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A Review of the Effect of HLA Genotype on COVID-19 Severity

Natalie Chalfant - Southern Maine Community College

Abstract:
The human leukocyte antigen (HLA) super-locus includes at least 132 protein coding genes that play important roles in the regulation of the immune system, as well as other molecular and cellular processes. Research has demonstrated that variations in alleles of some of these HLA loci can have a significant effect on the severity of COVID-19 infection. This literature review poster focuses on two genes of particular interest: HLA-DPA1 and HLA-E. Both genes are primarily expressed in the cell membrane of macrophages, specialized cells in the immune system involved in the detection, phagocytosis, and destruction of bacteria, infected cells, and dead cells. DPA1 binds peptides derived from antigens and presents them for recognition by CD4 T-cells that play a role in immune system activation and suppression. A small study of COVID-19 positive individuals in India identified a DPA1 allele, HLA-DPA1*01:03:01:02, that significantly increased the risk of severe COVID-19 infection. HLA-E is involved in immune self-nonself discrimination and plays a role in the activation of natural killer (NK) cells through activation of KLRC2, which is found in the cell membrane of NK cells. When activated, NK cells destroy physiologically stressed cells such as virus-infected cells and tumor cells. Researchers identified the allele HLA-E*01:01, which is present in European populations, as potentially interacting with KLRC2 mutations to increase the severity of COVID-19 infection. A better understanding of these mutations may lead to the development of biomarkers for assessing the probability of severe COVID-19 infection.

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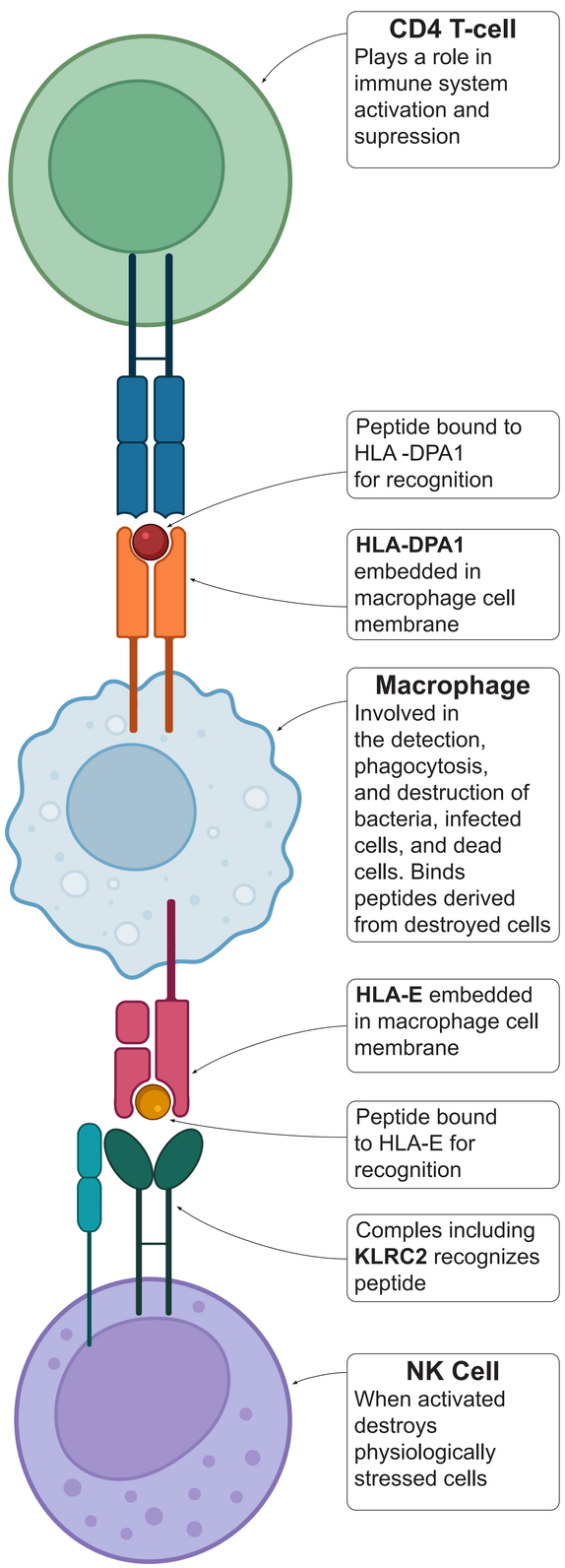
Fig. 1: HLA-DPA1 and HLA-E Pathways



(Created with BioRender.com)

Results:

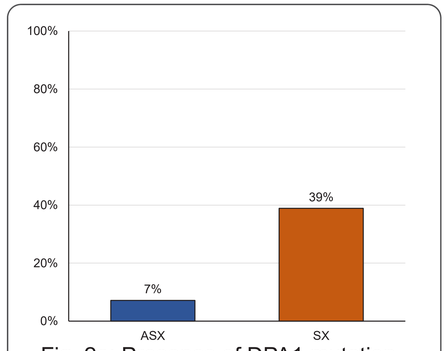


Fig. 2a: Presence of DPA1 mutation
n= 54, p= 0.0004
(Data from Vishnubhotla et al. 2021)

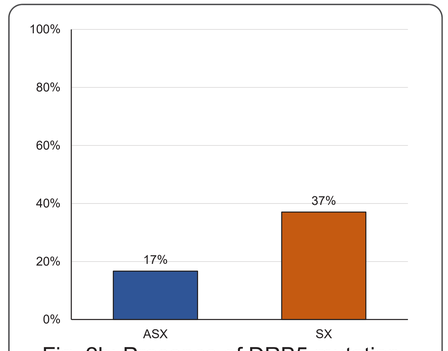


Fig. 2b: Presence of DRB5 mutation
n= 54, p= 0.02
(Data from Vishnubhotla et al. 2021)

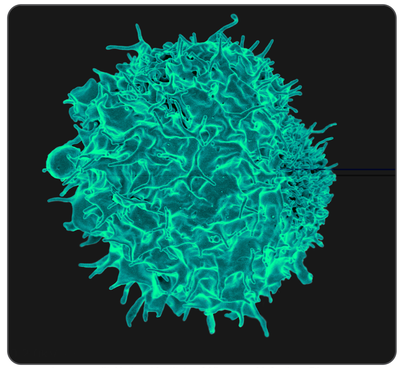


Image credit: National Institute of Allergy and Infectious Diseases

Fig. 2c: CD4 t-cell

A study an Indian cohort identified multiple alleles that were associated with severe COVID-19. The alleles which showed a significant difference between symtomatic and asymptomatic groups were HLA-C* 04:01:01:01, HLA-DRB5*01:01:01:02, HLA-DQA1*03:01:01:01, HLA-DPB1*04:01:01:04, and HLA-DPA1*01:03:01:02.[9]

- A potential explanation for the increased severity associated with these alleles is that they may be less effective at binding SARS-CoV-2 viral peptides than wild type alleles.
- HLA-C* 04:01:01:01 alleles are predominantly found in Central American populations as well as North American populations.[9]
- In Brazillian populations HLA-DQA1*03:01:01:01 is associated with the autoimmune disease Bullous pemphigoid, suggesting this allele may be more frequent in Brazillian populations.[1]

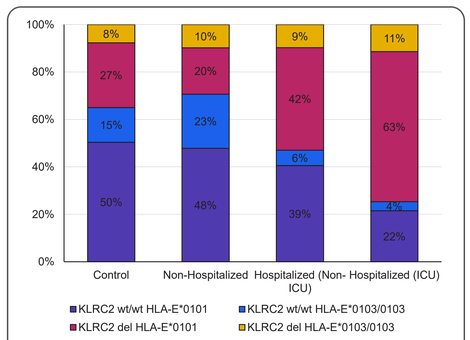


Fig. 3a: KLRC2 deletions and HLA-E alleles present in individuals with COVID-19
(Data from Vietzen et al. 2021)

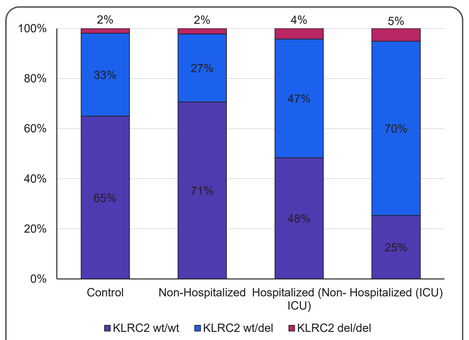


Fig. 3b: KLRC2 deletions in individuals with COVID-19
(Data from Vietzen et al. 2021)

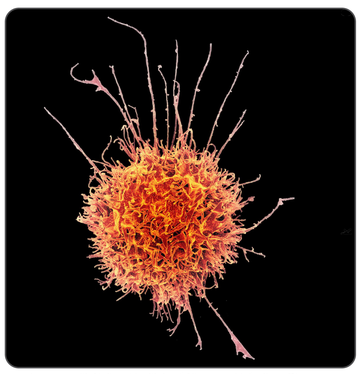


Image credit: National Institute of Allergy and Infectious Diseases

Fig. 3c: NK cell

A study of 316 Austrian COVID-19 patients found that KLRC2 (NKG2-C) deletions as well as the presence of an HLA-E*0101 allele were significantly associated with hospitalization for COVID-19. The association with increased severity became even stronger when looking at both of these mutations together.[8]

- Cell surface expression levels are lower for HLA-E*0101/0101 than they are for HLA-E*0103/0103, which may result in a slower or decreased NK cell response and explain the association with hospitalization.[7]
- Patients with severe COVID-19 had a significantly lower NK cell count when compared with patients with moderate COVID-19.[10] This suggests NK cells play an important role in controlling COVID-19 severity.

Discussion:
The results of the studies included in this literaure review as well as future studies could be used to identify biomarkers for severe COVID-19 which would allow greater targeting of treatments and vaccinations to ensure they went to the most vulnerable populations. Future studies with a larger sample size may reveal other genes within the HLA super locus that are associated with severe COVID-19 as well as potential interactions between genes. Additionally, studies including participants from multiple countries may show varying geographic distribution of these alleles.