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FC GAMMA RECEPTORS IN RESPIRATORY SYNCYTIAL VIRUS INFECTIONS: IMPLICATIONS FOR INNATE IMMUNITY

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SUMMARY

Respiratory syncytial virus infections are a major burden in infants less than 3 months of age. Newborns and infants express a distinct immune system that is largely dependent on innate immunity and passive immunity from maternal antibodies. Antibodies can regulate immune responses against viruses through interaction with Fc gamma receptors leading to enhancement or neutralization of viral infections. The mechanisms underlying the immunomodulatory effect of Fc gamma receptors on viral infections have yet to be elucidated in infants. Herein, we will discuss current knowledge of the effects of antibodies and Fc gamma receptors on infant innate immunity to RSV. A better understanding of the pathogenesis of RSV infections in young infants may provide insight into novel therapeutic strategies like vaccination.

Keywords

respiratory syncytial virus; fc gamma receptor; maternal antibodies; innate immunity

INTRODUCTION

Respiratory syncytial virus can cause bronchiolitis that is a major burden in infants because almost all children will have had an RSV infection by the age of two years [1, 2]. The severity of RSV infection ranges from mild upper respiratory symptoms to severe lower respiratory tract infection resulting in mechanical ventilation and admission to an intensive care unit. Strikingly, severe infections occur predominantly in infants below 6 months of age and usually involve primary infections. Risk factors such as prematurity, lung disease and congenital heart disease only account for ~50% of the severe cases [1]. It is currently unknown which other factors may account for the remaining 50% of patients with severe RSV infections.

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CONFLICTS OF INTEREST
None

Control of RSV infection in early life

Infants below 6 months of age are largely dependent on innate immunity and the presence of maternal antibodies (matAbs) during infectious diseases. As severe RSV cases involve primary infections, innate immunity and maternal Abs are likely to have an important role. This raises the question why severe RSV infections are highly prevalent in a population having matAbs. This lack of protection might be due to the matAb properties and/or inefficient interaction between these matAbs and the innate immune system.

Innate immunity comprises particular cells and mechanisms that are the first line of defense against infections after the physical barrier has been breached. It is comprised of innate immune cells and soluble components such as the complement system, antimicrobial proteins and peptides. Cells such as monocytes, macrophages, dendritic cells, NK cells and granulocytes contain specific pathogen-recognition molecules, e.g. Toll-like receptors (TLRs), which induce the production of cytokines and activate the adaptive immune response. The innate immune response is supported by a soluble biochemical host defense cascade known as the complement system. Upon activation, this system complements the ability of Abs and phagocytic cells to clear pathogens. Due to an immature adaptive immune system and limited antigen (Ag) encounter in utero, neonates and infants below 6 months of age rely particularly on their still maturing innate immune system to defend themselves against infectious diseases [3]. The importance of innate immune receptors at this age is illustrated by the fact that deficiencies in TLR signaling increase susceptibility to infections with *Streptococcus* spp., *Listeria monocytogenes*, respiratory syncytial virus and *Toxoplasma gondii* in the first years of life [4].

MatAbs are produced by the mother after infection or vaccination. The induction of high affinity Ag-specific Abs is called affinity maturation and leads to high avidity, neutralizing Abs. During pregnancy, matAbs are transferred across the placenta to the fetus and remain in the serum of infants during the first months of life. Immunoglobulins, mainly IgG1, IgG3 and IgG4, cross the placenta actively and are the most important maternal antibodies [5]. IgM is a molecule too large to be transported across the placenta and IgA is transferred to the neonate in small amounts through breast milk [6]. The importance of matAbs is illustrated in newborns with a genetic inability to produce Abs such as agammaglobulinemia. These patients are usually protected against invasive bacterial infections up to 6 months when matAbs are still present [7].

Fc gamma receptors (FcγRs) are essential for the recognition of IgG and internalization of immune complexes to induce an immune response. FcγRs can be divided into either activating or inhibitory receptors and all innate immune cells contain their own specific set of FcγRs. B cells only express the inhibitory FcγRIIB (Table 1). The balance between activating and inhibitory FcγRs together with the avidity of this binding determines the threshold to immune activation [8]. Interaction between FcγRs and pathogen-recognition receptors and the complement system as components of the innate immune system has been described and the role of IgG in this cross-talk is currently being elucidated [9–11] (Figure 1.)

In this review, we will discuss the presence and the properties of RSV-specific Abs in infants and elaborate on the interaction between Abs, FcγRs and the innate immune system, both in general and in RSV infections.

RSV SPECIFIC ANTIBODIES IN INFANTS

RSV-specific matAbs are present during the first 6 months of life and have an estimated half-life of 1.5 months [12–15]. IgG1 (66%) and IgG3 (5.3%) are the predominant subtypes

present in infants [16–20]. These titers are highest among infants < 6 months and infants > 24 months, possibly indicating matAbs and “self made antibodies” respectively. Furthermore, RSV-specific IgG2 and IgG4 are not detected in the sera [20].

The clinical relevance of RSV-specific IgG is unknown at this moment and conflicting evidence is present regarding the effects of matAbs. Several studies observed that matAbs do not have a clinically beneficial effect and high anti-RSV Ab levels are associated with an increased risk of recurrent wheezing [21–23]. Other studies indicate that high titers of maternal IgG are associated with protection against RSV infection [23–27]. These studies calculated the amount of IgG by investigating the neutralizing effect of the sera via plaque reduction or the reduction of the RSV-induced cytopathic effect in in vitro cell culture systems. The amount and effect of non-neutralizing Abs are not measured by these methods. An EIA without pre-selecting neutralizing Abs might more accurately represent the total amount of RSV-specific IgG. By using an EIA, a marginal increased risk of hospitalization has been associated with moderate levels of matAbs compared to low levels [28]. RSV infected infants have comparable amounts but significantly lower avidity of RSV-specific IgG1 compared to non-RSV infected infants. These data indicate that Ab properties, like avidity, might play a role in RSV infections [20].

A more pronounced Ab response after RSV infection in individuals with low titers of matAbs has been observed, indicating that maternal Abs can inhibit the B-cell response and the production of Abs [29, 30]. Further, passive transfer of RSV-specific Abs in mice attenuates the titer and the neutralizing activity of Abs against F and G-proteins expressed by vaccinia virus recombinants [31–33]. All together, these data suggest that matAbs alter the humoral response against RSV resulting in a non-protective immune response.

Besides Ab properties, another important aspect to consider is the different epitopes that Abs can be directed to. RSV has several epitopes recognized by the immune system; the F protein, a surface glycoprotein, causes immune cell membranes to merge and mediates cell entry. The G protein is either membrane bound (mG) or secreted in a soluble form (sG) and has been implicated in immune evasion. The role of other viral proteins, like the small hydrophobic (SH) protein and the non-structural proteins (NS1 and NS2), are less well defined and currently being investigated.

The protective role of RSV-specific Abs is demonstrated by the introduction of palivizumab. Palivizumab is a mAb against the F protein of RSV and reduces hospitalization and decreases the total number of wheezing days in high-risk groups and preterm infants [34, 35]. In mice, mAbs against the RSV G protein offer protection against respiratory disease. Both neutralizing and non-neutralizing anti-RSV G protein mAbs induce protection by inhibition of replication or reduction of pulmonary inflammation [36, 37]. Given a half-life of 20 days, mAbs offer short-term protection and should be administered monthly. Therefore, the induction of a persistent protective immune response against RSV through vaccination has been a topic of interest for decades. The failure of a vaccine trial with formalin-inactivated RSV shows the complexity of inducing a proper immune response against RSV. Proper affinity maturation and the induction of neutralizing Abs are important for an adequate immune response against RSV [38, 39]. Formalin-inactivated RSV induces non-neutralizing Abs and thereby causes an enhanced respiratory disease after concurrent RSV infection [39]. This process is mediated through insufficient stimulation of TLR on B cells and is dependent on the formation of immune complexes. Inactivation of RSV with formalin induces reactive carbonyl groups that may alter immunogenicity and favor a Th2 response possibly resulting in pulmonary eosinophilia and a deleterious immune responses [40]. An important regulatory role of CD8 T cells has been suggested because these cells

inhibit RSV vaccine-enhanced disease and eosinophilia [41]. Consequently a novel vaccine should induce a balanced CD4 and CD8 T cell response to minimize immunopathology.

Overall, the clinical and immunological effects of RSV-specific Abs on RSV infection are still unclear. Studies have reported either a protective or deleterious effect of matAbs (Table 2). Future research on the specific properties of matAbs is needed to interpret this contradictory data.

THE EFFECT OF FC GAMMA RECEPTORS ON INNATE IMMUNITY

Fc gamma receptors and monocytes, macrophages and dendritic cells

FcγRI, FcγRIIA and FcγRIIIA are involved in Ab-mediated phagocytosis of pathogens by monocytic cells like monocytes, macrophages and dendritic cells. Phagocytosis is important for the activation of Syk kinase and the induction of the immune response by release of inflammatory cytokines [42]. The down-side of Ab-mediated phagocytosis is shown in the context of several viral infections and is called Ab-dependent enhancement (ADE). ADE has been observed in secondary dengue infections of both monocytes and dendritic cells in which Abs increase infectivity via FcγRI and FcγRIIA [43]. Furthermore, the ligation of dengue virus particles with Abs reduces the expression of TLR and shifts the formation of cytokines towards anti-inflammatory cytokines [44, 45]. The same principle has been observed in the context of HIV infection and is dependent on FcγRs [46, 47]. These data suggest a mechanism by which ADE in the context of viral infections increases infectivity and impairs the innate immune response [43, 48]. A comprehensive review has been published concerning the different mechanisms of ADE in viral infections after secondary infections or vaccination [49].

Beside initiating phagocytosis, FcγRIII has been implicated in cross-talk with TLRs. The presence of immune complexes results in the association between TLR4 and FcγRIII. Furthermore, the activation of FcγR requires the presence and integrity of TLR4 because both FcγRIII-deficient mice and TLR4-deficient mice were unable to elicit an immune response upon stimulation of macrophages with IgG [11].

FcγRIIB is known as an inhibitory receptor resulting in immunosuppression and decreased phagocytosis by monocytic cells [50]. Pre-treatment of macrophages with IgG1 inhibits the TLR4 response induced by lipopolysaccharide, a process dependent on the activation of FcγRIIB. [51]. In dendritic cells, blockage of FcγRIIB leads to dendritic cell maturation, up-regulation of the type I interferon genes and increased amounts of CCL-5 (chemokine C-C motif ligand 5) which underlines the inhibitory effects of FcγRIIB on the immune response [52, 53].

The role of Fc gamma receptors expressed on monocytes, dendritic cells and macrophages in RSV infections

In animal studies, macrophages are essential for the restriction of RSV replication in the lungs. ADE after vaccination has been observed in RSV infections in vitro with both human and a mouse monocyte-like cell line and macrophages. Monoclonal Abs can have a neutralizing effect, a disease enhancing effect or both [54]. The concentration of IgG and the simultaneous presence of different mAbs determine whether the Abs are neutralizing or disease enhancing [54, 55]. The enhancing activity of RSV-specific Ab levels is confined to sera from infants aged 0 to 6 months and acts via FcγR [56]. This suggests that matAbs may contribute to ADE of RSV infection ADE has not yet been investigated in the context of disease severity of RSV infections. Dendritic cells are the most important antigen presenting cells and function as a bridge between innate and adaptive immunity. RSV can infect DCs but reduces T cell activation by impairment of the immunological synapse between DCs and

T cells [57]. RSV-specific T cell activation and release of IFN-γ are enhanced when mouse DCs are exposed to RSV immune complexes. The use of FcγR-deficient mice showed that this process is dependent on activating FcγRs. The authors conclude that the presence of antibodies might induce a more efficient T cell response through the phagocytosis of opsonized virus particles by DCs [58].

RSV has evolved different mechanisms to alter or counteract the antiviral effect of monocytic cells. RSV evades Ab neutralization by the production of sG which acts as a decoy antigen. The use of FcγR-deficient mice shows that the production of sG decreases the antiviral effect of cells bearing FcγRs underlining the role of Abs in this process [59, 60]. Other structural and non-structural proteins alter the antiviral immune response through direct interaction with recognition receptors [61–65]. All experiments in the context of human cells were performed in a serum-free environment. Therefore, the role of antibodies in the immune evasion mechanisms of RSV is unknown.

Fc gamma receptors and NK cells

NK cells are activated by virus-infected cells directly through activation receptors or through immune complexes. FcγRIIIA is the most important FcγR present on NK cells [66]. In the context of Abs, CD56dim NK cells are of interest considering their abundant presence in peripheral blood and their expression of FcγRIIIA. IgG is able to enhance the production of cytokines by CD56dim NK cells upon encountering target cells [67]. Binding of immune complexes to FcγRIIIA induces antibody-dependent cellular cytoxicity (ADCC) through CD56dim NK cells by degranulation and perforin-dependent targeted cell lysis [68, 69]. In the absence of a pathogen, IgG is able to inhibit NK cell activity [70]. ADCC has extensively been studied in the context of HIV infections in which the interaction of anti-HIV Abs with NK cells offers protection and even predicts viral load and clinical outcome [71, 72]. ADCC against herpes simplex virus and HIV is decreased in neonates compared to adults possibly reflecting, in part, deficient interaction of matAbs and NK cells in the neonatal period [73–75].

FcγRIII is aided in its cytotoxic effect by FcγRIIC. Not all individuals express FcγRIIC on their NK cells. The FcγRIIC gene originates from the unequal crossover between IIA and IIB genes, which results in an FcγR that is homologous to FcγRIIB extracellularly and to FcγRIIA intracellularly [76]. When FcγRIIC is expressed on NK cells, it mediates IFN-γ production and aids FcγRIII in its cytotoxic effect [68, 77]. Finally, the inhibitory FcγRIIB was detected in only a few individuals and was able to suppress NK cell function [76, 78].

The role of Fc gamma receptors expressed on NK cells in RSV infections

In RSV infected mice, NK cells accumulate in the lung upon RSV infection and cause acute lung injury through the production of IFN-γ [79, 80]. RSV infection induces ADCC via NK cells as shown by the cytotoxic effect of NK cells on a RSV-infected human cell line. This process is already present in young infants, implying a role of matAbs [81, 82]. Recent studies are unraveling the specific subsets of NK cells responsible for the RSV-induced ADCC. Lung tissues from fatal RSV infections showed a near absence of NK cells [83]. These low amounts of NK cells, however might represent the end-stage values of NK cells considering the use of lung tissue samples after the patients died. In the acute phase of RSV infection, increased amounts of NK cells are found. CD56+/FcγRIIIA+ NK cells and IFN-γ production are increased in the acute phase of hospitalized RSV-infections compared to control patients without RSV-infection [84]. The increased presence of FcγRIIIA+ NK cells, IFN-γ and lung damage in severe RSV infections, raises the possibility that IgG, as a ligand for FcγRIIIA, negatively influences the immune response in RSV infections.

Fc gamma receptors and granulocytes

Neutrophils—Resting neutrophils express FcγRIIA in a low-avidity state which is functional inactive [85, 86]. fMLP and PMA are two well-known neutrophil activators that regulate the functionality of FcγRIIA in an opposing manner. Whereas fMLP increases the binding of IgG-coated particles, PMA suppresses this process and thereby the functionality of FcγRIIA. These data indicate that the functionality of FcγRIIA is not merely dependent on the activation of neutrophils, but that a stimulus-specific signal determines whether FcγRIIA on activated neutrophils becomes functionally active. [87]. Future research investigating the effects of specific infectious agents, such as RSV, on the functionality of FcγRIIA is needed to translate these findings to understand its role in the pathophysiology of infectious diseases. The activation of FcγRIIIB leads to increased phagocytosis and the recruitment of neutrophils to inflammatory sites [88–90]. As stated before in the context of macrophages, stimulation of neutrophils with IgG results in the association between TLR4 and FcγRIII. PMN from TLR4-deficient mice are unable to elicit an immune response upon stimulation with IgG. However, the effect of immune complexes on PMN from FcγRIII-deficient mice was not investigated [11]. The precise role of the inhibitory FcγRIIB in human neutrophils is as yet unknown. Resting human neutrophils express FCGR2B2 mRNA, but express low levels of FcγRIIB on the cell surface. FcγRIIB might inhibit phagocytosis, superoxide production and neutrophil adhesion [91].

The role of Fc gamma receptors expressed on neutrophils in RSV infections

Neutrophils play an important role in the development of lung pathology in severe primary RSV infections in infants below 6 months [92]. Neither RSV alone nor specific RSV-Abs alone are able to activate neutrophils. The presence of RSV and RSV-specific Abs results in the formation of RSV immune complexes [93]. After phagocytosis of the immune complexes, profound activation of neutrophils and increased amounts of interleukin 8, oxygen radicals and thromboxane B2 are observed. These products cause immune complex-mediated lung pathology and bronchoconstriction in RSV infections [93–95].

Mast cells—IgG Abs have been known to activate mast cells, long before the currently established correlation between IgE, mast cells and allergic reactions [96]. Upon stimulation with IFN-γ, FcγRI expression on mast cells is upregulated and IgG has an activating effect. The increased expression of FcγRI allows IgG, and particularly IgG1, to cause degranulation and prolonged survival of mast cells [97–99].

FcγRIIIA expression is present on mast cells and induces IgG-mediated degranulation [100, 101]. Inhibition of Kit-induced mast cell proliferation upon activation of FcγRIIB has been observed and bone marrow-derived mast cells do not respond to IgG unless they are FcγRIIB-deficient [102]. These data suggest that IgG does bind to bone marrow-derived mast cells, but has an inhibitory effect through FcγRIIB that was confirmed by the increased sensitivity of mast cells from FcγRII-deficient mice upon stimulation with IgG [96, 103].

Currently, there is compelling evidence of a role for mast cells in the immune response against viral infections [104]. Studies observed that viral infection of mast cells leads to the recruitment of monocytes, NK cells and T lymphocytes [105]. The addition of dengue-specific Abs to dengue infected mast cells leads to increased expression of RIG-I and MDA-5 and induces a profound and possibly harmful release of cytokines and chemokines. It has been concluded that FcγRIIA plays a role in the ADE of dengue infections in mast cells [106–108].

The role of Fc gamma receptors expressed on mast cells in RSV infections

Mast cells express TLR4 suggesting direct recognition of pathogens including RSV. RSV infection of rodents and cows has been associated with mast cell activation. In humans, RSV bronchiolitis is associated with an increased number of mast cells [109]. Pre-treatment of mast cells with purified human total IgG results in increased amounts of chemokines compared to stimulation with RSV alone [110].

Eosinophils—Although eosinophils are mostly involved in allergic reactions, they also possess antimicrobial properties [111–113]. FcγRII is responsible for Ab-mediating killing of tumor cells and antibodies are able to enhance the killing ability and activate FcγRII-dependent degranulation of eosinophils against a variety of pathogens like *Toxoplasma gondii* and *Candida albicans* [111, 114, 115]. Abs, particularly IgG1 and IgG3 but not IgE, activate eosinophils resulting in their degranulation and causing bronchial hyperreactivity as seen in asthma patients, a process dependent on FcγRII [116]. Interestingly, immobilized IgG induces death of eosinophils and soluble IgG is able to prolong survival of eosinophils [117].

After activation with chemoattractants or IFN-γ, FcγRI and FcγRII become membrane-expressed on eosinophils. FcγRIII is mainly present intracellular in resting eosinophils. Upon activation however, FcγRIII becomes membrane-expressed transiently before secretion of the receptor takes place [118, 119]. The exact role of FcγRIII in eosinophils is yet to be determined.

The role of Fc gamma receptors expressed on eosinophils in RSV infections

Increased amounts of eosinophils are observed in nasopharyngeal aspirates of RSV infected infants compared to non-infected infants [120]. RSV replication in eosinophils results in the release of infectious virions and the pro-inflammatory mediator interleukin 6 [121]. Eosinophils inactivate RSV by the release of a specific protein called eosinophil cationic protein (ECP) [122, 123]. Infants with elevated levels of ECP during a primary RSV infection are ten times more likely to develop wheezing later in childhood [124]. Pulmonary eosinophilia attracted in response to primary RSV infection is particularly evident in the youngest human infants and in neonatal mouse models [125, 126]. Currently no data are available concerning the effect of Abs or immune complexes on RSV-infected eosinophils. In the context of RSV vaccination, Polack *et al*. showed that IgG mediates increased activation of eosinophils and enhanced respiratory disease after challenge with formalin inactivated RSV [38]. Therefore, abundant eosinophilic acitivation or ECP release might play a role in the immunopathology of RSV infections.

Basophils—Basophils are a sparse subset in the population of leukocytes and they are involved in allergic reactions. Only recently, the role of FcγR on basophils is being elucidated. IgG is not able to activate basophils probably due to the high expression of the inhibitory FcγRIIB in this cell type. A low degree of basophil activation is achieved by selectively activating FcγRIIA and thereby bypassing FcγRIIB [127–130].

The role of Fc gamma receptors expressed on basophils in RSV infections

RSV induces basophil accumulation in a mouse model. Furthermore, basophils were the only cells responsible for the release of interleukin 4, a cytokine which might contribute to the pulmonary pathogenesis of RSV infections [131]. No published data are available on the role of Abs and basophils in the context of RSV.

FC GAMMA RECEPTORS AND B CELLS

The B cell compartment is predominantly known for its adaptive aspects in the immune defense. However, the expression of TLRs and the internalization of viruses upon binding with the B cell receptor (BCR) suggest that B cells are involved in directly sensing infectious agents [132]. A specific B cell population, called B1 cells, is already present during the fetal period. A progressive loss of B1 cells was shown with a fourfold difference between cord blood and adults above 20 years of age that indicates a specific role of B1 cells in childhood [133]. Natural Abs are spontaneously produced by B1 cells without prior infection or immunization and are a major recognition molecule of innate immunity [134–136]. In mice, natural Abs activate the complement system, facilitate antigen uptake and protect against *S. pneumoniae*, *Listeria monocytogenes* and influenza virus [134, 137–140].

B cells only express the inhibitory FcγRIIB and the expression of FcγRIIB varies among the different subtypes of B cells. Engagement of FcγRIIB to BCR leads to inhibition of cellular proliferation and induces apoptosis. B cells that express high-affinity BCR will receive signals from both BCR and FcγRIIB, whereas B cells that have low-affinity BCR will predominantly receive signals via FcγRIIB resulting in apoptosis. Plasma cells express high levels of FcγRIIB and are therefore susceptible to the induction of apoptosis by Abs [141]. Thus, overall, FcγRIIB acts as a regulator of humoral immunity.

The role of Fc gamma receptors expressed on B cells in RSV infections

B cell responses may contribute to the protective and/or pathological effect of primary RSV infections and are increased in the acute and convalescent phase of RSV infection [142, 143]. Some characteristics of RSV-specific B cells from RSV infected individuals have been determined. B cells from RSV infected infants younger than 3 months express fewer somatic mutations after both a primary and a secondary infection compared to individuals older than 3 months. Somatic mutation is an important property of B cells in order to produce neutralizing Abs upon encountering a pathogen [144]. These data suggest that inefficient somatic mutation underlies the poor Ab response in neonates against RSV infections. As mentioned before, high levels of matAbs reduce the Ab response of infants against RSV [30]. Although B cells are the main source of Abs, no study so far has investigated the effect of antibodies on the humoral response in natural RSV infections. The insufficient TLR stimulation on B cells resulting in the lack of a protective Ab response upon formalin-inactived RSV vaccine highlights the importance of adequate activation of B cells [39].

FC GAMMA RECEPTORS AND THE COMPLEMENT SYSTEM

The complement system is a cascade that aids Abs in the clearance of pathogens. IgG1, IgG2 and IgG3 are capable of activating the classical pathway of complement. In this cascade, the formation of complement factors C3a and C5a allows induction of phagocytosis and pro-inflammatory cytokines through complement receptors (C3aR and C5aR) [145]. The interplay between complement and FcγR is essential in this process (Figure 1). Pre-treatment with IgG1 is able to shift this balance by selectively activating FcγRIIB and thereby limiting the inflammatory response [146, 147]

The role of Fc gamma receptors and complement in RSV infections

The complement system is important in the pathogenesis of RSV infections. RSV activates the complement system and induces the production of C3a and C5a [148]. C3aR-deficient mice show decreased viral replication suggesting a non-protective role of C3aR. The disease enhancing effect of C3aR has been confirmed in the context of the formalin-inactivated RSV vaccine. Vaccinated C5-deficient mice express an upregulation of C3aR and enhanced

respiratory disease upon infection with RSV [149]. Moreover, C3 is increased in enhanced respiratory disease caused by vaccination with formalin-inactivated RSV [38]. Both studies conclude that C3aR might contribute to the pathogenesis of RSV infection [150]. Indeed, increased complement activation has been observed in patients who died from RSV bronchiolitis [38]. The effects of pre-existent RSV-specific Abs has been studied by injecting naïve mice with RSV-specific Abs to mimic infants having matAbs. The following Ab-mediated viral restriction is dependent on the complement system [60]. IgG1 is the predominant RSV-specific Ab present in infants with RSV-infections and suppresses complement-mediated inflammation. This predominant interaction of IgG1 with FcγRIIB as stated by Karsten *et al*. is yet to be investigated in the context of RSV infections [147]. Studies on the effect of Abs on the adaptive immune response against RSV show that FcγR and complement contribute to the Ab-mediated induction of CD4+ T cells resulting in a high ratio of CD4+/CD8+ T cells [58]. The balance between CD4+ and CD8+ T cells might be important considering patients with severe RSV infections have relatively low amounts of CD4+ T cells compared to CD8+ T cells [72, 151]. A role of complement and the induction of neutralizing versus non-neutralizing Abs in shaping the CD4+/CD8+ ratio and disease severity has been suggested [58].

CONCLUSIONS

This review has presented the extensive evidence for the immunomodulatory effect of Abs and FcγRs on innate immunity. All cells of the innate immune system express FcγRs and are affected by the presence of antibodies. Circulating matAbs should be taken into account when contemplating disease pathogenesis of infectious diseases in young infants. Most of these mechanisms are present in the context of RSV (Figure 2). Therefore, it is likely that these pathways play a significant role in the development of severe RSV infections. Currently, clinical evidence is lacking and future research is necessary to investigate how the balance between activating and inhibitory FcγRs determines the resulting immune response during severe RSV infections. Elucidating the Ab properties, like the neutralizing capacity, the avidity and the titers of matAbs against RSV in young infants could explain why matAbs are either protective or disease enhancing. In vitro experiments using primary cells represent an important approach to studying these pathways. Characterizing the effect of Abs and activated FcγRs on neutralization of RSV in vitro, cytokine production and the adaptive immune response could advance our knowledge on this subject. Cross-talk between Abs and innate immune receptors, such as TLRs will be of particular interest in the context of an infection that frequently strikes young infants. Studies of FcγR-deficient mice can be used to study the effect of FcγRs in vivo. Although immune evasion mechanisms of RSV are currently being unraveled, the presence of Abs has not been investigated when contemplating clinical relevance. These mechanisms will give more insight into the effects of matAbs on the immune response and disease severity during RSV infections in infants. Secondly, it will provide essential knowledge relevant to the induction of protective Abs during maternal or neonatal immunization. Therefore, characterizing matAbs and the role of FcγRs will provide new insights in the pathogenesis of RSV infections and the development of novel preventive strategies.

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Abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ADE	antibody-dependent enhancement
BCR	B cell receptor
C3aR	complement 3a receptor
CCL-5	chemokine c-c motif ligand 5
ECP	eosinophil cationic protein
FcγR	Fc gamma receptor
fMLP	formyl-methionyl-leucyl-phenylalanine
matAbs	maternal antibodies
mG	membrane bound G protein
NS protein	non structural protein
PMA	phorbol 12,13-dibutyrate
sG	soluble G protein
SH protein	small hydrophobic protein
TLR	Toll-like receptor

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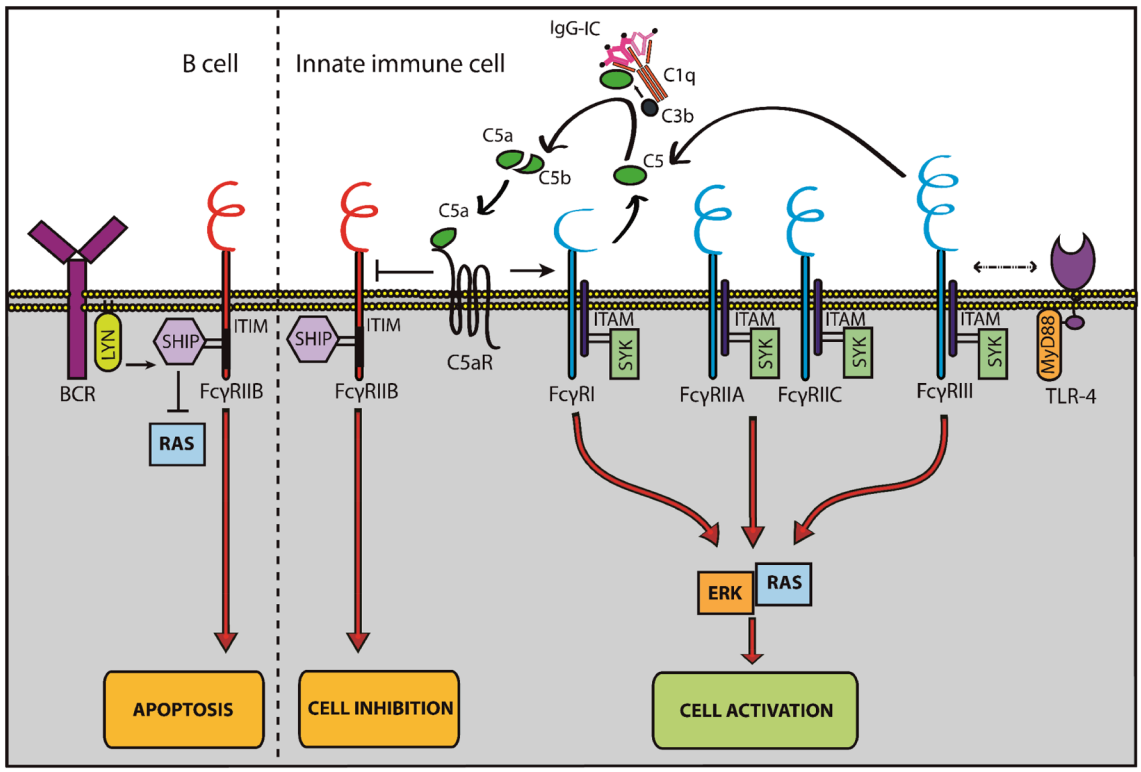

Figure 1. Interplay between FcγRs and other receptors on innate immune cells and B cells

FcγRs are expressed on APCs, NK cells, granulocytes and B cells. Depending on the ITAM or ITIM motif, FcγRs can be divided in activating (blue) or inhibitory (red) receptors. Activating receptors are able to initiate cell activation and induce phagocytosis, ADCC and the oxidative burst. Cross-talk with TLR-4 has been suggested for a proper immune response. The inhibitory FcγR, FcγRIIB, induces cell inhibition.

Cross-talk between the complement system and activating FcγRs creates a positive feedback loop. Activating FcγRs (FcγRI and FcγRIII) promote the complement system to generate C5a. C5a binds C5aR which is co-expressed on the cell. This binding induces increased expression levels of activating FcγRs and decreased levels of inhibitory FcγRs.

B cells only express the inhibitory FcγR, FcγRIIB. Engagement of FcγRIIB to BCR leads to inhibition of cellular proliferation and induces apoptosis. (BCR: B cell receptor; C5aR: complement 5a receptor; ERK: extracellular-signal-regulated kinases; FcγR: Fc gamma receptor; IgG-IC; immune complex; ITAM: immunoreceptor tyrosine-based activation motif; ITIM: immunoreceptor tyrosine-based inhibition motif; LYN: member of src-related family of protein-tyrosine kinases; MyD88: myeloid differentiation primary response gene 88; RAS: member of small GTPase proteins; SHIP: SH2 domain containing inositol-5 phosphatase; Syk: spleen tyrosine kinase)

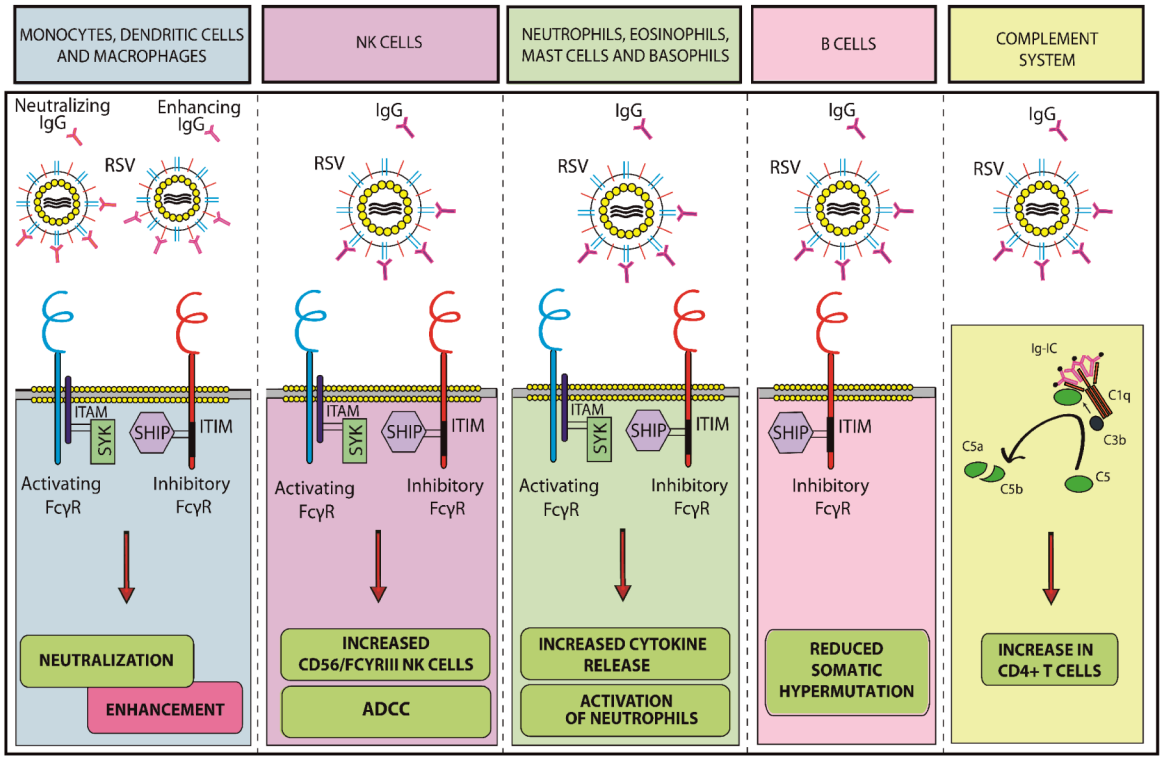

Figure 2. Summary of the interaction between RSV, antibodies, FcγRs and the innate immune system

In monocytic cells, the interaction between Abs and FcγRs has a neutralizing or a disease enhancing effect on RSV. FcγRIIIA+ NK cells are responsible for ADCC, induce higher amounts of cytokines in the presence of Abs and increased amounts of FcγRIIIA+ NK cells are observed in severe RSV infections. Profound activation of neutrophils and increased cytokine release against RSV are induced in the presence of RSV-specific Abs. B cells from RSV infected infants younger than 3 months of age express fewer somatic mutations compared to older individuals. The complement system is involved in the Ab-mediated induction of CD4+ T cells upon RSV infection.

Table 1

Expression of different types of FcγR on innate cells and B cells and its proposed effect in the immune response against pathogens

The right hand column, separated by a dated vertical line, indicates inhibitory receptors.

Type	FcγRI	FcγRIIA	FcγRIIC	FcγRIIIA	FcγRIIIB	FcγRIIB
Expression	Monocyte Macrophage Dendritic cell Neutrophil Eosinophil Mast cell[1]	Monocyte Macrophage Dendritic cell Neutrophil Basophil Eosinophil	NKcell	Monocyte Macrophage Dendritic cell NK cell Mast cell	Neutrophil Eosinophil[1]	Monocyte Macrophage Dendritic cell Neutrophil Basophil Mast cell NK cell B cell
Effect	Phagocytosis Cytokine release ADE[2] Degranulation[3] Complement activation[4]	Phagocytosis Cytokine release ADE[2] ADCC[5]	Cytokine release ADCC[5 6]	Phagocytosis Cytokine release Cross-talk TLR-4 Complement activation[4] ADCC[5]	Phagocytosis Chemoattractants Cross-talk TLR-4 Degranulation[3] ADCC	Reduced phagocytosis Reduced TLR sigaling Reduced proliferation Apoptosis[7]

[1] Upon stimulation with IFN-γ;

[2] Antibody-dependent enhancement of disease;

[3] Mast cells;

[4] In mice models;

[5] Antibody-dependent cellular toxicity;

[6] Interaction with FcγRIII;

[7] B cells

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Table 2

Clinical relevance of IgG in RSV infections in young infants

RSV-specific IgG can be divided into IgG1, IgG2, IgG3, IgG4 and mAb IgG1. Contradictory data is present regarding the protective effects of total maternal IgG. Low avidity maternal IgG1 has been associated with an increased susceptibility to RSV infections. Palivizumab (mAb IgG1) has a protective effect against severe RSV infection in high-risk infants. IgG2-4 are either undetectable or only detected in the minority of young infants below the age of 6 months.

Type	Total IgG	IgG1	mAb IgG1 (Palivizumab)	IgG2	IgG3	IgG4
Clinical relevance	**High titer:** • Increased wheezing and hospitalization[1] • Reduced wheezing and hospitalization[2] • Reduced Ab response	**Low avidity:** • Increased susceptibility to RSV infection[3]	**Monthly administration:** • Reduced wheezing and hospitalization[4]	Not detectable	Detectable in the minority of young infants	Not detectable

[1] Amount of IgG measured by plaque reduction or reduction of RSV-induced cytopathic effect in in vtiro cell culture system;

[2] Amount of IgG measured by EIA;

[3] Avidity measured by using an antibody eluting agent (sodium thiocyanate);

[4] Administered to high-risk and preterm infants