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HLA-A*02 affinity to SARS-CoV-2 and susceptibility to COVID-19

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ABSTRACT: Coronavirus disease 2 (SARS-CoV-2) was declared by the World Health Organization as a global public health urgency. Considering the crucial role of HLA molecules in emerging infections, the interference of different HLA alleles on susceptibility to COVID-19 has been questioned in the scientific academy. Intending to elucidate the target ligand interactions, this present work selected the genotypes HLA-A*02, HLA-B*15, HLA-B*35 and HLA-B*44, as the most frequent in the Bahian population and the viral epitopes YLQPRTFLL, QYIKWPWYI, LTDEMIAQY, NYNYLYRLF, FIAGLIAIV, the most immunogenics of the spike glycoprotein peak. For protein selection, modeling and molecular docking was used the Allele Frequency Net Database (AFND), Immune Epitope Database and Analysis Resource (IEDB), the HADDOCK online server and the PEP-FOLD 3. Our findings suggest that HLA-A*02:01 is a risk genotype, since it showed lower energy affinity compared to HLA-B*15, HLA-B*35 and HLA-B*44.

Keywords: HLA; COVID-19; Molecular Docking.

1. INTRODUCTION

In December 2019, a new virus emerged in the seafood market in Wuhan, Hubei province, China, and after genetic sequencing, it was determined that it belonged to the Coronaviridae family [1]. Soon after, in the first quarter of 2020, the World Health Organization (WHO) declared the new coronavirus disease (COVID-19) a global public health emergency and suggested that all countries take measures to control the pandemic. To date, coronaviruses have caused four explosive illnesses: Severe Acute Respiratory Syndrome (SARS) between 2002 and 2003, in China, Middle East Respiratory Syndrome (MERS) in 2012 and the current COVID-19 between 2019 and 2022 [2].

Thus, COVID-19 mobilized the international scientific community in search of answers about susceptibility factors to the disease, among which the influence associated with the interaction of the virus with human proteins has been reported previously [3]. According to Deb et al. [4] variations in the molecules of the Human Leukocyte Antigen (HLA) complex have shown significant associations related to the strength of interaction between the HLA-Antigen (Ag)-T Cell Receptor (TCR) complex. The elucidation of these molecular mechanisms became possible due to technological advances in bioinformatics, statistics and omics sciences [5].

As a relevant genetic factor, the author Galisa (2021) [6] brings the idea that the HLA system plays a role of paramount importance in regulating the immune response, thus, various polymorphisms in the HLA genes associated with viral infections, including SARS-CoV-2, are described. As for the virus, Vieira [7] explains that the entire genome of SARS-CoV-2 is inscribed in only one single RNA (ribonucleic acid) strand, and because of this, this virus has a higher rate of mutations compared to viruses that have DNA (deoxyribonucleic acid) in their genome, because DNA has a greater ability to correct any transcription errors.

At the 3' end of SARS-CoV-2, there are the Spike (S), membrane (M), nucleocapsid (N) and envelope (E) proteins [8]. Among these, the S protein plays a crucial role in the virus entering the cell and, due to its location, in the host's immune responses. Thus, it is the main target of prophylactic and therapeutic interventions, the S1 subunit has 672 amino acids organized in four domains: N-Terminal (NTD), Receptor Binding Domain (RBD), and two subdomains SD1 and SD2. The S2 subunit has 588 amino acids and with the N-terminal hydrophobic fusion peptide (FP), two heptad repeats (HR1 and HR2), a transmembrane domain (TM) and a cytoplasmic tail (CT), organized as FP-HR1-HR2-TM-CT [9].

Therefore, due to the current pandemic urgency, it is necessary to clarify the genetic factors of susceptibility to infection by SARS-CoV-2, including the prospecting of new molecules for drug production. In this sense, the objective of this work is to describe the interaction strength of HLA-A1, HLA-A2, HLA-A24 and HLA-B35 with validated epitopes of SARS-CoV-2 in the Brazilian population.

2. MATERIALS AND METHODS

2.1. Selection of genotypes and HLA proteins

The four genotypes with the highest allele frequency in the Brazilian population of the state of Bahia of HLA Class I, locus A and B, were selected from the Allele Frequency Net Database (AFND) (version website: 3.37.0) available on the website allelefrequencies.net/.

2.2. SARS-CoV-2 viral epitope selection

The public access website www.iedb.org was used, which has robust experimental literature on epitopes expressed on HLA/MHC molecules that are recognized by T cells, studied in humans and other animal species, funded by the United States National Institute of Allergy and Infectious Diseases. The tool is widely used to search for molecular targets in order to elucidate adaptive immune responses [10]. The search strategy consisted of selecting the epitopes available for T cells, with restriction for MHC Class I, specific for the S glycoprotein of the SARS-CoV-2 viral source, targeted at the human host and the COVID-19 disease. After this active search, the epitopes were selected based on the highest immunogenicity presented by the website, which were respectively: YLQPRTFLL [11], QYIKWPWYI [12], LTDEMIAQY [13], NYNYLYRLF [14] and FIAGLIAIV [15].

2.3. Molecular modeling

For the process of modeling Spike protein peptides, the PEP-FOLD 3 software, version 3.5 was used (https://bioserv.rpbs.univ-paris -diderot.fr/services/PEP-FOLD3/) [16-18]. For the modeling process, the HLA molecule available on the website was obtained from Protein Data Bank (PDB) (https://www.rcsb.org/structure/7mkb), from this structure, peripheral regions not relevant for docking were removed and the AlphaFold 1 software was used for modeling [19], available on Google Colab (https://colab.research.google.com/github/sokrypton/ColabFold/blob/main/AlphaFold2.ipynb) [20].

2.4. Molecular docking

The HADDOCK (High Ambiguity Driven protein-protein DOCKing) (Utrecht Bioinformatics Center, Version: 2.4) (https://wenmr.science.uu.nl/haddock2.4/) webserver was used for docking, using the HADDOCK Score (HS) metric which is defined as "HS = 1.0 * van der Waals + 0.2 * intermolecular electrostatic energy + 1.0 * empirical desolvation energy + 0.1 * AIR energy" [21, 22] the active residues required for Docking were obtained by Cport. To define active residues, the entire length of the SARS-CoV-2 epitopes were defined as active amino acids, and for HLA the entire canonical region of interaction between the SARS-COV-2 epitope and the HLA cleft delimited between amino acids 25-200 [23].

3. RESULTS AND DISCUSSION

3.1. HLA-A*02 has a higher allele frequency in the Baiian population

After the active search, it was found that HLA-A02 has the highest allele frequency in the Bahian population, around 23.67%, in second place HLA-B15 with 11.02%, in third place HLA-B35 has 11.01% and in fourth place HLA-B44 has 11.01% (Figure 1).

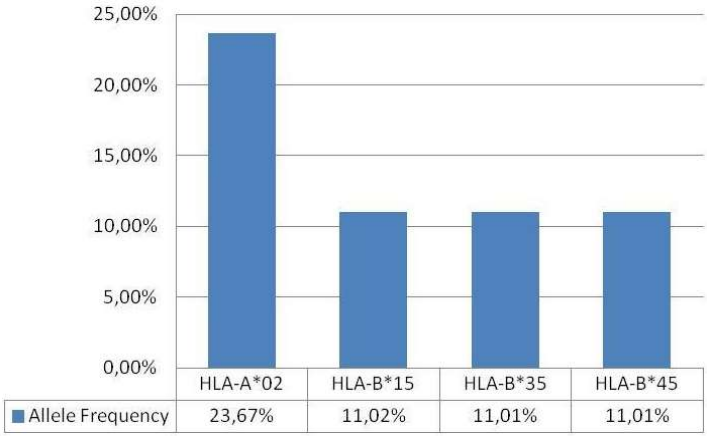

Figure 1. Most frequent HLA Class I allele genotypes in Bahian population (n=47,399).

The HLA allele frequency has been analyzed by the scientific community in order to investigate population-level immunological coverage. For example, the work of Wang et al. [24] evaluated the allele frequency distribution in 82 Chinese individuals with COVID-19 using Next Generation Sequencing (NGS), this study suggested that some HLA alleles may be associated with the occurrence of COVID-19.

In Europe, in a similar perspective, Novelli et al. [25] analyzed the frequency of HLA in a group of 99 Italian patients affected by the severe or extremely severe form of COVID-19, the authors claim that this approach can help to individualize alleles that may reflect a higher susceptibility to the disease. After applying

the Bonferroni correction for multiple tests, a significant association was found for HLA-DRB1*15:01, -DQB1*06:02 and -B*27:07. Although they admit that there are controversial results on the role of single HLA alleles in patients with COVID-19, they claim that increased frequencies can contribute to identifying potential susceptibility markers to the disease.

However, there are some authors who contest the relevance of HLA, Schetelig et al. [26] suggested in their work that HLA-A, HLA-B, HLA-C and HLA-DRB1 are not important factors for the severity of COVID-19, also suggests that the Spike glycoprotein alone allows T cells to mount robust responses not limited to HLA genotype. Shachar et al. [27] also stated that if there is any relationship between HLA and COVID-19, it is very weak and has a limited effect on the pandemic, their conclusions are based on their large-scale analysis of Israeli individuals who tested positive for SARS-CoV-2 by Polymerase Chain Reaction (PCR), in which no association was found.

However, authors like these, who contest the relevance of HLA in understanding COVID-19, are going against other evidence in the literature. At the Third People's Hospital of Shenzhen, China, the whole-genome association study by Wang et al. [28] concluded that HLA-A11;01, B51:01 and C14:02 significantly predispose to worse outcomes in patients. Another in silico association study by Sakuraba et al. [29] concluded that the allelic frequency of HLA-C05 and the distribution pattern with its receptor KIR2DS4fl strongly correlate with COVID-19 mortality in 74 countries.

In this context, the search for new evidence is constant. To obtain allelic frequencies, the Allele Frequency Net (AFND) database provides the scientific community with a widely used public and free repository in studies of the relationship between HLA and COVID-19. As in the work of Requena et al. [30], which conducted a literature review on allelic frequency of HLA by country and identification of new candidate epitopes in SARS-COV-2 proteins for South America, using AFND and the Immune Epitope Database and Analysis Resource (IEDB). According to these authors, updating HLA allelic frequencies has a crucial impact on the quality of immunogenetic studies.

3.2. YLQPRTFLL is the most immunogenic epitope of spike glycoprotein peak

Upon searching for viral epitopes in the IEDB, it was found that the epitope YLQPRTFLL has 30 references in literature and 95 immunological assays, followed by QYIKWPWYI with 17 references and 25 immunological assays, LTDEMIAQY with 13 references and 22 immunological assays, NYNYLYRLF with 12 references and 18 immunological assays, and FIAGLIAIV with 9 references and 1 immunological assay (Figure 2).

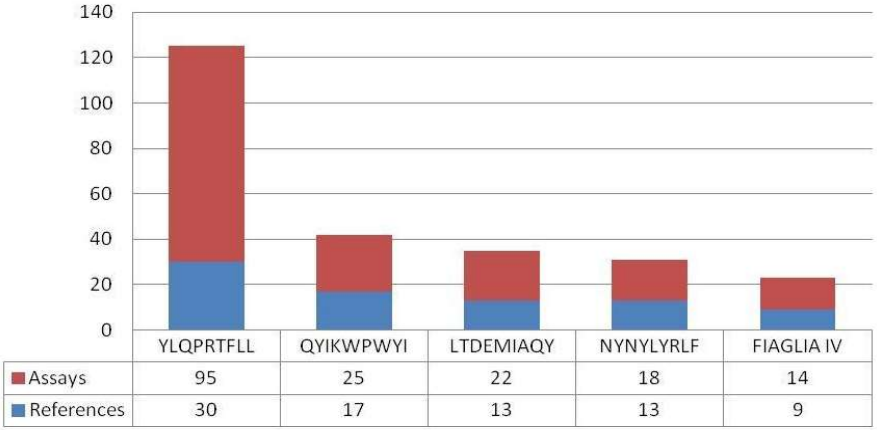

Figure 2. Most immunogenic viral epitopes of the SARS-COV-2 Spike glycoprotein spike found in the Immune Epitope Database and Analysis Resource (IEDB).

According to the official website iedb.org, the IEDB is a freely available resource funded by the National Institute of Allergy and Infectious Diseases of the United States (NIAID), which catalogs experimental data on epitopes, antibodies, and T cells studied in humans, other non-human primates, and other species in the context of infectious diseases, also bringing together epitope analysis and prediction tools.

In the context of the COVID-19 pandemic, this tool has been helping researchers worldwide in understanding the specific T cell receptors (TCR) of SARS-COV-2, as well as in MHC restriction and immunodominance. As the study of Wu et al. [31], which aimed to determine the public and private TCR structures in complex with HLA-A2 and two epitopes of the SARS-COV-2 spike protein (YLQ and RLQ), according to the authors, the structures reveal the basis for selection of specific genes.

According to Parker et al. [32], the spike glycoprotein (composed of the S1 and S2 subunits) is highly immunogenic for T cells, constituting not only the main vaccine target but also the top of the antigenic hierarchy of the entire viral proteome. In the study by Titov et al. [33], a panel of immunogenic epitopes was created for obtaining cellular responses to SARS-COV-2. According to the authors, the evaluation of T-cell responses contributes to a more comprehensive characterization of immunity to the pathogen. In this study, 118 epitopes were evaluated, of which 75 were identified as immunogenic and 24 immunodominant. The authors also point out that the most dominant MHC-I epitope of the S protein, with almost 100% response, was YLQ/A*02:01.

However, the prospecting of new epitopes is dynamic, that is, it needs to keep up with viral evolution. Dolton et al. [34] present an emergency in the immunological escape of SARS-COV-2 through the Spike P272L mutation (sequence YLQPRTFLL), which appeared in at least 112 different strains, including so-called worrying variants. After sequencing 747 isolates, Agerer et al. [35] alerts in their study that SARS-COV-2 mutations in epitopes restricted to MHC-I avoid CD8+ T cell responses, being, in addition, the reduced binding of MHC-1 to mutant peptides, associated with decreased cell proliferation and IFN-γ production.

In light of this problem, although the epitope YLQPRTFLL has been widely cited in the literature, robust immune responses are based on multiple epitopes. This was well defined in the study by Luz et al. [36], in which the diversity of T-cell responses was associated with mild symptoms, this knowledge helps in the development of preventive, diagnostic and therapeutic measures. Especially when mutations in the S protein of SARS-COV-2 that avoid immunity and increase infectivity are already being reported, the study by Motozono et al. [37] demonstrated that the L452R variant had a higher affinity for the host entry receptor (ACE2) and escaped cellular immunity restricted to HLA-A24.

3.3. According to HLA-A*02, it has lower energy affinity when compared to other variants

The comparative HS between the epitopes demonstrated greater conformity between the epitopes YLQPRTFLL and QYIKWPWYI, with the variants from best to worst performance being HLA-B 44, HLA-B 35, HLA-B 15 and HLA 02 (Figure 3).

According to some authors, HLA variability can help to understand the susceptibility, severity, mortality, and clinical heterogeneity of COVID-19. In this context, the binding affinity-based approach is widely used, in a pilot study, Iturrieta-Zuazo et al. [38] evaluated the binding affinity of 66 HLA class I alleles and SARS-COV-2 viral peptides, and their association with severity in a total of 45 Spanish patients, their results suggested that patients with mild disease present class I HLA molecules with higher theoretical binding capacity. Therefore, it is crucial to evaluate the HLA's ability to bind to SARS-COV-2.

In this perspective, given the importance of the S protein, evaluating epitopes of this protein recognized by the most frequent MHC-I alleles, has been crucial for evaluating the immunity trend of populations. In a similar approach to this study, also done in the Brazilian population, Moura et al. [39] performed molecular

modeling, measurement of binding affinity, prediction of antigenicity, peptide docking and molecular dynamics of MHC-I/S protein complexes. Identifying, in this way, 24 immunogenic epitopes that could interact with 17 MHC-I alleles, although recognizing the limitations of in silico analyses, the authors believe that this approach can improve the understanding of the immune response against the virus.

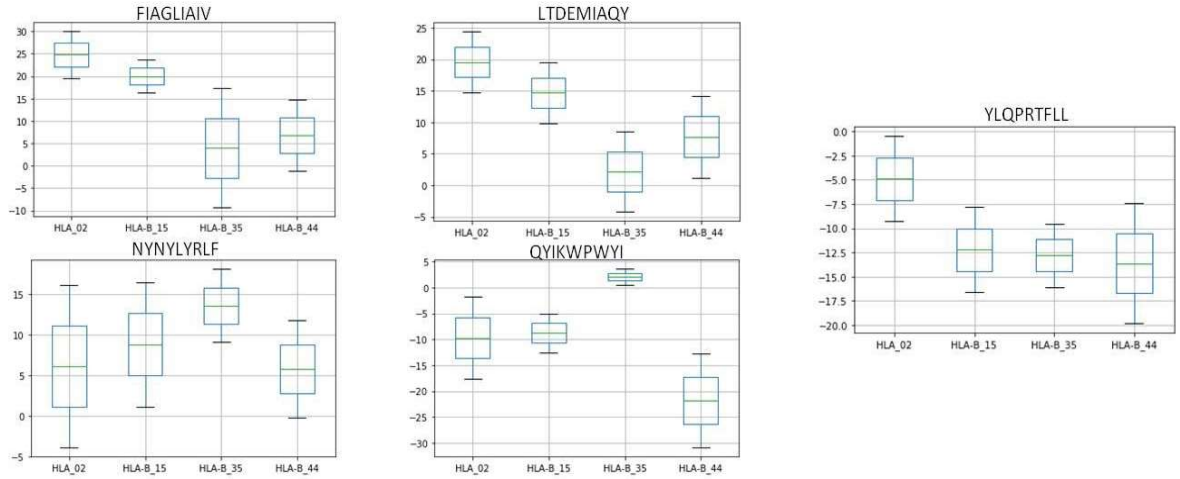

Figure 3. Haddock Score HLA variants with SARS-COV-2 epitopes.

In this sense, bioinformatic predictions of binding affinity began in 2020, often inspired by the work of Hsieh and his collaborators [40]. In the study Map of susceptibility to HLA for coronavirus 2 (2020), this author and his collaborators found that HLA-15:03 showed a greater ability to present SARS-COV-2 antigens, antigens that are conserved and shared in other human coronaviruses, suggesting, therefore, a possibility of cross-immunity. Additionally, they also highlighted that the prediction of high-risk HLA individuals could guide public policies, such as vaccination priority.

The in silico analysis by Tomita et al. [41] also relied on binding affinity to associate HLA polymorphisms with COVID-19 mortality. The authors' hypothesis is that the most common HLA genotypes in the population could influence morbidity and mortality. In order to assess the issue, they compiled HLA frequency data from 19 countries with high and low mortality. They conducted an analysis of covariance using R software. Afterward, they computationally predicted in silico the binding of HLA class I alleles to SARS-COV-2 peptides using IEDB algorithms. The results of the present study reinforce the results of the authors, Tomita T and his collaborators [41], who found that HLA-A*02:01 had a lower capacity to bind to SARS-COV-2 when compared to HLA-A*11:01 or HLA-A *24:02, already in this work, it was found that HLA-A*02:01 also has a lower binding capacity when compared to HLA-B 44, HLA-B 35, HLA-B 15. However, unlike this work, Tomita T and his collaborators [41] also associated HLA-A-02:01 with an increased risk of COVID-19.

3.4. Positions 97, 70, 147 and 156 are the most relevant; ARG97 and TRP147 are retained in all variants

In reference to the amino acids, the most relevant ones were those located in positions 97, 70, 147, and 156, interacting respectively with 18, 17, 17 and 16 experiments out of a total of 20. The most conserved were ARG97 and TRP147, which were conserved in all variants, with position 97 being located in the center of the active site on beta 3 strand, the other amino acids are located in the alpha structures that delimit the site, 70 in alpha 2, 147 in alpha 3, 156 in alpha 4 (Figure 4).

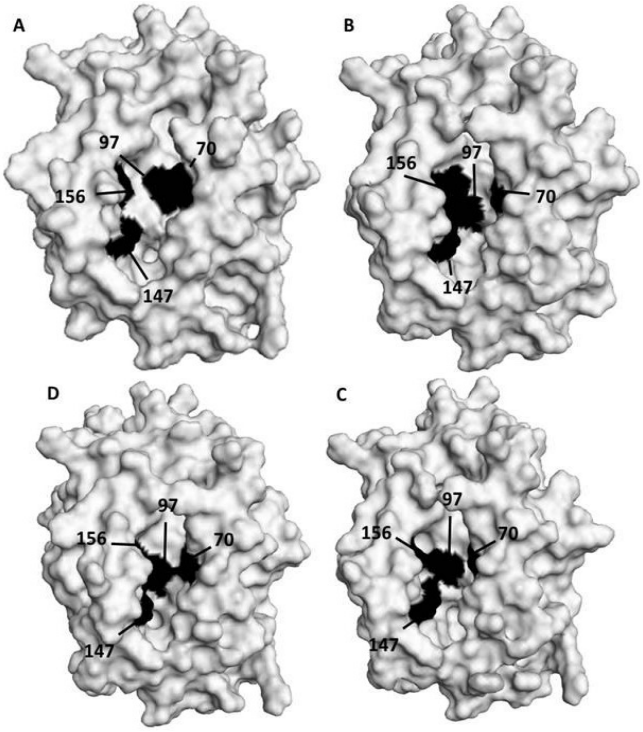

Figure 4. Amino acids 97, 70, 147 and 156 in HLA variants.

4. CONCLUSIONS

The results of this study suggest that the most frequent allele in Bahia state, HLA-A02, has lower affinity for SARS-COV-2 compared to other HLA variants, in particular the YLQPRTFLL epitope of the S protein stands out. In terms of variant structure, ARG97 and TRP147 remained conserved, and further studies are needed to determine if this conservation holds true in other populations. The literature suggests that the low affinity of HLA-A02 may possibly be associated with an increased risk for COVID-19, therefore more robust studies are needed to clarify this issue, adjusting for other variables that may create confusion such as age, gender, and ancestry.

Author Contributions: F.M.A. and M.V.C.M.S. did the conception and design of the study; L.N.R., F.S.S., V.M.L., M.S., M.S.G. and F.M.A.O. did the acquisition of data; F.M.A., M.V.C.M.S., F.S.S. and V.M.L did the analysis and the interpretation of data; F.M.A., M.V.C.M.S. and M.S. did the draft of the article or critical review for important intellectual content. All authors read and approved the final version of the manuscript.

Conflict of Interest: The authors declare no potential conflict of interest.

Availability of data and materials: The datasets used and analyzed in this study are available from the corresponding author upon reasonable request.

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