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Short Communication

Innate cellular immunity for suppressing viral infections

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ABSTRACT

Innate immunity is our first-line, generic/non-specific host defense mechanism against viral infections, regardless of the type of virus. This component of anti-viral immunology could potentially provide initial protection of host cells against viral infections, but it is generally overlooked as a potential candidate for pharmacological enhancement. Although immunization against individual pathogens provides protection against specific infections and reduces disease severity, the ongoing emergence of new pathogenic viruses, variant strains, and mutants will continue to pose difficult challenges for vaccines. This brief perspective emphasizes the opportunity to explore new approaches to enhancing the generic protective function of innate cellular immunity against viruses. Evaluations of strategies to activate or stimulate these generic/non-specific cellular defense responses may provide a useful approach to help mitigate a broad range of novel deadly viral infections, epidemics, and even pandemics such as COVID-19.

KEYWORDS: innate immunity, viral infections, viral epidemics, pandemics, HO-1, SARS-CoV-2, COVID-19.

ABBREVIATIONS

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019 (COVID-19); HO-1, heme oxygenase-1.

INTRODUCTION

Immunization against specific pathogens is a powerful and cost-effective health intervention, and mass-scale vaccination during pre-pandemic outbreaks may be efficacious, as recently reported for a vaccine for Ebola virus [1]. However, a relatively unexplored potential alternative or complementary approach would be the activation of innate immunity, an important facet of the immune system that can be active against numerous viral pathogens [2, 3]. This generic, non-pathogen-specific innate defense mechanism, the first line of host defense against any invading pathogen, precedes the secondary or adaptive humoral responses that are generated against a specific pathogen. Although the innate immune response can act immediately, the adaptive immune response is not generated for days or weeks after infection, even as viral loads and pathogenesis increase rapidly. Despite the potential of the innate host defense system to attempt initial resistance to all types of invading pathogens, it is rapidly overwhelmed by deadly viruses such as SARS-CoV-2, Ebola, and HIV. There is subsequent overall failure of the immune system to protect against such viruses, posing serious medical consequences [4], particularly for novel viral diseases with limited options for effective post-infection treatment. Under these circumstances, induction or enhancement of nascent innate cellular defense responses could provide an alternative or concurrent strategy for ameliorating infections due to novel viral pathogens.

Perspectives on stimulated innate cellular immunity to resist viral infections

The functional link between viruses and host cell regulation is a well-known critical element in the initial response to infections and subsequent pathogenic events. Since viruses utilize host

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factors for replication in infected cells and may additionally alter the immune system directly or indirectly during inflammatory responses, induction of innate cellular immune responses may provide a promising therapeutic approach to reduce the severity of infections. Examples of such mechanisms might include not only interferons – classical antiviral biologics induced early in infections [5, 6], but also the newer type of physiologically stimulated cellular cytoprotective agent – heme oxygenase-1 (HO-1), a widely distributed and inducible enzyme present in all cells. In model studies, induction of HO-1 has recently been shown to mediate cellular resistance to a broad range of viral infections, including HIV-1, hepatitis B virus, hepatitis C virus, Ebola virus, vaccinia virus, Zika virus, and SARS-CoV-2 [7-15]. Therefore, interventions by activating a robust cellular response using soluble modulators such as interferons or by inducing intracellular physiological modulators such as HO-1 could provide additional options for minimizing the severity of infection and disease progression resulting not only from existing viruses, but especially from new viral pathogens and their emerging mutants or variants.

The speculative diagram shown in Figure 1 is a graphical conceptualization of the potential benefit of rapidly inducing or stimulating the innate cellular response to reduce viral load and to retard disease progression, as well as to permit time for the generation of the secondary (or adaptive humoral) immune response. The patterns of viremia and subsequent generation of IgM and IgG responses shown in the diagram are similar to those typically seen in most viral infections [16-18]. As depicted in this diagram, activation of the innate host defense system might provide substantial generic suppression of virus replication in the cells of early or mildly symptomatic infected patients to maintain a low level of the virus, as has already been shown *in vitro*. Although interferon treatment can produce side-effects, HO-1-mediated innate immune responses could potentially be induced by non-toxic treatment with hemin, an agent FDA-approved for another disease, that has minimal side-effects. Because innate immune activation might also enhance antigen-specific adaptive immune responses [3], it could potentially enhance the effectiveness of the humoral immune response, either naturally in recovering patients or even possibly in individuals administered vaccines.

CONCLUSION

Research on pharmacological activation or stimulation of the innate immune systems seems promising because of its generic, non-specific nature, particularly considering the ongoing new appearance and evolution of deadly viral pathogens

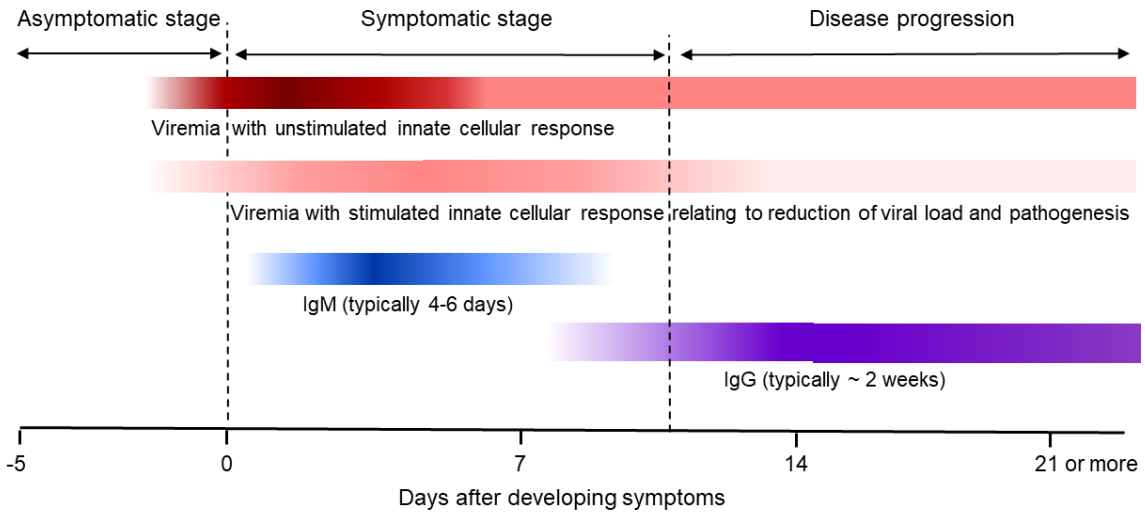

Figure 1. A schematic speculative model depicting the potential importance of a stimulated innate cellular protective response against novel viral infections by reducing viral loads, retarding disease progression, and permitting time for the generation of subsequent secondary (or adaptive) humoral responses.

and mutants that pose significant threats to human health. In the absence of effective approved antiviral drugs to reduce the replication of a broad range of deadly viruses, plus the narrow pathogen-specificity of vaccines, and the limited choice of other therapeutic options to treat viral infections and subsequent severe complications – particularly due to novel viral pathogens – there is urgency to evaluate the practicality of enhancing innate cellular immunity to complement existing medical modalities for more effective control of viral epidemics or pandemics.

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CONFLICT OF INTEREST STATEMENT

The author declares no conflict of interest.

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