Thromboses and Hemostasis Disorders Associated with COVID-19: The Possible Causal Role of Cross-Reactivity and Immunological Imprinting

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Abstract

By examining the issue of the thromboses and hemostasis disorders associated with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) through the lens of cross-reactivity, it was found that 60 pentapeptides are shared by SARS-CoV-2 spike glycoprotein (gp) and human proteins—when altered, mutated, deficient or, however, improperly functioning—cause vascular diseases, thromboembolic complications, venous thrombosis, thrombocytopenia, coagulopathies, and bleeding, inter alia. The peptide commonality has a relevant immunological potential as almost all of the shared sequences are present in experimentally validated SARS-CoV-2 spike gp-derived epitopes, thus supporting the possibility of cross-reactions between the viral gp and the thromboses-related human proteins. Moreover, many of the shared peptide sequences are also present in pathogens to which individuals have previously been exposed following natural infection or vaccinal routes, and of which the immune system has stored imprint. Such an immunological memory might rapidly trigger anamnestic secondary cross-reactive responses of extreme affinity and avidity, in this way explaining the thromboembolic adverse events that can associate with SARS-CoV-2 infection or active immunization.

Keywords

► COVID-19
► SARS-CoV-2 spike gp
► cross-reactivity
► immunological imprinting
► thromboses-related proteins
► thromboses
► vascular diseases
► bleeding

Introduction

Clinical studies have shown that severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection can lead to an increased incidence of disorders such as thrombosis, venous thrombosis, and pulmonary embolism.1–3 A main conclusion of these studies is that, although it cannot be proven that the hypercoagulable state is a direct causative effect of SARS-CoV-2 infection, nonetheless it is apparent that patients with SARS-CoV-2 could have a predilection to the occurrence of thromboembolic events.1 However, currently there are no hypotheses or data that might suggest a molecular mechanism that relates to such SARS-CoV-2-related thromboembolic events. Searching for possible mechanisms, the present study analyzes the SARS-CoV-2 spike glycoprotein (gp) for peptide sharing, that is, molecular mimicry, with human proteins, alterations of which may cause thromboses and hemostasis diseases. The underlying scientific rationale is that peptides common to a pathogen and the human host may lead to autoimmune pathologies through cross-reactivity phenomena following pathogen infection.4–6 The results indicate that several linear
sequences shared between the SARS-CoV-2 spike gp and human proteins related to thromboembolic events can possibly generate pathogenic autoantibodies via cross-reactivity and immunologic imprinting phenomena, in this way leading to thromboses and hemostasis disorders.

**Materials and Methods**

Peptide sharing between spike gp (NCBI, GenBank Protein Accession, ID: QHD43416.1) from SARS-CoV-2 and human proteins related to thromboses and hemostasis disorders was analyzed as previously detailed. In brief, pentapeptides were used as sequence probes since a peptide grouping formed by five amino acid (aa) residues defines a minimal immune determinant that can (1) induce highly specific antibodies, and (2) determine antigen–antibody specific interaction. Human proteins linked to thromboses and hemostasis disorders were retrieved from UniProtKB database (www.uniprot.org). Methodologically the spike gp primary sequence was dissected into pentapeptides offset by one residue (i.e., MFVFL, FVFLV, VFLVL, FLVLL, and so forth) and the resulting viral pentapeptides were analyzed for occurrences within the human proteins related to thromboses and hemostasis disorders. Then, the shared peptides were also controlled for occurrences in the pathogens *Bordetella pertussis*, *Corynebacterium diphtheriae*, *Clostridium tetani*, *Haemophilus influenzae*, and *Neisseria meningitidis*.

The immunological potential of the peptides shared between SARS-CoV-2 spike gp and thrombosis-related proteins was analyzed by searching the Immune Epitope Database (IEDB [www.iedb.org/]) for immunoreactive SARS-CoV-2 spike gp-derived epitopes hosting the shared pentapeptides.

**Results and Discussion**

**Peptide Sharing between SARS-CoV-2 Spike Glycoprotein and Thromboses-Related Human Proteins**

Table 1 shows that 60 minimal immune determinants are shared between SARS-CoV-2 spike gp and 44 human proteins that—when altered, mutated, deficient or, however, improperly functioning—may cause diseases that include blood diseases.

| Shared peptides | Human proteins and associated functions/pathologies | References |
|-----------------|-----------------------------------------------------|------------|
| MTKTS, NLLLQ   | ADTRP (androgen-dependent TPPI-regulating protein)  | 11         |
|                 | Regulates the anticoagulant activity of the tissue factor pathway inhibitor, dysfunctions of which lead to vascular diseases |           |
| TQLPP, PRTFL   | ALG12: Dol-P-Man: Man(7)GlcNAc(2)-PP-Dol α-1,6-mannosyltransferase | 12         |
|                 | Psychomotor retardation, hypotonia, coagulation disorders, and immunodeficiency |           |
| SAICK           | ALG8: Dolichyl pyrophosphate Glc1Man9GlcNAc2 α-1,3-glucosyltransferase | 13         |
|                 | Pathologies: see ALG12 above |           |
| AEIRA           | ANXA6 (annexin A6) | 14         |
|                 | Anticoagulant protein from human placenta |           |
| QLIRA, IRASA   | AP3B1 (AP-3 complex subunit β-1) | 15         |
|                 | Associates with Hermansky–Pudlak syndrome. Bleeding diathesis resulting in bruising, epistaxis, gingival bleeding, postpartum hemorrhage, bleeding |           |
| LIGAE           | APLP2 (amyloid-like protein 2) | 16         |
|                 | The soluble form may have inhibitory properties toward coagulation factors and regulates cerebral thrombosis |           |
| VLLPL           | B3AT (band 3 anion transport protein) | 17         |
|                 | Involved in venous thrombosis of unknown origin |           |
| FGGVVS          | B4GTT1 (β-1,4-galactosyltransferase 1) | 18         |
|                 | Defects in the nervous system development, psychomotor retardation, dysmorphic features, hypotonia, coagulation disorders |           |
| KGYHL           | C4BPB (C4b-binding protein β chain) | 19,20       |
|                 | Controls complement activation; binds as a cofactor to C3b/C4b inactivator; possibly involved in the susceptibility to venous thrombosis |           |
| LTCLP           | CBS (cystathionine β-synthase) | 21         |
|                 | CBS-deficient patients are prone to vascular thrombosis |           |
| NSVAY           | CO1A1 (collagen α-1(I) chain) | 22,23       |
|                 | Connective tissue disorders characterized by fragile, bruisable skin |           |
| PGQTG, NGLTG   | CO1A2 (collagen α-2(I) chain) | 22,23       |
|                 | Pathology: see CO1A1 above |           |
| TQSLL, GTGVL   | COG1 (conserved oligomeric Golgi's complex subunit 1) | 24         |
|                 | Psychomotor retardation, hypotonia, coagulation disorders, and immunodeficiency |           |

(Continued)
### Table 1 (Continued)

| Shared peptides | Human proteins and associated functions/pathologies\(^{a,b}\) | References |
|-----------------|---------------------------------------------------------------|------------|
| STNLV, GAISS    | COG2 (conserved oligomeric Golgi’s complex subunit 2) | 25         |
|                 | Pathology: as for COG1                                       |            |
| PINLV           | COG5 (conserved oligomeric Golgi’s complex subunit 5) | 26         |
|                 | Pathology: as for COG1                                       |            |
| LPFQQ, PFQQ, IGKIQ | ENTP1 (ectonucleoside triphosphate diphosphohydrolase 1) | 27,28      |
|                 | Implicated in the prevention of platelet aggregation         |            |
| YTSAL           | EPHB2 (ephrin type-B receptor 2) | 29         |
|                 | Regulation of platelet activation and blood coagulation      |            |
| VLNDI           | F13A (coagulation factor XIII A chain)                      | 30         |
|                 | Relates to hematologic disorders characterized by bleeding tendency |     |
| DPLQP           | FAS (coagulation factor V)                                   | 31–34      |
|                 | Central regulator of hemostasis. Parahemophilia, i.e., poor clotting; pregnancy loss, ischemic stroke, thrombophilia |     |
| PPLLIT, FVTQR   | FA8 (coagulation factor VIII)                                | 35         |
|                 | Hemophilia                                                   |            |
| NSYEC           | FA9 (coagulation factor IX)                                  | 35         |
|                 | Hemophilia                                                   |            |
| SSANN           | FIBA (fibrinogen \(\alpha\) chain)                         | 36–38      |
|                 | Bleeding, amyloidosis, arterial hypertension, hepatosplenomegaly, cholestasis, petechial skin rash; thromboembolic complications | |
| CAGAA           | GATA4 (transcription factor GATA-4)                         | 39–41      |
|                 | Regulates factor X, a vitamin K-dependent serine protease that functions in blood coagulation. Can predispose to dilated cardiomyopathy, and to premature death | |
| NDPFVL          | GP1BA (platelet glycoprotein lb \(\alpha\) chain)            | 42         |
|                 | Epistaxis; hemorrhage; menorrhagia; purpura; congenital bleeding diathesis; large platelets; thrombocytopenia; long bleeding time | |
| ALLAG           | GPIX (platelet glycoprotein IX)                              | 42         |
|                 | Epistaxis; hemorrhage; menorrhagia; purpura; congenital bleeding diathesis; large platelets; thrombocytopenia; long bleeding time | |
| KLIAN           | HABP2 (hyaluronan-binding protein 2)                         | 43         |
|                 | Serine protease involved in coagulation fibrinolysis and inflammatory pathways | |
| TQLPP           | HPS4 (Hermansky–Pudlak syndrome 4 protein)                  | 44         |
|                 | Epistaxis; reduced visual acuity; horizontal nystagmus; iris transillumination; restrictive lung disease; bruising; bleeding tendency; menorrhagia; absence of platelet dense bodies; lack of secondary aggregation response of platelets | |
| HTSPD           | HPS5 (Hermansky–Pudlak syndrome 5 protein)                  | 45         |
|                 | As HPS4 above                                                |            |
| FNATR, DRLIT    | HS3SS (heparan sulfate glucosamine 3-O-sulfotransferase 5)  | 46         |
|                 | Catalyzes a crucial step in the biosynthesis of the anticoagulant heparan sulfate | |
| SASFS           | ITA2 (integrin \(\alpha\)-2)                               | 47,48      |
|                 | Associates with increased ischemic stroke risk; thrombophilia | |
| VRDLP           | ITB3 (integrin \(\beta\)-3)                               | 49         |
|                 | Thrombasthenia, characterized by mucocutaneous bleeding      |            |
| FGTTL, YDPLQ, GDISG | JAK2 (tyrosine-protein kinase JAK2) | 50,51       |
|                 | Thrombophilia, thrombocytosis                               |            |
| VNLIT, GDSSS, VTYVP | MMRN1 (multimerin-1)                                     | 52         |
|                 | Deficiency in multimerin-1 associates with bleeding disorder | |
| LLPLV           | PLF4 (Platelet factor 4)                                    | 53         |
|                 | Involved in thrombosis                                      |            |
| TFGAGG          | PLMN (plasminogen) may be associated with susceptibility to thrombosis | 54         |
| TVEKG, TGTGV    | PROS: vitamin K-dependent protein S                          | 55,56      |
|                 | Anticoagulant plasma protein. Helps to prevent coagulation and stimulates fibrinolysis. Deficiency leads to impaired blood coagulation and a tendency to venous thrombosis | |
coagulation disorders, bruising, bleeding, hemorrhages, retinal vessel occlusion, cerebral thrombosis, venous thrombosis, ischemic stroke, and thrombophilia, inter alia.

Immunological Potential of the Viral versus Human Peptide Sharing

The data shown in Table 1 are quantitatively impressive and become strikingly preeminent from a pathological perspective when analyzed for their immunological potential. Indeed, exploration of the IEDB reveals that nearly all the shared pentapeptides described in Table 1 are also dissemnated among SARS-CoV-2 spike gp-derived epitopes that have been experimentally validated as immunoreactive and are cataloged at the IEDB database (http://www.iedb.org).

That is, Table 2 concretely supports the possibility that autoimmune cross-reactions may be triggered by SARS-CoV-2 infection/active immunization and hit human proteins related to thrombophilic/thromboembolic disorders and coagulopathies, inter alia. Clinically, the vasty of the potential immunological cross-reactivity that emerges from Table 2 indicates that mild-to-moderate and severe forms of thrombosis and coagulopathy may unavoidably accompany SARS-CoV-2 infection/active immunization.

Autoimmunity Potential and the Immunological Memory

As already highlighted also in other infection models, one has to consider that immunologic memory can powerfully enhance and amplify the autoimmune cross-reactivity potential because of interpathogen peptide sharing. Indeed, as a rule, the immune system recalls preexisting memory responses toward past infections rather than inducing ex novo responses toward the recent ones since hallmarking of the immune system is the memory for the immune determinants it has previously encountered.

Here, comparative sequence analyses show that 31 out of the 60 minimal immune determinants common to SARS-CoV-2 spike gp and human proteins related to thromboses are also widespread in pathogens, such as B. pertussis, C. diphtheriae, C. tetani, H. influenzae, and N. meningitidis, that are in pathogens with which, in general, an individual has already come into contact during his life due to infections or by vaccination (Table 3).

Hence, Table 3 indicates the possibility that a preexisting immune response to previously encountered pathogens (in the present case: B. pertussis, C. tetani, C. diphtheriae, H. influenzae, and/or N. meningitidis) might be magnified and intensified following SARS-CoV-2 infection/active immunization. That is, immunological imprinting can start a chain of events according to which followings can be measured:

- Following exposure to SARS-CoV-2, the primary response to the virus can turn into a secondary response to previously encountered pathogens of which the immune system has stored an immunological memory.
- The anamnestic secondary and, by definition, extremely powerful response against immune determinants previously encountered implies not only that a low or no immune response will fail to be evoked against the pathogen lastly encountered, that is, SARS-CoV-2, but also entails that the anamnestic secondary reaction against the early sensitizing pathogens—in the case in point, B. pertussis, C. tetani, C. diphtheriae, and/or N. meningitidis—will fail...
**Table 2** Distribution of peptides shared between SARS-CoV-2 spike gp and human proteins related to thromboses and hemostasis disorders among 94 experimentally validated SARS-CoV-2 spike gp-derived epitopes

| IDa | Epitopeb | IDa | Epitopeb |
|-----|----------|-----|----------|
| 1069137 | aqYTSALLAGtitsg | 1309555 | qcVNLTrTQlPPaytnsft |
| 1069290 | ctksfTVEKGIyqt | 1309558 | qfnSAIGKIQdSlssatal |
| 1071585 | nIVRDLPqgfsalep | 1309564 | qtraqcLIGAEhvnNSYECd |
| 1071723 | patvcgpkSTNLVnknc | 1309573 | rLFKSNlkpfrdstoney |
| 1072807 | skhtPILVRLDPqg | 1309595 | tnfivstvteilpsMTKTS |
| 1072965 | svteitelsMTKTS | 1309598 | tvYDPLQPeldskeelddky |
| 1073281 | tesnnkflPFQQQFrldia | 1309599 | Tyypaqknfittapacdhg |
| 1073938 | vqiDLRITgrIqlqslq | 1309600 | tvytqQLIRAeIRASAnla |
| 1074201 | ylyrlFRRSNlkpe | 1309602 | vqcpkSTNLVnkncvnfnf |
| 1074838 | AEIRASAnlaatk | 1309603 | vnkncvnfnNGTGTGVlt |
| 1074925 | hVYYPaqeknf | 1309604 | VLDNDsrldkveaeqjd |
| 1074969 | lgaenSVAYesnn | 1309621 | yskhtPILVRLDPqgfsal |
| 1074974 | ILALHRSyl | 1310254 | aeNSVAYsnnsaiap |
| 1075005 | nqKLIAnqf | 1310281 | aphpgvflhVYYPa |
| 1075031 | rLFKSNlk | 1310303 | caqkfnLTVLPPLL |
| 1075039 | rqiPCQGTGkiadnykl | 1310336 | dskTQLLSvnnatn |
| 1075066 | sVLNDIsrl | 1310392 | FGTLdskTQSLLiv |
| 1075079 | tPILVRLd | 1310401 | fkiyskhtPILNvrd |
| 1075085 | tvYDPLQPeldsfk | 1310415 | fnqLTVLPPLLdtem |
| 1075094 | vLPLDtemiaqyqt | 1310434 | GAISVLDNDsrlrd |
| 1075125 | ysvlynSASFStfk | 1310444 | givntvYDPLQPel |
| 1075131 | yyvgylqPRTFLI | 1310487 | igiintrfqTLLALh |
| 1087680 | PINLVRDLPqgfsalepl | 1310506 | irqiwFGTTdskstkq |
| 1125063 | gLTVLPPLL | 1310513 | itrqTQLLSvHRSyl |
| 1309117 | ggynynylyrLFRRSnn | 1310592 | ILALHRsytpgdss |
| 1309118 | gpkkSTNLVnkncvn | 1310611 | JPLLDTemiaqyts |
| 1309123 | khtPILVRLDLPqgf | 1310633 | lyenqKLIAnqfsna |
| 1309140 | tdemiaqYTASSLAG | 1310787 | SASFStfkcyvgyspt |
| 1309147 | ylyqPRTFLI | 1310828 | svlynsASFStfcky |
| 1309148 | AEIRASAnlaatkmsecvlg | 1310852 | tlvkqlssnGAISS |
| 1309442 | ayyvgylqPRTFLKyneng | 1310865 | trfqTQLLSvH Rylt |
| 1309450 | dpIsetkctlkftVEKGtGy | 1310899 | VLLPVSSQCVNLTt |
| 1309451 | dsfkeeldkyfknHTSPDvdr | 1310909 | VNLTrTQLLPPaytn |
| 1309461 | ehvnNSYECdipagiacas | 1310927 | vtqnvlyenqKLIAN |
| 1309464 | esnkflLPFQQqfrgriadt | 1310947 | wTFGAALQipfam |
| 1309469 | fkkHTSPDvIGDISHGinas | 1310979 | yyyvqlqPRTFLKyn |
| 1309470 | fknidgyfkiyskhtPILNv | 1311657 | ccSGCScckffedclosedpvlkvgvl |
| 1309475 | gccSGSCcckffeddedsepv | 1311813 | rLFKSNlkp |
| 1309492 | ilpltcsffGvGSvitpgtn | 1313244 | nSASFStfk |
| 1309506 | kvggynylyrLFRRSnlkp | 1313285 | PINLVRDLPqgfsal |
| 1309515 | lhysltpGDSSSwtagaag | 1313286 | PINLVRDLPeqlwal |
| 1309516 | litgrlqsiqtytvqQLIARA | 1314023 | ynylyrLFRRSnlkp |
because those early sensitizing pathogens are no more present in the organism.

- As a final result, the anamnestic, high affinity, high avidity, and extremely powerful secondary immune response triggered by the lastly encountered pathogen (SARS-CoV-2) and addressed toward past infections may find an outlet by hitting available human targets, that is, in the case in object, the human proteins related to thromboses and hemostasis diseases (►Table 1).

**Conclusion**

The last decades witnessed the emerging of infectious diseases and, consequently, intensive application of immunization procedures. Concomitantly, concerns about possible adverse events have increased. A recent crucial example is the immunization campaign with the dengue vaccine that highlighted the risk of enhanced disease after vaccination.74

Today, the clinical context associated with SARS-CoV-2 infection/active immunization is no different. Actually, understanding whether undesired collateral events, such as the thrombotic manifestations and bleeding disorders discussed in this study, may causally associate with the viral infection/active immunization is a fundamental step for fighting the current pandemic. In this context, the present study:

- Analyzed the hypothesis that infectious agents can induce cross-reactive autoantibodies capable of hitting and altering human proteins that regulate hemostasis and coagulation.
- Showed that numerous peptides endowed with an immunologic potential are common to SARS-CoV-2 spike gp and human proteins, when mutated, altered, deficient or improperly functioning, are associated with thromboses and hemostasis diseases (►Tables 1 and 2).
- Documented that the peptide commonality extends to pathogens that usually have been already encountered by an individual during his life (►Table 3).

Scientifically, the data indicate that peptide sharing–associated cross-reactivity and, in conjunction, immunological imprint might help explain some of the thromboembolic events that rapidly, massively, and violently may arise following SARS-CoV-2 infection/active immunization.

Clinically, the present data warrant testing of patients’ sera for autoantibodies against the peptide targets described in ►Tables 1–2 and 3, and reiterate the suggestion advanced already in 200075 that immunotherapies should take advantage of the principle of peptide uniqueness, that is, of peptides present in the antigen of interest and absent in the human proteome.71,76–81

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Conflict of Interest
None declared.
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