LETTER TO THE EDITOR
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The Association between Proportion HLA-BW4 or HLA-BW6 May Causes Immunity Failure in COVID-19

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Dear Editor

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) induce Coronavirus disease 2019 (COVID-19) that appeared globally with a mortality rate of 3, 232, 062 on the 30th of April 2020, and the rate of new cases increased every day, according to the centers for disease control and prevention. The immunity reaction to this virus is different case by case. Accordingly, some are recognized with mild symptoms or moderate, while some are in critical status.[1] Hence, what causes this amount of fluctuation in different populations?

Acute respiratory distress syndrome (ARDS) is the cause of mortality in most serious cases. Also, hyper-inflammation and hypercytokinemia accompanied by multiple organ failure are the endotypes in this viral pneumonia.[2] Therefore, if we turn back to discover the starting point of inflammation spark, undoubtedly, we would reach out to Natural killer cells (NK).

NK cells are regarded as the primary defense in innate immunity against viruses. The first immune cells which trigger such hypercytokinemia and cytokine storm and therefore cause pro-inflammatory cytokine production is NK cells. Moreover, these cells play a critical role in sepsis through secretion of interferon-Y and are regarded as a promising factor in the therapeutic benefits. There are some inhibitory and stimulatory receptors on NK cells by which their interaction with human leukocyte antigens type I (HLA-I) defines NK cells' mission.[3] Killer immunoglobulin-like receptors (KIRs), by their division to have a long cytoplasmic tail with two immune tyrosin-based inhibitory motifs or the short form, are characterized as inhibitory or stimulatory receptors. Some of these receptors have two immunoglobulin domains outside of the cell, and some have three of them. Collectively, KIR2DL and KIR3DL are inhibitory ones, and KIR2DS and KIR3DS are regarded as the stimulatory receptors for deactivation or activating of NK cells, respectively.[4]

As it is defined, HLA molecules are from the ones with intensely high polymorphism. Possibly, the type of HLA-I and the kind of motif it possesses between individuals might be the answer to the variation in immune response in populations. Here we discuss that a particular motif is highly tied to the people of a geographical region. Understanding if these motifs, their frequencies, and their affinities to KIRDL or KIRDS define the intensity of the immune response is highly remarkable. HLA-B has two alleles of HLA-BW4 and HLA-BW6.[5] HLA-BW4 interaction to KIR-3DL1 of NK cells has been studied in a great deal. In patients with kidney cancer, it is reported that the KIR-3DL1 and HLA-BW4 are much more frequent. This might be attributable to the weak immune response in subjects with cancer.[6] Zhen et al, showed that the HLA-Bw4 ligand and KIR3DL1-HLA-Bw4 combination could confer a protective effect against MDS in Chinese Southern Han.[7] Also, Jorge R Oksenberge et al, reported the correlation between

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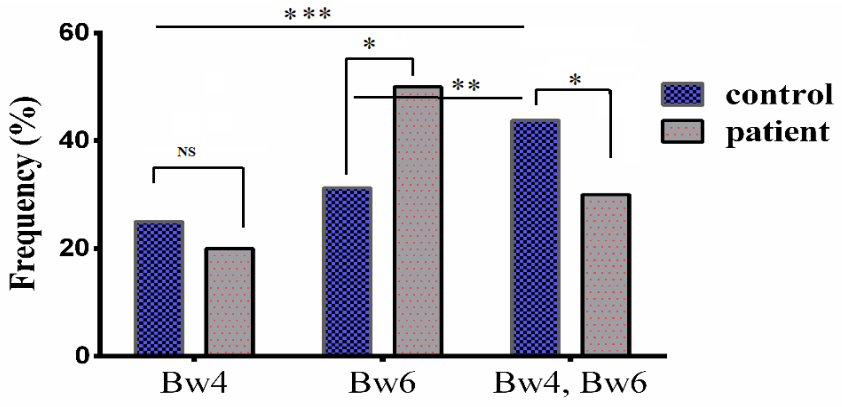
KIR-3DL1 and HLA-BW4 combination and protectivity against multiple sclerosis in African Americans.[8] It seems like HLA-BW6 does not have anything to do with NK cells but causes cytotoxic T cells (CTLs) to escape from killing the target cells. So it raises this hypothesis that HLA-BW4 with low frequency might not be enough to inhibit NK cells from hyperactivity against viral infection. On the other hand, HLA-BW6 contributes to CTL activity failure. Altogether, these diversities in HLA-BW4 or HLA-BW6 expression in individuals might lead to an unsuccessful response toward viral infection in which one side is NK cells with high activity but not enough to kill the cells, and the other side is CTL with low efficiency.

In the recent research in Iran performed on patients who died of COVID-19 (20 patients and 32 normal cases), the type of HLA-BW4 and HLA-BW6 was assessed by PCR-SSP technique. Compared to normal cases with around 25% HLA-BW4, the amount of HLA-BW6 in patients was recorded at 50% (Figure 1). From these data, we can hypothesize that the cases that represent HLA-BW6 are at high risk and most likely indicate severe hyper-inflammation but inefficient cytotoxicity effect of CTLs.

Taken together, our hypothesis will provide baseline information about the HLA-BW4 and HLA-BW6 diversity and their relation to the hyper-activation of immunity through the high activity of NK cells.

One of the limitations of this study was that It was better to investigate other effective allotypes. Due to limitations in laboratory facilities and regents, we were not able to perform other allotypes (HLA-C1, C2). It is recommended to study (effective allotypes HLA-BW4, HLA-BW6, HLA-C1, and C2) in populations with other races.



HLA Typing	Control	Patient
HLA- Bw4	8 (25%)	4 (20%)
HLA- Bw6	10 (31.25%)	10 (50%)
HLA- Bw4, Bw6	14 (43.75%)	6 (30%)
Total	32 (100%)	20 (100%)
P value = 0.0129		

Figure 1. Investigation of the frequency of genotypes (Bw4, Bw6, and Bw4/Bw6) in patients and control groups (*p<0.05, **p<0.01, ***p<0.001).

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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There is no acknowledgment to declare.

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