Open Access Journal [doi: 10.46683/jmvi.2021.34] Review Article

Journal of Molecular Virology and Immunology

An Overview of Innate Immune Response to Human Rhinovirus Infection

Human Rhinovirus Enfeksiyonuna Doğuştan Gelen Bağışıklık Tepkisine Genel Bakış

Shuaibu Abdullahi HUDU[1] [ID]

[1]Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, Nigeria.

Article Info: Received: 25.05.2021. Accepted: 11.06.2021.
Correspondence: Shuaibu Abdullahi Hudu; PhD, Department of Medical Microbiology and Parasitology, Faculty of Basic Clinical Sciences, College of Health Sciences, Usmanu Danfodiyo University, Sokoto, 840232 Sokoto State, Nigeria. E-mail: hudu.shuaibu@udusok.edu.ng

Abstract

Human rhinoviruses (HRV) are mainly associated with catarrh or the common cold and quite possibly cause one of the most unavoidable diseases in human beings. Although the HRV infections of the upper respiratory tract are generally somewhat harmless, there is increasing proof that HRV pave the way for more hazardous infections, promote asthmatic intensifications, and lead to severe diseases in the lower respiratory tract. Respiratory tract epithelial cells are the essential targets for rhinovirus and other respiratory pathogens. In the presence of rhinovirus, respiratory tract epithelial cells mount both supportive of provocative reactions and antiviral natural invulnerable reactions to clear the infection effectively. A portion of antiviral reactions include the expression of interferons (IFNs) and endoplasmic reticulum stress-actuated unfolded protein reaction and autophagy. In patients with chronic (*persistent*) lung diseases, these reactions may be either imperfect or incited in overabundance prompting insufficient getting free from infection and supported aggravation. In this review, components hidden behind innate antiviral invulnerability and the dysregulation of a portion of these instruments will be examined in patients with chronic lung diseases.

Keywords: Human rhinovirus, Catarrh, Common cold, Immunology.

Özet

İnsan rinovirusları (HRV) esas olarak nezle veya soğuk algınlığı ile ilişkilidir ve büyük olasılıkla insanlarda en kaçınılmaz hastalıklardan birine neden olurlar. Üst solunum yollarının HRV enfeksiyonları genellikle bir şekilde zararsız olsa da HRV'nin daha tehlikeli enfeksiyonların önünü açtığına, astım şiddetini artırdığına ve alt solunum yollarında ciddi hastalıklara yol açtığına dair artan kanıtlar vardır. Solunum yolu epitel hücreleri, rinovirus ve diğer solunum yolu patojenleri için temel hedeflerdir. Rinovirus varlığında, solunum yolu epitel hücreleri, enfeksiyonu etkili bir şekilde temizlemek için hem provokatif reaksiyonları hem de antiviral doğal bağışıklığın koruyucu reaksiyonlarını destekler. Antiviral reaksiyonların bir kısmı, interferonların (IFN) ekspresyonunu ve endoplazmik retikulum stresle harekete geçen katlanmamış (*unfolded*) protein reaksiyonunu ve otofajiyi içerir. Kronik (*persistan*) akciğer hastalığı olan hastalarda, bu reaksiyonlar yetersiz olabileceği gibi aşırı reaksiyonlara da neden olabilir, bu durum enfeksiyonun temizlenmesini güçleştirirken ve alevlenmesini destekler. Bu derlemede, kronik akciğer hastalığı olan hastalarda doğuştan gelen antiviral yanıttaki savunma açıklarının arkasına gizlenmiş bileşenler ve bu araçların bir kısmının düzensizliği (*disregülasyonu*) incelenecektir.

Anahtar Kelimeler: İnsan rinovirusu, Nezle, Soğuk algınlığı, İmmünoloji.

Introduction

Human rhinoviruses (HRV) are the most widely recognized viral agents of infection in people and constitute the major cause of the common cold. A rhinovirus infection replicates optimally at a temperatures between 33 and 35°C, which is found in the nose [1]. Rhinoviruses belong to the genus of *Enterovirus* in the family *Picornaviridae* [2]. The induction of proinflammatory cytokines and subsequent recruitment and activation of both innate and adaptive immune cells following the infection of respiratory epithelial cells by the virus are important phases of host response against the virus, which can also be involved in the exacerbation of both chronic obstructive pulmonary disease (COPD) and asthma. The detection of pathogen-associated molecular patterns (PAMPs) by specific host cell receptors triggers pathogen-host interactions. Pattern recognition receptors (PRRs), which are expressed in innate immune cells, play a pivotal role in the specific identification of microbial pathogens and activation of intrinsic signaling pathways. The subsequent production of various cytokines and chemokines result in innate immune responses, such as inflammatory response constituting the foundation to eliminate infective pathogens. The innate immune system helps to direct adaptive immune responses to fight against pathogens [3].

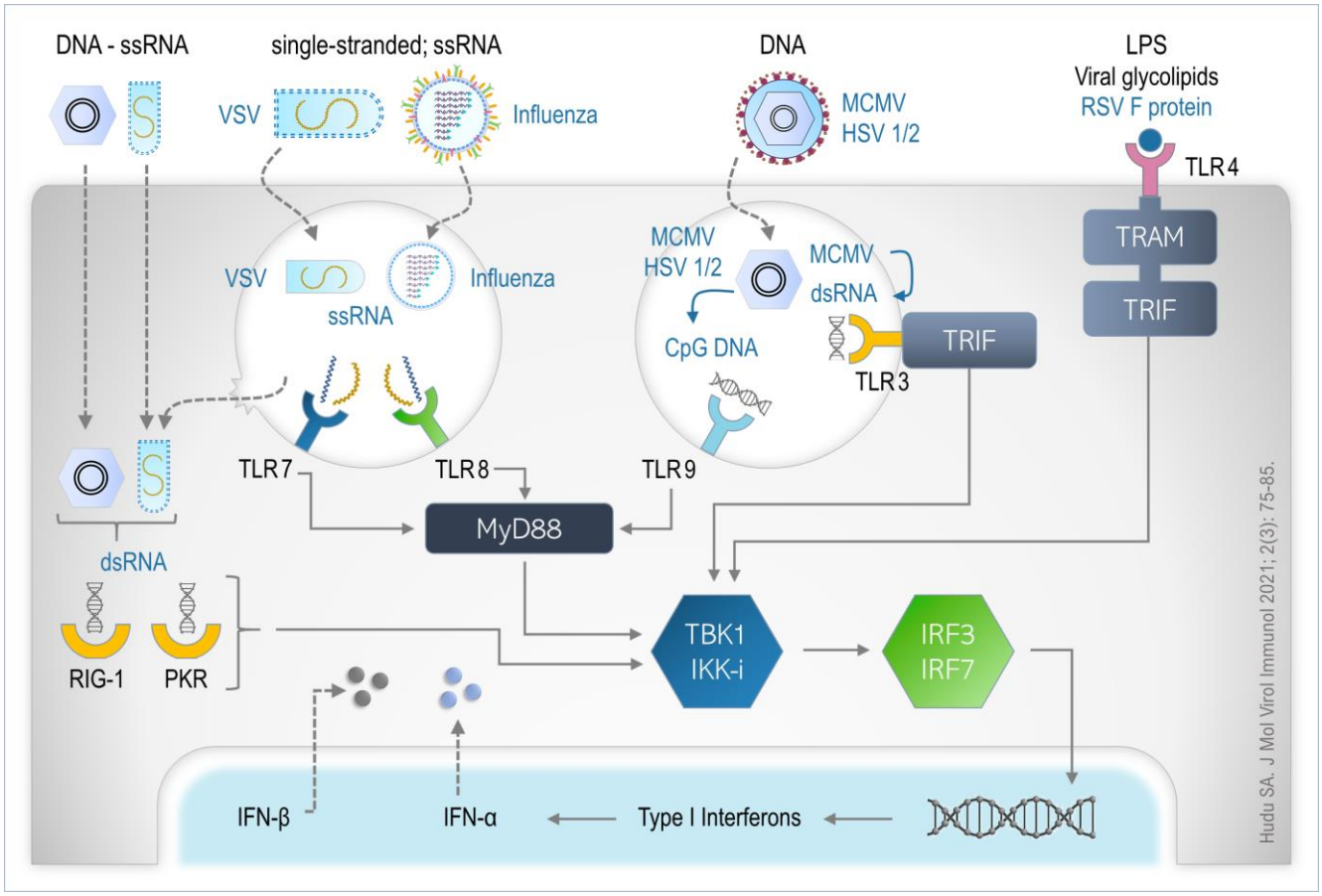

Figure 1. Pathways involved in type I interferon (IFN) production. Toll-like receptors (TLRs) recognize viruses located in the endocytic compartment. ssRNA (single-stranded ribonucleic acid) viruses are recognized by TLR7 and TLR8, and double-stranded ribonucleic acid (dsRNA) viruses are recognized by TLR3. RIG-1 and dsRNA-dependent protein kinase R (PKR) recognize dsRNA produced by viruses in the cytoplasm compartment. Adapted from reference [4]. Other abbreviations: MyD88 [Myeloid differentiation factor 88], TRIF [TIR (Toll/interleukin-1 receptor)-domain-containing adapter-inducing interferon-β], TRAM [TRIF- related adaptor molecule], TBK [TANK-binding kinase], IKK-I [inducible IκB kinase], IRF [interferon-regulatory-factor], RSV [respiratory syncytial virus], HSV [herpes simplex virus], VSV [vesicular stomatitis virus], and MCMV [murine cytomegalovirus]

In addition to the activation of host immune pathways, the excessive production of inflammatory cytokines by activated PRRs can pose extensive damage to the infected cell and tissue. PPRs can identify pathogen specific components, such as viral antigens, lipopolysaccharides of bacteria, and genomes of infectious agents. Toll-like receptors (TLRs), retinoic acid-inducible gene (RIG)-I-like receptors (*RIG-1-like receptor* - RLR family) and nucleotide-binding oligomerization domain (NOD)-like receptors (*NOD-like receptor* - NLR family) and DNA (*deoxyribonucleic acid*) receptors (cytosolic sensors for DNA) constitute common platforms of PRR as shown in Figure 1 [5]. Signaling pathways including type I interferon (IFN) response, natural killer kappa B (NK-κB) and mitogen-activated protein kinases (MAPKs) are activated following endogenous stimuli or pathogen interactions with PRR, leading to the induction of proinflammatory and antiviral responses [6]. Novel therapeutics for the treatment of diseases associated with respiratory viruses can be achieved through the complete understanding of virus recognition and subsequent cell signaling mechanisms leading to the production of pro-inflammatory cytokines and IFNs [7]. New therapeutic agents can also be developed with the deeper understanding of persistent inflammation mechanisms.

Transmembrane sensors

TLRs are type I transmembrane proteins that are associated with either cell membrane or intracellular vesicles. The secretion of type I IFNs (α and β), as well as proinflammatory cytokines and chemokines [tumor necrosis factor-α, interleukin (IL)-1, IL-6, and IL-8] is initiated upon the detection of PAMPs including various viral components by TLRs leading to the direct elimination of pathogens through the recruitment of immune cells, such as neutrophils and macrophages and the stimulation of IFN-related genes or induction of the adaptive branch of the immune system [6,8]. In addition, viral infections are dominantly detected by the innate immune system through nucleic acid identification, but several studies have also demonstrated that the recognition of certain viruses occurs in nucleic acid in an independent manner [9-11]. TLRs 3, 7, 8 and 9 reside almost exclusively in intracellular compartments, such as endosomes, which can recognize nucleic acid of viral pathogens. The TLR3 recognition of double-stranded ribonucleic acid (dsRNA), an intermediate product produced during the replication of most viruses in the cell, induces the production of proinflammatory cytokines and chemokines [12], as well as type I IFN (IFN-β) antiviral response induced through the activation of nuclease factor-κB (NF-κB) [13,14]. Hewson et al. [15] showed that the HRV infection of human bronchial epithelial cells induced TLR3 expression using the BEAS-2B cell-line. In that study, TLR3 was also found as a potent inducer of antiviral response (IFN-β) against rhinovirus by strengthening the innate immune arm of host response. The deficient expression of TLR3 could have a link to deficient IFN-β responses and increased susceptibility to HRV infections in asthmatics. On the other hand, TLR7 and TLR8 are activated via interaction with single-stranded RNA (ssRNA). This type of activation may be an important mechanism for enveloped viruses which access cytosol through endosomes [6]. Kurt-Jones et al. [10] demonstrated that the recognition of the fusion protein of human respiratory syncytial virus (RSV) through TLR4 mediated innate immune response against the virus. RSV persisted longer in the lungs of TLR4-deficient mice with higher viral propagation compared with normal healthy individuals, which also showed a lower level of virus elimination due to reduced monocyte infiltration and IL-12 production. The activation of TLR2 through the sensing of the hemagglutinin protein of measles virus (MV) not only induce proinflammatory cytokines, such as IL-6 but also upregulate the expression of the MV receptor (CD150), which contributes to the spread and pathogenicity of the virus [11]. The activation of TLR2 following interaction with viral fusion protein has also been reported for glycoprotein B of human cytomegalovirus [9]. Studies have shown that the interaction of HRV with intercellular adhesion molecule 1 (ICAM-1) plays an important role in cytokine production in addition to viral entry and replication [16]. The p38 kinase, a serine-threonine kinase, is a member of the MAPK superfamily that is activated through

phosphorylation by the direct interaction of virus with the cell during an early HRV infection, independent of virus replication and protein production. This is reported to result in the activation of the NF-κB transcription pathway and peak cytokine expression during the early hours of post-infection [17]. Wang et al. [18] showed that immunoregulatory protein tyrosine kinase, Syk, which is the downstream of the ICAM-1 signaling pathway, plays a crucial role in the activation of p38 MAPK and inflammatory cytokine production before virus replication [18]. Therefore, ICAM-1 signal transduction initiates proinflammatory response upon HRV interaction.

Cytosolic receptors

RIG-1 and melanoma differentiation-associated protein 5 (MDA5) are RNA helicases located in cytosol and play critical antiviral roles in the elimination of replicating the virus through the identification of dsRNA in cell cytoplasm [4]. Yoneyama et al. [19] showed that the production of IFNα/β was induced following the Newcastle disease virus infection and dsRNA transfection. The critical regulators of innate immune response including transcription factors NF-κB and IRF-3 are activated in response to the interaction of the RNA helicase domain with dsRNA through the caspase recruitment domain. DsRNA is a main virus genome produced in the cytosol of HRV-infected cells upon receptor-mediated endocytosis and subsequent virus conformational changes and genome injection into the cytoplasm and acts as an important mediator of innate response stimulation [20]. However, the recognition of dsRNA by these PRRs appears to be specific to cell and virus types. For instance, Wang et al. [20] demonstrated that the maximum sensing of rhinovirus dsRNA and the subsequent IFN response are achieved through MDA5 and TLR3 but not RIG-I using both the BEAS-2B human bronchial epithelial cell line and primary tracheal epithelial cells isolated from lung transplant donors. Further experiments showed that IRF3 was used by both PRRs as a common downstream intermediate to regulate the expression of IFN. In that study, both major and minor serotype groups showed similar immune responses, which is in agreement with the gene expression patterns of both minor and major HRV groups reported in a study by Chen et al. [21]. In contrast, the infection of the A549 cell line by RSV quickly induced the expression of both RIG-I and TLR3, further demonstrating virus-type specific recognition by PRRs. The binding of the RSV genome to RIG-I, as a primary sensor, induced early antiviral response through the activation of IRF3 and NF-κB. Here, TLR3 expression is secondary to the RIG-I pathway, which only affects late-phase gene expression [22]. Although other studies have shown that rhinovirus group A infections of primary bronchial epithelial cells induce a high level of type I IFN and a variety of IFN-stimulated genes (ISGs) [20,21], Kotla et al. reported that the infection of the A549 cell line with the HRV group B strain (HRV14) failed to elevate type I IFN [23]. The low level of IFN-β mRNA in that study can be explained by the impaired activation of IRF3 in the presence of activated NF-κB and ATF-2, which seems to contradict intact innate immunity in virus group A. MDA5 is degraded in poliovirus-infected cells, as well as in rhinovirus type 1a, although it is stable in rhinovirus type 16 and 14 [23,24]. A recent in-depth study by Slater et al. [7] demonstrated the role of RIG-1 in addition to TLR-3 and MDA5 in the recognition of major and minor HRV groups and innate response based on both in vitro and in vivo models. The authors showed that the endosomal sensing of HRV through TLR-3 subsequently induced cytoplasmic RIG-I and MDA5 expressions early in the infection to reach maximal IFN and pro-inflammatory cytokine induction.

Inflammasome

Inflammasome is another type of cytoplasmic PRRs, which regulates the activation of the proinflammatory cytokines, including pro-IL-1β and pro-IL-18 through the conversion of procaspase-1 to caspase-1. They recognize pathogen components and danger-associated molecular patterns. They are multiplex molecules consisting of the NLR family, apoptosis-associated speck-like protein containing a CARD-caspase recruitment domain, and apoptotic protease-activating factor-1 (Apaf-1) [25]. Several studies have demonstrated that inflammasome activation is regulated by the concentration of intracellular

ions. The perturbation of cell membrane and the subsequent drop in cytosolic potassium levels by some microbial toxins induce NLRP3 inflammasome activation [26]. The ion homeostasis of cells can be modulated by viroporins, a group of proteins commonly produced by respiratory viruses. A wide range of stimuli, such as ultraviolet irradiation and virus infections activate NLRP3 through an increase in the intracellular Ca^{2+} concentration. In 2013, Triantafilou et al. [27] demonstrated that the infection of primary bronchial cells by rhinovirus activated NLRP3 and NLRC5 inflammasomes, and caspase 1, and led to IL-1β secretion. Viroporin 2B disturbed the homeostasis of calcium by targeting the Golgi complex and endoplasmic reticulum and reduced Ca^{2+} in these organelles. The detection of NLRP3 and NLRC5 inflammasome activation may explain stronger inflammation and exacerbations in the respiratory tract [27].

Viperin is the most induced protein in the class of antivirals. The antiviral activity of viperin has been reported against several viruses [28]. Viral proteins required for viral assembly and maturation are inhibited by viperin, which is highly elevated in HRV infections [21]. In a previous study, there was a significant correlation between the mRNA level of viperin and the symptomatic period of the HRV infection [28]. Viperin induction was dependent on time and HRV replication. Induction started at 12 hours after infection and significantly increased at 48 hours [28]. The role of viperin may be more prominent in the late stage of the infection, and this protein may act as a member of antiviral response to HRV infections [28]. Human β-defensin 2 and inducible nitric oxide synthase are antiviral proteins that have been shown to be induced in HRV in both in vitro and in vivo studies [29,30]. Phospholipid scramblase 1, which plays an indirect role in antiviral response, is also induced in HRV infections [31].

Interferon response

IFN was first discovered more than half a century ago as a factor released by the chick chorioallantoic membrane challenged by influenza virus [32]. There are three classes of IFNs designated as type I (13 α subtypes, β, κ, ε, ο, τ and δ), II (IFNγ), and III (IFNλ) [33]. NF-κB, IRF-3, and ATF-2-c-Jun are important transcription factors in the expression regulation of type I IFN [19]. Type I IFNs are important components of antiviral response with direct antiviral effects on infected and adjacent cells. It has been shown that more than 300 ISGs are activated following the interaction of type I IFN with the corresponding receptor. However, small numbers of ISGs are directly involved in antiviral response [34]. The attenuated induction of the IFN-induced genes related to apoptosis, innate immunity, and antigen processing, especially in the early stage of viral infections may be a reason for failure in virus elimination, resulting in severe cases of the disease. On the other hand, the pathogenicity of different virus strains can be determined by the early induction of ISGs [35].

Type I IFNs (α/β) play an important role in mounting a robust antiviral response of cells through several ISG-mediated pathways, including protein kinase R (PKR), Mx GTPase pathway (myxovirus resistance 1), 2′,5′-oligoadenylte-synthetase-directed ribonuclease L (RNaseL) pathway and ISG15 ubiquitin-like pathway as shown in Figure 2 and controlling virus propagation in all steps including the inhibition of virus transcription and translation [33]. An in vitro study using primary respiratory tract epithelial cells showed that IFN-α and IFN-γ were not induced in HRV-infected cells, but IFN-β was detected in HRV16-infected cells [21]. The detection of phosphorylated signal transducer and activator of transcription 1 demonstrated the role of IFN in the induction of intracellular signaling, but the IFN-β signaling pathway only had a partial effect on the expression of genes in HRV-infected cells [21]. In that study, the importance of IFN-β in antiviral gene expression was consistent with the increase of HRV production in asthmatic patients with deficient cell antiviral response, including impaired RV-induced IFN-β production [21].

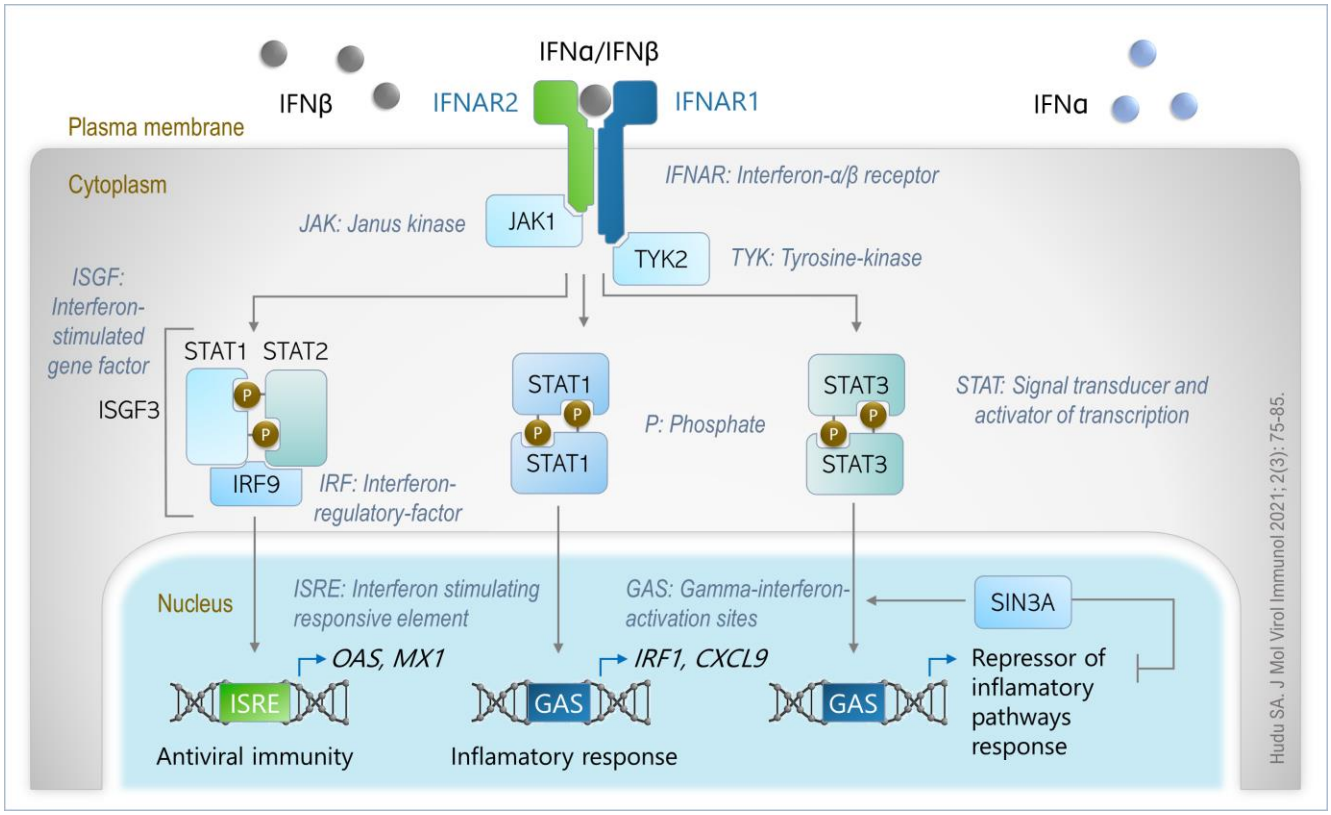

Figure 2. Jak/STAT signaling cascade. This cascade is activated by INF-α/β binding to the type I IFN receptor. This results in the production of antiviral proteins, such as 2′-5′-oligoadenylate synthase (OAS) and IFN-induced GTP-binding protein Mx1. Adapted from references [33,36].

One of the critical stages of innate antiviral responses in cells infected with a virus is the swift elimination of infected cells by the induction of apoptosis. Virus replication and establishment is prevented by the early apoptosis and subsequent phagocytosis of virus-infected cells before the initiation of cellular lysis. In a study by Takaoka et al. [37], it was shown that IFNs also played an important role in antiviral responses through the regulation of apoptosis in vesicular stomatitis virus infections in mice. The production of IFN-α/β by infected cells enhances apoptosis by inducing tumor suppressor p53. Therefore, p53 is considered as a critical element of host defense in viral infection and early cell apoptosis in innate antiviral response. A subsequent study showed that increased HRV virus replication in cultured primary bronchial epithelial cells obtained from asthmatic subjects compared with normal healthy individuals was related to deficient type I IFN response and resistance to the early apoptosis of virus-infected cells. This could explain the more severe symptoms associated with the lower respiratory tract among patients with asthma, which may be due to decreased virus elimination at the early stage of the infection, further confirming the critical role of type I IFNs and apoptosis related to HRV infections [38]. On the other hand, Bochkov et al. [39], who compared the genes involved in HRV-infected primary bronchial epithelial cells from asthmatic donors with HRV-infected cells from normal individuals showed no significant differences in the production of INFs type I and III between the two groups. Type I IFN was reported to prime infected and neighboring cells to an antiviral state and early apoptosis with the subsequent phagocytic removal of the replicating virus, which confined the extent of inflammatory responses in the respiratory tract upon infection [40]. Therefore, type I IFN is a potential therapeutic for treating the exacerbations of asthma of virus origin, limiting virus replication by restoring cell apoptosis response to the normal level [40].

PKR is a constitutively expressed serin/threonine protein kinase and IFN-induced protein, which regulates protein synthesis in response to stress signal, mostly by viral

infection. In addition to antiviral protection, PKR plays an important role in cell growth regulation and differentiation. PKR is a main regulator of the antiviral response of the cell. It can inhibit virus replication through the inhibition of protein synthesis through eukaryotic translation initiation factor 2A (EIF2A), induction of antiviral genes through NF-κB, and triggering of apoptosis in virus-infected cells [41]. Phosphorylated serine residue 51 of EIF2A inhibits GDP recycling and leads to impairment in protein synthesis. Phosphorylation of EIF2Aα is associated with the antiproliferative and antiviral activity of PKR [33]. DsRNA can activate or inhibit PKR following binding and exerting conformational changes. Viruses have developed mechanisms to escape the immune system through the inhibition of PKR at different levels [42]. The DsRNA-binding domain of influenza virus nonstructural protein 1 inhibits the activation of PKR, as well as type I IFN synthesis [43]. The E3L and K3L proteins of Vaccinia virus inhibit the PKR pathway through the sequestering of dsRNA molecules and inhibition of PKR autophosphorylation, respectively [44]. Chen et al. [21] showed that HRV infections significantly induced the PKR system in addition to the Mx pathway, viperin, and the coupled 2′-5′-oligoadenylate synthetase (OAS)/RNase L pathway. PKR plays an important role in HRV antiviral response.

The replication of the virus is eliminated through another innate pathway called the 2′,5′-(OAS)/RNase L system. The OAS gene is induced by IFN signaling through IFN-stimulated response elements. In this system, cytoplasmic viral dsRNA is recognized by OAS as PRRs, which is constitutively expressed in the cell. Activated OAS produces 2-5A from ATP. The binding of 2-5A to RNase L monomers converts them into activated dimers with RNase activity, degrading the single-stranded RNAs of both viral and cellular origin [45]. Some viruses develop a potent inhibitor for RNase L, which may play a role in the in vivo pathogenesis of the virus [46]. The antiviral role of OAS has been investigated against picornaviruses, including coxsackieviruses, poliovirus, and encephalomyocarditis virus [45]. All four types of OAS (OAS1, 2, 3 and L) have been shown to be significantly induced in human tracheobronchial cells infected with both major and minor HRV groups [21].

Mx proteins comprising Mx1 and Mx2 play an antiviral role against a wide variety of viruses. Type I IFN stimulates the expression of Mx proteins through an IFN-stimulated response element present in the gene promoter. MxA proteins accumulate in intracellular membranes, including the endoplasmic reticulum in cell cytoplasm and target both cytoplasmic and nuclear viruses. They inhibit viral replication at early stages, which prevents the generation of mechanisms by the virus to escape the Mx antiviral. Mx proteins inhibit viral replication by inhibiting virus RNA synthesis and nucleocapsid transport. Viral components, mostly nucleocapsids, are trapped and degraded by MxA monomers [33]. Turan et al. [47] showed that the transcription step of influenza virus was efficiently interfered through the interaction of nuclear Mx with PB2-NP proteins. Both subtypes of Mx proteins, Mx1 and Mx2, are significantly induced by HRV infections [21].

HRV-induced inflammatory response

In addition to molecules with direct anti-viral effects, HRV infections induce pro-inflammatory mediators that clear infections through immune cells recruitment to the site of infection. The production of cytokines contributes to the eradication of pathogens in vivo, but the insufficient induction of proinflammatory cytokines can cause systemic inflammatory response syndrome, and it is associated with the pathophysiology of inflammation [3,48]. Three types of inflammatory mediators are released in response to HRV infections: those that recruit and activate specific leukocytes, such as IL-8 and IL-6, those involved in anti-viral defense, such as IFNβ and IFNα, and those like IL-1 which amplify local inflammation [49]. The induction of respiratory tract inflammation and initiation of the exacerbation of respiratory tract diseases have been associated with the significant elevation of inflammatory mediators, including IL-1, 6 and 8, granulocyte-macrophage colony-stimulating factor (GM-CSF), regulated on activation, normal T cell expressed and secreted (RANTES), and eotaxin [21].

IL-1 family mediators are produced by respiratory tract epithelial cells during the very early stage of the HRV-induced inflammatory cascade and play an important role in the establishment of inflammation. Piper et al. [50] showed that HRV infections induced the release of IL-1α, IL-β and IL-18 by epithelial cells, and autocrine IL-1 signaling had an undeniable role in the production of pro-inflammatory cytokines in HRV infections. The upregulation of pro-inflammatory cytokines was reported to be inhibited by IL-1 blockage without contributing to IFN and INF-driven responses induced by HRV infections. Therefore, the inhibition of the IL-1 pathway can be considered as an optimal therapeutic strategy to moderate inflammatory responses in acute exacerbations.

IL-8 has been shown to be involved in several inflammatory disorders. Studies have reported an increased level of IL-8 in nasal aspirates during the virus-induced exacerbation of respiratory tract diseases. IL-8 plays an important role in neutrophil chemotactic activity and recruitment, which may be involved in virus-induced respiratory pathogenesis and clinical outcome. Studies have also demonstrated a positive link between the severity of respiratory tract symptoms and an increase in the respiratory tract hypersensitivity of asthmatic patients and the level of neutrophil chemoattractants, such as IL-8, as well as neutrophil counts in nasal secretions [51,52]. Although studies indicate that individuals with asthma have defective IFN-β production in response to HRV infections, which results in a subtle defect in immune response, the production of IL-6, RANTES, IL-8 and GM-CSF in this group was similar to healthy individuals, suggesting that proinflammatory response to viral infections remains intact and is necessary to eliminate infections from the respiratory tract [40].

The rapid induction of granulocyte colony-stimulating factor (G-CSF) followed by IL-8 in the nose upon infection is associated with an increase in neutrophils in blood and nasal fluid, respectively. Sputum neutrophilia is followed by upper respiratory neutrophilia and also correlated with changes in G-CSF and IL-8, suggesting that the HRV infection gradually moves to the lower part of the respiratory tract [53]. Johnston et al. [54] showed the induction of IL-8 in the low-grade rhinovirus infection of the transformed lower respiratory tract epithelial cell (A549). The authors found that IL-8 release was time- and dose-dependent and increased for up to five days in the post-infection period depending on virus receptor interaction and partially on viral replication. Both in vitro and in vivo studies have reported that CXCL10 is induced by HRV infections [55]. Other respiratory viruses have been shown to induce CCL2 and CXCL11. CXCL13, which is traditionally limited to lymphoid organs, is markedly elevated in respiratory tract epithelial cells, although its role in the pathogenesis of the virus requires further investigations [28].

Intranasal challenging of volunteers with HRV showed a significant decrease in peripheral T lymphocytes, which was associated with severe cold symptoms and frequent virus shedding [56]. In a study by Gern et al. [53], the pattern of Th1- and Th2-like cytokine responses (as indicated by IFN-γ and IL-5 sputum mRNA, respectively) was compared to the virological and clinical outcomes of HRV infections in asthmatic individuals. Both branches were observed to be activated during the acute phase. Time required to eliminate the virus from sputum and peak symptom scores during the acute phase were inversely related to the IFN-γ/IL-5 ratio. Therefore, profound Th1-like cytokine response during the HRV-induced common cold would play a critical role in restricting virus propagation and respiratory symptoms. However, impaired immune response to this viral infection may occur as a result of Th2-like responses in asthmatic patients. The simultaneous elevation of IFN-γ and IL-5 may be strong inflammatory stimuli [53]. Therefore, exogenous IFN-γ may have a potential therapeutic effect on reducing respiratory tract dysfunctions.

Conclusion

Conductive respiratory tract epithelial cells that function as both a barrier for and a trigger of appropriate immune responses are the main target of HRV. Respiratory tract epithelial cells are outfitted with layers of invulnerable antiviral instruments. Nitric oxide produced following contamination has intense antiviral activity and

adjusts excessive cytokine articulation to prevent irritation. Type I and type III IFN-reinforced qualities, as well as meddling with viral replication additionally limit infection instigated favourable to incendiary cytokines to forestall unreasonable aggravation.

Notwithstanding uncertain, a few investigations associated diminished IFN articulation with higher viral load in patients with asthma. Despite new advances in the field of inborn resistant reactions to HRV, the fundamental components of HRV-related exacerbations in patients with persistent lung diseases are not yet fully understood. While patients with COPD regularly show Th1 irritation, the majority patients with asthma have Th2 aggravation in light of viral diseases.

Consequently, significant factors underlying HRV-related aggravation in asthma and COPD may be completely different, and this should be considered when evaluating discoveries to foster new treatments.

Conflict of interest: The author declares that there is no conflict of interest. The author alone is responsible for the content and writing of the paper. **Financial disclosure:** There is no financial support to this study.

References

1. Moriyama M, Hugentobler WJ, Iwasaki A. Seasonality of Respiratory Viral Infections. Annu Rev Virol 2020; 7(1): 83-101. [Crossref]

2. Zell R. Picornaviridae-the ever-growing virus family. Arch Virol 2018; 163(2): 299-317. [Crossref]

3. Kimura H, Yoshizumi M, Ishii H, Oishi K, Ryo A. Cytokine production and signaling pathways in respiratory virus infection. Front Microbiol 2013; 4: 276. [Crossref]

4. Perry AK, Chen G, Zheng D, Tang H, Cheng G. The host type I interferon response to viral and bacterial infections. Cell Res 2005; 15(6): 407-22. [Crossref]

5. Kumar H, Kawai T, Akira S. Pathogen recognition by the innate immune system. Int Rev Immunol 2011; 30(1): 16-34. [Crossref]

6. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell 2006; 124(4): 783-801. [Crossref]

7. Slater L, Bartlett NW, Haas JJ, Zhu J, Message SD, Walton RP, et al. Co-ordinated role of TLR3, RIG-I and MDA5 in the innate response to rhinovirus in bronchial epithelium. PLoS Pathog 2010; 6(11): e1001178. [Crossref]

8. Kawai T, Akira S. Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 2011; 34(5): 637-50. [Crossref]

9. Boehme KW, Guerrero M, Compton T. Human cytomegalovirus envelope glycoproteins B and H are necessary for TLR2 activation in permissive cells. J Immunol 2006; 177(10): 7094-102. [Crossref]

10. Kurt-Jones EA, Popova L, Kwinn L, Haynes LM, Jones LP, Tripp RA, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol 2000; 1(5): 398-401. [Crossref]

11. Bieback K, Lien E, Klagge IM, Avota E, Schneider-Schaulies J, Duprex WP, et al. Hemagglutinin protein of wild-type measles virus activates toll-like receptor 2 signaling. J Virol 2002; 76(17): 8729-36. [Crossref]

12. Rudd BD, Burstein E, Duckett CS, Li X, Lukacs NW. Differential role for TLR3 in respiratory syncytial virus-induced chemokine expression. J Virol 2005; 79(6): 3350-7. [Crossref]

13. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature 2001; 413(6857): 732-8. [Crossref]

14. Doyle SE, O'Connell R, Vaidya SA, Chow EK, Yee K, Cheng G. Toll-like receptor 3 mediates a more potent antiviral response than Toll-like receptor 4. The Journal of Immunology 2003; 170(7): 3565-71. [Crossref]

15. Hewson CA, Jardine A, Edwards MR, Laza-Stanca V, Johnston SL. Toll-Like Receptor 3 Is Induced by and Mediates Antiviral Activity against Rhinovirus Infection of Human Bronchial Epithelial Cells. Journal of Virology 2005; 79(19): 12273-9. [Crossref]

16. Guo-Parke H, Linden D, Weldon S, Kidney JC, Taggart CC. Mechanisms of Virus-Induced Airway Immunity Dysfunction in the Pathogenesis of COPD Disease, Progression, and Exacerbation. Front Immunol 2020; 11: 1205. [Crossref]

17. Griego SD, Weston CB, Adams JL, Tal-Singer R, Dillon SB. Role of p38 Mitogen-Activated Protein Kinase in Rhinovirus-Induced Cytokine Production by Bronchial Epithelial Cells. The Journal of Immunology 2000; 165(9): 5211-20. [Crossref]

18. Wang X, Lau C, Wiehler S, Pow A, Mazzulli T, Gutierrez C, et al. Syk is downstream of intercellular adhesion molecule-1 and mediates human rhinovirus activation of p38 MAPK in airway epithelial cells. The Journal of Immunology 2006; 177(10): 6859-70. [Crossref]

19. Yoneyama M, Kikuchi M, Natsukawa T, Shinobu N, Imaizumi T, Miyagishi M, et al. The RNA helicase RIG-I

has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 2004; 5(7): 730-7. [Crossref]

20. Wang Q, Nagarkar DR, Bowman ER, Schneider D, Gosangi B, Lei J, et al. Role of double-stranded RNA pattern recognition receptors in rhinovirus-induced airway epithelial cell responses. J Immunol 2009; 183(11): 6989-97. [Crossref]

21. Chen Y, Hamati E, Lee PK, Lee WM, Wachi S, Schnurr D, et al. Rhinovirus induces airway epithelial gene expression through double-stranded RNA and IFN-dependent pathways. Am J Respir Cell Mol Biol 2006; 34(2): 192-203. [Crossref]

22. Liu P, Jamaluddin M, Li K, Garofalo RP, Casola A, Brasier AR. Retinoic acid-inducible gene I mediates early antiviral response and Toll-like receptor 3 expression in respiratory syncytial virus-infected airway epithelial cells. J Virol 2007; 81(3): 1401-11. [Crossref]

23. Kotla S, Peng T, Bumgarner RE, Gustin KE. Attenuation of the type I interferon response in cells infected with human rhinovirus. Virology 2008; 374(2): 399-410. [Crossref]

24. Barral PM, Morrison JM, Drahos J, Gupta P, Sarkar D, Fisher PB, et al. MDA-5 is cleaved in poliovirus-infected cells. J Virol 2007; 81(8): 3677-84. [Crossref]

25. Triantafilou K, Triantafilou M. Ion flux in the lung: virus-induced inflammasome activation. Trends Microbiol 2014; 22(10): 580-8. [Crossref]

26. Pétrilli V, Papin S, Dostert C, Mayor A, Martinon F, Tschopp J. Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. Cell Death Differ 2007; 14(9): 1583-9. [Crossref]

27. Triantafilou K, Kar S, van Kuppeveld FJ, Triantafilou M. Rhinovirus-induced calcium flux triggers NLRP3 and NLRC5 activation in bronchial cells. Am J Respir Cell Mol Biol 2013; 49(6): 923-34. [Crossref]

28. Proud D, Turner RB, Winther B, Wiehler S, Tiesman JP, Reichling TD, et al. Gene expression profiles during in vivo human rhinovirus infection: insights into the host response. Am J Respir Crit Care Med 2008; 178(9): 962-8. [Crossref]

29. Sanders SP, Proud D, Permutt S, Siekierski ES, Yachechko R, Liu MC. Role of nasal nitric oxide in the resolution of experimental rhinovirus infection. J Allergy Clin Immunol 2004; 113(4): 697-702. [Crossref]

30. Proud D, Sanders SP, Wiehler S. Human rhinovirus infection induces airway epithelial cell production of human beta-defensin 2 both in vitro and in vivo. J Immunol 2004; 172(7): 4637-45. [Crossref]

31. Dong B, Zhou Q, Zhao J, Zhou A, Harty RN, Bose S, et al. Phospholipid scramblase 1 potentiates the antiviral activity of interferon. J Virol 2004; 78(17): 8983-93. [Crossref]

32. Isaacs A, Lindenmann J. Virus interference. I. The interferon. Proc R Soc Lond B Biol Sci 1957; 147(927): 258-67. [Crossref]

33. Sadler AJ, Williams BR. Interferon-inducible antiviral effectors. Nat Rev Immunol 2008; 8(7): 559-68. [Crossref]

34. Der SD, Zhou A, Williams BR, Silverman RH. Identification of genes differentially regulated by interferon alpha, beta, or gamma using oligonucleotide arrays. Proc Natl Acad Sci U S A 1998; 95(26): 15623-8. [Crossref]

35. Muramoto Y, Shoemaker JE, Le MQ, Itoh Y, Tamura D, Sakai-Tagawa Y, et al. Disease severity is associated with differential gene expression at the early and late phases of infection in nonhuman primates infected with different H5N1 highly pathogenic avian influenza viruses. J Virol 2014; 88(16): 8981-97. [Crossref]

36. Ivashkiv LB, Donlin LT. Regulation of type I interferon responses. Nat Rev Immunol 2014; 14(1): 36-49. [Crossref]

37. Takaoka A, Hayakawa S, Yanai H, Stoiber D, Negishi H, Kikuchi H, et al. Integration of interferon-alpha/beta signalling to p53 responses in tumour suppression and antiviral defence. Nature 2003; 424(6948): 516-23. [Crossref]

38. Acosta PL, Byrne AB, Hijano DR, Talarico LB. Human Type I Interferon Antiviral Effects in Respiratory and Reemerging Viral Infections. J Immunol Res 2020; 2020: 1372494. [Crossref]

39. Bochkov YA, Hanson KM, Keles S, Brockman-Schneider RA, Jarjour NN, Gern JE. Rhinovirus-induced modulation of gene expression in bronchial epithelial cells from subjects with asthma. Mucosal Immunol 2010; 3(1): 69-80. [Crossref]

40. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med 2005; 201(6): 937-47. [Crossref]

41. Williams BR. PKR; a sentinel kinase for cellular stress. Oncogene 1999; 18(45): 6112-20. [Crossref]

42. García MA, Meurs EF, Esteban M. The dsRNA protein kinase PKR: virus and cell control. Biochimie 2007; 89(6-7): 799-811. [Crossref]

43. Hatada E, Saito S, Fukuda R. Mutant influenza viruses with a defective NS1 protein cannot block the activation of PKR in infected cells. J Virol 1999; 73(3): 2425-33. [Crossref]

44. Davies MV, Elroy-Stein O, Jagus R, Moss B, Kaufman RJ. The vaccinia virus K3L gene product potentiates translation by inhibiting double-stranded-RNA-activated protein kinase and phosphorylation of the alpha subunit of eukaryotic initiation factor 2. J Virol 1992; 66(4): 1943-50. [Crossref]

45. Silverman RH. Viral encounters with 2',5'-oligoadenylate synthetase and RNase L during the interferon antiviral response. J Virol 2007; 81(23): 12720-9. [Crossref]

46. Drappier M, Michiels T. Inhibition of the OAS/RNase L pathway by viruses. Curr Opin Virol 2015; 15:19-26. [Crossref]

47. Turan K, Mibayashi M, Sugiyama K, Saito S, Numajiri A, Nagata K. Nuclear MxA proteins form a complex with influenza virus NP and inhibit the transcription of the engineered influenza virus genome. Nucleic Acids Res 2004; 32(2): 643-52. [Crossref]

48. Xu PB, Lou JS, Ren Y, Miao CH, Deng XM. Gene expression profiling reveals the defining features of monocytes from septic patients with compensatory anti-inflammatory response syndrome. J Infect 2012; 65(5): 380-91. [Crossref]

49. Kim J, Schleimer R. Epithelial Cell Innate Responses to Rhinovirus Infection. In: Pawankar R, Holgate ST, Rosenwasser LJ (eds), Allergy Frontiers: Classification and Pathomechanisms. 2009, Springer, Tokyo. pp:267-84. [Crossref]

50. Piper SC, Ferguson J, Kay L, Parker LC, Sabroe I, Sleeman MA, et al. The role of interleukin-1 and interleukin-18 in pro-inflammatory and anti-viral responses to rhinovirus in primary bronchial epithelial cells. PLoS One 2013; 8(5): e63365. [Crossref]

51. Grünberg K, Timmers MC, Smits HH, de Klerk EP, Dick EC, Spaan WJ, et al. Effect of experimental rhinovirus 16 colds on airway hyperresponsiveness to histamine and interleukin-8 in nasal lavage in asthmatic subjects in vivo. Clin Exp Allergy 1997; 27(1): 36-45. [Crossref]

52. Teran LM, Johnston SL, Schröder JM, Church MK, Holgate ST. Role of nasal interleukin-8 in neutrophil recruitment and activation in children with virus-induced asthma. Am J Respir Crit Care Med 1997; 155(4): 1362-6. [Crossref]

53. Gern JE, Vrtis R, Grindle KA, Swenson C, Busse WW. Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. Am J Respir Crit Care Med 2000; 162(6): 2226-31. [Crossref]

54. Johnston SL, Papi A, Bates PJ, Mastronarde JG, Monick MM, Hunninghake GW. Low grade rhinovirus infection induces a prolonged release of IL-8 in pulmonary epithelium. J Immunol 1998; 160(12): 6172-81.

55. Spurrell JC, Wiehler S, Zaheer RS, Sanders SP, Proud D. Human airway epithelial cells produce IP-10 (CXCL10) in vitro and in vivo upon rhinovirus infection. Am J Physiol Lung Cell Mol Physiol 2005; 289(1): L85-95. [Crossref]

56. Levandowski RA, Ou DW, Jackson GG. Acute-phase decrease of T lymphocyte subsets in rhinovirus infection. J Infect Dis 1986; 153(4): 743-8. [Crossref]