Innate Immune Response in Respiratory System: A Double-edged Sword Against Virus Infection

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Introduction

Respiratory virus infection, as a leading cause of newly emerging or re-emerging infectious diseases, is undoubtedly a primary threat for global public health. Nevertheless, among various respiratory viruses, namely adenovirus, influenza virus, rhinovirus, respiratory syncytial virus as well as coronavirus, most of them cause self-limited diseases with mild symptoms. However, a few may progress into severe morbidity and even mortality. For example, α-coronavirus HCoV-229E, HCoV-NL63 and β-coronavirus HCoV-OC43, HCoV-HKU1 only cause mild common cold, whereas the β-coronavirus SARS-CoV, MERS-CoV, and SARS-CoV-2 could result in fatal infection and pose great threat to human public health with global pandemics.[1] Similar observations exist for influenza viruses, as low pathogenic seasonal influenza (H3N2) versus high pathogenic avian influenza (H5N1 and H7N9) and 1918 pandemic influenza (H1N1). The mechanisms underlying the nature of different respiratory viral infections should be urgently explored to develop effective intervention approaches.

Innate immune responses to respiratory viruses: an early and effective interferon responses is critical for containment of viral replication

As the first line of defense, respiratory innate immune system presents elaborate mechanisms against invading respiratory viruses. Innate immune cells are the first cells responding to viruses in respiratory tract, namely, macrophages, neutrophils, monocytic, dendritic cells, natural killer cells as well as innate lymphoid cells, containing the viruses and protecting the airway epithelium. In addition, upper respiratory tract represents a mucosal compartment which is relatively separated from systemic compartment, and as a niche exempted from systemic adaptive immunity, therefore, the fine tuning of respiratory innate immune responses is critical to determine the outcomes of viral infection.

Innate immune responses will be activated when viral RNA or their conserved components called pathogen associated molecular patterns (PAMPs) are recognized by host pathogen recognition receptors (PRRs), such as Toll-like receptors (TLRs), retinoic acid-inducible gene I (RIG-I) receptors, and NOD-like receptors (NLRs), triggers downstream transduction signaling including interferon regulatory factor 3 (IRF3) and nuclear factor kappa-light chain-enhancer of activated B cells (NF-κB), leading to production and release of a variety of interferons and pro-inflammatory mediators such as cytokines and chemokines. Early and effective interferon responses will restrain viral replication and even clear viruses, thereby tune down the virus-driving innate immune responses and play as a negative feedback mechanism.[2] Elevated cytokines or chemokines will recruit inflammatory immune cells including monocytes, macrophages, dendritic cells, and neutrophils, subsequently adaptive responses will be elicited and play a critical role in the clearance of viral pathogens if the infection persists. All those responses are well orchestrated and balanced, consequently, the majority of respiratory viral infections are cleared by innate immune responses in the absence of immune pathogenesis, and only cause a self-limited disease [Figure 1 upper panel]. Overall, an early and effective interferon responses is critical for containment of viral replication and ensures a proper innate immune response, delayed or insufficient interferon responses could result in the failure to keep virus in check and thereafter, persistent viral replication will drive the excessive inflammatory responses and lead to the occurrence of severe morbidity and even mortality infection.

Imbalanced interferon and inflammatory responses result in high pathogenic respiratory virus infection

The unprecedented global pandemic COVID-19 triggered by SARS-CoV-2 continues to threat global public health. Several researches have tried to characterize the infections which developed aggravated clinical symptoms and even death. A highly significant feature is the cytokine release syndrome (CRS), patients who developed into critical status commonly display an uncontrolled and life-threatening host immune responses concomitant with markedly elevated serum proinflammatory cytokines and chemokines, such as IL-6, IL-8, TNF-α, CCL2, CCL5, and CXCL10. Those factors precipitate and sustain the aberrant systemic or local inflammatory responses, mediating excessive recruitment of immune cells into respiratory tract, lung or other organs, which in turn will lead to acute respiratory distress syndrome (ARDS) and multiple organ failure, represents a major factor contributing to mortality.[3] In addition, the second distinct feature observed in severe patients, appears a highly impaired interferon type I response, which is characterized by no IFN-β and low IFN-α production and activity.[4] Growing evidences demonstrated that SARS-CoV-2 perturbs host virus clearance by interfering or delaying interferon
activation to evade anti-virus immune responses. For example, blocking IRF3/7 or RIG-I pathway on different levels leads to inefficient production of interferons and impaired antiviral response [Figure 1 down panel]. Similar to highly pathogenic coronavirus, a cohort study on a highly pathogenic influenza revealed that hypercytokinemia as well as interferon dysfunction was associated with the fatal prognosis of H7N9 infections. In addition, study demonstrates that early administration of type I interferon kappa (IFN-k) profoundly protects mice from fetal influenza infection. Altogether, an imbalanced interferon and inflammatory responses was observed in highly pathogenic coronavirus and influenza virus infection, the early administration of type I interferon could gear back the imbalance and thereby turn down the pathogenesis.

**Strengthening the interferon responses and dampening the excessive inflammatory responses: an optimized strategy against respiratory virus infection**

The viral evolution has developed multiple escaping mechanisms from interferon control, which practically results in the imbalanced innate immune responses of low or delayed interferon and excessive inflammatory responses. Therefore, strengthening the early interferon responses is highly important for treatment of respiratory viral infection, which will reconstitute the negative feedback pathway and restructure the balance between interferon and inflammatory responses. However, in clinical practice, patient admitted into hospital usually have developed hypercytokinemia. As we described above, excessive inflammatory responses are the direct cause of immune pathogenesis, the suppression of inflammation is equivalent critical to the containment of viral replication by interferon. Furthermore, several studies demonstrated that interferons can be significant drivers of pathological inflammatory responses in SARS-CoV-2 mouse model. Thus, the inflammation suppressor has to be coupled upon the application of interferon. We have identified a potent anti-inflammatory natural cytokine IL-37 and proved its strong correlation in dampening inflammation and consequently favorable prognosis in SARS-CoV-2 infections. We have also evaluated the safety and efficacy of a combined treatment with IFN-k and anti-inflammatory protein Trefoil Factor 2 (TFF2) in COVID-19 patients, and verified the combination can significantly promote clinical outcomes. In conclusion, a combination of interferon and inflammation suppressor, such as TFF2 and IL-37, is a rationalized regimen for treatment of respiratory viral infection, this regimen targets both viral replication and immune pathogenesis and thereby preferentially reconstitute the immune balance and will be likely to facilitate a favorable clinical outcome.

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**Conflicts of Interest**

None.
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