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Leonardo Ferreira Oliveira

ABSTRACT

Throughout history, the ABO system has been used as an element for clinical reasoning to analyze the relationship of different blood groups with different pathologies. There is ample evidence on the association between SARS-CoV-2 infection and polymorphism in the ABO system. Bioinformatics has revolutionized the scientific world, allowing the systematic study of biomolecules. The present work aims to clarify the relationship between the glycosition of the SARS-COV-2 spike protein and blood groups of the ABO system, using bioinformatics tools and systematic literary review. The SARS-CoV-2 spike protein is intensely glycosylated and plays a key role in the success of viral fixation, entry and fusion of the virus membrane into host cells. The N-glycans in this protein are related to the proper folding of proteins and also to the escape of innate and adaptive immune responses. It can be seen that the glycosylation of the spike protein is extremely important for SARS-Cov-2 to perpetuate its cycle and, probably, that is the explanation of the relationship with susceptibility related to groups in the ABO system.

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SUMMARY

Throughout history, the ABO system has been used as an element for clinical reasoning to analyze the relationship of different blood groups with different pathologies. There is ample evidence on the association between SARS-CoV-2 infection and polymorphism in the ABO system. Bioinformatics has revolutionized the scientific world, allowing the systematic study of biomolecules. The present work aims to clarify the relationship between the glycosition of the SARS-COV-2 spike protein and blood groups of the ABO system, using bioinformatics tools and systematic literary review. The SARS-CoV-2 spike protein is intensely glycosylated and plays a key role in the success of viral fixation, entry and fusion of the virus membrane into host cells. The N-glycans in this protein are related to the proper folding of proteins and also to the escape of innate and adaptive immune responses. It can be seen that the glycosylation of the spike protein is extremely important for SARS-Cov-2 to perpetuate its cycle and, probably, that is the explanation of the relationship with susceptibility related to groups in the ABO system.

Keywords: ABO. Glycosylation. Spike. SARS-CoV-2.

I. INTRODUCTION

Bioinformatics has revolutionised biological and biomedical research as it allows researchers to systematically study genomes, the assemblage of RNA molecules and proteins. The wealth of data generated by genomics, transcriptomics and proteomics has enabled researchers to innovate and advance scientific knowledge [1].

Glycoproteomics is a branch of proteomics that identifies, catalogues and characterises proteins containing carbohydrates as post-translational modifications. Recently assays in glycoproteomics address the separation and enrichment of glycoproteins and glycopeptides, structural and functional analysis of glycoproteins and analysis of protein glycosylation sites [2].

Throughout history the ABO system has been used as an element for clinical reasoning, being employed for decades to analyse the relationship of the different blood groups with bacterial, viral infections [6; 7; 8; 9], caused by protozoa [10; 11; 12] and helminths [13; 14; 15], tumours [16; 17; 18; 19; 20] among others [21; 22].

The rapid global spread of SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19), has culminated in considerable morbidity and mortality, along with social and economic disruption worldwide [23].

Severe acute respiratory syndrome is a highly contagious disease with clinical symptoms of fever, dry cough, fatigue, and shortness of breath. Nucleic acid tests of respiratory tract samples and stool samples are the basis of laboratory confirmation of COVID-19, although serological tests are being used due to improved specificity and sensitivity. The production of IgM antibodies specific for SARS-CoV-2 commonly occurs about 3-5 days after the onset of symptoms, followed by the production of IgG antibodies [24]. The production of IgM antibodies specific for SARS-CoV-2 commonly occurs about 3-5 days after the onset of symptoms, followed by the production of IgG antibodies [24].

The existing evidence on the association between SARS-CoV-2 infection and ABO system polymorphism is preliminary and controversial [25]. However, meta-analysis studies [26; 27; 28; 29] and genome-wide association analysis have been able to elucidate the potential factors involved in the development of Covid-19 [30]. In addition, trials have sought to elucidate the relationship between ABO system antibodies and their influence on the interaction of SARS-CoV-2 and the host [31].

A group of researchers conducting a genetic study found that blood group O was associated with a lower risk of acquiring Covid-19 than non-O blood groups, while blood group A was associated with a higher risk than non-A blood groups. The authors ponder that one of the biological mechanisms justifying these findings relates to the development of neutralizing antibodies against protein-bound N-glycans [30].

Guillon et al. [32] hypothesized that since SARS-CoV replicates in cells that have the ability to synthesize ABO system epitopes, the S protein of virions produced by A or B individuals could be decorated with A or B carbohydrate epitopes, respectively. Thus natural anti-A or anti-B antibodies from individuals of blood groups O, B and A could bind to the S protein and interfere with the interaction with ACE2, thus preventing infection.

Based on the same assumption of the aforementioned authors, the present work aims to clarify the relationship between glycosylation of the spike protein of SARS-COV-2 and blood groups of the ABO system, using bioinformatics tools and systematic literature review.

II. MATERIALS AND METHOD

A bibliographical survey was conducted in PubMed using the descriptors in Health Sciences; ABO Blood Groups System, Coronavirus Infections, Glycosylation and Betacoronavirus, and their respective correlates in English. Articles describing the relationship between SARS-Cov-2 and ABO system blood groups were included, as well as papers referring to the theme of betacoronavirus protein glycosylation.

Free bioinformatics resources available on the internet were used. Two spike proteins, namely P59594 (SARS-Cov) and P0DTC2 (SARS-Cov-2), were selected from the Uniprot website (https://www.uniprot.org/). A three-dimensional structure of the protein sequences was produced using UCSF Chimera software, after previous identification and exclusion of signal peptide and transmembrane domains in TOPCONS website (https://topcons.cbr.su.se/).

The two proteins were also aligned using Uniprot resources, identifying glycosylation sites and similarity patterns between them. The analysis of O and N-glycosylation site prediction was performed in NetOGlyc 4.0 Server (http://www.cbs.dtu.dk/services/NetOGlyc/) and NetNGlyc 1.0 Server (http://www.cbs. dtu.dk/ services/NetNGlyc/), respectively.

III. RESULTS AND DISCUSSIONS

The most significant post-translational modification is glycosylation, which consists of the enzymatic addition of sugars to asparagine residues, called N-glycans, and/or serine and threonine residues, called O-glycans [33]. The heterogeneity related to protein glycosylation is related to the location of one or more sites where glycosylation occurs (macroheterogeneity), as well as due to the great variety and complexity of glycans that can be expressed in a given glycosylation site (microheterogeneity) [34]. Glycosylation can affect how a protein is secreted and packaged, as well as its stability, solubility and conformation, which culminates in biological activity and antigenicity [35].

The set of the great variety of glycans in an organism is called glycomome. Glycans participate in the regulation of cellular and humoral immune responses, including the constitution of MHC antigens and immune cell receptors, participation in endocytosis and the functions of immunoglobulins. In addition, some glycan motifs act as hazard-associated molecular patterns or pathogen-associated molecular patterns. Thus, glycosylation participate in the processes of diapedesis and chemotaxis, pathogen

recognition, activation of immune cells as well as immunosuppression [33; 36].

The antigens of the ABO system represent a classic example of glycosylated proteins. The antigenicity of this system is attributed to the terminal sugars present in glycoproteins on the surface of blood cells, tissues and in secretions. The variety of phenotypes of the antigens of this system is conferred by the different genes that express glycosyltransferases encoded in the ABO locus that is located on the long arm of chromosome 9 (9q34.2) [37].

H-transferase (FUT1) is responsible for synthesising a structure known as the H antigen by adding a fucose to terminal galactose residues of oligosaccharide precursors. In epithelial tissues and salivary glands, a second fucosyltransferase (FUT2) synthesizes antigen H. In individuals of blood group A, B or AB, antigen H can be targeted by specific glycosyltransferases to form antigens A and B [38].

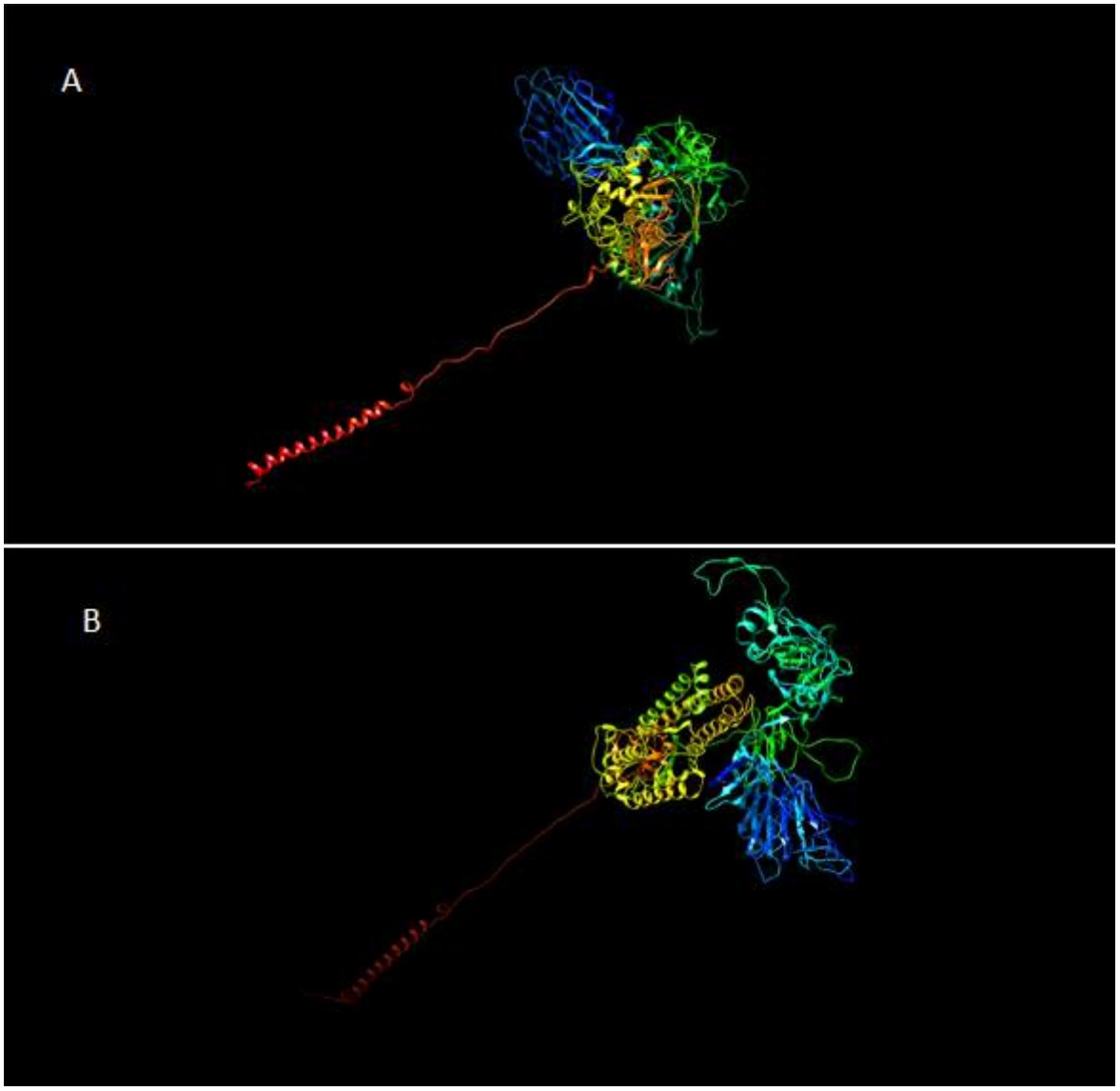
The glycosyltransferases of the ABO system, belong to the CAZy 6 family and are represented of more homologous group of enzymes that transfer distinct naturally occurring donor substrates, differing from each other by only four amino acids out of 354. Glycosyltransferase A (GTA) is an α-(1→3)-N-acetylgalactosaminyltransferase (EC 2.4.1.40) transfers GalNAc from UDP-GalNAc to antigen H , producing antigen A. Glycosyl tranferase B (GTB), on the other hand, is an α-(1→3)-galactosyltransferase (EC 2.4.1.37) transfers Gal from UDP-Gal, also to antigen H, producing antigen B [38].

The ABO system antibodies are absent at birth and can be detected after a few months of life. Heteroimmunization is responsible for the appearance of these antibodies, mainly due to contact with microorganisms of the intestinal bacterial flora. These antibodies are potent IgM and/or IgG, capable of agglutinating red blood cells and of activating the complement cascade, causing intravascular hemolysis [39].

Although the mechanism of ABO blood type in COVID-19 infection has not yet been elucidated, esearch related to other viruses may direct towards clarification. Since SARS-Cov and SARS-Cov-2 have similar nucleic acid sequence and also exhibit the same binding tropism to ACE2, comparing them may advance scientific knowledge [29].

The P59594 protein (FIGURE 1A) originating from SARS-Cov with 1255 amino acid residues and P0DTC2 (FIGURE 1B) protein from SARS-Cov-2 with 1273 amino acid residues, present 207 similar positions, making an identity of 75.881%, both with 22 possible glycosylation sites (FIGURE 2). The analysis performed on glycosylation prediction servers showed agreement with Uniport site alignment with the same amount of N-glycosylation sites (FIGURE 3A and 3B). O-glycosylation prediction showed three probable glycosylation sites for SARS-Cov-2 protein, and one site for SARS-Cov.

Guillon et al, [32] used a cellular model of adhesion to investigate the effect of natural antibodies of the ABO system on the interaction and blockade of SARS-CoV spike protein and angiotensin-converting enzyme 2. For this, an eGFP (green fluorescent protein) labelled spike protein at the C-terminus was expressed in CHO co-transfected with an α1,2-fucosyltransferase and a GTA to co-express the ectodomain of the spike glycoprotein and the A antigen on the cell surface. It was observed that the S/ECA2 protein-dependent adhesion of these cells to a cell line expressing ACE2 was specifically inhibited by monoclonal or natural human anti-A antibodies, indicating that these antibodies can block the interaction between the virus and its receptor, providing protection.



source: prepared by the author

Figurae 1: Three-dimensional structure of SARS-Cov and SARS-Cov-2 spike proteins

The spike protein of SARS-CoV-2 is highly glycosylated and plays a key role in the successful viral attachment, entry and membrane fusion of the virus to host cells. This protein plays a key role in the host immune response and is therefore the main target of research for vaccine production [40].

The N-glycans in the spike protein are related to proper protein folding as well as initiation by host proteases. In addition, these glycans may protect antigenic sites, preventing recognition by defence cells and antibodies. Thus glycosylation may allow coronavirus to evade innate and adaptive immune responses [41].

Source: Adapted by authors

Figure 2: Alignment of spike proteins P59594 and P0DTC2

A

SeqName	Position	Potential	Jury agreement	N-Glyc result	
sp_P59594_SPIKE_SARS	29	NYTQ	0.7751	(9/9)	+++
sp_P59594_SPIKE_SARS	65	NVTG	0.8090	(9/9)	+++
sp_P59594_SPIKE_SARS	73	NHTF	0.4327	(6/9)	-
sp_P59594_SPIKE_SARS	109	NKSQ	0.6081	(7/9)	+
sp_P59594_SPIKE_SARS	118	NNST	0.4711	(4/9)	-
sp_P59594_SPIKE_SARS	119	NSTN	0.7039	(9/9)	++
sp_P59594_SPIKE_SARS	158	NCTF	0.5808	(7/9)	+
sp_P59594_SPIKE_SARS	227	NITN	0.7517	(9/9)	+++
sp_P59594_SPIKE_SARS	269	NGTI	0.6910	(9/9)	++
sp_P59594_SPIKE_SARS	318	NITN	0.6414	(9/9)	++
sp_P59594_SPIKE_SARS	330	NATK	0.6062	(8/9)	+
sp_P59594_SPIKE_SARS	357	NSTF	0.5746	(8/9)	+
sp_P59594_SPIKE_SARS	589	NASS	0.5778	(6/9)	+
sp_P59594_SPIKE_SARS	602	NCTD	0.6882	(9/9)	++
sp_P59594_SPIKE_SARS	691	NNTI	0.4604	(5/9)	-
sp_P59594_SPIKE_SARS	699	NFSI	0.5357	(7/9)	+
sp_P59594_SPIKE_SARS	783	NFSQ	0.6348	(9/9)	++
sp_P59594_SPIKE_SARS	1056	NFTT	0.4342	(5/9)	-
sp_P59594_SPIKE_SARS	1080	NGTS	0.5806	(7/9)	+
sp_P59594_SPIKE_SARS	1116	NNTV	0.5106	(5/9)	+
sp_P59594_SPIKE_SARS	1140	NHTS	0.3739	(9/9)	--
sp_P59594_SPIKE_SARS	1155	NASV	0.4001	(8/9)	-
sp_P59594_SPIKE_SARS	1176	NESL	0.6796	(9/9)	++

B

SeqName	Position	Potential	Jury agreement	N-Glyc result	
sp_P0DTC2_SPIKE_SARS2	17	NLTT	0.6606	(8/9)	+
sp_P0DTC2_SPIKE_SARS2	61	NVTW	0.7820	(9/9)	+++
sp_P0DTC2_SPIKE_SARS2	74	NGTK	0.7192	(9/9)	++
sp_P0DTC2_SPIKE_SARS2	122	NATN	0.6781	(8/9)	+
sp_P0DTC2_SPIKE_SARS2	149	NKSW	0.6318	(7/9)	+
sp_P0DTC2_SPIKE_SARS2	165	NCTF	0.6220	(8/9)	+
sp_P0DTC2_SPIKE_SARS2	234	NITR	0.7613	(9/9)	+++
sp_P0DTC2_SPIKE_SARS2	282	NGTI	0.7378	(9/9)	++
sp_P0DTC2_SPIKE_SARS2	331	NITN	0.5970	(7/9)	+
sp_P0DTC2_SPIKE_SARS2	343	NATR	0.5671	(8/9)	+
sp_P0DTC2_SPIKE_SARS2	603	NTSN	0.5783	(6/9)	+
sp_P0DTC2_SPIKE_SARS2	616	NCTE	0.7163	(9/9)	++
sp_P0DTC2_SPIKE_SARS2	657	NNSY	0.4724	(6/9)	-
sp_P0DTC2_SPIKE_SARS2	709	NNSI	0.3528	(9/9)	--
sp_P0DTC2_SPIKE_SARS2	717	NFTI	0.6426	(9/9)	++
sp_P0DTC2_SPIKE_SARS2	801	NFSQ	0.6146	(8/9)	+
sp_P0DTC2_SPIKE_SARS2	1074	NFTT	0.4084	(7/9)	-
sp_P0DTC2_SPIKE_SARS2	1098	NGTH	0.5496	(5/9)	+
sp_P0DTC2_SPIKE_SARS2	1134	NNTV	0.5800	(6/9)	+
sp_P0DTC2_SPIKE_SARS2	1158	NHTS	0.3730	(9/9)	--
sp_P0DTC2_SPIKE_SARS2	1173	NASV	0.3998	(8/9)	-
sp_P0DTC2_SPIKE_SARS2	1194	NESL	0.6791	(9/9)	++

Source: Adapted by authors

Figure 3a and 3b: Prediction of N-glycosylation in spike proteins P59594 and P0DTC2

According to Padhi et al. [42], when SARS-CoV-2 multiplies in host cells with its subsequent release to perpetuate the cycle, thus infecting new hosts, its proteins, especially spike, would have A and/or B antigens, depending on the blood group. Thus, as individuals of blood group O possess antibodies against antigens A and B, they would be able to protect, to a certain extent, from SARS-CoV-2 carrying A and/or B antigens, explaining the lower number of infected individuals in this group.

Gérard et al. [43] postulate that group O as it predominantly presents anti-B and anti-A immunoglobulin of the IgG isotype, differently from groups A, B and AB where the IgM isotype predominates, would explain the fact that group O presents lower susceptibility when compared with the other non-A groups. The authors suggest that the presence of anti-A antibodies in the serum and more specifically of the IgG class should be considered a more significant factor than the blood group itself with regard to the relationship

between COVID susceptibility to ABO blood groups.

IV. CONCLUSIONS

It can be inferred that glycosylation of the spike protein is extremely important for SARS-Cov-2 to evade immune responses and that it is probably the explanation for the relationship with susceptibility related to the ABO system groups. It is clear the importance of glycoproteomics and immunology knowledge in the search for both a vaccine and diagnostic tools, as well as the use of bioinformatics tools in the advancement of medical and biomedical sciences.

While the emergence of a new coronavirus puts the world under great pressure, the clarification of glycoproteins in the viral envelope opens up a wide range of possibilities for the application of lectins and glycosylation inhibitors that may participate in treatment and/or diagnosis.

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