The immunity and therapy of influenza virus infection

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Abstract

Influenza is a disease caused by influenza virus. There are three genera of influenza viruses: A, B and C. The influenza A and B viruses that routinely spread in people are responsible for seasonal flu epidemics each year. Influenza C virus infections cause a relatively mild respiratory illness and are not thought to cause epidemics. In this mini review, the immunity of influenza virus infection was briefly introduced. Both innate and adaptive immunity are involved in responding to viral infection. The binding of viral ligands to host sensors can induce multiple signaling pathways that activate cellular transcription factors controlling the expression of a diverse set of genes, which in turn coordinate both the innate and adaptive immune responses. The innate immune response can also activate the adaptive immune system through a process known as antigen presentation. Upon infection, cells induce early inflammatory proteins including type I interferon (IFN) and inflammatory cytokines. Type I IFNs are critical components of the innate antiviral response. Recent studies have clearly established that type I IFN has not only a critical role in the innate antiviral response but also in the pathogenicity of viral infection. For the treatment of influenza virus infection, the therapies that either directly target the influenza virus itself or instead may just offer relief to symptoms of the disease for the individual’s own immune system to recover from infection, including M2 protein inhibitors and neuraminidase inhibitors, biologics and immunobiologics, herbs, as well as Rhodiola and salidroside were also discussed.

Keywords: Immunity; Therapy; Influenza; Rhodiola; Salidroside

Introduction:

Influenza is a disease caused by influenza virus, a member of the Orthomyxoviridiae. Influenza spreads around the world in seasonal epidemics, resulting in the deaths about 250,000 people and up to millions every year [1]. There are three genera of influenza viruses: A, B and C. The influenza A and B viruses that routinely spread in people are responsible for seasonal flu epidemics each year. Influenza C virus infections cause a relatively mild respiratory illness and are not thought to cause epidemics. However, the emergence of a new and very different influenza virus to infect people can cause an influenza pandemic.

The influenza virus is spherical in shape and covered in an envelope made of a lipid bilayer. Inside the envelope is the helical symmetry capsid, which is the protein shell contains the genetic information. Viruses of this family contain 7 (influenza C) to 8 (influenza A and B) segments of linear gative-sense single stranded RNA, and each segment codes for a functionally important protein. In general, the influenza virus particles is 50 to 120 nm in diameter. There are some 500 distinct spike-like surface projections of the envelope each projecting 10 to 14 nm from the surface with some types (i.e. hemagglutinin esterase) densely dispersed over the surface, and with others (i.e. hemagglutinin (HA)) spaced widely apart. The major glycoprotein (HA) is interposed irregularly by clusters of neuraminidase (NA), with a ratio of HA to NA of about 4 to 1. Based on the antigenicity of these glycoproteins, influenza A viruses are further subdivided into sixteen H (H1-H16) and nine N (N1-N9) subtypes.

Immunology in viral infection

Viruses can modulate host responses through multiple mechanisms. Both innate and adaptive immunity are involved in responding to viral infection. The innate immune response, also known as the nonspecific immune system, is an important subsystem of the overall immune system that comprises of the cells and mechanisms that defend the host from infection by other organisms very early after infection, as well as for timely orchestration of virus-specific adaptive responses [2]. However, unlike
Mechanism Effective Against directly target the excelyticspublishers.com the disease for the individual’s own immune system works to recover from influenza virus infection. Treatments may either directly target the viruses.

Components of the host defense against invading pathogens, including proteins not only exert direct antiviral effects, but also induce maturation of the earliest cellular defense against viral infection and a potent stimulant has not only a critical role in the innate antiviral response but also in the antiviral response. Recent studies have clearly established that type I IFN of NFkB factors and the family of interferon regulatory factors (IRF). The stimulation of expression of these proteins: the well-characterized family of cytokines. Two families of transcriptional factors play a major role in the stimulation of expression of these proteins: the well-characterized family of NFkB factors and the family of interferon regulatory factors (IRF). The IRFs play a critical role in the induction of Type I IFN and chemokines as well as proteins mediating antiviral, antibacterial, and inflammatory responses. Type I IFNs are critical components of the innate antiviral response. Recent studies have clearly established that type I IFN has not only a critical role in the innate antiviral response but also in the pathogenicity of viral infection. It has been reported that IFN is the earliest cellular defense against viral infection and a potent stimulant for the subsequent adaptive immune response. Furthermore, these proteins not only exert direct antiviral effects, but also induce maturation of dendritic cells, recruitment of the immune cells to the sites of infection, and enhance the functions of macrophages, NK, T and B cells, and macrophages. In addition to interferon, the innate antiviral response also leads to expression of a large number of inflammatory cytokines. The increased understanding of the cross talk of IFN pathway with the other inflammatory cytokines, illustrates an increasing degree of complexity in the mechanism of IFN action. These regulatory networks are critical components of the host defense against invading pathogens, including viruses.

Treatment of influenza virus infection

A range of medications and therapies have been used in response to influenza virus infection. Treatments may either directly target the influenza virus itself; or instead they may just offer relief to symptoms of the disease for the individual’s own immune system works to recover from infection. These were summarized below and listed in Table 1.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Content</th>
<th>Effective Against</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>M2 protein inhibitors / neuraminidase inhibitors</td>
<td>amantadine, rimantadine, oseltamivir, zanamivir</td>
<td>Influenza A / Influenza A &amp; B viruses</td>
<td>M2 protein inhibitors /neuraminidase inhibitors</td>
</tr>
<tr>
<td>Biologics and immunobiologics</td>
<td>monoclonal antibodies, receptors, regulatory proteins, immune cells, and cytokines</td>
<td>Influenza virus</td>
<td>Activate/ suppress specific immune response and/or stimulate immune cells</td>
</tr>
<tr>
<td>Herbs</td>
<td>Ephedra, Withania somnifera ayurvedic, Paenio lactiflora Pall, Musa dohantia, Houta indigotica root, Echobaxia rugosula, and others</td>
<td>Influenza virus</td>
<td>directly target the influenza virus and/or through the immune response</td>
</tr>
<tr>
<td>Chemical from Rhodiol</td>
<td>salidroside</td>
<td>Influenza A &amp; B viruses</td>
<td>directly target the influenza virus and/or through the immune response</td>
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M2 protein inhibitors and neuraminidase inhibitors

Presently, the two classes of FDA approved antiviral drugs used against influenza are M2 protein inhibitors and neuraminidase inhibitors (adamantane derivatives)[8]. The M2 protein of influenza virus is a small integral membrane that functions as a proton channel and is essential to viral replication. For M2 protein inhibitors, both rimantadine (trade name Flumadine) and the similar drug amantadine (trade name Symmetrel) are derivatives of adamantane. Amantadine and rimantadine act by preventing the uncoating of the virus’s protective shells, which are the envelope and capsid. They inhibit viral uncoating by blocking the proton channel activity of the influenza A viral M2 protein. Limitations of the adamantanes include no activity against influenza B, toxicity in the elderly, and the development of resistance. For example, resistance to rimantadine can occur as a result of amino acid substitutions at certain locations in the transmembrane region of M2. This prevents binding of the antiviral to the channel. The CDC recommended against using M2 inhibitors during the 2005–06 and 2009 influenza seasons due to high levels of drug resistance [9, 10]. Bothamantadine and rimantadine are no longer recommended to prescribe for treatment of the influenza. As less toxic and more effective, neuraminidase inhibitors are currently preferred for flu virus infections[11]. Antiviral drugs such as oseltamivir (trade name Tamiflu) and zanamivir (trade name Relenza) are neuraminidase inhibitors that are designed to halt the spread of the virus in the body [12]. These drugs are often effective against both influenza A and B [13]. The ability of neuraminidase to break the bond with sialic acid makes it possible for the virus to disseminate in the respiratory tract in multiple ways. It facilitates the release of progeny virus from infected host cells and also prevents newly formed viral particles from aggregating once they have left the host cell. Because it also cleaves the sialic acid found in respiratory tract mucus, neuraminidase helps the virus pass through sialic acid-rich mucosal secretions that would otherwise protect epithelial cells of the respiratory tract. Since the neuraminidase molecule are critical to the spread of the influenza virus, an agent that binds to them could prevent the cycle of viral proliferation and clinical symptoms that follows influenza infection [14]. This is the concept of neuraminidase inhibition. However, different strains of influenza viruses have differing degrees of resistance against these antivirals, and it is impossible to predict what degree of resistance a future pandemic strain might have [15]. Like the development of bacterial antibiotic resistance, drug resistance can result from over-use of these drugs.

Biologics and immunobiologics

Biologics and immunobiologics including monoclonal antibodies, receptors, regulatory proteins, immune cells, and cytokines that designed to activate/suppress the specific immune response to virus particle or antigens. Generally, biologics stimulate immune cells including lymphocytes, macrophages, and/or antigen presenting cells, to drive an immune response towards cytotoxic effects against the virus but rather than target viral replication pathway like anti-viral drugs. A number of biologics and immunobiologics have been investigated for treatment of infection caused by viruses. The suppressors of cytokine signaling (SOCS) proteins are key negative regulators of the cytokine networks responsible for an adequate and efficient innate and adaptive immune response. Suppressor of cytokine signaling 4 (SOCS4) was suggested to protect against severe cytokine storm and enhances viral clearance during influenza infection [16]. Influenza virus infection was predicted to suppress special AT-rich sequence-binding protein-1 (SATB1) activity in dendritic cells. Suppression of the transcription factor SATB1 was also predicted as a novel effect of influenza-mediated immune antagonism, and validated experimentally [17]. Lymphocytic T-cell immune modulator inhibits viral growth in the murine model of influenza has been proposed to test the effects of prophylactic and therapeutic biologics [18]. Interferon stimulated genes are specifically suppressed in influenza virus-infected cells. Based on experiments in mice that suggested that type I interferons could enhance the effectiveness of influenza vaccines in mice, interferons have also been investigated as adjuvants to enhance to effectiveness of...
influenza vaccines [19]. However, a clinical trial in 2008 found that oral dosing of elderly patients with IFN-α actually reduced their immune response to an influenza vaccine [20].

Herbs

Herbs have been used not only for food but also for medicinal purposes for centuries across the world in every civilization. As treating viral disease with herb or plant derived compound which is accessible and do not require laborious pharmaceutical synthesis seems highly attractive, several herbs have been proposed to show antiviral activities and attempts have been made to isolate their active components. Ephedra,Withania somnifera ayurvedic, Paeciona lactiflora Pall. Mosla diaphan, Isatis indigota root and Elsholtzia rugulosahave been suggested to demonstrate promising anti-influenza activity [21-26]. Recently, a review discussing herbal and alternative medicines in influenza treatment details evidence suggesting that N-acetylcysteine, elderberry, or a combination of Eleutherococcus senticosus and Andrographis paniculata may help to shorten the course of influenza infection [27]. The limited evidence including animal or in vitro studies suggested possible benefit from vitamin C, DHEA, high lacticferinray he protein, Echinacea spp., Panax quinqufolium, Larix occidentalisarabinogalactans, elenolic acid (a constituent of olive leaf extract), Astragalus membranaceus, and Isatis tinctoria or Isatis indigota in influenza infection. However, another review by Guo et al. assessed the quality of evidence for alternative influenza treatments and concluded that there was “no compelling evidence” that any of these treatments were effective [28]. Moreover, the available data on these products is particularly weak, with trials in this area suffering from many shortcomings, such as being small and poorly-designed and not testing for adverse effects. Therefore, though some of the studies reported some benefits from use of antiviral herbal medicines, negative findings and risks of herb-drug interaction may also remained. There remains a need for larger, stringently designed, randomized clinical trials to provide conclusive evidence of their efficacy.

Chemical (salidroside) fromRhodiola

Rhodiola rosea (L.) is a precious traditional phytomedicine of the Rodiula genus that has grown in high altitudes and cold environments in Tibet and China. Rhodiola rosea extract was reported to exhibit anti-inflammatory effects and protect muscle tissue during exercise [29]. Animal tests have suggested a variety of beneficial effects of Rhodiola rosea extract (RRE) [30]. Recently, the efficacy of RRE in the treatment of inflammatory conditions was revealed through rat models of carrageenan-induced paw edema, formaldehyde-induced arthritis, and nystatin-induced paw edema [31].RRE was reported to exhibit inhibitory effects against acute and subacute inflammation at a dose of 250 mg/kg body weight. At 200 mg/kg daily, RRE also significantly decreased blood glucose and increased levels of reduced glutathione and the activities of glutathione reductase, glutathione S-transferase, glutathione peroxidase, catalase, and superoxide dismutase in the livers of mice [32].

Rhodiola rosea contains a variety of biologically active compounds that may contribute to its effects [33]. Among these compounds, rhodioloside (salidroside), a glycoside compound, and the class of rosavins including rosavin, rosarin, and rosin, which are mainly found in plant rhizomes [34], have demonstrated therapeutic effects. Among its active components, salidroside is the most widely investigated compound in Rhodiola rosea. Several studies have also suggested that salidroside is likely to be the most active component of Rhodiola rosea [35]. Salidroside was reported to dose-dependently restore the H₂O₂-induced loss of mitochondrial membrane potential and elevate intracellular calcium levels [36].

More recently, a study suggested that salidroside possesses antiviral activity against coxsackievirus B3 and may represent a potential therapeutic agent for viral myocarditis [37]. Based on the finding that salidroside from Rhodiola rosea significantly increased the mRNA expression of IL-10 and IFN-γ, but decreased tumour necrosis factor (TNF-α) and IL-2 mRNA expression, Wang et al. suggested that salidroside may prevent inflammatory responses and strengthen host resistance against virus infection by enhancing the expression of IL-10 and IFN-γ in heart tissues, and suppress myocardial apoptosis and myocardial dysfunction by inhibiting TNF-α and IL-2 mRNA expression [37]. However, we found that salidroside had immunomodulatory effects on both Th1 cytokines, i.e. IL-2 and IFN-γ, and Th2 cytokines, i.e. IL-4 and IL-10[38]. Our study suggested that increased in vivo secretion of both Th1 (IL-2 and IFN-γ) and Th2 (IL-4 and IL-10) cytokines can be achieved with salidroside treatment [38]. Interestingly, in our recent study using Rhodiola as a complementary therapy for chronic obstructive pulmonary disease (COPD) patients, our results showed that the serum levels of IL-2, IL-10, and IFN-γ in COPD patients were significantly higher than levels in non-COPD controls (p=0.05) [39]. Moreover, Rhodiola treatment in COPD patients was also shown to decrease the IFN-γ levels and CD8+ cell counts in blood but significantly increased the numbers of CD4+CD25+FOXP3+ and CD4+CD25+CD45+FOXP3+ cells. These results suggested that Rhodiola treatment had selected anti inflammatio effects [39]. Recently, the antiviral activity of salidroside and Rhodiola against influenza virus in vitro has been investigated in our lab. The results demonstrated salidroside from Rhodiola has low cytotoxicity (CC50:8.7mg/ml) and dose-dependent in hibitory effects on pandemic influenza A (H1N1) and B viruses replication in vitro(unpublished data). Further, salidroside exhibit more potent anti-influenza activity than oseltamivir in a bioassay platform (unpublished data). Noteworthy, the usage of Rhodiola and salidroside ininfluenza has been patented (No. 1419699,Taiwan, R.O.C). It is interesting to study the detailed anti-influenza virus mechanism of salidroside further.

Conclusions

There is emerging needs to develop therapeutics that can elicit more potent and protective immune responses, as well as reduce the impact of future pandemic outbreaks. To achieve this goal, new techniques and reliable animal models would be very helpful. For example, functional genomic analyses with microarray assays provide valuable knowledge about which components of the innate immune response the host activates to clear the pathogens, as well as the strategies the virus uses to defeat the immune response. Systemic approaches like these can identify innate immune signatures that may be used to assess the strength of the adaptive immune response and predict protective immunity after infection. The influenza mouse models allow for highly reproducible initial screening of therapeutic sufficiently and safely. Hopefully, the new and better strategies used to improve the clinical therapy of influenza infections can be developed in the near future.

References:

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