Evasion of Host Immune Defenses by Human Response Viruses

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Abstract: Infectious diseases caused by respiratory viruses are one of the important threats to human health, especially respiratory viruses such as H1N1, SARS-CoV, or SARS-CoV-2, which cause global pandemics and bring great challenges to global public health security. In addition to its high rate of infection, mutation, and worsening, respiratory viruses are difficult to prevent and multiple with seasonality, which brings great hinder to the effective prevention and treatment of viruses. Therefore, this paper discusses respiratory viruses in detail, especially the interaction mechanism among influenza virus that is easy to cause a pandemic, current novel coronavirus pandemics, and the immune system. Meanwhile, this paper analyzes the multiple ways and essence of virus evasion from the host immune system, putting forward new ideas for the prevention and control of respiratory viruses from a more novel perspective.

1. Introduction

There are many kinds of respiratory viruses, among which the infection of parainfluenza virus, measles virus, respiratory syncytial virus, and mumps virus in paramyxovirusdae will cause the common cold, measles, childhood bronchitis, mumps, and other diseases. Infection triggered by adenovirus, rubella virus, and rhinovirus will cause pneumonia, rubella, or the common cold in children. Orthomyxovirus can be subdivided into three types, namely A, B, and C. The typical representative of type A is the influenza virus, which can infect people, pigs, horses, birds, and some reptiles. For example, the H1N1 subtype triggered the Spanish pandemic in 1918. Because of its strong infectivity as well as the wide scope and fast speed of spread, it spread to Europe and eventually the whole world, causing about 2.5%-5% death of the global population at that time.[1] Human severe avian influenza[2] caused by H7N9 subtype 2 and other subtypes such as H3N2, H5N1, H9N2, etc. all lead to seasonal influenza of different degrees[3]. Because the two main components of the influenza virus are hemagglutinin (HA) H1-H16 and neuraminidase (NA) N1-N9 with RNA as its genetic material, it is easy to mutate through antigen drift and antigen transformation.[4] There are many kinds of variations, which bring great pressure to virus prevention. Nowadays, the World Health Organization (WHO) is still launching the latest global influenza strategy year after year. It can be seen that the influenza virus, which has been mutated step by step, is still the target of the human health system all over the world, and its potential harm should not be underestimated.

In addition to influenza viruses, pandemics caused by coronaviruses represented by SARS-CoV and SARS-CoV-2 are still worldwide. Because coronaviruses are easy to infect and spread with a long incubation period, they have caused a great burden on the public health of countries around the world. Common coronaviruses, including HCoV-229E, HCoV-OC43, etc., cause common infections[5]. However, the SARS-CoV virus, which triggers”atypical pneumonia”, can easily lead to severe acute respiratory distress syndrome because of its severe infection symptoms and then cause multiple organ failures, greatly damaging human health. As for the current globally SARS-CoV-2 novel coronavirus pandemic, its symptoms of the disease are relatively mild compared with SARS-CoV infection, but its infectivity is doubled and its incubation period is significantly prolonged. Thus, it has caused large-scale population infection, resulting in overwhelmed medical resources and heavy social and economic losses.[6]

Since respiratory viruses, especially influenza viruses and novel coronavirus, are easy to cause pandemics, we’re obliged to clarify the biological activities of these two extremely harmful viruses

after infecting the host, focusing on how the viruses evade the immune system, which will bring enlightenment to the prevention and control of infectious diseases.

2. Innate Immune Response of Evading Host

2.1 Antagonize the Antiviral Immune Response of Host Interferon

The innate immune system is a set of evolutionarily conserved cellular and chemical defense systems, which is significant to identify and limit pathogens and activate the adaptive immune response. The interferon response pathway is the most basic and crucial defense against broad-spectrum viruses, while influenza virus and novel coronavirus have evolved a series of means to antagonize interferon antiviral response.

The genome of influenza A virus consists of 8 single-stranded negative RNA gene fragments encoding 12 proteins, [7]NS1 is a nonstructural protein encoded by the smallest RNA fragment of IAV and NEP (NS mRNA), which is the main antagonist of the immune system during virus replication. NS1 directly interacts with the RIG-I receptor to inhibit the induction of IFN (a natural broad-spectrum antiviral protein in the innate immune system to inhibit virus replication). In addition, NS1 can also prevent the activation of interferon by interacting with PKR. NS1 and CPSF30 (lysis and polyadenylation specificity factor) can inhibit the processing of cell mRNA, thus inhibiting the antiviral activity of the host. NS1 also targets Kappa B kinase inhibitor and ultimately inhibits the NF-kB enhancer of activated B cell pathway to prevent the expression of antiviral genes in cells.[8]

PB1-F2 is the second protein encoded by ORF in the second fragment of the influenza virus genome, which is described as the promoter of apoptosis in the early stage. PB1-F2 can inhibit superoxide dismutase 1 (SOD1), which is related to the increase in reactive oxygen species (ROS) levels. It can also inhibit IFN reaction.[9]

M2 is a transmembrane protein, which can be immobilized in mitochondria of virus-infected cells and M2 overexpressed cells, accelerating the formation of MAVS autocorrelation and aggregation. M2 can prevent antiviral-related autophagy.[10]

Similar to the influenza virus playing an antagonistic role through its protein, SARS-CoV-2 in novel coronavirus have evolved various mechanisms to control this key antiviral response. Many proteins encoded by SARS-CoV-2 can antagonize IFN signal transduction, such as NS1, MDA-5, PKR, ORF3, ORF6, M protein, and nucleocapsid protein.[11] Secondly, novel coronavirus NSP8 protein can affect the expression and production of IFN-a/b by affecting the specific transcription factor IRF3/7.

When the host recognizes the virus antigen, MDA-5 and PKR begin to signal cascade, thus inducing the production of IFN-b. However, SARS-CoV-2 blocks the recognition function and activation ability of dsRNA sensors MDA5 and PKR by using endonuclease existing in the coronavirus complex. In addition, the double membrane vesicles (DMV) encoded by NSP3/4/6 encapsulate viral RNA to avoid the recognition of MDA5 and PKR sensors, so as to hide viral RNA and delay the antiviral response of interferon.

It has been reported that the M protein of SARS-CoV-2 interacts with TRAF3 to destroy the association of TRAF3-TBK1. [12] In addition, other studies have shown that the novel coronavirus receptor ACE2 is an interferon-stimulating gene, and SARS-CoV-2 may use the up-regulation of ACE2 driven by the interferon pathway to enhance infection.[13]

2.2 Killing of Evading Innate Immune Cells

In addition to interfering with innate immune signals through viral proteins, influenza A virus and novel coronavirus can also fight against innate immune cells.

Infection of monocytes with influenza virus will weaken their ability to mature into DCs.[14] Influenza A virus can also avoid NK reactions caused during infection. The glycosylation site of influenza virus HA protein gradually mutates. Free HA protein down receptor NKp46 with ζ chain regulates the zeta chain of NKp46 receptor, which leads to the damage of signal transduction, thus

reducing the cytotoxicity of NK cells.[16]

NK cell failure in SARS-CoV-2 patients increased. The expression of inhibiting receptor NKG2A on NK cells leads to its failure.[17] NKG2A receptor specifically originated from the HLA-I complex, which was involved in transmitting inhibitory signals of NK cells and preventing cell activation. The increased expression of this receptor was involved in the failure of NK cells to reduce their ability to virus infection. The possible mechanism is that some HLA-I molecules are used to up-regulate NKG2A in NK cells, which leads to the increase of the inhibitory signal and inhibits the toxicity of NK cells.[18] The above studies show that novel coronavirus can escape its killing by affecting the function of NK cells.

SARS-CoV-2 can infect macrophages, suggesting that SARS-CoV-2 can directly manipulate macrophages to evade immunity. MHC I were highly expressed in infected macrophages, but MHC II was lacking. [19] which impaired the function of macrophages and thus evaded its phagocytosis.

Similar to macrophages, dendritic cells play a decisive role in different stages of virus infection. When viruses invade alveolar cells, they can provide virus antigens or some dangerous stimulation signals to Naive T lymphocytes to provide activation signals, such as regulating adaptive immune response through cytokine secretion. Coronavirus mainly interferes with the function of DC in the following two ways: (1) Down-regulation of the expression of co-stimulating cell surface molecules on immature DC, which slows down the production of antibodies and increases the chance of virus replication. (2) The release of cytokines directly leads to the infiltration of the inflammatory environment in the infected site.

3. Adaptive Immune Response of Evading Host

3.1 Humoral Immune Response of Evading Host

Influenza viruses have many mechanisms to evade immune response of the host. The transcription of viral RNA is prone to errors, which leads to the wrong incorporation of nucleotides. Therefore, random mutations in the genome form viruses of similar species. After influenza virus infection and/or vaccination, mutations are actively selected from quasispecies of amino acid substitutions accumulated at HA antigenic sites. This phenomenon, known as antigen drift.[20]

Introducing a new influenza A virus subtype with unique antigenicity into the population is called antigenic transfer, which may lead to a pandemic outbreak. After the spread of zoonotic diseases, antigen-specific viruses can be introduced.

However, pandemics are caused by viruses that exchange gene fragments between human influenza A viruses. Other studies have shown that in addition to pigs, quails can also be used as a mixed container for newly emerging reclassified influenza A viruses. Moreover, fusion peptides, are unrecognized by antibodies because they are buried inside proteins. This evading strategy is also reflected in other viruses (such as human immunodeficiency virus (HIV).

The spike protein of SARS-CoV-2 in novel coronavirus is its main structural protein, which is embedded in the virus membrane in the form of homotrimer[23], recognizing human ACE2 as the receptor of virus entry and consisting of two subunits cleaved by host Furin.[24] The mutation of SARS-CoV-2 spike protein will significantly affect the conformational structure of spike protein, and then affect the binding affinity of neutralizing antibody, thus realizing the evasion of the humoral immune response.

SARS-CoV-2 has achieved strong humoral immune evading ability because of its extremely high mutation ability, especially many mutants evolved from the early stage of the pandemic. Virus mutation with different genes of has been recorded. The Omicron (B.1. 1.529) virus variant emerged, with significant clinical impact. The neutralizing activity of existing neutralizing antibodies against Omicron variants was detected, and the neutralizing titer was reduced by 17 to 22 times.[25]

3.2 Immune Response of Evading Host Cells

Neutralizing antibodies and CTLs were the main protective factors. CTLs are the key to

endowing immune memory and protecting viral pathogens. CTL kills infected cells after recognizing viral epitopes because they appear on the cell surface against the background of MHC-I. Certain positions of these epitopes are critical to the presentation of MHC-I, and mutations in these so-called anchoring residues may interfere with the binding of peptides to MHC-I.

Relatively more nonsynonymous mutations were observed in the CTL epitope region of NP, which indicated that the CTL epitope was under selection pressure. Amino acid substitution in CTL epitopes may affect the presentation of CTL epitopes. Amino acid substitution on the anchoring residue may result in complete loss of the epitope because it may no longer bind to the corresponding MHC Class I molecule. Mutations in TCR contact residues affect the recognition of specific T cells because epitopes no longer match the specificity of TCR. [26]

Influenza virus can evade the recognition of virus-specific CTL in the following ways: (1) Mutation of TCR contact residue of CTL epitope to prevent specific CTL from recognizing MHC class I complex; (2) Mutation of the anchoring residues of the CTL epitope; (3) Mutations affect proteasome processing of antigens or transport of antigens through TAP.

CTL showed high levels of cytotoxic effector molecules. Many HLAs with restricted CTL epitopes have been identified. The mutation of the virus epitope directly interferes with the recognition and killing of MHC-I restriction T cell antigen by CTL.[27] It is found that some mutations of SARS-CoV-2 are related to evading antibody response. SARS-CoV-2 may evade CTL monitoring through virus epitope mutation, which leads to the decrease of MHC-I binding and changes CTL response quantitatively and qualitatively. Viruses adopt various strategies to evade the immune response of $CD8^+$ T cells. ORF8 protein encoded by SARS-CoV-2 can down-regulate the surface expression of MHC-I molecule, and some reports suggest that the mutation of virus spike protein is related to evading neutralizing antibody response.

4. Conclusion and Perspective

The current situation of the virus pandemic still brings great challenges and burdens to the world public health security. Although many vaccines have been successfully developed, the virus remains prevalent and new mutations are still emerging. Understanding the interaction together with all links and main targets of the virus acting on the immune system can provide the theoretical basis for the development of targeted drugs. Meanwhile, clarifying how respiratory virus evades innate immune response is vital for grasping its pathogenicity and developing innovative treatment methods to limit virus infection. As for each invasion, we can develop specific antibody drugs. According to the characteristics of virus mutation, our traditional drugs may lead to ineffective treatment, so the drug development strategy should be changed to broad-spectrum antiviral drugs.

Although the influenza virus is one of the most deeply studied pathogens, the existing control scheme needs further improvement. The influenza vaccine must be updated regularly because the glycoprotein on the virus surface constantly undergoes antigen drift and antigen transfer. At present, influenza treatment is limited to neuraminidase inhibitors, so new drugs and vaccines are urgently needed.

In the process of co-evolution of host and virus, SARS-CoV-2 has been well adapted to avoid host innate immune response. Through this interaction, SARS-CoV-2 evades the host antiviral mechanism, hijacks the host innate immunity, and completes its life cycle.

At present, our progress in understanding the immune response and immune evading mechanism of coronavirus has also boosted many therapeutic approaches. These mechanisms include limiting virus entry and replication, promoting virus clearance, and inducing a highly effective antiviral immune response. Studying the mechanism may be helpful to enhance virus clearance and alleviate immunopathology.

Traditional design and screening of antiviral drugs usually target viral proteins, however, SARS-CoV-2 has a high mutation rate, which leads to the continuous production of many different strains. The immune evasion or drug-resistant protein changes of these strains may lead to ineffective treatment. Therefore, the development of new antiviral drugs against innate immune interaction provides great potential for alleviating virus infection and assisting the immune system

to eliminate virus infection.

By reviewing the interaction between virus and host innate immunity, this paper puts forward the following antiviral drug design strategies:

(1) Design a new IFN agonist, which has the same or better antiviral activity as IFN, but has less toxicity than IFN itself;

(2) Interferon stimulating genes targeting natural antiviral products;

(3) Targeting TLRs and NF-B pro-inflammatory pathway to prevent high inflammatory reaction of COVID-19 infection;κ

(4) Screening compounds that can target both viral protein and host innate immunity.

With people's in-depth understanding of the interaction between virus and host, the development of broad-spectrum antiviral drugs will play a guiding role in fighting respiratory viruses and regulating the host immune system. Clarifying how respiratory viruses evade the innate immune response is essential for understanding their pathogenicity and developing innovative treatments to limit viral infection. The discovery of key immune evading proteins paves the way for the development of more effective antiviral drugs against these viral proteins. In addition, the identification of key cellular antiviral pathways of respiratory virus infection is also helpful to develop strategies for these pathways to better prevent and treat epidemic respiratory virus infection.

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