Editorial

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The Arms Race in the War Between Virus and Host: Implications for Anti-Infection Immunity

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Viruses are recognized as the simplest form of life on earth, whereas humans are the most complex, flattered by ourselves. Nonetheless, warfare between viruses and human immunity is never ending. Some human organs, such as the respiratory tract and liver, appear to be fertile ground for specific viruses, leading to sometimes aggressive infection. The immune system acts as the human's army, shouldering the responsibility of defending the body. Military operations are carried out by a complex system, reflected in the intricacy of its components. The specialized troops, physical environment, battle strategy, precise timing, and so on constitute the ecosystem of war. Accordingly, even a simple immune response against a virus has these components, as millions of cells mobilize to the infected organs. Generally, we may recognize innate immunity as the advance force of the immune system, while the adaptive immune system can be likened to regular armies employing antibodies and T cells as its main forces.[1] This thematic issue is dedicated to the current scientific landscape of interactions between immunity and viruses in the context of respiratory tract and liver infections, which may provide guidance toward understanding Sun Tzu's art of war in antiviral immunity [Figure 1].

As the first line of defense, the respiratory innate immune system presents elaborate mechanisms against invading viruses. Innate immune cells, namely, macrophages, neutrophils, monocytes, dendritic cells, natural killer cells, and innate lymphoid cells, etc., contain the invading viruses and protect the airway epithelium. The innate immune response becomes activated when viral RNA or other conserved components, called pathogen associated molecular patterns, are recognized by the immune system's radar system, which includes host pathogen recognition receptors, such as Toll-like receptors, retinoic acid-inducible gene I receptors, and NOD-like receptors. Then, serving as the early-warning system, downstream signal transduction signaling, such as interferon regulatory factor 3 and nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB), are triggered. This leads to the production and release of a variety of interferons (IFNs) and proinflammatory mediators, such as cytokines and chemokines, which can be compared to the battle trumpet announcing the impending battle. Thus, the fine tuning of respiratory innate immune responses is critical to the outcome of viral infections. In a recent issue of the journal, Li et al. reviewed the mechanisms underlying the nature of different respiratory viral infections and proposed effective intervention approaches. They emphasized that strengthening of the early IFN response is crucial for the successful treatment of respiratory viral infections, which may reconstitute the negative feedback pathway, thereby reducing IFN expression and restoring the balance between IFN levels and inflammation.

Interferon kappa (IFN-κ) is a relatively ancient and evolutionally conservative host defense factor that has been shown to markedly inhibit the replication of RNA viruses *in vivo* in different animals, including bovines, chickens, and other poultry, during the early stages of infection. IFN-κ may function differently from the later-emerged IFN-α and β. Fu et al. investigated the localization, structure, and function of IFN-κ and compared the IFN stimulated gene (ISG) expression profiles and antiviral activities exerted by IFN-κ and IFN-α2. They found that human IFN-κ-induced anti-viral responses against respiratory viruses depended on cell-to-cell interactions. Additionally, IFN-κ induced more rapid effects during early infection, with less intensity and a shorter half-life, compared with IFN-α2; this led them to postulate that IFN-κ may constitute the first line of IFN-I against respiratory virus infections.[2]

Faced with the formidable defense of host innate immunity, viruses have evolved multifunctional proteins as weapons of resistance. Previous work demonstrated that the SARS-CoV-2 nucleocapsid (N) protein regulated innate immune responses; low-dose N protein suppressed IFN-I signaling and inflammatory cytokines.[3] Gao et al. found that SARS-CoV-2 N protein antigenemia occurred in patients with COVID-19 and was highly prevalent at early stages of the disease. Antigenemia was correlated with clinical severity and may be responsible for the delayed detection of SARS-CoV-2 antibodies. To compensate for the deficient antibody neutralization reaction, the host is forced to call for reinforcements in the form of antibody-dependent cellular cytotoxicity (ADCC) to combat SARS-CoV-2 infection. Cui et al. reported that high ADCC activity against the spike (S) protein and N protein was detected in patients with acute COVID-19; ADCC was observed to peak at 3 weeks post-disease onset. Interestingly, ADCC did not aggravate the severity of COVID-19 and was not correlated with neutralizing antibody titer or total immunoglobulin G titers against S and N proteins. These

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Figure 1: The arms race in the war between virus and host immunity. In order to conquer the emerging viruses, it is needed to develop vaccines, antibodies, drugs, and other intervention measures and bionics related to antiviral immunity with new strategies. Sun Tzu's art of war said that the supreme art of war is to subdue the enemy before fighting. Thus we need to forge ahead with science as in the war against viruses.

data demonstrated that ADCC may play an independent, protective role in anti-infection immunity.[4]

Virus-associated carcinoma is another weapon of mass destruction that may be employed during chronic infection by some viruses, such as hepatitis B virus (HBV) and human papillomavirus. HBV infection is the most prevalent etiological factor association with hepatocellular carcinoma (HCC), a highly aggressive cancer that ranks as the second leading cause of cancer-related death. A review by Xie et al. summarized recent progress on the use of multimodal methods, including genomic, transcriptomic, epigenomic, and proteomic methods, in mechanistic studies of HBV-associated HCC, highlighting advantages and challenges faced by multimodal studies in the field. They also propose that well-designed multimodal studies may facilitate the identification of molecular targets with wide biological impact across different "omes", which may lead to the development of therapeutics for reshaping the tumor microenvironment, delaying cancer progression, and ultimately curing this deadly disease.

Anti-viral and anti-tumor cytotoxic $CD8^+$ T cells are among the ultimate weapon systems of the host. When a virus successfully infects the target cells after escaping neutralization by antibodies, cytotoxic $CD8^+$ T cells recognize viral peptides presented by major histocompatibility complex (MHC) class I molecules and kill the infected cells. The assembly and secretion of MHC class I molecules with antigenic peptides in the endoplasmic reticulum/Golgi is a highly regulated process requiring the concerted action of cytosolic proteasomes, the transporter associated with antigen processing (TAP), and accessory chaperones, such as heat shock protein gp96. The study reported by Meng et al. elucidated the mechanism of assembly and HBV antigen-presenting function of MHC class I molecules by gp96, which is beneficial for designing immunotherapies and vaccines.

Peace is a universal wish; however, war has accompanied almost the whole of human history. Viruses have been at war with their hosts for millions of years, and this process plays an influential role in the evolution of different species.[5] Our struggle against viruses has taught us as much about the viruses as ourselves.[6] The development of new vaccines, antibody drugs, and other immunological interventions fueled by recent innovations has expanded and equipped our immune system inventory. However, the warfare against viruses appears to be endless, considering the continuous emergence of new viruses, such as SARS-CoV-2 and its variants. Thus, the study of bionics pertaining to antiviral immunity should be continuously advocated. Of course, many challenges stand in the way. First, we must consider the double-edged sword that is immunity; precise regulation of immune responses is required to achieve beneficial effects, as heightened or extended responses can inadvertently result in detrimental outcomes. Second, the T cell response is a complex process involving antigen processing and presentation and MHC polymorphisms; thus, the bionics of antiviral T cell immunity require significant breakthroughs before the development of T cell-oriented reagents, drugs, and vaccines can be realized.[7] Lastly, the realm of possibility as we know it today poses a significant challenge; is peace between viruses and immunity a possible outcome? Considering that the supreme art of war is to subdue the enemy before fighting, we must forge ahead with science as we seek to subdue our viral enemies.

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Conflicts of Interest

None.

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