

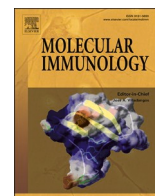


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Untangling COVID-19 and autoimmunity: Identification of plausible targets suggests multi organ involvement

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ABSTRACT

Underlying mechanisms of multi-organ manifestations and exacerbated inflammation in COVID-19 are yet to be delineated. The hypothesis of SARS-CoV-2 triggering autoimmunity is gaining attention and, in the present study, we have identified 28 human proteins harbouring regions homologous to SARS-CoV-2 peptides that could possibly be acting as autoantigens in COVID-19 patients displaying autoimmune conditions. Interestingly, these conserved regions are amongst the experimentally validated B cell epitopes of SARS-CoV-2 proteins. The reported human proteins have demonstrated presence of autoantibodies against them in typical autoimmune conditions which may explain the frequent occurrence of autoimmune conditions following SARS-CoV-2 infection. Moreover, the proposed autoantigens' widespread tissue distribution is suggestive of their involvement in multi-organ manifestations via molecular mimicry. We opine that our report may aid in directing subsequent necessary antigen-specific studies, results of which would be of long-term relevance in management of extrapulmonary symptoms of COVID-19.

1. Introduction

1.1. Autoimmune conditions following COVID-19

Even after a year of the pandemic's onset, several significant aspects of COVID-19 pathogenesis have remained unexplained. Severe COVID-19 cases are often associated with extrapulmonary tissue damage, multi-organ failure and death, precise immunological mechanisms for which are yet to be delineated. Over the course of the pandemic, cases of COVID-19 affected individuals developing autoimmune/auto-inflammatory conditions have also been reported frequently (Ehrenfeld et al., 2020; Galeotti and Bayry, 2020; Novelli et al., 2021; Rodríguez et al., 2020). Interestingly, children - the least susceptible age group for the viral disease, were affected by autoimmune conditions secondary to the actual disease. Incidences of Kawasaki disease (Ouldali et al., 2020; Verdoni et al., 2020), multisystem inflammatory syndrome in children (MIS-C) with symptoms overlapping those of Kawasaki disease (Gruber et al., 2020; Rowley, 2020) and paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) leading to paediatric ICU admissions (Davies et al., 2020) increased significantly in them upon SARS-CoV-2 exposure/infection. Older age groups displayed

a wider variety of autoimmune diseases like Guillain Barre Syndrome (GBS) (Mbchb et al., 2020), Graves' disease (Mateu-Salat et al., 2020), autoimmune and rheumatic musculoskeletal diseases (Shah et al., 2020), autoimmune haemolytic anaemia (Lazarian et al., 2020; Lopez et al., 2020), autoimmune thrombocytopenia (Revuz et al., 2020) and anti-phospholipid syndrome (Zhang et al., 2020b) with a wide-spread occurrence (Ehrenfeld et al., 2020; Novelli et al., 2021; Rodríguez et al., 2020). During the pandemic, these conditions precipitated in genetically predisposed individuals by exposure to or infection by SARS-CoV-2. The symptoms occurred simultaneously or at the end stage of infection. Woodruff et al.'s (2020) recent report of intersecting extrafollicular B cell responses indicates a more intimate relationship between COVID-19 and autoimmune conditions rather than a mere co-occurrence. The authors also pointed out the need for characterising mechanistic underpinnings of such autoimmune-like responses associated with severity of the disease. Hence, the initial notion of COVID-19 as a 'stand-alone infectious disease' has been extensively refined. Association of COVID-19 and autoimmunity is thus attracting significant attention.

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1.2. SARS-COV-2 as a trigger for autoimmunity

Multiple immunological changes associated with autoimmune/autoinflammatory conditions have been observed in critical COVID-19 patients (Rodríguez et al., 2020). An imbalanced adaptive immune response observed during COVID-19 is a known feature of pathogenesis for several autoimmune/autoinflammatory conditions (Ehrenfeld et al., 2020; Rodríguez et al., 2020; Woodruff et al., 2020). Additionally, overactivated innate immune cells, immune-mediated thrombotic and vascular events are shared features between several autoimmune conditions and COVID-19 (Liu et al., 2021). Along with these observations, the worldwide clinical reports of typical autoimmune conditions following COVID-19 (Liu et al., 2021; Novelli et al., 2021) suggest a causal link between the two.

Several viruses are known to act as environmental triggers for autoimmune and/or autoinflammatory conditions via molecular mimicry, bystander activation, epitope spreading or viral persistence (Smatti et al., 2019). SARS-CoV-2 was also known to elicit cross-reactive antibodies leading to autoimmune reactions (Salle, 2021). SARS-CoV-2 as a trigger for autoimmunity is thus emerging as a strong, rational hypothesis demanding further studies to delineate the intricacies involved.

The coronavirus disease is thought to progress on a trajectory of 4 overlapping stages (Rodríguez et al., 2020). After infecting host cells by fusion of spike protein with angiotensin converting enzyme 2 (ACE2) receptor, the first stage (the viral phase) is either asymptomatic or characterised by mild fever, cough, fatigue and headache. The second phase ensues after host-pathogen interactions which may result in hyperresponsiveness of the host's immune system. The third stage is hypercoagulability and the fourth is organ failure due to hyperinflammation. Towards the last stage i.e. hyperinflammation, cytokine storm syndrome causes the patient to move into critical zone, ensues organ damage, ARDS, thrombosis and potentially death. About 80 % of the infected individuals do not proceed beyond stage one and recover after presentation of mild or no symptoms (Chen et al., 2020; Fafi-Kremer et al., 2020; Team, n.d.). The clinical outcomes may be worse in individuals genetically susceptible to autoimmune conditions as the virus can trigger autoimmune reactions (Ehrenfeld et al., 2020; Rodríguez et al., 2020) by mechanisms hypothesised as -

a) Via bystander activation: Cytokine storm syndrome may trigger activation of T cells and B cells and lead to autoimmune conditions like ARDS. So far, no evidence for this particular hypothesis has been reported in the context of COVID-19 (Ehrenfeld et al., 2020; Rodríguez et al., 2020).

b) Via molecular mimicry: Preliminary reports mentioned below supported the hypothesized causal link between SARS-COV-2 infection and autoimmunity via cross-reactivity. The proteome of SARS-COV-2 shares three sequences (six amino acids length) GSQASS, LNEVAK, and SAAEAS with three proteins present in the human brainstem preBötC. The three sequences are housed on experimentally validated SARS-COV-2 epitopes (Lucchese and Flöel, 2020a). Another study investigated the spike glycoprotein and human surfactant related proteins for shared peptide sequences and found several shared sequences that could potentially be immunologically reactive regions (Kanduc and Shoefeld, 2020). Evidence for autoimmunity secondary to COVID-19 by molecular mimicry is rapidly accumulating and hence currently it appears to be the most likely mechanism.

c) Autoimmunity in critical COVID-19 cases can also be initiated by NETosis stimulated by SARS-COV-2 (Arcanjo et al., 2020) wherein autoantigens are exposed and could lead to expansion of autoreactive T cells (Shah et al., 2020). Viral persistence as a mechanism cannot be ruled out entirely but it is less likely as some cases infected with other

members of coronavirus family have reported complete clearance (Shah et al., 2020).

On this background, we hypothesise a role of autoreactivity via molecular mimicry at the basis of extrapulmonary manifestations and exacerbated inflammation observed in subpopulations of COVID-19 patients. Aim of the present study was to predict plausible human antigens involved in the pathogenesis of COVID-19 to better understand the autoimmune conditions and multiorgan involvement occurring post-SARS-CoV-2 infection. Our study differs from the other similar studies mentioned above as our results possess a broader scope of interpretation. In addition to potentially explaining the occurrence of typical autoimmune conditions post-infection, the tissue distribution of reported proteins hints at their involvement in multi-organ damage and hyper stimulating the immune system. Subject to experimental validation, our results have the potential of explaining an umbrella of yet unexplained, unusual clinical manifestations associated with COVID-19.

2. Methods

Sequences of immunogenic B-cell epitopes of SARS-CoV-2 were collected from the literature (with keywords “immunogenic regions SARS-CoV-2” and “B-cell epitopes SARS-CoV-2” for PubMed). The ones which were experimentally identified/validated were selected for further analysis. The BLASTp program (<https://blast.ncbi.nlm.nih.gov/Blast.cgi>) (Altschul et al., 1990) was used to search for human proteins homologous to the selected epitopes (with search set in UniProtKB/Swiss-Prot limited to *Homo sapiens*, algorithm parameters set to default and number of results limited to top 100 hits). Using Open Targets Platform (Carvalho-Silva et al., 2019) server, the proteins obtained from BLASTp were manually curated to identify the ones against which autoantibodies have been shown to be elicited in autoimmune conditions. The tissue-specific expression patterns of the human proteins reported here were obtained from the human protein atlas (<http://www.proteinatlas.org/>) (Uhlén et al., 2015).

3. Results

The SARS-COV-2 B-cell epitopes reported here homologous to regions on human proteins were collected from the literature. Though housed on multiple viral proteins, majority of them are present on the spike glycoprotein (Table 1). Out of the 11 viral epitopes found to be homologous with human autoimmunity-related proteins, 2 are on the nucleocapsid phosphoprotein (153-170 and 370-375) (Amrun et al., 2020; Lucchese and Flöel, 2020b), 1 on Orf1ab polyprotein (1205-1210) (Lucchese and Flöel, 2020b) and 8 on spike glycoprotein (221-245, 261-285, 450-469, 480-499, 542-566, 574-593) (Amrun et al., 2020; Yi et al., 2020; Zhang et al., 2020a). Two of them (450-469, 480-499) are within the receptor binding domain (RBD) (319-541). The above mentioned 11 epitopes are homologous to peptide sequences from total 28 human proteins with a widespread tissue distribution ranging from nervous system specific localisation to ubiquitous presence. These proteins are known to be acting as targets for autoantibodies generated during typical autoimmune conditions, as listed in Table 1. Multiple cases with some of the typical autoimmune conditions (from Table 1) occurring post SARS-COV-2 infection have also been reported (Table 2). This suggests that the human proteins reported here might be involved in the observed onset of post-COVID-19 autoimmune conditions. Moreover, the previously demonstrated presence of antibodies against such widely distributed targets also supports our speculation of ‘autoreactivity at the basis of multi-organ effects’. We have previously reported titin (TTN), ryanodine receptor 2 (RYR2) and heat shock protein

Table 1

Possible self-antigens homologous to B cell epitopes of SARS-CoV-2 (Minota et al., 1988; Mantej et al., 2019; Margutti et al., 2008; Labrador-Horrillo et al., 2014; Shi et al., 2015; Bartos et al., 2007; Oh et al., 2013; Fialová et al., 2013; Takahashi et al., 2010; Kurasawa et al., 2010; Oliveira et al., 2013; Nauert et al., 1997; Sasaki et al., 2001; Saxena et al., 1994; Mimouni et al., 2004; Foedinger et al., 1995; Hedstrand et al., 2001; Tsouris et al., 2020; Yamamoto et al., 2001; Sköldberg et al., 2002; Stojanov et al., 1996; Mygland et al., 1992; Rogers et al., 1994; Ooka et al., 2003; Landegren et al., 2015; Hagberg et al., 2015; Tsuruha et al., 2001; Maciejewska-Rodrigues et al., 2010; Shimizu et al., 2019; Lai et al., 2010; Mei et al., 2018).

SARS-COV-2 protein	Human protein with homologous sequence	SARS-COV-2 epitope sequence (homologous sequence in red, start and end residue numbers in parenthesis)	Autoimmune conditions with demonstrated presence of antibodies against the human protein	Cellular and tissue distribution of the human proteins
Nucleocapsid Phosphoprotein	Heat Shock Protein 90 (HSP90AB1)	KDKKKK (370-375)	Systemic Lupus Erythematosus (Minota et al., 1988), Rheumatoid Arthritis (Mantej et al., 2019)	Cytoplasmic expression in most tissues
Nucleocapsid Phosphoprotein	RalA Binding Protein 1 (RALBP1)	KDKKKK (370-375)	Behçet disease (Margutti et al., 2008), Systemic Lupus Erythematosus (Margutti et al., 2008)	Cytoplasmic and membranous expression in most tissues
Nucleocapsid Phosphoprotein	Interferon induced with helicase C domain 1 (IFIH1)	KDKKKK (370-375)	Dermatomyositis (Labrador-Horrillo et al., 2014)	Cytoplasmic expression in most tissues
Nucleocapsid Phosphoprotein	Prohibitin (PHB)	NNAAIVLQLPQGTTLPKG (153-170)	Rheumatoid Arthritis (Shi et al., 2015)	General cytoplasmic expression with a granular pattern
ORF1ab Polyprotein	Neurofilament medium (NEFM)	EIPKKE (1205-1210)	Multiple Sclerosis (Bartos et al., 2007)	Distinct cytoplasmic expression in CNS and peripheral nerves
ORF1ab Polyprotein	Coagulation factor VIII (F8)	EIPKKE (1205-1210)	Autoimmune Haemophilia (Oh et al., 2013)	Extracellular deposits and cytoplasmic expression in most tissues, secreted

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family A (Hsp70) member 5 (HSPA5) as possible autoantigens for antibodies in COVID-19 patients with neurological conditions (Mohkhedkar et al., 2020). The authors of the primary article had reported a unique immunofluorescence pattern on rodent tissues on staining with COVID-19 patients' sera (Schiaffino et al., 2020). The epitopes and associated autoimmune conditions reported in the above-mentioned correspondence article have been marked with asterisk in the table. Taken together, our observations strongly suggest molecular mimicry between SARS-CoV-2 and human proteins which may lead to varied clinical manifestations.

4. Discussion

Sufficient evidence for extrapulmonary aftermath of SARS-CoV-2 infection has accumulated (Gupta et al., 2020; Mbchb et al., 2020). For example, multiple studies have documented myocardial inflammation

and abnormal echocardiograms in a significant proportion of patients affected and recovered from COVID-19 (Dweck et al., 2020; Puntmann et al., 2020). There are also reports of GBS (Abu-Rumeileh et al., 2020) and thyroiditis (Mateu-Salat et al., 2020) secondary to COVID-19. Such multi-organ 'effects' don't necessarily stem from multi-organ 'infection'. Even though ACE2 and Transmembrane protease, serine 2 (TMPRSS2) are necessary for infecting cells, their presence isn't always sufficient (Muus et al., 2020). Hence, tissues expressing both might not be infected by the virus but can be damaged during the course of the disease. These reports together suggest existence of mechanisms other than direct viral infection for multiorgan effects. A prominently hypothesized mechanism is of autoimmunity via molecular mimicry triggered by SARS-CoV-2 (Angileri et al., 2020; Cappello, 2020; Sedaghat and Karimi, 2020). SARS-CoV (virus from the 2003 pandemic) is known to elicit cross-reactive autoantibodies (Lin et al., 2005). Similarly, SARS-CoV-2 was also hypothesized to possess cross-reactive epitopes that could

Table 1 (continued)

				into blood
ORF1ab Polyprotein	Neurofilament heavy (NEFH)	EIPKEE (1205-1210)	Multiple Sclerosis (Fialová et al., 2013)	Selective expression in CNS, peripheral nerves and glandular cells of prostate
ORF1ab Polyprotein	Angiotensin converting enzyme 2 (ACE2)	EIPKEE (1205-1210)	Connective tissue disorders (Takahashi et al., 2010)	Membranous expression in proximal renal tubules, intestinal tract, seminal vesicle, epididymis, exocrine pancreas and gallbladder. Expressed in Sertoli and Leydig cells, and trophoblasts. Membranous expression in ciliated cells in nasal mucosa, bronchus, and fallopian tube. Expressed in endothelial cells and pericytes in many tissues.
Spike glycoprotein (S2 subdomain)	Platelet derived growth factor receptor beta (PDGRFB)	GIAVEQDKNTQEVFAQVK (769-786)	Systemic Lupus Erythematosus (Kurasawa et al., 2010)	High expression in endothelial cells, decidual cells and fibroblasts with distinct positivity in connective tissue
Spike glycoprotein (S2 subdomain)	E-Cadherin (CDH1)	GIAVEQDKNTQEVFAQVK (769-786)	Pemphigus vulgaris (Oliveira et al., 2013)	Cytoplasmic and membranous expression in epithelial cells
Spike glycoprotein (S2 subdomain)	A-kinase anchoring protein 12 (AKAP12)	GIAVEQDKNTQEVFAQVK (769-786)	Myasthenia Gravis (Nauert et al., 1997; Sasaki et al., 2001)	Cytoplasmic expression mainly in seminiferous duct, endothelial cells and connective tissues
Spike glycoprotein (S2 subdomain)	Nidogen1 (NID1)	GIAVEQDKNTQEVFAQVK (769-786)	Systemic Lupus Erythematosus (Saxena et	Strong positivity in plasma

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lead to autoimmunity (Angileri et al., 2020). Multiple studies have already identified some of the shared epitopes between SARS-CoV-2 and human proteins, pointing to the linked autoimmune diseases. e.g. Autoimmune dermatomyositis (Megremis et al., 2020), GBS (Lucchese and Flöel, 2020b). Presence of autoantibodies has also been observed in COVID-19 patients' sera (Megremis et al., 2020; Schiaffino et al., 2020; Wang et al., 2021). We opine that our contemporaneous report of hitherto unknown potential self-antigens for autoreactive antibodies can aid in narrowing down the search for specific self-antigens contributing to multi-organ damage/hyperinflammation in severe COVID-19 via autoimmunity and direct subsequent antigen-specific studies. We have carried out the analysis also using experimentally mapped T cell epitopes from SARS-CoV-2 (Saini et al., 2021). Though regions that share homology with human peptides were found (Supplementary Table 1), it is difficult to gauge the potential involvement of these regions in instigating auto immune conditions post SARS-CoV-2 infection, as so far, to the best of our knowledge, there have been no direct reports of autoreactive T cells detected in severe COVID-19 cases.

Spanning analysis of possibilities of molecular mimicry between human and SARS-COV-2 is crucial at this stage. It will not only contribute to the understanding and better management of observed autoimmune reactions post-infection, but also aid in selecting virus-specific peptide sequences to be targeted for future vaccine designs to bypass undesirable autoimmune consequences of vaccination. Although epitopes on multiple other proteins can be recognized by the immune system (Grifoni et al., 2020), most of the vaccine development strategies utilize epitopes on receptor binding domain or spike protein. To ensure that deceptive imprinting and autoimmune/autoinflammatory reactions don't occur post-vaccination, a wholesome knowledge of epitopes and their capacity to generate auto-/neutralizing-/non-neutralizing- antibodies is necessary. Needless to say, our report calls for experimental studies to verify the proposed antigenic nature of the reported human proteins. Recording in vitro autoreactivity for extrapulmonary antigens, using sera from severe COVID-19 patients, would further indicate a role of autoimmunity at the basis of multiorgan involvement/damage in COVID-19. Additionally, long-term monitoring of the corresponding

Table 1 (continued)

			al., 1994)	
Spike glycoprotein (S2 subdomain)	Desmoplakin (DSP)	GIAVEQDKNTQEVFAQVK (769-786)	Pemphigus vulgaris (Mimouni et al., 2004), Erythema multiforme (Foedinger et al., 1995)	Cytoplasmic and membranous expression most abundant in squamous epithelia and intercalated discs
Spike glycoprotein (S2 subdomain)	SRY-box transcription factor 10 (SOX10)	PSKPSKRSFIEDLLFNKV (809-826)	Autoimmune polyendocrine syndrome type I (Hedstrand et al., 2001)	Nuclear expression mainly in glial cells and salivary glands
Spike glycoprotein (S1 subdomain)	Promyelocytic leukemia protein (PML)	SALEPLVDLPIGINITRFQTLALH (221-245)	Autoimmune Liver disease (Tsouris et al., 2020)	Nuclear expression in most tissues
Spike glycoprotein (S1 subdomain)	Titin (TTN)*	SALEPLVDLPIGINITRFQTLALH (221-245)	Myasthenia Gravis (Yamamoto et al., 2001)	Cytoplasmic expression in skeletal muscle and heart muscle.
Spike glycoprotein (S1 subdomain)	Desmoplakin (DSP)	SALEPLVDLPIGINITRFQTLALH (221-245)	Pemphigus vulgaris (Mimouni et al., 2004), Erythema multiforme (Foedinger et al., 1995)	Cytoplasmic and membranous expression most abundant in squamous epithelia and intercalated discs
Spike glycoprotein (S1 subdomain)	AHNAK nucleoprotein (AHNAK)	SALEPLVDLPIGINITRFQTLALH (221-245)	Systemic Lupus Erythematosus (Sköldbberg et al., 2002)	Ubiquitous cytoplasmic expression.
Spike glycoprotein (S1 subdomain)	Glycyl-tRNA synthetase 1 (GARS1)	SALEPLVDLPIGINITRFQTLALH (221-245)	Systemic Lupus Erythematosus (Stojanov et al., 1996)	General cytoplasmic expression in a granular pattern
Spike glycoprotein	Ryanodine receptor 2	SALEPLVDLPIGINITRFQTLALH	Myasthenia Gravis	Cytoplasmic expression in several

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autoantibodies can help to better understand the association of autoimmune conditions, exacerbation of inflammation and severity of COVID-19. The outcomes of such experimental studies would also be relevant in COVID-19 therapy for detecting the onset of multiorgan manifestations by using autoantibodies corresponding to the identified self-antigens as biomarkers and further aiding quality control in plasma therapy.

5. Conclusion

The present study traces the thread of known autoantigens, hoping to understand the dense mesh of COVID-19, autoimmune conditions, exacerbated inflammation and extrapulmonary damage associated with the disease. We have reported several hitherto unknown human proteins that may act as autoantigens for antibodies elicited due to SARS-COV-2 exposure/infection. Of interest is their widespread tissue distribution, which is suggestive of their involvement in multi-organ manifestations,

hyper stimulated immune system and exacerbated inflammation associated with the disease.

Contributions

V.J. contributed to concept, design, data analysis and editing of the manuscript. M.M. performed the work, contributed to data analysis and writing of the original draft of the manuscript. S.S.K.V. performed the work and contributed to data analysis and editing of the manuscript. All authors have read and approved the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

Table 1 (continued)

(S1 subdomain)	(RYR2)*	(221-245)	(Mygland et al., 1992)	tissues including heart muscle, placenta and CNS
Spike glycoprotein (S1 subdomain)	Interferon induced with helicase C domain 1 (IFIH1)	GAAAYVGYLQPRFTLLKYNENGTI (261-285)	Dermatomyositis (Labrador-Horrillo et al., 2014)	Cytoplasmic expression in most tissues
Spike glycoprotein (S1 subdomain)	Glutamate ionotropic receptor delta type subunit 2 (GRID2)	NYLYRFRKSNLKPFERDIS (450-469)	Rasmussen's encephalitis (Rogers et al., 1994)	Expression in neuropil of cerebellum and subset of cells in seminiferous ducts.
Spike glycoprotein (S1 subdomain)	Low density lipoprotein receptor 2 (LRP2)	CNGVEGFNCYFPLQSYGFQP (480-499)	Systemic autoimmune diseases (rheumatoid arthritis, Systemic Lupus Erythematosus, Behçet's disease, systemic sclerosis, and osteo arthritis) (Ooka et al., 2003)	Membranous expression mainly in renal tubules and parathyroid gland
Spike glycoprotein (S1 subdomain)	Transglutaminase4 (TGM4)	CNGVEGFNCYFPLQSYGFQP (480-499)	Autoimmune polyendocrine syndrome type 1 (Landegren et al., 2015)	Selective cytoplasmic expression in prostate and skeletal muscle.
Spike glycoprotein (S1 subdomain)	Killer cell lectin like receptor D1 (CD94)	CNGVEGFNCYFPLQSYGFQP (480-499)	Systemic Lupus Erythematosus (Hagberg et al., 2015)	Preferentially expressed on the surface of subsets of natural killer cells #
Spike glycoprotein (S1 subdomain)	Cartilage intermediate layer protein (CILP)	CNGVEGFNCYFPLQSYGFQP (480-499)	Rheumatoid Arthritis (Tsuruha et al., 2001)	Extracellular and cytoplasmic expression in several tissues.
Spike glycoprotein (S1 subdomain)	Serpin B3 (SERPINB3)	NFNGLTGTGVLTESNKKFLPFQQFG (542-566)	Rheumatoid Arthritis (Maciejewska-Rodrigues et al., 2010)	Selective cytoplasmic expression in squamous epithelia, respiratory epithelia and urinary bladder.
Spike glycoprotein (S1 subdomain)	Heat shock protein family A (Hsp70) member 5 (HSPA5)*	NFNGLTGTGVLTESNKKFLPFQQFG (542-566)	Neuromyotitis optica (Shimizu et al., 2019)	Ubiquitous cytoplasmic expression, highly abundant in immune, neuronal cells and thyroid follicular cells
Spike glycoprotein (S1 subdomain)	Titin (TTN)	DAVRDPQTEILDITPCSFG (574-593)	Myasthenia Gravis (Yamamoto et al., 2001)	Cytoplasmic expression in skeletal muscle and heart muscle
Spike glycoprotein (S1 subdomain)	Leucine-rich, glioma inactivated 1 (LGI-1)	DAVRDPQTEILDITPCSFG (574-593)	Limbic encephalitis (Lai et al., 2010)	Asymmetric distribution in human brain#
Spike glycoprotein (S1 subdomain)	Ribosomal protein lateral stalk subunit P0 (RPL P0)	DAVRDPQTEILDITPCSFG (574-593)	Systemic Lupus Erythematosus (Mei et al., 2018)	General cytoplasmic expression in all tissues

Footnote:

1. Tissue distribution data was obtained from the human protein atlas (Uhlén et al., 2015).
2. # - Conclusive data for expression patterns of CD94 (Valiante et al., 1997) and LGI-1 (Furlan et al., 2006) is unavailable in the human protein atlas and was sourced from the literature.
3. References cited adjacent to the autoimmune conditions are evidence for demonstrated presence of antibodies against the corresponding human protein.

Table 2

Reports of autoimmune conditions secondary to COVID-19.

Autoimmune condition	Report(s) of occurrence of the condition post SARS-CoV-2 infection
Systemic Lupus Erythematosus	Gracia-Ramos and Saavedra-Salinas (2021) and Zamani et al. (2021)
Rheumatoid Arthritis	Derksen et al. (2021)
Dermatomyositis	Gokhale et al. (2020) and Megremis et al. (2020)
Multiple Sclerosis	Fragoso et al. (2021) and Yavari et al. (2020)
Autoimmune Hemophilia	Franchini et al. (2020)
Myasthenia Gravis	Huber et al. (2020), Khedr et al. (2021), Restivo et al. (2020) and Sriwastava et al. (2020)
Neuromyelitis Optica	Batum et al. (2020) and de Ruijter et al. (2020)

Footnote: Autoimmune conditions mentioned here were selected based on their presence in Table 1. In addition to the above mentioned, multiple other autoimmune conditions have also been reported post SARS-CoV-2 infection.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.molimm.2021.06.021>.

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