Minireview

Respiratory viral infection and resolution of inflammation: Roles for specialized pro-resolving mediators

Luciana P Tavares, Julie Nijmeh and Bruce D Levy

Pulmonary and Critical Care Medicine Division, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02115, USA
Corresponding author: Luciana P Tavares. Email: lpaduatavares@bwh.harvard.edu

Impact Statement

Influenza A virus (IAV) and respiratory syncytial virus (RSV) are two highly contagious respiratory pathogens that can cause severe respiratory illnesses in humans, particularly in vulnerable populations, including infants and the elderly. Failure to control pathogen-evoked inflammation can lead to excess lung tissue damage. While antiviral therapies have been developed, they are not widely available and have limited effectiveness for many patients. Here, we review recent advances in our understanding of the impact of respiratory viral infection on homeostatic restraints for inflammation, including intriguing evidence on endogenous pro-resolving mediators and cellular mechanisms for resolution. In model experimental systems, specialized pro-resolving mediators (SPMs) and their receptors activate cell-type specific responses to dampen inflammation, accelerate viral clearance, and enhance host resilience to secondary bacterial infection. Harnessing endogenous pro-resolving mechanisms for viral pathogen-evoked inflammation holds promise as a novel therapeutic strategy to lessen the excess morbidity and mortality of viral pneumonia.

Abstract

Respiratory viral infections with influenza A virus (IAV) or respiratory syncytial virus (RSV) pose a significant threat to public health due to excess morbidity and mortality. Dysregulated and excessive inflammatory responses are major underlying causes of viral pneumonia severity and morbidity, including aberrant host immune responses and increased risk for secondary bacterial infections. Currently available antiviral therapies have not substantially reduced the risk of severe viral pneumonia for these pathogens. Thus, new therapeutic approaches that can promote resolution of the pathogen-initiated inflammation without impairing host defense would represent a significant advance. Recent research has uncovered the potential for specialized pro-resolving mediators (SPMs) to transduce multipronged actions for the resolution of serious respiratory viral infection without increased risk for subsequent host susceptibility to bacterial infection. Here, we review recent advances in our understanding of SPM production and SPM receptor signaling in respiratory virus infections and the intriguing potential of harnessing SPM pathways to control excess morbidity and mortality from IAV and RSV pneumonia.

Keywords: Specialized pro-resolving mediators, respiratory syncytial virus, influenza A virus, pneumonia

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Introduction

Respiratory viral infections pose a threat to public health due to excess morbidity and mortality. For decades, virus-induced pneumonia has been among the most common causes of death worldwide. Notably, influenza A virus (IAV) is a causative pathogen of annual epidemics and lethal pandemics,[1,2] and human respiratory syncytial virus (RSV) is a leading cause of community-acquired pneumonia in children younger than five years.[3] Excessive inflammatory responses to pathogens, including IAV and RSV, are an important underlying determinant of viral pneumonia severity and can lead to prolonged host immune dysfunction that increases the risk for secondary bacterial infections.[4] Currently, most available therapies have focused on antiviral strategies, yet in many patients they have not substantially reduced the risk for severe viral pneumonia from IAV and RSV. While anti-inflammatory strategies have been used to control virus-induced disease burden, they must be considered with caution due to an associated risk for immunosuppression in already critically ill patients.[5] As such, therapeutic approaches that modulate inflammation and promote host defense would represent a new paradigm.

Research in the last decade has established that resolution of inflammation is an active process, rather than a passive diminution of the response, in the context of host defense.[6] Resolution of inflammation is orchestrated, in part, by SPMs that are produced from essential polyunsaturated

fatty acids (PUFAs).[7] SPMs can regulate innate and adaptive immune responses, and unlike immunosuppressant molecules, SPMs promote host antimicrobial responses.[8] Here, we review recent advances in our understanding of the protective actions of SPMs in the lungs, especially in controlling host immune responses to respiratory viral infections.

Viral-induced pathogenesis

IAV

IAV is a deadly respiratory pathogen that has resulted in four pandemics since 1918,[9] with yearly deaths ranging from 290,000 to 650,000.[1] A recent outbreak in South America of the highly pathogenic avian influenza A H5N1 highlights the urgent need for research and development of new therapeutic approaches for IAV infections.[10] IAV is an enveloped negative-sense RNA virus belonging to the *Orthomyxoviridae* family.[11] In humans, IAV primarily infects and replicates in respiratory tract epithelial cells. Other cell types, including macrophages, can also be infected by IAV, but replication is usually abortive without release of viable progeny;[12] yet, highly pathogenic IAV strains can productively infect and kill macrophages, thus disabling an important innate host defense mechanism for infection.[12] Of note, IAV infection of macrophage-depleted mice leads to increased viral titers and disease severity, underscoring the protection that macrophages can provide in restraining the initial stages of IAV replication.[13] Most commonly, infection is restricted to the upper respiratory tract, leading to mild disease;[14] however, in some instances, IAV can lead to lower respiratory tract infection and pneumonia, which can be severe with extensive lung damage. Severity of IAV pneumonia is affected by various factors including the virus subtype, host co-morbidities, age, and host immune status.[15]

Infection is initiated with attachment of IAV to host epithelial cells, which is mediated by interaction between the viral hemagglutinin (HA) and sialic acid residues present on the host cell surface. The nature of sialic acid linkage to the underlying galactose moieties determines the susceptibility of cells to different strains of IAV. α2,3 and α2,6-linked sialic acid receptors are present in the human respiratory tract. α2,6-linked sialic acids are most abundant in the upper respiratory tract and the preferred receptors for seasonal IAV strains; however, highly pathogenic avian IAV strains have a higher affinity for binding to α2,3-linked sialic acids present in the lower respiratory tract.[16] IAV tropism and pathogenicity are also determined by susceptibility of the viral HA to airway proteases. For infectivity, HA is cleaved into HA1 and HA2 subunits for viral fusion to the host cell.[17] Different airway trypsin-type proteases can mediate HA cleavage and virus fusion, including Clara protease, human airway trypsin-like protease (HAT), mini-plasmin, transmembrane serine protease 2 (TMPRSS2), among others. These proteases are differentially distributed in the airways.[18,19] For example, Clara proteases are expressed by cells from the terminal and respiratory bronchioles while mini-plasmin is found in the upper airways.[18,19] Thus, IAV pathogenesis is, in part, affected by the tropism of the virus infecting the host, leading to a range of disease severity from mild upper respiratory infection or severe pneumonia in humans.[16] SPMs have not been shown to impact these initial pathogenic processes for IAV viral entry into host airway epithelial cells.

IAV replication in infected respiratory epithelial cells can ultimately lead to cell death by apoptosis, necrosis, and pyroptosis, as well as disruption of the alveolar barrier. While the pathogen-evoked inflammation is important for proper clearance of IAV and development of adaptive immunity, an exaggerated response can lead to increased lung injury, dysfunctional repair, and significant disease severity.[20] IAV-induced inflammation can also lead to impairment of host resistance to secondary bacterial infections, which can have lethal consequences.[21] Indeed, IAV disrupts the host microbiome leading to increase susceptibility to pathobionts[22] and can induce pulmonary epithelium denudation and fibrin deposition, exposing novel attachment sites for bacteria.[23] One report has indicated that SPMs can limit viral replication,[24] and a recent report of SPM actions to decrease host susceptibility to bacterial infection after IAV.[25] These findings and the role of inflammation during respiratory viral infections will be discussed in more detail later in the review.

RSV

RSV is a major cause of lower respiratory tract infection in young children, leading to substantial morbidity and mortality.[26] In adults, RSV has also been increasingly recognized as a cause of significant respiratory illness, particularly in the elderly.[27] RSV is an enveloped negative-sense RNA virus of the *Pneumoviridae* family, and unlike IAV, it has a non-segmented genome so is uncapable of undergoing antigenic shifts that could result in pandemic strains.[28] RSV is classified into RSVA and RSVB subgroups based on the antigenic variability, and both subgroups of RSV co-circulate worldwide.[29] While both subgroups can cause lung disease, RSVA has been associated with a slightly increased severity of illness in comparison to RSVB, especially in premature children.[30,31]

Airway epithelial cells are the primary site of infection and replication for RSV. In the lower respiratory tract, the virus has specific tropism for cells that line the bronchioles, including type 1 pneumocytes and intraepithelial dendritic cells.[32,33] In addition, RSV can infect basal cells, the precursors for airway epithelium, potentially impacting the development and structure of the airways.[32] Viral replication can lead to epithelial cell necrosis, airway edema, and mucus-overproduction. Although more common in immunocompromised patients, epithelial syncytial can also be observed.[34]

Typically, RSV infection is mild and self-resolving. In some patients, especially children younger than two years, an exaggerated inflammatory response can result in severe bronchiolitis that progresses to respiratory failure characterized by the obstruction of the airways with cellular debris and mucus.[35] RSV-induced bronchiolitis and wheezing in infants are highly associated with the development of asthma later in life.[36] At a cellular level, the overactivation of leukocytes, including lymphocytes and eosinophils, have been implicated in exacerbating pathogen-initiated lung injury in mouse models of RSV infection.[37] There is a growing array of therapeutic and preventive approaches for RSV

infection; however, an urgent need remains for additional treatment strategies.[38,39]

Virus-triggered inflammatory responses

Inflammation is fundamentally a protective response to infection. Respiratory viruses are detected by pattern recognition receptors (PRRs) in epithelial and immune cells that detect specific pathogen-associated molecular patterns (PAMPs) on the virus. Infected epithelial cells activate inflammatory responses, as genomic single-stranded RNA from either IAV or RSV can activate Toll-like receptors (i.e. TLR7 and TLR8), and double-stranded RNA formed during viral replication can activate TLR3. Overall, a myriad of surface and intracellular PRRs are activated during viral infection and can trigger intracellular signaling cascades that increase expression of several pro-inflammatory and antiviral genes.[20]

Type I interferons (INFs) (primarily IFN-α and IFN-β) and type III interferons (IFN-λ1 to IFN-λ4) are innate antiviral cytokines secreted by infected cells to trigger the transcription of IFN-stimulated genes (ISGs) that can disrupt the viral cycle of infection.[40] In addition to directly controlling the viral replication, IFN-α and IFN-β stimulate inflammation by recruiting and activated leukocytes.[41] IAV and RSV can hinder IFN production and evade IFN signaling by expressing non-structural proteins that can antagonize IFNs or ISGs.[42,43] Although an effective IFN response is crucial to restrain viral replication early during infection, the sustained or exacerbated production of type I and type III IFNs can inhibit repair of epithelial cells and impair macrophage-associated antibacterial responses postviral infection.[44,45] Resident alveolar macrophages (rAMs) serve as a primary line of defense for lung viral infection from IAV and RSV.[46,47] IAV infection impacts viability and functionality of rAMs, which secondarily increases susceptibility to pneumococcal pneumonia.[25,48] In addition, IAV infection induces macrophage polarization to a pro-phlogistic phenotype with heightened secretion of pro-inflammatory cytokines.[49]

Pro-inflammatory cytokines and pro-phlogistic lipid mediators, secreted by rAMs and epithelial cells during IAV and RSV infection, rapidly recruit leukocytes to the infected lung. Neutrophils are one of the first cells recruited upon infection, but their role in controlling viral replication is unclear. In experimental models of RSV infection in mice, depletion of neutrophils did not restrict viral replication nor impact disease severity.[50] Yet, a predominance of neutrophils in lung autopsy samples from fatal cases of pediatric RSV bronchiolitis suggests an immunopathogenic role for the excess recruitment of these cells.[51] In contrast, neutrophils were suggested to play an antiviral role during IAV infection in mice, including the development of adaptive responses.[52,53] For IAV and RSV infections, excessive recruitment and activation of neutrophils correlates with increased lung damage and disease severity.[54] When encountering a microorganism or other danger signals, neutrophils may undergo neutrophil extracellular trap (NET) formation, a response that is observed in pediatric RSV patients, suggesting a relationship between uncontrolled NET extrusion and airway obstruction.[55] NET formation in IAV is associated with increased severity in patients,[54] and worse IAV-associated lung injury in mouse models of infection.[56]

Innate lymphocytes serve important roles in mucosal immunity to viruses.[57] Natural killer (NK) cells are the most abundant innate lymphocytes and their recruitment and activation to the lung decreases virus-induced pathology.[33,58,59] NK cells can function as cytotoxic cells, so one important immune response is for these innate lymphocytes to target and kill infected cells – crucial for timely and effective viral clearance.[60] Decreased NK cell and $CD8^+$ T cell numbers and high viral titers were reported in infant lungs with severe RSV and IAV infections, associations that suggest important protective roles for these cells.[33] The immunopathogenic effect of NK cells is related to sustained cell activation, with intense cell killing and release of IFNγ within the delicate lung mucosa in IAV and RSV infections.[58,59] Therefore, in IAV and RSV pathogenesis, dysregulation of initially protective responses exacerbates inflammation, leading to increased disease severity even after the clearance of the pathogen. SPMs are potent regulatory signals for NK cell function,[61,62] which are reviewed in more detail below.

An interesting feature of some clinical strains of RSV is that there is a shift in the immune response from type 1 cytokines (such as IFN-γ) to type 2 cytokines (such as interleukin [IL]-4 and IL-13), which is linked to the immunopathology induced by the virus.[37] As such, $CD4^+$ Th2 lymphocytes that secrete type 2 cytokines lead to increased recruitment and activation of eosinophils that themselves can secrete proteases and mediators that contribute to RSV disease.[37] Regulatory T cells (Tregs) are crucial for counter-regulation of RSV-associated type 2 inflammation in preventing severe disease.[63] Of interest, RSV disrupts the immunosuppressive function of Tregs, converting them to pathological pro-inflammatory effectors.[64,65] Tregs are another target for SPMs to enhance resolution from viral pathogen-evoked inflammation.[65]

In summary, a well-balanced self-limited inflammatory response is crucial in controlling pathogen replication and promoting the development of adaptive immune responses. Nevertheless, in severe respiratory viral infections, this equilibrium is disrupted, resulting in an overactivation of various inflammatory pathways that contribute to tissue damage, pulmonary dysfunction, and even death.

Immunomodulatory and pro-resolving therapies

IAV

Different anti-inflammatory strategies have been proposed to control the IAV disease burden. Our research group and others have shown that excessive neutrophil infiltration into the lungs is directly associated with disease severity in mice[66,67] and humans.[54] The pharmacological inhibition of CXCR1/2 reduces recruitment of neutrophils into the lungs of IAV-infected mice, resulting in reduced tissue inflammation, injury, and weight loss.[66] Of interest, clinical trials investigating the safety of inhibiting CXCR2 in patients with IAV or SARS-CoV-2 infections showed that the treatment was well tolerated, did not impair viral clearance, and slightly improved clinical symptoms.[68,69] Larger studies are needed

to fully address the potential benefits of inhibiting CXCR2 in severe respiratory infections caused by either IAV.

Although blocking specific arms of the innate immune system might confer benefit to severe IAV patients, the imminent risk of immunosuppression must also be considered. For instance, inhibition of the CCR5:CCL5 axis, an important pro-inflammatory chemokine signaling pathway during IAV infection, can lead to defective lymphocyte recruitment, antibody production, and clearance of virus in the lungs.[70] In this regard, inhibiting ACKR2, a scavenger of CCL5, was reported to be protective from IAV infection in mice.[70] Hence, distinguishing harmful from protective inflammatory pathways is necessary to optimize potential anti-inflammatory therapeutic approaches for IAV disease.

Harnessing resolution of inflammation mechanisms represents an alternative approach to anti-inflammation in lessening the severity of respiratory viral infection. Resolution of inflammation is active homeostatic process with specific cellular and molecular mechanisms, which are governed, in part, by SPMs.[6] SPMs comprise a superfamily of mediators, enzymatically derived from omega-6 and omega-3 polyunsaturated essential fatty acids. SPMs are endogenously produced during inflammation to promote resolution of inflammation, tissue repair, and restoration of homeostasis.[7] Rather than solely blocking inflammatory pathways, SPMs serve as agonists for receptor-mediated activation of host antipathogen responses and regulation of inflammatory responses to the virus.[8] SPM families are biosynthesized via the stereo-selective, enzymatic conversion of arachidonic acid (AA) to lipoxins; docosahexaenoic acid (DHA) to D-series resolvins, protectins, maresins, and cysteinyl-SPMs; and eicosapentaenoic acid (EPA) to E-series resolvins.[6] Dysregulated or failed resolution of inflammation can contribute to pathogenesis. Pharmacologic administration of increased doses of SPMs or prevention of SPM further metabolism can counter-regulate the excessive inflammatory responses associated with severe IAV disease.

Evidence from preclinical studies in mice shows that IAV infection can disrupt production and action of select SPMs. For example, in a mouse model of severe IAV, the level of select SPMs, such as protectin D1 (PD1) and lipoxin A_4 (LXA_4), is significantly reduced in the lungs.[24] Similarly, the highly pathogenic IAV H5N1 results in considerable inhibition of lipoxin signaling, overly exuberant inflammation, and high mortality in mice.[71] In humans, the levels of Alox12-derived SPMs were shown to be inversely correlated with heightened clinical symptoms during IAV infection.[72] Mice treated with the DHA-derived PD1 showed significant reduction in IAV replication and associated mortality, highlighting the potential pharmacological value for SPMs in treating IAV disease.[24]

SPMs can boost host adaptive immune responses to IAV infection and vaccination. 17-HDHA promotes human B cell differentiation and antibody secretion *in vitro* and, when used as a vaccine adjuvant in a mouse model, increased antibody production and decreased lethality for IAV infection.[73,74] In addition to 17-HDHA, lipoxin B_4 (LXB_4), an AA-derived SPM, can also exert similar effects on human B cells. Exposure of B cells to LXB_4 results in increased expression of BLIMP1 and XBP1, important transcription factors involved in plasma cell differentiation. Furthermore, LXB_4 enhances *in vitro* antibody production by memory B cells from IAV-vaccinated donors.[75] Thus, when present and available, SPMs can directly inhibit IAV replication, can signal for the development of adaptive immune responses to IAV, and enhance IAV antibody production. Recently, T-series resolvins were determined to modulate neutrophil responses by enhancing apoptosis or uptake of NETs by macrophages, thereby promoting NETs clearance.[76] Considering the association between uncontrolled NET formation and IAV severity,[54] SPMs might also exhibit a protective effect in that context.

Inadequate resolution can also result from prolonged functional impairment and phenotypical alterations of rAMs long after viral clearance.[25] This incomplete restoration of homeostasis postinfection can result in increased susceptibility to bacterial infections one to three weeks after IAV infection. These secondary bacterial infections, especially by *Streptococcus pneumoniae*, are an important contributor to IAV-related mortality.[77]

Alveolar macrophages are early responders to pulmonary pathogens[77] and, in addition to controlling bacterial proliferation, are important for regulating inflammation in the lung.[78] Of interest, a new family of macrophage-derived cysteinyl-containing (cys)-SPMs named the maresin conjugates in tissue regeneration (MCTRs) was recently shown to display protective actions in lung inflammation.[79] MCTR1, MCTR2, and MCTR3 are produced via series of enzymatic reactions. DHA is converted by 12-lipoxygenase (12-LO, *Alox12* gene) to an epoxy-maresin intermediate and, glutathione S-transferase μ4 (GSTM4) converts this intermediate to MCTR1 which is subsequently converted to MCTR2 by gamma-glutamyltransferase and then MCTR2 is further converted by dipeptidase to MCTR3.[80] Sustained reduction in mouse lung expression of *Alox12* occurs after IAV infection (Figure 1). Pulmonary levels of *Gstm4* are also significantly reduced at day 7 post-IAV, suggesting that IAV infection can regulate the MCTR biosynthetic pathway (Figure 1). Administration of MCTRs, especially MCTR3, post-IAV infection significantly improves resilience to secondary *S. pneumoniae* lung infection and bacteremia and decreases lung inflammation and damage, in part by reversing the IAV-induced changes in rAM phenotype and function.[25] Of interest, plasma SPM levels are reduced in patients with severe COVID-19 and correlate with a higher leukocyte activation phenotype and impaired phagocytosis.[81] Exogenous MCTR3 restores function and phenotype of phagocytes from COVID-19 patients.[81] In addition to MCTRs, aspirin-triggered RvD1 (AT-RvD1) when given during active IAV infection significantly reduces severity of *S .pneumoniae*-IAV co-infection by reducing overall inflammation and bacteria proliferation in the lungs of mice.[82] Notably, decreased RvD1 levels are associated with severity of COVID-19[83] and *in vitro* exposure to RvD1 decreases monocyte-mediated inflammation triggered by the SARS-CoV2 Spike protein.[84] Together, these findings suggest a shared host response to severe viral pneumonia that can be leveraged by MCTRs and other SPMs to promote resolution.

Pharmacologically harnessing SPMs and their pro-resolving mechanisms hold promise as a potential strategy to

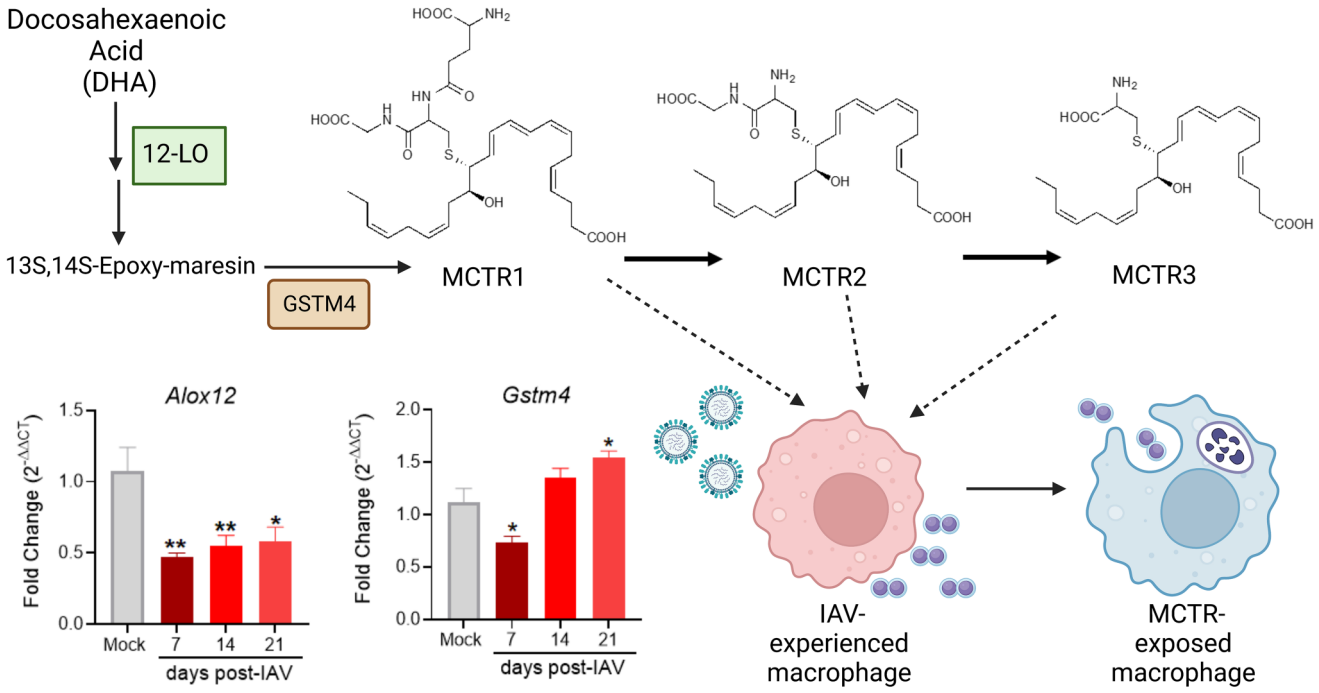

Figure 1. Expression of MCTR biosynthetic enzymes is temporarily regulated during IAV infection. MCTRs are biosynthesized by the 12-lipoxygenase (12-LO, *Alox12* gene) enzymatic conversion of docosahexaenoic acid (DHA) to an epoxy-intermediate that can be further converted to MCTR1 by the glutathione S-transferase μ4 (GSTM4). MCTR1 is subsequently converted by MCTR2 and can be further enzymatically processed to MCTR3. IAV infection of C57/BL6 mice (500 PFU; intranasally; IAV H1N1 WSN/33) leads to a significant reduction in the lung expression of Alox12 and Gstm4, the genes for 12-LO and GSTM4, by qPCR (Alox12: Fw: 5'-GAT CAC TGA AGT GGG GCT GT-3'; Rv: 5'-CAC ACA TGG TGA GGA AAT GG-3'; GSTM4: Fw: 5'-AGG CTA TGG ATG TCT CCA ATC AG-3'; Rv: 5'-TCC AGG GAG CTG CTC CAA-3'; and GAPDH: Fw: 5'-CGT CCC GTA GAC AAA ATG G-3'; Rv: 5'-TTG ATG GCA ACA ATC TCC AC-3'). A recent study from Tavares *et al.* has shown that MCTR exposure to IAV-experienced macrophages restores the viral-induced phagocytosis impairment, enhancing pneumococcal host defense and decreasing pathogen-initiated lung inflammation.[39]
Source: Created with Biorender.com.

augment host resilience to IAV and prevent post-IAV secondary bacterial infections. SPMs in the context of IAV disease can help in controlling exaggerated pulmonary inflammation and enhancing antipathogen responses to protect the host from the excess morbidity and mortality from these infections.

RSV

Although immunomodulatory therapies, including glucocorticoids, have been helpful in the treatment of certain inflammatory respiratory diseases, including pediatric severe RSV infection and asthma,[85] they impair viral clearance and predispose to secondary bacterial infections in patients infected with RSV.[86,87] As such, there is a clinical need to identify alternate approaches to glucocorticoids for RSV disease management, especially for severely affected patients.

In RSV infection, the production of pro-inflammatory prostaglandin E_2 (PGE_2) by epithelial cells is associated with increased virus replication.[88] Treating the human cell line A549 with the omega-3 fatty acids, DHA and EPA, which are substrates for SPM biosynthesis, significantly reduces RSV-induced PGE_2 production.[89] This suggests a potential immunoregulatory action for DHA and EPA-derived SPMs in RSV, leading to a decrease in viral replication and inflammation.

In mice, 5-lipoxygenase (5-LO)-mediated biosynthesis of lipoxins and resolvins can protect from the RSV-induced immunopathology.[90] More specifically, lipoxin A_4 and resolvin E_1 were shown to promote regulatory macrophage phenotypes that are associated with more potent control of lung inflammation and pathology during RSV infection. Of interest, circulating levels of LXA_4 are decreased in many severe asthma patients and in patients with uncontrolled asthma.[91] Given that asthma exacerbations are commonly associated with RSV and other respiratory viral infections, these studies suggest that harnessing endogenous counter-regulatory pathways in the airways might represent an interesting therapeutic strategy to lessen the morbidity of infection. More recently, expression of *ALOX5*, the gene for 5-LO, was shown to be downregulated in airway macrophages and dendritic cells from severe COVID-19 patients compared to healthy individuals suggesting that an impairment in biosynthesis of 5-LO-derived SPMs may be part of SARS-CoV-2 pathogenesis.[92]

More recently, infection with a human clinical strain of RSV was shown to disrupt SPM biosynthetic pathways in mouse lungs.[93] RSV-infected mice had reduced lung expression of LTC4S and GSTM4 – cys-SPM biosynthetic enzymes, including for protectin conjugates in tissue regeneration 1 (PCTR1).[93] In addition, reduced pulmonary levels of PCTR1 and PD1 were observed early during RSV infection.[93] Administration of exogenous PD1 and PCTR1 after RSV infection decreased type-2 pulmonary inflammation and engaged host antiviral responses including expression of antimicrobial peptides and IFN type III in the mouse

Table 1. Specialized pro-resolving mediators in IAV and RSV infections.

Virus	Mediator	Role	Reference
IAV	Lipoxins	Decreased lung levels of lipoxin A_4 are observed in mice infected with PR8 H1N1 virus	Morita *et al*.[24]
		Lipoxin B_4 enhances IgG production from human memory B cells and increases the expression of transcription factors involved in plasma cell differentiation	Kim *et al*.[75]
		Severity of H5N1 infection is associated with decreased lipoxin signaling, enhanced inflammation and virus dissemination	Cilloniz *et al*.[71]
	Protectin D1	Protectin D1 is suppressed in the lungs of mice infected with PR8 H1N1; treatment with protectin D1 in IAV-infected mice improves viral clearance and survival	Morita *et al*.[24]
	MCTRs	A mix of MCTR1, MCTR2, and MCTR3 or MCTR3 alone reverses the IAV-induced alterations in alveolar macrophage phenotype and function enhancing pneumococcal host defense and decreasing inflammation	Tavares *et al*.[25]
	17-HDHA	17-HDHA enhances antibody secretion and protects IAV-infected mice from mortality	Ramon *et al*.[73,74]
	AT-RvD1	AT-RvD1 mitigates the severity of *S. pneumoniae*-IAV co-infection in mice by attenuating overall inflammation and inhibiting bacterial proliferation in the lungs	Wang *et al*.[82]
RSV	Lipoxin A_4	5-lipoxygenase–derived lipoxin A_4 is required to promote alternatively activated macrophage polarization, leading to resolution of lung pathology	Shirey *et al*.[90]
	Resolvin E1	Resolvin E1 promotes macrophage polarization to alternatively activated cells contributing to resolution of lung pathology	Shirey *et al*.[90]
	PCTR1	PCTR1 treatment increases the levels of the antiviral IFNλ and the cathelicidin antimicrobial peptide leading to reduced viral burden and inflammation-induced lung pathology	Walker *et al*.[93]
	Protectin D1	Protectin D1 treatment increased the levels of the antiviral IFNλ and reduces viral burden and inflammation-induced lung damage	Walker *et al*.[93]
	Maresin 1	Maresin 1, acting through the LGR6 receptor, regulates pathologic type 2 immune responses to RSV infection in mouse and human lungs by restoring Treg immunosuppressive functions and reducing viral burden	Krishnamoorthy *et al*.[65]

IAV: influenza A virus; RSV: respiratory syncytial virus; MCTRs: maresin conjugates in tissue regeneration; AT-RvD1: aspirin-triggered RvD1; PCTR1: protectin conjugates in tissue regeneration 1; IgG: immunoglobulin G.

lung and human airway epithelial cells.[93] These findings with PCTR1 and PD1 were the first to identify this endogenous host protective mechanism for airway epithelial IFN type III induction for antiviral protection. Recent evidence uncovered relationships for IFN type I and SPM production, including 15-epi-LXA_4 and RvD1, highlighting the intricate crosstalk between antiviral and pro-resolving pathways during lung inflammation and infection.[94]

NK cells are crucial to host defense against viral infections, given their cytotoxic activity to help clear virus-infected cells. In addition, NK cells can assist in the resolution of pathogen-initiated inflammation by inducing apoptosis of activated granulocytes for macrophage clearance in the affected tissue. Glucocorticoids are still administered to many severely affected pediatric patients with RSV and recent evidence has uncovered an adverse impact for glucocorticoids on NK cell cytotoxic function.[61,62] In contrast, SPMs promote NK cell-mediated cytotoxicity and resolution of lung inflammation.[61,62,95] LXA_4 promotes human NK cell-directed apoptosis of activated granulocytes, and mouse NK cells cytotoxicity is increased by RvE1 for lymphocytes.[62,95] In sharp contrast to glucocorticoids, LXA_4 induces LIMK to promote NK cell-lytic granule mobilization to the immune synapse to facilitate cytotoxicity.[61] Together, these findings suggest that SPM activation of NK cell function could serve pro-resolving roles in IAV and RSV infection; however, these relationships are yet to be determined.

Recently, in the setting of RSV infection, the DHA-derived SPM maresin 1 (Mar1) was shown to increase IFN-β production in lungs of infected mice and human pediatric lung slices for a host-directed antiviral response.[65] The Mar1 actions were receptor dependent as Mar1 receptor (i.e. LGR6) knockout mice were not protected with Mar1 administration. Mar1 decreased RSV burden and lessened pathogen-initiated lung inflammation by activating the suppressive function of Tregs that decreased pro-phlogistic cytokine production. Mar1 also increased amphiregulin production. Together, these host-directed mechanisms for Mar1 enhanced the resilience of the lung to infection with RSV.[65] Of interest, a comprehensive feeding study of pregnant mothers with omega-3 fatty acids led to decreased risk for respiratory tract of their infants over five years of follow-up.[96]

Although mechanisms associated with onset of inflammation have been extensively studied in RSV pathogenesis, these reports and others provide for growing evidence that RSV can subvert pro-resolving pathways to avoid the host antiviral responses, and SPMs and other molecular or cellular pro-resolution mechanisms may be able to restore host resilience and lessen morbidity associated with this infection.

Conclusions

In summary, SPMs can play important roles in promoting host resistance and resilience to respiratory viral diseases (Table 1 and Figure 2). Disease outbreaks, epidemics, and pandemics caused by respiratory viruses such as IAV, RSV, and the recently emerged SARS-CoV-2 pose a great threat to public health. Severity of viral pneumonia is driven, in part, by robust and unrestrained inflammation in the lungs that can culminate in lung failure and death. Cell-specific and temporal production of SPMs in the lungs counter-regulates dysfunctional inflammatory responses while promoting the development of adaptive responses and repair.

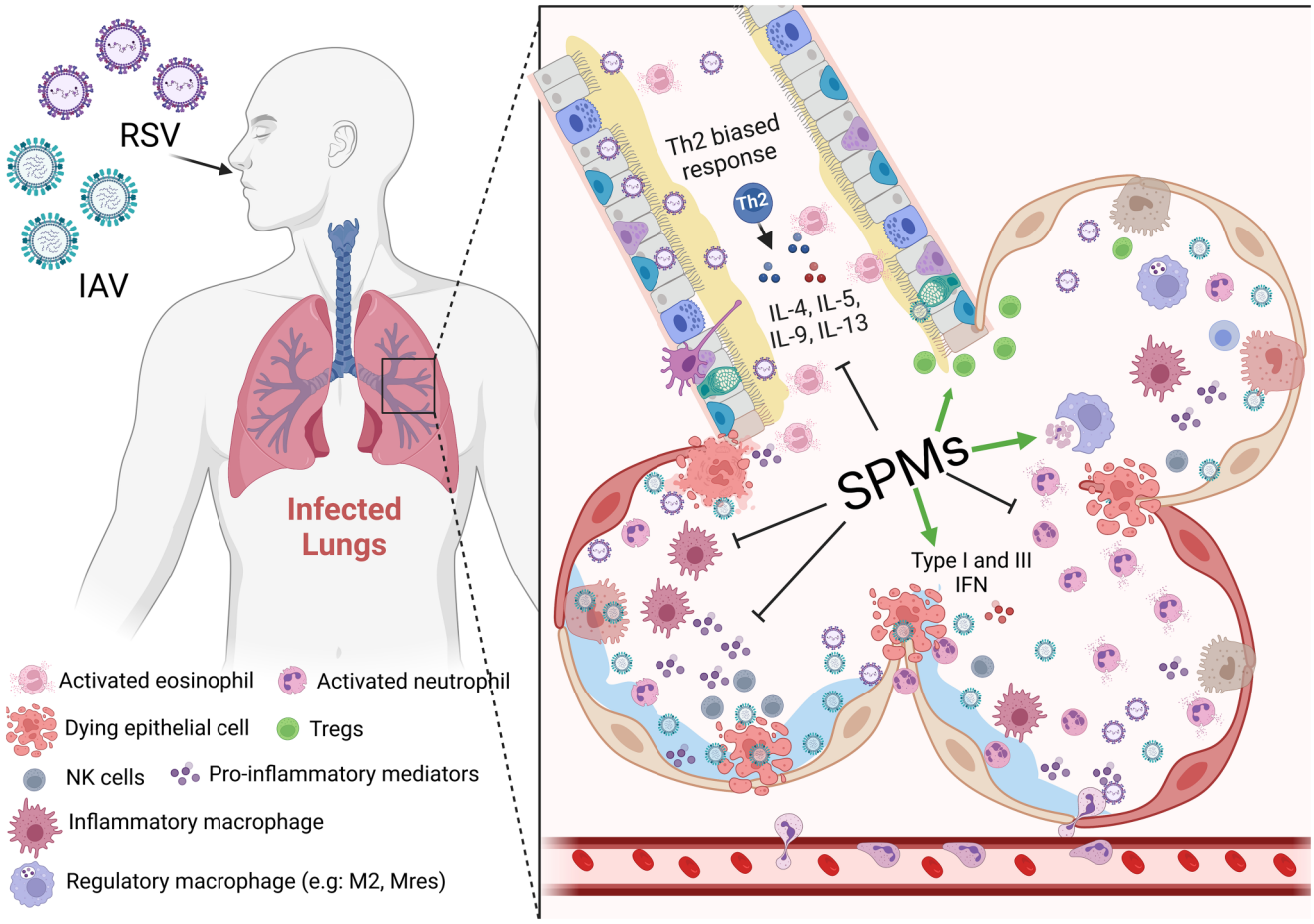

Figure 2. The role of SPMs in counter-regulation of the inflammatory responses in RSV and IAV diseases. The respiratory virus infection leads to (1) epithelial cell death with accumulation of necrotic and apoptotic debris and airway edema; (2) production of high quantities of pro-inflammatory mediators that will lead to an intense (3) recruitment and activation of granulocytes; (4) polarization of macrophages to pro-inflammatory phenotypes; (5) RSV can lead to a type 2 skewed response with hypersecretion of mucus and increased recruitment and activation of eosinophils. SPMs stimulate Tregs function, promote macrophage polarization to regulatory phenotypes, and enhance efferocytosis and clearance of cellular debris in the lungs. In addition, SPMs enhance antiviral host responses such as IFN type I and type III, while counter-regulating pro-inflammatory mediator production, excessive recruitment of leukocytes preventing intense tissue damage.
Source: Created with Biorender.com.

Throughout human history, the evolutionary challenge posed by viruses has given rise to elegant and remarkably effective immunological defense mechanisms to enable pathogen control and host survival. In parallel, viral pathogens have developed strategies to circumvent these host defense mechanisms by hindering antiviral and inflammatory responses to replicate and disseminate. SPMs are potent mediators conserved through evolution with increasing evidence of protective bioactions during infections, but their production or actions can be disrupted by respiratory viruses. The recently described interplay between type I and type III IFNs and specific SPMs indicates an intricate and likely ancient connection between host antiviral and immunoregulatory mechanisms. Hence, not surprisingly, respiratory viruses, such as IAV and RSV, have been shown to disrupt SPM production and signaling.

In preclinical models of IAV and RSV infections, pharmacological administration of SPMs counter-regulates excess inflammation while promoting host antipathogen mechanisms including production of IFNs, secretion of antibodies, and restoration of disrupted leukocyte function. In humans, omega-3 PUFA supplementation increases circulating levels of SPMs.[97] Two recent randomized clinical trials have evaluated the impact of supplementation with omega-3 PUFAs in COVID-19 patients. Although the studies were conducted in a relatively small cohort of patients, omega-3 supplementation improved clinical parameters of respiratory and renal function in critically ill COVID-19 patients[98] and decreased cellular interactions related to immunothrombosis, while improving leukocyte phagocytic functions in older COVID-19-hospitalized patients.[99] These studies highlight the potential promise for the use of SPMs in therapeutic strategies to treat the host response to respiratory viral diseases. Further clinical studies in IAV and RSV patients are warranted to evaluate the benefit of SPM precursors' supplementation in these diseases.

There is still much to be examined to fully understand the endogenous mechanisms triggered by SPMs to control pathogen-mediated inflammation and damage. The synergism between mediators, receptor-initiated signaling pathways, and the finely regulated control of SPM biosynthesis during infections are yet to be fully understood. Traditionally, the therapeutic approaches for respiratory virus diseases target the pathogen and are becoming more challenging due to the

increasing drug resistance. Host-targeted therapies focusing on harnessing the host's SPM pathways offer a novel strategy for consideration with the goal of addressing the excess morbidity and mortality associated with viral pneumonia.

AUTHORS' CONTRIBUTIONS

BDL and LPT conceived the idea of the article. LPT and JN wrote the manuscript, including the figures and table, LPT, JN, and BDL performed the literature search, drafted, and revised the work.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: BDL is an inventor on patents (specialized pro-resolving mediators [SPMs]) assigned to Brigham and Women's Hospital. LPT and JN have no conflicts of interest to declare.

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ORCID ID


Luciana P Tavares https://orcid.org/0000-0002-5319-0210

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