

Estimating the binding of Sars-CoV-2 peptides to HLA class I in human subpopulations using artificial neural networks

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Abstract

Epidemiological studies show that SARS-CoV-2 infection leads to severe symptoms only in a fraction of patients, but the determinants of the individual susceptibility to the virus are still unknown. The Major Histocompatibility Complex (MHC) class I exposes viral peptides in all nucleated cells and is involved in the susceptibility to many human diseases. Here we use artificial neural networks to analyze the binding of SARS-CoV-2 peptides with polymorphic human MHC class I molecules. In this way, we identify two sets of haplotypes present in specific human populations: the first displays weak binding with SARS-Cov-2 peptides, while the second shows strong binding and T cell propensity. Our work offers a useful support to identify the individual susceptibility to COVID-19 and illustrates a mechanism underlying variations in the immune response to SARS-CoV-2. A record of this papers Transparent Peer Review process is included in the Supplemental Information

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Introduction

SARS-CoV-2, the coronavirus causing the COVID-19 pandemic, is the seventh coronavirus known to infect humans. SARS-CoV, MERS-CoV and SARS-CoV-2 can cause severe disease, whereas HCoV-HKU1, HCoV-NL63, HCoV-OC43 and HCoV-229E are associated with mild symptoms (Corman et al., 2018). For a successful infection, multiple elements of the host immune response must be overcome, including both the innate and the adaptive immunity (Mandl et al., 2015). The Human Leukocyte Antigen (HLA) system or the Major Histocompatibility Complex (MHC) is a very polymorphic region of the human genome which plays an important role in the individual genetic susceptibility to human diseases (Dendrou et al., 2018). For example in infectious diseases, HIV infection was shown to be highly correlated with HLA-A*29, HLA-B*35, and HLA-B*57 (Hill, 1998; Mallal et al., 2002; Carrington et al., 1999; Goulder and Watkins, 2008; Mekue et al., 2019; Valenzuela-Ponce et al., 2018) and H1N1 flu was shown to be associated with several HLAs (Falfán-Valencia et al., 2018; Luckey et al., 2019). Association between disease severity and HLA was also reported in SARS-CoV patients (Lin et al., 2003; Ng et al., 2004; Chen et al., 2006; Keicho et al., 2009; Spínola, 2016).

According to the structure and function of its genes, the human MHC has been classified in three main regions: class I, class II and class III. The class I regions are located on the most telomeric part of the human MHC and include 3 highly polymorphic HLA genes, known as classical (Class Ia: HLA-A, HLA-B and HLA-C) and 3 lowly polymorphic HLA genes, known as non-classical (class Ib: HLA-E, HLA-F and HLA-G) (Shiina et al., 2009). These molecules display at the cell surface small protein fragments, mostly originated in the cytosol. Thus when a cell expresses foreign proteins, due for example to a viral infection, peptides created in the cytosol through proteasome-dependent processes could bind the MHC class I. This MHC-peptide complex can then be exposed on the cellular membrane, triggering the immune response if there is a recognition by CD8+ T cells (Maffei et al., 1997; Goldberg and Rizzo, 2015). Among HLA class I, HLA-B is the most polymorphic classical class I gene, with 4077 alleles identified to date in different human populations, followed by HLA-A (3285 alleles) and HLA-C (2801 alleles) (González-Galarza et al., 2015).

Due to the rapid spread of the SARS-CoV-2 virus, a crucial question is to understand why there is an individual susceptibility to the virus in

the population. Epidemiological studies show that only a fraction of the infected individual experiences severe respiratory symptoms due to SARS-CoV-2 (Wu et al., 2020), with an infection fatality ratio estimated for China at around 0.6% and increasing with age (Verity et al., 2020). Another recent work estimated that in France on average 2.6% of the infected individuals were hospitalized while 0.53% died, again with a dependence on the age of the patient (Salje et al., 2020). In light of these results, it would be extremely important to identify in advance possible susceptible subjects in order to protect them with adequate prevention strategies (Lipsitch et al., 2020).

In the present paper, we propose a method to identify the dependence on HLA class I polymorphic alleles of the individual immune response to SARS-CoV-2. We focus on this class of MHC since they are expressed by all nucleated cells, including antigen presenting cells. In practice, we estimate the aggressiveness of COVID-19 based on the compatibility between the specific HLA I polymorphism and SARS-CoV-2 peptides. Because experimental characterization of neoantigens is costly and time-consuming, there is a growing effort in the development of computational methods that are able to predict peptide-MHC binding and the subsequent immune response. Supervised neural network machine learning approaches are currently showing increasing performance and are widely used as *in silico* epitope prediction tools (Paul et al., 2020; Jurtz et al., 2017; O’Donnell et al., 2018). Here, we use two of these epitope prediction algorithms to compute binding affinities between SARS-CoV-2 peptides and 79 HLA class I. Similar calculations are performed to identify peptides for vaccine development (Campbell et al., 2020).

We compare our predictions for SARS-CoV-2 with analogous predictions for SARS-CoV and HCoV-OC43, a coronavirus responsible for the common cold. We also assess the stability and T cell propensity of these peptides for a smaller number of HLA alleles (Trolle and Nielsen, 2014). Using this method, we identify a set of weakly binding haplotypes and assess their prevalence in specific human subpopulations, as well as a set of strongly binding haplotypes for which we also compute peptide stability and T cell propensity (Trolle and Nielsen, 2014). All together, our strategy paves the way to the development of a general screening method to assess individual COVID-19 susceptibility in the population.

Results

To compute binding affinities of coronavirus peptides, we combine the predictions of two state-of-the-art methods (Paul et al., 2020): netMHCpan (Jurtz et al., 2017) and MHCflurry (O’Donnell et al., 2018)) both based on artificial neural networks. The combination of the two methods allows us to have a more robust result that is independent of the artificial neural networks used. We consider 79 common polymorphic HLA class I alleles supported by both methods and combine their predictions for the binding affinities for peptides of lengths 8-11. These 79 HLA alleles are present in a considerable fraction of the human population as illustrated in Fig. S1. We scan peptides that are produced by proteasome degradation (Nielsen et al., 2005) considering only the structural proteins of SARS-CoV-2, which are the most abundant proteins in coronaviruses (Bar-On et al., 2020). We then compared the results obtained from the structural proteins of SARS-CoV and HCoV-OC43.

As shown in Fig. S2, S3 and S4 for HLA-A, HLA-B and HLA-C alleles and SARS-CoV-2 peptides, binding affinities are broadly distributed with a peak at high affinities so that the majority of peptides display weak binding to the HLA. Furthermore, the distributions differ between the various alleles (Fig. S2, S3 and S4), confirming the presence of heterogeneous binding pattern. To encapsulate the binding affinity distributions into a simple parameter, we counted all the peptides displaying a strong binding affinity ($IC_{50} < 1000\text{Mm}$) for each of the 79 alleles. We carried out the same analysis for all the three coronaviruses. Fig. 1a displays the number of strongly binding peptides for each allele showing that there is a close similarity between SARS-CoV-2 and SARS-CoV. In particular, alleles with few strongly binding peptides in SARS-CoV-2 also display small numbers in SARS-CoV while alleles with many strongly binding peptides in SARS-CoV-2 also show many strong peptides in SARS-CoV (Fig. 1a). We can also observe similarities between SARS-CoV-2 and HCoV-OC43, but typically HCoV-OC43 displays more strongly binding peptides than SARS-CoV-2 or SARS-CoV (see Fig. 1a).

To confirm that our results do not depend on the particular cutoff chosen, we also repeat the analysis with a smaller cutoff for strong binding ($IC_{50} < 500\text{Mm}$). In Fig. S5, we compare the number of strongly binding peptides in SARS-CoV-2 for the two different cutoffs. The outcome is very similar, apart from small quantitative differences. To obtain a cutoff-independent as-

assessment of the binding of viral peptides to each HLA molecule, we compute a total binding affinity K_{tot} by weighting the binding affinity of all the peptides, as described in the Methods section. The value of K_{tot} for the binding between SARS-CoV-2, SARS-CoV and HCoV-OC43 peptides to all the considered HLA molecules is reported in Fig. S6. Comparing the patterns in 1a and Fig. S6, we can see that the HLA molecules with few strongly binding peptides are also those with higher values of K_{tot} , confirming the robustness of our results.

A visual representation of how much strongly binding peptides are shared among different HLA alleles is provided in Fig. 1b for the case of SARS-CoV-2. The figure shows that some peptides display strong affinity (in yellow) for a number of HLA molecules, but in general peptides only bind strongly to a relatively small number of HLA molecules, highlighting the heterogeneity of MHC-peptide interactions across human haplotypes.

To understand in more depth the similarities between SARS-CoV-2 or SARS-CoV, we report in Fig. S7a peptides that are common to both viruses and that are binding strongly to more than one HLA molecule. We observe that some peptides bind strongly to up to 8 HLA molecules. Conversely for each HLA molecule, there are strongly binding peptides that are unique to SARS-CoV-2 or SARS-CoV. The number of these peptides are summarized in Fig. S7b for each HLA molecule.

We then analyzed the stability between peptides and HLA class I as well as T cell propensity. To this end, we use a NetTepi (Trolle and Nielsen, 2014) to find putative T cell epitopes for SARS-CoV-2 and SARS-CoV considering all the 13 alleles available for this method. These alleles are widely frequent in human populations: the HLA-A alleles are present in around 60% of the populations, while the HLA-B are present in around 30% of the populations. As shown in Fig. S8a the number of highly ranked peptides are very similar in the case of SARS-CoV-2 and SARS-CoV. Highly ranked peptides that are common to the two coronaviruses are then reported in Fig. S8b together with their rank. In Fig. S9, we display distributions of binding stability, T cell propensity and T cell epitope score for the 13 supported HLA alleles and all the strongly binding peptides previously identified in SARS-CoV-2. By ranking the HLA molecules as based on the T cell epitope score, we can identify the list of HLA molecules that are most likely to bind SARS-CoV-2 peptides that are recognized by T cells.

Having characterized the binding propensity of each molecule to SARS-CoV-2 peptides, we thus investigate how individuals from different human

populations are likely to respond to SARS-CoV-2 infection in terms of peptide presentation by HLA class I. To this end, we collect haplotype frequencies from different human populations (i.e. Europeans, Chinese, Japanese, Hispanic and African Americans) and inspect the prevalence of weakly binding molecules, defined as those who display no strongly binding peptide from SARS-CoV-2 structural proteins. This list includes: HLA-A*25:01, HLA-A*26:03, HLA-A*66:01, HLA-B*08:02, HLA-B*14:02, HLA-B*15:09, HLA-B*27:02, HLA-B*27:03, HLA-B*27:04, HLA-B*27:06, HLA-B*37:01, HLA-B*39:06, HLA-B*46:01, HLA-B*83:01, HLA-C*04:01, HLA-C*08:02 and HLA-C*12:03. Since HLA is codominant and all the alleles (A, B and C) are expressed by each individual, we determine the haplotype that contain three, two or one of the alleles contained in the list. We then plot their prevalence in the different human populations (see Fig. 2b). The results show that haplotypes with three weakly binding alleles are generally quite rare, amounting to up to 2 individuals over 1000. The frequency of haplotypes with two weakly binding alleles is around 1-4% depending on the populations, with the exception of Japan where those haplotypes amount only to 0.16% and Germans of Chinese origin where this frequency is 0.59%. Finally, haplotypes with only one weakly binding peptide are more common, showing frequencies of around 20% with small variations among different populations.

We finally report the frequency of haplotypes containing either one or two of the HLA alleles that are most likely to bind SARS-CoV2 peptides and be recognized by T cells. Fig. 2a shows variations of the frequency in the populations, with Chinese and Japanese displaying the highest frequency of these haplotypes.

Discussion

The possibility to screen the population and predict a score of aggressiveness for each specific individual is a critical issue in order to develop personalized therapeutic strategies and to mitigate the effects of the infection in the shortest time. To reach this final goal, we focused on HLA class I which is involved in presenting viral peptides to CD8+ T cells, mounting the immune response. A more complete picture of the immune response could be obtained by studying HLA class II molecules, but the performance of peptide-HLA class II binding prediction algorithms is still inferior to that of HLA class I predictors (Andreatta et al., 2018).

SARS-CoV-2 and SARS-CoV share 80% of the genome, while the similarity between SARS-CoV-2 and HCoV-OC43 is only 50% (Bar-On et al., 2020). We have thus compared the variations in binding affinities between coronavirus-derived peptides and a large number of HLA class I molecules for SARS-CoV-2, SARS-CoV, and HCoV-OC43. Our results show that the binding patterns are similar for SARS-CoV-2 and SARS-CoV while they differ more for HCoV-OC43. We then identified a list of HLA class I alleles where the binding with SARS-CoV-2 peptides is particularly weak. This means that these HLA alleles have a smaller probability to start immediately an adaptive immune response. On the other hand, we also identified the list of HLA alleles where the binding with SARS-CoV-2 peptides is particularly strong and that are most likely to activate a T cells response.

Our results show clearly the heterogeneity of the human population in responding to SARS-CoV-2 infection. To quantify this heterogeneity, we computed the frequency of haplotypes that are predicted to display a weak SARS-CoV-2 peptide-HLA class I binding in different human populations. In particular, we measured the prevalence of haplotypes that contain one, two or three weakly binding alleles. Individuals with these haplotypes are likely to display a weaker immune response to SARS-Cov-2 infection. In this way, we developed a clear parameter that can be useful to screen the population.

Earlier studies in SARS-CoV revealed association between the presence of HLA-B*46:01, one of the weakly binding alleles in our list, and the observation of severe symptoms in a cohort of Taiwanese patients (Lin et al., 2003). Similar associations were found with HLA-B*07:01 (Keicho et al., 2009) and HLA-C*08:01 (Chen et al., 2006) that are, however, not among the alleles we were able to study with our method. Since SARS-CoV-2 and SARS-CoV share most of the genome and we show that they display similar HLA binding profiles, it is expected that the weakly binding HLA molecules are similar for both viruses. While these early study confirm the relevance of our approach, in light of our results it would be more appropriate to investigate the correlations between disease severity and the complete haplotype, instead of focusing on individual alleles.

Furthermore, we also identified the HLA haplotypes associated with a strong combined peptide affinity, stability and T cell propensity and measured their prevalence in different human populations. We found that these haplotypes are more present in Asian populations. This might be a relevant parameter to study the diffusion of the disease across the world. Simulations of diffusion of the virus might take this effect into account. All together,

our strategy could be the basis to develop individualized tests to assess the immune susceptibility to COVID-19 in the population. To reach this goal, it would be important to extend our analysis also to HLA class II molecules.

Author contributions

CAMLP and SZ designed the project, performed research, analyzed data and wrote the paper.

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Declaration of interests

Authors declare no conflicts of interest.

Figure 1: Characterization of binding heterogeneity of SARS-CoV-2 and SARS-CoV peptides are similar and differ for HCoV-OC43. The number of strongly binding peptides ($IC_{50} < 1000nM$) for SARS-Cov-2, SARS-Cov and HCoV-OC43 estimated for 79 Class I HLA alleles by combining predictions from netMHCpan and MHCflurry. b) The binding affinities (IC_{50}) of SARS-Cov-2 peptides are shown in the clustered colormap for 79 Class I HLA alleles. Only peptides with at least one binding affinity smaller than 1000nM are included.

Figure 2: Response to SARS-CoV-2 across human populations. a) Frequencies of haplotypes containing 1 or 2 strong alleles, defined as those with highly ranked T-cell epitopes. b) Frequencies of haplotypes containing 1,2 and 3 weakly binding alleles for SARS-CoV-2. Error bars are estimated 95% confidence intervals.

Supplemental items

- Supplementary information: pdf file containing 10 supplementary figures (related to Fig. 1)
- Data S1: Binding affinities for SARS-CoV-2, SARS-CoV and HCoV-OC43 peptides (related to Fig. 1).

STAR Methods

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Caterina A. M. La Porta (caterina.laporta@unimi.it).

Materials Availability

This study did not generate new unique reagents or materials.

Data and Code Availability

The source codes generated to obtain the results presented in this paper are available at <https://github.com/ComplexityBiosystems/hla-covid>. Binding affinities for SARS-CoV-2, SARS-CoV and HCoV-OC43 are reported in Supplementary data S1. The protein sequences used in this paper are also available at <https://github.com/ComplexityBiosystems/hla-covid/>. Haplotype frequencies for different population are retrieved from the Allele Frequency Net Database (<http://www.allelefrequencies.net/>) (González-Galarza et al., 2015) and available at <https://github.com/ComplexityBiosystems/hla-covid/>.

METHOD DETAILS

Calculation of binding affinities for individual peptides

We downloaded the fasta sequences for SARS-CoV-2 (GenBank: MN908947.3), SARS-CoV (NCBI Reference Sequence: NC_004718.3) and HCoV-OC43 (NCBI Reference Sequence: NC_006213.1). We restrict our analysis to the most abundant structural proteins (Bar-On et al., 2020): S,N,E,M for SARS-Cov and SARS-Cov-2 and S,N,E,M,HE for HCOV-OC43. In order to estimate binding affinities for peptides, we combine two recent algorithms based

on artificial neural networks (ANN): netMHCpan 4.0 (Jurtz et al., 2017) and MHCflurry (O'Donnell et al., 2018). NetMHCpan uses a pan-allele approach to provide predictions for binding affinities of peptides to any MHC molecule by an ANN trained on a combination of more than 180000 quantitative binding data (Jurtz et al., 2017). MHCflurry uses instead an allele specific algorithm where each MHC allele is associated with 8-16 neural networks trained on affinity measurements (O'Donnell et al., 2018). Here, we run netMHCpan 4.0 and MHCflurry on a set of 79 HLA-A, HLA-B and HLA-C alleles supported by both algorithm. We run netMHCpan 4.0 predictions on the DTU server (<https://services.healthtech.dtu.dk/service.php?NetMHCpan-4.0>) while MHCflurry predictions are obtained using the epitopepredict python code (<https://github.com/dmnfarrell/epitopepredict>). In both cases, we scan all the peptides of lengths 8-11 for the proteins of interest. We only consider peptides that are likely to be produced by proteasome degradation. To this end, we employ NetChop 3.1 (Nielsen et al., 2005) a neural network based algorithm that scans proteins for probable cleavage sites of the human proteasome. We next compare the predictions for the binding affinities obtained by netMHCpan 4.0 and MHCflurry for each peptide and MHC allele. As shown in Fig. S10, there is a strong correlation between the two predictions but in some cases the two predictions sometimes display large differences. We discard these values considering only peptides for which $|p_1 - p_2|/|p_1 + p_2| < 0.25$, where p_1 and p_2 are the predictions for binding affinity (IC_{50}) obtained by the two algorithms. The binding affinity is then taken to be the average of p_1 and p_2 . Finally, peptides for which both p_1 and p_2 are smaller than 1000 Nm are defined as strongly binding. We thus count the number of strongly binding peptides for each allele.

Calculation of the total binding affinity to HLA molecules

Consider a set of n peptides with concentrations $[P_i]$ with $i = 1, \dots, n$ that can bind with HLA molecules with dissociation constants K_i . We denote by $[H]$ the concentration of free HLA molecules and by $[HP_i]$ the concentration of HLA molecules bound to a peptide i . According to the law of mass action, we have that

$$K_i = \frac{[P_i][H]}{[HP_i]}. \quad (1)$$

The probability for a HLA molecule to be bound by any peptide i can be written as

$$p_b = \frac{\sum_i [HP_i]}{[H] + [\sum_i HP_i]} = \frac{\sum_i [P_i]/K_i}{1 + \sum_i [P_i]/K_i}. \quad (2)$$

For peptides with uniform concentration $[P_i] = P_0$, we can write

$$p_b = \frac{P_0/K_{tot}}{1 + P_0/K_{tot}}, \quad (3)$$

where $K_{tot} = 1/(\sum_{i=1}^n 1/K_i)$ is a measure of the total binding affinity of all the peptides to a given HLA molecule. To estimate K_{tot} , we use the predicted binding affinities as a proxy for the dissociation constants K_i . The binding affinity is strictly equal to the dissociation constant only for non-competitive binding, while the two quantities are just proportional in competitive binding assays (Yung-Chi and Prusoff, 1973; Lazareno and Birdsall, 1993).

Identification of T cell epitopes

To identify potential T cell epitopes, we use NetTepi 1.0 server (<https://services.healthtech.dtu.dk/service.php?NetTepi-1.0>) which combines estimates for peptide-MHC binding affinity, peptide-MHC stability and T cell propensity (Trolle and Nielsen, 2014). Peptides are then ranked against a set of 200000 natural peptides to obtain a global rank score. Here we scan all SARS-Cov-2 and SARS-Cov peptides with lengths 8-11 from the 4 structural viral proteins and retain the peptides with rank score lower than 2%. We perform the calculations for all the available class I MHC allele using the default values for the relative weight on stability prediction and the relative weight on T cell propensity prediction. The alleles supported by NetTepi are well represented in human populations. In particular, the supported HLA-A alleles are present in around 60% of the populations, while the HLA-B are present in around 30% of the populations.

QUANTIFICATION OF HAPLOTYPE FREQUENCIES AND STATISTICAL ANALYSIS

We consider populations with a sample size larger than 1000 individuals and containing data for all the three classical polymorphic HLA genes. We include data from the German Bone Marrow Donor File (Deutsche Knochen-MarkSpenderdate, DKMS) which provides thousands of haplotypes for Germans with different origins. We also include a large dataset from Japan, sample over more than 18000 individuals, and two large datasets from the United

States of America (African-Americans and Hispanics). Confidence intervals for haplotype frequencies f are estimated assuming binomial statistics (i.e. $CI = f \pm z \sqrt{f(1-f)/N}$, with $z = 1.96$ for a 95% confidence interval, where N is the sample size). When $f = 0$ we use instead the rule of three: $CI = 3/N$. Statistical analysis is implemented in python and available within the released code <https://github.com/ComplexityBiosystems/hla-covid>.

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