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The host response and molecular pathogenesis associated with respiratory syncytial virus infection

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Abstract

Since the isolation of respiratory syncytial virus (RSV) in 1956, its significance as an important human pathogen in infants, the elderly and the immunocompromised has been established. Many important mechanisms contributing to RSV infection, replication and disease pathogenesis have been uncovered; however, there is still insufficient knowledge in these and related areas, which must be addressed to facilitate the development of safe and effective vaccines and therapeutic treatments. A better understanding of the molecular pathogenesis of RSV infection, particularly the host-cell response and transcription profiles to RSV infection, is required to advance disease intervention strategies. Substantial information is accumulating regarding how RSV proteins modulate molecular signaling and regulation of cytokine and chemokine responses to infection, molecular signals regulating programmed cell death, and innate and adaptive immune responses to infection. This review discusses RSV manipulation of the host response to infection and related disease pathogenesis.

Keywords

adaptive immunity; disease; innate immunity; respiratory syncytial virus

Respiratory syncytial virus

The *Paramyxoviridae* family includes important human respiratory-tract pathogens, of which human respiratory syncytial virus (RSV) is a member. RSV is in the *Pneumovirinae* subfamily and type species member of the *Pneumovirus* genus. RSV was first isolated four decades ago from chimpanzees during an outbreak of respiratory illness [1]. Thereafter, RSV was isolated from infants with pneumonia and bronchitis [2], and was named RSV owing to its characteristic

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ability to induce syncytia in cell lines. RSV is a ubiquitous virus and the most important cause of serious lower respiratory-tract illness in infants and young children worldwide, as well as an important pathogen in the elderly and the immunocompromised [3–11]. RSV is the primary cause of hospitalization for respiratory tract illness in young children with infection rates approaching 70% in the first year of life [12]. In the USA, lower respiratory-tract disease develops in 20–30% of children infected with RSV, of which many require hospitalization [13].

RSV is a nonsegmented pleiomorphic negative-strand RNA virus containing two nonstructural (*NS1* and *NS2*) genes followed, in gene order, by nucleocapsid, phosphoprotein (*P*), matrix, small hydrophobic (*SH*), surface attachment glycoprotein (*G*), surface fusion glycoprotein (*F*), a *M2* gene, which encodes two proteins from M2-1/M2-2 open reading frames that have roles in RNA transcription and replication, and RNA-dependent RNA polymerase (*L*). The virus consists of a nucleocapsid surrounded by a lipid envelope derived from the host-cell plasma membrane during the budding process [14–16]. There are three virally encoded surface transmembrane proteins: G, F and SH, and all three of these proteins have been associated with modifying aspects of the host response to infection. The G protein, or attachment protein, is a type II glycoprotein with a single N-terminal hydrophobic region (amino acids 38–66) that serves as a signal peptide and membrane-anchor [17–20]. Proximal to the membrane anchor region is an extracellular ectodomain containing four cysteine residues that are highly conserved in all RSV isolates [21,22]. This cysteine region contains a CX3C chemokine motif (amino acids 182–186) that may facilitate virus attachment to cells expressing the CX3C chemokine receptor, and modify CX3CL1 (fractalkine)-mediated responses as an immune evasion strategy [23]. The G glycoprotein is expressed as both a membrane-bound (G_m) and secreted form (G_s) by initiation of translation at an alternate in-frame AUG codon located in the middle of the hydrophobic transmembrane region [19]. Approximately 15% is synthesized in infected cells as a soluble form lacking the cytoplasmic but G_s retains the same characteristics domain, as G_m, for example, glycosylation and antibody reactivity [24,25]. The SH protein is a minor surface protein that has been shown to have the ability to form cation-selective ion channels in planar lipid bilayers [26] and interact with the G protein [27]. In addition, the SH protein may inhibit TNF-α signaling [28]. Considering the other RSV proteins with known immune modulatory activities, the function of NS1 and NS2 proteins appear to act cooperatively to antagonize the type I IFN antiviral response [29–33]. Studies with recombinant RSV with deletions in the NS1 and NS2 have shown that these genes are dispensable for virus replication *in vitro*, however, through type I IFN antagonism, they provide auxiliary functions for efficient RSV replication *in vitro* and *in vivo* [34].

RSV replication

RSV attachment to cells primarily occurs via heparin-binding domains on the G protein with cell-surface glycosaminoglycans [35–37]. The G protein itself is not required for virion attachment as RSV mutant viruses lacking *G* and/or *SH* genes have been shown to infect cells likely through interaction with the F protein [38–41]; however, G protein appears to be necessary for efficient virus replication *in vivo* [40]. Following cell fusion and penetration mediated by the F protein [42], the nucleocapsid is released into the cytoplasm [43–46] where the L protein initiates viral transcription and replication proceeds [47]. Transcription of mRNA occurs in a 3′ to 5′ order from a single promoter near the 3′ end resulting in a series of subgenomic mRNAs [48–52]. mRNAs can be detected by 4 h postinfection with peak mRNA synthesis and protein expression occurring 12–20 h postinfection. Importantly, the level of protein expressed is related to mRNA abundance [49], thus there are decreased levels of mRNA proportional to the gene distance from promoter sequence. Virions assemble at the plasma membrane where nucleocapsids localize with the cell-membrane containing membrane viral

glycoproteins. The virions mature in clusters at the apical surface in a filamentous form associated with caveolin-1, and extend from the plasma membrane [53].

Regulation of the host-cell response to infection

RSV primarily infects respiratory epithelial cells lining the nasal passages and respiratory tract. RSV infection of host cells has been shown to alter the tempo and expression patterns of various genes related to protein metabolism, cell growth and proliferation, cytoskeleton organization, regulation of nucleotides and nucleic acid synthesis, and cytokine/chemokine genes linked with inflammation [54,55]. While a primary function of airway epithelium is to promote gaseous exchange, it also functions as the interface between the external environment and the host, thus acting as a first-line defense against pathogens. Given the unique position of airway epithelial cells in this regard, they also provide a close interface with various immune components including mucosal dendritic cells (DCs) and intraepithelial lymphocytes [56]. To overcome the repertoire of immune defenses encountered, it is not surprising that RSV enlists a variety of immune modulatory and evasion strategies to promote virus infection and replication.

RSV delays programmed cell death to facilitate virus replication

RSV infection does not induce substantial cytopathology in human airway epithelial cell models [57,58], a feature in part associated with the ability of RSV to delay programmed cell death or apoptosis of epithelial cells. It has been shown that RSV-infected cells have increased expression of the anti-apoptosis gene *IEX-1L* and increased expression of several Bcl-2 family members including myeloid cell leukemia-1 and Bcl-XL [59–62]. Recent studies have suggested other mechanisms that may contribute to delayed cell death that are linked to the inhibition of tumor suppressor p53 and Akt activation, leading to p53 proteosome degradation [63]. The delay of apoptosis has also been connected to the phosphatidylinositol 3-kinase-dependent pathway [64], and to increased ceramidase and sphingosine kinases leading to enhanced levels of anti-apoptotic proteins within cells [65]. In addition, the RSV NS and SH proteins have been shown to delay premature apoptosis, a feature that results in more robust viral titers [28,66].

Modulation of host-cell responses via pattern recognition receptors

A majority of respiratory epithelial cells express pattern recognition receptors (PRRs) or Toll-like receptors (TLRs), which aid in sensing infection and host-cell signaling and communication. RSV infection of respiratory epithelial cells has been shown to result in increased TLR4 expression on the cell surface within 24 h postinfection [67,68]. The upregulation of TLR4 leads to increased sensitivity to endotoxin, and upon stimulation with lipopolysaccharide, enhanced IL-6 and IL-8 production has been observed [67]. TLR4 expression in infants responding to RSV infection has also been examined. In one study, infants possessing two single-nucleotide polymorphisms encoding Asp299Gly and Thr399Ile substitutions in the TLR4 ectodomain were highly associated with symptomatic RSV disease, suggesting that heterozygosity of these two extracellular TLR4 polymorphisms is associated with symptomatic RSV disease in high-risk infants [69], supporting the role for TLR4 in host response to RSV infection. Furthermore, peripheral monocytes isolated from infants with severe RSV bronchiolitis also showed increased TLR4 expression [70]. Like lipopolysaccharide, the RSV F protein can interact with TLR4 and CD14 in human monocytes leading to the activation of NF-κB and the production of proinflammatory cytokines TNF-α, IL-6 and IL-12 [71]. While the mechanism is not yet clear, the RSV G protein may also suppress TLR3/4-mediated cytokine production by interfering with the TLR adaptor, TNF receptor-associated factor/Toll IL-1 receptor domain-containing adaptor molecule-1 or NF-κB activation, resulting in decreased proinflammatory cytokine production [72,73]. A recent study demonstrated that RSV promotes TNF-α, IL-6, monocyte chemotactic protein (MCP)-1 and

RANTES via interaction with TLR2 and TLR6 [74]. These findings indicate that TLR4 has a role in sensing RSV infection and contributing to protection from RSV infection.

RSV interferes with the host antiviral cytokine response

Several studies have shown that RSV nonstructural proteins, NS1 and NS2, are important in antagonizing the type I IFN response in infected epithelial cells as well as suppressing DC maturation [30,32,33,75–78]. NS2 is the principal type I IFN antagonist linked to STAT-2 signaling [76,79,80]. The NS1 protein contains elongin-C- and cullin-2-binding sequences and can potentially act as an ubiquitin E3 ligase to target STAT-2 to the proteasome [80,81]. Bovine RSV nonstructural proteins have also been shown to interfere in type I IFN signaling via a mechanism involving IFN regulatory factor (IRF)3 phosphorylation and subsequent activation [75]. Aside from the role for NS1 and NS2 in governing type I IFN expression, a recent study in mice epithelial-15 lung cells showed that by 24 h postinfection, in the absence of NS1 and NS2 proteins, type I IFN mRNA and IFN-β protein expression were suppressed [31]. In this study, a role for RSV G-protein inhibition of IFN-β was revealed and linked to the induction of suppressor of cytokine signaling (SOCS)1 and SOCS3 expression. SOCS proteins are negative regulators of cytokine expression [82,83], and act to inhibit the JAK–STAT pathway to regulate cytokine expression via a kinase inhibitory region [84]. While it remains unclear whether NS1 and NS2 directly affect SOCS expression, the net result of SOCS expression leads to a decreased antiviral response within the cell. RSV can also interfere with JAK–STAT signaling and chemokine transcription by inducing Bcl-3, which complexes with STATs in the nucleus, resulting in enhanced infection [85].

RSV infection modulates respiratory epithelial cell function

A consequence of severe RSV disease is fluid extravasation into the lung air spaces [86]. RSV infection of murine and human airway cells results in decreased sodium transport across epithelial cells leading to reduced alveolar fluid clearance in mice [64,87,88]. Evidence suggests that the RSV F protein and TLR4 have a role in this effect [89], and one recent study found that RSV infection of primary bronchial cells resulted in a loss of plasma-membrane integrity and cytoskeletal rearrangement dependent on MAPK signaling via p38 and heat shock protein-27 activation [86]. p38 MAPK activation and heat shock protein-27 phosphorylation may result in actin reorganization and an altered shape of the infected cell [90].

RSV infection also results in reduced levels of surfactant proteins (SP), particularly SP-A and SP-D, in bronchoalveolar lavage [91,92]. Nonciliated cells of the respiratory tract produce SP-A and SP-D, which are important in promoting opsonization of pathogens as well as apoptotic cells [93]. SP-A has been shown to bind to the RSV F protein and promote uptake of RSV-infected cells by macrophages [94,95], while SP-D binds to the RSV G protein to inhibit infection [96]. Although SP-A and SP-D bind viruses as part of the clearance mechanism, it is possible that RSV may use these innate host-defense proteins to sequester surfactant proteins during infection to prevent antibody neutralization or to limit the immune cell response to infection, an effect that may be linked to the decreased levels of SP-A and SP-D found in the lungs of infected infants [92].

Matrix metalloproteinases are involved in the digestion of extracellular matrix components such as gelatin, collagens (types IV, V, XI and XVII) and elastin [97]. RSV infection can enhance the expression of matrix metalloproteinase-9, which increases the rate of syncytium formation, leading to more efficient viral replication [98]. Furthermore, prostaglandin, which are implicated in many regulatory events including the differentiation of immune cells and regulation of immunological and inflammatory responses, are increased via increased cyclooxygenase-2 expression, which occurs during RSV infection [99–101]. Prostaglandin E2

is considered a potent proinflammatory mediator, and in the lung, has a role in limiting the immune inflammatory response as well as the tissue repair processes [102].

RSV G protein immune evasion

The RSV G protein was first recognized as an attachment protein involved in the binding of RSV particles to the host cell surface. Following RSV infection, the G protein is produced in two forms, G_m and G_s [24,103]. G protein is one of two major RSV proteins recognized in the antibody response to infection, the other being the F protein [104,105]. While the antibody response primarily recognizes epitopes within the C-terminal region of the G protein [106, 107], the glycosylation pattern of the RSV G protein changes depending on the specific cell type infected [108–111]. Thus, the altered glycosylation patterns are likely to be a feature linked to immune evasion associated with changes in the G protein antigenic profile [112,113].

The G protein has known attributes that contribute to host protein mimicry and immune evasion. For example, the G_m and G_s proteins both contain a central-conserved cysteine-rich region, homologous to the fourth subdomain of the TNF receptor, which can modulate the innate immune response to infection [23,72,114–116]. TNF-α/β are proinflammatory cytokines implicated in a large range of inflammatory conditions [117] and in the antiviral response to RSV infection [118]. It is possible that the G_s protein may bind to TNF-α or other homologs modulating the host antiviral response [24,116]. The central-conserved cysteine-rich region also contains a CX3C chemokine motif at amino acid positions 182–186, which binds to CX3CR1, the CX3CL1 (fractalkine) receptor [23]. CX3CR1 mimicry by the G protein has been shown to facilitate RSV infection and alter CX3CL1 chemotaxis of human and mouse leukocytes [23]. Expression of the G protein during RSV infection of mice has also been shown to decrease the number of activated and RSV-specific pulmonary $CX3CR1^+$ T cells, as well as natural killer (NK) cells [119]. Consistent with this finding, infection of mice with a RSV mutant virus lacking the *G* and *SH* genes results in enhanced numbers of NK cells recruited to the lung as well as increased IFN-γ and TNF-α production, suggesting that the G and/or SH surface proteins inhibit NK cell recruitment and proinflammatory cytokine production [41]. Together these studies suggest that RSV can modulate both the innate and adaptive immune responses to infection via G protein expression.

Cytokine response to RSV infection

Cytokines are a diverse group of secreted proteins produced *de novo* in response to immune stimuli that mediate and regulate immunity, inflammation and hematopoiesis. Chemokines, a constituent of the cytokine family, function to activate and attract leukocytes to sites of infection. Many cytokines are pleiotropic and may have multiple, overlapping or redundant actions that can be explained by the presence of receptors for a cytokine on multiple cell types or lineages, or by a cytokine having the ability to activate multiple signaling pathways that may differentially contribute to different cell functions. A wide range of cytokines and chemokines are produced by different cell types in response to RSV infection, some of which mediate proinflammatory functions to activate and recruit immune cells, and others that suppress or regulate the proinflammatory state. For example, RSV infection of airway epithelial cells has been shown to result in a cascade of signaling events mediated by NF-κB leading to the expression of proinflammatory cytokines and chemokines including RANTES, MCP, eotaxin, IL-9, TNF-α, IL-6, IL-1 and CX3CL1 (fractalkine) [120–127]. It has been suggested that certain patterns of cytokine and chemokine expression in a RSV-infected individual may be an indicator of disease severity [128]. Studies with RSV-infected patients have shown that increased levels of macrophage inflammatory protein (MIP)-1α, RANTES and IL-8 are often present in the upper and lower respiratory tract [121]. Likewise, bronchial epithelial cells infected with RSV have been shown to express high levels of IL-6, IL-8 and RANTES [129]. Blocking any one of these factors may result in less severe disease. For example, antibody-

mediated depletion of RANTES or eotaxin results in reduced airway hyper-reactivity and eosinophilia in mice infected with RSV [130,131]. Furthermore, the tempo and pattern of cytokine and chemokine expression has also been linked to age, as mice infected as neonates display higher illness scores, greater cell recruitment to the lungs and increased IL-4 production, and upon reinfection with RSV as adult mice, develop manifestations of severe disease associated with a Th2-type cytokine response [132].

RSV G-protein expression during acute infection in mice has been associated with altered CC and CXC chemokine mRNA expression and Th1/Th2-type cytokine responses by bronchoalveolar leukocytes [133,134]. Specifically, the G protein appears to inhibit early MIP-1α, MIP-1β, MIP-2, MCP-1 and IFN-inducible protein of 10 kDa mRNA expression, all important chemokines that attract immune cells to sites of infection or inflammation [133]. G-protein expression has also been linked with reduced IFN-β expression in mouse lung epithelial cells [31], thus RSV appears to modulate the balance or expression of cytokines to manipulate antiviral immunity, a feature that may contribute to RSV-mediated disease pathogenesis.

RSV activation & regulation of cellular transcription factors

Accumulating evidence suggests that RSV interacts with TLRs and PRRs and activates signaling and downstream cellular transcription pathways [68,71,73,74,135–138]. *In vitro* studies show that RSV infection upregulates TLR4 expression in A549 cells [68], and more specifically, that purified RSV F protein interacts with TLR4 in a CD14-dependent manner [71]. Signaling through TLR4 can lead to activation of TNF receptor-associated factor and the adaptor protein MyD88, which in turn activate downstream members IKKε/TANK-binding kinase-1 and IL-1 receptor-associated kinase-4, thereby initiating signaling pathways leading to the induction of an array of transcription factors (IRF3, IRF7, NF-κB, JNK, p38 MAPK and activator protein-1), which translocate to the nucleus and initiate transcription of various proinflammatory genes [139]. TLR3, the ligand of which is dsRNA, is upregulated in response to RSV infection [137,140]. Cellular signaling via TLR3 leads to the activation of downstream IKKε/TANK-binding kinase-1, which in turn induces the nuclear translocation of transcription factors such as IRF3, IRF7 and NF-κB. Activation of the TLR3 pathway in A549 airway epithelial cells was shown to control phosphorylation of RelA providing a mechanism for regulating RSV-induced NF-κB-dependent gene expression at the late phase of infection [138]. Similarly, retinoic acid-inducible gene (*RIG*)-*I*, is a cellular cytoplasmic helicase protein that recognizes the 5′ triphosphate ends of RNA generated by viral polymerases and when activated leads to the induction of IFN-α and IFN-β [141]. *In vitro* studies in A549 cells have shown that RSV infection induces RIG-I and TLR3 expression, and that TLR3 induction is regulated by RIG-I-dependent IFN-β and mediated by both IFN response-stimulated element and STAT sites within its proximal promoter [138]. These findings indicate distinct roles for RIG-I and TLR3 in mediating RSV-induced innate immune responses. Later stage signaling events suggest that paracrine signaling mechanisms may have an important role in the innate response to RSV infection. Recently, studies examining IFN-mediated monocyte-derived DC (mDC) TLR3/4 signaling showed that mDCs treated with live or UV-irradiated RSV showed no early (within 4 h) induction of IFN-β [73]. In this study, initial virus attachment to the cells blocked poly-I:C-mediated IFN-β induction. Furthermore, studies using IFN-stimulated response element reporter analysis in HEK293 cells demonstrated that RSV G protein inhibited TLR3/4-mediated IFN-stimulated response element activation. These findings are consistent with studies in mice epithelial-15 lung cells, which showed that RSV G protein modulates SOCS1 and SOCS3 expression associated with the type I IFN response, and in particular, inhibits IFN-β expression [31].

STAT proteins are a family of transcription factors that are activated following phosphorylation by JAK, translocated to the nucleus, where IFN-γ activation factor, a dimer of STAT1, binds

to, and initiates transcription of, genes containing IFN-γ-activated sites [142]. RSV proteins have been shown to modulate STAT signaling and transcription of IFN-regulated genes. For example, *in vitro* studies in A549 cells and human tracheobronchial epithelial cells have shown that RSV NS protein expression is linked to reduced levels of STAT2 [76,80], a feature that requires proteasomal activity. NS1 protein contains elongin-C- and cullin-2-binding consensus sequences, which allow NS1 to act as an E3 ligase, thereby targeting STAT2 for proteosome-mediated degradation [81]. Degradation of STAT2 suppresses formation of the IFN-stimulated gene factor-3 transcription factor complex [143,144]. The IFN-stimulated gene factor-3 transcription factor is a heterotrimer complex composed of STAT1, STAT2 and IRF9, which translocate to the nucleus and bind to ISRE leading to the transcription of IFN-regulated genes such as 2′5′OAS Mx, PKR, MHC, CD80, CD86, iNOS, *STAT1* and *IRF7* [145]. These studies provide a mechanism for NS antagonism of type I IFN responses to infection [76,78]. In addition, another mechanism that can negatively regulate type I IFN expression is SOCS regulation of the JAK-STAT signaling pathway [82]. Of the eight SOCS family members, SOCS1 and SOCS3 appear to be the most efficient at downregulating type I IFN expression [146], and SOCS1 and SOCS3 expression has been shown to be modulated during RSV infection, leading to type I IFN antagonism [31,147].

Innate immunity to RSV infection

Innate immunity constitutes an evolutionarily conserved, nonspecific primary defense strategy that is important for recruitment, activation and production of the virus-specific adaptive immune response that mediates long-lasting immunity. Viral recognition by the host is essential for regulating the functional consequences of infection. TLRs and PRRs recognize conserved pathogen-associated molecular patterns [148]. Viruses that trigger TLRs initiate a complex signaling cascade leading to the expression of a variety of genes and signaling through NF-κB [149]. It is likely that multiple TLRs and/or PRRs are involved in detecting RSV or RSV components as several TLRs and PRRs have been shown to be affected by RSV infection [68,71,73,74,135–138], and although not all TLRs or PRRs may be required to facilitate RSV clearance, it seems that some, for example TLR3, may be important for maintaining an immune environment by avoiding the development of Th2-mediated pathology in the lungs [150].

TLRs are broadly distributed along the airways by various cell types including respiratory epithelial cells, alveolar macrophages and DCs. Virus infection sensed by TLRs results in NF-κB activation and inflammatory chemokine and cytokine expression. These chemokines and cytokines can act directly or via an autocrine/paracrine feedback mechanism to regulate virus infection and replication. RSV has been shown to be a poor inducer of type I IFNs (IFN-α/β), and cells infected with RSV are resistant to the antiviral effects of IFN-α/β [30]. As noted previously, RSV NS1 and NS2 proteins have been shown to act cooperatively as type I IFN antagonists [30,32,33,75], and recent studies suggest that RSV G protein also inhibits IFN-β expression [31]. As type I IFNs have an important role in DC maturation, activation of NK cells, differentiation and function of T cells, as well as enhancing primary antibody responses [151,152], RSV-mediated inhibition of IFN production negatively impacts antiviral immunity and facilitates virus replication.

Dendritic cells

DCs are the major antigen-presenting cells following RSV infection [153,154]. The costimulatory or inhibitory surface molecules and cytokines secreted by DCs influence the T-cell response, such as whether T cells are activated or tolerized and whether they are polarized to Th1, Th2 or regulatory T cells [155]. Respiratory DCs are located within intraepithelial sites and below the respiratory epithelium where they encounter RSV and carry the RSV antigens to the draining lymph node. There are two main subsets of DCs: myeloid or conventional DCs expressing CD11b and CD11c, and plasmacytoid DCs (pDCs) expressing little or no CD11b

or B220 [156]. The balance between conventional DCs and pDCs in the lung and lymph nodes is essential for driving pulmonary immunity to RSV infection [157]. Increased pDC numbers have a protective impact on the nature of the overall immune environment, while depletion of pDCs from the lungs of RSV-infected mice results in a pathologic response characterized by increased Th2 cytokine profiles [157–159]. DCs in the lung can be infected by RSV. Although RSV-infected DCs can still differentiate and mature, they display impaired T-cell activation, an effect linked to altered IFN-α or IL-1 receptor-α expression [160,161]. It has also been shown that direct contact of T cells with RSV F protein expressed on cells inhibits T-cell activation [162]. Moreover, a recent study showed that RSV impairs T-cell activation by preventing T-cell receptor–DC synapse assembly on DCs [163]. Thus RSV-infected DCs expressing F protein may also inhibit T-cell activation by a related mechanism.

Macrophages

Macrophages, like DCs, are key effector cells in the innate immune response. The lower respiratory tract abounds with alveolar macrophages, which serve as significant sources of proinflammatory cytokines such as TNF-α, IL-6 and IL-8 following RSV infection [164]. In one study, a depletion of macrophages significantly inhibited the early release of inflammatory cytokines following RSV infection, an effect which resulted in enhanced virus titers in the lung [165]. In this study, a depletion of macrophages had little effect on the activated T-cell recruitment and overall lung disease, suggesting that macrophages may be more important in the earliest response to RSV infection. However, a recent study comparing RSV-mediated lung pathogenesis in BALB/c and New Zealand Black (NZB) mice showed that alveolar macrophages are central in the disease process because depletion of alveolar macrophages in BALB/c mice before RSV exposure resulted in airway occlusion, and a similar pathogenesis was observed in NZB mice deficienct in alveolar macrophages [166]. In this study, RSV infection yielded an increased viral load and enhanced expression of type I IFN genes at the height of disease, suggesting that innate, rather than adaptive, immune responses are critical determinants of the severity of RSV bronchiolitis.

Natural killer cells

NK cells constitute a major component of the innate immune system where they have a major role in the clearance of tumors and virus-infected cells by virtue of their natural cytotoxic ability. Chemokines, such as MIP-1α, are important for the recruitment of NK cells to the site of infection and inflammation [167]. During RSV infection, NK cells are recruited to the lungs very early after infection and reach peak levels at approximately day 3–4 postinfection [41, 114]. DCs are considered to be the primary cell types that potentiate NK-cell activation and cytotoxicity [168,169]; however, a recent study showed that alveolar macrophages are required to recruit and activate NK cells in response to RSV infection, and depletion of macrophages reduced the activation and recruitment of NK cells [165]. RSV G and/or SH proteins appear to regulate trafficking of NK cells to the lungs, as mice infected with a RSV mutant lacking *G* and *SH* genes exhibited greater pulmonary trafficking of NK cells compared with mice infected with wild-type RSV [41].

Natural killer T cells

Natural killer T (NKT) cells are a subpopulation of CD1d-restricted T cells that coexpress semi-invariant T-cell receptor and NK-cell markers [170]. NKT cells recognize glycosphingolipids presented by CD1d, an antigen-presenting molecule that is related to the classical MHC class I and class II glycoproteins [171,172]. These cells can produce Th1- and Th2-type cytokines and therefore have the potential to impact adaptive immune responses by governing aspects of the cytokine microenvironment. NKT cells have been implicated in immune responses against RSV infection; NKT cells were shown to have a role in early IFN-

γ production and efficient induction of CD8 T-cell responses during primary RSV infection [173].

Adaptive humoral immunity

RSV infection induces antibody responses against several viral antigens; however, only the two major surface glycoproteins (F and G proteins) induce antibodies that have a major role in protection [174]. Vaccination studies using recombinant vaccinia virus expressing various RSV proteins have shown that serum antibodies can be induced by F, G, M2 and P proteins, but only F and G proteins were the major determinants of protection [175]. The RSV F protein has two forms: a mature form, found in virions, and an immature folded form [176,177]. The immature F protein does not contain all the neutralizing epitopes found on the mature form of the F protein, thus if released from lysed cells or made available from a denatured mature F protein; it is possible that the immature form may induce an ineffective antibody response leading to the diversion or reduction of a protective antibody response. It has been shown that both forms of F protein are able to induce antibody responses of comparable magnitudes [178]. Comparing the F to G proteins among RSV isolates, reveals that the G protein is the more divergent protein [179]. Between the major antigenic subgroups of RSV, such as A and B strains, there is only a 53% identity for G protein but a 90% similarity for the F protein. Therefore, few G-specific monoclonal antibodies are cross-reactive, while the majority of F-specific monoclonal antibodies are cross-reactive [179]. Unexpectedly, very few individual G-protein-specific monoclonal antibodies efficiently neutralize RSV infectivity, and G-protein-specific antibody neutralization requires multiple antibodies [180]. Furthermore, the majority of G-protein-specific monoclonal antibodies are much less effective compared with F-protein-specific monoclonal antibodies in the neutralization of RSV. It appears that protective anti-G protein antibodies recognize the central-conserved cysteine-rich region of the G protein [181]. It is plausible that this feature may also be linked to antibody-mediated inhibition of G protein CX3C interaction with CX3CR1 and immune modulation [23].

Neutralizing antibodies have an important role in protection from RSV infection, although serum and mucosal neutralizing antibodies seem to provide different levels of protection. Serum antibodies, mainly composed of IgG, gain access to the lungs easier than to the nasal passages via transduction. Passive immunization studies in cotton rats have demonstrated that serum antibodies can provide complete protection against RSV replication in the lungs, but only a partial reduction in nasal virus titers [182]. Mucosal secretory IgA antibody may have a more important role in local protection, although this antibody is short-lived and has less neutralizing activity compared with serum IgG antibodies. Repeated RSV infection can induce a sustained antibody response associated with high levels of mucosal IgA in nasal secretions, a feature that can limit virus replication in the upper respiratory tract independent of the level of serum antibodies [183].

Cellular immunity

Although antibody responses are vital for protection again RSV infection, T-cell-mediated cellular immune responses have a greater role in virus clearance. In humans, $CD8^+$ T cells recognize F, matrix, M2 and NS2 proteins, but there is little or no recognition of G, phosphoprotein or NS1 protein [184]. In BALB/c mice, $CD8^+$ cytotoxic T lymphocyte primarily recognize F, nucleocapsid and M2 proteins [185]. Priming of different subsets of $CD4^+$ T cells appears to contribute to the quality and magnitude of the $CD8^+$ T-cell response and subsequent disease pathogenesis. Studies in BALB/c mice vaccinated with different recombinant vaccinia virus constructs expressing G or F proteins have shown that F and G proteins prime different subsets of $CD4^+$ T cells [186]. In BALB/c mice, F protein primes both $CD8^+$ and $CD4^+$ T cells toward a Th1-type biased cytokine response while G protein primes

only $CD4^+$ T cells that are biased towards the Th2-type cytokine response [187]. The Th1 and Th2 $CD4^+$ T-cells elicited react to a single region comprising amino acids 183–197 of the G protein [188]. Antigen-specific Th2-type CD4 T cells from mice have also been shown to respond to non-glycosylated immunodominant epitopes in the ectodomain of G protein, however, these epitopes have been shown to be poorly recognized by human $CD4^+$ T cells [189,190]. In a related study, it was reported that the immunodominant peptide in G protein is recognized by both Th1 and Th2 $CD4^+$ T cells in humans [191,192].

The importance of $CD4^+$ memory T cells to RSV reinfection has been investigated; however, the majority of studies have focused on the response to RSV G-protein priming. It has been shown that the memory $CD4^+$ T-cell response to the RSV G protein in the lungs of primed BALB/c mice challenged with RSV is dominated by effector T cells expressing a single TCR Vβ chain, such as Vβ14 [193]. $CD4^+$ T cells expressing TCR Vβ14 preferentially proliferate and expand into activated effector T cells in the lungs rather than the lymph nodes, which drain the site of infection [194]. Although this study is limited to a specific inbred strain of mice, these findings may be important as RSV-specific $CD4^+$ memory T cells have been shown to have a major role in RSV-induced immunopathology, a feature linked to polarizing for a Th2-type cytokine response and pulmonary eosinophilia [114,153,195–197]. It has recently been shown that RSV-specific memory CD8 T cells, when present in sufficient numbers, inhibit Th2-associated chemokines, CCL17 and CCL22, and may alter the trafficking of Th2-type cells and eosinophils into the lung [198]. Interestingly, the memory $CD4^+$ T-cell response to RSV F protein is much broader than that to RSV G protein. Immunization of mice with the F protein elicits a broad repertoire of RSV F-protein-specific $CD4^+$ T cells that predominantly express Th1-type responses; however, in the absence of IFN-γ, RSV F-specific memory $CD4^+$ T cells secrete IL-5 and develop pulmonary eosinophilia after RSV challenge, suggesting that IFN-γ can modulate the memory $CD4^+$ T-cell response to secondary RSV infection [199].

$CD8^+$ T cells have a major role in the clearance of a virus. RSV-specific $CD8^+$ T cells are found in the lungs and peripheral tissues after RSV infection. Studies have demonstrated that virus clearance is temporally associated with an increase of RSV-specific CD8 cytotoxic T-lymphocyte activity in the lungs [200]. Although T-cell responses to RSV infection predominantly occur in the lungs, it has been demonstrated in a mouse model that T-cell subsets can redistribute to secondary sites following RSV infection [201]. A higher proportion of RSV-specific $CD8^+$ T cells in the peripheral blood have been observed in older infants than younger infants, a feature that might be due to immune immaturity, the Th2-type environment in the lungs or the suppressive effect of maternal antibodies. It has been shown that young children are prone to develop a Th2-type cytokine biased response, which has also been associated with higher RSV pathology [202]. However, other studies have demonstrated a predominant Th1-type response [203].

$CD8^+$ memory T cells are important for clearing RSV reinfection. Studies of RSV-specific $CD8^+$ memory T cells in humans have demonstrated that most pulmonary $CD8^+$ T cells are retained in the lungs and a minority in the peripheral blood [204]. Consistent with these findings, it has been shown, following acute RSV infection in mice, that approximately 20% of pulmonary $CD8^+$ T cells secrete IFN-γ in response to immunodominant peptide stimulation compared with 2–3% in the draining lymph node [205]. It remains unclear whether resident or recruited RSV-specific $CD8^+$ T cells may be more important to control RSV reinfection; however, it has been demonstrated that although there is a higher proportion of $CD8^+$ memory T cells in the lungs, amplification of recall responses in the organized lymphoid tissue is more efficient [205]. These findings do not appear to be related to RSV-mediated suppression, as RSV does not impair the *ex vivo* functionality of RSV-specific $CD8^+$ T cells isolated from the lung during the acute and memory phase of murine RSV infection [206], suggesting that

functionality is likely to be affected by the lung environment. Consistent with these findings, it was recently shown that RSV-specific $CD8^+$ T cells isolated from the lungs were impaired in their ability to secrete IFN-γ compared with RSV-specific $CD8^+$ T cells isolated from the spleen, providing strong evidence that the decreased functionality of $CD8^+$ cytotoxic T lymphocyte is specific to a lung environment and is not dependent on the specific virus, viral antigen or route of infection [207]. The mechanisms contributing to pulmonary $CD8^+$ T-cell functional impairment are not well understood, but the effect may be linked to the cytokine microenvironment or other features. One study suggested that the functional inactivation of CD8 T cells is independent of RSV infection and is mediated by immunosuppressive agents in a basal lung environment [208]. It has been shown that the functional inactivation of $CD8^+$ T cells is associated with TCR signaling, and the activity could be improved by IL-2 expression in the lungs [209].

Disease pathogenesis

A variety of host factors affect RSV disease pathogenesis. Some of the known risk factors for severe disease include the age of the individual at the time of infection, congenital heart disease and immunodeficiency or suppression [210–212]. The state of immune maturation early in life is also important for susceptibility to RSV disease. Maternal antibodies appear to confer only partial protection from RSV infection, and have been shown to also suppress antibody and T-cell responses to primary RSV infection [213]. Furthermore, genetic-association studies have demonstrated that variations in certain genetic loci, such as haplotype and Th2-type cytokine genes, confer susceptibility to RSV disease [214–216]. RSV disease pathogenesis mechanisms are not well understood, but the virus itself likely contributes to the level of pathogenesis and there is abundant evidence that the early innate host response to primary infection is important. Although RSV disease phenotypes vary in humans and among animal models, inflammatory mediators have been strongly implicated in RSV pathogenesis. For example, numerous studies have established that RSV can cause asthma exacerbations and bronchiolitis [217], and that these conditions are associated with enhanced CD4 T-cell responses, inappropriate cytokine expression, inflammation and reduced immune regulation [217–219].

There is no single paradigm for how the cascade of inflammatory mediators and events that follow affect RSV disease pathogenesis. Numerous inflammatory mediators are expressed in the response to RSV infection in humans and in animal models, and there is controversy regarding the importance of inflammatory mediators, Th1- versus Th2-type cytokine responses and dysfunction induced by RSV. It appears that disease pathogenesis is a multifactorial process involving virus replication, innate responses to infection and aberrant immune responses linked to modification by RSV proteins. The often early onset of RSV disease severity suggests that features affecting innate immunity have an important role in the disease process, and it is likely that these features are linked to RSV activation of PRRs or TLRs [220]. How RSV recognition and the subsequent response is tailored by the individual PRRs or TLRs is not yet clear, but evidence suggests that RSV may be recognized by surface and cytoplasmic TLRs including TLR2, TLR3, TLR4 and RIG-I [71,74,137,138,221], and that RSV may inhibit TLR7- and TLR9-mediated type I IFN production in human pDCs [136].

Activation of the innate immune response to RSV infection is associated with the production of chemokines and cytokines, which signal and recruit immune cells to sites of infection. These cells and their constituents function to regulate virus replication, but over-exuberant or inappropriate production of immune mediators in the respiratory tract may exacerbate the inflammatory response and promote airway damage and pathogenesis during virus clearance. RSV has been shown to modify the tempo and magnitude of cytokine and chemokine expression patterns during infection [114,151,196,222–224], and these features likely contribute to immune dysregulation and aspects of disease pathogenesis. Consistent with this

view, *in vivo* chemokine blockade reduces RSV-associated lung pathology in mice treated with anti-RANTES antibodies [130], and treatment of RSV-infected mice with a competitor of the RANTES receptor (Met-RANTES) reduces recruitment of inflammatory cells to the lung [225].

The innate immune response interfaces with adaptive immunity and has an important role in defining the magnitude and quality of adaptive immunity to RSV infection and immunopathology. Inefficient or inappropriate innate and inflammatory responses triggered by RSV may contribute to the induction of inappropriate T-cell responses, and there is considerable evidence of a Th2-type biased immune response specific for some RSV antigens [151,196,224,226–228]. It is thought that efficient virus clearance requires Th1-type responses characterized by IFN-γ, IL-2 and IL-12 expression, and that Th2-type responses characterized by IL-4, IL-10 and IL-13 expression are mostly ineffective and can lead to allergic diseases and asthma. Th2-type cytokine responses have been linked to RSV vaccine-enhanced disease studies in mice and cotton rats immunized with formalin-inactivated RSV vaccine or vaccinia vectors expressing RSV F or G proteins [195,224,228–231]. In these studies, sensitization with the RSV G protein leads to Th2-type $CD4^+$ T-cell responses, and in many cases pulmonary eosinophilia, during subsequent challenge with RSV. In small animal models, ablation of either $CD4^+$ or $CD8^+$ T cells after RSV infection has been shown to decrease disease severity and illness [224,232], indicating the important role of T cells in immune pathology. Interestingly, RSV-specific memory $CD8^+$ T cells appear to have an important role in regulation of the aberrant $CD4^+$ T-cell response associated with vaccine-enhanced disease [198,233,234], but may have less of a role in other allergy-related pathologies such as airway hyper-responsiveness to RSV infection [235].

Conclusion

Numerous host and several virus components have been connected with disease pathogenesis following RSV infection; however, the importance of a single component against the spectrum of mediators is difficult to identify as being singularly important. It is apparent that RSV causes an atypical host response to infection with attributes of altered innate and inadequate immune memory responses where individuals may be repeatedly infected with the same or different strains of RSV, and where RSV may reinfect despite the presence of specific neutralizing antibodies [153,236–239]. Experimental animal models and *in vitro* studies of RSV infection have helped to identify and differentiate aspects of the host response to infection, and to identify RSV proteins that modulate these responses, however, the features of molecular pathogenesis remain poorly understood. A better understanding of the interplay between RSV and the host response to infection is needed to facilitate vaccine and antiviral drug development, although accumulating evidence suggests that regulating aspects of innate immunity may be more important in controlling disease pathogenesis.

Future perspective

Understanding the host response and molecular pathogenesis of RSV infection is critical for the development of vaccines, antivirals and other disease intervention approaches. It is clear that we must understand the problem if we are to prevent or correct it. Fundamental to this understanding is the biology behind RSV infection. RSV first infects respiratory epithelial cells during infection. The host response to infection is sensed by PRRs or TLRs that induce a network of host cell gene products, which profoundly affect the cascade of inflammatory and immune signals and functions. RSV-specific gene products have been shown to modulate the tempo, pattern and magnitude of the signaling cascade in the early elements of innate immunity. These early elements in innate immunity are required to properly orchestrate the adaptive immune response as well as regulate airway inflammation and disease pathogenesis. It is clear

that the identification of host pathways affected by RSV proteins will be fundamental to achieving rationally designed antiviral drugs and vaccines. Despite decades of effort toward an efficacious RSV vaccine, there are still no clear contenders on the horizon. It is likely that the vaccine focus will shift from current vaccine approaches toward the development of mucosal RSV vaccine strategies and antiviral drug approaches toward novel strategies that encumber RNA interference or antisense approaches that could be used to specifically target the virus or airway epithelium host genes early after infection. It is likely that interceding in the earliest events following RSV infection may offer a clearer path toward drug-based disease intervention, and generating antibody responses that target RSV proteins more effectively may provide greater efficacy for RSV disease pathogenesis.

Executive summary

Respiratory syncytial virus

- Respiratory syncytial virus (RSV) is a paramyxovirus.
- Nonsegmented negative-strand RNA virus containing two nonstructural (*NS2* and *NS1*) genes followed, in gene order, by nucleocapsid, phosphoprotein, matrix, small hydrophobic, surface attachment glycoprotein (G), surface fusion glycoprotein (F), a M2 gene encoding two proteins from M2–1/M2–2 and RNA-dependent RNA polymerase.
- Transcription of mRNA occurs in a 3′ to 5′ order from a single promoter near the 3′ end resulting in a series of subgenomic mRNAs.
- The level of protein expressed is related to mRNA abundance.
- Virions assemble at the plasma membrane where nucleocapsids localize with the cell membrane containing membrane viral glycoproteins.

Regulation of host-cell responses to infection

- RSV primarily infects respiratory epithelial cells lining the nasal passages and respiratory tract.
- Following infection, RSV delays apoptosis by enhancing IEX-1L, several Bcl-2 family members, proteins within the phosphatidylinositol 3-kinase pathway, and by inhibiting tumor suppressor p53 and oncogene Akt.
- RSV proteins modulate host-cell responses through pattern recognition receptors and Toll-like receptors (TLRs); RSV F protein interacts with TLR4; G protein potentially with TLR2.
- RSV interferes with the host antiviral cytokine response; NS1 and NS2 are important in type I IFN antagonists.
- RSV induces suppressor of cytokine signaling (SOCS)1 and SOCS3 negative regulation of type I IFNs.
- RSV infection modulates respiratory epithelial-cell function, surfactant protein (SP)-A and SP-D are decreased, and matrix metalloproteinases are increased.
- RSV G protein contains a CX3C chemokine motif which can bind to the CX3CR1 and impede CX3CR1 responses and CX3CR1-mediated leukocyte chemotaxis.

Cytokine responses to RSV infection

- RSV infection of airway epithelial cells results in a cascade of signaling events mediated by NF-κB leading to the expression of proinflammatory cytokines and chemokines.
- RSV G-protein expression during acute infection in mice has been associated with altered CC and CXC chemokine mRNA expression and Th1/Th2-type cytokines.
- RSV G protein inhibits IFN -β and IFN-stimulated gene-15.

Regulation of cellular transcription factors

- RSV infection induces many transcription factors including IFN regulatory factor (IRF)3, IRF7, NF-κB, p38 MAPK and AP-1.
- RSV G protein interferes with Toll IL-1 receptor domain-containing adaptor molecule-1 or NF-κB activation leading to reduced levels proinflammatory cytokines.
- Interferon antagonism by NS1/NS2 is mediated by inhibiting STAT2 and IRF3 activation.
- NS1 contains elongin-C- and cullin-2-binding sequences that provide ubiquitin E3 ligase activity to target proteins, specifically STAT2, to the proteosome.
- RSV G protein induces SOCS1 and SOCS3 proteins which negatively regulate cytokine signaling cascades, particularly type I IFNs.

Innate immunity to RSV infection

- Host cells recognize RSV infection via TLR4, TLR3, TLR2 and retinoic acid-inducible gene-I resulting in the expression of proinflammatory cytokines and chemokines.
- The balance between conventional dendritic cells (DCs) and plasmacytoid DCs in the lung and lymph nodes is important for driving pulmonary immunity to RSV infection.
- DCs infected with RSV lose their ability to stimulate RSV-specific T cells.
- RSV G protein has a role in modulating natural killer cells and other cell trafficking to the lung through inhibition of cytokines and chemokines.

Adaptive humoral & cellular immunity

- RSV F and G surface proteins induce neutralizing antibody production, and these are the major antigenic determinants of protection.
- T-cell responses have an important role in viral clearance.
- RSV F protein may polarize both $CD4^+$ and $CD8^+$ T-cell responses toward a Th1-type response.
- RSV G protein may prime $CD4^+$ T cells toward a Th2-biased response.

Disease pathogenesis

- A variety of host factors affect RSV disease pathogenesis; known risk factors for severe disease include the age of infection, congenital heart disease and immune deficiency or suppression.
- The state of immune maturation early in life is important for susceptibility to RSV disease.
- Genetic-association studies indicate that variations in certain genetic loci confer susceptibility to RSV disease.

▪ Disease pathogenesis is a multifactorial process.

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Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

1. Morris JAJ, Blount RE, Savage RE. Recovery of cytopathogenic agent from chimpanzees with coryza. Proc Soc Exp Biol Med 1956;92:544–550. [PubMed: 13359460]
2. Chanock RM, Finberg L. Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent CCA. II Epidemiological aspects of infection in infants and young children Am J Hygiene 1957;66:291–300.
3. Staat MA. Respiratory syncytial virus infections in children. Semin Respir Infect 2002;17:15–20. [PubMed: 11891515]
4. Respiratory syncytial virus activity – United States, 2000–2001 season. Morb Mortal Wkly Rep 2002;51:26–28.
5. Falsey AR, Walsh EE. Respiratory syncytial virus infection in adults. Clin Microbiol Rev 2000;13:371–384. [PubMed: 10885982]
6. Simoes EA. Respiratory syncytial virus infection. Lancet 1999;354:847–852. [PubMed: 10485741]
7. Hall CB. Respiratory syncytial virus: a continuing culprit and conundrum. J Pediatr 1999;135:2–7. [PubMed: 10431132]
8. Falsey AR. Respiratory syncytial virus infection in older persons. Vaccine 1998;16:1775–1778. [PubMed: 9778756]
9. Couch RB, Englund JA, Whimbey E. Respiratory viral infections in immunocompetent and immunocompromised persons. Am J Med 1997;102:2–9. [PubMed: 10868136]discussion 25–26
10. Billings JL, Hertz MI, Wendt CH. Community respiratory virus infections following lung transplantation. Transpl Infect Dis 2001;3:138–148. [PubMed: 11493396]
11. Fixler DE. Respiratory syncytial virus infection in children with congenital heart disease: a review. Pediatr Cardiol 1996;17:163–168. [PubMed: 8662029]
12. Glezen P, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973;288:498–505. [PubMed: 4346164]
13. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among USA children, 1980–1996. JAMA 1999;282:1440–1446. [PubMed: 10535434]
14. Bachi T, Howe C. Morphogenesis and ultrastructure of respiratory syncytial virus. J Virol 1973;12:1173–1180. [PubMed: 4128827]
15. Joncas J, Berthiaume L, Pavilanis V. The structure of the respiratory syncytial virus. Virology 1969;38:493–496. [PubMed: 4308056]

16. Norrby E, Marusyk H, Orvell C. Ultrastructural studies of the multiplication of RS (respiratory syncytial) virus. Acta Pathol Microbiol Scand B Microbiol Immunol 1970;78:268. [PubMed: 5275087]

17▪. Wertz GW, Collins PL, Huang Y, Gruber C, Levine S, Ball LA. Nucleotide sequence of the G protein gene of human respiratory syncytial virus reveals an unusual type of viral membrane protein. Proc Natl Acad Sci USA 1985;82:4075–4079. [PubMed: 3858865]The amino acid sequence of the glycoprotein (G) backbone is determined and the protein shown to contain a combination of structural features that make it unique among many viral glycoproteins

18. Vijaya S, Elango N, Zavala F, Moss B. Transport to the cell surface of a peptide sequence attached to the truncated C-terminus of an N-terminally anchored integral membrane protein. Mol Cell Biol 1988;8:1709–1714. [PubMed: 3380095]

19▪ . Roberts SR, Lichtenstein D, Ball LA, Wertz GW. The membrane-associated and secreted forms of the respiratory syncytial virus attachment glycoprotein G are synthesized from alternative initiation codons. J Virol 1994;68:4538–4546. [PubMed: 8207828]Shows that respiratory syncytial virus (RSV) synthesizes two mature forms of G protein, an anchored type II integral membrane form and a smaller form that is secreted

20. Lichtenstein DL, Roberts SR, Wertz GW, Ball LA. Definition and functional analysis of the signal/anchor domain of the human respiratory syncytial virus glycoprotein G. J Gen Virol 1996;77 (Pt 1): 109–118. [PubMed: 8558117]

21. Teng MN, Collins PL. The central conserved cystine noose of the attachment G protein of human respiratory syncytial virus is not required for efficient viral infection *in vitro* or *in vivo*. J Virol 2002;76:6164–6171. [PubMed: 12021350]

22. Sullender WM, Mufson MA, Anderson LJ, Wertz GW. Genetic diversity of the attachment protein of subgroup B respiratory syncytial viruses. J Virol 1991;65:5425–5434. [PubMed: 1895391]

23▪▪ . Tripp RA, Jones LP, Haynes LM, Zheng H, Murphy PM, Anderson LJ. CX3C chemokine mimicry by respiratory syncytial virus G glycoprotein. Nat Immunol 2001;2:732–738. [PubMed: 11477410] Shows RSV G protein CX3C chemokine mimicry, binding to the CX3CR1-specific receptor and induction of leukocyte chemotaxis, suggesting that G-protein interaction with CX3CR1 probably plays a key role in the biology of RSV infection

24. Hendricks DA, McIntosh K, Patterson JL. Further characterization of the soluble form of the G glycoprotein of respiratory syncytial virus. J Virol 1988;62:2228–2233. [PubMed: 3373568]

25. Hendricks DA, Baradaran K, McIntosh K, Patterson JL. Appearance of a soluble form of the G protein of respiratory syncytial virus in fluids of infected cells. J Gen Virol 1987;68(Pt 6):1705–1714. [PubMed: 3585282]

26. Gan SW, Ng L, Lin X, Gong X, Torres J. Structure and ion channel activity of the human respiratory syncytial virus (hRSV) small hydrophobic protein transmembrane domain. Protein Sci 2008;17:813–820. [PubMed: 18369195]

27. Low KW, Tan T, Ng K, Tan BH, Sugrue RJ. The RSV F and G glycoproteins interact to form a complex on the surface of infected cells. Biochem Biophys Res Commun 2008;366:308–313. [PubMed: 18036342]

28. Fuentes S, Tran KC, Luthra P, Teng MN, He B. Function of the respiratory syncytial virus small hydrophobic protein. J Virol 2007;81:8361–8366. [PubMed: 17494063]

29▪. Gotoh B, Komatsu T, Takeuchi K, Yokoo J. Paramyxovirus accessory proteins as interferon antagonists. Microbiol Immunol 2001;45:787–800. [PubMed: 11838896]Review of how Paramyxovirus accessory proteins circumvent the interferon response by inhibiting interferon signaling

30. Schlender J, Bossert B, Buchholz U, Conzelmann KK. Bovine respiratory syncytial virus nonstructural proteins NS1 and NS2 cooperatively antagonize α/β interferon-induced antiviral response. J Virol 2000;74:8234–8242. [PubMed: 10954520]

31▪ . Moore EC, Barber J, Tripp RA. Respiratory syncytial virus (RSV) attachment and nonstructural proteins modify the type I interferon response associated with suppressor of cytokine signaling (SOCS) proteins and IFN-stimulated gene-15 (ISG15). Virol J 2008;5:116. [PubMed: 18851747] Shows suppressor of cytokine signaling (SOCS)1 and SOCS3 regulation of type I IFN and the IFN-stimulated gene (*ISG*)-15 response follows RSV infection of mouse lung epithelial cells, and a novel

role for RSV G protein manipulation of SOCS3 and modulation of ISG15 and IFN-β mRNA expression

32. Spann KM, Tran KC, Collins PL. Effects of nonstructural proteins NS1 and NS2 of human respiratory syncytial virus on interferon regulatory factor 3, NF-κB, and proinflammatory cytokines. J Virol 2005;79:5353–5362. [PubMed: 15827150]

33▪. Spann KM, Tran KC, Chi B, Rabin RL, Collins PL. Suppression of the induction of α, β, and λ interferons by the NS1 and NS2 proteins of human respiratory syncytial virus in human epithelial cells and macrophages. J Virol 2004;78:4363–4369. [PubMed: 15047850]Results with NS1 and NS2 single and double gene-deletion viruses indicates that the two proteins function independently as well as coordinately to antagonize IFN, with NS1 having a greater independent role

34. Jin H, Zhou H, Cheng X, Tang R, Munoz M, Nguyen N. Recombinant respiratory syncytial viruses with deletions in the *NS1*, *NS2*, *SH*, and *M2-2* genes are attenuated *in vitro* and *in vivo*. Virology 2000;273:210–218. [PubMed: 10891423]

35. Bourgeois C, Bour JB, Lidholt K, Gauthray C, Pothier P. Heparin-like structures on respiratory syncytial virus are involved in its infectivity *in vitro*. J Virol 1998;72:7221–7227. [PubMed: 9696816]

36. Krusat T, Streckert HJ. Heparin-dependent attachment of respiratory syncytial virus (RSV) to host cells. Arch Virol 1997;142:1247–1254. [PubMed: 9229012]

37. Feldman SA, Hendry RM, Beeler JA. Identification of a linear heparin binding domain for human respiratory syncytial virus attachment glycoprotein G. J Virol 1999;73:6610–6617. [PubMed: 10400758]

38. Techaarpornkul S, Collins PL, Peeples ME. Respiratory syncytial virus with the fusion protein as its only viral glycoprotein is less dependent on cellular glycosaminoglycans for attachment than complete virus. Virology 2002;294:296–304. [PubMed: 12009871]

39. Karron RA, Buonagurio DA, Georgiu AF, et al. Respiratory syncytial virus (RSV) SH and G proteins are not essential for viral replication *in vitro*: clinical evaluation and molecular characterization of a cold-passaged, attenuated RSV subgroup B mutant. Proc Natl Acad Sci USA 1997;94:13961–13966. [PubMed: 9391135]

40. Teng MN, Whitehead SS, Collins PL. Contribution of the respiratory syncytial virus G glycoprotein and its secreted and membrane-bound forms to virus replication *in vitro* and *in vivo*. Virology 2001;289:283–296. [PubMed: 11689051]

41▪▪ . Tripp RA, Moore D, Jones L, Sullender W, Winter J, Anderson LJ. Respiratory syncytial virus G and/or SH protein alters Th1 cytokines, natural killer cells, and neutrophils responding to pulmonary infection in BALB/c mice. J Virol 1999;73:7099–7107. [PubMed: 10438795]First study to show an immune modulatory role of RSV G protein on innate immune and cytokine responses

42. Bachi T. Direct observation of the budding and fusion of an enveloped virus by video microscopy of viable cells. J Cell Biol 1988;107:1689–1695. [PubMed: 3182934]

43. Levine S, Hamilton R. Kinetics of the respiratory syncytial virus growth cycle in HeLa cells. Arch Gesamte Virusforsch 1969;28:122–132. [PubMed: 5369728]

44. Hierholzer JC, Tannock GA. Respiratory syncytial virus: a review of the virus, its epidemiology, immune response and laboratory diagnosis. Aust Paediatr J 1986;22:77–82. [PubMed: 3524530]

45. Arslanagic E, Matsumoto M, Suzuki K, Nerome K, Tsutsumi H, Hung T. Maturation of respiratory syncytial virus within HEp-2 cell cytoplasm. Acta Virol 1996;40:209–214. [PubMed: 9014011]

46. Routledge EG, Willcocks MM, Morgan L, Samson AC, Scott R, Toms GL. Expression of the respiratory syncytial virus 22K protein on the surface of infected HeLa cells. J Gen Virol 1987;68 (Pt 4):1217–1222. [PubMed: 3553424]

47. Fearns R, Collins PL. Model for polymerase access to the overlapped L gene of respiratory syncytial virus. J Virol 1999;73:388–397. [PubMed: 9847343]

48▪▪ . Huang YT, Collins PL, Wertz GW. Characterization of the 10 proteins of human respiratory syncytial virus: identification of a fourth envelope-associated protein. Virus Res 1985;2:157–173. [PubMed: 3993233]The largest RSV proteins, which include RNA-dependent RNA polymerase, surface attachment glycoprotein, surface fusion glycoprotein, nucleocapsid, phosphoprotein and matrix, are clearly identified as virion structural proteins

49. Dickens LE, Collins PL, Wertz GW. Transcriptional mapping of human respiratory syncytial virus. J Virol 1984;52:364–369. [PubMed: 6492254]
50. Kuo L, Grosfeld H, Cristina J, Hill MG, Collins PL. Effects of mutations in the gene-start and gene-end sequence motifs on transcription of monocistronic and dicistronic minigenomes of respiratory syncytial virus. J Virol 1996;70:6892–6901. [PubMed: 8794332]
51. Harmon SB, Megaw AG, Wertz GW. RNA sequences involved in transcriptional termination of respiratory syncytial virus. J Virol 2001;75:36–44. [PubMed: 11119571]
52. Krempl C, Murphy BR, Collins PL. Recombinant respiratory syncytial virus with the *G* and *F* genes shifted to the promoter-proximal positions. J Virol 2002;76:11931–11942. [PubMed: 12414935]
53. Brown G, Aitken J, Rixon HW, Sugrue RJ. Caveolin-1 is incorporated into mature respiratory syncytial virus particles during virus assembly on the surface of virus-infected cells. J Gen Virol 2002;83:611–621. [PubMed: 11842256]
54. Zhao D, Peng D, Li L, Zhang Q, Zhang C. Inhibition of G1P3 expression found in the differential display study on respiratory syncytial virus infection. Virol J 2008;5:114. [PubMed: 18838000]
55. Martinez I, Lombardia L, Garcia-Barreno B, Dominguez O, Melero JA. Distinct gene subsets are induced at different time points after human respiratory syncytial virus infection of A549 cells. J Gen Virol 2007;88:570–581. [PubMed: 17251576]
56. Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. Nat Rev Immunol 2008;8:193–204. [PubMed: 18301423]
57. Zhang L, Peeples ME, Boucher RC, Collins PL, Pickles RJ. Respiratory syncytial virus infection of human airway epithelial cells is polarized, specific to ciliated cells, and without obvious cytopathology. J Virol 2002;76:5654–5666. [PubMed: 11991994]
58. Wright PF, Ikizler MR, Gonzales RA, Carroll KN, Johnson JE, Werkhaven JA. Growth of respiratory syncytial virus in primary epithelial cells from the human respiratory tract. J Virol 2005;79:8651–8654. [PubMed: 15956607]
59. Domachowske JB, Bonville CA, Mortelliti AJ, Colella CB, Kim U, Rosenberg HF. Respiratory syncytial virus infection induces expression of the anti-apoptosis gene *IEX-1L* in human respiratory epithelial cells. J Infect Dis 2000;181:824–830. [PubMed: 10720500]
60. Kotelkin A, Prikhod'ko EA, Cohen JI, Collins PL, Bukreyev A. Respiratory syncytial virus infection sensitizes cells to apoptosis mediated by tumor necrosis factor-related apoptosis-inducing ligand. J Virol 2003;77:9156–9172. [PubMed: 12915532]
61. Lindemans CA, Coffer PJ, Schellens IM, de Graaff PM, Kimpen JL, Koenderman L. Respiratory syncytial virus inhibits granulocyte apoptosis through a phosphatidylinositol 3-kinase and NF-κB-dependent mechanism. J Immunol 2006;176:5529–5537. [PubMed: 16622022]
62. Monick MM, Cameron K, Staber J, et al. Activation of the epidermal growth factor receptor by respiratory syncytial virus results in increased inflammation and delayed apoptosis. J Biol Chem 2005;280:2147–2158. [PubMed: 15542601]
63. Groskreutz DJ, Monick MM, Yarovinsky TO, et al. Respiratory syncytial virus decreases p53 protein to prolong survival of airway epithelial cells. J Immunol 2007;179:2741–2747. [PubMed: 17709487]
64. Thomas KW, Monick MM, Staber JM, Yarovinsky T, Carter AB, Hunninghake GW. Respiratory syncytial virus inhibits apoptosis and induces NF-κB activity through a phosphatidylinositol 3-kinase-dependent pathway. J Biol Chem 2002;277:492–501. [PubMed: 11687577]
65. Monick MM, Cameron K, Powers LS, et al. Sphingosine kinase mediates activation of extracellular signal-related kinase and Akt by respiratory syncytial virus. Am J Respir Cell Mol Biol 2004;30:844–852. [PubMed: 14742298]
66. Bitko V, Shulyayeva O, Mazumder B, et al. Nonstructural proteins of respiratory syncytial virus suppress premature apoptosis by an NF-κB-dependent, interferon-independent mechanism and facilitate virus growth. J Virol 2007;81:1786–1795. [PubMed: 17151097]
67. Xie XH, Law HK, Wang LJ, Li X, Yang XQ, Liu EM. Lipopolysaccharide induces IL-6 production in respiratory syncytial virus-infected airway epithelial cells through the Toll-like receptor 4 signaling pathway. Pediatr Res 2009;65(2):156–162. [PubMed: 18948841]
68. Monick MM, Yarovinsky TO, Powers LS, et al. Respiratory syncytial virus up-regulates TLR4 and sensitizes airway epithelial cells to endotoxin. J Biol Chem 2003;278:53035–53044. [PubMed: 14565959]

69. Awomoyi AA, Rallabhandi P, Pollin TI, et al. Association of TLR4 polymorphisms with symptomatic respiratory syncytial virus infection in high-risk infants and young children. J Immunol 2007;179:3171–3177. [PubMed: 17709532]

70. Gagro A, Tominac M, Krsulovic-Hresic V, et al. Increased Toll-like receptor 4 expression in infants with respiratory syncytial virus bronchiolitis. Clin Exp Immunol 2004;135:267–272. [PubMed: 14738455]

71▪▪. Kurt-Jones EA, Popova L, Kwinn L, et al. Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol 2000;1:398–401. [PubMed: 11062499]First report to show that RSV surface fusion glycoprotein is a ligand for Toll-like receptor (TLR)4 and CD14, and that a common receptor activation pathway can initiate innate immune responses to both bacterial and viral pathogens

72. Polack FP, Irusta PM, Hoffman SJ, et al. The cysteine-rich region of respiratory syncytial virus attachment protein inhibits innate immunity elicited by the virus and endotoxin. Proc Natl Acad Sci USA 2005;102:8996–9001. [PubMed: 15956195]

73. Shingai M, Azuma M, Ebihara T, et al. Soluble G protein of respiratory syncytial virus inhibits Toll-like receptor 3/4-mediated IFN-β induction. Int Immunol 2008;20:1169–1180. [PubMed: 18611945]

74▪▪. Murawski MR, Bowen GN, Cerny AM, et al. RSV activates innate immunity through Toll-like receptor 2. J Virol 2008;83(3):1492–1500 . [PubMed: 19019963]First report to show that RSV activates innate immunity through TLR2

75. Bossert B, Marozin S, Conzelmann KK. Nonstructural proteins NS1 and NS2 of bovine respiratory syncytial virus block activation of interferon regulatory factor 3. J Virol 2003;77:8661–8668. [PubMed: 12885884]

76. Lo MS, Brazas RM, Holtzman MJ. Respiratory syncytial virus nonstructural proteins NS1 and NS2 mediate inhibition of STAT2 expression and α/β interferon responsiveness. J Virol 2005;79:9315–9319. [PubMed: 15994826]

77. Valarcher JF, Furze J, Wyld S, Cook R, Conzelmann KK, Taylor G. Role of α/β interferons in the attenuation and immunogenicity of recombinant bovine respiratory syncytial viruses lacking NS proteins. J Virol 2003;77:8426–8439. [PubMed: 12857912]

78. Munir S, Le Nouen C, Luongo C, Buchholz UJ, Collins PL, Bukreyev A. Nonstructural proteins 1 and 2 of respiratory syncytial virus suppress maturation of human dendritic cells. J Virol 2008;82:8780–8796. [PubMed: 18562519]

79. Ramaswamy M, Shi L, Monick MM, Hunninghake GW, Look DC. Specific inhibition of type I interferon signal transduction by respiratory syncytial virus. Am J Respir Cell Mol Biol 2004;30:893–900. [PubMed: 14722224]

80. Ramaswamy M, Shi L, Varga SM, Barik S, Behlke MA, Look DC. Respiratory syncytial virus nonstructural protein 2 specifically inhibits type I interferon signal transduction. Virology 2006;344:328–339. [PubMed: 16216295]

81. Elliott J, Lynch OT, Suessmuth Y, et al. Respiratory syncytial virus NS1 protein degrades STAT2 by using the Elongin-Cullin E3 ligase. J Virol 2007;81:3428–3436. [PubMed: 17251292]

82▪ . Croker BA, Kiu H, Nicholson SE. SOCS regulation of the JAK/STAT signaling pathway. Semin Cell Dev Biol 2008;19(4):414–422. [PubMed: 18708154]Useful review of the role of SOCS protein in governing the JAK/STAT cytokine signaling pathway

83▪ . Yoshimura A, Naka T, Kubo M. SOCS proteins, cytokine signaling and immune regulation. Nat Rev Immunol 2007;7:454–465. [PubMed: 17525754]Succinct review of immune regulation mediated through negative feedback of SOCS proteins

84. Starr R, Willson TA, Viney EM, et al. A family of cytokine-inducible inhibitors of signalling. Nature 1997;387:917–921. [PubMed: 9202125]

85. Jamaluddin M, Choudhary S, Wang S, et al. Respiratory syncytial virus-inducible Bcl-3 expression antagonizes the STAT/IRF and NF-κB signaling pathways by inducing histone deacetylase 1 recruitment to the interleukin-8 promoter. J Virol 2005;79:15302–15313. [PubMed: 16306601]

86. Singh D, McCann KL, Imani F. MAPK and heat shock protein 27 activation are associated with respiratory syncytial virus induction of human bronchial epithelial monolayer disruption. Am J Physiol Lung Cell Mol Physiol 2007;293:L436–L445. [PubMed: 17557802]

87. Davis IC, Lazarowski ER, Chen FP, Hickman-Davis JM, Sullender WM, Matalon S. Postinfection A77–1726 blocks pathophysiologic sequelae of respiratory syncytial virus infection. Am J Respir Cell Mol Biol 2007;37:379–386. [PubMed: 17541010]
88. Davis IC, Lazarowski ER, Hickman-Davis JM, et al. Leflunomide prevents alveolar fluid clearance inhibition by respiratory syncytial virus. Am J Respir Crit Care Med 2006;173:673–682. [PubMed: 16387801]
89. Kunzelmann K, Sun J, Meanger J, King NJ, Cook DI. Inhibition of airway Na^+ transport by respiratory syncytial virus. J Virol 2007;81:3714–3720. [PubMed: 17287265]
90. Landry J, Lambert H, Zhou M, et al. Human HSP27 is phosphorylated at serines 78 and 82 by heat shock and mitogen-activated kinases that recognize the same amino acid motif as S6 kinase II. J Biol Chem 1992;267:794–803. [PubMed: 1730670]
91. van Schaik SM, Vargas I, Welliver RC, Enhorning G. Surfactant dysfunction develops in BALB/c mice infected with respiratory syncytial virus. Pediatr Res 1997;42:169–173. [PubMed: 9262218]
92. Kerr MH, Paton JY. Surfactant protein levels in severe respiratory syncytial virus infection. Am J Respir Crit Care Med 1999;159:1115–1118. [PubMed: 10194154]
93. Pastva AM, Wright JR, Williams KL. Immunomodulatory roles of surfactant proteins A and D: implications in lung disease. Proc Am Thorac Soc 2007;4:252–257. [PubMed: 17607008]
94. Ghildyal R, Hartley C, Varrasso A, et al. Surfactant protein A binds to the fusion glycoprotein of respiratory syncytial virus and neutralizes virion infectivity. J Infect Dis 1999;180:2009–2013. [PubMed: 10558959]
95. Barr FE, Pedigo H, Johnson TR, Shepherd VL. Surfactant protein-A enhances uptake of respiratory syncytial virus by monocytes and U937 macrophages. Am J Respir Cell Mol Biol 2000;23:586–592. [PubMed: 11062136]
96. Hickling TP, Bright H, Wing K, et al. A recombinant trimeric surfactant protein D carbohydrate recognition domain inhibits respiratory syncytial virus infection *in vitro* and *in vivo*. Eur J Immunol 1999;29:3478–3484. [PubMed: 10556802]
97. Atkinson JJ, Senior RM. Matrix metalloproteinase-9 in lung remodeling. Am J Respir Cell Mol Biol 2003;28:12–24. [PubMed: 12495928]
98. Yeo SJ, Yun YJ, Lyu MA, et al. Respiratory syncytial virus infection induces matrix metalloproteinase-9 expression in epithelial cells. Arch Virol 2002;147:229–242. [PubMed: 11890521]
99. Liu T, Zaman W, Kaphalia BS, Ansari GA, Garofalo RP, Casola A. RSV-induced prostaglandin E2 production occurs via cPLA2 activation: role in viral replication. Virology 2005;343:12–24. [PubMed: 16153673]
100. Richardson JY, Ottolini MG, Pletneva L, et al. Respiratory syncytial virus (RSV) infection induces cyclooxygenase 2: a potential target for RSV therapy. J Immunol 2005;174:4356–4364. [PubMed: 15778400]
101. Bryan DL, Hart P, Forsyth K, Gibson R. Modulation of respiratory syncytial virus-induced prostaglandin E2 production by n-3 long-chain polyunsaturated fatty acids in human respiratory epithelium. Lipids 2005;40:1007–1011. [PubMed: 16382572]
102. Vancheri C, Mastruzzo C, Sortino MA, Crimi N. The lung as a privileged site for the beneficial actions of PGE2. Trends Immunol 2004;25:40–46. [PubMed: 14698283]
103. Hendricks DA, Baradaran K, McIntosh K, Patterson JL. Appearance of a soluble form of the G-protein of respiratory syncytial virus in fluids of infected-cells. J Gen Virol 1987;68:1705–1714. [PubMed: 3585282]
104. Wu H, Pfarr DS, Losonsky GA, Kiener PA. Immunoprophylaxis of RS infection V: advancing from RSV-IGIV to palivizumab and motavizumab. Curr Top Microbiol Immunol 2008;317:103–123. [PubMed: 17990791]
105. Welliver RC, Ogra PL. Immunology of respiratory viral infections. Annu Rev Med 1988;39:147–162. [PubMed: 2453154]
106. Rueda P, Palomo C, Garciabarreno B, Melero JA. The 3 C-terminal residues of human respiratory syncytial virus G-glycoprotein (long strain) are essential for integrity of multiple epitopes distinguishable by antiidiotypic antibodies. Viral Immunol 1995;8:37–46. [PubMed: 8546803]

107. Martinez I, Dopazo J, Melero JA. Antigenic structure of the human respiratory syncytial virus G glycoprotein and relevance of hypermutation events for the generation of antigenic variants. J Gen Virol 1997;78:2419–2429. [PubMed: 9349460]

108. Garcia-Beato R, Melero JA. The C-terminal third of human respiratory syncytial virus attachment (G) protein is partially resistant to protease digestion and is glycosylated in a cell-type-specific manner. J Gen Virol 2000;81:919–927. [PubMed: 10725417]

109. Garcia-Beato R, Martinez I, Franci C, Real FX, Garcia-Barreno B, Melero JA. Host cell effect upon glycosylation and antigenicity of human respiratory syncytial virus G glycoprotein. Virology 1996;221:301–309. [PubMed: 8661440]

110. Palomo C, Cane PA, Melero JA. Evaluation of the antibody specificities of human convalescent-phase sera against the attachment (G) protein of human respiratory syncytial virus: influence of strain variation and carbohydrate side chains. J Med Virol 2000;60:468–474. [PubMed: 10686032]

111. Palomo C, Garcia-Barreno B, Penas C, Melero JA. The G protein of human respiratory syncytial virus: significance of carbohydrate side-chains and the C-terminal end to its antigenicity. J Gen Virol 1991;72(Pt 3):669–675. [PubMed: 2005433]

112. Cane PA. Analysis of linear epitopes recognised by the primary human antibody response to a variable region of the attachment (G) protein of respiratory syncytial virus. J Med Virol 1997;51:297–304. [PubMed: 9093944]

113▪ . Cane PA. Molecular epidemiology of respiratory syncytial virus. Rev Med Virol 2001;11:103–116. [PubMed: 11262529]Provides a classic review of the molecular epidemiology of RSV infection

114▪. Tripp RA. Pathogenesis of respiratory syncytial virus infection. Viral Immunol 2004;17:165–181. [PubMed: 15279697]Provides a timely review of the mechanisms associated with RSV disease pathogenesis

115. Arnold R, Konig B, Werchau H, Konig W. Respiratory syncytial virus deficient in soluble G protein induced an increased proinflammatory response in human lung epithelial cells. Virology 2004;330:384–397. [PubMed: 15567433]

116. Langedijk JP, de Groot BL, Berendsen HJ, van Oirschot JT. Structural homology of the central conserved region of the attachment protein G of respiratory syncytial virus with the fourth subdomain of 55-kDa tumor necrosis factor receptor. Virology 1998;243:293–302. [PubMed: 9568029]

117. Bradley JR. TNF-mediated inflammatory disease. J Path 2008;214:149–160. [PubMed: 18161752]

118. Openshaw PJ. Potential therapeutic implications of new insights into respiratory syncytial virus disease. Respir Res 2002;3(Suppl 1):S15–S20. [PubMed: 12119053]

119. Harcourt J, Alvarez R, Jones LP, Henderson C, Anderson LJ, Tripp RA. Respiratory syncytial virus G protein and G protein CX3C motif adversely affect $CX3CR1^{+}$ T-cell responses. J Immunol 2006;176:1600–1608. [PubMed: 16424189]

120. Bitko V, Velazquez A, Yang L, Yang YC, Barik S. Transcriptional induction of multiple cytokines by human respiratory syncytial virus requires activation of NF-κB and is inhibited by sodium salicylate and aspirin. Virology 1997;232:369–378. [PubMed: 9191851]

121. Harrison AM, Bonville CA, Rosenberg HF, Domachowske JB. Respiratory syncytical virus-induced chemokine expression in the lower airways: eosinophil recruitment and degranulation. Am J Respir Crit Care Med 1999;159:1918–1924. [PubMed: 10351940]

122. Noah TL, Becker S. Chemokines in nasal secretions of normal adults experimentally infected with respiratory syncytial virus. Clin Immunol 2000;97:43–49. [PubMed: 10998316]

123. Haeberle HA, Casola A, Gatalica Z, et al. IκB kinase is a critical regulator of chemokine expression and lung inflammation in respiratory syncytial virus infection. J Virol 2004;78:2232–2241. [PubMed: 14963119]

124. Haeberle HA, Takizawa R, Casola A, et al. Respiratory syncytial virus-induced activation of nuclear factor-κB in the lung involves alveolar macrophages and Toll-like receptor 4-dependent pathways. J Infect Dis 2002;186:1199–1206. [PubMed: 12402188]

125. Miller AL, Bowlin TL, Lukacs NW. Respiratory syncytial virus-induced chemokine production: linking viral replication to chemokine production *in vitro* and *in vivo*. J Infect Dis 2004;189:1419–1430. [PubMed: 15073679]

126. Zhang Y, Luxon BA, Casola A, Garofalo RP, Jamaluddin M, Brasier AR. Expression of respiratory syncytial virus-induced chemokine gene networks in lower airway epithelial cells revealed by cDNA microarrays. J Virol 2001;75:9044–9058. [PubMed: 11533168]

127. McNamara PS, Flanagan BF, Baldwin LM, Newland P, Hart CA, Smyth RL. Interleukin-9 production in the lungs of infants with severe respiratory syncytial virus bronchiolitis. Lancet 2004;363:1031–1037. [PubMed: 15051283]

128. Hoffman SJ, Laham FR, Polack FP. Mechanisms of illness during respiratory syncytial virus infection: the lungs, the virus and the immune response. Microbes Infect 2004;6:767–772. [PubMed: 15207824]

129. Yoon JS, Kim HH, Lee Y, Lee JS. Cytokine induction by respiratory syncytial virus and adenovirus in bronchial epithelial cells. Pediatr Pulmonol 2007;42:277–282. [PubMed: 17245736]

130. Tekkanat KK, Maassab H, Miller A, Berlin AA, Kunkel SL, Lukacs NW. RANTES (CCL5) production during primary respiratory syncytial virus infection exacerbates airway disease. Eur J Immunol 2002;32:3276–3284. [PubMed: 12555673]

131. Matthews SP, Tregoning JS, Coyle AJ, Hussell T, Openshaw PJ. Role of CCL11 in eosinophilic lung disease during respiratory syncytial virus infection. J Virol 2005;79:2050–2057. [PubMed: 15681407]

132▪ . Culley FJ, Pollott J, Openshaw PJ. Age at first viral infection determines the pattern of T-cell-mediated disease during reinfection in adulthood. J Exp Med 2002;196:1381–1386. [PubMed: 12438429]Examins whether age at first infection determines the balance of cytokine production and lung pathology during subsequent challenge, and shows that the environment of the neonatal lung is a major determinant of cytokine production and disease patterns in later life.

133. Tripp RA, Jones L, Anderson LJ. Respiratory syncytial virus G and/or SH glycoproteins modify CC and CXC chemokine mRNA expression in the BALB/c mouse. J Virol 2000;74:6227–6229. [PubMed: 10846112]

134. Tripp RA, Moore D, Anderson LJ. TH(1)- and TH(2)-TYPE cytokine expression by activated T lymphocytes from the lung and spleen during the inflammatory response to respiratory syncytial virus. Cytokine 2000;12:801–807. [PubMed: 10843768]

135. Gagro A, Tominac M, Krsulovic-Hresic V, et al. Increased Toll-like receptor 4 expression in infants with respiratory syncytial virus bronchiolitis. Clin Exp Immunol 2004;135:267–272. [PubMed: 14738455]

136. Schlender J, Hornung V, Finke S, et al. Inhibition of Toll-like receptor 7- and 9-mediated α/β interferon production in human plasmacytoid dendritic cells by respiratory syncytial virus and measles virus. J Virol 2005;79:5507–5515. [PubMed: 15827165]

137. Groskreutz DJ, Monick MM, Powers LS, Yarovinsky TO, Look DC, Hunninghake GW. Respiratory syncytial virus induces TLR3 protein and protein kinase R, leading to increased double-stranded RNA responsiveness in airway epithelial cells. J Immunol 2006;176:1733–1740. [PubMed: 16424203]

138. 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;81:1401–1411. [PubMed: 17108032]

139. Liew FY, Xu D, Brint EK, O'Neill LA. Negative regulation of Toll-like receptor-mediated immune responses. Nat Rev Immunol 2005;5:446–458. [PubMed: 15928677]

140. Ritter M, Mennerich D, Weith A, Seither P. Characterization of Toll-like receptors in primary lung epithelial cells: strong impact of the TLR3 ligand poly(I:C) on the regulation of Toll-like receptors, adaptor proteins and inflammatory response. J Inflamm (Lond) 2005;2:16. [PubMed: 16316467]

141. Komuro A, Bamming D, Horvath CM. Negative regulation of cytoplasmic RNA-mediated antiviral signaling. Cytokine 2008;43:350–358. [PubMed: 18703349]

142. Decker T, Kovarik P, Meinke A. GAS elements: a few nucleotides with a major impact on cytokine-induced gene expression. J Interferon Cytokine Res 1997;17:121–134. [PubMed: 9085936]

143. Fu XY, Schindler C, Improta T, Aebersold R, Darnell JE Jr. The proteins of ISGF-3, the interferon α-induced transcriptional activator, define a gene family involved in signal transduction. Proc Natl Acad Sci USA 1992;89:7840–7843. [PubMed: 1502204]

144. Reich NC. STAT dynamics. Cytokine Growth Factor Rev 2007;18:511–518. [PubMed: 17683973]

145. Noppert SJ, Fitzgerald KA, Hertzog PJ. The role of type I interferons in TLR responses. Immunol Cell Biol 2007;85:446–457. [PubMed: 17667935]

146. Krebs DL, Hilton DJ. SOCS: physiological suppressors of cytokine signaling. J Cell Sci 2000;113 (Pt 16):2813–2819. [PubMed: 10910765]

147. Zhao DC, Yan T, Li L, You S, Zhang C. Respiratory syncytial virus inhibits interferon- α-inducible signaling in macrophage-like U937 cells. J Infect 2007;54:393–398. [PubMed: 16978698]

148. Medzhitov R, Janeway CA Jr. Innate immunity: the virtues of a nonclonal system of recognition. Cell 1997;91:295–298. [PubMed: 9363937]

149. Kawai T, Akira S. TLR signaling. Semin Immunol 2007;19:24–32. [PubMed: 17275323]

150. Rudd BD, Smit JJ, Flavell RA, et al. Deletion of TLR3 alters the pulmonary immune environment and mucus production during respiratory syncytial virus infection. J Immunol 2006;176:1937–1942. [PubMed: 16424225]

151. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy – a review. Virus Genes 2006;33:235–252. [PubMed: 16972040]

152. Bruder D, Srikiatkhachorn A, Enelow RI. Cellular immunity and lung injury in respiratory virus infection. Viral Immunol 2006;19:147–155. [PubMed: 16817757]

153. Bueno SM, Gonzalez PA, Pacheco R, et al. Host immunity during RSV pathogenesis. Int Immunopharmacol 2008;8:1320–1329. [PubMed: 18687294]

154. Lukacs NW, Smit JJ, Schaller MA, Lindell DM. Regulation of immunity to respiratory syncytial virus by dendritic cells, toll-like receptors, and notch. Viral Immunol 2008;21:115–122. [PubMed: 18419253]

155. de Jong EC, Smits HH, Kapsenberg ML. Dendritic cell-mediated T-cell polarization. Semin Immunopathol 2005;26:289–307.

156. Belz G, Mount A, Masson F. Dendritic cells in viral infections. Handb Exp Pharmacol 2009:51–77. [PubMed: 19031021]

157. Smit JJ, Lindell DM, Boon L, Kool M, Lambrecht BN, Lukacs NW. The balance between plasmacytoid DC versus conventional DC determines pulmonary immunity to virus infections. PLoS ONE 2008;3:e1720. [PubMed: 18320041]

158. Smit JJ, Rudd BD, Lukacs NW. Plasmacytoid dendritic cells inhibit pulmonary immunopathology and promote clearance of respiratory syncytial virus. J Exp Med 2006;203:1153–1159. [PubMed: 16682497]

159. Wang H, Peters N, Schwarze J. Plasmacytoid dendritic cells limit viral replication, pulmonary inflammation, and airway hyperresponsiveness in respiratory syncytial virus infection. J Immunol 2006;177:6263–6270. [PubMed: 17056556]

160. Preston FM, Beier PL, Pope JH. Identification of the respiratory syncytial virus-induced immunosuppressive factor produced by human peripheral blood mononuclear cells *in vitro* as interferon- α. J Infect Dis 1995;172:919–926. [PubMed: 7561210]

161. Salkind AR, McCarthy DO, Nichols JE, Domurat FM, Walsh EE, Roberts NJ Jr. Interleukin-1-inhibitor activity induced by respiratory syncytial virus: abrogation of virus-specific and alternate human lymphocyte proliferative responses. J Infect Dis 1991;163:71–77. [PubMed: 1984478]

162. Schelender, JWG.; Conzelmann, K-K. Contact inhibition of PBL proliferation by respiratory syncytial virus(RSV) fusion (F) protein. Presented at 11th International Conference on Negative Strand Viruses; Quebec City, Canada. 24–29 June; 2000.

163▪ . Gonzalez PA, Prado CE, Leiva ED, et al. Respiratory syncytial virus impairs T-cell activation by preventing synapse assembly with dendritic cells. Proc Natl Acad Sci USA 2008;105:14999–15004. [PubMed: 18818306]Demonstrates that RSV may impair immunity by inhibiting the synapse between dendritic cells and T cells.

164. Becker S, Quay J, Soukup J. Cytokine (tumor necrosis factor, IL-6, and IL-8) production by respiratory syncytial virus-infected human alveolar macrophages. J Immunol 1991;147:4307–4312. [PubMed: 1753101]

165. Pribul PK, Harker J, Wang B, et al. Alveolar macrophages are a major determinant of early responses to viral lung infection but do not influence subsequent disease development. J Virol 2008;82:4441–4418. [PubMed: 18287232]

166. Reed JL, Brewah YA, Delaney T, et al. Macrophage impairment underlies airway occlusion in primary respiratory syncytial virus bronchiolitis. J Infect Dis 2008;198:1783–1793. [PubMed: 18980502]

167. Taub DD, Ortaldo JR, Turcovski-Corrales SM, Key ML, Longo DL, Murphy WJ. β-chemokines costimulate lymphocyte cytolysis, proliferation, and lymphokine production. J Leukoc Biol 1996;59:81–89. [PubMed: 8558072]

168. Moretta A, Marcenaro E, Parolini S, Ferlazzo G, Moretta L. NK cells at the interface between innate and adaptive immunity. Cell Death Differ 2008;15:226–233. [PubMed: 17541426]

169. Moretta L, Ferlazzo G, Bottino C, et al. Effector and regulatory events during natural killer-dendritic cell interactions. Immunol Rev 2006;214:219–228. [PubMed: 17100887]

170. Brutkiewicz RR, Lin Y, Cho S, Hwang YK, Sriram V, Roberts TJ. CD1d-mediated antigen presentation to natural killer T (NKT) cells. Crit Rev Immunol 2003;23:403–419. [PubMed: 15030309]

171. Bendelac A, Rivera MN, Park SH, Roark JH. Mouse CD1-specific NK1 T cells: development, specificity, and function. Annu Rev Immunol 1997;15:535–562. [PubMed: 9143699]

172. Brigl M, Bry L, Kent SC, Gumperz JE, Brenner MB. Mechanism of CD1d-restricted natural killer T-cell activation during microbial infection. Nat Immunol 2003;4:1230–1237. [PubMed: 14578883]

173. Johnson TR, Hong S, van Kaer L, Koezuka Y, Graham BS. NKT cells contribute to expansion of $CD8^+$ T cells and amplification of antiviral immune responses to respiratory syncytial virus. J Virol 2002;76:4294–4303. [PubMed: 11932395]

174. Groothuis JR. The role of RSV neutralizing antibodies in the treatment and prevention of respiratory syncytial virus infection in high-risk children. Antiviral Res 1994;23:1–10. [PubMed: 8141588]

175. Connors M, Collins PL, Firestone CY, Murphy BR. Respiratory syncytial virus (RSV) F, G, M2 (22K), and N proteins each induce resistance to RSV challenge, but resistance induced by M2 and N proteins is relatively short-lived. J Virol 1991;65:1634–1637. [PubMed: 1995956]

176. Lawless-Delmedico MK, Sista P, Sen R, et al. Heptad-repeat regions of respiratory syncytial virus F1 protein form a six-membered coiled-coil complex. Biochemistry 2000;39:11684–11695. [PubMed: 10995236]

177. Lopez JA, Bustos R, Orvell C, et al. Antigenic structure of human respiratory syncytial virus fusion glycoprotein. J Virol 1998;72:6922–6928. [PubMed: 9658147]

178. Sakurai H, Williamson RA, Crowe JE, et al. Human antibody responses to mature and immature forms of viral envelope in respiratory syncytial virus infection: significance for subunit vaccines. J Virol 1999;73:2956–2962. [PubMed: 10074145]

179▪ . Collins, PL.; Chanock, RM.; Murphy, BR. Respiratory syncytial viruses. In: Knipe, DM.; Hawley, PM., editors. Fields Virology. Lippincott-Raven; Philadelphia, PA, USA: 2001. Excellent chapter providing a comprehensive review of the biology of RSV infection and replication

180. Melero JA, Garcia-Barreno B, Martinez I, Pringle CR, Cane PA. Antigenic structure, evolution and immunobiology of human respiratory syncytial virus attachment (G) protein. J Gen Virol 1997;78 (Pt 10):2411–2418. [PubMed: 9349459]

181. Trudel M, Nadon F, Seguin C, Binz H. Protection of BALB/c mice from respiratory syncytial virus infection by immunization with a synthetic peptide derived from the G glycoprotein. Virology 1991;185:749–757. [PubMed: 1720589]

182. Prince GA, Horswood RL, Chanock RM. Quantitative aspects of passive immunity to respiratory syncytial virus infection in infant cotton rats. J Virol 1985;55:517–520. [PubMed: 4020957]

183. Mills JT, van Kirk JE, Wright PF, Chanock RM. Experimental respiratory syncytial virus infection of adults Possible mechanisms of resistance to infection and illness. J Immunol 1971;107:123–130. [PubMed: 5091954]

184. Cherrie AH, Anderson K, Wertz GW, Openshaw PJ. Human cytotoxic T cells stimulated by antigen on dendritic cells recognize the N, SH, F, M, 22K, and 1b proteins of respiratory syncytial virus. J Virol 1992;66:2102–2110. [PubMed: 1548754]

185. Openshaw PJ, Anderson K, Wertz GW, Askonas BA. The 22,000-kilodalton protein of respiratory syncytial virus is a major target for Kd-restricted cytotoxic T lymphocytes from mice primed by infection. J Virol 1990;64:1683–1689. [PubMed: 2319650]

186. Alwan WH, Openshaw PJ. Distinct patterns of T- and B-cell immunity to respiratory syncytial virus induced by individual viral proteins. Vaccine 1993;11:431–437. [PubMed: 8470427]

187. Johnson TR, Graham BS. Secreted respiratory syncytial virus G glycoprotein induces interleukin-5 (IL-5), IL-13, and eosinophilia by an IL-4-independent mechanism. J Virol 1999;73:8485–8495. [PubMed: 10482601]

188. Varga SM, Wissinger EL, Braciale TJ. The attachment (G) glycoprotein of respiratory syncytial virus contains a single immunodominant epitope that elicits both Th1 and Th2 $CD4^+$ T-cell responses. J Immunol 2000;165:6487–6495. [PubMed: 11086089]

189. Hancock GE, Tebbey PW, Scheuer CA, Pryharski KS, Heers KM, La Pierre NA. Immune responses to the nonglycosylated ectodomain of respiratory syncytial virus attachment glycoprotein mediate pulmonary eosinophilia in inbred strains of mice with different MHC haplotypes. J Med Virol 2003;70:301–308. [PubMed: 12696122]

190. Tebbey PW, Hagen M, Hancock GE. Atypical pulmonary eosinophilia is mediated by a specific amino acid sequence of the attachment (G) protein of respiratory syncytial virus. J Exp Med 1998;188:1967–1972. [PubMed: 9815273]

191. de Graaff PM, Heidema J, Poelen MC, et al. HLA-DP4 presents an immunodominant peptide from the RSV G protein to CD4 T cells. Virology 2004;326:220–230. [PubMed: 15302208]

192. de Waal L, Yuksel S, Brandenburg AH, et al. Identification of a common HLA-DP4-restricted T-cell epitope in the conserved region of the respiratory syncytial virus G protein. J Virol 2004;78:1775–1781. [PubMed: 14747542]

193. Varga SM, Wang X, Welsh RM, Braciale TJ. Immunopathology in RSV infection is mediated by a discrete oligoclonal subset of antigen-specific $CD4^+$ T cells. Immunity 2001;15:637–646. [PubMed: 11672545]

194. Wissinger EL, Stevens WW, Varga SM, Braciale TJ. Proliferative expansion and acquisition of effector activity by memory $CD4^+$ T cells in the lungs following pulmonary virus infection. J Immunol 2008;180:2957–2966. [PubMed: 18292518]

195▪ . Castilow EM, Olson MR, Varga SM. Understanding respiratory syncytial virus (RSV) vaccine-enhanced disease. Immunol Res 2007;39:225–239. [PubMed: 17917067]Comprehensive review of the factors contributing to RSV vaccine-enhanced disease

196. Graham BS, Johnson TR, Peebles RS. Immune-mediated disease pathogenesis in respiratory syncytial virus infection. Immunopharmacology 2000;48:237–247. [PubMed: 10960663]

197. Graham BS. Pathogenesis of respiratory syncytial virus vaccine-augmented pathology. Am J Respir Crit Care Med 1995;152:S63–S66. [PubMed: 7551416]

198. Olson MR, Hartwig SM, Varga SM. The number of respiratory syncytial virus (RSV)-specific memory CD8 T cells in the lung is critical for their ability to inhibit RSV vaccine-enhanced pulmonary eosinophilia. J Immunol 2008;181:7958–7968. [PubMed: 19017987]

199. Castilow EM, Olson MR, Meyerholz DK, Varga SM. Differential role of γ-interferon in inhibiting pulmonary eosinophilia and exacerbating systemic disease in fusion protein-immunized mice undergoing challenge infection with respiratory syncytial virus. J Virol 2008;82:2196–2207. [PubMed: 18094193]

200. Taylor G, Stott EJ, Hayle AJ. Cytotoxic lymphocytes in the lungs of mice infected with respiratory syncytial virus. J Gen Virol 1985;66(Pt 12):2533–2538. [PubMed: 2866227]

201. Kimpen JL, Ogra PL. T-cell redistribution kinetics after secondary infection of BALB/c mice with respiratory syncytial virus. Clin Exp Immunol 1993;91:78–82. [PubMed: 8419089]

202. Roman M, Calhoun WJ, Hinton KL, et al. Respiratory syncytial virus infection in infants is associated with predominant Th-2-like response. Am J Respir Crit Care Med 1997;156:190–195. [PubMed: 9230746]

203. Bont L, Heijnen CJ, Kavelaars A, et al. Peripheral blood cytokine responses and disease severity in respiratory syncytial virus bronchiolitis. Eur Respir J 1999;14:144–149. [PubMed: 10489842]

204. de Bree GJ, van Leeuwen EM, Out TA, Jansen HM, Jonkers RE, van Lier RA. Selective accumulation of differentiated $CD8^+$ T cells specific for respiratory viruses in the human lung. J Exp Med 2005;202:1433–1442. [PubMed: 16301748]

205. Ostler T, Hussell T, Surh CD, Openshaw P, Ehl S. Long-term persistence and reactivation of T-cell memory in the lung of mice infected with respiratory syncytial virus. Eur J Immunol 2001;31:2574–2582. [PubMed: 11536155]

206. Ostler T, Ehl S. Pulmonary T cells induced by respiratory syncytial virus are functional and can make an important contribution to long-lived protective immunity. Eur J Immunol 2002;32:2562–2569. [PubMed: 12207340]

207. Di Napoli JM, Murphy BR, Collins PL, Bukreyev A. Impairment of the $CD8^+$ T-cell response in lungs following infection with human respiratory syncytial virus is specific to the anatomical site rather than the virus, antigen, or route of infection. Virol J 2008;5:105. [PubMed: 18816384]

208. Arimilli S, Palmer EM, Alexander-Miller MA. Loss of function in virus-specific lung effector T cells is independent of infection. J Leukoc Biol 2008;83:564–574. [PubMed: 18079210]

209. Chang J, Choi SY, Jin HT, Sung YC, Braciale TJ. Improved effector activity and memory CD8 T-cell development by IL-2 expression during experimental respiratory syncytial virus infection. J Immunol 2004;172:503–508. [PubMed: 14688360]

210▪ . Falsey AR. Respiratory syncytial virus infection in adults. Semin Respir Crit Care Med 2007;28:171–181. [PubMed: 17458771]Inclusive review of RSV disease pathogenesis in the elderly

211. Everard ML. The role of the respiratory syncytial virus in airway syndromes in childhood. Curr Allergy Asthma Rep 2006;6:97–102. [PubMed: 16566858]

212. De Vincenzo JP. Factors predicting childhood respiratory syncytial virus severity: what they indicate about pathogenesis. Pediatr Infect Dis J 2005;24:S177–S183. [PubMed: 16378043]

213. Crowe JE Jr, Williams JV. Immunology of viral respiratory tract infection in infancy. Paediatr Respir Rev 2003;4:112–119. [PubMed: 12758048]

214. Forton JT, Rowlands K, Hanchard N, Herbert M, Kwiatkowski DP, Hull J. Genetic association study for RSV bronchiolitis in infancy at the 5q31 cytokine cluster. Thorax. 2009(Epub ahead of print)

215. Wilson J, Rowlands K, Rockett K, et al. Genetic variation at the IL-10 gene locus is associated with severity of respiratory syncytial virus bronchiolitis. J Infect Dis 2005;191:1705–1709. [PubMed: 15838798]

216. Choi EH, Lee HJ, Yoo T, Chanock SJ. A common haplotype of interleukin-4 gene IL4 is associated with severe respiratory syncytial virus disease in Korean children. J Infect Dis 2002;186:1207–1211. [PubMed: 12402189]

217. Sikkel MB, Quint JK, Mallia P, Wedzicha JA, Johnston SL. Respiratory syncytial virus persistence in chronic obstructive pulmonary disease. Pediatr Infect Dis J 2008;27:S63–S70. [PubMed: 18820581]

218. Gern JE. Mechanisms of virus-induced asthma. J Pediatr 2003;142:S9–S13. [PubMed: 12584514]

219. Kallal LE, Lukacs NW. The role of chemokines in virus-associated asthma exacerbations. Curr Allergy Asthma Rep 2008;8:443–450. [PubMed: 18682112]

220. Pasare C, Medzhitov R. Toll-like receptors: linking innate and adaptive immunity. Adv Exp Med Biol 2005;560:11–18. [PubMed: 15932016]

221. Haynes LM, Moore DD, Kurt-Jones EA, Finberg RW, Anderson LJ, Tripp RA. Involvement of Toll-like receptor 4 in innate immunity to respiratory syncytial virus. J Virol 2001;75:10730–10737. [PubMed: 11602714]

222. Moore ML, Peebles RS Jr. Respiratory syncytial virus disease mechanisms implicated by human, animal model, and in vitro data facilitate vaccine strategies and new therapeutics. Pharmacol Ther 2006;112:405–424. [PubMed: 16820210]

223. Tripp RA, Oshansky C, Alvarez R. Cytokines and respiratory syncytial virus infection. Proc Am Thorac Soc 2005;2:147–149. [PubMed: 16113483]

224. Durbin JE, Durbin RK. Respiratory syncytial virus-induced immunoprotection and immunopathology. Viral Immunol 2004;17:370–380. [PubMed: 15357903]

225. Culley FJ, Pennycook AM, Tregoning JS, et al. Role of CCL5 (RANTES) in viral lung disease. J Virol 2006;80:8151–8157. [PubMed: 16873271]

226. Martinez FD. Respiratory syncytial virus bronchiolitis and the pathogenesis of childhood asthma. Pediatr Infect Dis J 2003;22:S76–S82. [PubMed: 12671456]

227. van Schaik SM, Welliver RC, Kimpen JL. Novel pathways in the pathogenesis of respiratory syncytial virus disease. Pediatr Pulmonol 2000;30:131–138. [PubMed: 10922135]

228▪ . Openshaw PJ. Immunity and immunopathology to respiratory syncytial virus. The mouse model. Am J Respir Crit Care Med 1995;152:S59–S62. [PubMed: 7551415]Provides a good overview of immunity and disease pathogenesis in a mouse model of RSV infection

229. Waris ME, Tsou C, Erdman DD, Zaki SR, Anderson LJ. Respiratory synctial virus infection in BALB/c mice previously immunized with formalin-inactivated virus induces enhanced pulmonary inflammatory response with a predominant Th2-like cytokine pattern. J Virol 1996;70:2852–2860. [PubMed: 8627759]

230. Prince GA, Jenson AB, Hemming VG, et al. Enhancement of respiratory syncytial virus pulmonary pathology in cotton rats by prior intramuscular inoculation of formalin-inactiva ted virus. J Virol 1986;57:721–728. [PubMed: 2419587]

231. Connors M, Kulkarni AB, Firestone CY, et al. Pulmonary histopathology induced by respiratory syncytial virus (RSV) challenge of formalin-inactivated RSV-immunized BALB/c mice is abrogated by depletion of $CD4^+$ T cells. J Virol 1992;66:7444–7451. [PubMed: 1433525]

232. Graham BS, Bunton LA, Wright PF, Karzon DT. Role of T lymphocyte subsets in the pathogenesis of primary infection and rechallenge with respiratory syncytial virus in mice. J Clin Invest 1991;88:1026–1033. [PubMed: 1909350]

233. Hussell T, Baldwin CJ, O'Garra A, Openshaw PJ. $CD8^+$ T cells control Th2-driven pathology during pulmonary respiratory syncytial virus infection. Eur J Immunol 1997;27:3341–3349. [PubMed: 9464822]

234. Srikiatkhachorn A, Braciale TJ. Virus-specific $CD8^+$ T lymphocytes downregulate T helper cell type 2 cytokine secretion and pulmonary eosinophilia during experimental murine respiratory syncytial virus infection. J Exp Med 1997;186:421–432. [PubMed: 9236194]

235. Schwarze J, Cieslewicz G, Joetham A, Ikemura T, Hamelmann E, Gelfand EW. CD8 T cells are essential in the development of respiratory syncytial virus-induced lung eosinophilia and airway hyperresponsiveness. J Immunol 1999;162:4207–4211. [PubMed: 10201948]

236. Hall CB, Walsh EE, Long CE, Schnabel KC. Immunity to and frequency of reinfection with respiratory syncytial virus. J Infect Dis 1991;163:693–698. [PubMed: 2010624]

237. van der Poel WH, Brand A, Kramps JA, van Oirschot JT. Respiratory syncytial virus infections in human beings and in cattle. J Infect 1994;29:215–228. [PubMed: 7806887]

238. Handforth J, Friedland JS, Sharland M. Basic epidemiology and immunopathology of RSV in children. Paediatr Respir Rev 2000;1:210–214. [PubMed: 12531081]

239. Bont L, Versteegh J, Swelsen WT, et al. Natural reinfection with respiratory syncytial virus does not boost virus-specific T-cell immunity. Pediatr Res 2002;52:363–367. [PubMed: 12193668]