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SUPPLEMENT ARTICLE

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Immunological basis of virus-host interaction in COVID-19

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Abstract

COVID-19 is a complex new viral disease, in which a strict balance between antiviral immune response and the ensuing organ inflammation has a critical role in determining the clinical course. In adults, compelling evidence exists indicating that an uncontrolled inflammatory response ("cytokine storm") is pivotal in determining disease progression and mortality. Children may rarely present with severe disease. Modulating factors related to the host's genetic factors, age-related susceptibility, and the capability to mount appropriate immune responses might play a role in control virus load at an early stage and regulating the inflammatory reaction. Elucidating these mechanisms seems crucial in developing target therapies according to patient's age, immunologic status, and disease evolution in COVID-19.

KEYWORDS

children, COVID-19, cytokine storm, immunopathogenesis, Kawasaki disease

1 | INTRODUCTION

COVID-19 pandemic has quickly spread worldwide, becoming a frightful global threat for health and economy. Two main features characterize this new disease: (a) Children have a milder or even asymptomatic clinical course as compared to adults,[1] and (b) in severe cases, an exaggerated host immune response leads to acute lung injury (ALI) and a systemic vascular dysfunction syndrome. Data from adult COVID-19 suggest that severe cases evolve through a "four-stage" disease progression.[2] The first stage is characterized by upper airway involvement and the second by interstitial pneumonia; patients evolving to the third stage develop complications due to a cytokine-driven hyperinflammatory condition, associated with acute respiratory distress syndrome (ARDS) and/or a hypercoagulability state, ultimately leading (fourth stage) to multi-organ failure (MOF) and death. This brief review will focus on the complex interplay between SARS-CoV-2, host's innate and adaptive immune responses, and endogenous factors potentially implicated in the modulation of the phenotype and evolution of COVID-19 in children.

Key Message

COVID-19 presents a better clinical course in children. This might be due to lower intracellular response of SARS-CoV-2/(ACE2) receptor binding, a higher number of memory B cells generating natural antibodies, trained immunity (vaccinations), and lower androgen-depending TMPRSS2 activity.

2 | BASIS OF VIRUS-HOST INTERACTION

SARS-CoV-2 is a zoonotic RNA virus, with 79% genetic similarity with SARS-CoV.[2,3] The spike protein (protein S), expressed on its surface, is composed of 2 subunits, S1 and S2. S1 contains the receptor-binding domain that recognizes ACE2 receptors and the cellular serine protease TMPRSS2, implicated in S2 protein priming, that allows the fusion of viral and cellular membranes. Intriguingly, androgen receptor activity is required for TMPRSS2 gene transcription.[2] Alveolar epithelial type II cells represent 83% of all ACE2-expressing cells, explaining the higher severity of COVID-19 compared to other respiratory viral infections (eg, influenza). ACE2 receptors are also expressed on the kidney, heart, enterocytes, keratinocytes, and other cell types. SARS-CoV-2 is a cytopathic virus, but it also induces an ALI downregulating ACE2.

ACE2 regulates the renin-angiotensin system, whose dysfunction results in impaired blood pressure and fluid/electrolyte balance, enhanced airway inflammation, and vascular permeability. ALI, in turn, triggers the innate immune response. Alveolar endothelial cells and macrophages recognize virus pathogen-associated molecular patterns (PAMPs) through a variety of pattern-recognition receptors (PRRs) and release Th1-polarized proinflammatory cytokines and chemokines.[2] Type I interferons (IFNs) and IFN-stimulated genes control viral spreading and modulate the immune response. Other innate components, including NK cells, complement and coagulation system, natural antibodies, and other cytokines, may also be implicated in the immune response to SARS-CoV-2. Upon the release of proinflammatory cytokines, monocytes and lymphocytes are recruited and thus depleted from the periphery. Adaptive immune response develops within one week after symptom onset and involves both T and B cells. CD8+ T cells kill infected cells, while CD4+ T cells drive CD8+

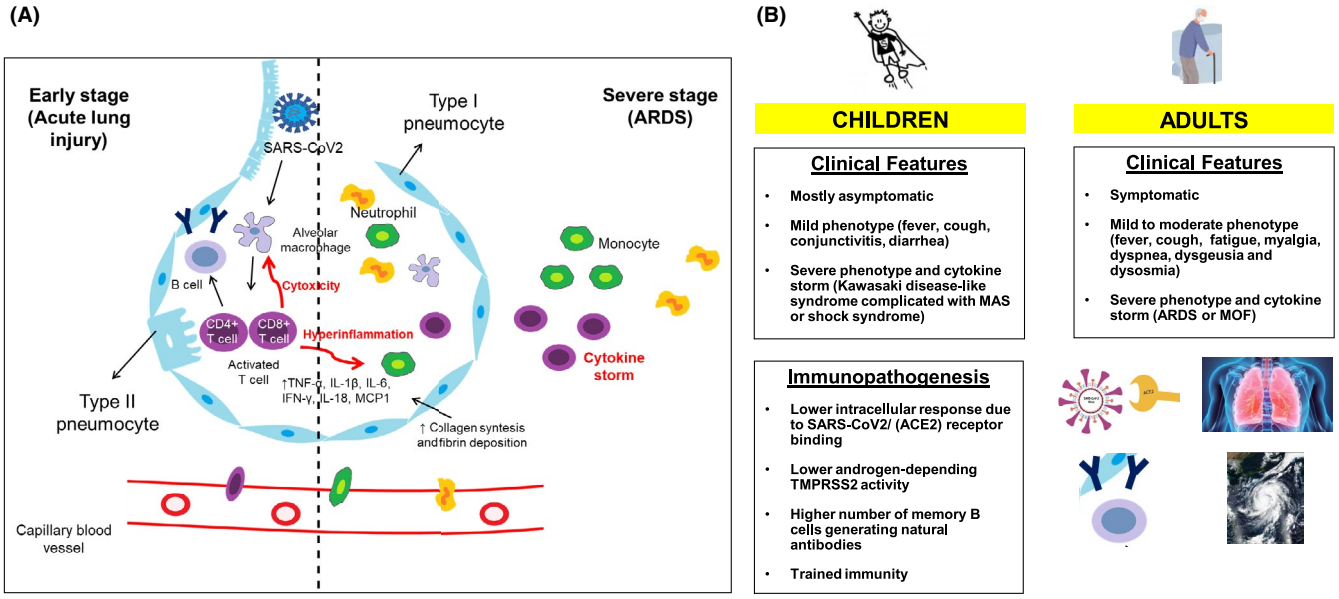

FIGURE 1 A, Immunopathogenesis of covid-19 B, Differences in COVID-19 between children and adults [Colour figure can be viewed at wileyonlinelibrary.com]

T- and B-cell responses (Figure 1).[2] T cells terminate the immune response preventing inflammatory complications. Antibodies to SARS-CoV-2 increase during the first three weeks after symptom onset. The efficacy of convalescent serum in the treatment of COVID-19 suggests their neutralizing efficiency. However, it remains unknown how long they are lasting. Evidence from agammaglobulinemic patients suggests that B-cell response might be less important than expected and may be paradoxically deleterious in COVID-19 inasmuch, promoting a robust inflammatory response through IL-6-mediated mechanisms.[3,4]

3 | HYPERINFLAMMATION AND CYTOKINE STORM

Besides the direct cytopathic effect of the virus, the host's immune response and lung inflammation play an important role in COVID-19 and may be implicated in disease severity and mortality, being a potential target for the treatment.[5] Increased acute-phase reactants, cytopenias (thrombocytopenia and lymphopenia), coagulopathy (elevated D-dimer), hepatitis (elevated LDH, AST, ALT), and macrophage activation (elevated ferritin) correlate with severity and mortality. There are several hypotheses on how the virus might induce inflammation. Pyroptosis, related to viral infection and replication in airway epithelial cells, leads to cytokine release and consequent vascular leakage. As expected, IL-1β, released during pyroptosis, resulted in elevated during SARS-CoV-2 infection.[2] Viral infection of monocytes and macrophages can also result in aberrant cytokine production. These proinflammatory cytokines and chemokines, including IL-6, IFNγ, MCP1, and IP-10, attract immune cells, notably monocytes and T lymphocytes, but not neutrophils.[2] SARS-CoV-2 patients also exhibited high levels of IFNγ and IL-18, which are key players in the cytokine storm syndrome.[5] Elevated levels of cytokines, such as TNF-α, can cause septic shock and MOF.[2,5] Hyperinflammation is similar to, but not fully overlapping with other well-known clinical entities, such as macrophage-activated syndrome (MAS), or hemophagocytic lymphohistiocytosis (HLH) and other forms of viral-induced cytokine storm, in that ferritin increase is modest and severe end-organ disease is limited to the lung. Nonetheless, it is becoming more and more evident that it has a central role in disease severity and outcome. Experience from hyperinflammation in HLH, MAS, and cytokine release syndrome suggests that early intervention is essential to avoid irreversible tissue damage.[5]

4 | DIFFERENCES IN THE IMMUNOPATHOGENESIS OF COVID-19 INFECTION BETWEEN HEALTHY ADULTS AND CHILDREN

Why SARS-CoV-2 affects individuals with different severity is still unclear. Genetic factors can facilitate life-threatening COVID-19 in previously healthy individuals without any overt comorbidities. In adults, polymorphisms in innate immune genes (eg, mannose-binding lectin) have been linked to susceptibility to SARS-CoV.[6] Although children are usually vulnerable to respiratory infections, they rarely show severe COVID-19 disease, being mostly asymptomatic or presenting with a mild phenotype. Potential explanations may include a better and healthier lifestyle in children and a reduced viral load due to competition with other common viruses of childhood. When focusing on host-virus interaction, it has been shown that SARS-CoV-2 S1 protein by binding cell entry receptor (ACE2) induces a lower intracellular response in children's alveolar epithelial cells compared to adults.[7] Interestingly, given a general lack of preexisting immunity in the human population, the study of immune system ontogeny may unravel possible immune response differences. Severe COVID-19 cases are more frequent in elderly or adults with coexisting underlying conditions whose suboptimal immune response might interfere with the initial kinetics of infection, leading to disease progression with consequent host hyperinflammatory response.

On the contrary, the children's immune system may react better to novel pathogens because of a higher number of memory B cells that can rapidly generate natural antibodies independently of previous antigen encounters. These antibodies, mostly of the IgM isotype, display a broad reactivity, which is probably able to contain SARS-CoV-2 infection in the early phases before it progresses toward a severe disease.[8] Another age-dependent protective mechanism may be associated with live vaccinations routinely administered in childhood (eg, measles) that might protect beyond their target antigen by induction of innate immune mechanisms called nonspecific heterologous effects (trained immunity).[9] Also, SARS-CoV-2 spread might be limited in children because of lower androgen-depending TMPRSS2 activity. Finally, controversial data are reported on the possibility that previous respiratory coronavirus infections in children may induce a cross-protection toward SARS-CoV-2, being possibly responsible, on the contrary, of a progression of the disease. Of note, severe illness in children is mostly linked to life-threatening inflammation, presenting with different immune dysregulatory manifestations, sharing some similarities with Kawasaki disease.[10] In these cases, respiratory symptoms can be absent, and pediatricians should be alerted by other clinical presentations.

5 | CONCLUSION

In this review, we summarized the immunologic basis of virus-host interaction in COVID-19. Further studies on the host's immune response to SARS-CoV-2, including a detailed investigation of the determinants of children versus adulthood clinical presentation and outcomes, will help unravel the disease's pathogenesis, paving the way for novel targeted therapies.

CONFLICT OF INTEREST

We declare no competing interests and no financial support for this study.

AUTHOR CONTRIBUTIONS

FLT, LL, and GG contributed equally to write the manuscript. SV, SF, and AS performed a systematic literature search in PubMed and EMBASE and contributed to write the manuscript. CC, VL, RC, SC, and FC revised critically and contributed to write the manuscript. All authors have read and agreed to the published version of the manuscript.

PEER REVIEW

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