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# Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons

*To the Editor:*

The novel coronavirus SARS-CoV2 is causing a global pandemic. The syndrome associated with the infection, COVID-19, encompasses fever, coughing, dyspnea and severe pneumonia with respiratory failure [1]. Severity of structural lung involvement appears not to be the only factor contributing to respiratory failure and respiratory failure in COVID-19 appears to be characterized by a dissociation between well-preserved lung mechanics and severity of hypoxemia [2]. These observations suggest that additional factors beyond direct pulmonary damage might play a role in the most critical cases.

Brainstem involvement has been proposed as a possible cause of respiratory failure in SARS-CoV-2 infection, given that the virus appears to have potential for inducing neurological damage, a number of neurological symptoms have been described, and SARS-CoV has been reported to massively infect the brainstem in both patients and experimental animals [3]. Of relevance, a retrospective study on moderately to critically ill COVID-19-patients found that 22% of the patients who died showed disorders of consciousness at admission compared to 1% of the recovered patients [1]. In addition, autoimmune neurological complications of SARS-CoV-2 have already been reported [4,5]. Moreover, COVID-19 appears to be associated with hyper-activation of the immune system and cytokine storm thus resembling other clinical conditions characterized by immune dysregulation [6,7]. Cytokine storm is a possible pathogenic mechanism of the acute necrotizing encephalopathy reported in COVID-19 [7,8].

In light of the above, damage to the respiratory pacemaker in the brainstem, also known as pre-Bötzinger complex (preBötC) [9], might contribute to respiratory failure in COVID-19 as a consequence of mimicry between viral and neuronal proteins of the preBötC. Indeed, the proteome of the virus (https://www.ncbi.nlm.nih.gov/nuccore/MN908947) shares three sequences of six amino acids (GSQASS, LNEVAK, and SAAEAS) with three proteins, namely DAB1, AIFM, and SURF1 (as catalogued at www.uniprot.org) that are present in the human brainstem preBötC (Table 1) and are part of experimentally validated epitopes [10]. Interestingly, the three sequences are absent in other human Coronaviruses (hCoV-HKU-1 and hCoV-OC-43) that can cause lung damage but are not typically associated with respiratory failure [11].

DAB1 belongs to the Reelin signalling pathway [12]. Three main points bear relevance for the potential involvement of DAB1 in preBötC-dysfunction and respiratory failure:

- DAB1-mutant mice show the same phenotype as Reelin-mutants, and both proteins need to be concurrently expressed in humans for the signal pathway to function properly [12].
- Reelin is a specific marker of preBötc neurons [9].
- Reelin-mutations are associated with impaired response to hypoxia [9].

AIFM1 and SURF1 are involved in mitochondrial metabolism and, when altered as consequence of mutations, cause Leigh syndrome [13].

**Table 1**
Hexapeptides of immunologic relevance shared between SARS-CoV-2 and proteins related to the preBötC. The experimentally validated immunogenic epitopes containing the shared motifs are presented in the last column.

| Shared 6-mer | SARS-CoV-2 protein | Human protein [UniProt-ID] | Epitopes [IEDB-ID; Protein; Organism] |
|---|---|---|---|
| GSQASS | nucleocapsid phosphoprotein | DAB1 Disabled homolog 1 [O75553] | PKGFYAEGSRG**GSQASS**R [48067; Nucleoprotein; SARS-CoV] SRG**GSQASS**RSSSRSR [60669; Nucleoprotein; SARS-CoV] |
| LNEVAK | surface glycoprotein | AIFM1 Apoptosis-inducing factor 1, mitochondrial [O95831] | R**LNEVAK**NL [54680; Spike glycoprotein; SARS-CoV] EIDR**LNEVAK**NLNESLIDLQELGKYEQY + ACET(E1) [12426; Spike glycoprotein; SARS-CoV] EIDR**LNEVAK**NLNESLIDLQELGKYEQY [558417; Spike glycoprotein; SARS-CoV] |
| SAAEAS | nucleocapsid phosphoprotein | SURF1 Surfeit locus protein 1 [Q15526] | KK**SAAEAS**KKPRQKRTA [31692; Nucleoprotein; SARS-CoV] KK**SAAEAS**KKPRQKRTATKQYNVTQ [31693; Nucleoprotein; SARS-CoV] QQQGQTVTKK**SAAEAS**KK [52117; Nucleoprotein; SARS-CoV] |

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Of relevance for the present hypothesis, death in Leigh syndrome results most often from respiratory failure and, crucially, mouse models of the disease show pathological functioning of the preBötC [14]. Leigh syndrome is indeed the eponym of a subacute necrotizing encephalopathy that closely resembles morphologically the acute necrotizing encephalopathy associated with COVID-19 [15].

In the context of this peptide sharing between the preBötc, and SARS-CoV-2, it appears possible that immunological targeting of DAB1, AIFM1, and SURF1 might contribute to brainstem-related respiratory failure in COVID-19 patients and that a therapeutic benefit might come from immunomodulatory agents. To test this hypothesis, sera and cerebrospinal fluid from COVID-19 patients suffering from respiratory distress and/or neurological symptoms might be examined for immunoreactivity against the shared protein sequences. Evidence of causality can be obtained from animal models by immunizing the individuals with the same protein sequences.

## References


[1] Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020:368.

[2] Gattinoni L, Coppola S, Cressoni M, Busana M, Chiumello D. Covid-19 Does Not Lead to a "Typical" Acute Respiratory Distress Syndrome [published online ahead of print, 2020 Mar 30]. Am J Respir Crit Care Med 2020. https://doi.org/10.1164/rccm.202003-0817LE.

[3] Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol 2020. https://doi.org/10.1002/jmv.25728.

[4] Toscano G, Palmerini F, Ravaglia S, Ruiz L, Invernizzi P, Cuzzoni MG, et al. Guillain–Barré syndrome associated with SARS-CoV-2. New Eng J Med 2020. https://doi.org/10.1056/NEJMc2009191.

[5] Gutiérrez-Ortiz C, Méndez A, Rodrigo-Rey S, et al. Miller Fisher Syndrome and polyneuritis cranialis in COVID-19 [published online ahead of print, 2020 Apr 17]. Neurology 2020. https://doi.org/10.1212/WNL.0000000000009619.

[6] Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4. https://doi.org/10.1016/S0140-6736(20)30628-0.

[7] Shoenfeld Y. Corona (COVID-19) time musings: Our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning [published online ahead of print, 2020 Apr 5]. Autoimmun Rev 2020:102538. https://doi.org/10.1016/j.autrev.2020.102538.

[8] Poyiadji N, Shahin G, Noujaim D, Stone M, Patel S, Griffith B. COVID-19-associated Acute Hemorrhagic Necrotizing Encephalopathy: CT and MRI Features [published online ahead of print, 2020 Mar 31]. Radiology 2020:201187. https://doi.org/10.1148/radiol.2020201187.

[9] Tan W, Sherman D, Turesson J, Shao XM, Janczewski WA, Feldman JL. Reelin demarcates a subset of pre-Bötzinger complex neurons in adult rat. J Comp Neurol 2012;520:606–19. https://doi.org/10.1002/cne.22753.

[10] Vita R, Overton JA, Greenbaum JA, et al. The immune epitope database (IEDB) 3.0. Nucleic Acids Res 2015;43:D405–12. https://doi.org/10.1093/nar/gku938.

[11] Gaunt ER, Hardie A, Claas EC, Simmonds P, Templeton KE. Epidemiology and clinical presentations of the four human coronaviruses 229E, HKU1, NL63, and OC43 detected over 3 years using a novel multiplex real-time PCR method. J Clin Microbiol 2010;48(8):2940–7. https://doi.org/10.1128/JCM.00636-10.

[12] Deguchi K, Inoue K, Avila WE, et al. Reelin and disabled-1 expression in developing and mature human cortical neurons. J Neuropathol Exp Neurol 2003;62:676–84. https://doi.org/10.1093/jnen/62.6.676.

[13] Lake NJ, Compton AG, Rahman S, Thorburn DR. Leigh syndrome: one disorder, more than 75 monogenic causes. Ann Neurol 2016;79(2):190–203. https://doi.org/10.1002/ana.24551.

[14] Quintana A, Zanella S, Koch H, et al. Fatal breathing dysfunction in a mouse model of Leigh syndrome. J Clin Invest 2012;122(7):2359–68. https://doi.org/10.1172/JCI62923.

[15] Wu X, Wu W, Pan W, Wu L, Liu K, Zhang HL. Acute necrotizing encephalopathy: an underrecognized clinicoradiologic disorder. Mediators Inflamm 2015;2015:792578. https://doi.org/10.1155/2015/792578.



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