Possible auto-antigens that may explain the post-infection autoimmune manifestations in COVID-19 patients displaying neurological conditions

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To the editor-

We read with interest the article 'Immunoserologic detection and diagnostic relevance of cross-reactive autoantibodies in Coronavirus disease 2019 patients' by Schiaffino *et al.,* [1]. They reported a unique immunofluorescence (IF) pattern on rat tissues for 12 hospitalized COVID-19 patients' sera. The observed COVID-19 specific IF pattern (COVID-IF) suggested the presence of non-organ specific autoreactive antibodies in affected patients. Furthermore, the COVID-IF patients displayed neurological and thrombotic conditions with a strong temporal association with COVID-19. Of the three patients with neurological conditions, one with Guillain-Barre syndrome (GBS) was also found to possess autoantibodies in cerebrospinal fluid (CSF-positive for COVID-IF). Evidence presented for seroconversion from negative to positive in a patient's pre- and post-COVID-19 serum samples respectively, suggested a causal relationship between generation of autoreactive antibodies and COVID-19. The authors postulatedmolecular mimicry as a possible mechanism for the observed neurological and thrombotic manifestations [1].

Here, we report 4 human proteins involved in autoimmunity that potentially act as autoantigens in COVID-19 patients with neurological damage. We screened for shared B cell epitopes between humans and SARS-CoV-2. To collect B cell epitopes on SARS-CoV-2, a search was performed on PubMed using the keywords "immunogenic regions SARS-CoV-2" and "B-cell epitopes SARS-CoV-2". B cell immunogenic epitopes (from papers published before 8 Aug 2020) reported through various computational prediction methods and/or experimental verification methods were compiled to create a library. For further analysis, it was ensured that the epitopes selected from the library were experimentally identified/validated. BLASTp program

(https://blast.ncbi.nlm.nih.gov/Blast.cgi)[2] was used to search for human encoded proteins that shared homologous sequences with the immunogenic peptides. The search set was limited to *Homo sapiens* in the UniProtKB/Swiss-Prot database. Default BLASTp algorithm parameters were used and the results were limited only to the top 100 hits.The protein list obtained from the BLAST search was manually curated using the Open Targets Platform[3] server to identify if a given protein had been previously reported to have autoantibodies generated against it in autoimmune conditions.

Our results include 4 human proteins homologous to SARS-COV-2 that could possibly be acting as autoantigens in COVID-19 patients displaying neurological conditions. One of them is Heat Shock Protein 90 alpha family class B member 1 (HSP90AB1, known to be involved in GBS [4]), as previously reported [5]. The other three are heat shock protein family A (Hsp70) member 5 (HSPA5/GRP78, involved in neuromyelitis optica [6]), titin (TTN, involved in myasthenia gravis [7]) and ryanodine receptor 2 (RYR2, involved in myasthenia gravis [8]). Epitope sequences on SARS-CoV-2 and homologous human self-antigen sequences are as given in the table.

Cases reported by Schiaffino *et al.,* [1] had no previous history of autoimmune conditions and displayed post-infection generation of non-organ specific autoreactive antibodies. In that context, our report of experimentally validated epitope sequences on HSP5A, HSP90AB1, Titin and RYR2 possibly acting as auto-antigens may support the hypothesis of 'autoimmunity via molecular mimicry triggered by SARS-CoV-2 infection and causing multi-organ damage'.

Table 1. Possible self-antigens in neurological conditions arising due to autoimmunity via molecular mimicry triggered by SARS-COV-2 infection.

SARS-COV-2 Protein	Sequence in SARS-CoV-2 (Homologous sequences in red)	Homologous human protein	Autoimmune condition
Spike protein	NFNGLTGTGVLTESNKKFLPFQQFG[9]	HSPA5[a]	Neuromyelitis optica
Spike protein	SALEPLVDLPIGINITRFQTLLALH[9]	TTN[b]	Myasthenia gravis
Spike protein	SALEPLVDLPIGINITRFQTLLALH[9]	RYR2[c]	Myasthenia gravis
Nucleocapsid phosphoprotein	KDKKKK [5]	HSP90AB1[d]	GBS

Table Footnote: superscripts indicate subcellular location as obtained from the Human Protein Atlas (http://www.proteinatlas.org) [10]

a – cytosol, b – predicted to be intracellular and membrane for different isoforms, c – nucleoplasm, plasma membrane, cytosol, d – cytosol

Abbreviations: GBS: Guillain Barre Syndrome, HSPA5: heat shock protein family A (Hsp70) member 5, HSP90AB1: Heat Shock Protein 90 alpha family class B member 1, RYR2: ryanodine receptor 2, TTN: titin.

Notes

Potential conflicts of interest
Authors declare that there are no competing interests.

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