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SARS-CoV-2: The Self-Nonself Issue and Diagnostic Tests

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Abstract

Objective At present, false negatives/positives have been reported in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) diagnostics. Searching for the molecular basis of such tests' unreliability, this study aimed at defining how specific are the sequences used in serological and polymerase chain reaction (PCR) tests to detect SARS-CoV-2.

Materials and Methods Analyses were performed on the leading SARS-CoV-2 biomarker spike glycoprotein (gp). Sharing of peptide sequences between the spike antigen and the human host was analyzed using the Peptide Search program from Uniprot database. Sharing of oligonucleotide sequences was investigated using the nucleotide Basic Local Alignment Search Tool (BLASTn) from National Center for Biotechnology Information (NCBI).

Results Two main points stand out: (1) a massive pentapeptide sharing exists between the spike gp and the human proteome, and only a limited number of pentapeptides (namely 107) identify SARS-CoV-2 spike gp as nonself when compared with the human proteome, and (2) the small phenetic difference practically disappears at the genetic level. Indeed, almost all of the 107 pentadecameric nucleotide sequences coding for the pentapeptides unique to SARS-CoV-2 spike gp are present in human nucleic acids too.

Conclusion The data are of immunological significance for defining the issue of the viral versus human specificity and likely explain the fact that false positives can occur in serological and PCR tests for SARS-CoV-2 detection.

Keywords
- SARS-CoV-2 spike gp
- self-nonself
- serological tests
- PCR tests
- false positives

Introduction

Canonical immunology lays on the concept that the human immune system evolved to attack and destroy extraneous entities such as infectious pathogens (that is, the "nonself"), in this way defending the human host (that is, the "self") from harmful infections.[1] Accordingly, self-reactive lymphocytes that might react with peptides/structures present in the human host are selectively deleted from the immune repertoire to protect the host from self-reactivity.[1,2]

Hence, identification and mathematical definition of self and nonself entities are a *conditio sine qua non* for furthering our still incomplete understanding of the immune system,[3] exploiting the immunogenic potential of vaccines in fighting

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infectious agents, and formulating specific diagnostic tools.[4] Indeed, discriminating self from nonself currently is all the more necessary at the molecular level because in silico comparative sequence analyses[5,6] have documented that a high level of peptide sharing exists between pathogens and the human host. Immunologically, this peptide sharing highlights the risk that serological immunoassays for measuring patients' immune responses against a pathogen might actually reflect the extent of cross-reactivity phenomena targeting human proteins.[7]

In this scientific framework, taking the clue from recent data on the peptide sharing between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and *Homo sapiens*,[8–12] the present study used SARS-CoV-2 spike glycoprotein (gp) as a research model and mathematically quantified the phenetic and genetic sequence differences that characterize the viral antigen as nonself when compared with the human host. That is, the entire human proteome was searched for peptide sequences shared with the viral gp. Pentapeptides were used as scanning probes to determine the exact viral versus human peptide sharing because a five amino acid grouping is the minimal antigenic and immunogenic space sufficient to specify an immune reaction, that is five amino acids represent the immune measurement unit.[13–20] Specifically, the research was addressed to find pentapeptide identities, i.e., perfect matches, between SARS-CoV-2 gp and human proteins. This is because for a perfect peptide match (i.e., 5/5 identities and no gaps allowed) there is one and only one corresponding nucleotide sequence while for a homologous peptide (i.e., a peptide where four out of five amino acids are identical but there is a gap) there would be more corresponding nucleotide sequences depending on the gap position.[20]

Following whole human proteome analyses, data were obtained showing that only a handful of pentapeptides (exactly 107 out of 1,269 pentapeptides) are uniquely present in the viral protein antigen and absent in the human host, in this way specifying the SARS-CoV-2 spike gp as nonself when compared with the human proteome. However, this phenetic difference disappears at the genetic level. Indeed, furthering at the nucleotide level the sequence analyses revealed that the pentadecameric oligonucleotides coding for the 107 pentapeptides present in the SARS-CoV-2 spike gp and not expressed in the human proteome actually are present in human nucleic acids too.

Materials and Methods

SARS-CoV-2 spike amino acid and nucleotide sequences were retrieved from isolate Wuhan-Hu-1, GenBank: MN908947.3. The viral protein antigen, which is 1,273 amino acids long, was dissected into 1,269 pentapeptides offset by 1 residue, that is, overlapped each other by 4 residues (i.e., MFVFL, FVFLV, VFLVL, and so forth). Next, for each viral pentapeptide, the entire human proteome was searched for occurrences of the same pentapeptide match by using PIR Peptide match (https://research.bioinformatics.udel.edu/peptidematch/index.jsp) and Peptide Search program (https://www.uniprot.org/peptidesearch/).[21]

Viral pentapeptides that are absent in the human proteome were further investigated at the genetic level using the nucleotide Basic Local Alignment Search Tool (BLASTn) program (http://blast.ncbi.nlm.nih.gov).[22,23] That is, for each pentapeptide unique to SARS-CoV-2 spike gp, the corresponding coding pentadecameric oligonucleotide sequence was used as a probe to scan the entire human NCBI (National Center for Biotechnology Information) nucleotide collection searching for instances of the same identical oligonucleotide sequence (i.e., 15/15 identities and no gaps allowed).

Results

SARS-CoV-2 Spike gp versus the Human Proteome: Self-Nonself at the Phenetic Level

Following PIR matching analyses of the SARS-CoV-2 spike gp versus the entire human proteome, the SARS-CoV-2 spike gp self could be defined as a set of 107 pentapeptide perfect matches. That is, only 107 out of 1,269 viral pentapeptides uniquely occur in the SARS-CoV-2 antigen and represent the molecular signature of the viral antigen, while the remaining 1,162 viral pentapeptides occur in the human proteome. ►**Table 1** describes the pentapeptides unique to SARS-CoV-2 spike gp.

Hence, a first datum provided from this study is that serological tests to measure the extent of the antiviral immune response might equate mostly to measuring the immune response against proteins of the human host.

SARS-CoV-2 Spike Gene versus the Human Genome: Self-Nonself at the Genetic Level

As a second step, the 107 pentapeptides that are absent in the human proteome and uniquely present in the spike gp were controlled at the genetic level for oligonucleotide sharing. The scientific rationale at the basis of such control analyses is the following. If the absence of the 107 pentapeptides described in ►**Table 1** marks and differentiates the viral gp antigen from the human proteome, as a logical consequence such an absence must exist at the nucleic acid level too, by being nucleic acids the ultimate repository of the information that specifies and identifies proteins and organisms.

On that account, human nucleic acids were searched for oligonucleotide sequences coding for the SARS-CoV-2 spike gp pentapeptides not expressed in the human proteome. The results obtained by using the BLASTn program are illustrated in ►**Table 2** that shows that practically all pentadecameric oligonucleotide sequences corresponding to the unique 107 SARS-CoV-2 spike gp pentapeptides occur and often repeatedly recur in coding and/or noncoding human nucleic acids. Exception is the pentapeptide YSSAN (amino acid position: 160–164), the corresponding oligonucleotide of which was repeatedly found at the 13mer level.

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Table 1 SARS-CoV-2 spike gp pentapeptides that are absent in the human proteome

Pos[a]	Sequence[b]	Pos[a]	Sequence[b]	Pos[a]	Sequence[b]	Pos[a]	Sequence[b]
34	RGVYY	230	PIGIN	538	CVNFN	901	MAYRF
35	GVYYP	257	GWTAG	617	CTEVP	904	RFNGI
36	VYYPD	264	AYYVG	651	IGAEH	1028	MSECV
37	YYPDK	280	NENGT	674	YQTQT	1045	GYHLM
61	NVTWF	297	SETKC	675	QTQTN	1046	YHLMS
62	VTWFH	311	GIYQT	693	IAYTM	1072	KNFTT
63	TWFHA	350	VYAWN	694	AYTMS	1078	PAICH
65	FHAIH	351	YAWNR	734	TSVDC	1097	NGTHW
85	PFNDG	361	CVADY	737	DCTMY	1098	GTHWF
101	IRGWI	375	STFKC	739	TMYIC	1099	THWFV
102	RGWIF	377	FKCYG	740	MYICG	1100	HWFVT
105	IFGTT	378	KCYGV	745	DSTEC	1101	WFVTQ
130	VCEFQ	379	CYGVS	759	FCTQL	1104	TQRNF
131	CEFQF	393	TNVYA	793	PIKDF	1107	NFYEP
132	EFQFC	418	IADYN	836	QYGDC	1129	IGIVN
136	CNDPF	420	DYNYK	837	YGDCL	1134	NTVYD
143	VYYHK	421	YNYKL	838	GDCLG	1209	IKWPW
148	NNKSW	433	VIAWN	848	DLICA	1210	KWPWY
149	NKSWM	435	AWNSN	849	LICAQ	1211	WPWYI
152	WMESE	436	WNSNN	850	ICAQK	1214	YIWLG
153	MESEF	477	STPCN	851	CAQKF	1215	IWLGF
160	YSSAN	479	PCNGV	868	MIAQY	1224	IAIVM
166	CTFEY	485	GFNCY	883	SGWTF	1233	LCCMT
184	GNFKN	486	FNCYF	885	WTFGA	1234	CCMTS
199	GYFKI	493	QSYGF	897	FAMQM	1236	MTSCC
203	IYSKH	534	VKNKC	899	MQMAY	1253	CCKFD
204	YSKHT	536	NKCVN	900	QMAYR		

[a]Position along the SARS-CoV-2 spike gp.
[b]Amino acid sequence in one-letter code.

Discussion

This study analyzes the pentapeptide sharing between SARS-CoV-2 spike gp and the human proteome, and mathematically defines the identity of the viral antigen as a set of 107 pentapeptides uniquely present in the spike gp and absent in the human proteins. Crucially, this viral versus human phenetic specificity disappears at the genetic level. The data have relevant implications in SARS-CoV-2 immunology, vaccinology, and clinical diagnostics.

Indeed, in the immunological context described under Introduction, the presence in human nucleic acids of the oligonucleotide sequences coding for the 107 pentapeptides that phenetically specify the viral antigen fails to support the deterministic hypothesis according to which the immune system evolved to discriminate infectious nonself from noninfectious self.[1–3] Rather, ►**Tables 1** and **2** suggest that SARS-CoV-2 and humans derived their genetic information from common ancestral templates. In this regard, this study supports the viral eukaryogenesis hypothesis, according to which the primordial eukaryotic cell was a consortium consisting of a viral ancestor of the nucleus, an archaeal ancestor of the eukaryotic cytoplasm, and a bacterial ancestor of mitochondria.[24–26]

Moreover, the present data confirm and strengthen the concept[27–32] that only vaccine formulations based on peptide sequences uniquely present in infectious pathogens and absent in the host proteins have the potential to selectively hit the pathogens and halt infections. In the case in point, by being absent in the human proteome, the unique SARS-CoV-2 spike gp peptides described in ►**Table 1** represent an ideal basic peptidome platform that could result in effective and highly specific anti-SARS-CoV-2 vaccines exempt from harmful cross-reactivity.

Clinically and of utmost importance in diagnostics, the viral versus human pentapeptide and oligonucleotide sharing shown in ►**Table 1** and **2**, respectively, could have a

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Table 2 Occurrences in human nucleic acids of the pentadecameric oligonucleotides coding the 107 pentapeptides uniquely present in SARS-CoV-2 spike gp

Pentapeptide[a]	5′-Oligodeoxynucleotide-3′[b,c]	Occurrences in human nucleic acids	
		Plus strand	Minus strand
RGVYY	CGTGGTGTTTATTAC	1	1
GVYYP	GGTGTTTATTACCCT	4	–
VYYPD	GTTTATTACCCTGAC	2	–
YYPDK	TATTACCCTGACAAA	13	4
NVTWF	AATGTTACTTGGTTC	7	7
VTWFH	GTTACTTGGTTCCAT	5	11
TWFHA	ACTTGGTTCCATGCT	12	14
FHAIH	TTCCATGCTATACAT	13	9
PFNDG	CCATTTAATGATGGT	8	12
IRGWI	ATAAGAGGCTGGATT	3	7
RGWIF	AGAGGCTGGATTTTT	41	59
IFGTT	ATTTTTGGTACTACT	13	11
VCEFQ	GTCTGTGAATTTCAA	15	21
CEFQF	TGTGAATTTCAATTT	46	64
EFQFC	GAATTTCAATTTTGT	46	43
CNDPF	TGTAATGATCCATTT	20	21
VYYHK	GTTTATTACCACAAA	17	19
NNKSW	AACAACAAAAGTTGG	18	19
NKSWM	AACAAAAGTTGGATG	22	31
WMESE	TGGATGGAAAGTGAG	29	25
MESEF	ATGGAAAGTGAGTTC	6	19
YSSAN	TATTCTAGTGCGAAT	–	–
CTFEY	TGCACTTTTGAATAT	2	7
GNFKN	GGTAATTTCAAAAAT	30	45
GYFKI	GGTTATTTTAAAATA	54	71
IYSKH	ATATATTCTAAGCAC	18	30
YSKHT	TATTCTAAGCACACG	5	2
PIGIN	CCAATAGGTATTAAC	4	20
GWTAG	GGTTGGACAGCTGGT	5	11
AYYVG	GCTTATTATGTGGGT	18	21
NENGT	AATGAAAATGGAACC	28	10
SETKC	TCAGAAACAAAGTGT	21	27
GIYQT	GGAATCTATCAAACT	3	10
VYAWN	GTTTATGCTTGGAAC	2	2
YAWNR	TATGCTTGGAACAGG	5	8
CVADY	TGTGTTGCTGATTAT	10	15
STFKC	TCCACTTTTAAGTGT	19	17
FKCYG	TTTAAGTGTTATGGA	13	15
KCYGV	AAGTGTTATGGAGTG	2	1
CYGVS	TGTTATGGAGTGTCT	2	–
TNVYA	ACTAATGTCTATGCA	5	6
IADYN	ATTGCTGATTATAAT	44	43
DYNYK	GATTATAATTATAAA	63	46

(*Continued*)

Table 2 (*Continued*)

Pentapeptide[a]	5′-Oligodeoxynucleotide-3′[b,c]	Occurrences in human nucleic acids	
		Plus strand	Minus strand
YNYKL	TATAATTATAAATTA	71	82
VIAWN	GTTATAGCTTGGAAT	6	13
AWNSN	GCTTGGAATTCTAAC	17	4
WNSNN	TGGAATTCTAACAAT	15	23
STPCN	AGCACACCTTGTAAT	7	6
PCNGV	CCTTGTAATGGTGTT	9	4
GFNCY	GGTTTTAATTGTTAC	10	13
FNCYF	TTTAATTGTTACTTT	50	29
QSYGF	CAATCATATGGTTTC	10	27
VKNKC	GTTAAAAACAAATGT	35	56
NKCVN	AAAAACAAATGTGTC	19	44
CVNFN	TGTGTCAATTTCAAC	60	42
CTEVP	TGCACAGAAGTCCCT	21	9
IGAEH	ATAGGGGCTGAACAT	1	3
YQTQT	TATCAGACTCAGACT	37	21
QTQTN	CAGACTCAGACTAAT	9	7
IAYTM	ATTGCCTACACTATG	1	4
AYTMS	GCCTACACTATGTCA	1	1
TSVDC	ACATCAGTAGATTGT	12	8
DCTMY	GATTGTACAATGTAC	–	1
TMYIC	ACAATGTACATTTGT	18	32
MYICG	ATGTACATTTGTGGT	13	21
DSTEC	GATTCAACTGAATGC	1	2
FCTQL	TTTTGTACACAATTA	9	12
PIKDF	CCAATTAAAGATTTT	26	22
QYGDC	CAATATGGTGATTGC	1	–
YGDCL	TATGGTGATTGCCTT	3	–
GDCLG	GGTGATTGCCTTGGT	3	5
DLICA	GACCTCATTTGTGCA	5	2
LICAQ	CTCATTTGTGCACAA	6	12
ICAQK	ATTTGTGCACAAAAG	19	37
CAQKF	TGTGCACAAAAGTTT	23	19
MIAQY	ATGATTGCTCAATAC	1	5
SGWTF	TCTGGTTGGACCTTT	53	42
WTFGA	TGGACCTTTGGTGCA	1	–
FAMQM	TTTGCTATGCAAATG	26	15
MQMAY	ATGCAAATGGCTTAT	5	9
QMAYR	CAAATGGCTTATAGG	4	1
MAYRF	ATGGCTTATAGGTTT	9	10
RFNGI	AGGTTTAATGGTATT	1	5
MSECV	ATGTCAGAGTGTGTA	6	6
GYHLM	GGCTATCATCTTATG	1	–
YHLMS	TATCATCTTATGTCC	–	4
KNFTT	AAGAACTTCACAACT	5	8
PAICH	CCTGCCATTTGTCAT	17	13

(*Continued*)

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Table 2 (*Continued*)

Pentapeptide[a]	5′-Oligodeoxynucleotide-3′[b,c]	Occurrences in human nucleic acids	
		Plus strand	Minus strand
NGTHW	AATGGCACACACTGG	14	11
GTHWF	GGCACACACTGGTTT	4	11
THWFV	ACACACTGGTTTGTA	5	4
HWFVT	CACTGGTTTGTAACA	5	5
WFVTQ	TGGTTTGTAACACAA	52	54
TQRNF	ACACAAAGGAATTTT	47	62
NFYEP	AATTTTTATGAACCA	22	35
IGIVN	ATAGGAATTGTCAAC	3	1
NTVYD	AACACAGTTTATGAT	15	15
IKWPW	ATAAAATGGCCATGG	27	25
KWPWY	AAATGGCCATGGTAC	5	3
WPWYI	TGGCCATGGTACATT	12	5
YIWLG	TACATTTGGCTAGGT	2	4
IWLGF	ATTTGGCTAGGTTTT	18	14
IAIVM	ATTGCCATAGTAATG	9	5
LCCMT	CTTTGCTGTATGACC	4	14
CCMTS	TGCTGTATGACCAGT	2	6
MTSCC	ATGACCAGTTGCTGT	11	2
CCKFD	TGCTGCAAATTTGAT	11	21

[a]Pentapeptides uniquely present in SARS-CoV-2 spike gp when compared with the human proteome.
[b]Oligodeoxynucleotide sequences coding for pentapeptides unique to SARS-CoV-2 spike gp.
[c]Each pentadecameric oligodeoxynucleotide sequence was used as a probe to scan the entire human NCBI nucleotide collection for exact 15/15 identities with no gaps allowed, using BLASTn program.[22,23] Further data and details are available at http://blast.ncbi.nlm.nih.gov.

severe impact on the validity of the current polymerase chain reaction (PCR) tests for SARS-CoV-2 spike detection. In fact, claims have been reported about the rates of false negatives/positives in SARS-CoV-2 detection by means of serological and PCR tests,[33–38] in this way raising numerous concerns. As observed by Viswanathan et al,[39] healthy individuals may be falsely identified as positive, requiring confirmatory testing and potentially leading to the unnecessary isolation of these individuals. In agreement, Gubbay et al[40] suggested that large-scale SARS-CoV-2 screening testing initiatives among low pretest probability populations should be evaluated thoroughly prior to implementation given the risk of false positives and consequent potential for harm at the individual and population levels, and this not to mention the enormous waste of economic resources that might be caused by unreliable large-scale SARS-CoV-2 tests. As a matter of fact, data from ►**Table 1** clearly suggest that serological immunoassays for measuring antipathogen antibody response might actually be indicative of cross-reactions with human proteins. In line with ►**Table 1**, ►**Table 2** indicates that SARS-CoV-2 spike detection by PCR might be affected by the risk that human nucleotide sequences can be amplified, thus generating false-positive results with consequent wrong medical diagnoses. Such a risk is real in light of the fact that oligonucleotide sequences have been shown to be shared between the human genome and primers that have been proposed/used for SARS-CoV-2 detection by PCR.[41] Therefore, this study might be of help not only to understand cross-reactivity phenomena and to address new specific peptide-based approaches in anti-SARS-CoV-2 vaccinal protocols but also to define a specific and precise diagnostics of SARS-CoV-2 infection and disease.

In closing, it is also worth noting that, in agreement with reports from this laboratory,[8,10,11,42–44] Khavinson et al[45] have recently described an intense peptide sharing between almost all the SARS-CoV-2 proteins and human proteins, with hepta- and octamers scattered along the entire length of the SARS-CoV-2 spike protein molecule, thus furtherly supporting the possibility of cross-reactivity and consequent autoimmunity between SARS-CoV-2 and the human host.[7]

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Conflicts of Interest
None declared.

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