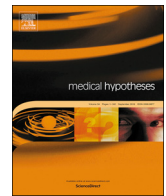




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COVID-19: Loss of bridging between innate and adaptive immunity?

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ABSTRACT

COVID-19 has spread to most countries in the world. However, there are some striking differences in how COVID-19 is behaving in different age groups. While data on COVID-19 is limited, children appear to be less susceptible to severe disease. These unique characteristics may be considered as a potential link to understanding the immune system and response in COVID-19 and lead to an effective cure to the disease. We suggest a possible role of loss of bridging between innate and adaptive immunity in COVID-19 and a potential treatment modality also discussed.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) is a threat to the health and well-being of millions of lives across the globe. The potential source for its widespread disruption is a global travel and close personal contact that has allowed the virus to propagate. The emergence, re-emergence, mutations spread and effects of and from animals of this mysterious and cryptic virus has become the focus of the media across the world. Researchers are working relentlessly to study the virus and its effects [1]. The host inflammatory response and the cytokine storm-generated reflects its predominant attack on the lungs, heart, liver and kidney [1].

The SARS-CoV2 is the pathogen causing COVID-19, a pandemic threatening millions of lives globally [2]. While in most individuals SARS-CoV2 infections are unapparent or associated with mild to moderate symptoms, as many as 10–20% develop the severe or life-threatening disease [2]. Surprisingly, the morbidity and mortality report of the Centers for Disease Control (CDC) showed that compared to adults, children under 18 years of age are less likely to experience the typical symptoms of infection, including fever, cough and difficulty breathing, and are also less likely to need hospitalization and less likely to die of COVID-19 [3]. The overall mortality rate observed was low, at about 0.18% compared to 4.3% in adults [4–6]. One possible explanation for the difference in the disease profiles is the repeated exposure to viral infections improves the children's response to SARS CoV 2 infection

[4,5]. It has also been suggested that children could get relative protection because they have immature angiotensin-converting enzyme 2 (ACE-2) receptors, which the SARS-CoV-2 protein appears to bind for pathogenic effects [4–6]. These unique characteristics could help find answers to its potential link to the immune system and in turn, an effective cure to the disease.

It is noteworthy that the immune system of older patients resembles that of the new-born, with reduced antimicrobial activity by neutrophils and macrophages, reduced antigen presentation by dendritic cells (DCs), decreased natural killer (NK) cell cytotoxicity, and compromised adaptive lymphocyte responses [7–9]. Furthermore, both the very young and old immune systems are similarly compromised in coping with a typical viral infection. Why then are children responding better? These unique characteristics may help find answers to its potential link to the immune system and in turn, an effective cure to the disease.

Hypothesis

The severity of COVID-19 infection in children is less than it is in adults in terms of symptoms, lung consolidation as visualized by computed tomography (CT), and most laboratory abnormalities. The underlying mechanism remains unknown. It is speculated that this may be due to a fully functional thymus in children. The lung is the most severely affected organ in COVID-19 infection [10]. The thymus plays a

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vital role in both lymphatic and endocrine function and serves as a setting where T-cells develop, the lymphocytes responsible for adaptive immunity [10]. With this background, we hypothesise that the increased morbidity in COVID-19 affected older adults is primarily due to the decline in the immune system secondary to dysregulated adaptive immunity. This validates our fact that focusing on adaptive IFN gamma is logical.

The innate immune system is the first active and general line of defence against viral infections. Interferon (IFN) molecules are produced and secreted from infected cells upon virus infection. The IFN- α (alpha) and IFN- β (beta) act as signalling molecules and activate an antiviral response in surrounding cells, turning them refractory to infection. A few hours after a viral infection, both α and β IFNs are rapidly and efficiently produced by macrophages [11]. SARS coronavirus (SARS-CoV) which is similar SARS-CoV-2, is known to suppress the induction of antiviral type I interferons (IFN- α/β). If the innate immunity, the very first line of defence against any invasion of the human body is unsuccessful in eliminating the pathogens, the specific adaptive immune response sets in by the 4th to 7th day following the infection [12]. This correlates with the average time duration at which the patient develops worsening symptoms in COVID-19 infection. The hypothesis might explain why older adults are more commonly affected by SARS CoV-2 when compared to children. It may be that in children, the thymus-derived immunity bridges the gap between innate and adaptive immunity. The innate response is delayed in the elderly, and this makes them vulnerable to the complication in COVID-19 infection. The immune system declines with age, thereby increasing the susceptibility of the elderly to viral infections. Production of innate interferons constitutes the most prompt and dominant immune response to eliminate viral infections. The decline of plasmacytoid dendritic cells in the elderly and a further reduction in the frail elderly population with comorbidities depletes the immune envelope.

Elderly patients are unable to mount a stable immune response against all types of viral infections due to the decreased interferon production or its inhibition through viral non-structural protein 1 (NS1) which in turn increases the relentlessness of viral infection [7,8,11]. Furthermore, new-born babies have limited bacterial exposure, reduced antigen presentation by the dendritic cells, decreased lethal action by the NK cells and compromised adaptive lymphocyte response [11]. However, the paediatric clinical manifestations of COVID-19 are not typical, mild in severity and presents faster recovery [2]. A reasonable explanation to this would be that thymus-derived early innate immunity as a critical factor for host fortification.

The key to successfully decreasing the disease fatality could be the stimulation of the immune responses in the early stages of infection. This could be done through the administration of Interferons (IFNs) which plays a vital role in inducing and modulating an array of immune responses in a controlled manner. It has been shown to play a crucial role in bridging innate and adaptive immunity [13].

Recently, Du and Yuwan [14] through a mathematical model postulated that the interaction between host innate and adaptive immune response could be the likely cause for the severity and mortality in COVID-19 patients. Further, mismatch in the timing between the two immune responses has a significant impact on the disease progression. The adaptive immune response in COVID-19 patients is likely to emerge before the peak viral load. And this causes delayed depletion of vulnerable epithelial cells in the lungs in COVID-19 patients. This mismatch in timing and the resulted interference with innate immunity, leads to incomplete clearance of the exposed cells, thereby providing a source of uninfected target cells for continued infection. This sequentially can induce overactive immune responses, secondary complications with fatal outcomes [14].

While we agree with the view that the interaction between host innate and adaptive immune response is critical in deciding the severity

in COVID-19 infection, we are not in accord with the 'immune response timing mismatch theory'. The hypothesis fails to explain the differing severity or mortality across age group. However, our hypothesis constructively explains why children are spared, and old age individuals are at higher risk of complications and fatality in COVID-19.

Conclusion

SARS-CoV2 exhibits the potential to escape the host's immune response. A greater emphasis should be laid on researching how this virus interacts with immunity and the resultant devastating disease affects children and elderly individuals. With this knowledge, studies should be directed to produce an "antiviral state" with innate-adaptive immune cell responses which helps in containment and clearance of the pathogen. We recommend a clinical trial for activation of T-cells from healthy donors and to develop an enriched cocktail of cytokines, rich in IFN's predominantly TH1 type cells. This cocktail, when administered to an infected patient, can result in a controlled surge of cytokines in the body of the infected person and help boost his ability to fight the virus. Currently, the clinical trial to test the safety and efficacy of this cytokine cocktail in COVID-19 patients is underway at our COVID-19 hospital.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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