Minireview

Influence of polymorphic variations of IFNL, HLA, and IL-6 genes in severe cases of COVID-19

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Impact Statement

The establishment of pathologies and the development of pathological conditions with diverse clinical outcomes, even in phenotypically similar individuals, demonstrate a great need to understand which factors may be associated beyond commonly related risk factors such as sex, age, and comorbidities. With the emergence of COVID-19, it was possible to visualize a scenario where factors such as host genetics influence the establishment and progression of the disease, just as genetics characterize individuality, and its study can elucidate new paths for prognosis and new therapies in different populations, as already done for other diseases. The present study aims to address the main genetic variants for the mentioned targets from a review of studies carried out to demonstrate the influence of single-nucleotide polymorphisms (SNPs) on severe cases of the disease, providing relevant information on the knowledge of genetic diversity and its influence on the immune response in COVID-19.

Abstract

The administration of vaccination doses to the global population has led to a decrease in the incidence of COVID-19. However, the clinical picture developed by infected individuals remains extremely concerning due to the great variability in the severity of cases even in vaccinated individuals. The clinical progression of the pathology is characterized by various influential factors such as sex, age group, comorbidities, and the genetics of the individual. The immune response to viral infections can be strongly influenced by the genetics of individuals; nucleotide variations called single-nucleotide polymorphisms (SNPs) in structures involved in the innate and adaptive immune response such as interferon (IFN)-λ, human leukocyte antigen (HLA), and interleukin (IL)-6 are frequently associated with pathological progression. In this study, we conducted a review of the main SNPs of these structures that are associated with severity in COVID-19. Searches were conducted on some platforms of the National Center for Biotechnology and Information (NCBI), and 102 studies were selected for full reading according to the inclusion criteria. IFNs showed a strong association with antiviral function, specifically, IFN-λ3 (IL-28B) demonstrated genetic variants commonly related to clinical progression in various pathologies. For COVID-19, rs12979860 and rs1298275 presented frequently described unfavorable genotypes for pathological conditions of hepatitis C and hepatocellular carcinoma. The high genetic variability of HLA was reported in the studies as a crucial factor relevant to the late immune response, mainly due to its ability to recognize antigens, with the HLA-B*46:01 SNP being associated with susceptibility to COVID-19. For IL-6, rs1554606 showed a strong relationship with the clinical progression of COVID-19. In addition, rs2069837 was identified with possible host protection relationships when linked to this infection.

Keywords: Immunogenetic, IFN-λ, HLA, IL-6, polymorphism, COVID-19

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Introduction

The incidence of coronavirus disease 2019 (COVID-19) cases, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was strongly reduced due to the interpositions of vaccination doses and mass immunization actions of the population.[1] However, the clinical picture developed by infected individuals remains obscure and concerning due to the high variability of severity even among vaccinated individuals.[2,3]

The high viral variability is an important and relevant factor and RNA viruses are characterized by a highly mutagenic profile,[4,5] a reflection of the viral replicative and adaptive process. SARS-CoV-2 is a highly mutagenic virus,[6] despite having a nucleotide proofreading mechanism mediated by the non-structural NSP14 protein complexed with its cofactor NSP10.[7,8] Variabilities still occur resulting in the emergence of several lineages of SARS-CoV-2,[9,10] such mutations directly affect its mechanisms of infection and transmission, its pathogenicity, virulence, and can influence immune escape.[11]

The clinical progression of COVID-19 is intrinsically related to several factors such as age, sex, comorbidities, and mainly the host's immunogenetic response.[12–15] Genetic variability is characterized mainly by single-nucleotide polymorphisms (SNPs) in the human genome.[16] In humans, the immune response produced through infection by a pathogen is mediated by the recognition and antigen presentation through the human leukocyte antigen (HLA).[17] For SARS-CoV-2, the action of the immune response is investigated through the study of HLA alleles to understand which factors may be associated with clinical progression,[17,18] as there is a great heterogeneity of the disease, and variability can act as an influencing factor for severity.[18] Through these studies, it is possible to elucidate the divergent pathological behavior in different populations.

Just as for HLA, interferon (IFN)-λ3 has also been strongly linked to susceptibility to severe COVID-19,[19] with a recent study demonstrating a higher association of the mutant allele for rs8099917 with up to a 36-fold increase in the risk of severity among study participants.[20] In addition, the cytokine storm, an event resulting from the increase of inflammatory cytokines in response to SARS-CoV-2 infection, is importantly relevant to better understanding the genetic influence on immune response.[21]

Studies indicate that interleukin (IL)-6 is one of the key cytokines involved in the process of progression to severe COVID-19 mediated by hyperinflammation,[18,22,23] with its use as a severity marker for cases of the disease being discussed.[12,15] SNPs in the IL-6 gene have shown a strong association with increased expression as well as contributing to the development of comorbidities such as hypertension, diabetes, cardiovascular diseases, and obesity, with different allele distributions observed in various populations.[24]

Therefore, this article aims to discuss the immunological behavior in the context of genetic influence, addressing the polymorphic variability of the HLA, IFN-λ3, and IL-6 to understand the underlying mechanisms and relate their roles in clinical progression toward either worsening or recovery from COVID-19 while demonstrating the main associated SNPs.

IFN-λ and the antiviral immune response

The IFN-λ, found in humans, is encoded on chromosome 19,[25] from which it is composed of the ILs IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28B), and IFN-λ4,[26] and has a strong association with the innate antiviral immune response,[27] contributing to the expression of genes whose antiviral and immunoregulatory properties are stimulated during the infectious process.[28,29] There are two families of IFNs that directly act on the innate antiviral response in human mucosal barriers, type I (IFN-α and IFN-β) and type III (IFN-λs).[30]

Linked to mucosal defense activities, IFN-λ type III activates a cascade of reactions after binding to the heterodimeric receptor (IFNLR1/IL10Rβ)[31] as represented in Figure 1. These properties mediate high levels of expression specifically in epithelial cells present in various organs such as the lungs, liver, and intestines, where they directly reduce the likelihood of systemic side effects and minimize the risk of promoting a cytokine storm.[32]

There is a possible relationship between the harmful role of IFNs when found at elevated levels in the blood, coupled with their influence on the clinical progression toward severity of cases,[33] as well as antiviral dysfunction and induction of angiotensin-converting enzyme 2 (ACE2) expression,[34] a viral tropism protein of SARS-CoV-2 used for entry into host cells.[35] In the immune process, the activation of IFNs only occurs after the recognition of structures called pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs),[36] thus initiating chemical signaling cascades through the production of IFNs, chemokines, and some cytokines such as IL-6.[27,36]

IFN-λ3 and the regulation of the immune response in COVID-19

In the immune response mediated by SARS-CoV-2 infection, the responses of IFN-λ1 and IFN-λ3 are fundamental in viral innate immunity,[30] with the latter being related to the inhibition of infection in bronchial epithelial cells;[30,37] however, compared to the immune response induced by IFN-1, it ends up being characterized as less inflammatory due to its functional location.[29]

Studies indicate that the innate immune response is critical for combating virus infection and the establishment of COVID-19;[38–40] however, SARS-CoV-2, due to mutations, has developed strategies that block the induction and action of IFNs by inhibiting the activation of PRRs downstream of the PAMP detection stage,[41] thus suppressing the IFN response at different levels, giving it a greater advantage for viral replication.[37,42] Despite this blockade, *in vitro* and *in vivo* studies have shown that exogenous IFN treatment has positive effects in inhibiting viral production in cultured lung cells,[37,43] thus suggesting that IFN-λ may be an effective preventive or therapeutic antiviral to treat human SARS-CoV-2 infection.[43]

Genetic variation of IFN-λ3 and pathological clinical progression

In addition to the immune response, a better understanding of the crosstalk between the host and pathogen is fundamental to understanding the pathophysiology of the disease and establishing therapeutic targets.[44,45] Among the spectrum of point mutations characterizing genetic variability in individuals are SNPs.[16] Genetic diversity may characterize, among many factors, susceptibility or resistance to pathological clinical progression;[45] there is a strong association between genetics and pathology in order to elucidate factors that may influence the development of severe clinical conditions of

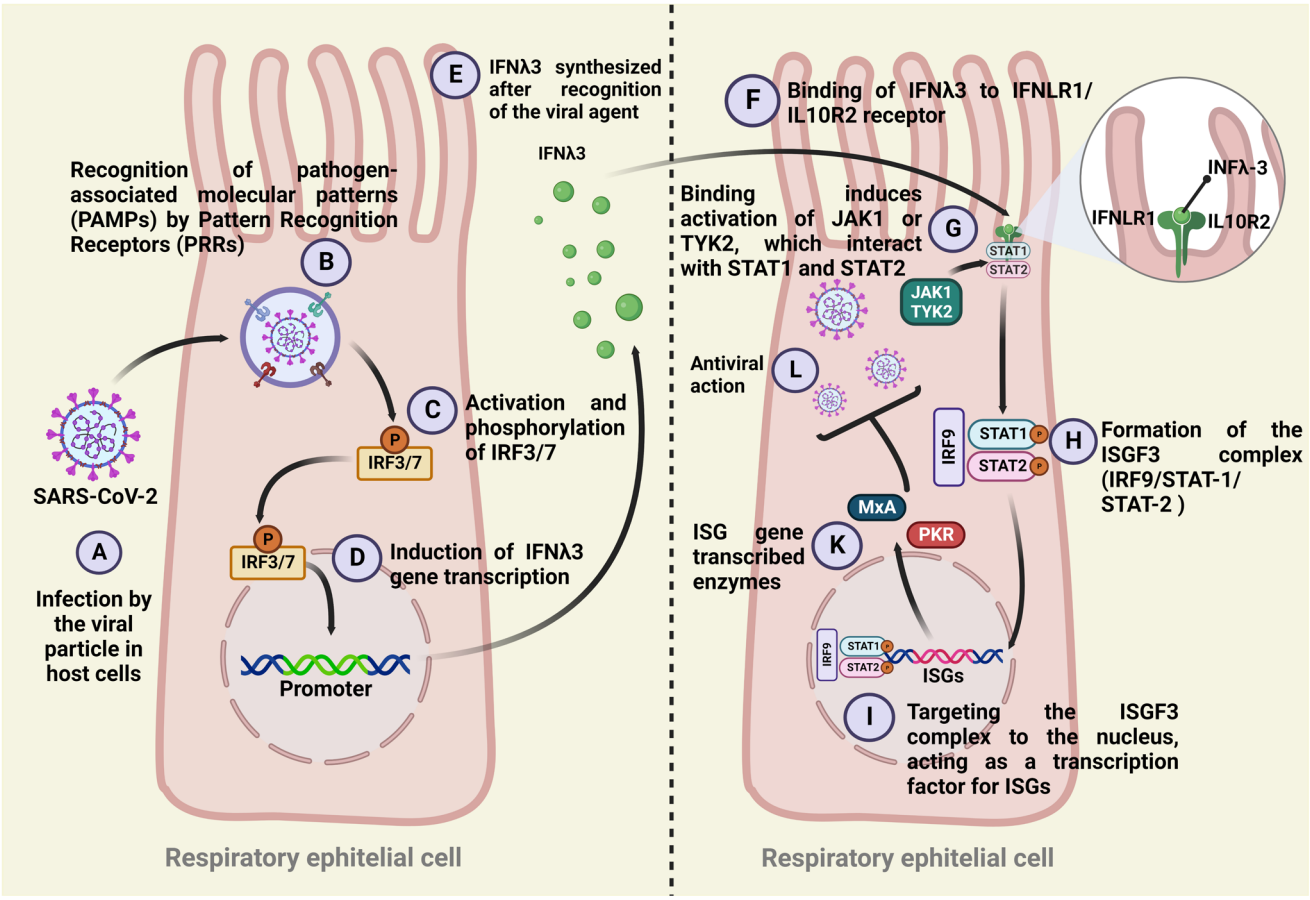

Figure 1. Gene expression and antiviral action of IFNL3. From the binding process to the tropism protein, the viral particle is internalized in the cytoplasm of the host cell, the pathogen-associated molecular patterns (PAMPs) by the pattern recognition receptors (PRRs); subsequently, there is the phosphorylation and activation of IRF3/7 that will act as a transcription factor of the IFNL3 gene. After the transcription of interleukins, there is the binding on the IFNLR1/IL10R2 receptor that induces the activation of some proteins that result in the formation of the ISGF3 complex that will be directed to the nucleus and will act as transcription factor for interferon-stimulated genes (ISGs). The transcription products of ISGs like MxA and PKR act in the antiviral action.
Source: Created with BioRender.com.

diseases such as hepatocellular carcinoma, HIV-associated ischemic stroke, and more recently, the disease caused by the SARS-CoV-2 virus through Genome-Wide Association Studies (GWAS).[46–49] With this, several SNPs are related to the clinical progression of COVID-19 as shown in Table 1.

IFN-λ3, particularly IL-28B, may be associated with clinical severity in some pathologies such as hepatitis B,[73] as well as other viral infections.[74,75] In COVID-19, there is an association of various SNPs in monitoring the clinical condition of infected individuals and in sustained antiviral action in the regulation of the immune response.[76] The genotypes of rs12979860 (CC) and rs12980275 (AA) were considered strong contributors to resistance in SARS-CoV-2 infection;[73,76] however, among this variation, there was unfavorable genotypic discrimination with influence on clinical progression to severity in the rs12979860 (TT) SNP, which is the same genotype associated with disease aggravation such as hepatitis C in the development of hepatocellular carcinoma.[36]

HLA: recognition and antigenic presentation in the immune response

Another marker that may be associated with the severity of COVID-19 is the HLA, which comprises molecules from the major histocompatibility complex (MHC) corresponding to the set of specialized glycoproteins that distinguish foreign peptides, expressed on the surface of human cells.[77] In its origin, the gene encoding the HLA classes is located on the short arm of chromosome 6p21.3,[78] one of the most polymorphic regions of the human genome.[79] This characteristic results in a high phenotypic variability of the complex, highlighting the diversity of responses to various pathologies in different ethnic groups.[80,81]

There are several HLA haplotypes, with three genes from HLA class I (HLA-A, HLA-B, and HLA-C) mainly related to peptide presentation and activation of CD8+ T cells, and three other genes from HLA class II (HLA-DP, HLA-DQ, and HLA-DR), which differ from class I, are intrinsically linked to CD4+ T-cell peptide presentation.[82,83] In addition, there is also class III HLA, which has genes encoding proteins in the immune system, such as the complement system and cytokines.[84]

Studies show the association between some MHC complex genes with increased susceptibility or protective factor in relation to their action against some infections,[85] as well as the analysis of the ability of HLA class I and class II proteins to present their peptides and their potentially stronger or weaker ligands, including in SARS-CoV-2 infection.[86]

Table 1. Genes associated with clinical progression to severity in COVID-19.

Gene	chr:position	SNP	A1	A2	References
ACE2	chrX:15592225	rs2285666	C	T	50–52
ACE2	chrX:15564667	rs2074192	C	T	51,53
ACE2	chrX:15600857	rs73635825	A	G	54,55
ACE2	chrX:15581305	rs143936283	T	C	55
FURIN	chr15:90883330	rs4702	A	G	56
IFNL3	chr19:39252525	rs8099917	G	T	19
IFNL3	chr19:39241143	rs12980275	A	G	19
IFNL4	chr19:39248147	rs12979860	C	T	19,57
IFITM3	chr11:321001	rs6598045	A	G	58
IL6	chr3:45823240	rs1800795	C	G	21,59
IL10	chr1:206773289	rs1800871	C	T	60
IL10	chr1:206773062	rs1800872	A	C	60
MX1	chr21:41446003	rs469390	G	A	61
TMPRSS2	chr21:41470061	rs2070788	A	G	62–66
TMPRSS2	chr21:41507982	rs75603675	C	A	67,68
TMPRSS2	chr21:41480570	rs12329760	C	T	66,69–71
TMPRSS2	chr21:41486440	rs383510	T	C	66,72

HLA-mediated immune response to SARS-CoV-2

In humans, among the main proteins of the immune response, the HLA plays one of the fundamental roles: the regulation of the host's immune response.[87] HLA acts in the recognition of endogenous and exogenous structures but is mainly responsible for the presentation of antigenic peptides for the activation of immune system cells.[87,88]

Among the various HLA molecules, those of classes I and II are the most important, with the former inducing the cytotoxic action of CD8+ T cells by inducing programmed cell death of infected cells[89] and the latter characterized by their high specificity in binding and presenting antigens to CD4+ T cells (Figure 2).[90] The process of binding to antigens is mediated by interaction in the peptide-binding grooves of the complex proteins, followed by proteolysis of the epitopes and finally their presentation.[87]

The extensive number of polymorphisms in HLA genes characterize a large variability in the immune response produced, making possible genotypes strong markers that impact susceptibility to viral infections.[91] Studies have indicated that the highly polymorphic profile of this region may result from natural selection among individuals,[18,92] resulting in the composition of distinct haplotypes. Through this, genetically diverse populations would have a greater chance of survival in epidemics of new diseases.[87]

Given the highly mutagenic profile that SARS-CoV-2 has,[93] in addition to the characteristic variability of HLA,[94] infection with new viral variants may induce non-recognition by the binding grooves present in the proteins of the complex, this being an activity linked to loss of peptide affinity that results in a delayed immune response (Figure 3).[95,96]

Alterations in peptide affinity in the MHC, specifically for HLA, have been previously reported in several pathologies and associated with the progression of the pathological picture.[96] Recent studies have evaluated the antigen–HLA relationship in the Delta and Omicron variants, and it was possible to conclude that there is a great loss of recognition affinity for HLA proteins,[93] where class II is impaired and does not promote in a timely manner the differentiation of TCD4+ cells, therefore, an immune escape.[95,96]

Genetic variability and the influence on HLA antigen recognition

There are several polymorphic associations between HLA and COVID-19, addressing the allelic frequency of different genotypes and some genes of the complex in different geographic regions,[87,97] elating them to susceptibility to SARS-CoV-2 infection and influence severity in COVID-19.[98,99] Antigen presentation by HLA molecules present on the surface of antigen-presenting cells (APCs) and recognition by structures of the immune system are strongly associated with clinical progression by COVID-19;[100] the recognition or not of antigenic structures is what mediates the emergence of asymptomatic and symptomatic pictures (Figure 4) and is intrinsically related to the genetic variability of these structures.

Some of the HLA genes have thousands of variants and are now called hyperpolymorphic.[101] Many SNPs in the HLA region have been associated with viral infections, including hepatitis B and C, HIV,[102] and SARS-CoV-2. Several studies have sought to find an association between the various HLA genotypes and the severe form of SARS-CoV-2 infection in different regions of the world.[91,103,104] An *in silico* analysis of the affinity between binding peptides of SARS-Cov-2 and genotypes of MHC I molecules showed that individuals presenting the SNP HLA-B*46:01 may be more susceptible to COVID-19, whereas the HLA-B*15:03 allele was associated with a protective factor.[103] Another study indicated that the high mortality rates from COVID-19 observed in some countries seem to be related to a low MHC class II presentation.[105]

IL-6 and the inflammatory process in the immune response

IL-6 is a pro-inflammatory and anti-inflammatory cytokine consisting of 212 amino acids, being encoded by the IL-6

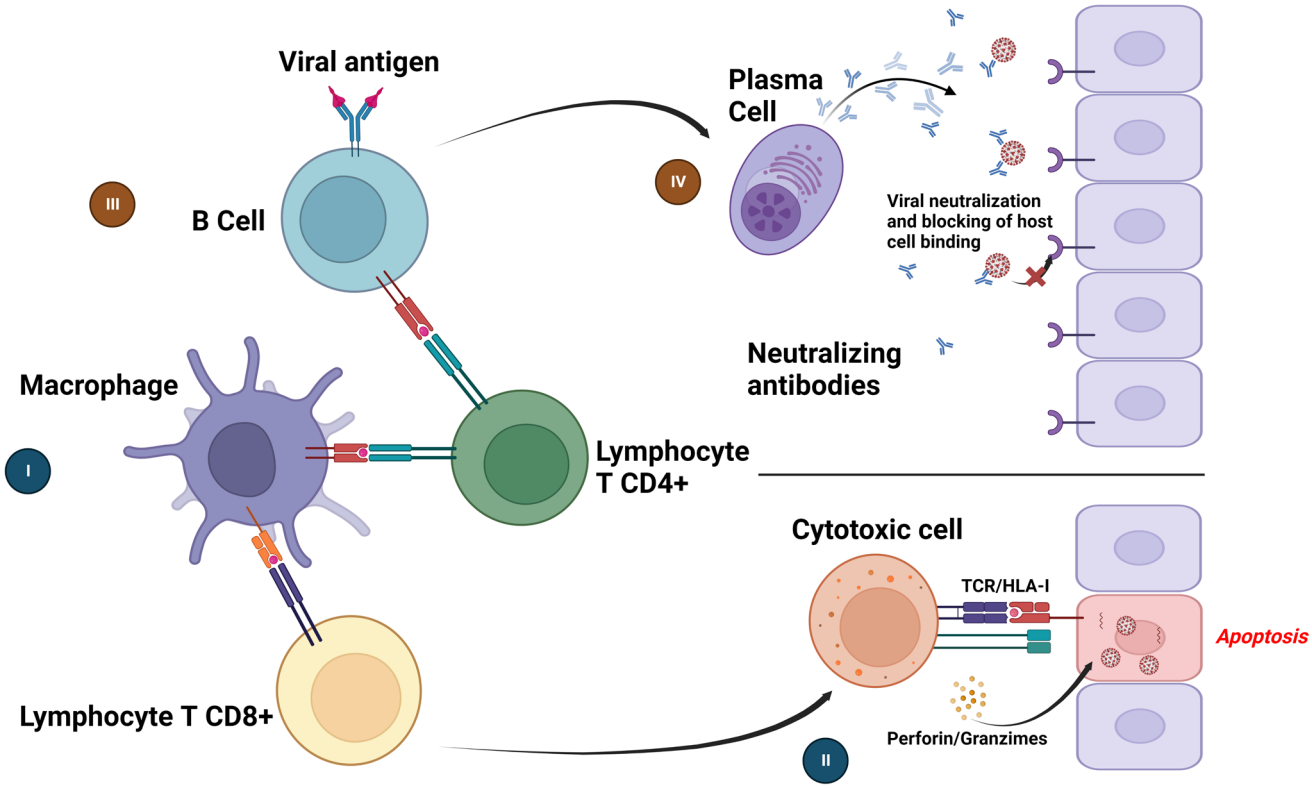

Figure 2. (I) Macrophage antigenic presentation through HLA class I molecules to CD8+ and CD4+ T cells of the immune system; (II) with antigenic presentation through APC, there was CD8+ T-cell activation, and its cytotoxic action is performed in cells that present similar antigens on their surface inducing programmed cell death (apoptosis); (III) after antigenic presentation by APC, the viral antigen is presented to B cells, which results in their differentiation into plasma cells; and (IV) the plasma cell excretes neutralizing antibodies to the viral antigen presented, interrupting the viral infection process by neutralizing the SARS-CoV-2.
Source: Created with BioRender.com.

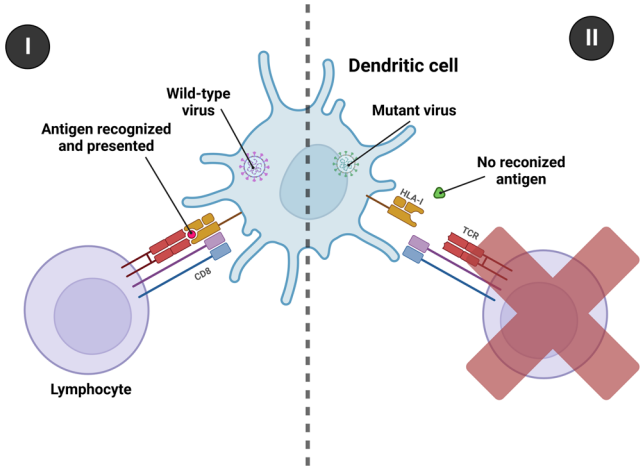

Figure 3. (I) Antigenic recognition by HLA class I molecules from a viral wild type and (II) non-recognition by HLA class I of the viral peptides due to virological variation and non-affinity with the molecules of the complex.
Source: Created with BioRender.com.

gene on chromosome 7p21 is classified as pleiotropic due to its ability to affect the function of various cell types.[106] In addition, it is considered a marker of inflammatory diseases and plays an important role in antiviral immunity.[107,108]

The increase of cytokine IL-6 in the human organism occurs due to the range of cells of the immune system having the ability to release it when they are acting on infections.[109] Researchers conducted a study with an Italian population of hospitalized patients for COVID-19 that showed associations with the outcome of severe pneumonia occurring due to the storm of cytokines; in face of this, it was noted the importance of analyzing drugs that act against these cytokines.[110] Among them is the drug tocilizumab that acts competing for the IL-6 receptor, which is responsible for inducing lung failure and fibrosis formation in the severe course of the disease.[111]

Cytokine storm: effect of IL-6 over-reaction

Cytokine storm or cytokine release syndrome is a picture of hyperinflation and over-production of cytokines in an exacerbated and negative way for the organism.[112,113] This occurs due to a failure in the immune system function, causing severe inflammation and possibly evolving to multiple organ failure.[114] This scenario encompasses several cytokines, among them IL-1, IL-6, IL-8, IL-10, tumor necrosis factor (TNF)-α, and IFN-γ.[115] The clinical picture of cytokine release syndrome is characteristic of COVID-19 disease, in which this increase in pro-inflammatory cytokines is directly correlated with the worsening of the disease and its lethality.[112,116]

IL-6 and its role in the clinical progression of severity in COVID-19

The severe clinical evolution of COVID-19 was related to an exacerbated host immune response, called hyperinflammatory syndrome, which occurs due to the action of

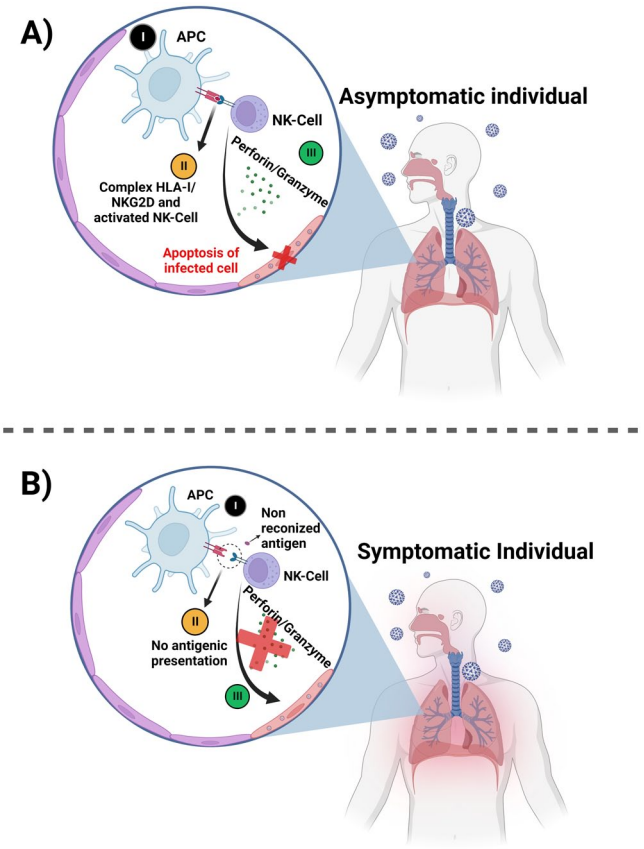

Figure 4. Influence of the immune response on the symptomatology of COVID-19. (A) Viral infection with asymptomatic clinical picture – (I) APC recognizes and presents viral antigenic peptide to the natural-killer cell, (II) formation of the binding complex of the HLA class I molecule and the NKG2D receptor activating NK cells, (III) upon their activation, natural-killer cells secrete enzymes such as perforin and granzymes, inducing cell death of the infected cell. (B) Viral infection and symptomatic clinical picture – (I) the HLA class I molecule present in APC does not recognize the viral antigen, (II) due to antigenic non-recognition, there is no presentation to the immune system, (III) the cascade of enzyme release does not happen due to non-activation of the responsible cells; therefore, the infected cell remains contributing to viral replication, occurring the emergence of symptoms.
Source: Created with BioRender.com.

the immune system in response to infection through the release of inflammatory cytokines, a phenomenon known as cytokine storm.[117] Among the main cytokines related to the clinical severity of SARS-Cov-2 infection is IL-6, which promotes a highly specific reaction of adaptive immunity by stimulating CD8+ T and B cells, which also favors the survival of phagocytic neutrophils. However, there is tissue damage by deregulation of the extracellular matrix and by attraction of pro-inflammatory macrophages and neutrophils to the tissues.[118] A study of 1472 patients hospitalized for COVID-19 infection showed a positive relationship between IL-6 levels and neutrophil, monocyte, and white cell counts, as well as C-reactive protein levels.[119]

The expression of IL-6 is increased in many malignancies,[120] and it is also highly involved in inflammatory processes.[121,122] IL-6 family cytokines induce specific and enforced molecular responses in endothelial cells, in addition to regulating genes and proteins involved in angiogenesis and immune cell recruitment.[121] Several genes have been associated with IL-6 levels in the bloodstream, and a large number of these genes are involved in the inflammatory cascade and red blood cell function.[123] In addition, another trial that looked at patients with elevated C-reactive protein levels from different inflammatory conditions found an association between elevated IL-6 levels and atrial electrical remodeling.[124]

Genetic variants of IL-6 are strongly associated with clinical progression of COVID-19 due to their differential expression.[125] An associative study between IL-6 and critical cases of the disease identified the SNP rs2069837 with genotypes strongly associated with the influence on the clinical picture of individuals, with the A allele being characterized as high risk; however, the G allele was related to a protective action in patients with COVID-19 and respiratory failure directly affecting protein expression.[126,127] Concomitantly, the rs1554606 SNP was also associated with severe COVID-19 patients, and there was an association of IL-6 gene expression at serum levels also in cases of disease severity.[128]

AUTHORS' CONTRIBUTIONS

All authors contributed to the production of the paper. Conceptualization: AMPS and DV; data processing and analysis: AA and AMPS; methodology: AA and AMPS; writing – original draft: AA, AMPS, LEA, KST, MHMCC, and GS; writing – review and editing: DV, JMVS, AMPS, and GS.

DECLARATION OF CONFLICTING INTERESTS

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