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Research Article

SARS-CoV-2 and Autoimmunity: From Myocarditis to Arrhythmia and Cardiac Death

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ABSTRACT

Background: Clinical attention has focused recently on an unexplained insurgence of Cardiovascular Diseases (CVDs) in concomitance with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Here, this study aimed at defining the possible role of autoimmune cross-reactivity and immunologic memory as mechanisms that might link the viral infection to CVDs.

Methods: Human proteins that, when altered, associate with CVDs were searched for pentapeptide immune determinants that are shared with SARS-CoV-2 spike glycoprotein (gp) and also recur in common pathogens to which the general population is frequently exposed.

Results: Comparative sequence analyses show that: 1) a high level of peptide sharing exists between SARS-CoV-2 spike gp and human proteins related to CVDs; 2) the shared peptides are endowed with an immunological potential because they are also part of experimentally validated SARS-CoV-2 spike gp-derived epitopes, and 3) most of the shared peptides are also present in infectious pathogens to which population, in general, has been already exposed.

Conclusion: Peptide sharing and cross-reactivity appear to be, respectively, the molecular platform and the basic mechanism linking SARS-CoV-2 infection to CVDs, with the past history of the individual's infections having a role in determining and specifying the immune response as well as the pathologic autoimmune sequelae.

Keywords: SARS-CoV-2 infection; SARS-CoV-2 spike gp; Cross-reactivity; Autoimmunity; Immunologic imprinting; Cardiovascular diseases; Arrhythmias; Acute congestive heart failure; Acute coronary syndrome; Hypertension; Myocarditis

INTRODUCTION

SARS-CoV-2 infection may be accompanied by cardiovascular complications such as arrhythmia, acute congestive heart failure, acute coronary syndrome, hypertension, myocarditis, and other disorders that, in the end, configurate a significant risk of heart failure and rise in death cases [1-4]. The causal link between SARS-CoV-2 infection and the cardiovascular disease is ill-defined. Indeed, thus far, it has been proposed a multifactorial etiology that includes the inflammatory cytokine storm, direct viral myocardial damage, hypoxia, angiotensin-converting enzyme 2-receptors downregulation, endogenous catecholamine adrenergic status, and drug toxicity [5-7]. In addition, autoimmunity as a pathogenic factor in cardiovascular syndrome following SARS-CoV-2) infection might be possible. Indeed, a role for Auto Antibodies (AAbs) in CVDs has been proposed following basic research using disease model and clinical studies based on the removal of AAbs from patients with dilated cardiomyopathy [8].

Searching for the possible link between SARS-CoV-2 infection and autoimmunity, this study follows the hypothesis advanced since 2000 [9] that peptide commonality between pathogens and the human host may lead to autoimmune pathologies through cross-reactivity phenomena following pathogen infection [10-14]. Accordingly, the SARS-CoV-2 spike gp was analyzed for peptide sharing i.e., molecular mimicry with human proteins, alterations of which may cause CVDs. Results indicate a high level of molecular mimicry between the viral spike gp and human proteins crucially involved in myocardial injuries, from arrhythmias to cardiac death. Moreover, inter-pathogen peptide sharing seems to contribute to the pathologic burden. Indeed, comparative sequence analyses show that many of the peptide sequences shared between the viral gp and the cardiovascular-related proteins are also present in microbial agents to whom individuals have been already exposed in their life following infection or immunization.

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MATERIALS AND METHODS

Peptide sharing between spike gp (NCBI, GenBank Protein Accession Id=QHD43416.1) from SARS-CoV-2 and human proteins related to cardiovascular syndrome was analyzed as previously detailed using the pentapeptide as minimal immune determinant unit [10-14]. Pentapeptides were used as sequence probes since a peptide grouping formed of five amino acid residues defines a minimal immune determinant that can i) induce highly specific antibodies, and ii) determine antigen-antibody specific interaction [15,16]. Human proteins linked to CVDs, arrhythmias and sudden death were obtained from UniProtKB database [17].

Methodologically the spike gp primary sequence was dissected into pentapeptides offset by one residue (that is: MFVFL, FVFLV, VFLVL, FLVLL, and so forth) and the resulting viral pentapeptides were analyzed for occurrences within the human proteins related to CVDs. Then, the shared peptides were also controlled for occurrences in the pathogens *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Haemophilus influenzae*, and *Neisseria meningitides*. Peptide match and peptide search programs that are available [17].

The immunological potential of the peptides shared between SARS-CoV-2 spike gp and CVDs-related proteins was analyzed by searching the Immune Epitope DataBase (IEDB) [18] for immune reactive SARS-CoV-2 spike gp-derived epitopes hosting the shared pentaptides.

RESULTS

Peptide sharing between Sars-CoV-2 spike gp and human proteins related to CVDs

Table 1 shows that 61 pentapeptide immune determinants are shared between Sars-CoV-2 spike gp and 42 human proteins that when altered, mutated, deficient or, however, improperly functioning may cause diseases that include arrhythmias, atherosclerosis, cardiac ischemia-reperfusion, congestive heart failure, coronary artery disease, collapse, heart failure, impaired systolic function, limb ischemia, myocardial infarction, valve problems, ventricular dilation, syncope, ventricular hypertrophy, palpitations, chest pain, long QT syndrome, sinus bradycardia, polyphasic T waves and atrial fibrillation [19-73]. Also, Table 1 shows that, mostly, these various CVDs and symptoms may also be harbingers of sudden unexpected death.

Table 1: Peptide sharing between SARS-CoV-2 spike gp and CVDs-related human proteins.

Peptides	Human proteins and functions and/or pathologies	Refs.
LQDVV, ANLAA	ABCA1. Phospholipid-transporting ATPase ABCA1 Associates with coronary artery disease; protects against atherosclerosis	19-21
DLQEL	ABCC9. ATP-binding cassette sub-family C member 9 Ventricular dilation, impaired systolic function, congestive heart failure, arrhythmia, and risk of premature death	22
DLQEL	ABCC9. ATP-binding cassette sub-family C member 9 Ventricular dilation, impaired systolic function, congestive heart failure, arrhythmia, and risk of premature death	22
YGVSP	ABL1. Tyrosine-protein kinase ABL1 Myocardial infarction; stroke; critical limb ischemia.	23, 24
VVVLS,	ACADV. Very long-chain specific acyl-CoA dehydrogenase, mitochondrial Cardiomyopathy and sudden death	25
FRSSV	ACE2. Angiotensin-converting enzyme 2 Regulation of blood volume; cardiovascular homeostasis	26
KNIDG, TTDAV, ITTDN	AKAP9. A-kinase anchor protein 9 Long QT syndrome, ventricular arrhythmias, syncope and sudden death in response to exercise or stress.	27
AGAAA	ALPK3. Alpha-protein kinase 3 Ventricular hypertrophy. Dyspnea, syncope, collapse, palpitations, and chest pain.	28
AGAAL	ANF. Natriuretic peptides A Regulation of blood pressure. Involved in atrial fibrillation. Ischemic stroke.	29-31
LDSKT, EDDSE	ANK2. Ankyrin-2 Long QT syndrome, sinus bradycardia, polyphasic T waves and atrial fibrillation.	32
NRKRI, LPPLL	ANPRA. Atrial natriuretic peptide receptor 1 Myocardial infarction	33
VFRSS	APJ. Apelin receptor Susceptibility to brain infarction and risk of hypertension	34, 35
SALGK	APOA1. Apolipoprotein A-I Myocardial infarction, acute coronary syndrome, severe carotid stenosis	36
FRSSV	BAG3. BAG family molecular chaperone regulator 3 Myofibrillar myopathy; dilated cardiomyopathy; congestive heart failure; arrhythmia. Risk of premature death	37, 38
STGSN, EELDK	CAC1C. Voltage-dependent L-type calcium channel subunit alpha-1C Brugada syndrome with tachyarrhythmia characterized by right bundle branch block and ST segment elevation on an electrocardiogram.	39
LPDPSK	CLOCK. Circadian locomoter output cycles protein kaput Stroke	40
LTTRT	DESM. Desmin Myofibrillar myopathies that also include dilated cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy	41
KLQDV, KEIDR	DMD. Dystrophin Myofibrillar myopathy. Ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Risk of premature death.	41,42
TGTGV, FGAGAA	ELN. Elastin Structural protein of aorta. Biomarker for ruptured intracranial aneurysm. Elastolysis associates with the formation of abdominal aortic aneurysms.	43-45

PPAYT, TVLPP, LQELG	ERBB4. Receptor tyrosine-protein kinase erbB-4 Heart failure	46
CALDP, CGKGY, SNGTH	FBN1. Fibrillin-1 Fibrillinopathies; risk of aortic dissection or aortic root dilatation	47, 48
GAGAA	FOXC1. Forkhead box protein C1 Coarctation of the aorta	49
GAGAA	GATA4. Transcription factor GATA-4 Increased risk of hypertension, arrhythmia, aortopathy, and heart failure.	50
NTFVSG	GNB5. Guanine nucleotide-binding protein subunit beta-5 Severe intellectual disability with poor speech, and bradycardia and/or cardiac sinus arrhythmias. Visual abnormalities, seizures, hypotonia, and gastric reflux.	51
RLQSL	HCN4. Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 4 Sick sinus syndrome. Brugada syndrome and long QT syndrome with bradycardia.	52, 53
TNGVG, FGAGAA	IRS1. Insulin receptor substrate 1 Heart failure	54
PCSFG	JAG1. Protein jagged-1 Stenosis/hypoplasia of the branch pulmonary arteries	55
GAGAA	JPH2. Junctophilin-2 Hypertrophic cardiomyopathy, which often involves the interventricular septum. Dyspnea, syncope, collapse, palpitations, chest pain. High risk of cardiac death	56
LTESNK	KCNB1. Potassium voltage-gated channel subfamily B member 1 Contributes to regulate the duration of both the action potential of cardiomyocytes and the heart ventricular repolarization QT interval.	57, 58
VSVIT	KCND3. Potassium voltage-gated channel subfamily D member 3 Tachyarrhythmia characterized by right bundle branch block and ST segment elevation on an electrocardiogram. Sudden death.	59
EDDSE	KCNJ2. Inward rectifier potassium channel 2 Heart disorder characterized by a prolonged QT interval and polymorphic ventricular arrhythmias. Syncope and sudden death.	60
RSVAS, GGFNF, SLSSTA	LAMA4. Laminin subunit alpha-4 Dilated cardiomyopathy ventricular dilation,impaired systolic function, congestive heart failure and arrhythmia. Risk of death.	61
SVAYS, TTAPA	LDB3. LIM domain-binding protein 3 Ventricular dilation and impaired systolic function, resulting in congestive heart failure and arrhythmia. Risk of death	62
KEELD, DLQEL	LMNA. Prelamin-A/C Hypergonadotropic hypogonadism, ovarian failure, and dilated cardiomyopathy.	63
KLQDV	MYLK. Myosin light chain kinase, smooth muscle Aortic dissections	64
KFNGL	NOTC1. Neurogenic locus notch homolog protein 1 Aortic valve anomalies and severe valve calcification	65
VYSSA, VDLPI, TLLAL, LLLQY, QQLIR, YFKNH	RYR2. Ryanodine receptor 2 Arrhythmogenic right ventricular cardiomyopathy; catecholaminergic polymorphic ventricular tachicardia	66, 67
PQTLE, PLQPE	SPEG. Striated muscle preferentially expressed protein kinase Myopathy with dilated cardiomyopathy	68
AGAAA	TBX2. T-box transcription factor TBX2 Syndromic cardiovascular and skeletal developmental disorder	69
SNLLL, TVLPP	THSD1. Thrombospondin type-1 domain-containing protein 1 Intracranial aneurysms or saccular aneurysms that are the common cause of non-traumatic subarachnoid hemorrhage that can lead to severe disability and death.	70
ELDKY	TPM1. Tropomyosin alpha-1 chain Ventricular hypertrophy, dyspnea, syncope, collapse, palpitations, and chest pain.	71
VSPTK	TRDN. Triadin Ventricular tachicardia, syncope, sudden death after physical activity or stress.	72
FTVEK	VINC. Vinculin Ventricular dilation, impaired systolic function, congestive heart failure and arrhythmia. Risk of premature death	73

Autoimmunity potential of the viral *vs* human peptide sharing

The quantitatively remarkable viral *vs* human peptide overlap shown in Table 1 has also a high immuno-pathological potential. Indeed, inspection of the Immune Epitope DataBase (IEDB) reveals that the 61 shared pentapeptides described in Table 1 are also repeatedly disseminated throughout 339 SARS-CoV-2 spike gp–derived immune reactive epitopes that have been experimentally validated as immunoreactive and are cataloged at the IEDB (Table S1). A snapshot of the peptide sharing between spike gp-derived epitopes and CVDs-related proteins is given in Table 2.

Table 2: Sixty-one pentapeptides shared between SARS CoV-2 spike gp and CVDs-related human proteins also recur throughout immune reactive spike gp-derived epitopes.

IEDB ID	Epitope Sequence
10112	dsfkeeldky
26710	iittdntfv
36724	litgrlqsl
38831	LQDVVNQNAQALNTL

43316	nasvvniqkeidrlnev
51999	qpyrvvvlsf
52057	QQLIRAAEIRASANL
54725	RLQSLQTYV
56252	rvdfcgkgy
71771	vvniqkeidrlnev
530936	asvvniqkeidrlne
533447	raaeirasanlaatk
533643	scgscckfdeddsep
1069290	ctlksftvekgiyqt
1069445	epqiittdntfvsgn
1069550	fnfngltgtgvltes
1069816	ginasvvniqkeidr
1071580	nlllqygsfctqlnr
1073276	tdntfvsgncdvvig
1073280	TESNKKFLPFQQFGR
1073281	TESNKKFLPFQQFGRDIA
1073912	vniqkeidrlnevak
1073938	vqidrlitgrlqslq
1074900	fvfknidgy
1074928	ilpdpskpsk
1074949	KEIDRLNEV
1074967	leplvdlpi
1074980	lppaytnsf
1075025	regvfvsngthw
1075075	tldsktqsl
1075085	tvydplqpeldsfk
1087346	fqptngvgy
1087385	nlttrtql
1087679	pikdfggfnfsqilpdps
1087780	vkqiyktppikdfggfnf
1087806	ynsasfstfkcygvsptk
1125063	gltvlppll
1125138	slidlqel
1309113	efvfknidgyfkiys
1309120	gvsptklndlcftnv
1309125	lidlqelgkyeqyi
1309132	nfsqilpdpskpskr
1309139	stecsnlllqygsfc
1316945	fsqilpdpskpskrsfie
1317137	fvsngthwf

In this way, Tables S1 and S2 experimentally prove the possibility that autoimmune cross-reactions may be triggered by SARS-CoV-2 infection or immunization and can hit human proteins that, on the whole, relate to a vast cardiovascular disease as detailed in Table 1.

Autoimmunity potential of the viral *vs* human peptide sharing and the immunological memory

Clinically, the viral *vs* human peptide sharing described in in Table 1 is characterized by an extensive and intensive cross-reactivity potential as illustrated in Tables S1 and S2, thus indicating that CVDs and myocardial injuries might well be the autoimmune pathologic sequelae of SARS-CoV-2 infection or immunization. In addition, as has long been known [74] and already highlighted in previous reports [75-78], the autoimmune cross-reactivity potential of the peptide sharing can powerfully be enhanced and amplified because of the immunologic imprinting phenomenon. Indeed, hallmark of the immune system is the memory for the immune determinants it has encountered so that, as a rule, the immune system recalls pre-existing memory responses towards past infections rather than inducing *ex novo* responses towards the recent ones [74]. In the case in object, if peptides shared between the virus and the CVDs-related human proteins were also present in previously encountered pathogens, then an anamnestic immune response against the previous pathogens might occur.

DISCUSSION

De facto, comparative sequence analyses show that 36 out of the 61 minimal immune determinants common to SARS-CoV-2 spike gp and CVDs-related human proteins also recur in pathogens such as *B. pertussis, C. diphtheriae, C. tetani, H. influenzae, and N. meningitides*, that is in pathogens with which, in general, an individual has already come into contact during his life due to infections (Table 3).

Table 3: Occurrence in microbial pathogens of pentapeptides common to SARS-CoV-2 spike gp, SARS-CoV-2 spike gp-derived epitopes, and human proteins related to CVDs.

Organism	Shared peptides
B. pertussis	AGAAA, AGAAL, ANLAA, DLQEL, GAGAA, LQELG, LTTRT, PQTLE, RLQSL, RSVAS, TGTGV, VSVIT
C. tetani	AGAAA, AGAAL, ANLAA, DLQEL, EELDK, KEELD, LQDVV, LQELG, LTESN, SVAYS
C. diphtheriae	AGAAA, AGAAL, ANLAA, EELDK, GAGAA, KEIDR, SALGK, VSVIT, VVVLS
H. influenzae	AGAAA, AGAAL, ANLAA, EELDK, GAGAA, GGFNF, KNIDG, LDSKT, LPPLL, LQDVV, LQELG, LSSTA, LTESN, PQTLE, RLQSL, SALGK, SLSST, SNLLL, TLLAL, TNGVG, TTAPA, TTDAV, TVLPP, VSVIT, VVVLS
N. meningitidis	AGAAA, AGAAL, ANLAA, DLQEL, EDDSE, EELDK, GAGAA, KEELD, LLLQY, LPPLL, LQELG, PDPSK, TLLAL, VSPTK

Hence, the inter-pathogen peptide sharing shown in Table 3 supports the possibility that a prior immune response towards previously encountered pathogens such as *B. pertussis, C. tetani, C. diphtheriae, H. influenzae*, and/or *N. meningitides*, might be magnified and intensified following SARS-CoV-2 infection or immunization [74-78]. That is, immunologic imprinting can modify the primary response to SARS-CoV-2 into a quantitatively high and qualitatively extremely intense secondary response to a previously encountered pathogens at the expense of an attack against SARS-CoV-2.

Conveying immune responsiveness towards early sensitizing pathogens may have the following logical consequences: Firstly, a low or no immune response will be evoked against the pathogen lastly encountered, i.e., SARS-CoV-2; secondly, on the other hand, also the anamnestic secondary reaction against the early sensitizing pathogens –in the case in point, *B. pertussis, C. tetani, C. diphtheriae, H. Influenzae* and/or *N. meningitides* –will fail because the previously encountered infectious agents are no more present in the organism; and thirdly, the rapid anamnestic, high affinity, high avidity, and extremely intense secondary immune response triggered by SARS-CoV-2 and deviated by the immune memory towards past infections may find an outlet in attacking available human targets, i.e., in the case in object, the CVDs-related human proteins.

CONCLUSION

Cardiomyopathies, myocarditis, ischemic heart disease, cardiac channelopathies, and sudden death, inter alia, inexplicably occur following SARS-CoV-2 infection and immunization. The etiology of the cardiac jnjuries remains unknown. This study supports the hypothesis that molecular mimicry between SARS-CoV-2 and CVDs-related human proteins may induce cross-reactive AAbs capable of binding and altering human cardiac proteins and, in this way, causing CVDs, thus confirming results obtained using as a research model SARS-CoV-2 spike gp and the cardiac human protein Titin. On the whole, the data indicate peptide sharing, i.e., molecular mimicry, as the likely molecular platform underlying SARS-CoV-2-associated CVDs and substantiate cross-reactivity as the mechanism linking SARS-CoV-2 infection to CDVs.

Moreover, comparative sequence analyses highlight that numerous pentapeptide immune determinants shared by SARS-CoV-2 and CVDs-related proteins are also present in pathogens to which an individual has been already exposed during his life. Such an inter-pathogen peptide overlap indicates that immunologic imprinting phenomena can occur. That is, a preexisting immune response to a first pathogen can be boosted by a successive exposure to a second different pathogen having the same determinants. Simply put, the effective possibility exists that immune reactivity against the SARS-CoV-2 minimal determinants may be affected by previous immune responses and addressed towards the same determinants present in other pathogens.

In synthesis show that the pentapeptide sharing occurring among CVDs-related human proteins and the analyzed pathogens may be involved in an intense and complex autoimmune cross-reactivity network that is specifically and temporally determined by the immunological history of the individual. Crucially offer a list of possible cardiac protein targets of autoimmunity in SARS-CoV-2 infection and immunization and, from a clinical perspective, the results make mandatory the testing of patients' sera for AAbs against these protein targets.

Finally, in agreement with previous studies this report warns that using entire pathogen antigens in immunization procedures can associate with multiple and severe autoimmune manifestations, and further supports the concept of peptide uniqueness for designing safe and effective anti-SARS-CoV-2 immunotherapies.

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Conflicts of Interest

The author declare that there is no conflict of interest

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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