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Host immunity during RSV pathogenesis

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Abstract

Infection by respiratory syncytial virus (RSV) is the leading cause of childhood hospitalization as well as a major health and economic burden worldwide. Unfortunately, RSV infection provides only limited immune protection to reinfection, mostly due to inadequate immunological memory, which leads to an exacerbated inflammatory response in the respiratory tract promoting airway damage during virus clearance. This exacerbated and inefficient immune-inflammatory response triggered by RSV, has often been attributed to the induction of a Th2-biased immunity specific for some of the RSV antigens. These features of RSV infection suggest that the virus might possess molecular mechanisms to enhance allergic-type immunity in the host in order to prevent clearance by cytotoxic T cells and ensure survival and dissemination to other hosts. In this review, we discuss recent findings that contribute to explain the components of the innate and adaptive immune response that are involved in RSV-mediated disease exacerbation. Further, the virulence mechanisms used by RSV to avoid activation of protective immune responses are described.

1. Introduction

Respiratory syncicial virus (RSV) is the leading cause of viral bronchiolitis and pneumonia worldwide, infecting more than 70% of children in the first year of life and 100% of children by age 2 [1]. RSV is an enveloped, negative strand RNA virus belonging to the *Paramyxoviridae* family with a genome that encodes for 11 proteins [2]. Among these proteins, two on the virion surface: F and G, and two non-structural proteins:

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NS1 and NS2, constitute key viral components that contribute to the infective cycle and to the evasion of the host immune response [3–5]. The F protein mediates the fusion between the virus and the target cell surface and promotes the formation of syncytia – a phenomenon that originates the virus name [3].

Despite being highly infective, RSV does not induce an effective immunological memory and repeated infections are therefore very frequent [6,7]. Although common RSV symptoms manifest as rhinitis in adults, severe RSV infection is frequently observed in premature infants, the elderly and immunosuppressed individuals [8,9]. Furthermore, it has been proposed that exposure to RSV infection early in life can lead to an increased susceptibility to suffer from recurrent allergic wheezing and asthma [10]. Considering epidemiological data, RSV is responsible for causing a health problem that is extremely expensive for individuals, governments and health care systems. Unfortunately, to date there are no commercially available vaccines against this pathogen. Efforts aimed to develop a vaccine against RSV were first carried out with a formalin-inactivated RSV formulation (FI-RSV) in vaccine trials in the mid 1960s [11]. However, vaccinated children experienced exacerbated pulmonary disease and required hospitalization upon subsequent RSV infection, while non-vaccinated control children experienced significantly milder symptoms [11,12]. The failure of FI-RSV remained unexplained for at least two decades, primarily because of a poor understanding of the immune responses triggered by RSV infection. However, recent studies have suggested that the FI-RSV vaccine failed because of its ability to induce an allergic-like T cell helper-2 (Th2) immune response against the virus [13–15]. This particular Th2 type response is characterized by the activation and proliferation of $CD4^+$ T cells that secrete a pattern of cytokines promoting the infiltration of eosinophils and neutrophils into the lung tissues. This inflammatory-allergic cellular environment dampens $CD8^+$ cytotoxic T cell activation and effector functions, such as the secretion of IFN-γ [16]. As a result, clearance of RSV is delayed and virus spreading promoted. Studies with sera obtained from children immunized with FI-RSV vaccine have shown that antibodies to the F and G proteins were generated but they had low neutralizing capacity [17]. These findings could be due to a possible disruption of critical epitopes by formalin during the process of virus inactivation. Furthermore, excess of these antibodies may enhance disease by promoting immune complex deposition and complement activation [17]. Effecting clearance of RSV would require the induction of a balanced Th1/Th2 adaptive immune response that is able to promote the production of neutralizing antibodies (preferably mucosal IgA), in addition to the induction of IFN-γ secreting cytotoxic $CD8^+$ T cells.

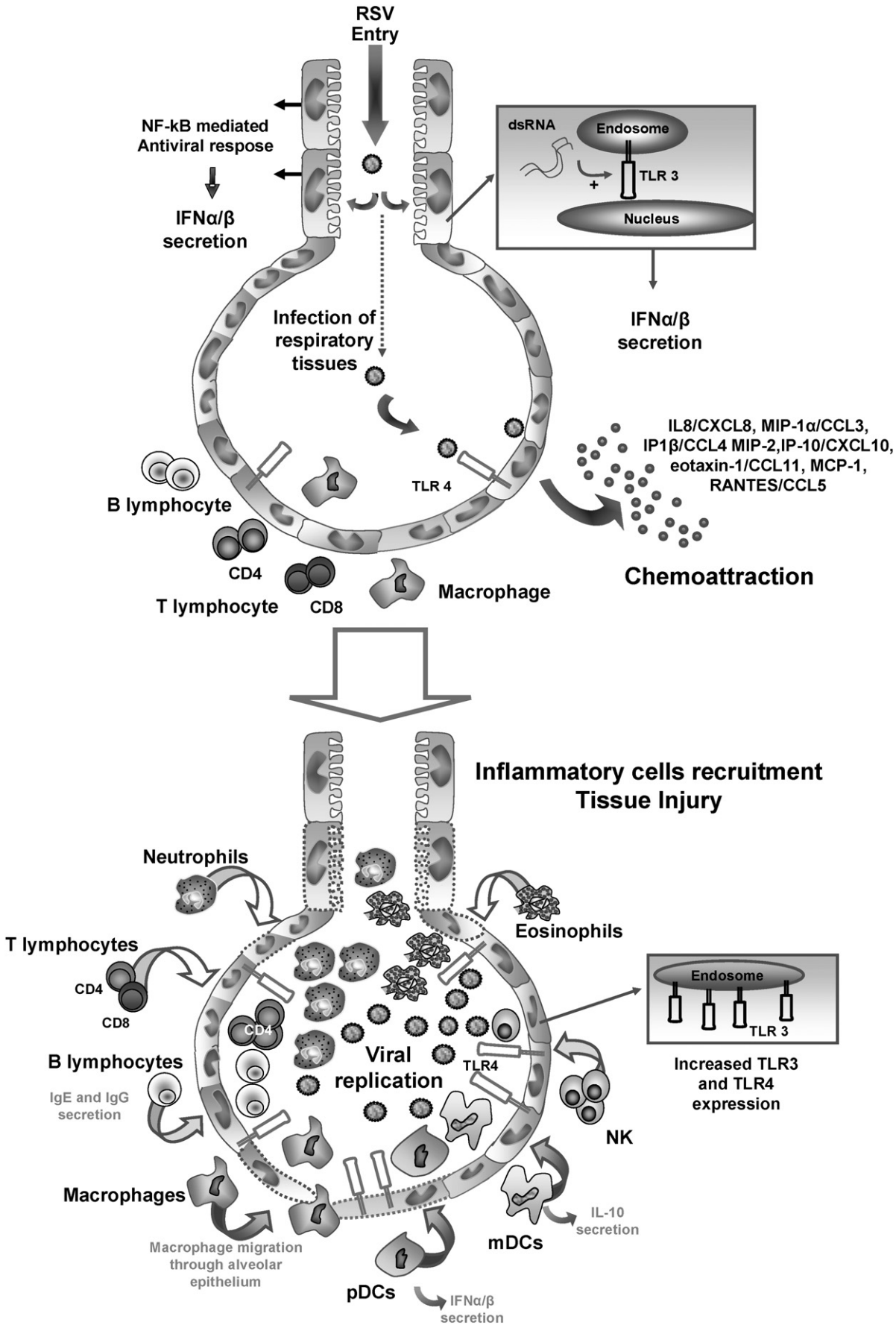
Several recent studies have contributed to explain the impaired adaptive immune response to RSV. Here we discuss experimental evidence providing support for a model for RSV-induced immunopathology and describe virulence features and mechanisms used by this virus to avoid activation of an appropriate, protective immune response.

2. RSV infection and innate immune response

Airway epithelial cells are initial targets for RSV infection, as well as the first site for the activation of an innate immune response. After attaching to epithelial cells, RSV induces NF-kB-mediated transcription of genes promoting an anti-viral response [18,19]. Accordingly, during the first hours after infection, an enhanced expression of genes related with local inflammatory responses, antigen processing and chemoattraction are observed in the lung epithelium [20]. These processes promote the production of chemokines and the recruitment of eosinophils, NK cells and $CD4^+$ T cells to the airways (Fig. 1) [21].

Once RSV contacts respiratory epithelial cells, the virus is recognized by cell surface Toll-like Receptors (TLRs), promoting the secretion of inflammatory cytokines. Among the TLRs expressed on the surface of respiratory epithelial cells, the TLR4/CD14 complex is the main extracellular receptor recognizing RSV, through the binding of the Fusion (F) protein present on the viral envelope [22]. TLR4/CD14 engagement by F protein leads to an NF-kB-mediated cytokine response, including the secretion of IL-8, IL-10, and IL-6 [22,23] and an increase in TLR4 expression on epithelial cells [24]. In addition, several reports have demonstrated that RSV can also be recognized by TLR3 on respiratory epithelial cells [18,25,26]. TLR3 is an intracellular receptor that recognizes viral replication intermediates, such as dsRNA. Although it has been suggested that TLR3 is not required for viral clearance, its expression might be necessary to regulate the immune environment in the lung epithelia. A recent study has shown that RSV infection in mice lacking TLR3 translates into increased secretion of Th2 cytokines and mucus in the lung, as well as enhanced eosinophil recruitment as compared to wild-type mice [25]. In addition, increased TLR3 expression is observed on respiratory epithelial cells after RSV infection, which probably can contribute to an increased sensitivity and secretion of inflammatory cytokines upon contact with RSV or even other microbial components, such as LPS or dsRNA [18]. These observations are consistent with the notion that RSV might be able to predispose lung tissues to enhanced inflammatory responses to later challenges with virus or bacteria [27,28].

In vitro studies performed on respiratory epithelial cells have shown that RSV infection promotes the secretion of chemokines, such as IL-8/CXCL8, MIP-1α/CCL3, MIP-1β/CCL4, MIP-2, IP-10/CXCL10, eotaxin-1/CCL11, macrophage chemoattractant protein 1 (MCP-1) and RANTES/CCL5. Accordingly, expression of these chemokines has been shown increased in nasal washes from RSV-infected individuals at the time of virus shedding [29–37]. Chemokines secreted by RSV-infected epithelia promote activation and recruitment, from blood into infected tissues, of neutrophils (IL-8/CXCL8), monocytes, memory T cells (RANTES/CCL5) and eosinophils (eotaxin-1/CCL11). The recruited immune cells secrete both pro-inflammatory cytokines, such as TNF, IL-6 and IL-8, as well as inhibitory cytokines, such as IL-10 [38–40]. Increased secretion of these cytokines probably contributes to the airway damage caused by RSV infection. Consistent with this notion, *in vitro* studies have shown that bronchial epithelial cells secrete higher amounts of IL-8, IL-6 and RANTES/CCL5 in response to RSV infection, when compared to other respiratory virus [16]. Accordingly, *in vivo* chemokine blockade can reduce lung pathology and damage, as observed in mice treated with anti-RANTES antibodies, which showed a significant decrease in airway


RSV
Entry
NF-kB mediated
Antiviral respose
IFNα/β
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Infection of
respiratory
tissues
TLR 4
IL8/CXCL8, MIP-1α/CCL3,
IP1β/CCL4 MIP-2,IP-10/CXCL10,
eotaxin-1/CCL11, MCP-1,
RANTES/CCL5
Chemoattraction
B lymphocyte
CD4
T lymphocyte
CD8
Macrophage
Inflammatory cells recruitment
Tissue Injury
Neutrophils
Eosinophils
T lymphocytes
CD4
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CD4
B lymphocytes
IgE and IgG
secretion
Viral
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and TLR4
expression
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IL-10
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Macrophage migration
through alveolar
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hyperreactivity [37]. Similarly, treatment of mice with Met-RANTES (a competitor for RANTES receptor) reduced the recruitment of inflammatory cells to the lung [32]. Interestingly, treatment with RANTES/CCL5 can reduce RSV infection of HEp-2 cells, probably by blocking the interaction between RSV fusion (F) protein and epithelial cell surface proteins [41]. Similarly, infection was also decreased by a biologically inactive N-terminally modified Met-CCL5 [41]. In another study, mice treated with a blocking antibody against CCL11 showed reduced lung eosinophilia and disease severity [31]. Unexpectedly, treatment with this molecule also caused inhibition of $CD4^+$ but not $CD8^+$ T cell infiltration into the lungs [31]. In agreement with the observations discussed above, MIP-1α KO mice infected with RSV showed a significant reduction in lung histopathology as compared to wild-type mice. However, no differences on lung viral titers were observed between MIP-1α KO and WT mice [36]. Taken together, these data suggest that secretion of chemokines by airway epithelium and infiltrating immune cells can be detrimental to the host by promoting immunopathology and tissue damage with a minor contribution to viral clearance. Thus, the chemokine milieu is beginning to be considered as an important component during RSV infection and therefore an attractive pharmacological target.

Upon RSV infection, epithelial cells and infiltrating leukocytes produce large amounts of anti-viral molecules, such as type I IFN [42]. These cytokines signal through the IFNAR receptor on the target cell surface and, activate several intracellular signaling pathways that involve the activity of STAT-1 and STAT-2 proteins [42]. Activated STAT-1 and -2 bind to Interferon regulatory factor 9 (IRF-9) to assemble an activator complex that translocates to the nucleus and initiates the expression of multiple genes, known as Interferon-stimulated genes (ISGs) [42]. Expression of these genes triggers several anti-viral functions; such as the activation of ribonuclease L (RNAseL) that degrades host and viral RNA. Furthermore, ISGs promote the proliferation and activation of NK cells, as well as their anti-viral capacity [43]. Although plasmacytoid dendritic cell (pDCs) are main producers of IFN-α, as described below, epithelial cells also can produce significant amounts of type I interferons [44].

However, type I IFNs have been shown to also influence other immune process during RSV infection. Mice deficient on STAT-1 and -2, two proteins required for IFN α/β and IFN-γ induced signaling, suffer severe inflammation, increased eosinophil infiltration to the airways and increased Th2 cytokines in the lungs in response to RSV infection. [45]. Further, it has been observed that IFN-α/β and IFN-γ produced during the innate immune response could also contribute to the recruitment of inflammatory cells to the lungs during RSV infection [46]. Mice lacking IFNα/β and IFNγ receptors ($IFN\alpha\beta\gamma R^{-/-}$) showed eosinophilia but reduced lymphocyte infiltration to the lungs after a challenge with RSV. However, mice that only lack the IFN-γ receptor, showed only moderate eosinophilia within the lung [46]. Thus, type I IFNs seems to be critical for the recruitment of inflammatory cells to the lungs, triggered by RSV.

Interestingly, RSV infection promotes a weakened type I IFN response in infected tissues by blocking IFNα/β signaling. Studies using recombinant deletion approaches have demonstrated that RSV proteins NS-1 and NS-2 are necessary to impair IFN-α/β secretion by epithelial cells [47]. These two viral proteins act coordinately to decrease STAT-2 mediated-signaling by selectively targeting this receptor for proteasomal degradation [48]. Recently, it has been suggested that NS-1 binds to the proteasome-related proteins elongin C and cullin 2 to form an E3 ubiquitin ligase complex, which probably promotes STAT-2 degradation with the assistance of NS-2 [49]. This mechanism used by RSV to down-regulate type I IFN signaling and response probably allows successful viral replication within infected tissues. However, RSV also reduces secretion of type I IFN in RSV-infected tissues, which could promote bystander recruitment of inflammatory cells to the airways contributing to lung damage upon viral infection.

3. Dendritic cell function during the immune response to RSV

Dendritic cells (DCs) are ubiquitous professional antigen presenting cells (APCs) found in lymphoid tissues and non-lymphoid tissues located strategically to capture a diverse array of antigens and present them to T cells as peptides bound to either MHC class I or class II molecules [50–52]. Upon recognition of pathogen associated molecular patterns, DCs undergo a phenotypic change, known as maturation. As a result of maturation, DCs downmodulate their phagocytic capacity and up-regulate the expression of surface peptide-major histocompatibility complexes (pMHC) and co-stimulatory molecules such as CD80 and CD86 [53]. Additionally, mature DCs increase their migratory capacity and secrete modulatory cytokines involved in host defense, such as IL-12 and type I and type II interferons [54,55]. Concomitantly, DCs undergoing maturation migrate to lymphoid tissues where antigen presentation to specific T cells takes place and initiate an adaptive immune response [51,56]. Because DCs are key components for the clearance of pathogens, virulent microorganisms can interfere with DC function as a mechanism to impair the proper function of adaptive immunity [57–60].

However, dendritic cells are a heterogeneous group of cells, which show phenotypic and functional differences at

Figure. 1 RSV infection modifies the inflammatory environment in the airways. Early after RSV infection, viruses reach alveoli and infect airway epithelial cells. As a defense mechanism against viral spreading, infected cells are induced to secrete IFNα/β after the activation of NF-kB and intracellular TLR3 by RSV-derived PAMPs (dsRNA). Simultaneously, engagement of surface TLR4 by RSV induces the secretion of several chemokines and cytokines. Under normal conditions, lymphocytes and macrophages can only be found circulating in the blood outside alveoli (top panels). Later on infection, viral replication is accompanied by massive infiltration of inflammatory cells into the lungs, which is promoted by the chemokine- and cytokine-rich environment. At this point, neutrophils, eosinophils, NK cells, mDCs, pDCs, macrophages, B lymphocyes and $CD4^+$ T lymphocytes can be observed in alveoli, as well as surrounding bronchial tubes. Although $CD8^+$ T lymphocyte infiltration can be observed, their effector capacity is widely hampered (lower panels). Furthermore, increased expression of TLR3 and TLR4 by epithelial cells is observed after RSV infection.

priming adaptive immunity [61]. Among the diverse DC lineages, two of them predominate and have been extensively characterized, myeloid DCs (mDCs) and plasmacytoid DCs (pDCs). These two DC subtypes work synergistically at inducing efficient anti-viral immune responses [54]. By stimulating $CD4^+$ and $CD8^+$ T cells, IL-12-producing mDCs are critical inducers of Th1-polarized adaptive immune responses, which can promote efficient effector responses against viruses and other intracellular pathogens [54,61]. On the other hand, IFN-α secreting pDCs promote anti-viral and immunomodulatory effects by acting over wider range of cell types [54,62]. mDCs and pDCs residing at the airways play pivotal roles during innate immune responses against viruses, as well as a regulatory roles in the polarization of T cell effector mediated responses [63]. Considering their key functions as promoters of immunity, it is important to define how mDCs and pDCs can contribute to development of immune responses to RSV, as well as the potential virulence mechanisms developed by this virus to interfere with DC function.

In vitro experiments have shown that RSV can infect DCs and replicate within these cells [64,65] (Gonzalez and Kalergis, unpublished results). DC-RSV interaction can lead to the upregulation of maturation markers on the DC surface, such as CD86 and MHC-II [64–67]. However, RSV-infected DCs seem unable to efficiently prime antigen-specific T cells for IFN-γ secretion [67] (Gonzalez and Kalergis, unpublished results), a phenomenon that could be explained by the reduced capacity of RSV-infected DCs to secrete Th1-polarizing cytokines. For example, virulent RSV strains inhibit IFN-α and IL-12p70 secretion by mDCs [65,68,69], which are key cytokines necessary to promote $CD8^+$ T cell effector functions as well as the induction of memory $CD8^+$ T cells [70]. Accordingly, another study has demonstrated that RSV can block IFN-α secretion derived from pDCs *in vivo*, thus evading the development of a proper anti-viral immune response [44]. However, other studies have shown that RSV-infected pDCs can secrete considerable amounts of IFN-α [66]. These differences might be accounted to the different strains of RSV used in these studies.

In vivo studies have shown that, after viral exposure, increased amounts of both myeloid and plasmacytoid DCs with mature phenotypes are observed in the respiratory airways of mice [71,72]. Moreover, sustained increase for both mDCs and pDCs is observed in the lungs of mice up to 30 days after RSV infection [69,72,73]. It is possible that proliferation of DC precursors at the site of infection in the lungs in response to GM-CSF secreted by epithelial cells upon RSV infection could contribute to the increased numbers of DCs [29]. This notion is supported by the expression of proliferation markers, such as Ki67, by DCs in infected lungs [74]. Interestingly, upon RSV infection, DC precursors in the lung are depleted and thus DC expansion in lungs is not observed following further viral infections [15].

Recent studies suggest that pulmonary pDCs could play an important role at modulating the immune response induced by RSV infection [73]. The selective depletion with pDC-specific antibodies leads to enhanced lung immunopathology [73,74]. As described above, type I IFN might play an important role at regulating the immune environment during RSV infection. Since pDCs are the most important IFN-α producing cells, depletion of these cells might further facilitate the Th2-biased immune response induced by RSV. In addition, activation of pDCs residing at the airways reduces RSV replication and inflammation after infection [15]. Therefore, although *in vitro* studies have shown that RSV modulates DC function by reducing its capacity to secrete key cytokines and prime an efficient anti-viral T cell response, *in vivo* studies would suggest that pulmonary DCs are relevant to control RSV infection and to counteract the immunopathology induced by this virus. Further studies are needed to conciliate both *in vitro* and *in vivo* observations regarding the role of DCs during RSV infection.

4. Role of adaptive immunity on RSV infection and immunopathology

To date, several experimental models and different approaches suggest that RSV can modulate the activation of the adaptive immune response in at least two ways. First, RSV seems to block the production/function of cytotoxic memory T cells against viral antigens. Thus, primary infection does not confer protection to subsequent re-infections with antigenically similar RSV strains [75,76]. Second, RSV infection and/or vaccination with inactivated virus can induce a detrimental, Th2 immune memory that promotes lung injury after a second exposure to the virus [77–79].

Early studies reported that monocytes/macrophages secrete inhibitory molecules that suppress T cells responses *in vitro* in response to challenge with RSV [80]. The absence of efficient murine adaptive immune responses is evidenced by the persistence of RSV in the lungs, despite the presence of RSV-specific $CD4^+$ and $CD8^+$ T cells in infected tissues [72]. Interestingly, it has become clear that the T cell responses are specifically impaired in the respiratory tract during RSV infection [7,81]. It is thought that efficient viral clearance requires Th1 polarization driven partially by IL-12 secreting mDCs, which promote activation of IFN-γ-producing $CD4^+$ T cells. IFN-γ in turn promotes cytotoxic T cell function by stimulating $CD8^+$ T cells and NK cells to clear virus-infected cells, stimulates macrophage phagocytic activity to promote clearance of dead cells and induces production of neutralizing IgG antibodies by B cells [82]. However, RSV infection seems able to evade cytotoxic immunity by blocking IFN-γ secretion by RSV-specific T cells [81]. In Balb/c mice, at least two immunodominant peptides derived from RSV proteins have been described to bind class I MHC molecules [6]. These epitopes have allowed tracking *in vivo* virus-specific $CD8^+$ T cells and their activation after RSV infection. These peptides, $M2_{82-90}$ and F_{85-93}, are bound to $H\text{-}2K^d$ molecules and can be used for flow cytometry detection of specific T cells infiltrating tissues, using MHC-I tetramers [6,81,83]. Using this methodology, it has been observed that M2-specific T cells expand, activate and localize in the lungs after RSV infection. However, these cells showed an impaired effector activity [81]. A similar behavior was described for F-specific $CD8^+$ T cells [6]. Interestingly, these cells localize in pulmonary tissues for short periods of time and secrete low amounts of IFN-γ, which contribute to their limited effector activity [81]. However, this unresponsiveness of specific $CD8^+$ T cells can be overcome by a treatment with IL-2, both *in vitro* and *in vivo* [81,84]. Additional immunodominant epitopes derived from RSV proteins have been recognized

for C57BL/6 mice, which have allowed further studies on the dynamics of T cell activation after RSV infection [85]. These studies have shown that M2-specific T cells were predominantly expanded and activated after RSV infection and showed no impairment of IFN-γ secretion after one week of primary infection. However, a reduction in the number of activated M2-specific $CD8^+$ T cells producing IFN-γ was observed in the lung at 21 and 28 days post-infection [85]. These observations support the notion that RSV infection in mice leads to inactivation of T cells, specifically in tissues infected with the virus or where it replicates actively, independently of host genetic background.

Evaluation of T cell function *in vitro* has provided new alternative explanations for the inability of RSV-specific T cells to produce efficient effector responses. A recent study has shown that inactivation of human T cells was caused by direct contact of T cells with cells expressing RSV F protein on the surface [86]. However, the molecular mechanisms responsible for this phenomenon have not been yet elucidated. Further studies have described that RSV hinders the secretion of pro-inflammatory cytokines from DCs, which lead to an impaired capacity of T cells to become activated and secrete IFN-γ [67]. On the other hand, soluble factors secreted by DCs in response to RSV challenge can also inhibit T cell proliferation [64]. This notion is supported by a recent study showing that human monocyte-derived DCs secrete IFN-λ and IFN-α in response to RSV, which impairs polyclonal T cell activation [87]. Consistently with these observations, blockade of both IFN-λ and IFN-α receptors can overcome T cell inhibition after co-culture with RSV-infected DCs [87]. However, it seems contradictory that while IFN-α might be contributing to T cell inhibition, RSV NS-1 and NS-2 gene products appear to suppress secretion of this molecule, as mentioned above [88]. Nevertheless, the simultaneous production of both IFN-α and IFN-λ seems to synergistically impair T cell activation [87].

5. Exacerbation of RSV immunopathology by immunization with inactivated virus

Another important feature of RSV infection is the induction of a $CD4^+$ mediated, Th2-biased T cell memory in the host, after either RSV infection or vaccination with formalin-inactivated RSV [89]. Administration of inactivated virus to humans leads to an enhanced disease progression after a subsequent encounter with RSV [12]. Equivalent observations have been made in animal models for RSV-caused disease [90]. An excess of eosinophil recruitment to the airways, deposition of immune complexes and complement activation is quickly observed on respiratory tissues after a challenge with RSV [15,90]. A recent study has suggested that the enhanced capacity to promote Th2 immunity shown by the inactivated RSV vaccine could be due to an excessive carbonylation of viral proteins after formalin treatment [15]. Accordingly, chemical reduction of carbonyl groups in formalin-inactivated vaccines can contribute to reduce excessive inflammation after RSV infection of vaccinated mice [15]. This feature might be particular for RSV proteins, since other formalin-inactivated virus vaccines do not induce damaging Th2-allergic immune responses [91,92]. In a similar way, several studies have shown that immunization with RSV G protein is sufficient to trigger a Th2-biased memory, which mediates enhanced inflammatory injury upon subsequent RSV infection [93–95]. G protein is a glycoprotein expressed on the RSV surface, which promotes attachment of the virus to host cells [96]. This protein contains a CX3C chemokine motif at amino acids 182–186 that binds to the CX3CR1 chemokine receptor, modulating $CX3CR1^+$ T cell responses [97]. It was observed that RSV G protein expression or the G protein CX3C motif within RSV virions can reduce the frequency of $CX3CR1^+/CD4^+$ and $CX3CR1^+/CD8^+$ T cells within lungs and reduce the frequency of $CX3CR1^+$/RSV-specific IFN-γ expressing cells during primary RSV infection [97]. Importantly, $CX3CR1^+$ T cells were shown to represent a major cytotoxic component responding to RSV infection [97].

Recently it was shown that immunization with purified G protein or Vaccinia virus expressing this RSV protein leads to enhanced disease after a subsequent RSV challenge [93–95]. This damaging immune response is characterized by secretion of cytokines such as IL-4 and IL-5 from activated $CD4^+$ T cells [5,89]. Such a cytokine pattern is known to promote eosinophil and basophil recruitment to lungs and IgE production. As a result, granule secretion by inflammatory cells is enhanced and an aggressive inflammatory hyperresponsiveness is established at the respiratory tract without an efficient clearance of RSV [98]. In Balb/c mice, an oligoclonal $Vβ14^+$, $CD4^+$ T cell population is expanded upon RSV G protein immunization, which is probably responsible for the enhanced tissue injury after RSV infection [79]. This notion is supported by experimental deletion of these cells, which reduces lung immunopathology, weight loss and eosinophil infiltration in the airways of G-primed mice after RSV infection [79].

6. Specific immune response to RSV antigens in humans

Although Th2 immune response can be observed in mouse models after intranasal RSV infection, the human immune response is apparently different and not well understood. Studies performed with young infants have shown that normal or increased IFN-γ producing T cells are found in the respiratory tract following RSV infection, regardless of the patient's clinical severity [99]. In contrast, other studies showed increased IL-4 responses in the infant respiratory tract, as well as eosinophilia and the establishment of Th2 type responses [100,101]. Thus, RSV infection seems able to induce either a Th1- or Th2-type adaptive immunity, depending on the genetic background of the individual. However, in most cases neither type of the immune response triggered by RSV infection seems to be appropriate for efficient virus clearance and host welfare. Therefore, RSV is not exclusively responsible for the immediate generation of the severe symptoms described above, but is rather the abnormal Th2-like immune response often induced against RSV.

7. Concluding remarks

To date, a large body of data on the immune response to RSV has contributed to explain several important features on RSV-

induced pathology. Its seems clear that the overreacting immune response triggered in some hosts by RSV proteins, which leads to an excessive inflammation and infiltration of immune cells into the airways, can be considered as the main cause of tissue damage. Damaging immunity can indeed be observed upon subsequent RSV infection after vaccination with FI-RSV of G protein. In addition, the establishment of protective and efficient adaptive immune memory is impaired probably because RSV infection impedes the activation of virus-specific T cell within the lungs. Therefore, efforts aimed to design an effective and safe vaccine against RSV need to evaluate both, the type of immune response induced after vaccination to avoid immunopathology, as well as the capacity to generate a long-lasting protective immune memory. In addition, further studies are required to underscore the molecular mechanisms used by RSV to interfere with T cell activation, which could contribute to the design of new therapeutic tools to treat or prevent the respiratory disorders caused by the virus.

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