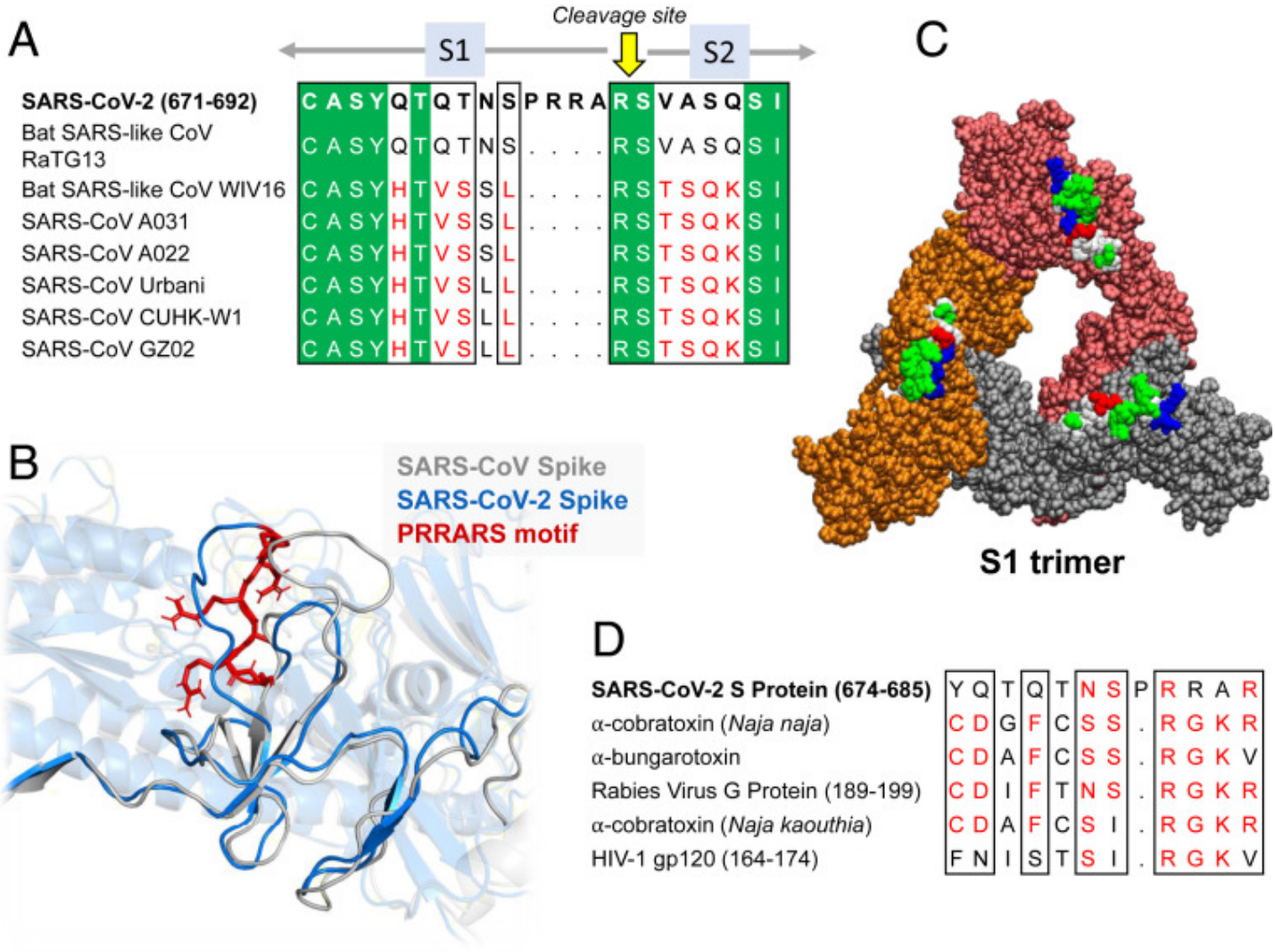
Twitter Thread by Billy Bostickson ■■&■ ■

Billy Bostickson ■■&■ ■
@BillyBostickson

Keep dwelling on this:
Further Examination of the Motif near PRRA Reveals Close Structural Similarity to the SEB Superantigen as well as Sequence Similarities to Neurotoxins and a Viral SAg.

The insertion PRRA together with 7 sequentially preceding residues & succeeding R685 (conserved in β-CoVs) form a motif, Y674QTQTNSPRRAR685, homologous to those of neurotoxins from Ophiophagus (cobra) and Bungarus genera, as well as neurotoxin-like regions from three RABV strains

(20) (Fig. 2D). We further noticed that the same segment bears close similarity to the HIV-1 glycoprotein gp120 SAg motif F164 to V174.
https://t.co/EwwJOSa8RK



In (B), the segment S680PPRAR685 including the PRRA insert and highly conserved cleavage site *R685* is shown in van der Waals representation (black labels) and nearby CDR residues of the TCRVβ domain are labeled in blue/white https://t.co/BsY8BAIzDa

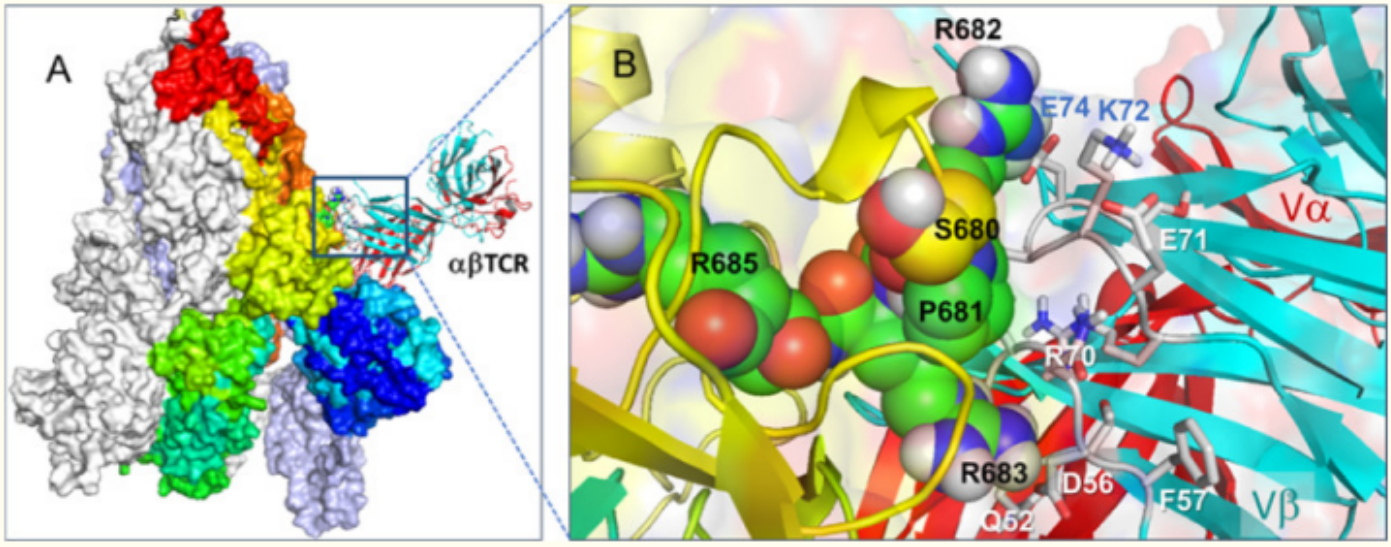


Figure 1:

Binding of TCR to SARS-CoV-2 spike trimer near the "PRRA" insert region.

Overall (**A**) and closeup (**B**) views of the complex and interfacial interactions. In (**B**) the spike monomers are colored *white*, *ice blue*, and spectrally from *blue* (N-terminal domain) to *red*, all displayed in surface representation. For better visualization, the spike trimer is oriented such that its receptor binding domains (RBDs) are at the bottom. TCR α- and β-chains are in *red* and *cyan ribbons*. In (**B**), the segment S_{680}PPRAR$_{685}$ including the PRRA insert and highly conserved cleavage site R685 is shown in van der Waals representation (*black labels*) and nearby CDR residues of the TCRVβ domain are labeled in *blue/white*.

Sequence Identity %

https://t.co/BsY8BAIzDa

Y674 - QTQTNSPRRA - R685

Similar to neurotoxins from Ophiophagus (cobra) & Bungarus genera & neurotoxin-like regions from three RABV strains

T678 - NSPRRA- R685

Superantigenic core, consistently aligned against bacterial or viral SAgs

A	Sequence	Residues	Sequence Identity
1	VIPFKDGIYFAATEKSNVVRGWVFGSTM	80-107	68%
	VLPFNDGVYFASTEKSNIIRGWIFGTTL	83-110	
2	QTHTMIFDNAFNCTFEYISDAFSLDVS	147-173	37%
	ESEFRVYSSANNCTFEYVSQPFLMDLE	154-180	
3	NITNFRAILT---AF-SPAQDI---WGTSA	227-249	30%
	NITRFQTLLALHRSYLTPG-DSSSGWTAGA	234-262	
4	YDENGTITDAVDCSQNPLAELKC	266-288	74%
	YNENGTITDAVDCALDPLSETKC	279-301	
5	LKCSVKSFEIDKGIYQTSNFRVVPSGDVVRFPNITNLCPFGEVFNATKFPSVY	286-338	75%
	TKCTLKSFTVEKGIYQTSNFRVQPTESIVRFPNITNLCPFGEVFNATRFASVY	299-351	
6	GCLIGAEHVDTSYECDIPIG	634-653	90%
	GCLIGAEHVNNSYECDIPIG	648-667	
7	NTREVFAQVKQMYKTPTLKYFGGFNFSQILP	759-789	84%
	NTQEVFAQVKQIYKTPPIKDFGGFNFSQILP	777-807	
8	EAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQAAPHGVVF LHVTYVPS	970-1052	98%
	EAEVQIDRLITGRLQSLQTYVTQQLIRAAEIRASANLAATKMSECVLGQSKRVDFCGKGYHLMSFPQSAPHGVVF LHVTYVPA	988-1070	
9	LQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQ	1123-1183	100%
	LQPELDSFKEELDKYFKNHTSPDVDLGDISGINASVVNIQKEIDRLNEVAKNLNESLIDLQ	1141-1201	

Figure S2: Motifs associated with superantigen, toxin, cytokine, and membrane surface proteins predicted for SARS-CoV spike and mapped onto SARS-CoV-2 spike sequence and structure. (**A**) Sequence alignment of these motifs on SARS-CoV (*upper rows*) and SARS-CoV-2 spikes *(lower rows),* corresponding residue numbers (3rd column) and sequence identity (4th/last column). Superantigenic and toxic-like motifs are highlighted in *pink*. Residues that interact with TCR Vα are marked in *red*. (**B**) Predicted motifs mapped onto the trimeric structure of SARS-CoV-2 spike, with one of its subunit colored in *yellow*. The motifs are colored *red* (superantigenic and toxic-like) or *orange* (others). Mutation sites reported in recent work[5,6] are shown in *spheres*. The mutation site D839Y/N/E is

Y674QTQTNSPRRAR685
Reference 21:
A nicotinic hypothesis for Covid-19
https://t.co/EWmVWI5jYr

Further examination of the motif near PRRA reveals close structural similarity to the SEB superantigen as well as sequence similarities to neurotoxins and a viral SAg.

The insertion **PRRA** together with the sequentially preceding seven amino acids and succeeding Arg (fully conserved among β-coronaviruses) have been pointed out to form a motif, Y_{674}QTQTNS**PRRA**R_{685}, homologous to that of neurotoxins from *Ophiophagus* (cobra) and *Bungarus genera*, as well as neurotoxin-like regions from three RABV strains ([21]) (Fig. 2C). We further noticed that the same segment bears close similarity to HIV-1 glycoprotein gp120 superantigenic motif F164-V164.

Above all, fantastic news for chain smokers! (if true)
Keep on Puffing, Ignore the Guys in White Coats!
https://t.co/EWmVWI5jYr
Anyway, this is where Cheng et al (2020) got the neurotoxin motifs from
Superantigenic character of insert unique to SARS-CoV-2
https://t.co/EwwJOSa8RK

Nicotine may be suggested as a potential preventive agent against Covid-19 infection. Both the epidemiological/clinical evidence and the in silico findings may suggest that Covid-19 infection is a nAChR disease that could be prevented and may be controlled by nicotine. Nicotine would then sterically or allosterically compete with the SARS-CoV-2 binding to the nAChR. This legitimates the use of nicotine as a protective agent against SARS-CoV-2 infection and the subsequent deficits it causes in the CNS. Thus, in order to prevent the infection and the retro-propagation of the virus through the CNS, we plan a therapeutic assay against Covid-19 with nicotine (and other nicotinic agents) patches or other delivery methods (like sniffing/chewing) in hospitalized patients and in the general population.

Reference 22 (from preprint) reveals more...

Bracci L., Ballas S. K., Spreafico A., Neri P., Molecular mimicry between the rabies virus glycoprotein and human immunodeficiency virus-1 GP120: cross-reacting antibodies induced by rabies vaccination.

https://t.co/UZbe658OGR

RESULTS

Several experimental data described previously by our group indicate the presence of a molecular mimicry between HIV-1 gp120 and the rabies virus glycoprotein.[1,6] The sequence 160-170 of HIV-1 gp120 is highly homologous to the sequence 189-199 of the rabies virus glycoprotein and to the sequence 30-40 of snake venom neurotoxins[1] (Fig 1). We found that immunization of mice with a synthetic peptide reproducing the sequence 160-173 of HIV-1 gp120 induces the production of anti-gp120 antibodies efficiently cross-reacting with both rabies virus glycoprotein and α-bgt.[6]

Something important here but I can't connect the dots

(apart from being good news for smokers...)

Maybe someone else can unravel the implications?

@Parsifaler @w_mccairn @Rossana38510044

The cross-reactivity of antirabies virus glycoprotein antibodies with HIV-1 gp120 confirms the data previously obtained through immunization of mice with the gp120 peptide B2: antipeptide antibodies were reacting with both gp120 and rabies virus glycoprotein.[6] Analogous cross-reacting antibodies seem to be induced by vaccination with rabies virus, thus confirming the existence of a similar structural motif between the rabies virus glycoprotein and HIV-1 gp120. This common structural motif is probably related to a common functional feature that is binding to nicotinic receptors.

The Rubber Policeman..

"For binding experiments, cells were harvested mechanically with a rubber policeman & centrifuged"

Binding of HIV-1 gp120 to the nicotinic receptor (1992)

https://t.co/6veoEkVbVp

Referenced in Bracci et al (1997)

https://t.co/UZbe658OGR

Volume 311, number 2, 115–118 FEBS 11637 October 1992

Binding of HIV-1 gp120 to the nicotinic receptor

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Received 14 July 1992; revised version received 2 September 1992

We previously described a significant sequence homology between HIV-1 gp120 and the functional sites responsible for the specific binding of snake curare-mimetic neurotoxins and rabies virus glycoprotein to the nicotinic acetylcholine receptor. Here we report findings about the existence of a mechanism of functional molecular mimicry which could enable the binding of HIV-1 gp120 to nicotinic acetylcholine receptors in muscle cells and neurons.

Acetylcholine receptor; HIV-1; gp120; α-Bungarotoxin; Mimicry

1. INTRODUCTION

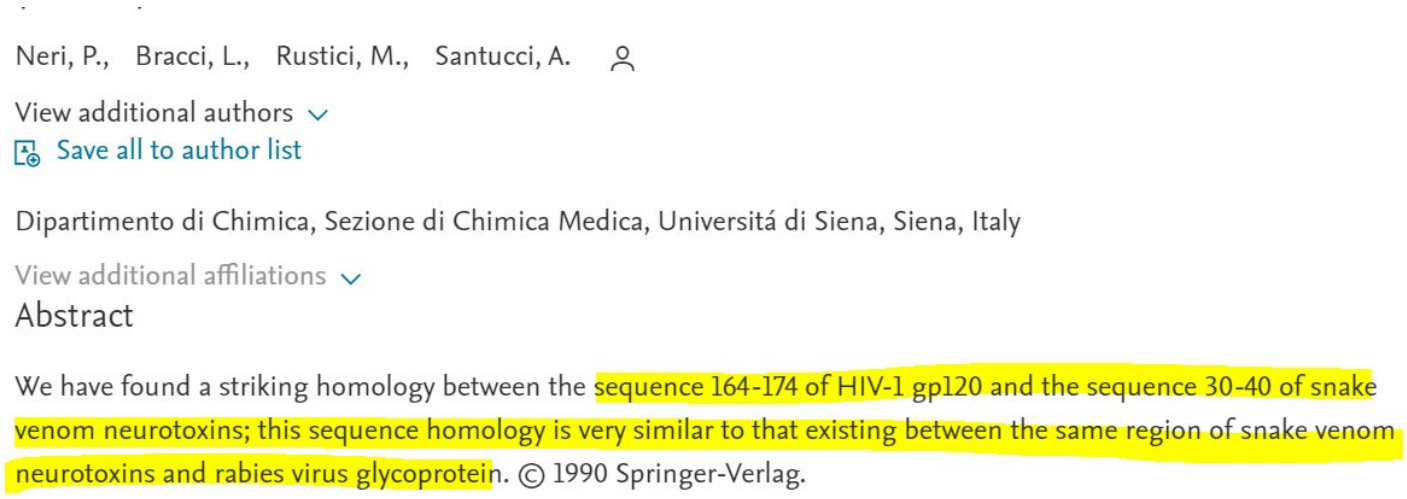
In a previous paper [1] we reported a significant homology between the sequence, 164–174 [2], of HIV-1 gp120 and the putative active sites of snake curare-mimetic neurotoxins and rabies virus (RV) glycoprotein, which specifically bind to the nicotinic acetylcholine receptor (AChR). Curare-mimetic neurotoxins from Elapid snakes bind with high affinity to AChR and competitively block acetylcholine-induced membrane depolarization [3]. On the other hand the rabies virus binds to the muscle nicotinic receptor and this 178 of gp120, homologous to snake neurotoxins and rabies virus glycoprotein, is also able, once conjugated to keyhole limpet hemocyanin (KLH), to inhibit the binding of α-Bgt to TE671 nicotinic acetylcholine receptor. Further, immunization of mice with the same gp120-derived peptide gave rise to antibodies efficiently cross-reacting with rabies virus glycoprotein and α-Bgt.

2. MATERIALS AND METHODS

2.1. *Cell culture*

The human cell line, TE671, was obtained from the American Type

earliest reference to this would be in 1990 by same authors (Bracci et al)
Sequence homology between HIV gp120, rabies virus glycoprotein, and snake venom neurotoxins - Is the nicotinic acetylcholine receptor an HIV receptor?
https://t.co/XGVUNyORP3


Neri, P., Bracci, L., Rustici, M., Santucci, A.

View additional authors

Save all to author list

Dipartimento di Chimica, Sezione di Chimica Medica, Universitá di Siena, Siena, Italy

View additional affiliations

Abstract

We have found a striking homology between the sequence 164-174 of HIV-1 gp120 and the sequence 30-40 of snake venom neurotoxins; this sequence homology is very similar to that existing between the same region of snake venom neurotoxins and rabies virus glycoprotein. © 1990 Springer-Verlag.

HIV GP120 /Snake Venom/Rabies GP Neurotoxin loop confirmed
(Sönnerborg & Johansson, 1993)
The neurotoxin-like sequence of human immunodeficiency virus GP120: A comparison of sequence data from patients with and without neurological symptoms
https://t.co/s8DIeMNMmD

The neurotoxin-like sequence of human immunodeficiency virus GP120: A comparison of sequence data from patients with and without neurological symptoms

Anders Sönnerborg & Bo Johansson

Virus Genes **7**, 23–31(1993) | Cite this article

Abstract

A region of the human immunodeficiency virus type 1 (HIV-1) envelope glycoprotein gp120 has been claimed previously to be homologous to parts of snake venom neurotoxins and rabies virus glycoprotein ("the neurotoxic loop"). We have determined DNA sequences directly from a polymerase chain reaction amplified fragment corresponding to this region of HIV-1 gp120 and have translated these to protein sequences. This was performed with the prototype HIV_{SF_2} isolate and several Swedish HIV-1 strains, which were precultivated from blood cells or cerebrospinal fluid (CSF) or were directly obtained from CSF cells of patients with and without neurological symptoms. The results show that there are sequence similarities between a short segment of gp120 of clinical HIV-1 strains and the neurotoxic loop. The strains of patients with neurological symptoms did not, however, show a genetic shift of their sequences towards a greater similarity to the sequences of snake venom neurotoxins and rabies virus glycoprotein as compared to the strains of asymptomatic individuals.

Some loose references I don't have time to explore now:
1. Molecular mimicry of HIV gp120 (2005) https://t.co/KzfEpbjbvk
2. McCoy cell line as a possible model containing CD4+ receptors for the study of HIV-1 replication
https://t.co/iG8NSrGrlI

Some loose references I don't have time to explore now:
3. Snake envenomation https://t.co/uJy1bi7NEU
4. Modified venom and venom components as anti-retroviral agents (PATENT)
https://t.co/VRH0gJlbqM

Loose references I don't have time to explore now:
5. Recombinant Newcastle disease virus (NDV) strain rL-RVG expressing the rabies virus glycoprotein
https://t.co/31SNcPXNYJ
6. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein
https://t.co/Ce9cAEOCQH

One way that SARS-COV-2 gets in your brain
Role of HIV gp120 in crossing blood brain barrier
Interactions of SARS-CoV-2 with the Blood–Brain Barrier
https://t.co/oZWRqn5cGr

HIV-1 protein gp120 crosses the blood-brain barrier role of adsorptive endocytosis
https://t.co/9pdkqSt0xz

157. Banks W.A., Kastin A.J., Akerstrom V. HIV-1 protein gp120 crosses the blood-brain barrier: Role of adsorptive endocytosis. *Life Sci.* 1997;61:PL119–PL125. doi: 10.1016/S0024-3205(97)00597-3. [PubMed] [CrossRef] [Google Scholar]

Jack Sim's Final Thesis before something happened to him down at the Cardiff Docks...
Final Thesis Jack Sim
In-vitro Characterisation of Targeting Ligands for
Enhanced Delivery Across the Blood-Brain Barrier
https://t.co/GAURhTA376

A potential interaction between the SARS-CoV-2 spike protein and nicotinic acetylcholine receptors
https://t.co/XQ71CTh93k

Based on the early observations of the lower-than-expected smoking prevalence in hospitalized COVID-19 patients, Changeux and colleagues suggested a role for nicotinic acetylcholine receptors (nAChRs) in the pathophysiology of COVID-19 via a direct interaction between these receptors and the viral spike glycoprotein ([20]). This suggestion was based on the fact that the spike protein contains a sequence motif similar to known nAChR antagonists ([20]) (Fig. S1), such as α-bungarotoxin from *Bungarus multicinctus* and glycoprotein from *Rabies lyssavirus* (formerly *Rabies virus*). Changeux et al. and others also proposed that COVID-19 might be controlled or mitigated by the use of nicotine, if the latter can compete with the virus for binding to these receptors (e.g., ([9,18,20, 21, 22, 23, 24])). If interactions with nAChRs are important, they may be relevant for some of the systemic effects observed in COVID-19.

Binding Confirmed Again
Simulations support the interaction of the SARS-CoV-2 spike protein with nicotinic acetylcholine receptors and suggest subtype specificity
https://t.co/umDn3S549X

Changeux et al. recently suggested that the SARS-CoV-2 spike (S) protein may interact with nicotinic acetylcholine receptors (nAChRs). Such interactions may be involved in pathology and infectivity. Here, we use molecular simulations of validated atomically detailed structures of nAChRs, and of the S protein, to investigate this 'nicotinic hypothesis'. We examine the binding of the Y674-R685 loop of the S protein to three nAChRs, namely the human α4β2 and α7 subtypes and the muscle-like αβγδ receptor from Tetronarce californica. Our results indicate that Y674-R685 has affinity for nAChRs and the region responsible for binding contains the PRRA motif, a four-residue insertion not found in other SARS-like coronaviruses. In particular, R682 has a key role in the stabilisation of the complexes as it forms interactions with loops A, B and C in the receptor's binding pocket. The conformational behaviour of the bound Y674-R685 region is highly dependent on the receptor subtype, adopting extended conformations in the α4β2 and α7 complexes and more compact ones when bound to the muscle-like receptor. In the α4β2 and αβγδ complexes, the interaction of Y674-R685 with the receptors forces the loop C region to adopt an open conformation similar to other known nAChR antagonists. In contrast, in the α7 complex, Y674-R685 penetrates deeply into the binding pocket where it forms interactions with the residues lining the aromatic box, namely with TrpB, TyrC1 and TyrC2. Estimates of binding energy suggest that Y674-R685, forms stable complexes with all three nAChR subtypes, but has highest affinity for the muscle-type receptor. Analyses of the simulations of the full-length S protein show that the Y674-R685 region is accessible for binding, and suggest a potential binding orientation of the S protein with nAChRs.

Above paper also here:
Simulations support the interaction of the SARS-CoV-2 spike protein with nicotinic acetylcholine receptors
https://t.co/1Qg0tKg3YI
Media Review:
https://t.co/2yyYJw3zVv

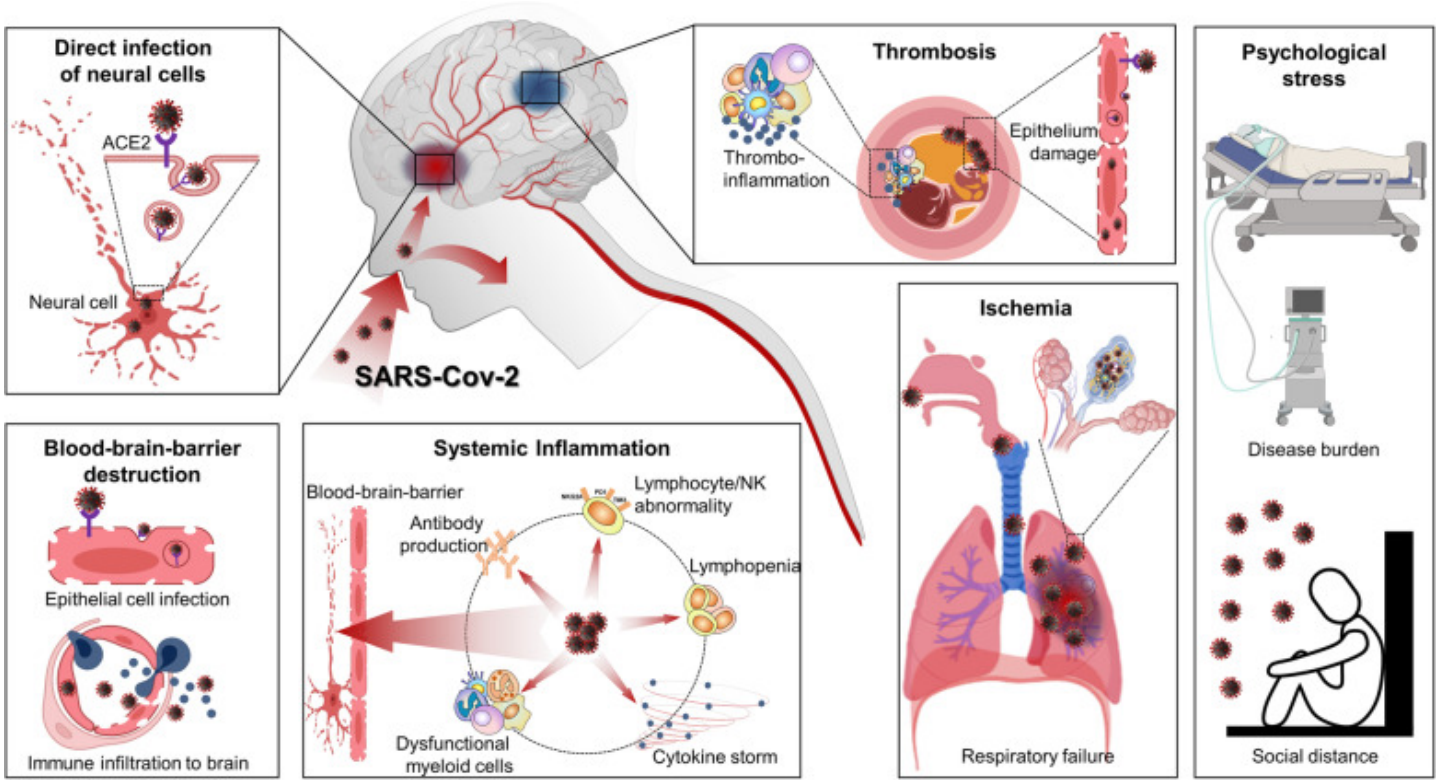
1. SAg-like motif on SARS-CoV-2 spike distinguished by its high sequence- & structural-similarity to a segment of SEB.
2. SARS-CoV-2 spike may act as a superantigen to trigger the development of MIS-C as well as cytokine storm in adult COVID-19 patients
https://t.co/sXQyd7kMx5

Using structure-based computational models, we recently demonstrated that the SARS-CoV-2 spike glycoprotein has a unique insert that displays a SAg-like sequence motif that exhibits a high-affinity for binding TCRs, and may form a ternary complex with MHCII (Cheng et al., 2020). Furthermore, we identified that this SAg-like motif has high sequence and structural similarity to a motif in SEB (Cheng et al., 2020). We further reported TCR Vβ-skewing in adult COVID-19 patients with severe hyperinflammation, consistent with a SAg immune response (Cheng et al., 2020).

SAg and SEB gonna get you!
COVID-19–associated multisystem inflammatory syndrome in children (MIS-C): A novel disease that mimics toxic shock syndrome—the superantigen hypothesis
https://t.co/NxmPM719VB

Through structure-based computational modeling, we discovered that the SARS-CoV-2 spike protein encodes a high-affinity SAg-like sequence motif near the S1/S2 cleavage site of the spike protein. The region containing this motif exhibits a high affinity to bind to T-cell receptors (TCRs) by closely associating with the variable domains' complementarity-determining regions of both the α and β chains(Fig 1).[5 , 6] Notably, this region (containing the SAg-like motif) is highly similar in sequence and 3-dimensional structure to a fragment of the superantigenic *Staphylococcal Enterotoxin B* (SEB), which is known to interact with the TCR and CD28.[6] SEB triggers large-scale T-cell activation and proliferation, resulting in massive production of a proinflammatory cytokine profile typical of TSS, similar to that which entails severity and death from COVID-19. Next-generation immunosequencing analysis of T-cell repertoires from patients with COVID-19 indicated that severe COVID-19 was associated with a TCRVβ skewing, enrichment of selected Vβ genes, and increased J diversity, consistent with SAg activity.[5] These data support our hypothesis that MIS-C, as well as cytokine storm observed in adult patients with severe COVID-19, is mediated by SAg activity of the SARS-CoV-2 spike protein. Additional, prospective studies in adult and pediatric cohorts are warranted to test this hypothesis.

Can COVID-19 pandemic boost the epidemic of neurodegenerative diseases?
https://t.co/b8PssOG6my
SEB confirmed again



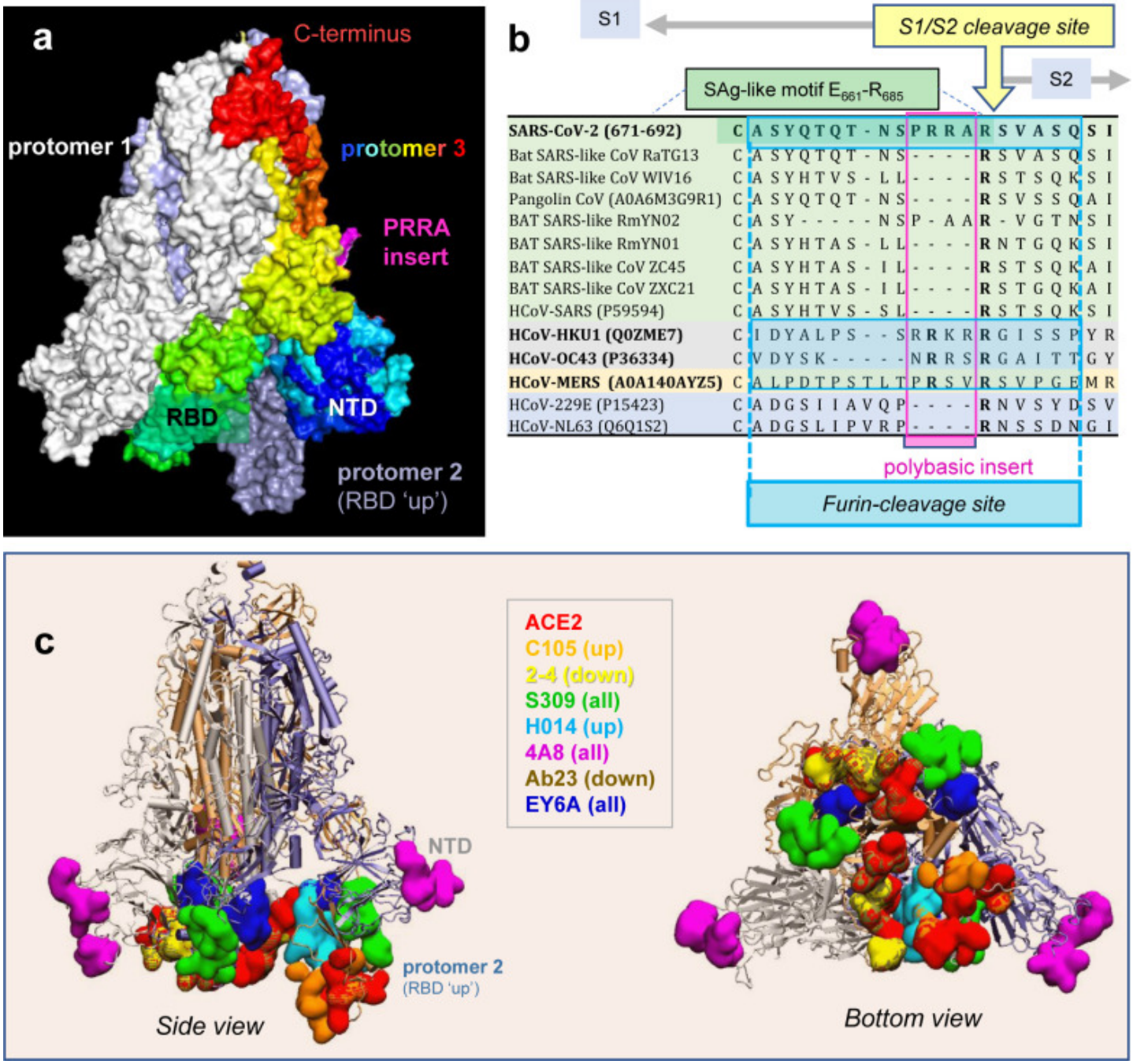
Smoking Break
1. What is Happening with Smokers and COVID-19?
https://t.co/wXGYU9EjAp
2. Cytokine Release Syndrome (CRS) and Nicotine in COVID-19 Patients
https://t.co/3oA9sWOTaU
and
https://t.co/4yGz47igy2
3. Involvement of nicotine receptors in COVID-19

https://t.co/0GtJwhu9tU

Abstract

SARS-CoV-2 is a new coronavirus that has caused a worldwide pandemic. It produces severe acute respiratory disease (COVID-19), which is fatal in many cases, characterised by cytokine release syndrome (CRS). According to the World Health Organization (WHO), those who smoke are likely to be more vulnerable to infection. Here, in order to clarify the epidemiologic relationship between smoking and COVID-19, we present a systematic literature review until 28 April 2020 and a meta-analysis. It includes 18 recent COVID-19 clinical and epidemiological studies based on smoking patient status from 720 initial studies in China, USA, and Italy. The percentage of hospitalised current smokers was 7.7% (95%CI: 6.9-8.4) in China, 2.3% (95%CI: 1.7-2.9) in the USA and 7.6% (95%CI: 4.2-11.0) in Italy. These percentages were compared to the smoking prevalence of each country and statistically significant differences were found in them all ($p < 0.0001$). By means of the meta-analysis, we offer epidemiological evidence showing that smokers were statistically less likely to be hospitalised (OR=0.18, 95%CI: 0.14-0.23, $p<0.01$). CRS and exacerbated inflammatory response are associated with aggravation of hospitalise patients. In this scenario, we hypothesise that nicotine, not smoking, could ameliorate the cytokine storm and severe related inflammatory response through the cholinergic-mediated anti-inflammatory pathway.

Back to the SEB Mystery - @w_mccairn @Parsifaler
Who put the Benzedrine in Mrs Murphy's Ovaltine?
Who put SAg & SEB in SARS COV-2's Spike Protein?
Note:
A monoclonal antibody against staphylococcal enterotoxin B superantigen inhibits SARS-CoV-2 entry
https://t.co/x7iAVt4Zvm



Nasty, very Nasty!

But a solution is proposed...

A monoclonal antibody against staphylococcal enterotoxin B superantigen inhibits SARS-CoV-2 entry in vitro

https://t.co/x7iAVt4Zvm

and

https://t.co/NgZ7aNd2KS

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause severe interstitial pneumonia with hyperinflammation[1,2], as well as many extrapulmonary manifestations[3]. Furthermore, a novel multisystem inflammatory syndrome (MIS), reported in both children (MIS-C) and adults (MIS-A), has been observed in patients that either tested positive for, or had epidemiological links to, COVID-19[4–7]. MIS-C manifests as persistent fever and hyperinflammation with multi-organ system involvement[4–7]. The clinical similarity between MIS-C or severe COVID-19 and the toxic shock syndrome (TSS) caused by bacterial superantigens (SAg) led to the hypothesis that SARS-CoV-2 might possess a SAg-like motif that acts acutely or via an autoimmune-like mechanism to trigger hyperinflammation[8,9]. Comparison with bacterial toxins revealed a motif in the SARS-CoV-2 spike (S) protein whose sequence and structure are highly similar to a segment of a bacterial SAg, staphylococcal enterotoxin B (SEB). T cell receptor (TCR) skewing observed in severe COVID-19 patients further supported the SAg-like character of the S protein[8].

A nice summary of the issue of mimicry between HIV-1 gp120, Rabies Glycoprotein, Snake Neurotoxin, as well as the role of Nicotinic Receptors, hence smoking as prophylaxis:

Molecular mimicry between rabies virus glycoprotein & HIV-1 GP120
https://t.co/Ahp5mE27uI

Abstract

The 160-170 sequence of human immunodeficiency virus (HIV)-1 gp120 mimics a nicotinic receptor-binding motif of rabies virus glycoprotein and snake neurotoxins. This sequence has been proposed to be involved in the binding of HIV-1 gp120 to the acetylcholine binding sites of nicotinic receptors. By using biomolecular interaction analysis (BIA) technology we have found that HIV-1 gp120 can bind to detergent-extracted nicotinic receptor from fetal calf muscle. The binding is inhibited by nicotine and by a synthetic peptide reproducing the gp120 160-170 sequence. The molecular mimicry between gp120 and rabies virus glycoprotein is confirmed by cross-reacting antibodies. We have found that vaccination against rabies can induce the production of anti-HIV-1 gp120 antibodies in humans. The cross-reacting antibodies are directed to the gp120 sequence involved in the mimicry with the rabies virus glycoprotein. The cross-reactivity between the rabies virus and HIV-1 has important implications in transfusion medicine. Moreover, the presence of cross-reacting antibodies between the nicotinic receptor binding site of rabies virus glycoprotein and a fragment of HIV-1 gp120 strengthens the hypothesis about the possible role of nicotinic receptors as potential receptors for HIV-1 in the central nervous system.

Similar articles

Binding of HIV-1 gp120 to the nicotinic receptor.

This concept has even evolved into a vaccine
A Novel Vaccine Employing Non-Replicating Rabies Virus Expressing Chimeric SARS-CoV-2 Spike Protein Domains: Functional Inhibition of Viral/Nicotinic Acetylcholine Receptor Complexes
https://t.co/Zp6gHLPE1x

Abstract

The emergence of the novel ß-coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in a global pandemic of coronavirus disease 2019 (COVID-19). Clinical studies have documented that potentially severe neurological symptoms are associated with SARS-CoV-2 infection, thereby suggesting direct CNS penetration by the virus. Prior studies have demonstrated that the destructive neurological effects of rabies virus (RABV) infections are mediated by CNS transport of the virus tightly bound to the nicotinic acetylcholine receptor (nAChR). By comparison, it has been hypothesized that a similar mechanism exists to explain the multiple neurological effects of SARS-CoV-2 via binding to peripheral nAChRs followed by orthograde or retrograde transport into the CNS. Genetic engineering of the RABV has been employed to generate novel vaccines consisting of non-replicating RABV particles expressing chimeric capsid proteins containing human immunodeficiency virus 1 (HIV-1), Middle East respiratory syndrome (MERS-CoV), Ebolavirus, and hepatitis C virus (HCV) sequences. Accordingly, we present a critical discussion that integrates lessons learned from prior RABV research and vaccine development into a working model of a SARS-CoV-2 vaccine that selectively targets and neutralizes CNS penetration of a tightly bound viral nAChR complex.

Superantigens and Long Covid?

Persistent SARS-2 infections contribute to long COVID-19

https://t.co/R5UI7pOynJ

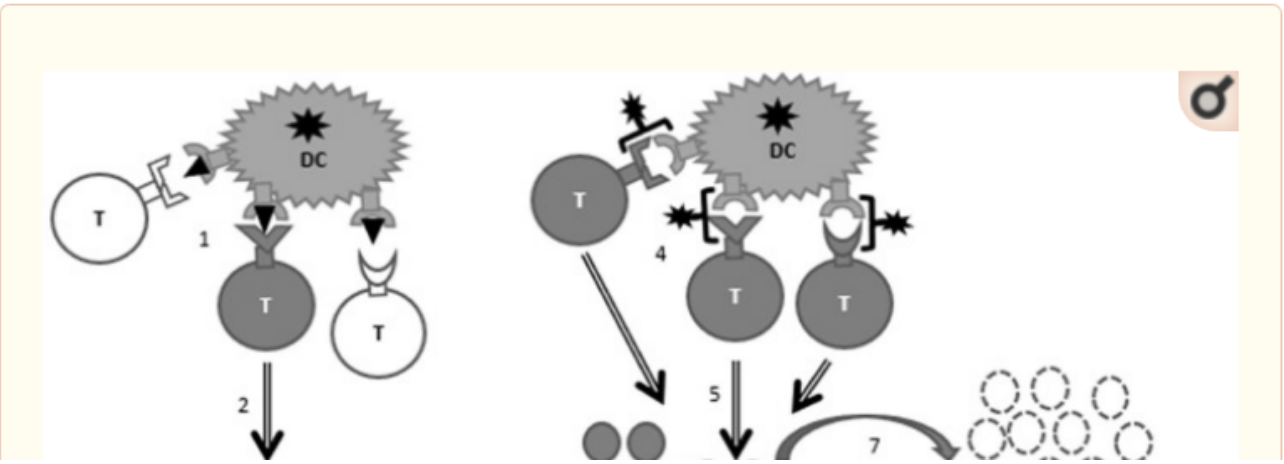
For the Curious:

Dampened Bat Immune System Interferon Response?

Outline of the hypothesis

Go to:

Superantigens are described for SARS-CoV-2 [22], [23], and superantigens are known to cause cytokine storm, by a polyclonal T cell activation [24]. SARS-CoV-2 induces a very strong immune response [25], which could be due to its superantigen(s). Down regulation of the immune system by corticosteroid treatment reduces mortality in severe COVID-19 [26], indicating the need for immune suppression. In most patients down-regulation of superantigen responses occurs naturally, and therefore superantigen-induced immune responses are all but efficient in generating immune response [27]. The negative immunological feedback loop could allow the virus to reproduce in the body, especially where the immune response is relatively weak. Fig. 1 shows the delicate balance between immune activation and suppression in case of a superantigen infection.



Let's finish with a question:
Why COVID-19 Transmission Is More Efficient and Aggressive Than Viral Transmission in Previous Coronavirus Epidemics?
https://t.co/yNTOP9Lf37
Good Luck with finding the answers!

Serial passage is likely a factor in this issue, as @Harvard2H pointed out:
https://t.co/9iQQBiUjaS
References 145, 146 & 147 for the curious:
https://t.co/yNTOP9Lf37
Host resistance influences patterns of experimental viral adaptation
https://t.co/gnLm32z0G6

Often, the viruses emerging from more resistant hosts have lower overall virulence than viruses emerging from more susceptible hosts. There is correlative evidence supporting the link between the host resistance and virulence evolution [142,143,144]. For example, since virulent strains can be favored over avirulent pathogen strains as a result of the within-host competition, resistant hosts may limit competitive interactions between co-infecting pathogens, thereby hampering the evolution of virulence [145]. The largest adaptive responses in a viral pathogen are achieved via the serial passage of the virus through resistant vs. susceptible hosts, and such adaptive responses are often linked to the most dramatic increases in virulence [146]. It is also possible that the optimal environment for virus adaptation is provided by the hosts with intermediate levels of immunity. This is because such individuals represent an appropriate environment for the optimization of both the pathogen population size and the strength of the immune-mediated selection [147]. All the accumulated data indicate that SARS-CoV-2 may gain some adaptation and enhanced virulence, which globally contributes to its pathogenicity and transmission.