Review Article
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Immunopathology of SARS–CoV–2: a review

Abstract

Knowledge of the dynamics of the virus and the host's response against it, are essential aspects to adopt effective measures for the antiviral treatment, vaccination and epidemiological control of COVID–19. The present review aimed to analyze publications about the dynamics of the immune response in individuals infected with SARS–CoV–2. The immune response in COVID–19 begins with the interaction between SARS–CoV–2 protein S and the angiotensin II converting enzyme (ACE2) on the host cell surface. This interaction leads to the production of type I interferons (IFN–α and IFN–β) and pro–inflammatory cytokines which are important in protecting uninfected cells. However, the immune response against SARS–CoV–2 is primarily responsible for the clinical picture of COVID–19 because cytotoxic T cells promote the destruction of alveolar cells, compromising the functioning of the lungs and the fact that the virus stimulates production of a storm of pro–inflammatory cytokines responsible for the vasodilation of small blood vessels and the constriction of the body's smooth muscle, which can lead to a multiorgan failure. Therefore, we can see that the production of specific antibodies (IgM and IgG) occurs between 14–21 days after the first symptoms of the disease and decline around 2 to 5 weeks after infection, showing a short duration of IMMUNOPROTECTION, which can lead recovered individuals a susceptibility to reinfection after this period.

Keywords: SARS–CoV–2, COVID–19, immune system, humoral immunity, antibodies

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Abbreviations: SARS–CoV–2, severe acute respiratory syndrome–related Coronavirus 2; ICTV, international committee for virus taxonomy; CSG, Coronavirus study group

Introduction

SARS–CoV–2 (*Severe Acute Respiratory Syndrome–related Coronavirus 2*) can cause a severe respiratory disease which has been called by the WHO as coronavirus–19 disease (COVID–19).[1,2]

According to studies carried out by the coronavirus study group (CSG) of the International Committee for Virus Taxonomy (ICTV), SARS–CoV–2 is a virus belonging to the order *Nidovirales*, suborder *Comidovirineae*, family *Coronaviridae*, subfamily *Orthocoronavirinae*, genus *Betacoronavirus*, subgenus *Sabecovirus*.[3,4]

Coronaviruses have structural proteins such as: protein S, which is a fusion protein that intermediates the interaction of the virus with the host cell; glycoprotein M which is a membrane protein; the envelope protein E which is a small protein with membrane permeabilization activities. This protein plays an important role in the assembly of the new particles and has been identified as a virulence factor for SARS–CoV. The N nucleocapsid protein is already involved in RNA synthesis and has antagonistic actions to type I interferon.[4,5] SARS–CoV–2 has a positive–sense linear RNA genome with a size of 27–32 kb considered the largest genome of all RNA viruses.[6]

Immune response against SARS–CoV–2

Knowledge of the dynamics of the virus and the host's response against it are essential aspects to adopt effective measures for the antiviral treatment, vaccination and epidemiological control of COVID–19.

The immune system is the body's main defense mechanism against different antigens, whether microbial or not. This system is governed by innate immunity as the first line of defense and acquired immunity. Both immunities interact in a synchronized way through different cellular and protein components responsible for the immune responses capable of controlling the replication of the virus and consequently its elimination.[7]

Innate immune response to SARS–CoV–2

Innate immunity always responds immediately against invading microorganisms and damaged cells. Immunity receptors are specific to structures that are common to a group of related microorganisms and do not distinguish specific differences between microorganisms. The main reactions of innate immunity against invading microorganisms are the inflammatory response and the blocking of viral replication or destruction of virus–infected cells without the need for an inflammatory response.[7]

The main route by which innate immunity blocks viral infections is to induce the expression of type I interferon whose most important action is the inhibition of viral replication. Therefore, different pattern recognition receptors, including TLRs (Toll Like Receptors), NLRs (NOD Like Receptors) and RLRs (RIG Like Receptors) generate signals that stimulate the expression of IFN–α and IFN–β genes in different cells. These type I interferons, secreted by cells, act on other cells to prevent the spread of viral infection.[8,9]

The immune response in COVID–19 begins with the interaction between SARS–CoV–2 protein S and the angiotensin II converting enzyme (ACE2) on the host cell surface, thereby inducing viral particle endocytosis and catalyzing fusion between the host and the viral membrane, allowing the penetration of the viral genome into the cytoplasm of the host cell.[9]

SARS–CoV–2 infects macrophages and these in turn present the virus to T cells. This process leads to the activation and differentiation of T cells, including the production of cytokines associated with

different subtypes of T cells such as helper T 17 (Th17), followed by a massive release of cytokines for the amplification of the immune response.[8,10]

The interaction of SARS–CoV–2 on the surface of the host cell through protein S leads to the appearance of viral genomic RNA in the cytoplasm of the host cell. Studies by Cao; Channappanavar et al. and Henderson et al., showed that after entering the alveolar epithelium, the virus is detected by endosomal sensors (TLR7/8) and cytosolic sensors (RIG/MDA–5) and, consequently, the IRF3/7 and NF–κB transcription factors are activated which produce type I interferons (IFN–α and IFN–β) and pro–inflammatory cytokines respectively.[11–13] The production of type I interferon is important in order to increase the release of antiviral proteins for the protection of uninfected cells. Subsequently, the virus through proteins E and 3a, activates the inflammatory sensor, NLRP3, resulting in the secretion of the highly inflammatory cytokine IL–1β.[13]

Other recent studies involving patients with COVID–19, have shown high serological levels of pro–inflammatory cytokines such as IL–6 and IL–1β, as well as IL–2, IL–8, IL–17, G–CSF, GM– CSF and TNF, characterized as a cytokine storm. Therefore, high levels of pro–inflammatory cytokines can lead to shock and tissue damage in the heart, liver and kidneys, as well as respiratory failure or multiorgan failure.[11–13]

Acquired immune response to SARS–CoV–2

Dendritic cells (DCs) play an important role in the acquired immune response. As professional antigen presenting cells, they are involved in the effective stimulation and activation of naïve T cells and B cells. T cells, particularly $CD4^+$ and $CD8^+$ cells, play a significant antiviral role in balancing the fight against pathogens and risk to develop autoimmunity. CD4+ cells promote the production of virus–specific antibodies through the activation of T–dependent B cells. However, $CD8^+$ cells are cytotoxic and can destroy infected cells.[7,10]

Patients with COVID–19, have presented profound lymphopenia, particularly in severe cases. This lymphopenia is characterized by a drastic reduction in $CD4^+$ cells, $CD8^+$ B cells, natural killer cells (NK), as well as a reduction in the percentage of monocytes, eosinophils and basophils.[14,15] This suggests that COVID–19 can compromise lymphocytes, particularly T lymphocytes and as a consequence the immune system is negatively affected during the disease period, impairing its action against the virus.

Furthermore, humoral immunity is essential in controlling persistent infection. Studies in patients with COVID–19 have demonstrated the presence of antibodies between 14–21 days or more after the first symptoms, which suggests an effective humoral response in controlling the virus.[16,17]

In their studies on the antibody response to SARS–CoV–2 in patients with COVID–19, Long et al., observed that in some patients the seroconversion of IgM and IgG occurred simultaneously and sequentially, while in another group the seroconversion of IgM occurred before that of IgG and in a third group the seroconversion of IgM occurred long after the seroconversion of IgG. Therefore, seroconversion of these immunoglobulins in all patients occurred within 20 days after the onset of symptoms.[17]

Another study in asymptomatic individuals with a confirmed diagnosis of SARS–CoV–2 demonstrated significantly low IgG levels specific to SARS–CoV–2 compared to symptomatic individuals. These results suggest that asymptomatic individuals have a weak immune response to SARS–CoV–2 infection. The same study also demonstrated that the levels of neutralizing antibodies decrease significantly in the initial phase of convalescence in both symptomatic and asymptomatic individuals. Therefore, these results suggest that neutralizing antibodies in recovered individuals decrease significantly between 2–5 weeks after infection, which demonstrates a short duration of immunity after SARS–CoV–2 infection.[8,18,19]

Evasion of SARS–CoV–2 to the immune system

The virus to induce a disease must be able to escape the host's defenses.[7] In the case of SARS–CoV–2, during replication, the virus covers the viral intermediate products within a double vesicular layer, preventing their arrest by the host cell's PRRs. Furthermore, viral proteins such as M and *PLpro* protease are able to actively inhibit host sensors in order to prevent the expression of type I interferons by inactivating IRF3 transcription factors. The virus can also directly block the interferon signaling cascade, preventing STAT1 phosphorylation and translocation of the STAT1/2–IRF9 complex, in that way preventing the activation of the antiviral state of uninfected cells and increasing the response of the interferon.[20–22]

Conclusions

The immune response against SARS–CoV–2 is primarily responsible for the clinical picture of COVID–19, because cytotoxic T cells promote the destruction of alveolar cells, compromising the functioning of the lungs and the fact that the virus stimulates the production of a storm of proinflammatory cytokines responsible for vasodilation of small blood vessels and constriction of the smooth muscle of the organism, thus leading to a multiorgan failure. Furthermore, we can see that the humoral response responsible for the production of specific antibodies (IgM and IgG) occurs between 14–21 days after the first symptoms of the disease and decline around 2 to 5 weeks after infection. This fact suggest a short durability of the IMMUNOPROTECTION which can lead to recovered individuals a susceptibility to reinfection after this period. Despite the efforts of the immune systems to try to control the virus, SARS–CoV–2 has escape mechanisms in order to prevent its destruction by the immune system, which includes mainly the inactivation of transcription factors responsible for the synthesis of type I interferons responsible by activating the antiviral status of uninfected cells.

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Conflicts of interest

I declare that there is no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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