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.

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Molecular mimicry may explain multi-organ damage in COVID-19

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To the Editor,

Molecular mimicry has been proposed as a cause of the autoimmune phenomena observed in COVID-19 [1–4], the syndrome associated with the infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Lucchese and Flöel [4] have recently reported three human proteins (namely DAB1, AIFM, and SURF1, as catalogued at www.uniprot.org) – that are present in neurons of the respiratory pacemaker in the brainstem – that share potentially antigenic epitopes with SARS-CoV-2, as shown by in silico analysis.

Particularly, they postulated that damage to the brainstem pacemaker may contribute to respiratory failure in COVID-19 as a consequence of molecular mimicry between neuronal and viral proteins, in turn causing the clinical dissociation between well-preserved lung mechanics and severity of hypoxemia.

Here, we would like to direct attention to some features of COVID-19 – such as anosmia, leukopenia, and multi-organ failure brought about by vascular damage – that could also be the consequence of molecular mimicry phenomena (Table 1).

Observations

1. Odorant Receptor 7D4 (OR7D4) is one of the most important odorant receptors on the plasma membrane of olfactory sensory neurons, responding to sex steroid-derived odours, e.g., androstenone and androstadienone [5]. Its alterations have been associated with anxiety and depression [6].
2. Poly (ADP-Ribose) Polymerase Family Member 9 (PARP9), also known as mono-ADP-ribosyltransferase (ARTD)-9, is a protein involved in differentiation and function of immune cells such as B lymphocytes [7] and macrophages [8].
3. Solute Carrier Family 12 Member 6 (SLC12A6) is a member of the K−Cl cotransporters (KCC), integral membrane proteins that lower intracellular chloride concentrations [9]. Alternative splicing in its gene results in multiple transcript variants encoding different isoforms, the most important one being KCC3 [10]. The latter has been found in endothelial cells of various organs, including vessels, heart, brain, kidney, liver, and lung [11].

Working hypothesis

We hypothesize that anosmia, leukopenia, and vascular damage with multi-organ damage are associated with molecular mimicry of the following proteins:

OR7D4: Anosmia. It could also be implicated in the mood disorders observed in these patients.

PARP9: Leukopenia. It could be implicated in plaque destabilization in patients with atherosclerosis.

SLC12A6: Vascular damage, in turn inducing thrombosis, disseminated intravascular coagulation, and multiorgan failure. It could also induce Kawasaki vasculitis. Interestingly, the shared epitope SSRSSSR in SLC12A6 (Table 1) was found to be highly immunogenic by SVMTriP (http://sysbio.unl.edu/SVMTriP/), a tool used to predict protein surface regions that are preferentially recognized by antibodies (i.e., antigenic epitopes), that is helping in the design of vaccine components [12].

Although plasma membrane localization has been demonstrated only for OR7D4 and SLC12A6, we cannot exclude that, after cell stress, post-translational modifications could induce PARP9 trafficking to plasma membrane and its exposure on the cell surface, as for other intracellular proteins [13]. Other studies, including the analysis of anatomical specimens from autopsies of subjects who died from severe forms of COVID-19, are necessary to verify these predictions.

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Table 1
Peptides of immunologic relevance shared between SARS-CoV-2 and human proteins.

Shared ≥6 mer (amino acids)	SARS-CoV-2 protein	Human protein	Putative Epitopes [NCBI Reference, SARS-CoV-2]	Localization of human protein [predicted by uniprot.org]
IIFWFSL	ORF7b	OR7D4 [Q8NG98]	LVLIML**IIFWFSL**ELQ [YP_009725318.1]	**Cellular**: olfactory receptor. **Subcellular**: plasma membrane.
VVNAAN	ORF1ab	PARP9 [Q8IXQ6]	**VVNAAN**VYLKHGGGVAG [YP_009724389.1]	**Cellular**: B cells; macrophage. **Subcellular**: cytosol, nucleus.
SSRSSSR	Nucleocapsid phosphor-protein	SLC12A6 [Q8NG98]	**SSRSSSR**SRNSSRNSTP [YP_009724397]	**Cellular**: endothelial cells; heart; brain; kidney; liver; lung. **Subcellular**: plasma membrane.

References

[1] Cappello F Is. COVID-19 a proteiform disease inducing also molecular mimicry phenomena? Cell Stress Chaperones 2020 May;25(3):381–2. https://doi.org/10.1007/s12192-020-01112-1.

[2] Sedaghat Z, Karimi N. Guillain Barre syndrome associated with COVID-19 infection: A case report. J Clin Neurosci 2020 Apr 15. https://doi.org/10.1016/j.jocn.2020.04.062. pii: S0967-5868(20)30882-1.

[3] Cappello F. COVID-19 and molecular mimicry: The Columbus' egg? J Clin Neurosci 2020 May 6. https://doi.org/10.1016/j.jocn.2020.05.015. pii: S0967-5868(20)31156-5.

[4] Lucchese G, Flöel A. Molecular mimicry between SARS-CoV-2 and respiratory pacemaker neurons. Autoimmun Rev 2020 May 1:102556https://doi.org/10.1016/j.autrev.2020.102556.

[5] Zhuang H, Chien MS, Matsunami H. Dynamic functional evolution of an odorant receptor for sex-steroid-derived odors in primates. Proc Natl Acad Sci U S A 2009 Dec 15;106(50):21247–51. https://doi.org/10.1073/pnas.0808378106.

[6] Sookoian S, Burgueño A, Gianotti TF, Marillet G, Pirola CJ. Odor perception between heterosexual partners: its association with depression, anxiety, and genetic variation in odorant receptor OR7D4. Biol Psychol 2011 Mar;86(3):153–7. https://doi.org/10.1016/j.biopsycho.2010.11.003.

[7] Robert I, Gaudot L, Yélamos J, Noll A, Wong HK, Dantzer F, et al. Robust immunoglobulin class switch recombination and end joining in Parp9-deficient mice. Eur J Immunol 2017 Apr;47(4):665–76. https://doi.org/10.1002/eji.201646757.

[8] Iwata H, Goettsch C, Sharma A, Ricchiuto P, Goh WW, Halu A, et al. PARP9 and PARP14 cross-regulate macrophage activation via STAT1 ADP-ribosylation. Nat Commun 2016 Oct 31;7:12849https://doi.org/10.1038/ncomms12849.

[9] Howard HC, Mount DB, Rochefort D, Byun N, Dupré N, Lu J, et al. The K-Cl cotransporter KCC3 is mutant in a severe peripheral neuropathy associated with agenesis of the corpus callosum. Nat Genet 2002 Nov;32(3):384–92. [Epub 2002 Oct 7].

[10] Mercado A, Vázquez N, Song L, Cortés R, Enck AH, Welch R, et al. NH2-terminal heterogeneity in the KCC3 K + -Cl- cotransporter. Am J Physiol Renal Physiol 2005 Dec;289(6):F1246–61.

[11] Shen MR, Chou CY, Hsu KF, Liu HS, Dunham PB, Holtzman EJ, et al. The KCl cotransporter isoform KCC3 can play an important role in cell growth regulation. Proc Natl Acad Sci U S A 2001 Dec 4;98(25):14714–9.

[12] Yao B, Zhang L, Liang S, Zhang C. SVMTriP: a method to predict antigenic epitopes using support vector machine to integrate tri-peptide similarity and propensity. PLoS One 2012;7(9):e45152https://doi.org/10.1371/journal.pone.0045152.

[13] Guzel E, Arlier S, Guzeloglu-Kayisli O, Tabak MS, Ekiz T, Semerci N, et al. Endoplasmic reticulum stress and homeostasis in reproductive physiology and pathology. Int J Mol Sci 2017 Apr 8;18(4). https://doi.org/10.3390/ijms18040792. pii: E792.

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