Short Communication

Mortality in COVID-19 disease patients: Correlating the association of major histocompatibility complex (MHC) with severe acute respiratory syndrome 2 (SARS-CoV-2) variants

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A B S T R A C T

Genetic factors such as the HLA type of patients may play a role in regard to disease severity and clinical outcome of patients with COVID-19. Taking the data deposited in the GISAID database, we made predictions using the IEDB analysis resource (TepiTool) to gauge how variants in the SARS-CoV-2 genome may change peptide binding to the most frequent MHC-class I and –II alleles in Africa, Asia and Europe. We characterized how a single mutation in the wildtype sequence of of SARS-CoV-2 could influence the peptide binding of SARS-CoV-2 variants to MHC class II, but not to MHC class I alleles. Assuming the ORF8 (184S) mutation is biologically significant, selective pressure from MHC class II alleles may select for viral variants and subsequently shape the quality and quantity of cellular immune responses against SARS-CoV-2. MHC 4-digit typing along with viral sequence analysis should be considered in studies examining clinical outcomes in patients with COVID-19.

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Introduction

As the 2019 (COVID-19) pandemic caused by the novel coronavirus, SARS-CoV-2 spreads globally, differences in adverse clinical management outcomes have been associated with age >65 years, male gender, and comorbidities such as smoking, diabetes, hypertension, cardiovascular comorbidity, and immunosuppression. Ethnicity has been the focus of attention after data from the United Kingdom showed a disproportionate number of deaths among healthcare workers from Black, Asian, and other ethnic minority backgrounds (Khunti et al., 2020). In addition to ethnicity, socioeconomic factors, prior vaccinations, exposure to other
coronaviruses, and other factors need to be considered to explain the geographical and regional variations in susceptibility and severity of the clinical expression of COVID-19 disease and outcomes. In the United States, there have been disproportionate COVID-19 death rates among African Americans at around 2.6 times higher than that of other groups. Although these data could be due to multiple cultural and socioeconomic factors an underlying genetic susceptibility to SARS-CoV-2 infection may be a factor.

Genetic factors were thought to play a causative role in the SARS outbreak's pathogenesis in 2003 in a group of Taiwanese patients, where the HLA-B*4601 haplotype was associated with the severity of the SARS infection (Lin et al., 2003). In Hong Kong Chinese patients, a strong association was shown between HLA*0703 and HLA-DRB1*0301 alleles and increased susceptibility to SARS infection (Ng et al., 2004). In contrast, L-SIGN homozygote individuals seemed to have a significantly lower risk of SARS infection (Chan et al., 2006).

**Covid-19, HLA, and ethnicity**

Generally, peripheral blood lymphocytes counts of Black Americans show lower neutrophil counts and a proportionally higher frequency of lymphocytes compared to the rest of the population (Freedman et al., 1997). HLA-association studies of SARS-CoV-1 with HLA-antigens for SARS-CoV-2 have been compiled (Sanchez-Mazas, 2020a). The biological and clinical relevance of immune responses to SARS-CoV-2 requires further discussion:

**Autoimmune associations with COVID-19**

Some individuals with COVID-19 experienced neurological symptoms, e.g., Guillain Barre Syndrome (Zhao et al., 2020), suggesting an autoimmune background, which has been associated with MHC alleles (Hasan et al., 2014). The role of MHC variants in increased susceptibility to infections or, vice versa, immune protection, is well known for a number of viral diseases, e.g., the role of MHC alleles in HIV-control, or increased risk for chronic hepatitis B (Matzarakis et al., 2017).

**MHC variants impact the quality of cellular immune responses and the potential for increased inflammation**

For instance, DRB1*15:01-DQA1*01:02-DQB1*06:02 (abbreviated ‘DR2’) dampens autoimmune responses and confers protection from type I Diabetes (Noble and Valdes, 2011; Siebold et al., 2004) associated with strong IFN-γ production. HLA-DQB1*06:02 has been selected for increased resistance to Yersinia pestis in immigrants from Africa to Europe; the engagement of CD4+ T-cells to HLA-DQB1*06:02 leads to increased, pro-inflammatory IL-17 production, independent of MHC class II presented peptides (Mangalam et al., 2013) and confers increased risk to the development of anti-myelin directed autoimmune responses (Kaushansky and Ben-Nun, 2014). The haplotypes HLA-DR2-DQ6, DR4-DQ8, and DR3-DQ2 accommodate peptides from infectious pathogens to CD4+ T-cells from Europeans who survived the bottleneck of different, life-threatening infections prevalent in Europe (Matzarakis et al., 2017). These alleles have also been shown to be associated with increased risk for autoimmune diseases, for instance, to dietary antigens (celiac disease) (Cecilio and Bonatto, 2015) in part due to their intrinsic capacity to stimulate more robust IL-17 production, that facilitates Central Nervous System (CNS) associated disease manifestations (Pierson et al., 2012). Perhaps the most prominent example for MHC association with infection is the development of HLA-DQ*06:02 associated narcolepsy following H1N1 infection and H1N1-vaccination efforts in 2009/2010 (Mahlios et al., 2013). Such aspects should be considered while examining neurological symptoms in patients after COVID-19 recovery, and also in SARS-CoV-2 vaccination efforts. Thus, certain MHC class II alleles are associated, in part independent of their antigenic peptides, with stronger inflammatory responses that are manifested as increased risks to the development of autoimmune diseases.

**Binding of (variant) antigenic peptides to certain MHC class I or class II alleles are the prerequisite for the quality of anti-virus directed cellular immune responses**

A prime example is the oncogene E6 from HPV 16, the causative agent of cervical cancer. European HPV-16 E6 variants, such as the E6 variant LB3V (at the nucleotide position 350) is associated with increased risk of HPV infection and progression to malignant transformation (de Araujo Souza et al., 2009). HPV E6 variability and clinical outcome are associated with different DRB1*04-DQB1*03 MHC haplotypes in the Swedish compared to other, e.g., Italian, populations: the association is between a viral variant and MHC haplotypes (de Araujo Souza et al., 2009; Zehbe et al., 2003). Such associations ought to be explored in SARS-CoV-2 variants as well. The tremendous impact of single amino acid substitutions in viral pathogens and MHC-restricted T-cell recognition has been described for over 30 years (Rothbard et al., 1989). Single mutations in HIV (Klenerman et al., 1994) and Hepatitis B (Bertoletti et al., 1994) annual cytolytic activities of epitope-specific T-cells. The mutant epitope still binds to the MHC molecule, yet serves as a T-cell antagonist. A similar phenomenon is called a partial agonist, where a mutation in the nominal T-cell epitope leads to the dissociation of IL-4 production and T-cell proliferation (Evavold and Allen, 1991).

Not only do peptide variants from the identical viral pathogen lead to abrogation or dissociation of immune functions in T-cells, but also in very similar peptides (regarding their amino acid composition), that stem from different, unrelated pathogens. This has been previously described for T-cell responses for cross-reactive T-cell responses to M. tuberculosis and HIV (Hohn et al., 2003) associated with differential cytokine production. A different example is the cross-reactivity of HPV-specific T-cells to SARS-CoV-1 (Nilges et al., 2003). Thus, not only differential MHC-binding and T-cell responses should be considered in examining SARS-CoV-2 variants, but also potential similar ‘cross-reactive’ epitopes from other pathogens or ‘self’-proteins should be studied.

The question arises, would single mutations in the wildtype of SARS-CoV-2 (or the so-called B strain (Forster et al., 2020) or L strain (Tang et al., 2020)) have an impact on potential MHC presentation?

In order to test this possibility, we analyzed the most frequent MHC class I and II alleles in Europe, Asia, and Africa for binding to the mutations in ORF8 (L84S) and ORF3a (G251V) (see supplementary data sets). The MHC class I binding predictions were made with the IEDB analysis resource (TepiTool; Paul et al., 2016) using a consensus method (Wang et al., 2010) which employs a Stabilized Matrix, Artificial Neural Networks and combinatorial library methods; the MHC Class II binding predictions were done with the IEDB analysis resource (TepiTool; Paul et al., 2016) using the NetMHCIpan method (Karowski et al., 2013; Nielsen et al., 2008). These resources have been shown to produce satisfactory results for MHC binding predictions for SARS-CoV-1 and bona fide T-cell recognition and MHC class I-predictions of SARS-CoV-2 epitopes (Sanchez-Mazas et al., 2020b). For MHC class I, starting with a peptide with the mutation site in the middle (flanked by seven amino acid residues to the left and right, resulting in a 15mer peptide) for ORF8 (L84S) (GNYTVSCLPFTINQC and GNYTVSCLPFTINQC) and for...
Table 1

ORF8 variants and differential peptide binding.

| Protein | Peptide | Rank wt | Rank mut | Allele |
|---------|---------|---------|----------|--------|
| HA      | PKVVKQNT[K]LKLATGM | 1.50 | 41.00 | HLA-DRB1*04:01 |
| HA      | CPKVVKQNT[K]LKLATG | 1.60 | 41.00 | HLA-DRB1*04:01 |
| HA      | ACPKVVKQNT[K]LKLAT | 1.70 | 41.00 | HLA-DRB1*04:01 |
| HA      | GACPKVVKQNT[K]LKLK | 1.80 | 41.00 | HLA-DRB1*04:01 |
| HA      | VCAKVKVQNT[K]LKLK | 2.00 | 41.00 | HLA-DRB1*04:01 |
| HA      | YVQKQNT[K]LKLATGCMRN | 7.80 | 32.00 | HLA-DRB1*04:01 |
| HA      | KYVKQN[T[K]LKLATGMR | 8.50 | 51.00 | HLA-DRB1*04:01 |
| ORF8    | DIGNYTVSL[5]PTITN | 9.60 | 19.00 | HLA-DRB1*01:03/DPB1*02:01 |
| ORF8    | IDIGNYTVSL[5]PTIT | 9.60 | 22.00 | HLA-DRB1*01:03/DPB1*02:01 |
| ORF8    | IGNTVSCL[5]PTTINC | 9.60 | 19.00 | HLA-DRB1*01:03/DPB1*02:01 |
| ORF8    | PIQYIDIGNYTVSL[5] | 9.60 | 16.00 | HLA-DRB1*15:01 |
| ORF8    | DIGNYTVSCL[5]PTITN | 17.00 | 4.40 | HLA-DRB3*02:02 |
| ORF8    | IGNTVSCL[5]PTTINC | 18.00 | 4.50 | HLA-DRB3*02:02 |
| ORF8    | IDIGNYTVSL[5]PTIT | 19.00 | 5.30 | HLA-DRB3*02:02 |
| ORF8    | GNYTVSCL[5]PTTINCQ | 21.00 | 6.20 | HLA-DRB3*02:02 |
| ORF8    | YIDIGNYTVSL[5]PTFT | 24.00 | 6.70 | HLA-DRB1*04:01 |
| ORF8    | IDIGNYTVSCL[5]PTIT | 28.00 | 4.90 | HLA-DRB1*09:01 |
| ORF8    | DIGNYTVSCL[5]PTITN | 29.00 | 5.60 | HLA-DRB1*09:01 |
| ORF8    | YIDIGNYTVSCL[5]PTFT | 30.00 | 5.80 | HLA-DRB1*09:01 |
| ORF8    | IGNTVSCL[5]PTTINCQ | 30.00 | 7.10 | HLA-DRB1*09:01 |
| ORF8    | GNYTVSCL[5]PTTINCQ | 30.00 | 8.20 | HLA-DRB1*09:01 |
| ORF8    | IDIGNYTVSCL[5]PTIT | 39.00 | 7.90 | HLA-DRB1*04:01 |
| ORF8    | GNYTVSCL[5]PTTINCQ | 43.00 | 9.30 | HLA-DRB1*04:01 |
| ORF8    | DIGNYTVSCL[5]PTITN | 44.00 | 8.30 | HLA-DRB1*04:01 |
| ORF8    | IGNTVSCL[5]PTTINCQ | 45.00 | 8.60 | HLA-DRB1*04:01 |

A lower ranking value designates better MHC class II binding; we used the default recommended rank \(-10\) as the cutoff value for binding. Two MHC class II alleles accommodate the ORF8 wildtype, yet not the variant (L84S). Three MHC class II alleles predict binding to the SARS-CoV-2 ORF8 mut (L84S) variant. For comparison (top of the table), a well-characterized Flu A hemagglutinin epitope showing strong binding of the wildtype, but not the mutant variant to HLA-DRB1*04:01; this epitope is also recognized by T-cells. In bold and underlined, the amino acid in the wildtype sequence, and in parentheses, the amino acid in the mutant variant.

ORF3a (G251V) (VQIHTIDGSSGVVNP and VQIHTIDVSSGVVNP), we tested all possible combinations of length from 8 to 14 residues for MHC class I binding. For MHC class II, starting with a peptide with 33 residues with the mutation site in the middle for ORF8 (L84S) (KSPIQYIDIGNYTVSCL[5]PTTINCQPKLGSLVV) and for ORF3a (G251V) (KIVDEEPEEHHVQIDIGNYTVSCL[5]PTTINCQPKMVMEP), we tested all possible combinations to bind to MHC class II alleles listed in the supplementary data set since MHC class II molecules can accommodate longer peptides, and nominal epitopes may ‘glide’ within the MHC class II peptide binding cleft (Rammensee, 1995).

We could not identify differences in MHC class I or class II binding characteristics (see Appendix- supplementary data sets Tables S1, S2 and S3) except for three MHC class II alleles, i.e., DRB3*02:02, DRB1*09:01, and DRB1*04:01, that do not allow binding of the wildtype, but accommodate the SARS-CoV-2 ORF8 (L84S) variant (Table 1) and also two MHC class II alleles HLA- DPB1*01:03/DPB1*02:02 that do the opposite: they accommodate the wildtype but not the SARS-CoV-2 ORF8 (L84S) variant (Table 1).

In order to show the validity of the peptide prediction methodology, we examined the literature for viral variants that

Figure 1. Distribution of the SARS-CoV-2 ORF8 S residue at position 84. 11970 SARS-CoV-2 sequences deposited in the GISAID database by April 27th, 2020. 87% have the Leucine amino acid at position 84 and 13% exhibit Serine. In the countries that submitted more than 100 sequences where the proportion is different: in China, 38% SARS-CoV-2 sequences account for ORF8 (S84L), in Spain 43%, in the USA 32% and in Canada 31%.
bind differently to one of these alleles and identified the epitope PKYVKQNTLKLATGM, representing the wildtype hemagglutinin sequence from Influenza A virus subtype H3N2 that is recognized by a well-characterized T clone (Hennecke and Wiley, 2002). For this prediction we used a 33 residue peptide with the mutation site in the middle (VNKITYGACPKYVKQNTLKLATGMRNVPỆKQTR) and the best fitting peptide with 15 residues that were predicted to bind to HLA-DRB1*04:01, is exactly the peptide reported earlier (Hennecke and Wiley, 2002) recognized by a Flv epitope-specific T-cell clone. In contrast, one of the Flv variant (T314K) peptides does not bind to to HLA-DRB1*04:01 (Table 1).

Of the 11,970 SARS-CoV-2 sequences deposited in the GISAID database by April 27th, 2020, 85% exhibit the amino acid Leucine at the position 84 and 15% exhibit Serine. From the countries that have submitted more than 100 sequences, there are four where the distribution of ORF8 (L84S) is different from the worldwide trend: in China, 38% SARS-CoV-2 sequences account for ORF8 (L84S), in Spain 43%, in the USA 32% and in Canada 31% (Figure 1). Based on the information from previous studies (Solberg et al., 2008), the allele frequency of HLA-DRB1*04:01 is around 0.03 in Spain, around 0.02 in other ethnicities in the USA, around 0.01 in China, and 0.008 in Canada.

**Figure 2.** Frequency of HLA-DRB1*04:01 that allows binding of the ORF8 variant epitope. Based on previous studies (Solberg et al., 2008), the allele frequency of HLA-DRB1*04:01 is around 0.03 in Spain, around 0.1 in Caucasians in the USA, but around 0.02 in other ethnicities in the USA, around 0.01 in China, and 0.008 in Canada.

**Figure 3.** Frequency of HLA-DRB1*09:01. Based on previous studies (Solberg et al., 2008) for HLA-DRB1*09:01, the allele frequency is around 0.008 in Spain, approximately 0.1 in Asians in the USA, but around 0.01 in other ethnicities in the USA, and approximately 0.07 in Canada.
Appendix A: Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jiid.2020.07.016.

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