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Short Communication

Necessity for the evaluation of stimulated cellular immunity against SARS-CoV-2 infection

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ABSTRACT

Innate immunity is the first-line of non-specific host defense mechanism against pathogens, regardless of the type of strains and mutants. This pivotal component of viral immunology, extremely critical for protecting host cells against infections, has largely been overlooked for SARS-CoV-2 infection. While effective immunization against SARS-CoV-2 reduces the severity of the disease, constantly emerging viral mutants and variant strains continue to pose difficult challenges for effective development of vaccines. This perspective emphasizes the necessity to assess the involvement of the innate cellular immunity against SARS-CoV-2 infection. This most critical aspect of the generic host defense system deserves consideration to broaden the therapeutic scope for effectively mitigating SARS-CoV-2 infection and related pathogenic consequences.

KEYWORDS: COVID-19, SARS-CoV-2, innate immunity, viral infections, infectious diseases.

ABBREVIATIONS

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

INTRODUCTION

A novel class of coronavirus SARS-CoV-2 causes deadly severe upper respiratory illness, the coronavirus disease 2019 (COVID-19), and many serious secondary health complications was first identified in 2019 [1, 2]. It has now become a clinical threat to the general population and healthcare workers worldwide. The COVID-19 has thus far infected nearly 159 million individuals worldwide claiming more than 3 million lives with 33 million infections and in excess of 580,000 deaths in the United States. Frequent travel continues to present an immense global health concern for the spread of this deadly disease. In addition, emergence of rapid mutational changes in the viral genome resulting in new potentially more contagious and deadly variants has worsened the pandemic situation, resulting in difficult clinical challenges to effective treatment [3-6].

Three vaccines are authorized for emergency use by the U.S. Food and Drug Administration (FDA). While these vaccines may not prevent the vaccinees from acquiring SARS-CoV-2 infection, they have been evaluated by the FDA for their safety and efficacy to reduce the severity of COVID-19 in the infected patients, hospitalizations, and deaths. This significant medical intervention is optimistically expected to meet a major milestone of vaccinating 70-85% of the U.S. population for the anticipated herd immunity against SARS-CoV-2. The ongoing studies on the duration of circulating neutralizing antibodies in the individuals recovered from COVID-19 or in the vaccine recipients will be crucial for establishing future protective measures against COVID-19.

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Potential of stimulated innate immunity in mitigating SARS-CoV-2 infection

Immunization is a powerful and cost-effective medical preventive intervention against specific pathogens, for example, as recently reported for Ebola virus [7]; therefore, successful mass-scale vaccination for SARS-CoV-2 in the current COVID-19 pandemic outbreak may be possible. While vaccines against the SARS-CoV-2 are believed to reduce the severity of the disease, hospitalizations and deaths, constantly emerging viral mutants and variant strains continue to pose difficult challenges to assess the efficacy of the existing vaccines. Another most important aspect of the immune system, the innate immunity, against SARS-CoV-2 infection has thus far remained largely unaddressed. The "non-specific" characteristic of the innate defense mechanism, the first line of host defense against any invading pathogen, precedes the secondary immune response that is generated only against a "specific" pathogen. In addition, while the innate immune response is immediate, the adaptive immune response is not generated until days or weeks after infection. Despite crucial and powerful capacity of the initial innate host defense mechanism in resisting all invading pathogens, it has not yet been fully appreciated in defining its involvement against SARS-CoV-2 infection.

The innate immune response acts immediately to resist all types of pathogens and to retard rapid disease progression [8, 9]. It precedes the humoral responses against a specific pathogen that are generated days (IgM ~ 5 days) or weeks (IgG ~ 2 weeks) after initial exposure to the invading pathogens. Despite its strong potential to initially resist invading pathogens, the innate immune system is swiftly overwhelmed by infections with deadly viruses such as SARS-CoV-2, Ebola, Zika, and HIV. This failure of the immune system to protect against such viruses, poses serious medical consequences [10], especially for deadly viral diseases, such as COVID-19, with limited medical options to effectively treat post-infection conditions. The innate immune response becomes eventually less effective in providing sufficient natural protection against pathogens after they circumvent the host defense mechanism. Such failure of the immune system to defend itself against an invading pathogen poses serious challenges in managing the medical consequences, particularly when there are limited options for effective treatment of infections. In these circumstances, induction of nascent innate cellular defense responses may be necessary to provide an alternative or concurrent therapeutic strategy for treating viral infections [11].

In addition to classical cytokines and other modulators of the innate system [12-14], an interesting concept of BCG-induced non-specific activation of the innate immunity to likely provide protection against COVID-19 has recently been presented [15]. Adding to these potentially useful strategies, a novel class of physiologically stimulated cellular cytoprotective enzyme, heme oxygenase-1 (HO-1), a widely distributed functional protein present in all cells, has received recognition in recent years for its involvement in mediating cellular resistance to a broad range of viral infections [16-18, and references therein]. The compelling beneficial natural antiviral outcomes described in these studies present this inducible enzyme as "a unique generic non-specific host defense system" against viral infections. Therefore, evaluation of pharmacological activation of the ubiquitous HO-1 or any other inducers of the innate immunity may pave a way for new key insights into disrupting the replication cycle between the viruses and host factors to effectively ameliorate infections by novel emerging viral pathogens.

The model presented in Figure 1 depicts a graphical presentation of the potential of the inducible innate cellular response to reduce viral load to retard disease progression allowing sufficient time for the subsequent generation of the secondary or adaptive humoral response. The patterns of viremia and generation of IgM and IgG immune responses shown in this model diagram are similar to those typically seen in most viral infections [19-21]. As shown in the model, activating the innate host defense system could substantially reduce virus replication in early or mildly symptomatic COVID-19 patients to maintain a low level of SARS-CoV-2. Because innate immune activation triggers the generation of the antigen-specific adaptive immune response [8], it could also potentially enhance the

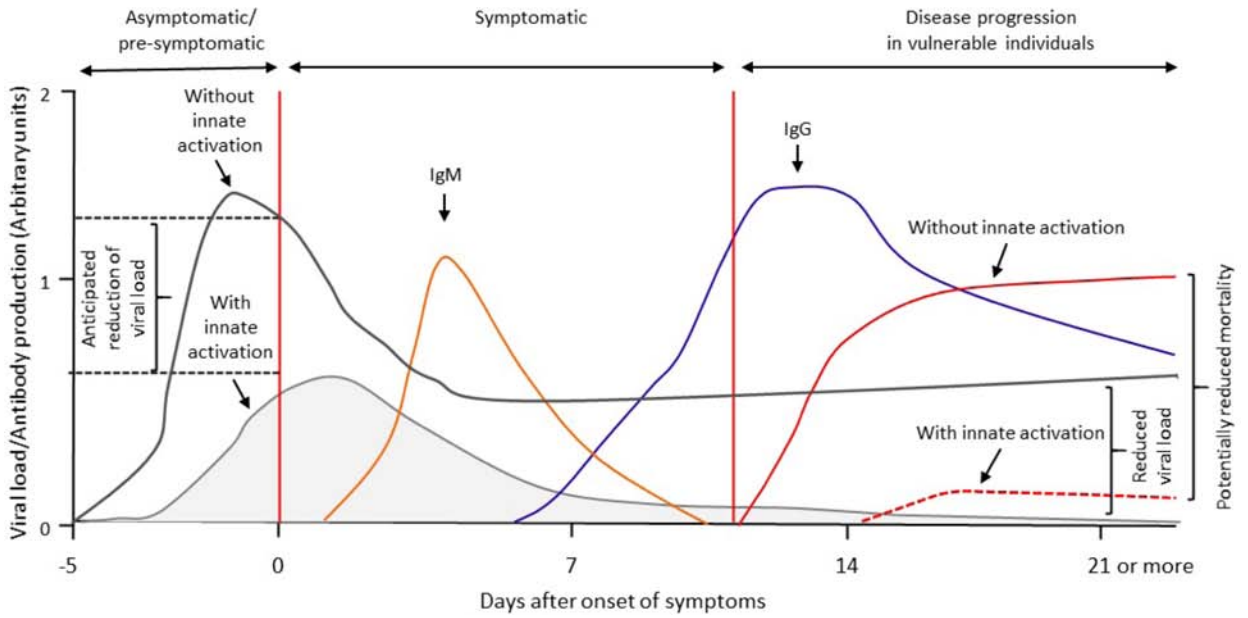

Figure 1. A model depicting the importance of inducible innate cellular protective response against SARS-CoV-2 infection. This model presents the concept of the stimulated innate immunity for reducing the viral load, retarding disease progression, and generation of the secondary humoral immune response.

effectiveness of the humoral immune response produced in the individuals administered vaccines. Stimulation of the innate immune system along with mass vaccination could potentially facilitate the herd immunity against SARS-CoV-2 than vaccines alone. Thus, a robust innate cellular response may afford additional necessary clinical options to minimize the severity of SARS-CoV-2 infection and retard disease progression.

Although the proposal for stimulated innate cellular protection presented in this perspective report can be generally applicable for all viral infections by virtue of its capacity to promote non-specific cellular resistance, it is particularly relevant to the prevailing concerns of SARS-CoV-2 genetic variants. A number of identified SARS-CoV-2 variants have been associated with reduced capacity of neutralization by antibodies generated against individual viral strains [22] in addition to their increased transmissibility and related pathogenicity. A dramatic decline in the number of COVID-19-positive cases, hospitalizations and deaths in the recent months are on the rise again, despite vaccination. These serious concerns warrant evaluation of the potential of the stimulated innate immune defense response along with the continued vaccination program. Physiologically induced innate response might also help facilitate the development of herd immunity against constantly emerging pathogens than vaccines alone by substantially reducing viral loads and hence minimizing transmissions. The enhanced cellular resistance can be expected to complement current medical modalities for more effective control of the COVID-19 pandemic, especially with the narrow pathogen-specificity of vaccines and the limited therapeutic options to treat post-infection conditions and associated severe complications [23-26].

CONCLUSION

The rationale for the development of therapeutics based on innate immune principles is now more realistic than ever before because of the constant evolution of new deadly virulent pathogens posing a significant threat to human health. In the absence of an effective antiviral drug to reduce SARS-CoV-2 replication and the limited choice of therapeutic options to treat COVID-19-related complications, there is an urgency for an alternative strategy that can aid the existing medical modalities for effectively controlling

the COVID-19 pandemic. Interventions involving non-specific activation of the innate immune system by exogenous soluble or cellular inducers could enable additional safe viable options for reducing the severity of SARS-CoV-2 infections and disease progression. Recognizing a limited choice of currently available therapeutics, evaluation of the stimulated innate host protective response presents an essential, unmet, and urgent public health need for the development of potentially novel, effective, and safe therapeutic approaches to resist SARS-CoV-2 infections and to control the COVID-19 pandemic.

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The scientific views in this article reflect the author's own independent opinion.

CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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