



Impact of genetic polymorphisms related to innate immune response on respiratory syncytial virus infection in children

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Abstract

Respiratory syncytial virus (RSV) causes lower respiratory tract infections and bronchiolitis, mainly affecting children under 2 years of age and immunocompromised patients. Currently, there are no available vaccines or efficient pharmacological treatments against RSV. In recent years, tremendous efforts have been directed to understand the pathological mechanisms of the disease and generate a vaccine against RSV. Although RSV is highly infectious, not all the patients who get infected develop bronchiolitis and severe disease. Through various sequencing studies, single nucleotide polymorphisms (SNPs) have been discovered in diverse receptors, cytokines, and transcriptional regulators with crucial role in the activation of the innate immune response, which is implicated in the susceptibility to develop or protect from severe forms of the infection. In this review, we highlighted how variations in the key genes affect the development of innate immune response against RSV. This data would provide crucial information about the mechanisms of viral infection, and in the future, could help in generation of new strategies for vaccine development or generation of the pharmacological treatments.

Keywords Respiratory syncytial virus · Bronchiolitis · Innate immunity · Polymorphisms

Introduction

Respiratory syncytial virus (RSV) infection is one of the main causes worldwide of acute respiratory infections (ARIs) among children under 5 years. 22% of ARIs are associated with this virus, being clinically manifested as

bronchiolitis from 40 to 90% [1, 2]. In 2015, 3.2 million of hospitalizations were globally associated to RSV, of which 59,600 cases resulted in deaths [2, 3]. RSV has a seasonal behavior with outbreaks mainly from early autumn to late spring in the North Hemisphere [4]. Viral spreading shows an important reduction during the summer, although rare outbreaks have been reported [5]. Importantly, co-infection of RSV and SARS-CoV-2 might have an important effect on the treatment and prognosis of the disease, since this viral coinfection may be associated to a higher level of care,

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increased hospital stay, and progression to acute respiratory distress syndrome [6]. Currently, no vaccine has been licensed against RSV [7], and the search for an effective and safe preventive method for RSV infection continues to be one of the greatest challenges for the scientific community. Most treatment options are inaccessible, such as palivizumab which is used in severe disease, and in some cases, infected children are mainly treated with palliative treatments, such as oxygen and bronchodilators [8]. This suggests that there is need for an effective and safe treatment strategy against RSV infection. In this review, we have discussed general biological characteristics of RSV and further focused on the genetics of main components of the innate immune response activated during RSV infection. We have revised the polymorphism in various genes of innate immune response associated with disease severity, particularly those that impact the probabilities of hospital care and co-infections among the infected individuals.

General characteristics of respiratory syncytial virus (RSV)

RSV was isolated in 1955 from a colony of 20 chimpanzees suffering from infectious coryza in the Walter Reed Army Institute of Research, Maryland, USA [9]. Two years later, similar viruses were isolated from children with respiratory illness (bronchopneumonia and laryngotracheobronchitis) [10]. RSV is a representative member of the order *Mononegavirales*, family *Pneumoviridae*, and subfamily *Orthopneumovirus* [11]. RSV is typically rounded (diameter 150–250 nm) or filamentous (diameter 90–100 nm × length 10 μm) [12]. The genome is 15.2 kb single stranded, non-segmented, negative-sense RNA and contains ten genes that encode eleven different proteins, which are classified as structural, regulatory, and non-structural [13]. The F (fusion) and G (attachment) envelope glycoproteins, the M, M2-1, M2-2 matrix proteins, SH, N and P proteins, give structure to the virion. The large polymerase protein (L) is responsible for the viral RNA synthesis. Finally, the NS (non-structural)1 and NS2 proteins are important disruptors and regulators of the expression of cellular responses against the RSV [14, 15] (Fig. 1).

The G and F proteins are the major glycoproteins on the surface of the virion and have important roles in the virus entry to the host cell [12]. The G glycoprotein works as an attachment protein that binds virions to the surface molecules in the target cells. The F glycoprotein also facilitates attachment and mediates fusion of the viral and host cell membranes [16–19]. Diverse molecules have been proposed as receptor for RSV in the host cells, such as the intercellular adhesion molecule-1 which binds the F protein [20], heparin which interacts with the G and F proteins [21, 22],

annexin II which binds to G protein [23], and recently, and still controversial, nucleolin which binds to the viral F protein [24–26]. Although Toll-like receptor (TLR)4 and fractalkine receptor can recognize viral proteins and have been associated with the innate antiviral response against RSV, their possible involvement in viral attachment and entry is still elusive [27, 28]. Once the viral RNA is located into the host cell, transcription and translation of the viral genome occurs in a well-coordinated mechanism [29]. The three viral glycoproteins are anchored to the cell membrane to facilitate the release of viral particles, while the assembly of nucleocapsid is achieved in the cytoplasmic inclusions [30]. Finally, viral assembly occurs in plasma membrane, where the viral particle acquires its viral envelope [30, 31] (Fig. 2).

Innate immune response in respiratory syncytial virus (RSV) infection and associated polymorphisms

Polymorphisms in the genes of immune system is considered as an important aspect behind the resistance or susceptibility of the host to an infectious disease. Over the years, researchers have explored many genetic factors having role in immune surveillance against infectious diseases [32]. Among them, single genetic mutations (such as single nucleotide polymorphisms -SNPs-) has been associated to the predisposition and development of the severe forms of the infections [33].

Different components of the innate immune response participate in the control of RSV infection, including various pattern recognition receptors (PRRs), diverse cell types, and a large array of cytokines and chemokines. An appropriate innate immune response has an essential role in the resolution of RSV infection, as it promotes virus clearance, avoids virus replication and spreading to the lower respiratory tract, and promotes the development of an adequate adaptive immune response [34].

The panoply of molecules giving structure to the RSV and those implied in its replicative cycle are classified as pathogen-associated molecular patterns (PAMPs) and share common general characteristics with those expressed by other viral pathogens. They are recognized by PRRs that promote the innate immune response leading to the activation of an antiviral state. These PRRs are anchored to the cell membrane or located in the intracellular vesicles, such as TLRs, but could also be dispersed in the cytoplasm, as in the case of RIG-I-like receptors, and NOD-like receptors. Thus, different viral molecules at each step of their infection cycle can be recognized by the host cells for inducing an immune response.

Once host cells recognize the presence of RSV components, such as the cytoplasmic viral RNA by the RIG-I

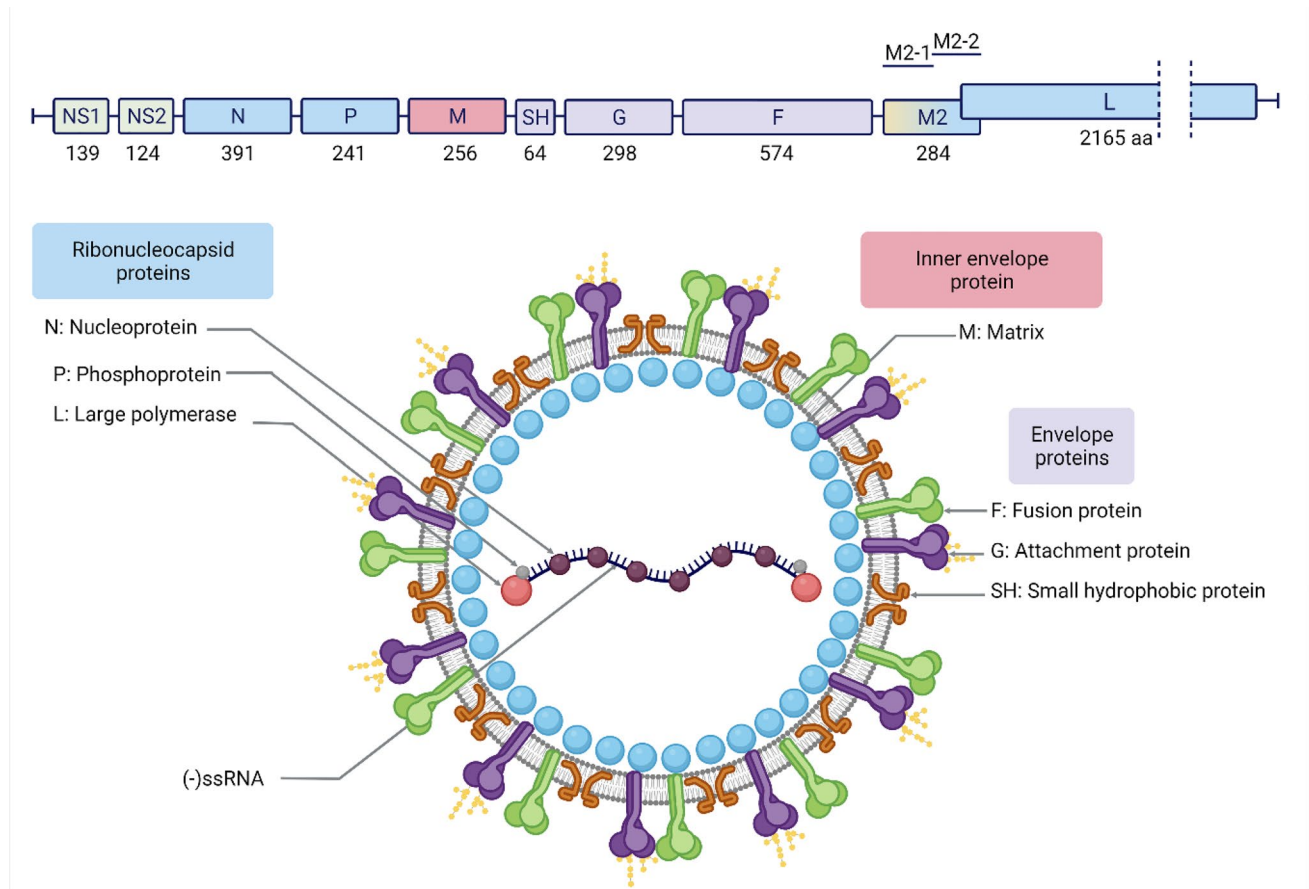


Fig. 1 Schematic representation of respiratory syncytial virus (RSV) genome and structure. The length of the genome is more than 15 kb, encoding 11 proteins. The negative-sense ssRNA is attached to N, P,

and L proteins forming a nucleocapsid, which is covered by M proteins and enveloped with a membrane consisting of G, F, and SH proteins. Created with BioRender.com (access date: March 25th, 2022)

receptor, the production of type I interferons (IFNs) is triggered. These innate anti-viral cytokines are represented by various isoforms such as IFN- α , IFN- β , and recently described IFN- ϵ , - κ , - ω [35–38]. Besides, upon RSV infection, diverse innate immune cells are activated to produce inflammatory mediators that orchestrate a type 1 antiviral response, characterized by production of IFN- γ (type II IFN) by natural killer (NK) and NKT cells. This response is combined with a type 2 response, which is accomplished by the group 2 innate lymphoid cells, mast cells, and airway epithelial. These cells release interleukin (IL)-5, IL-13, IL-25, IL-33, thymic stromal lymphopoietin (TSLP), CXCL8 (IL-8), CXCL10, CCL4, regulated on activation normal T cell expressed and presumably secreted (RANTES, CCL5), and the high mobility group box I alarmin [39–42]. Among the primary cytokines produced by airway epithelial cells after RSV infection, tumor necrosis factor (TNF)- α , IL-1 α , and IL-1 β induce the secretion of IL-6, IL-8, and CCL5 in an autocrine manner [43]. Altogether, these mediators attract eosinophils, neutrophils, monocytes, NK, NKT, dendritic cells (DC), and T cells to the airways, which are involved

in the immune response against RSV and viral clearance [39, 41].

Nevertheless, many of these cells are also involved in the severity of the RSV-associated respiratory disease. Bronchoalveolar lavage fluid (BALF) or nasopharyngeal aspirates of infants with severe RSV bronchiolitis are characterized by a predominance of neutrophils [44], a significant increase in the activated conventional DC [45–47], and accumulation of granzyme B-expressing NK cells [48]. Pro-inflammatory cytokines IL-1 β , IL-6, IL-8, and TNF- α are also significantly higher in the BALF of RSV cases [47]. Additionally, a lower number of plasmacytoid DC (pDC) producing anti-viral IFN- α in BALF has been found in preterm infant with RSV bronchiolitis [47]. Various studies have suggested the crucial role of pDCs and type I IFN responses in limiting the viral load and pulmonary inflammation, and in promoting viral clearance as an early response to RSV [49, 50].

It is also known that genetic polymorphism in the immune system genes influence the ability to respond to the RSV and also influences the severity of the infection.

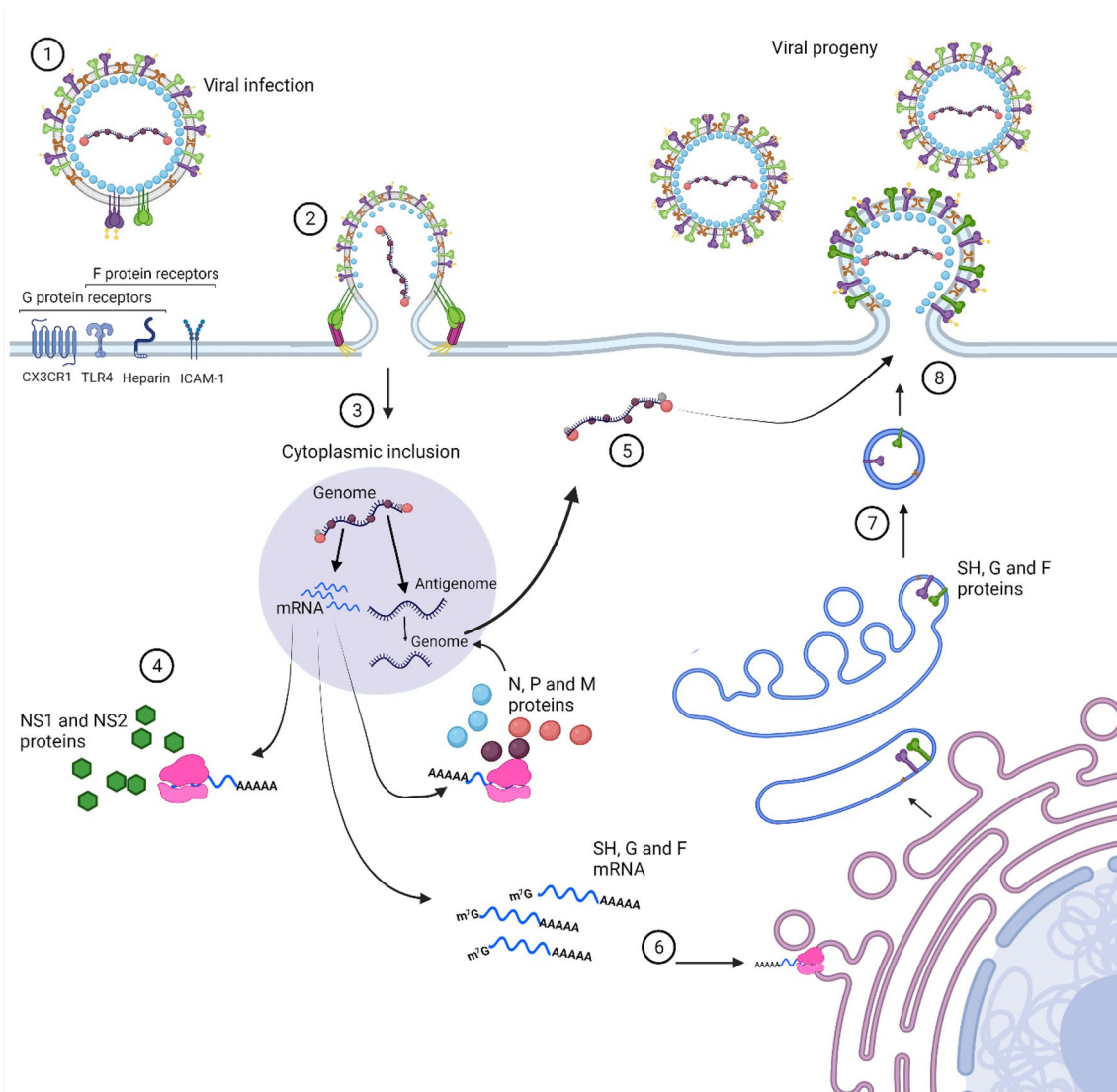


Fig. 2 Life cycle of RSV. For attachment and recognition of the virion mediated by glycoprotein (G) and fusion (F), proteins in the virion interact with the receptors in the host cell surface (1). The fusion (F) protein exposes the fusion peptide and change to a pre-harping conformation which facilitates the fusion of the virus to the host cell membrane and leads to nucleocapsid delivery (2). Viral genome is thereafter, contained in the cytoplasmic inclusions where

primary transcription occurs (3). This is followed by translation of genome in the cytoplasmic ribosomes (4) and replication (5). The SH, F, and G proteins are sorted via endoplasmic reticulum (6) and Golgi apparatus (7). Viral proteins are assembled into viral filaments for viral budding process (8). Created with BioRender.com (Access date: March 25th, 2022)

In this section, we reviewed the polymorphism in important genes of innate immune system which have been associated with disease severity. For all the discussed genes in this study, we explored the role of protein encoded by those genes in host response to RSV infection and the signaling pathway involved. We have further described the genetic studies in pediatric population which have correlated genetic polymorphism with RSV disease, emphasizing their protective or predisposing participation.

Pattern recognition receptors (PRRs)

One of the initial contacts between RSV and the host cell is mediated by the recognition of the F protein through TLR4. This interaction is proposed as an initiator of the innate immune response, that probably facilitates the virus entry and has been considered as one of the pathogenic triggers, which exacerbates airway inflammation by the release of cytokines and chemokines during RSV infection [43, 51, 52]. Besides, when human lung epithelial cells are infected

with RSV, the expression of TLR4 mRNA is increased, suggesting that RSV plays a role in the inflammatory sensitization of the airway epithelium [53]. Innate inflammatory cytokines are expressed once cell activation is initiated by TLR4 through MyD88-dependent or -independent signaling pathways [54]. It has been observed that in splenocytes of TLR4^{-/-} or MyD88^{-/-} mice, the production of IFN- β or TNF- α is highly diminished, which negatively impacts the RSV-specific antibody levels [55]. Moreover, cytokine and chemokine production is also dependent on the nuclear transcription factor kappa-light-chain-enhancer of activated B cells (NF- κ B), once the TLR4/CD14 complex has been activated [45, 56]. Genetic polymorphisms alter the function of TLR4, and these alterations have been associated with the severity of RSV infection. Two of the most studied polymorphisms in *TLR4* gene are 299Gly and 399Ile, due to their importance in the establishment of an effective immune response. The change of A to G at the position 896 generates a modification of Asp to Gly at the position 299, and the change of C to T at the position 196 leads to substitution of Thr to Ile, although the molecular effect of these changes is still elusive [57]. Both genetic polymorphisms are present in high frequency (in a heterozygous genotype) in ethnically diverse premature infants with symptomatic RSV infection [58]. In 1–12 months old Israeli infants, severe RSV bronchiolitis is significantly associated with polymorphisms 299Gly and/or 399Ile in *TLR4*, with increased odd ratios (OR) of 4.9 (299Gly/399Ile), 5.1 (299Gly), and 4.0 (399Ile) of hospital admission [59]. On the contrary, the peripheral blood mononuclear cells from Canadian pediatrics subjects (7–9 years old) heterozygous for 299Gly and 399Ile, and acutely exposed to RSV, showed no difference in the production of IFN- γ , CXCL10, IL-10, and CCL5, when compared to that obtained from normal homozygous infants [60]. The role of these alleles has been evidenced in human bronchial epithelial cells which express *TLR4* gene with 299Gly or 399Ile polymorphisms. These cells showed reduced production of IL-8, IL-10, IL-12p35, IL-8, and CCL8, indicating that impaired TLR4-response may affect the establishment of an effective immune responses against RSV [57].

TLR2 receptor recognizes common viral motif in RNA viruses, such as dengue virus, human immunodeficiency virus, hepatitis C virus, and rhinovirus, through the dimerization with either TLR1 or TLR6 [61–64]. Heterodimers TLR2/TLR1 and TLR2/TLR6 recruit MyD88 to the Toll/IL-1 receptor (TIR) domain, which is located in the cytosolic C-terminal region [65, 66]. It has been shown in a study that peritoneal macrophages from C57BL/6 mice stimulated with RSV elicited TNF- α production, which was found to be significantly reduced in TLR2 knock-out and TLR6 knock-out mice. This indicated that only TLR2/TLR6 heterodimers are responsible for RSV recognition and activation of the innate immune responses

[67]. Human primary small airway epithelial cells exposed to viral G protein have been found to activate the TLR2/TLR6 signaling and further expression of TNF- α [68]. In the human macrophage cell line U937 infected with RSV, TLR2/MyD88/NF- κ B signaling is required for pro-IL-1 β and *NLRP3* gene expression. This has been found to later on trigger the inflammasome assembly and the subsequent caspase-1 activation and mature IL-1 β secretion. After this, a coordinated participation of different pathways is required to orchestrate the innate immune response [69]. Although some *TLR2* polymorphisms have been associated with the severity of viral infections, the contribution or mechanism of some of them have not been clearly described yet. The polymorphism rs18998830, known as -15,607 A/G and laid on the first intron of the *TLR2* gene, has been significantly associated to severe bronchiolitis induced by RSV with fatalities in the Brazilian infants [70, 71]. Another polymorphism in *TLR2* gene, named as rs3804099, which is a synonymous SNPs in the single exon that means a C/T change coding Asn, was associated to a reduced proinflammatory cytokine secretion in hepatitis B virus chronic infection in a Chinese population [72]. In a study conducted in Germany with 156 infants suffering from severe RSV infection, no association of disease severity with rs3804099 polymorphism was reported [73].

During its life cycle, the RSV synthesizes a positive-sense RNA antigenome and various subgenomic mRNAs, which generate an intermediate double-stranded (ds)RNAs within cytosolic inclusions in the host cell [74]. Endosomal TLR3 recognizes dsRNA produced during viral replication [75]. The sensing of dsRNA is crucial to achieve an antiviral state during viral infection, which is characterized by the expression of IFN- α and IFN- β , and other proinflammatory cytokines, such as TNF- α , IL-6, IL-8, and IL-12 [76–79]. The induction of antiviral cytokine genes is triggered via the TIR domain-containing adaptor-inducing interferon- β (TRIF) signaling, which activates the interferon regulatory factor 3 (IRF3), NF- κ B and the activator protein (AP)-1 [80, 81]. Nevertheless, TLR3 activation has also been found to cause RSV-induced airway hyperreactivity and eosinophilia, since IL-33 production is partly TLR3-dependent in alveolar macrophages [82, 83]. There is limited evidence for the presence of polymorphic variants of the *TLR3* gene in association with the severity of RSV infection. In the previously mentioned study where 156 German infants were analyzed for TLRs polymorphisms, no association was found between severity of RSV infection and polymorphisms in *TLR3* gene rs3775291 (Leu412Phe G/A in exon 4), rs3775290 (F459F in exon 4 1337C/T), rs3775296 (in exon 2, untranslated region 299698T/G) [73]. Moreover, in 129 full-term Finn infants hospitalized for bronchiolitis, there were no significant association between rs3775291 SNP and RSV infection [84]. Although the association between *TLR3* polymorphisms and

severity of RNA virus infection has been suggested [85–87], more data are needed to clarify it.

Finally, it is worthy to consider that RSV RNA can also be recognized by the retinoic acid-inducible gene-I (RIG-I), that facilitates the oligomerization of the mitochondrial activator of signaling (MAVS) on the mitochondrial surface. Thereafter, diverse adaptors, like I κ B kinase γ (IKK γ) and TNF receptor-associated factors (TRAFs), are activated with the subsequent activation of NF- κ B [88–90]. It has been shown that after RSV infection of A549 cells, RIG-I activates the dimerization of the IRF3 and its translocation to the nucleus, leading to the expression of type I IFNs [91, 92]. Based on the biochemical and structural modeling approaches, two variants of human *RIGI* gene have been identified: the P229fs, a frameshift mutation that generates a truncated constitutively active receptor; and the S183I (a Ser to Ile mutation), which drastically inhibits antiviral signaling due to unintended stable complexes of RIG-I with itself and with MAVS [93]. However, these genetic alterations have not been detected in RSV-infected patients till date. Moreover, the information about SNPs in the RIG-I receptor in these patients is scarce. A study conducted in Canada detected rs10813831 (C/T Arg7Cys) and rs17217280 (T/A Asp580Glu) SNPs, however the differences in particular genotype or allele frequency between the children hospitalized with severe RSV bronchiolitis ($n = 140$) and children who tested positive for RSV but without hospitalization ($n = 100$) were not significant [94]. Thus, the possibility of detecting changes in this receptor in diverse childhood populations with severe RSV infection remains open and important to be studied as genetic variants of the *RIGI* gene have been reported to favor severe infections with other RNA viruses, like hepatitis C virus [95].

Cytokines and chemokines

Type I interferon (IFN)

IFN- α has 13 different subtypes in humans, while there is only one subtype of IFN- β [96]. Once, type I IFNs, are released from the initially infected cells, they induce an antiviral state in the neighboring uninfected cells. To accomplish this, IFNs bind to the IFN- α receptors consisting of IFNAR1 and IFNAR2 chains which further activates JAK-STAT signaling [97, 98]. Type I IFN binding drives the assembly of the two IFNAR chains and the consequent phosphorylation of IFNAR1-associated Tyk2 and IFNAR2-associated Jak1 tyrosine kinases, which phosphorylate IFNAR1 and IFNAR2 [99]. Phosphorylation of the IFNAR1 chain results in phosphorylation of STAT1 and STAT2, which translocate into the nucleus and together with IRF9 form the interferon-stimulated gene factor 3 (ISGF3) transcriptional complex. ISGF3 recognizes the type I IFN-stimulated response elements in

promoters of interferon-stimulated genes (ISGs). This initiates transcription and translation of various genes having antiviral activity, antiproliferative activity and have potential to induce robust adaptive immune response [99–103]. RSV has the potential to evade IFN type I-mediated immune response. NS1 binds to RIG-I, thereby inhibiting the activation of MAVS pathway and disrupting the downstream IFN antiviral and inflammatory response [104]. It has been shown in a study that NS2 expression in airway epithelial cells via vaccinia vector decreases the STAT2 levels in human tracheobronchial epithelial cells (hTBE) [98]. The genes coding for type I IFNs are grouped in a *locus* at the chromosome 9 and consists of 17 different functional genes, among which main are *IFNA5* and *IFNA13* [104]. The effect of these genes on the severity of infection caused by RSV has been studied. Genetic resistance to severe RSV infection has been associated to the polymorphism rs10757212 of *IFNA5* gene. The minor allele T was found to provide a protective effect to the hetero- and homozygous carriers (ORs C/T 0.80 and T/T 0.53, respectively) in a cohort of Dutch children [105]. Additionally, in other study conducted in The Netherlands, the change c.-603G/A (rs643070) of *IFNA13* gene conferred protection against RSV bronchiolitis in preterm children (OR 0.68) [106]. In the same study, but in context of IFN- α receptor genes, it was described that the polymorphism of rs7279064 of *IFNAR2* gene, which changes Phe10Val, increases the risk of severe RSV infection (OR 1.64) in the same population [106]. Despite the great importance of an adequate and timely type I IFN response to control viral replication and spreading, no other polymorphisms of type I IFN genes that impact RSV severity have been described so far.

Regulated on activation normal T cell expressed and previously secreted (RANTES)

Nasal epithelial cells, fibroblasts, and mast cells produce RANTES protein after RSV infection [39, 107]. RANTES plays a critical role during RSV infection and pathophysiology of bronchiolitis, since it induces chemotaxis of eosinophils, T cells, and monocytes [108]. RANTES levels are associated with risk of recurrent wheezing in RSV bronchiolitis [109]. In an animal model of RSV-infected mice, RANTES production was found to be dependent on the RSV infection, and neutralization of RANTES with anti-RANTES antibody reduced the airway hyperreactivity [110]. Genetic predisposition to severe bronchiolitis has been associated to the variations in the *RANTES* gene. The mutations -403G/A and -28C/G in the promoter were found to increase the transcription of *RANTES* which was evident by the serum levels of RANTES [111–113]. These variants have been related to increased risk of RSV bronchiolitis in two studies in China. One study analyzed 320 children with RSV bronchiolitis in Southern China, and found

that the heterozygous genotype G/A in -403 G/A polymorphism was associated with increased recurrent wheezing risk after RSV bronchiolitis [113]. The second study evaluated 238 infants (under 12 months) in the Nanjing Children's Hospital, and the results showed that the presence of -28G allele increased the risk of RSV bronchiolitis to 2.09, showing an absolute eosinophil count in peripheral blood of RSV-infected children higher than that of control infants [114]. On the contrary, in a study conducted in 106 Greek infants (1–24 months old), there was no association of two SNPs (-403G/A, -28C/G,) in the promoter region of the *RANTES* gene to severity of RSV [115]. These results suggest that more studies are needed to determine the possible association of polymorphism in these genes in different population with a sufficient population size.

Interleukin (IL)-8

During RSV infection, neutrophil recruitment is dependent on the IL-8 production. Neutrophil influx is a remarkable characteristic among the patients with severe RSV infection as the increased concentration of plasma levels of IL-8 has been associated with severe RSV infection in the children [116–118]. Neutrophils have been found to show protective effect during RSV infection, such as reduction of viral dissemination [119], or production of the anti-viral cathelicidin LL-37 [120, 121]. Nevertheless, many reports have evidenced a detrimental role of this innate immune cell in the pathogenesis of severe cases of RSV infection, mainly mediated through the release of elastase [122], mucin production [123], or NETosis [124]. The *IL8* gene has polymorphic variations that may contribute to the severity of RSV infection. The SNP -251A/T is located in the promoter and has been associated with a higher risk of severe symptoms in RSV infection. In a cohort of 117 infants in the United Kingdom, the presence of allele -251A was increased in patients with RSV bronchiolitis. As a functional approach, the authors also reported that the -251A allele was related to the increased IL-8 secretion after stimulating whole blood cells with LPS [125]. In a cohort of 320 Chinese children with severe bronchiolitis for RSV, the 54.6% presented wheeze and had increased prevalence of the -251A allele [126]. On the contrary, the allele -251T showed increased frequency in 101 Chinese children with severe RSV pneumonia, which increased the OR to 2.08 [127].

Transcriptional factors

Nuclear transcription factor κ -light-chain-enhancer of activated B cells (NF- κ B)

The NF- κ B is a transcription factor with pivotal role in the regulation of the expression of hundreds of genes that participate in the immune responses, such as enzymes, receptors,

chemokines, cytokines [128]. Structurally, NF- κ B consist of a family of dimeric transcriptional factors formed of two class of proteins. One is represented by RelA (p65), RelB and c-Rel subunits, that contain the DNA-binding/dimerization domain called Rel homology domain (RHD), and the transcriptional activation domain. The other class comprises of p50 and p52 subunits, which are expressed as large precursors p105 and p100, respectively, and contains the RHD and, additionally, an ankyrin repeat domain. In a canonical pathway, p105 is cleaved with the participation of a phosphorylation-mediated activation of IKK complexes. This releases the inhibitory κ B (I κ B) proteins and C-terminal ankyrin repeats from p105, thereafter allowing the release of the heterodimers RelA:p50 (prominently), RelA:c-Rel and c-Rel:p50, which drive the expression of diverse genes of immune response [129–131]. RSV evades immune response by redirecting the RelA protein to the cytoplasmic inclusions, making it unavailable to translocate to the nucleus for the transcriptional transactivation [132]. In this context, IL-8 expression after RSV infection has been found to be dysregulated. It has been shown by an in vitro study that this dysregulation is dependent on the translocation of RelA into the nucleus and binding to the IL-8 promoter [133]. It has also been found that host genetics might influence the activity of NF- κ B during RSV infection. The promoter of the *NFKBIA* gene (coding I κ B protein) possesses variants that influence the grade of response after stimuli. The polymorphism rs2233406 (-839 C/T) alters the binding regions for CCAAT/enhancer binding protein α (C/EBP α). In 352 Canadian children the minor allele was more prevalent in the group with severe RSV infection and significantly increased the OR to 1.83 [134].

Activator protein (AP)-1

The activator protein-1 (AP-1) is a dimeric transcriptional factor consisting of the members of the family Jun (c-Jun, JunB, JunD) and Fos (c-Fos, FosB, Fra-1, Fra-2) proteins, that after their interaction bind to AP-1 regulatory elements located in the promoters and enhancers of diverse genes related to the immune response [135, 136]. The increased expression of AP-1 in A549 cells (human type II pulmonary epithelial cells) infected with RSV demonstrated the importance of AP-1 in RSV infection. Binding of AP-1 to a region located from -132 to -99 in the *IL8* promoter was found to induce the expression of IL-8 [45, 137]. The silent polymorphism rs11688 (c.750 G/A) in *JUN* gene, which encodes the c-Jun protein, has been recognized as a gene marker for the predisposition of severe forms of RSV bronchiolitis. This was evident in a cohort of 480 children in The Netherlands, in whom this allele increased the OR to 1.48 and 3.45 in hetero- and homozygous patients, respectively [105].

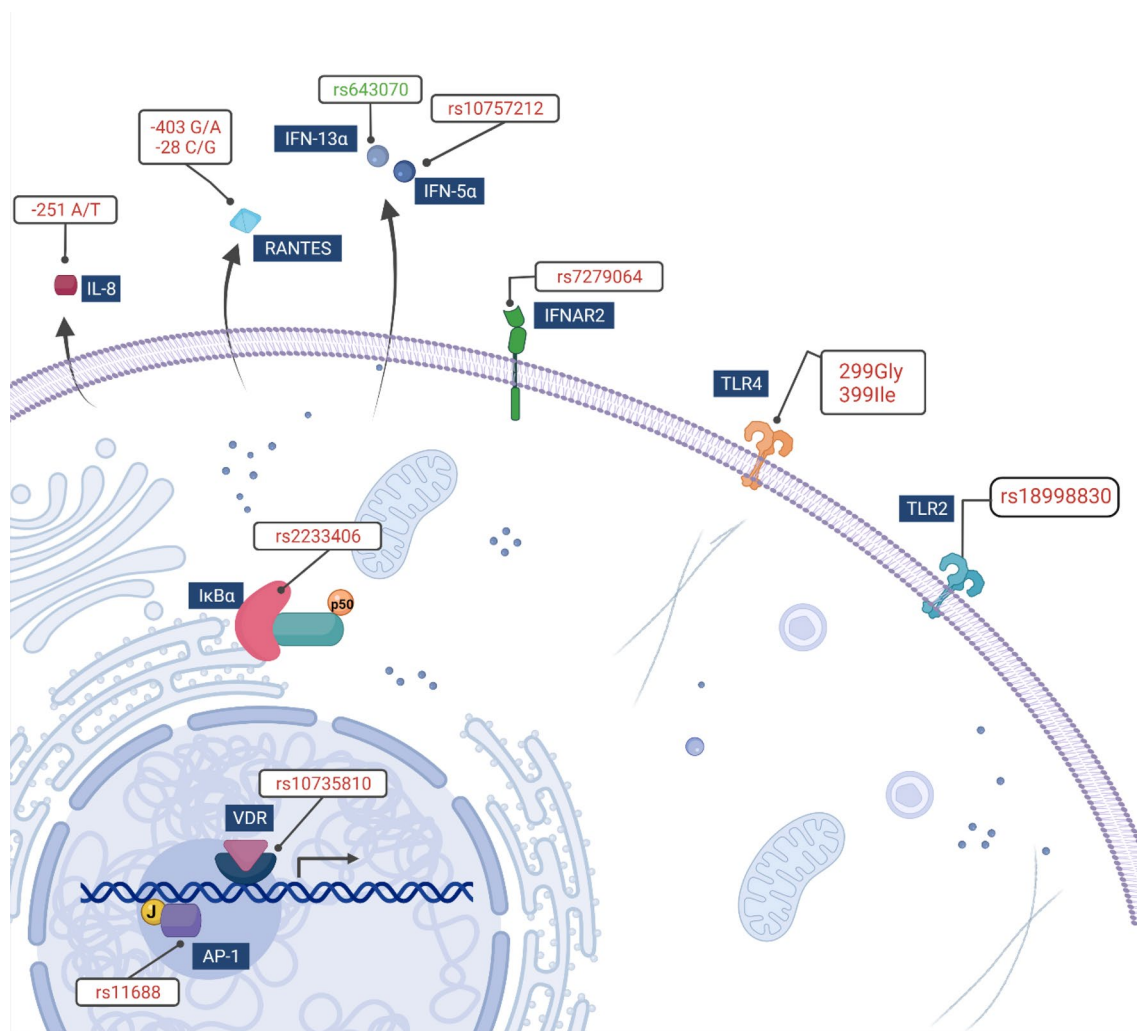


Fig. 3 Genetic variations in the innate immune response genes that alter the severity of RSV infection. Polymorphisms associated to an increased severity of RSV infection (red letters) and to protection (green letters). Created with BioRender.com (Access date: March 25th, 2022)

Vitamin D receptor

Vitamin D is a steroid hormone obtained from dietary constituents such as oily fish, and endogenous sources including photochemical transformation of precursor 7-dehydrocholesterol [138, 139]. The active form of vitamin D is produced when CYP27B1 hydroxylates 25-hydroxyvitamin D₃ into 1,25-dihydroxyvitamin D₃ (1,25D), which has been found to induce the production of antimicrobial molecules cathelicidin and LL-37 in macrophages and monocytes [140, 141]. Vitamin D might play a regulatory role in RSV-induced inflammation. The hTBE cells have reduced activation of NF-κB in presence of 1,25D due to the increased expression of *NFKBIA* mRNA. This effect was found to alter the response in RSV-infected hTBE, since the treatment with 1,25D reduced the levels of *IFNB*, *CXCL10*, and *ISG15* mRNA. However, the reduction of IFN-β did not alter the

viral replication [142]. The effects of vitamin D are facilitated by the binding of vitamin D to the vitamin D receptor (VDR), which once complexed act as transcriptional factor triggering the expression of vitamin D responsive genes [143, 144]. Some genetic variations in the *VDR* gene have been described to alter the response to vitamin D in diverse pathologies [145]. In terms of RSV infection, the polymorphism rs10735810 has been found to be significantly involved. It causes a change C/T (Thr1Met), which can be determined with the restriction enzyme *FokI*, and generates a new start codon located three codons upstream from the wild-type start site (ATG). Then, the polymorphic version of VDR contains three amino acids extra in the N-terminal side [146–148]. The role of the polymorphism rs10735810 in RSV severity was indicated in 470 children hospitalized in The Netherlands, by its significant association with bronchiolitis as evident by OR of 1.30 [105]. Similar results have

been found in a study conducted among 296 South African children with an average age of 3 months, reporting that patients with allele T were more susceptible to severe RSV infection [149].

Conclusion

As most cases of severe RSV infection occur in otherwise healthy infants who have no identifiable risk factors, it is suggested that additional subclinical factors, such as population genetic variations, should also be studied as these might also influence the course of RSV infection. As we highlighted in this review, various studies have shown that different polymorphisms associated with innate immune genes play crucial roles in the physiopathology, susceptibility, or protection to RSV infection in children (summarized in Fig. 3).

Overall, literature suggests that the identification of more SNPs associated with RSV infection would help to decipher the mechanisms involved in the severity of RSV infection. This mechanistic elucidation could further lead to development of novel therapeutic strategies against RSV infection. Since until now there are no vaccine for protection or specific treatment for helping to patient during infection, an accurate and properly modulation of the children immune response against the virus might be key in the prompt clearance of RSV from the host.

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Declarations

Conflict of interest The authors declare no conflict of interest.

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