B-cells, plasma cells |
| QHI73974        | ORF1ab protein | VATLQAEVNTGKLDCSKVI       | NP_001339255 | la-related protein 4 (LARP4) | EEEVGLFKSENCPKVI | ubiquitous |
| QIA98594         | ORF1ab polyprotein | DRRATCFSTASDTYACWHHS      | AIT38911  | IGHJCVR             | DTYACW                | B-cells, plasma cells |
| QIA98597         | ORF5a protein | YQIGGYTEKWESGVKCCV       | AAH82244  | PH domain and leucine rich repeat protein phosphatase 1 (EPPP1) | GYTEASAVKNKCV | brain, lung, kidney |
| QIA98604         | ORF7a protein | GVKHVYQLRARSVSPKLRFR      | XP_016871107 | soritlin related VPS10 domain containing receptor 1 (SORCS1) | GIKHVVQ | brain, gastrointestinal tract, kidney |
| QIA98601         | ORF8 protein | FYSKWIYRIGARKSAPLIE      | EAX03800  | ankyrin repeat and sterile alpha motif domain containing 1A (ANKS1A) | RVGVRKSAVPL | eye, lung, gastrointestinal tract, liver |
| YP_009725310     | endoRNAse | LGIEAVKTPFNYYKCDVGGV      | 3SWR_A   | DNA methyltransferase | VGEAVTDGGKSSYKKV | brain, lung, gastrointestinal tract, liver |
| YP_009725308     | helicase | ATNYDLSVSNAARLKHYYH      | MOQ41699  | B-cells, plasma cells |
| YP_009725297     | leader protein | LPQLEQYPYVFIRSDRTAP      | 5S2F_L    | Chain L, 2A10 antibody FAB fragment light chain glutamate ionotropic receptor kainate type subunit 2 (GRIK2) | PVFGGKGTRKRAADAAP | brain, kidney |
| QHO62114         | matrix protein | FIASFRLFARKRSMWSFNP       | MCD74337  | BHCJ                | ARERGSWSFDP | B-cells, plasma cells |
| QIA98599         | membrane glycoprotein M protein | FIASFRLFARTRSMWSFNP       | MCD74337  | BHCJ                | ARERGSWSFDP | B-cells, plasma cells |
| QIH45026         | M protein | FIASFRLFARKRSMWSFNP       | MCD74337  | BHCJ                | ARERGSWSFDP | B-cells, plasma cells |
| YP_009725298     | nonstructural protein NS2 | DGSIQYSLLRLDAMMFTSDL      | NP_001165883 | VANGL planar cell polarity protein 1(VANGL1) | GIVQYAVSLVDALLF | ubiquitous |
| YP_009725298     | nonstructural protein NS2 | VEKKKLDGFMRIRSVYPVA      | EAW65335  | adaptor protein containing pH domain, PTB domain and leucine zipper motif 1, isoform CRA_a | LVDAMMF | brain, kidney |
| YP_009725299     | nonstructural protein NS3 | LGYVHTHGLNEAARYMRSLSL    | AAC64695  | supervillin (SVIL) | VTHRLLEEDTPRYM | ubiquitous except eye, blood |
| EEVGHTDMAAYVDNSSLTI | Rap guanine nucleotide exchange factor 2 (RAGP2E) | XP_016864345 | MASYVDNS | brain, bone marrow (RNA) |
| EEVGHTDMAAYVDNSSLTI | Rap guanine nucleotide exchange factor 2 (RAGP2E) | XP_016864345 | ESSSLT | brain, bone marrow (RNA) |
| QTTLKGVAAVMYMTLSYEQ | T-cell receptor beta chain variable region N-acetyltransferase 9 isoform | ANO56871 | MYLCASSLSYEQ | lung, bone marrow, blood |
| QTTLKGVAAVMYMTLSYEQ | N-acetyltransferase 9 isoform | NP_001292017 | GTEAVLAM--LSYE | spleen |

(continued on next page)
Table 1 (continued)

| Protein Name                  | Accession | Immunogenetic epitope(s) | Accession | Human Protein Name | Putative pathogenic priming peptide (self-antigen) | Tissue RNA/Protein Expression |
|-------------------------------|-----------|--------------------------|-----------|-------------------|---------------------------------------------------|-------------------------------|
| SARS-CoV-2 nonstructural protein NS4 |          | VQESDGYIATNGPLKVG GCC    | CAA56042  | protein-tyrosine-phosphatase | IGJHCVR                          | ubiquitous                     |
|                               |          |                          |           |                   |                                                   |                               |
| 18 YP_009725304               | nonstructural protein NS8 | AVANGSEVVLKRLKSLNV       | AAH11491  | Promodomain and WD repeat domain containing 3(BRWD3) |                                                     |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 19 YP_009725305               | nonstructural protein NS9 | AKVTSAQMFTLMRLKLDN       | IA4P_A    | S100 calcium binding protein A10(S100A10) Antigen 3-like protein 1 |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 20 YP_009725306               | nonstructural protein NS10 | TLKNTVCTVCGMWKGYGGSC     | EAW66814  | Cartilage oligomeric matrix protein | KGYYGSC                          | adaptose tissue, muscle       |
|                               |          |                         |           |                   |                                                   |                               |
| 21 YP_009725307               | RNA-dependent RNA polymerase | QYIRLHDELTGHMLDMYSV      | NP_001271153 | Elongator acetyltransferase complex subunit 3 (ELP3) |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 22 QIH45023                   | S protein | LNEVAKNNLSELDQELGG       | EAW96281  | Hedgehog acetyltransferase (HHTAT) |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 23 QIA98596                   | Spike protein | LNEVAKNLSELDQELGG       | XP_011535432 | Coiled-coil domain-containing protein 175 |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 24 YP_009725301               | 3C-like proteinase | AENVTELGFKDCSVTGLHP      | AAH22377  | ribonucleoprotein domain family member 4 (LARP4) |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 25 QIA98602                   | nucleocapsid phosphoprotein | HLSYDTFKTFKTEGLCVDIPG  | XP_024308868 | Titin |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 26 QHR63265                   | nucleocapsid phosphoprotein | RRGPEQGFGQDGDFQERBQG     | MOO20493  | heart muscle, skeletal muscle |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 27 QHR63267                   | nucleocapsid phosphoprotein | VGVHIVYQLRARSVPKLFIR    | XP_016871107 | VPS10 domain-containing receptor |                                                   |                               |
|                               |          |                         |           |                   |                                                   |                               |
| 28 QIA98602                   | nucleocapsid phosphoprotein | QQQQGQTFTKSAAEASKPX    | n/a       | Ankyrin repeat and sterile alpha motif domain containing 1A |                                                   |                               |

(continued on next page)
used in humans.

Declaration of competing interest

Dr. Lyons-Weiler has, in the past, served as expert witness in the National Vaccine Injury Compensation Program.

Acknowledgements

This research was funded by private donations from the public to The Institute for Pure and Applied Knowledge.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtauto.2020.100051.

Statement of interests

The author has served as an expert witness in the US National Vaccine Injury Compensation Program.

References

[1] H. Shi, et al., Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet (2020), https://doi.org/10.1016/S1473-3099(20)30086-4.
[2] D. Deming, T. Sheahan, M. Heise, Vaccine efficacy in senescent mice challenged with recombinant SARS-CoV bearing epidemic and zoonotic spike variants, PLoS Med. 3 (12) (2006) e525, 2006 Dec.
[3] H. Weingartl, M. Czub, S. Czub, Immunization with modified vaccinia virus Ankara-based recombinant vaccine against severe acute respiratory syndrome is associated with enhanced hepatitis in ferrets, J. Virol. 78 (22) (2004 Nov) 12672-12676.
[4] B. Yao, L. Zhang, S. Liang, C. Zhang SVMTrilP, A method to predict antigenic epitopes using support vector machine to integrate tri-peptide similarity and propensity, PloS One 7 (9) (2012), e45152.
[5] S.S. Ahmed, W. Volkmuth, J. Duca, Antibodies to influenza nucleoprotein cross-react with human hypocretin receptor 2, Sci. Transl. Med. 7 (294) (2015 Jul 1), https://doi.org/10.1126/scitranslmed.aab2354, 294ra105.
[6] A.S. Agrawal, X. Tao, A. Algaissi, Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus, Hum. Vaccines Immunother. 12 (9) (2016 Sep) 2351-2356, https://doi.org/10.1080/21645515.2016.1177688, Epub 2016 Jun 7.

| Protein Accession | SARS-CoV-2 Protein Name | Immunogenic epitope(s) | Accession | Human Protein Name | Putative pathogenic priming peptide (self-antigen) | Tissue RNA/Protein Expression |
|-------------------|-------------------------|-----------------------|-----------|--------------------|-----------------------------------------------|-----------------------------|
| QIA98603          | ORF10 protein           | MGYINVFAPFPTYSSL-LCRMNSRN1AQVDVVNFNLTV | n/a       | n/a                | n/a                                           | n/a                         |
| QHR63254          | nonstructural protein NS6 | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |
| QHR63276          | nonstructural protein NS7b | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |
| QHW06053          | orf6 protein            | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |
| QIA20050          | ORF7b protein           | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |
| YP.009725311      | 2'-O-ribose methyltransferase | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |
| YP.009725309      | 3'-to-5' exonuclease E protein | n/a                   | n/a       | n/a                | n/a                                           | n/a                         |

immunoglobulin heavy chain region