



REVIEW

Chemokine regulation of inflammation during respiratory syncytial virus infection [version 1; peer review: 3 approved]

Rinat Nuriev ^{1,2}, Cecilia Johansson ¹

¹National Heart and Lung Institute, Imperial College London, London, UK
²I. Mechnikov Research Institute for Vaccines and Sera, Moscow, Russian Federation

v1 First published: 31 Oct 2019, 8(F1000 Faculty Rev):1837 (<https://doi.org/10.12688/f1000research.20061.1>)
 Latest published: 31 Oct 2019, 8(F1000 Faculty Rev):1837 (<https://doi.org/10.12688/f1000research.20061.1>)

Abstract

Respiratory syncytial virus (RSV) can cause severe lower respiratory tract infections especially in infants, immunocompromised individuals and the elderly and is the most common cause of infant hospitalisation in the developed world. The immune responses against RSV are crucial for viral control and clearance but, if dysregulated, can also result in immunopathology and impaired gas exchange. Lung immunity to RSV and other respiratory viruses begins with the recruitment of immune cells from the bloodstream into the lungs. This inflammatory process is controlled largely by chemokines, which are small proteins that are produced in response to innate immune detection of the virus or the infection process. These chemokines serve as chemoattractants for granulocytes, monocytes, lymphocytes and other leukocytes. In this review, we highlight recent advances in the field of RSV infection and disease, focusing on how chemokines regulate virus-induced inflammation.

Keywords

RSV, chemokines, lung inflammation

Open Peer Review

Reviewer Status

	Invited Reviewers		
	1	2	3
version 1 published 31 Oct 2019			

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- 1 **Ralph A Tripp** , University of Georgia, Georgia, USA
- 2 **Leo Carlin**, Cancer Research UK Beatson Institute, Glasgow, UK
University of Glasgow, Glasgow, UK
- 3 **Steven M Varga**, University of Iowa, Iowa, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Cecilia Johansson (c.johansson@imperial.ac.uk)

Author roles: Nuriev R: Conceptualization, Writing – Original Draft Preparation; Johansson C: Conceptualization, Writing – Original Draft Preparation

Competing interests: No competing interests were disclosed.

Grant information: We thank the Rosetrees Trust (M370) and Cancer Research UK (A27217) for support of the lab and the UK-Russia Young Medics Association supported by Sechenov First Moscow State Medical University and the British Embassy Moscow for support of RN's fellowship.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2019 Nuriev R and Johansson C. This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Nuriev R and Johansson C. **Chemokine regulation of inflammation during respiratory syncytial virus infection [version 1; peer review: 3 approved]** F1000Research 2019, 8(F1000 Faculty Rev):1837 (<https://doi.org/10.12688/f1000research.20061.1>)

First published: 31 Oct 2019, 8(F1000 Faculty Rev):1837 (<https://doi.org/10.12688/f1000research.20061.1>)

Introduction

Respiratory syncytial virus (RSV) can cause upper and lower respiratory tract infections. Lower respiratory tract RSV infections are particularly common in young children, resulting in a spectrum of illnesses, including bronchiolitis and viral pneumonia¹. Infections caused by RSV occur worldwide, and it is estimated that over 3.2 million children under 5 years of age are hospitalised annually because of RSV infection². Moreover, RSV can cause lower respiratory tract infections in adults, especially in the elderly and immunocompromised, who are prone to more severe disease^{1,3,4}. Natural RSV infections result in incomplete immunity and therefore recurrent infections are common throughout life. The determinants of the outcome of RSV disease are not fully known, but both viral and host factors play a part⁵. Among the latter are the immune responses elicited during RSV infection, which are crucial for efficient clearance of the virus but, if uncontrolled, can cause immunopathology. This can be detrimental for the lung tissues and result in impaired lung function and reduced oxygen exchange. Chemokines are crucial for the initiation of immune responses to RSV as they regulate leukocyte infiltration and localisation in the lungs⁶. Alterations in the chemokine profile may therefore result in substantial dysregulation of immune responses. Insufficient or misdirected immunity may lead to increased viral replication and direct viral damage to the lung tissue. In contrast, unnecessarily hyperactive immune responses may have subsequent immunopathologic consequences.

Innate immune responses during RSV infection

RSV infection often starts in the nasopharyngeal epithelium and rapidly spreads to the lower airways. The main cellular hosts for viral replication are the epithelial cells lining the airways and alveoli. When the virus reaches the lower airways, lung-resident cells such as epithelial cells, dendritic cells (DCs) and alveolar macrophages (AMs) initiate the innate immune response to the infection with the secretion of cytokines and chemokines^{1,5}. AMs are crucial for the initial anti-viral responses as they are the main type I interferon (IFN) producers in the lung during RSV infection⁷. Type I IFNs are cytokines that are important for inducing interferon-stimulated genes (ISGs) that limit viral replication and for priming and sustaining overall inflammatory cytokine and chemokine production^{8,9}. The inflammatory chemokines orchestrate recruitment of blood leukocytes into the lung. *In vitro* studies show that epithelial cells and macrophages can produce chemokines (see details in Table 1). However, there is no clear evidence that AMs are the main source of most chemokines during RSV infection^{10,11} and many other cell types are likely involved in chemokine production. Interestingly, chemokine production is bi-phasic in mice^{12,13} and humans¹⁴ after RSV infection; the first wave of chemokines is induced after sensing of the virus, and the second wave of chemokines is induced a few days after the initiation of infection. The second wave of chemokines correlates with the disease severity and the recruitment of T cells. The types of chemokines produced in the two waves are overall similar, but the underlying mechanism for the regulation and initiation of the two waves of chemokine production is not known. Therefore, increased knowledge of the regulation of chemokine production is important for the possibility to develop targeted therapies to reduce lung inflammation in the future.

In this review, we describe the major chemoattractants (Table 1) considered to be important during RSV infection. We have summarised work from *in vivo* studies in mice and from human patient samples and describe the cell recruitment into the lungs after RSV infection based on timing, starting with the cell types infiltrating the lungs within hours of a primary infection and ending with the events occurring during secondary exposure, after re-encountering RSV (Figure 1).

Neutrophils during RSV infection

Neutrophils are the first cell type to arrive at a site of infection or tissue damage and they infiltrate the lung in both mice and humans in large numbers during RSV infection^{8,15–17}. Neutrophils are attracted into the lung tissue by a wide range of different molecules. These include not only several chemokines but also cytokines, eicosanoids and small peptides¹⁸. In this review, only the chemokines will be discussed. CXCR2 and CCR1 are the most abundantly expressed chemokine receptors on neutrophils. CXCR2 is able to interact with a number of different chemokines, but CXCL1, CXCL2 and CXCL8 have been studied the most. Similarly, CCR1 can bind several distinct chemokines such as CCL3 and CCL5¹⁸.

CXCL1 (KC) and CXCL2 are considered to be some of the earliest chemokines expressed in the lungs of mice after RSV infection, detectable as early as 4 to 8 hours after virus exposure^{7,8,17,19}. Moreover, recombinant CXCL1 can recruit large numbers of neutrophils into the lungs if given intranasally to mice¹⁷. CXCL1 has been suggested to be produced by several different cell types, including epithelial cells²⁰ but not AMs¹⁰. Recently, it was shown that a stromal cell type—that is, a non-epithelial (AT-II) and non-endothelial cell—is the main source of CXCL1 during RSV infection of mice¹⁷.

CXCL8 (IL-8) has no orthologue in mice and can be studied in humans only. Many studies have found elevated CXCL8 levels in bronchoalveolar (BAL) fluid or nasal washes from RSV-infected children (for example, 20–26) and from RSV-challenged healthy adult volunteers¹⁴. The origin of CXCL8 during RSV infection is not clear, but an *in vitro* model showed that primary paediatric bronchial epithelial cells can produce CXCL8 after RSV infection²⁷. Furthermore, RSV can directly trigger the release of CXCL8 from neutrophils²⁸. A recent study revealed links between viral load, CXCL8 levels and changes in the microbiome during RSV infection²⁹. In that study, the abundance of bacteria of the *Haemophilus* genus in nasopharyngeal aspirates of RSV-infected hospitalised infants was a predictor for CXCL8 levels and higher viral load²⁹.

CCL3 can recruit many different cell types such as neutrophils, monocytes, natural killer (NK) cells and T cells. CCL3 production in the lungs increases soon after RSV infection in mice^{8,13,19,30} and in infants^{22,23,25}. Although CCL3 can be produced by AMs¹⁰, two studies using AM-depleted mice show different results: one shows a reduction in CCL3³¹ and the other no difference¹¹ when AMs are depleted during RSV infection. In addition, after RSV infection of BALB/c mice, CCL3 was detected in alveolar epithelial cells and endothelial cells³². This suggests that CCL3 can originate from several cell types in the lung.

Table 1. The most common chemokines produced during respiratory syncytial virus infection, their receptors, cell types they attract and possible sources.

Chemokine	Receptors	Cells attracted	Possible cellular sources	Study type	References
CXCL1 (KC)	CXCR1, CXCR2	Neutrophils	Stromal cells, neutrophils, ECs	Murine	7,8,17,19
CXCL2 (MIP-2 α)	CXCR2	Neutrophils	AMs?	Murine	12,19
CXCL8 (IL-8)	CXCR1, CXCR2	Neutrophils	ECs, macrophages, neutrophils	Human	14,20–28
CXCL9 (MIG)	CXCR3	NK cells, T cells	?		8,33
CX3CL1 (Fractalkine)	CX3CR1	Monocytes, NK cells, T cells	?	Murine	34
CXCL10 (IP-10)	CXCR3	Monocytes?, DCs, T cells	AMs, stromal cells?, ECs?	Human and murine	8,10,14,23,33,35,36
CCL2 (MCP-1)	CCR2, CCR4	Monocytes, NK cells, eosinophils?	ECs?, macrophages?	Human and murine	7,10,12,22,23,25
CCL3 (MIP-1 α)	CCR1, CCR4, CCR5	Neutrophils, monocytes, NK cells, T cells	AMs, ECs, stromal cells	Human and murine	8,10,13,14,19,22,23,25,30
CCL5 (RANTES)	CCR1, CCR3, CCR5	Neutrophils, monocytes, DCs, NK cells, T cells	ECs, AMs	Human and murine	11,12,14,20,31,37
CCL7 (MCP-3)	CCR2	Monocytes	?	Murine	7
CCL8 (MCP-2)	CCR1, CCR2, CCR3, CCR5	Monocytes, eosinophils, NK cells, T cells	?		
CCL11 (Eotaxin-1)	CCR2, CCR3, CCR5	Eosinophils, T cells	?	Murine	19,38,39
CCL12 (MCP-5)	CCR2	Monocytes, eosinophils, lymphocytes	Macrophages?	Murine	7
CCL17 (TARC)	CCR4	Th2 cells, Treg cells	?	Human	40
CCL20 (MIP-3a)	CCR6	DCs, T cells	?		
CCL22	CCR4	Th2 cells, Treg cells	DCs, macrophages		

AM, alveolar macrophage; DC, dendritic cell; EC, epithelial cell; NK, natural killer; Treg, regulatory T.

Neutrophils phagocytose microbes and release granules containing oxygen radicals, elastases and proteolytic enzymes^{41–43}. In addition, they form neutrophil extracellular traps (NETs), which serve to stop pathogens from propagating^{44,45}. Although the role of neutrophils is well defined during bacterial or fungal infections, their role during RSV infection remains unclear. It is not yet known whether they have a beneficial role limiting the spread of the virus or a detrimental role damaging the lung tissue^{46,47}. The viral load does not change if neutrophils are depleted during RSV infection⁴⁸, suggesting that neutrophils do not have a substantial direct anti-viral role. However, the inflammatory environment in the lung, induced by RSV infection, results in neutrophil activation¹⁷, and *in vitro* studies suggest that activated neutrophils augment the detachment of epithelium infected with RSV^{49,50}. Furthermore, a detrimental role of excessive neutrophilic response is suggested by the fact that the degree of neutrophilic infiltration into the lungs correlates positively with severity of RSV-induced bronchiolitis^{15,16,51}. Also, infants with RSV-induced bronchiolitis

have increased levels of neutrophil elastase^{21,52} and signs of oxidative burst⁵³, which can promote oxidative stress and tissue injury⁵⁴. NETs can be secreted by neutrophils from RSV-infected children and have also been detected in lungs of RSV-infected calves⁵⁵. *In vitro* studies have shown that RSV fusion protein can interact with TLR4, an innate immune receptor expressed on neutrophils and other cells, to trigger formation of NETs⁵⁶. It has also been suggested that NETs can capture RSV and that NET formation can contribute to lung damage during RSV infection⁵⁵. In sum, neutrophils are a key population of cells recruited into the lungs after RSV infection, but more studies are needed to confirm whether they are beneficial or detrimental to the host during RSV infection.

Monocytes during RSV infection

Monocytes are the second cell type to infiltrate the lung after RSV infection. Human and murine monocytes are divided into two main subsets on the basis of their chemokine receptor expression. Their functions seem to be more or less similar, but

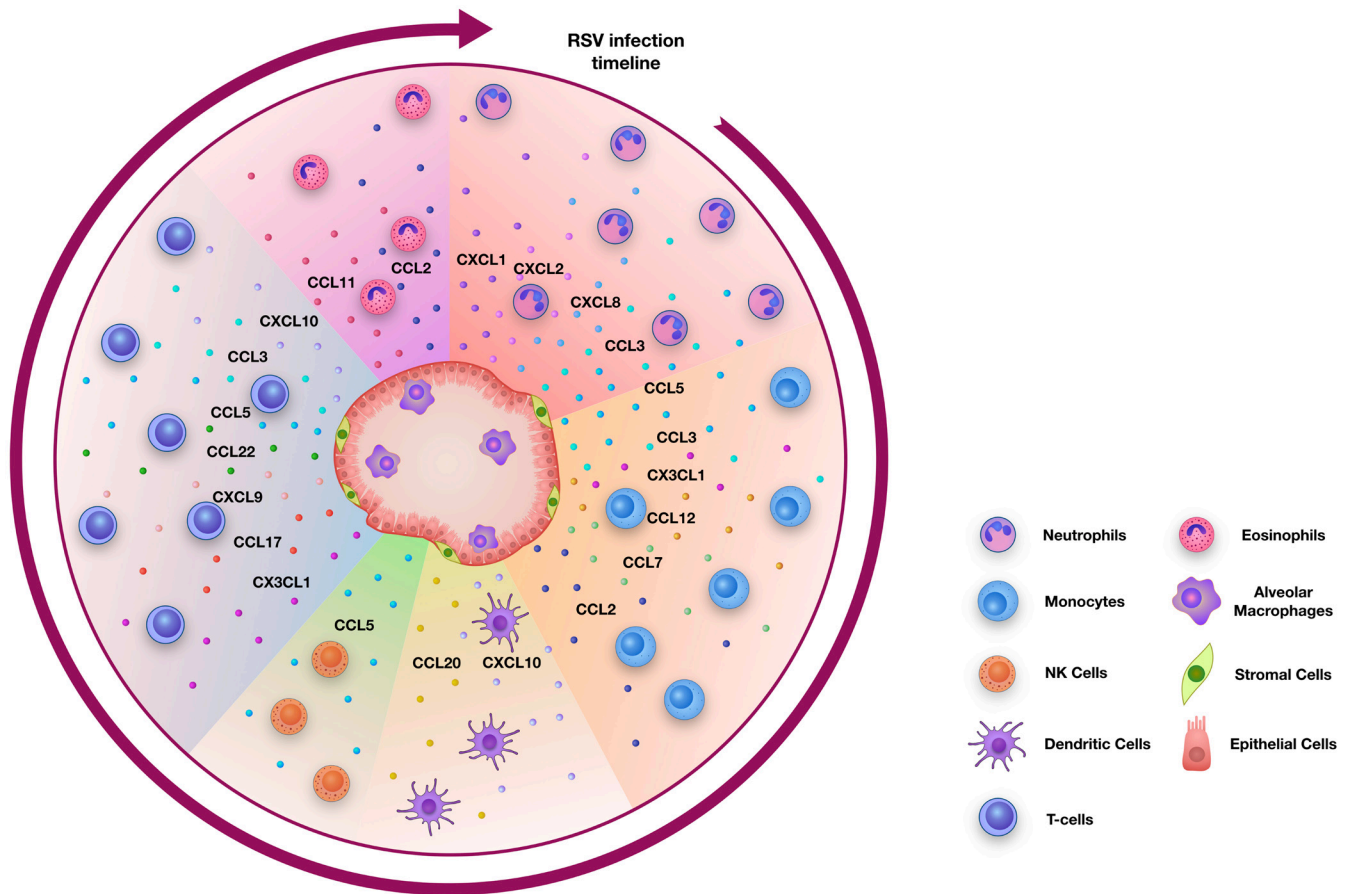


Figure 1. Chemokines as drivers of cell infiltration into the lung during respiratory syncytial virus (RSV) infection. Cells of the lung, such as alveolar macrophages, epithelial cells and stromal cells, produce chemokines during RSV infection to initiate and drive inflammation. During a primary RSV infection, neutrophils are the first cells to be recruited into the lung, followed by monocytes and dendritic cells. This is followed by the infiltration of natural killer (NK) cells and then T cells. During a secondary infection, tissue-resident and circulating memory T cells respond to the infection. In some cases, eosinophils can also infiltrate the lungs during RSV infection.

one subset expresses high levels of CCR2 and low levels of CX3CR1 (CCR2^{hi} subset) and the other subset expresses high levels of CX3CR1 and low levels of CCR2 (CX3CR1^{hi} subset)⁵⁷. CX3CR1 is also expressed on T cells and airway epithelial cells⁵⁸. CX3CR1 binds to its ligand, CX3CL1, which is important for the chemotaxis of CX3CR1^{hi} monocytes as well as T cells. Furthermore, CX3CR1 expression on monocytes is important for their survival⁵⁹. During RSV infection of mice, CX3CR1 deficiency is associated with reduced innate immune cell recruitment, notably a significant decrease in NK cells and CD11b⁺ cells (which may represent a monocytic subpopulation)³⁴. Interestingly, RSV G protein can bind directly to CX3CR1 and influence chemotaxis of lymphocytes⁶⁰, and CX3CR1 has been suggested to be a receptor used by RSV to infect cells^{1,58}.

CCR2 is also an important receptor expressed on monocytes. CCR2 binds to CCL2, CCL7, CCL8 and CCL12, and the first two chemokines are generally considered to be the most important for monocyte recruitment^{57,61}. However, both human and murine

monocytes express CCR1 and CCR5, which means that they can also be recruited by the chemokines CCL3 and CCL5⁵⁷. CCL2, CCL3, CCL5 and CX3CL1 have all been found in nasal samples or lung tissues of human and mice infected with RSV (for example, [7, 12, 14, 22, 23, 25]).

In mouse models, CCL2, CCL7 and CCL12 are produced early after RSV infection^{7,12}. In humans, CCL2 levels correlate positively with disease severity: infants with RSV bronchiolitis who required mechanical ventilation show significantly elevated levels of CCL2 in BAL fluid compared with control infants intubated for non-infective causes^{22,23}, and children with severe RSV disease displayed higher levels of CCL2 in nasopharyngeal wash samples than controls²⁵. The source of CCL2 during pulmonary inflammation has been under investigation but remains controversial. Experiments in *Mavs*^{-/-} and *Ifnar1*^{-/-} mice show that CCL2 expression is promoted by type I IFNs produced by AMs⁷. *In vitro* studies show that CCL2 can be produced by murine airway epithelial cells but not by AMs^{10,12}.

However, it is still unclear whether AMs can produce CCL2 *in vivo* or whether they simply promote chemokine expression by producing type I IFNs.

CCL5 (RANTES), another monocyte chemoattractant, is also considered to be important during initial responses to RSV infection. This chemokine binds to a wide range of receptors, including CCR1, CCR3 and CCR5, expressed on different types of immune cells: Th1 T cells, macrophages, DCs, neutrophils and NK cells⁶. Moreover, it has been proposed that CCL5 has a direct anti-viral effect against RSV by blocking RSV fusion protein interactions with epithelial cells⁶². Surprisingly, recent studies show that the levels of CCL5 are higher in nasal fluid samples of children with moderate RSV bronchiolitis compared with children with severe disease³⁷. AMs play a role in CCL5 production during RSV infection as AM depletion in mice results in decreased levels of CCL5^{11,31}. It is possible that AMs do not produce CCL5 themselves but exert their effects through the production of mediators such as type I IFNs that subsequently act on other cells to increase CCL5 production. Furthermore, *in vitro* studies show that human cord blood-derived mast cells⁶³ and human airway and bronchial epithelial cells can produce CCL5 and that CCL5 release depends on live virus^{12,20}.

Monocyte-derived cells consist of inflammatory monocytes and monocyte-derived DCs and can constitute up to 40% of total lung leukocytes in the mouse model of RSV infection⁷. Furthermore, monocyte-derived cells play a direct role in limiting RSV replication⁷. Monocytes exhibit their anti-bacterial effects through the production of tumour necrosis factor (TNF) and inducible nitric oxide synthase⁶⁴, but how they limit RSV replication is not yet understood. Contrary to their anti-viral activities, monocytes can also have harmful effects on lung tissue. In an influenza virus–*Streptococcus pneumoniae* co-infection mouse model, inflammatory monocytes induced damage to the lung barrier by killing epithelial cells via a TNF-related apoptosis-inducing ligand (TRAIL)-dependent mechanism, resulting in decreased control of the infection and reduced animal survival⁶⁵. However, there are no studies revealing a harmful role of monocytes during RSV infection. Given that viral–bacterial and viral–viral co-infections can occur in immunocompromised children or when several viruses such as RSV, rhinovirus and influenza virus co-circulate at the same time^{66–69}, it would be very interesting to investigate the exact role of monocytes during RSV infections.

Dendritic cells during RSV infection

DCs are the main antigen-presenting cells that initiate the adaptive immune responses to infections. This function makes DCs especially important for the clearance of viral infections such as RSV. DCs are resident in the lung during homeostasis and can respond to RSV immediately. However, immature DCs (not clear whether these are monocyte-derived) can also be recruited to sites of inflammation by many inflammatory chemokines binding to CXCR1, CXCR3, CCR1, CCR2, CCR5 and CCR6^{6,70,71}, and DCs are recruited to the nasal tissue in children with RSV infection⁷². One chemokine associated with DC recruitment during RSV infection is CXCL10 as

antibody-mediated neutralisation of CXCL10 results in impaired DC recruitment and maturation with reduced levels of type I IFN and IL-12p70 in the lungs of RSV-infected mice³⁵. Similar responses were observed after neutralisation of CXCR3, the only known receptor for CXCL10³⁵. Additionally, RSV-infected mice treated with neutralising antibodies against CCL20 or CCR6^{-/-} mice, another DC chemoattractant and chemokine receptor respectively, recruit fewer conventional DCs but show reduced lung pathology³⁶. These data suggest that DCs can have both a beneficial and detrimental role in the lungs.

Innate lymphoid cells during RSV infection

NK cells, part of the innate lymphoid cell 1 (ILC1) group, are important anti-viral innate lymphoid cells that activate other immune cells or kill virus-infected cells. NK cells, like other immune cells, express an extensive variety of chemokine receptors and can be attracted to the sites of inflammation via several distinct pathways^{6,73}. The CCR5/CCL5 axis plays an important role in the accumulation of NK cells at virally infected sites, and during influenza virus infection, both CXCR3 and CCR5 have been shown to be important for NK cell recruitment⁷⁴.

NK cells are recruited to the lungs of RSV-infected mice and get activated to produce IFN- γ ⁷⁵. *Ex vivo*, human NK cells can be infected by RSV, especially in the presence of RSV-specific antibodies⁷⁶. However, the number of human NK cells has also been shown to decrease with severe RSV disease⁷⁷, and if NK cells are depleted from mice, IFN- γ production is suppressed and more of a Th2 response develops⁷⁸.

RSV has also been shown to activate IL-13–producing ILC2s via the production of TSLP⁷⁹, and STAT-1 signalling was shown to be important for the activation of ILC1s and the repression of ILC2s and ILC3s⁸⁰. Overall, very little is known of the recruitment of ILCs during RSV infection, and more information will aid in the understanding of how they are recruited and their contribution to viral clearance or lung damage.

Adaptive immune responses during RSV infection

Cells of the adaptive immune response infiltrate the lung both during primary and secondary infections. These are mostly T cells: CD8⁺ (CTL) T cells and CD4⁺ T cells (both T helper cells and regulatory T [Treg] cells)¹. After naïve T cells have been primed in lymph nodes, they migrate to the lungs in response to chemotactic signals. In mice, it is known that RSV infections lead to increased numbers of T cells in the lung tissue, which typically peak at day 7 or 8 following a primary infection^{81,82}. T cells accumulate at a similar time (8 to 10 days after infection) in the human airways after RSV infection of healthy volunteers⁸³. Interestingly, the final lung viral clearance, both in mice and humans, occurs on days 8 to 10 after RSV infection, corresponding to the peak of adaptive immune responses^{1,83,84}.

Chemokines, such as CCL3, CXCL9 and CXCL10, regulate the infiltration of effector T cells into the lungs and they are all produced during RSV infection in mice and humans^{8,13,19,23,33,82}. Memory T cells are formed after the first encounter with

RSV. These are both effector memory cells and lung-resident memory T cells (Trm cells). The Trm cells provide a quick response during subsequent infections⁸⁵, whereas the effector memory cells need to be recruited upon re-infection^{1,84}. Chemokine signalling is therefore considered to be an important regulatory mechanism in the formation of, especially, long-term memory CD8⁺ T-cell populations in the lung⁸⁶. It has been observed that, following influenza virus infection, mice deficient in either CXCR3 or CCR5 have significantly elevated numbers of memory CD8⁺ T cells. Although it is not completely clear for RSV infections, these data suggest that chemokine signalling through CXCR3 and CCR5 can regulate the effector versus memory T cell recruitment into the lung⁸⁶.

Interestingly, CCL17 and CCL22 can recruit both Th2 cells and Treg cells into the lungs⁸⁷. CCL17 recruits Th2 cells, especially in mice sensitised by vaccinia virus expressing the RSV G protein before RSV infection⁸⁸, and serum CCL17 is increased in RSV-infected children compared with children with other respiratory infections or healthy controls⁴⁰. Furthermore, RSV-specific CD8⁺ T cells present in the lung can inhibit the production of CCL17 and CCL22 and therefore limit the recruitment of Th2 cells⁸⁹.

Thus, chemokines are important during both primary and secondary RSV infection as they regulate effector, memory T and Treg cell recruitment and thereby can determine the extent of disease severity during RSV infection. More detailed studies of how the chemokines also determine the exact localisation of effector, Treg and memory T cells and thereby direct their effector functions will be important for future work.

Eosinophils during RSV infection

Generally, eosinophils are not considered to have an important role during primary viral infections. However, during memory responses to RSV infection, eosinophils can infiltrate the lungs. This was especially the case when children, or mice, were vaccinated with formalin-inactivated RSV (FI-RSV). This vaccination induced a Th2-biased memory response with Th2 cells and pulmonary eosinophilia following RSV challenge, resulting in increased disease severity^{1,90-92}. For a long time, it was believed that lung eosinophilia was the driving factor of the FI-RSV vaccine-enhanced disease. However, more recent studies and re-evaluation of the initial vaccine trials revealed that eosinophilic infiltration was not the only characteristic component of vaccine-enhanced disease, suggesting that other factors may be important^{91,93}.

Eosinophils can be attracted to the lungs by chemokines such as CCL2 or CCL11. CCL2 and its role in chemotaxis of monocytes were extensively discussed above. CCL11, also called eotaxin, is considered to be the main chemokine for eosinophil recruitment. Mice sensitised by vaccinia virus expressing the RSV G protein showed eosinophils in the lungs following subsequent RSV infection but after administration

of anti-CCL11 antibodies showed significantly reduced lung eosinophil numbers. Moreover, CCL11 depletion resulted in subsequent decrease in CD4⁺ T-cell influx to the lungs and decreased IL-5 production with no influence on the viral load^{19,38}. However, more recent studies of vaccine-enhanced RSV disease suggest that eosinophils are pro-inflammatory and have direct anti-viral functions during RSV infection. Experiments in eotaxin knockout mice show complete absence of eosinophils in the lungs of FI-RSV immunised mice following RSV infection with reduced lung inflammation. However, the eotaxin knockout mice had significantly higher lung RSV titres compared with wild-type mice, and when lung eosinophilia was restored, by either intratracheal rCCL11 administration or adoptive transfer of eosinophils, this resulted in increased viral clearance³⁹. These data raise the question again, do eosinophils have a positive or negative influence on the course of RSV infection?

Conclusions

Chemokines are key drivers of the anti-viral inflammatory response during RSV infection. Many chemokines are produced during the infection, and specific cell types are recruited via several unique chemokine/chemokine receptor interactions. The redundancy of chemokines in cell recruitment denotes the importance for the host of being able to attract immune cells into the lungs to help combat the infection. We still know very little about the cellular sources of chemokines in the lung, and in order to identify the main cellular source (or sources) of a chemokine during the course of infection, several lung cell types have to be compared side by side which can be performed only *in vivo* or from biopsies. Also, how chemokines direct the migration of immune cells within the lung tissue to determine their precise localisation, which will have implications for their effector functions, is an important future research avenue.

Almost all chemokines correlate positively with disease severity during RSV infection^{25,26}. This observation is most likely explained by the scenario that excessive inflammatory responses in the delicate lung tissue will drive immunopathology via cell activation and mediator release. We are still far from being able to use chemokine receptor blockade as a treatment for RSV-induced disease (as discussed in more detail in 94). However, greater in-depth knowledge of which cell types act as the main sources of chemokines and how chemokine production is regulated will help the understanding of the initiation and maintenance of inflammation in the lung and possibly a more targeted approach for reducing lung inflammation via chemokine/chemokine receptor inhibition in the future.

Acknowledgement

We thank Caetano Reis e Sousa (The Francis Crick Institute) for critically reading the manuscript.

References



1. Openshaw PJM, Chiu C, Culley FJ, *et al.*: **Protective and Harmful Immunity to RSV Infection.** *Annu Rev Immunol.* 2017; **35**: 501–532.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Shi T, McAllister DA, O'Brien KL, *et al.*: **Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study.** *Lancet.* 2017; **390**(10098): 946–958.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
3. Falsey AR, McElhaney JE, Beran J, *et al.*: **Respiratory syncytial virus and other respiratory viral infections in older adults with moderate to severe influenza-like illness.** *J Infect Dis.* 2014; **209**: 1873–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
4. Falsey AR, Hennessey PA, Formica MA, *et al.*: **Respiratory syncytial virus infection in elderly and high-risk adults.** *N Engl J Med.* 2005; **352**(17): 1749–59.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Johansson C: **Respiratory syncytial virus infection: an innate perspective [version 1; peer review: 4 approved].** *F1000Res.* 2016; **5**: 2898.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
6. Sokol CL, Luster AD: **The chemokine system in innate immunity.** *Cold Spring Harb Perspect Biol.* 2015; **7**(5): pii: a016303.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
7. Goritzka M, Makris S, Kausar F, *et al.*: **Alveolar macrophage-derived type I interferons orchestrate innate immunity to RSV through recruitment of antiviral monocytes.** *J Exp Med.* 2015; **212**(5): 699–714.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
8. Goritzka M, Durant LR, Pereira C, *et al.*: **Alpha/beta interferon receptor signaling amplifies early proinflammatory cytokine production in the lung during respiratory syncytial virus infection.** *J Virol.* 2014; **88**(11): 6128–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
9. Makris S, Paulsen M, Johansson C: **Type I Interferons as Regulators of Lung Inflammation.** *Front Immunol.* 2017; **8**: 259.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
10. Makris S, Bajorek M, Culley FJ, *et al.*: **Alveolar Macrophages Can Control Respiratory Syncytial Virus Infection in the Absence of Type I Interferons.** *J Innate Immun.* 2016; **8**(5): 452–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
11. Kolli D, Gupta MR, Sbrana E, *et al.*: **Alveolar macrophages contribute to the pathogenesis of human metapneumovirus infection while protecting against respiratory syncytial virus infection.** *Am J Respir Cell Mol Biol.* 2014; **51**(4): 502–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
12. 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**(8): 1419–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
13. Tregoning JS, Pribul PK, Pennycook AMJ, *et al.*: **The chemokine MIP1alpha/CCL3 determines pathology in primary RSV infection by regulating the balance of T cell populations in the murine lung.** *PLoS One.* 2010; **5**(2): e9381.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
14. Noah TL, Becker S: **Chemokines in nasal secretions of normal adults experimentally infected with respiratory syncytial virus.** *Clin Immunol.* 2000; **97**(1): 43–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
15. McNamara PS, Ritson P, Selby A, *et al.*: **Bronchoalveolar lavage cellularity in infants with severe respiratory syncytial virus bronchiolitis.** *Arch Dis Child.* 2003; **88**(10): 922–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
16. Everard ML, Swarbrick A, Wright M, *et al.*: **Analysis of cells obtained by bronchial lavage of infants with respiratory syncytial virus infection.** *Arch Dis Child.* 1994; **71**(5): 428–32.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
17. Kirsebom FCM, Kausar F, Nuriev R, *et al.*: **Neutrophil recruitment and activation are differentially dependent on MyD88/TRIF and MAVS signaling during RSV infection.** *Mucosal Immunol.* 2019; **12**(5): 1244–55.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
18. Sadik CD, Kim ND, Luster AD: **Neutrophils cascading their way to inflammation.** *Trends Immunol.* 2011; **32**(10): 452–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
19. Culley FJ, Pennycook AM, Tregoning JS, *et al.*: **Differential chemokine expression following respiratory virus infection reflects Th1- or Th2-biased immunopathology.** *J Virol.* 2006; **80**(9): 4521–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Becker S, Reed W, Henderson FW, *et al.*: **RSV infection of human airway epithelial cells causes production of the beta-chemokine RANTES.** *Am J Physiol.* 1997; **272**(3 Pt 1): L512–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Abu-Harb M, Bell F, Finn A, *et al.*: **IL-8 and neutrophil elastase levels in the respiratory tract of infants with RSV bronchiolitis.** *Eur Respir J.* 1999; **14**(1): 139–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Bertrand P, Lay MK, Piedimonte G, *et al.*: **Elevated IL-3 and IL-12p40 levels in the lower airway of infants with RSV-induced bronchiolitis correlate with recurrent wheezing.** *Cytokine.* 2015; **76**(2): 417–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
23. McNamara PS, Flanagan BF, Hart CA, *et al.*: **Production of chemokines in the lungs of infants with severe respiratory syncytial virus bronchiolitis.** *J Infect Dis.* 2005; **191**(8): 1225–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Noah TL, Ivins SS, Murphy P, *et al.*: **Chemokines and inflammation in the nasal passages of infants with respiratory syncytial virus bronchiolitis.** *Clin Immunol.* 2002; **104**(1): 86–95.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Tabarani CM, Bonville CA, Suryadevara M, *et al.*: **Novel inflammatory markers, clinical risk factors and virus type associated with severe respiratory syncytial virus infection.** *Pediatr Infect Dis J.* 2013; **32**(12): e437–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
26. Russell CD, Unger SA, Walton M, *et al.*: **The Human Immune Response to Respiratory Syncytial Virus Infection.** *Clin Microbiol Rev.* 2017; **30**(2): 481–502.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
27. Villenave R, Thavagnanam S, Sarlang S, *et al.*: **In vitro modeling of respiratory syncytial virus infection of pediatric bronchial epithelium, the primary target of infection in vivo.** *Proc Natl Acad Sci U S A.* 2012; **109**(13): 5040–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
28. Tang FS, van Ly D, Spann K, *et al.*: **Differential neutrophil activation in viral infections: Enhanced TLR-7/8-mediated CXCL8 release in asthma.** *Respirology.* 2016; **21**(1): 172–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
29. Ederveen THA, Ferwerda G, Ahout IM, *et al.*: **Haemophilus is overrepresented in the nasopharynx of infants hospitalized with RSV infection and associated with increased viral load and enhanced mucosal CXCL8 responses.** *Microbiome.* 2018; **6**(1): 10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
30. Salimi V, Ramezani A, Mirzaei H, *et al.*: **Evaluation of the expression level of 12/15 lipoxygenase and the related inflammatory factors (CCL5, CCL3) in respiratory syncytial virus infection in mice model.** *Microb Pathog.* 2017; **109**: 209–13.
[PubMed Abstract](#) | [Publisher Full Text](#) | **F1000 Recommendation**
31. 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**(9): 4441–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
32. Haebler HA, Kuziel WA, Dieterich HJ, *et al.*: **Inducible expression of inflammatory chemokines in respiratory syncytial virus-infected mice: role of MIP-1alpha in lung pathology.** *J Virol.* 2001; **75**(2): 878–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
33. Goritzka M, Pereira C, Makris S, *et al.*: **T cell responses are elicited against Respiratory Syncytial Virus in the absence of signalling through TLRs, RLRs and IL-1R/IL-18R.** *Sci Rep.* 2015; **5**: 18533.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
34. Johnson CH, Miao C, Blanchard EG, *et al.*: **Effect of chemokine receptor CX3CR1 deficiency in a murine model of respiratory syncytial virus infection.** *Comp Med.* 2012; **62**(1): 14–20.
[PubMed Abstract](#) | [Free Full Text](#)
35. Lindell DM, Lane TE, Lukacs NW: **CXCL10/CXCR3-mediated responses promote immunity to respiratory syncytial virus infection by augmenting dendritic cell and CD8(+) T cell efficacy.** *Eur J Immunol.* 2008; **38**(8): 2168–79.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
36. Kallal LE, Schaller MA, Lindell DM, *et al.*: **CCL20/CCR6 blockade enhances immunity to RSV by impairing recruitment of DC.** *Eur J Immunol.* 2010; **40**(4): 1042–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
37. Thwaites RS, Coates M, Ito K, *et al.*: **Reduced Nasal Viral Load and IFN Responses in Infants with Respiratory Syncytial Virus Bronchiolitis and Respiratory Failure.** *Am J Respir Crit Care Med.* 2018; **198**(8): 1074–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
38. Matthews SP, Tregoning JS, Coyle AJ, *et al.*: **Role of CCL11 in eosinophilic lung disease during respiratory syncytial virus infection.** *J Virol.* 2005; **79**(4): 2050–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
39. Su YC, Townsend D, Herrero LJ, *et al.*: **Dual proinflammatory and antiviral properties of pulmonary eosinophils in respiratory syncytial virus vaccine-enhanced disease.** *J Virol.* 2015; **89**: 1564–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
40. Vojvoda V, Savić Mlakar A, Jergović M, *et al.*: **The increased type-1 and type-2 chemokine levels in children with acute RSV infection alter the development of adaptive immune responses.** *Biomed Res Int.* 2014; **2014**: 750521.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
41. Geerdink RJ, Pillay J, Meyaard L, *et al.*: **Neutrophils in respiratory syncytial virus infection: A target for asthma prevention.** *J Allergy Clin Immunol.* 2015; **136**(4):

- 838–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
42. Nicolás-Ávila JÁ, Adrover JM, Hidalgo A: **Neutrophils in Homeostasis, Immunity, and Cancer.** *Immunity*. 2017; **46**(1): 15–28.
[PubMed Abstract](#) | [Publisher Full Text](#)
43. Aulakh GK: **Neutrophils in the lung: “the first responders”.** *Cell Tissue Res*. 2018; **371**(3): 577–588.
[PubMed Abstract](#) | [Publisher Full Text](#)
44. Jenne CN, Kubes P: **Virus-induced NETs—critical component of host defense or pathogenic mediator?** *PLoS Pathog*. 2015; **11**(1): e1004546.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. **F** Papayannopoulos V: **Neutrophil extracellular traps in immunity and disease.** *Nat Rev Immunol*. 2018; **18**(2): 134–147.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
46. Galani IE, Andreaskos E: **Neutrophils in viral infections: Current concepts and caveats.** *J Leukoc Biol*. 2015; **98**(4): 557–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. **F** Bardeel BW, Kenny EF, Sollberger G, *et al.*: **The balancing act of neutrophils.** *Cell Host Microbe*. 2014; **15**(5): 526–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
48. Stokes KL, Currier MG, Sakamoto K, *et al.*: **The respiratory syncytial virus fusion protein and neutrophils mediate the airway mucin response to pathogenic respiratory syncytial virus infection.** *J Virol*. 2013; **87**(18): 10070–82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. **F** Deng Y, Herbert JA, Smith CM, *et al.*: **An *in vitro* transepithelial migration assay to evaluate the role of neutrophils in Respiratory Syncytial Virus (RSV) induced epithelial damage.** *Sci Rep*. 2018; **8**(1): 6777.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Wang SZ, Xu H, Wraith A, *et al.*: **Neutrophils induce damage to respiratory epithelial cells infected with respiratory syncytial virus.** *European Respiratory Journal*. 1998; **12**(3): 612–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Yasui K, Baba A, Iwasaki Y, *et al.*: **Neutrophil-mediated inflammation in respiratory syncytial viral bronchiolitis.** *Pediatr Int*. 2005; **47**(2): 190–5.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Emboriadou M, Hatzistilianou M, Magnisali C, *et al.*: **Human neutrophil elastase in RSV bronchiolitis.** *Ann Clin Lab Sci*. 2007; **37**(1): 79–84.
[PubMed Abstract](#)
53. Bataki EL, Evans GS, Everard ML: **Respiratory syncytial virus and neutrophil activation.** *Clin Exp Immunol*. 2005; **140**(3): 470–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Hosakote YM, Liu T, Castro SM, *et al.*: **Respiratory syncytial virus induces oxidative stress by modulating antioxidant enzymes.** *Am J Respir Cell Mol Biol*. 2009; **41**(3): 348–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. **F** Cortjens B, de Boer OJ, de Jong R, *et al.*: **Neutrophil extracellular traps cause airway obstruction during respiratory syncytial virus disease.** *J Pathol*. 2016; **238**(3): 401–11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
56. **F** Funchal GA, Jaeger N, Czepielewski RS, *et al.*: **Respiratory syncytial virus fusion protein promotes TLR4-dependent neutrophil extracellular trap formation by human neutrophils.** *PLoS One*. 2015; **10**(4): e0124082.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
57. **F** Shi C, Pamer EG: **Monocyte recruitment during infection and inflammation.** *Nat Rev Immunol*. 2011; **11**(11): 762–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
58. **F** Johnson SM, McNally BA, Ioannidis I, *et al.*: **Respiratory Syncytial Virus Uses CX3CR1 as a Receptor on Primary Human Airway Epithelial Cultures.** *PLoS Pathog*. 2015; **11**(12): e1005318.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
59. **F** Landsman L, BarOn L, Zernecke A, *et al.*: **CX₃CR1 is required for monocyte homeostasis and atherogenesis by promoting cell survival.** *Blood*. 2009; **113**(4): 963–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
60. Tripp RA, Jones LP, Haynes LM, *et al.*: **CX3C chemokine mimicry by respiratory syncytial virus G glycoprotein.** *Nat Immunol*. 2001; **2**(8): 732–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
61. **F** Tsou CL, Peters W, Si Y, *et al.*: **Critical roles for CCR2 and MCP-3 in monocyte mobilization from bone marrow and recruitment to inflammatory sites.** *J Clin Invest*. 2007; **117**(4): 902–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
62. Elliott MB, Tebbey PW, Pryharski KS, *et al.*: **Inhibition of respiratory syncytial virus infection with the CC chemokine RANTES (CCL5).** *J Med Virol*. 2004; **73**(2): 300–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
63. **F** AIAfif A, Alyazidi R, Oldford SA, *et al.*: **Respiratory syncytial virus infection of primary human mast cells induces the selective production of type I interferons, CXCL₁₀, and CCL₄.** *J Allergy Clin Immunol*. 2015; **136**(5): 1346–54.e1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
64. Serbina NV, Jia T, Hohl TM, *et al.*: **Monocyte-mediated defense against microbial pathogens.** *Annu Rev Immunol*. 2008; **26**: 421–52.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
65. **F** Ellis GT, Davidson S, Crotta S, *et al.*: **TRAIL+ monocytes and monocyte-related cells cause lung damage and thereby increase susceptibility to influenza–Streptococcus pneumoniae coinfection.** *EMBO Rep*. 2015; **16**(9): 1203–18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
66. **F** Petrarca L, Nenna R, Frassanito A, *et al.*: **Acute bronchiolitis: Influence of viral co-infection in infants hospitalized over 12 consecutive epidemic seasons.** *J Med Virol*. 2018; **90**(4): 631–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
67. **F** Liu P, Xu M, He L, *et al.*: **Epidemiology of Respiratory Pathogens in Children with Lower Respiratory Tract Infections in Shanghai, China, from 2013 to 2015.** *Jpn J Infect Dis*. 2018; **71**(1): 39–44.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
68. **F** Meskill SD, Revell PA, Chandramohan L, *et al.*: **Prevalence of co-infection between respiratory syncytial virus and influenza in children.** *Am J Emerg Med*. 2017; **35**(3): 495–498.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
69. Martínez-Roig A, Salvadó M, Caballero-Rabasco MA, *et al.*: **Viral Coinfection in Childhood Respiratory Tract Infections.** *Archivos de Bronconeumología (English Edition)*. 2015; **51**(1): 5–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
70. Banchereau J, Briere F, Caux C, *et al.*: **Immunobiology of dendritic cells.** *Annu Rev Immunol*. 2000; **18**: 767–811.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Caux C, Vanbervliet B, Massacrier C, *et al.*: **Regulation of dendritic cell recruitment by chemokines.** *Transplantation Journal*. 2002; **73**(1 Suppl): S7–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. Gill MA, Long K, Kwon T, *et al.*: **Differential recruitment of dendritic cells and monocytes to respiratory mucosal sites in children with influenza virus or respiratory syncytial virus infection.** *J Infect Dis*. 2008; **198**(11): 1667–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Bernardini G, Gismondi A, Santoni A: **Chemokines and NK cells: regulators of development, trafficking and functions.** *Immunol Lett*. 2012; **145**(1–2): 39–46.
[PubMed Abstract](#) | [Publisher Full Text](#)
74. **F** Carlin LE, Hemann EA, Zacharias ZR: **Natural Killer Cell Recruitment to the Lung During Influenza A Virus Infection Is Dependent on CXCR3, CCR5, and Virus Exposure Dose.** *Front Immunol*. 2018; **9**: 781.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
75. Li F, Zhu H, Sun R, *et al.*: **Natural killer cells are involved in acute lung immune injury caused by respiratory syncytial virus infection.** *J Virol*. 2012; **86**(4): 2251–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. **F** van Erp EA, Feyaerts D, Duijst M, *et al.*: **Respiratory Syncytial Virus Infects Primary Neonatal and Adult Natural Killer Cells and Affects Their Antiviral Effector Function.** *J Infect Dis*. 2019; **219**(5): 723–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. Larrañaga CL, Ampuero SL, Luchsinger VF, *et al.*: **Impaired Immune Response in Severe Human Lower Tract Respiratory Infection by Respiratory Syncytial Virus.** *Pediatr Infect Dis J*. 2009; **28**(10): 867–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
78. **F** Kaiko GE, Phipps S, Angkasekwinai P, *et al.*: **NK cell deficiency predisposes to viral-induced Th2-type allergic inflammation via epithelial-derived IL-25.** *J Immunol*. 2010; **185**(8): 4681–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
79. **F** Stier MT, Bloodworth MH, Toki S, *et al.*: **Respiratory syncytial virus infection activates IL-13–producing group 2 innate lymphoid cells through thymic stromal lymphopoietin.** *J Allergy Clin Immunol*. 2016; **138**(3): 814–824.e11.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
80. **F** Stier MT, Goleniewska K, Cephus JY, *et al.*: **STAT1 Represses Cytokine-Producing Group 2 and Group 3 Innate Lymphoid Cells during Viral Infection.** *J Immunol*. 2017; **199**(2): 510–519.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
81. Lukens MV, Claassen EAW, de Graaff PMA, *et al.*: **Characterization of the CD8+ T cell responses directed against respiratory syncytial virus during primary and secondary infection in C57BL/6 mice.** *Virology*. 2006; **352**(1): 157–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Loebbermann J, Thornton H, Durant L, *et al.*: **Regulatory T cells expressing granzyme B play a critical role in controlling lung inflammation during acute viral infection.** *Mucosal Immunol*. 2012; **5**: 161–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Jozwik A, Habibi MS, Paras A, *et al.*: **RSV-specific airway resident memory CD8+ T cells and differential disease severity after experimental human infection.** *Nat Commun*. 2015; **6**: 10224.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Chiu C, Openshaw PJ: **Antiviral B cell and T cell immunity in the lungs.** *Nat Immunol*. 2015; **16**(1): 18–26.
[PubMed Abstract](#) | [Publisher Full Text](#)

85. **F** Masopust D, Soerens AG: **Tissue-Resident T Cells and Other Resident Leukocytes.** *Annu Rev Immunol.* 2019; **37**: 521–546.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
86. Kohlmeier JE, Reiley WW, Perona-Wright G, *et al.*: **Inflammatory chemokine receptors regulate CD8⁺ T cell contraction and memory generation following infection.** *J Exp Med.* 2011; **208**(8): 1621–34.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Loebbermann J, Durant L, Thornton H, *et al.*: **Defective immunoregulation in RSV vaccine-augmented viral lung disease restored by selective chemoattraction of regulatory T cells.** *Proc Natl Acad Sci U S A.* 2013; **110**(8): 2987–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Monick MM, Powers LS, Hassan I, *et al.*: **Respiratory Syncytial Virus Synergizes with Th2 Cytokines to Induce Optimal Levels of TARC/CCL17.** *J Immunol.* 2007; **179**(3): 1648–58.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
89. Olson MR, Varga SM: **CD8 T cells inhibit respiratory syncytial virus (RSV) vaccine-enhanced disease.** *J Immunol.* 2007; **179**(8): 5415–24.
[PubMed Abstract](#) | [Publisher Full Text](#)
90. Murphy BR, Sotnikov AV, Lawrence LA, *et al.*: **Enhanced pulmonary histopathology is observed in cotton rats immunized with formalin-inactivated respiratory syncytial virus (RSV) or purified F glycoprotein and challenged with RSV 3-6 months after immunization.** *Vaccine.* 1990; **8**(5): 497–502.
[PubMed Abstract](#) | [Publisher Full Text](#)
91. **F** Knudson CJ, Hartwig SM, Meyerholz DK, *et al.*: **RSV vaccine-enhanced disease is orchestrated by the combined actions of distinct CD4 T cell subsets.** *PLoS Pathog.* 2015; **11**(3): e1004757.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
92. Waris ME, Tsou C, Erdman DD, *et al.*: **Respiratory syncytial 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**(5): 2852–60.
[PubMed Abstract](#) | [Free Full Text](#)
93. **F** Moghaddam A, Olszewska W, Wang B, *et al.*: **A potential molecular mechanism for hypersensitivity caused by formalin-inactivated vaccines.** *Nat Med.* 2006; **12**(8): 905–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
94. Thomas LH, Friedland JS, Sharland M: **Chemokines and their receptors in respiratory disease: a therapeutic target for respiratory syncytial virus infection.** *Expert Rev Anti Infect Ther.* 2014; **5**: 415–25.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review


Current Peer Review Status: 

Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

- 1 **Steven M Varga**
Department of Microbiology and Immunology, University of Iowa, Iowa, USA
Competing Interests: No competing interests were disclosed.
- 2 **Leo Carlin**
1 Cancer Research UK Beatson Institute, Glasgow, UK
2 Institute of Cancer Sciences, University of Glasgow, Glasgow, UK
Competing Interests: Dr Carlin and CJ were previously colleagues but had not collaborated on any research projects.
- 3 **Ralph A Tripp** 
Department of Infectious Diseases, University of Georgia, Georgia, USA
Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research