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Review article

Impact of inhaled pollutants on response to viral infection in controlled exposures

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Air pollutants are a major source of increased risk of disease, hospitalization, morbidity, and mortality worldwide. The respiratory tract is a primary target of potential concurrent exposure to both inhaled pollutants and pathogens, including viruses. Although there are various associative studies linking adverse outcomes to co- or subsequent exposures to inhaled pollutants and viruses, knowledge about causal linkages and mechanisms by which pollutant exposure may alter human respiratory responses to viral infection is more limited. In this article, we review what is known about the impact of pollutant exposure on antiviral host defense responses and describe potential mechanisms by which pollutants can alter the viral infection cycle. This review focuses on evidence from human observational and controlled exposure, *ex vivo*, and *in vitro* studies. Overall, there are a myriad of points throughout the viral infection cycle that inhaled pollutants can alter to modulate appropriate host defense responses. These alterations may contribute to observed increases in rates of viral infection and associated morbidity and mortality in areas of the world with high ambient pollution levels or in people using tobacco products. Although the understanding of mechanisms of interaction is advancing through controlled *in vivo* and *in vitro* exposure models, more studies are needed because emerging infectious pathogens, such as severe acute respiratory syndrome coronavirus 2, present a significant threat to public health. (J Allergy Clin Immunol 2021;148:1420-9.)

Key words: *Viral infection, pollution, inhaled*

Abbreviations used

ACE2:	Angiotensin-converting enzyme 2
e-cigarettes:	Electronic cigarettes
LAIV:	Live attenuated influenza vaccine
PM:	Particulate matter
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SP:	Surfactant protein
TMPRSS2:	Transmembrane protease, serine 2

Air pollutants are a major source of increased risk for disease, hospitalization, morbidity, and mortality worldwide.[1-3] Because the lungs filter more than 12,000 liters of air per day, they are a primary target of potential concurrent exposure to both inhaled pollutants and pathogens, including viruses. Although there are various associative studies linking adverse outcomes to co- or subsequent exposures to inhaled pollutants and viruses, causal linkages and mechanisms by which pollutant exposure may alter human respiratory response to viral infection are more limited.[4-7] The limited knowledge on how pollutants may impact response to viral infection has been acutely highlighted with the onset of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic and the resulting flurry of review articles that nicely summarize identified associations but do little to capture causal linkages.[8,9] In this article, we will focus on the impact of pollutant exposure on antiviral host defense responses and describe potential mechanisms by which pollutants can alter the viral infection cycle that have been identified through human observational and controlled exposure studies, as well as mechanistic *in vitro* studies.

POLLUTANT EXPOSURES AND LIVE ATTENUATED INFLUENZA VIRUS AS A MODEL VIRAL INFECTION

In addition to experimental inoculation with rhinovirus,[10] the Food and Drug Administration–approved live attenuated influenza virus (LAIV) vaccine presents a unique and underused model to mechanistically explore the interaction between pollutants and respiratory viruses in humans *in vivo*. The live, but attenuated virus replicates only at lower temperatures in the nasal passages, but causes similar innate and adaptive host defense responses, similar to community-acquired infections.[11] Hence, inoculation with LAIV allows the study of active viral infection and immune responses in the nasal passages of human volunteers, without risking the overall safety of the participants. The LAIV model is also ideal for studying the effects of viruses for whom the primary point of entry and activation is likely the nasal passage, such as influenza and SARS-CoV-2.[12] It should be noted that the use of the LAIV model is limited by contraindications in individuals with severe allergic reaction to its ingredients and

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children and adolescents on asprin therapy. However, the easy-to-use LAIV model of viral infection is well suited to determine the effects of ambient air pollutants, such as diesel exhaust and wood smoke, as well as use of tobacco products, including cigarettes and e-cigarettes on host defense responses.

Diesel exhaust

Diesel exhaust contributes a significant percentage of traffic-related air pollution in many cities, due to increased needs for transportation in urban areas.[13] Acute exposure effects include nose and eye irritation, fatigue, headache, and nausea, whereas chronic exposures increase respiratory symptoms, reduce lung function, and change inflammatory profiles.[13] Diesel exhaust is also known to enhance allergic inflammation and due to its contribution to ambient particulate matter (PM) is likely associated with increased susceptibility to viral infection. To explore this hypothesis, a study was conducted exposing adults who were healthy or had allergic rhinitis to diesel exhaust before inoculation with LAIV.[14] Diesel exhaust exposure was associated with increased LAIV-induced eotaxin-1, eosinophil cationic protein, and influenza RNA in nasal cells, supporting previous literature and animal studies,[15] suggesting that diesel exhaust can act as an allergic adjuvant, promoting inflammation and potentially reducing viral clearance, especially in individuals with underlying allergy.

Wood smoke

Wood smoke is a major and continually growing source of PM in the United States and globally as wildfire events occur with increasing frequency.[16] Furthermore, a substantial percentage of the world population uses wood and biomass for heating or cooking, resulting in up to 30% of ambient fine PM in some areas of the United States during the winter months, and greater percentages in developing countries.[17-19] Exposure to wood smoke and biomass is associated with increased morbidity, including reduced lung function, upper respiratory tract symptoms, and inflammation, and mortality due to respiratory infection in many populations.[20-25] The effects of wood smoke on LAIV were examined in healthy study participants exposed to either 500 $\mu g/m^3$ of wood smoke particulate or filtered air for 2 hours.[26] LAIV-induced IFN-γ–induced protein 10 levels, as measured in nasal lavage, were suppressed in the nasal mucosa of all participants. Furthermore, an Exposure by Sex interaction was observed, with males showing greater inflammation-related gene expression, whereas in females, host defense–related gene expression was mildly decreased in nasal lavage fluid cells. These results support sex-specific responses to viral infection, which can be augmented with the additional interaction of pollutant exposure, in this case wood smoke.

Tobacco products

Epidemiological evidence repetitively links tobacco smoke exposure to increased risk of viral infection.[7,27] To better understand the mechanisms of this association between tobacco product use and respiratory infection, various studies in users and nonusers have been conducted using the LAIV model. An observational cohort study was first conducted to understand differential responses in active cigarette smokers, nonsmokers, and those exposed to secondhand smoke after LAIV inoculation.[28] In this initial study, nasal lavage fluid IL-6 response was significantly suppressed in active smokers, along with decreased median IFN-γ–induced protein 10, and IFN-γ, whereas viral RNA levels were significantly increased in smokers as compared with nonsmokers. Individuals exposed to secondhand smoke generated responses that were intermediate between active smokers and nonsmokers, suggesting mechanisms for increased susceptibility to infection in tobacco product users and those exposed secondhand.

Most recently, the LAIV model has been used to investigate potential mechanisms by which electronic cigarettes (e-cigarettes) may affect susceptibility to viral infection.[29] Because e-cigarettes were deemed a tobacco product[30] and, similar to cigarettes, contain nicotine and other additives, it was hypothesized that e-cigarettes may also increase susceptibility to respiratory viral infection. Thus, a cohort of cigarette smokers, e-cigarette users, and nonsmokers was inoculated with LAIV and monitored for effects on immune gene expression and antibody response.[29] Overall, there was substantial downregulation of critical immune genes in nasal biopsy samples, especially in e-cigarette users compared with nonsmokers. In particular, altered host defense mediators, IFN-γ, IL-6, and IL12p40, were found in cigarette smokers and e-cigarette users when compared with nonsmokers. It was also found that nasal mucosal anti-LAIV IgA levels were significantly lower in cigarette smokers and e-cigarette users than in nonsmokers, demonstrating that e-cigarette use can alter response to viral infection, affecting host defense mediators and antibody production.

Although the LAIV model has provided significant insight into the effects of inhaled pollutants on viral infection in humans *in vivo*, there are still many aspects of the effects of inhaled pollutant exposures on response to viral infection that are poorly understood. For example, many of these studies focus on acute exposures, whereas most human population is exposed chronically to inhaled pollutants, which may impact response to viral infection. Furthermore, only a limited number of model pollutants have been investigated and more research is needed on pollutants such as PM, gaseous pollutants such as NO_2 and ozone, and pollutant mixtures. The field would also benefit from longer follow-up periods in LAIV-based studies to understand the effect of pollutant exposure on adaptive immunity and studies that include the exploration of potential targeted interventions to prevent pollution-induced effects (eg, therapeutics, dietary, and use of personal and household filtration devices).[31,32]

POTENTIAL MECHANISMS

Viral entry and activation

Many viral pathogens, including influenza, parainfluenza, and coronaviruses, including SARS-CoV-2, depend in part on proteolytic activation of the virus, regulating the ability of the virus to enter the host cell[33,34] (Fig 1, step 1). For example, attachment and subsequent entry of SARS-CoV-2 into the host cell occurs via binding of the virus spike (S)-protein to angiotensin-converting enzyme 2 (ACE2) receptors expressed on many different cell types. The S protein has 2 functional domains: the S1 domain, which binds to the ACE2 receptor, and the S2 domain, which mediates the fusion between the virus and the host cell membrane. Proteolytic cleavage of the S protein is required to enable the S2 domain to become active.[35] This can be

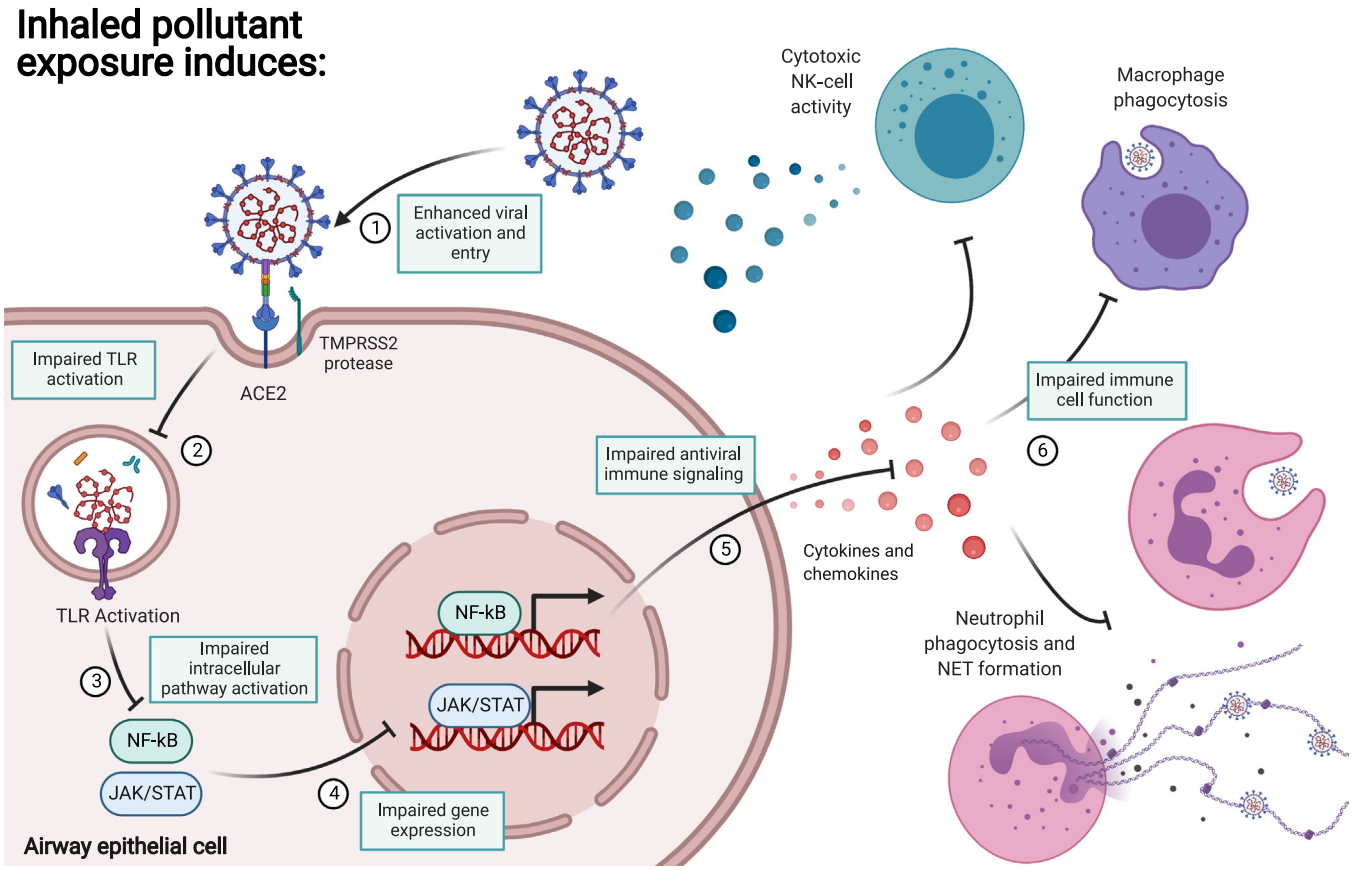

FIG 1. Potential mechanisms of inhaled pollutant interaction with viral life cycle. Controlled *in vivo*, *ex vivo*, and *in vitro* exposure studies indicate that inhaled pollutants can affect host defense response to viral infections in multiple ways. (1) Enhance the expression of receptors and the production or activity of proteases needed for viral entry, (2) impair TLR activation, (3) impair intracellular pathway activation (NF-kB and JAK/STAT), (4) impair gene expression (type I IFN, inflammatory, IFN inducible, and chemokine genes), (5) impair antiviral immune signaling molecule production including cytokines and chemokines, and (6) impair immune cell functions such as phagocytosis, NET formation, and cytotoxic NK-cell activity. Each of these disruptions of normal host defense responses result in increased viral replication and dysregulation of immune responses. Because inhaled pollutants affect the viral life cycle, it is important to reduce harmful exposures and explore prevention and mitigation strategies against these environmental pollutants. This figure shows SARS-CoV-2 as an example, but it is generally applicable to other types of viruses, such as influenza. *JAK/STAT*, Janus kinase/signal transducer and activator of transcription; *NET*, neutrophil extracellular trap; *NF-κB*, nuclear factor kappa-light-chain-enhancer; *NK*, natural killer; *TLR*, Toll-like receptor. The figure was created at BioRender.com.

accomplished by a number of proteases, such as transmembrane protease, serine 2 (TMPRSS2), furin, cathepsins, neutrophil elastase (reviewed in El-Shimy et al[35] and Meyer and Jaspers[36]), and potentially other proteases that prime and regulate viral entry of SARS-CoV-2 into the host cell. Human nasal and bronchial mucosa abundantly express ACE2 and are rich sources of proteases, such as TMPRSS2, furin, cathepsins, and other proteases.[33,37-40] Inhibition of protease activity in the respiratory mucosa has been explored as a therapeutic target, but can also be regulated endogenously by antiproteases, such as alpha 1 antitrypsin and secretory leukocyte protease inhibitor. Pollutant exposure has been shown to dysregulate the protease/antiprotease balance in the respiratory mucosa. For example, exposure to ozone increases secreted levels of TMPRSS2 and decreases levels of secretory leukocyte protease inhibitor, which was linked to increased viral entry of influenza virus.[41] Similarly, analysis of lung tissue from mice chronically exposed to ozone showed elevated expression of *Tmprss2*.[42] Many pollutants also enhance neutrophil elastase levels in the respiratory tract.

The effects of inhaling cigarette smoke on protease/antiprotease balance in the respiratory mucosa are well established and causally linked to smoking-related lung diseases.[43-46] Some groups have shown that expression of ACE2 and TMPRSS2 is similar in bronchial epithelial cells from current and never smokers,[47] whereas others have observed significant increases in either ACE2 and/or TMPRSS2 in cells from smokers.[48-50] Expression and activity of antiproteases, including secretory leukocyte protease inhibitor and alpha 1 antitrypsin, are also modified by smoking.[51,52] Controlled exposures to model particulate air pollutants, such as diesel exhaust,[53] demonstrate increased expression of ACE2 and TMPRSS2 in human pluripotent stem cell–derived alveolar epithelial cells and alveolar organoids. Expression of ACE2 and TMPRSS2 might be regulated by several consensus motifs for binding of the aryl hydrocarbon

TABLE I. Summary of described studies

LAIV controlled exposure studies				
Type of study	**Exposure**	**Participants**	**Outcomes**	**Citation**
Double-blind, randomized, placebo-controlled study	100 μg/m^3 of diesel exhaust or clean air and LAIV inoculation	Healthy adults and adults with allergic rhinitis	Exposure induced increased IFN-γ in nasal lavage fluid with no interaction with allergy and increased eotaxin-1, ECP, and influenza RNA sequences in nasal cells linked to allergy	Noah et al,[14] 2012
Randomized, placebo-controlled study	500 μg/m^3 wood smoke particles or filtered air and LAIV inoculation	Healthy adults	IP-10 suppression in nasal mucosa in all exposed participants. Increased inflammatory-related gene expression in male exposed subjects and decreased host defense–related gene expression in female exposed subjects, compared with controls	Rebuli et al,[26] 2019
Observational cohort study	LAIV inoculation	Healthy adult nonsmokers, cigarette smokers, and individuals exposed to secondhand smoke	Lower IL-6, IP-10, and IFN-γ in nasal lavage fluid in cigarette smokers compared with controls. Increased influenza viral subunit RNA in smokers compared with nonsmokers. Intermediate responses in secondhand smoke–exposed individuals	Noah et al,[28] 2011
Observational cohort study	LAIV inoculation	Healthy adult nonsmokers, cigarette smokers, and e-cigarette users	Downregulated host defense mediators including IFN-γ, IL-6, and IL12p40 in cigarette smokers and e-cigarette users compared with nonsmokers. Lower nasal mucosal IgA in cigarette smokers and e-cigarette users compared with nonsmokers	Rebuli et al,[29] 2021
Studies that inform mechanism of effects				
Type of study	**Exposure**	**Models**	**Outcomes**	**Citation**
In vivo animal controlled exposure	25 μL of diesel exhaust particles and influenza infection	Ovalbumin-sensitized C57BL/6 mice	Increased levels of lung lavage and tissue eosinophils; levels of IL-4, IL-13, CCL11, and CCR3 in lavage fluid; and levels of IL-1α in lung homogenates	Jaspers et al,[15] 2009
In vitro cell culture	0.4 ppm ozone and influenza infection	Primary human nasal epithelial cells	Increased levels of LDH, IL-6, influenza HA subunit expression, and viral titer postexposure. Increased viral entry postexposure. Decreased SLPI and increased HAT and TMPRSS2 production. Antioxidant supplementation suppresses viral replication	Kesic et al,[41] 2012
In vivo animal controlled exposure	0.8 ppm ozone	C57BL/6 mice	TMPRSS2 protein and transcripts were elevated in extrapulmonary airways, parenchyma, and alveolar macrophages in exposed mice	Vo et al,[42] 2020
Observational cohort study	Cigarette smoke and e-cigarette aerosol	Healthy adult humans	Elevations in neutrophil elastase, MMP2, and MMP9 in BAL of cigarette smokers and e-cigarette users. Nicotine induced dose-dependent increases in proteases in neutrophils and macrophages	Ghosh et al,[43] 2019

(Continued)

TABLE I. *(Continued)*

Studies that inform mechanism of effects				
Type of study	**Exposure**	**Models**	**Outcomes**	**Citation**
Observational cohort study	Cigarette smoke	Healthy adult humans	Greater alveolar macrophage presence, and alveolar macrophage–derived protease activity in BAL from cigarette smokers than from nonsmokers	Harris et al,[44] 1975
Observational cohort study	Cigarette smoke	Healthy adult humans	Elevated cathepsin L activity and mRNA in smokers compared with nonsmokers	Takahashi et al,[45] 1993
Observational cohort study	Cigarette smoke	Healthy adult humans	Elevated neutrophil elastase activity in smokers compared with nonsmokers	Weitz et al,[46] 1987
Meta-analysis	Cigarette smoke	Human bronchial epithelial cells	Similar ACE2 and TMPRSS2 expression in bronchial epithelial cells from smokers and nonsmokers	Voinsky and Gurwitz,[47] 2020
Meta-analysis	Cigarette smoke	Lung tissues: small and large airway epithelium	Upregulation of pulmonary ACE2 gene expression in ever-smokers compared with nonsmokers	Cai et al,[48] 2020
Meta-analysis	Cigarette smoke	Nasal and bronchial cells	Upregulation of lung airway ACE2 and TMPRSS2 in smokers compared with nonsmokers	Saheb Sharif-Askari et al,[49] 2020
In vitro cell culture and observational cohort study	Cigarette smoke	Primary human nasal epithelial cells and nasal lavage fluid	Increased SLPI expression in nasal epithelial cells and lavage fluid cells. Increased STAT1 gene expression and protein in nasal epithelial cells. Antiprotease activity of SLPI against neutrophil elastase is enhanced in cigarette smokers	Meyer et al,[51] 2014
Observational cohort study	Cigarette smoke	Healthy adult humans and individuals with COPD	Reduced A1AT antiprotease activity in smokers independent of disease state	Lockett et al,[52] 2012
In vitro cell culture	50 and 100 μg/mL diesel $PM_{2.5}$	Human pluripotent stem cell–derived alveolar epithelial cells and 3D alveolar organoids	Upregulated ACE2 and TMPRSS2 in exposed cells	Kim et al,[53] 2020
Meta-analysis	Comparative Toxicogenomics Database (15,681 chemicals)	Airway cells: intrapulmonary airway brushings, bronchial epithelial cells, small airway epithelium	50+ chemicals can modulate the expression of ACE2, and AhR can bind the promoters/enhancers of TMPRSS2 and cathepsin B, L, and V encoding genes	Watzky et al,[54] 2021
Review	PM	Role of AhR in PM-induced health effects	AhR activation by pollutant exposure can induce oxidative stress and inflammation	Lawal,[55] 2017
In vitro cell culture	0.01, 0.1, 1, 10 ppm ozone	Rat alveolar macrophages	SP-A functional activity was reduced in a dose-dependent manner with exposure	Han and Mallampalli,[56] 2015
Randomized, double-blind, cross-over, controlled exposure study	Diesel exhaust diluted to 300 $\mu g/m^3$ of $PM_{2.5}$	Allergen-sensitized human participants	Exposure dampened SP-D production in allergen-exposed individuals	Ryu et al,[58] 2020
In vivo animal controlled exposure	Diesel exhaust diluted to 0.5 or 2 mg/m^3	BALB/c mice	Increased susceptibility to influenza infection with exposure. Increased expression of IL-6 and decreased SP-A and SP-D with exposure	Ciencewicki et al,[59] 2007

(Continued)

TABLE I. *(Continued)*

Studies that inform mechanism of effects				
Type of study	**Exposure**	**Models**	**Outcomes**	**Citation**
Observational cohort study	Cigarette smoke	Healthy adult humans	Decreased BAL SP-A and SP-D with exposure	Honda et al,[60] 1996
In vitro cell culture	Cigarette smoke and SARS-CoV-2 infection	Primary human airway basal stem cells	Increased infection rates with exposure and reduced cellular proliferation	Purkayastha et al,[63] 2020
In vitro cell culture	Cigarette smoke extract	RAW264.7 macrophage cells	Inhibited TLR activation and production of IL-6, TNF-α, and IL-1β with exposure. Suppression of NF-κB at baseline and activity induced by LPS	Lee et al,[64] 2015
In vitro cell culture	Cigarette smoke	Primary human nasal epithelial cells	Increased rates of methylation (390 genes) with exposure, including IFN response genes	Rager et al,[65] 2013
In vitro cell culture	Cigarette smoke extract and human rhinovirus	Primary human bronchial epithelial cells	Suppression of antiviral defense, inflammation, viral signaling, and airway remodeling genes with exposure	Proud et al,[66] 2012
In vitro cell culture	Cigarette smoke– conditioned medium and polyI:C	Human embryonic lung fibroblasts, Beas-2B lung epithelial cells, and Vero kidney epithelial cells	Exposure decreases expression of ISG15, IRF-7, IRF-3, and NF-κB in fibroblast and epithelial cells	Bauer et al,[67] 2008
In vitro cell culture	Cigarette smoke extract	Primary human tracheobronchial epithelial cells	Exposure inhibited IFN-γ–dependent gene expression and type II IFN signal transduction. Exposure also decreased IFN-γ's inhibitory effects on RSV	Modestou et al,[68] 2010
In vitro cell culture	Cigarette smoke and poly I:C or influenza A	Primary human small airway epithelial cells	Exposure inhibited proinflammatory (IL-6 and IL-8) and antiviral protein (IP-10 and IFNs) production in response to viral infection. Influenza infection increased with exposure along with decreases in phosphorylation of IRF3. Exposure also inhibited TLR3 activation by impairing cleavage	Duffney et al,[69] 2018
In vitro cell culture	6.25 to 44 μg/cm^2 diesel exhaust and influenza A	Primary human nasal and bronchial epithelial cells and A549 cells	Exposure increased epithelial cell attachment at 2 h postinfection and the number of influenza-infected cells within 24 h postinfection. IFN-β, IFN-dependent signaling, and IFN-stimulated gene expression were enhanced by exposure. Exposure generated oxidative stress in epithelial cells	Jaspers et al,[70] 2005
In vitro cell culture and *in vivo* animal controlled exposure	50-400 μg $PM_{2.5}$	Pathogen-free C57BL/6 and peritoneal macrophages from wild-type C56BL/6 and NLRP3$^{-/-}$	Exposure decreased IL-1β and IFN-β production *in vitro* and downregulated *in vivo*. Exposure suppressed NLRP3 inflammasome activation and AhR-TIPARP signaling pathway	Tao et al,[71] 2020
In vitro cell culture	PM_{10} and H5N1 infection	A549 cell line	Exposure increased cellular damage and enhances pathogenic burden in A549 cells. Metabolic and immune response gene expression pathways were dysregulated by exposure during viral infection	Mishra et al,[72] 2020

(Continued)

TABLE I. *(Continued)*

Studies that inform mechanism of effects				
Type of study	**Exposure**	**Models**	**Outcomes**	**Citation**
Review	Air pollution (PM, ozone, nitrogen oxides, transition metals)	Pulmonary and cardiovascular systems	Air pollution induces oxidative stress, and oxidative stress can trigger redox-sensitive pathways that lead to inflammation and cell death, and ultimately pulmonary and cardiovascular injury	Lodovici and Bigagli,[73] 2011
Review	Air pollution	Immune system	Air pollution can induce proinflammatory immune responses in multiple immune cell classes (epithelium and macrophages), enhance T_H adaptive immune responses and dysregulate antiviral immune responses, and induce respiratory exacerbations in populations with disease	Glencross et al,[74] 2020
In vivo animal controlled exposure	0.5 mg/m^3 diesel exhaust and influenza A	BALB/c mice	Exposure induced increased viral titers, lung inflammation, cytokine expression, and pulmonary responsiveness to inhaled methacholine. Exposure also induced increased BAL neutrophils and protein. IFN-β was enhanced with exposure, along with IL-4, whereas IFN-γ and IL-12p40 were decreased	Gowdy et al,[75] 2010
Ex vivo exposure study	e-cigarette liquids and flavoring agent cinnamaldehyde	Human alveolar macrophages, neutrophils, and NK cells	Exposure, particularly to cinnamaldehyde containing e-liquids, induced immunosuppressive effects. Similarly, cinnamaldehyde alone suppressed macrophage and neutrophil phagocytosis, NK-cell killing, and neutrophil extracellular trap formation	Clapp et al,[77] 2017
In vitro cell culture	100 μg/μL diesel exhaust particles	Primary alveolar macrophages, RAW264.7 cells, and THP-1 cells	Exposure induces reactive oxygen radical-induced apoptosis, loss of surface membrane asymmetry, and DNA damage. Diesel exhaust particles with their organic constituents extracted had impaired apoptosis and ROR generation, but those with their organic extracts were able to induce apoptosis. Exposure induced stress-activated protein kinases	Hiura et al,[78] 1999

A1AT, Alpha 1 antitrypsin; *AhR*, aryl hydrocarbon receptor; *BAL*, bronchoalveolar lavage; *HA*, hemagglutinin; *HAT*, human airway trypsin-like protease; *IL-12p40*, IL-12 subunit p40; *IP-10*, IFN-γ–induced protein 10; *NF-κB*, nuclear factor kappa-light-chain-enhancer; *NK*, natural killer; *ROR*, receptor tyrosine kinase-like orphan receptor; *RSV*, respiratory syncytial virus; *SLPI*, secretory leukocyte protease inhibitor; *STAT1*, signal transducer and activator of transcription 1; *TLR*, Toll-like receptor.

receptor, a common pathway activated by ambient air pollutants.[54,55]

The pulmonary surfactant, which lines the alveoli, serves as another line of defense against pathogens. Surfactant proteins (SPs) SP-A and SP-D assist in the clearance of bacteria and virus from the lung by directly opsonizing pathogens and enhancing their uptake by phagocytic immune cells.[56] Air pollutants such as PM and ozone as well as cigarette smoke have all been shown to interfere with the pulmonary surfactant. Specifically, ozone exposure decreases the phagocytic index of SP-A.[57] Diesel exhaust

exposures dampened production of SP-D in allergen-sensitized individuals[58] and decreased SP-A and SP-D levels in mice, which was associated with increased influenza infections.[59] Finally, smokers, who are generally more susceptible to viral infections, have been reported to have less SP-A and SP-D present in bronchoalveolar lavage fluid compared with nonsmokers.[60]

Viral replication

Once the virus enters the host cell, it is met with an organized antiviral host defense response, aimed at limiting the replication and release of new virions.[61] Infection triggers a rapid antiviral signaling pathway, beginning by activation of Toll-like receptors and resulting in the secretion of type I and type III interferons (IFNs) by the infected cell (Fig 1, steps 2-4). Type I IFNs act in either an autocrine fashion or a paracrine fashion to stimulate the second wave of antiviral responses by activating the Janus kinase/signal transducer and activator of transcription signaling pathway and resulting in the expression of numerous IFN-stimulated genes, whose role is to shut off or limit the replication of the virus in the host cell.[61] Similarly, type III IFNs, which are massively induced in respiratory epithelium on viral infection, activate Janus kinase/signal transducer and activator of transcription pathways to upregulate expression of immunomodulatory genes.[62] The effects of cigarette smoke exposure on antiviral host defense responses have been well studied, including recent studies demonstrating that exposure to cigarette smoke increases SARS-CoV-2 infection.[63] Effects of smoking include inhibition of Toll-like receptor activation, inactivation of nuclear factor kappa-light-chain-enhancer response,[64] epigenetic modulation of IFN response genes,[65] decreased expression of antiviral host defense genes,[66,67] and decreased activation of IFN signaling pathways.[68,69] Much less is known about ambient air pollutant effects on antiviral host defense responses. In the context of model air pollutant exposures, such as diesel exhaust and ozone, type I IFN responses were not affected by the exposures and increase with the level of infection.[7,41,70] In contrast, exposure to ambient PM suppresses virus-induced IFN-β expression in macrophages and epithelial cells.[41,71,72] Hence, whether and to what extent inhalation of ambient air pollutants modulates the ability to mount an effective antiviral host defense response needs to be further explored.

Viral pathogenesis

Control of viral replication and pathogenesis depends on the ability of infected epithelial cells to limit spread of virus to neighboring cells while also increasing the production of cytokines and chemokines that recruit virus-specific immune effector cells to the infection site (Fig 1, step 5). However, increases in pollutant-induced oxidative stress, which has been observed after diesel exhaust, PM, and ozone exposures,[73] can result in epithelial cell damage, limiting their capacity to function.[7,9,74,75] Release of cytokines and chemokines, which recruit and activate immune cells, is also critical for coordinated innate and adaptive immune responses.[76] These include IFN-inducible cytokines, such as C-X-C motif chemokine ligand (CXCL)9/monokine induced by IFN-γ, CXCL10/IFN-γ–induced protein 10, and CXCL12/stromal cell–derived factor 1 alpha, as well as neutrophil chemokines (CXCL8/IL-8 and CXCL1/GROα), lymphocyte chemoattractants (C-C motif chemokine ligand 5/RANTES and CXCL16), and monocyte chemoattractants (C-C motif chemokine ligand 2/monocyte chemoattractant protein 1). The production of many of these inducible cytokines has been shown to be altered by pollutant exposure including tobacco products and wood smoke, indicating potentially impaired coordinated immune responses to infection.[26,29] Along with reduced production of important immune signaling molecules, the functions of innate immune cells recruited by these signals are also impaired by inhaled pollutant exposure (Fig 1, step 6). For example, neutrophil phagocytosis and neutrophil extracellular trap formation, macrophage phagocytosis, and cytotoxic natural killer cell responses were all altered *ex vivo* with e-cigarette exposure.[77] Furthermore, gaseous pollutants such as ozone have been shown to alter macrophage function[7,74] while diesel exhaust particle exposure induces apoptosis of human macrophages at levels that cause minimal cytotoxicity to bronchial epithelial cells.[78] In addition, critical to a coordinated response to future viral infection is the production of virus-specific antibodies, which have recently been shown to be impaired with exposure to e-cigarettes in an LAIV inoculation model.[29]

SUMMARY

Overall, there are a myriad of ways throughout the viral infection cycle that inhaled pollutants can alter appropriate host defense responses, which are summarized in Table I. These alterations may contribute to observed increases in rates of viral infection and associated morbidity and mortality in areas of the world with high ambient pollution levels or in people using tobacco products. There are limitations to using human controlled exposure models, such as the limitation of LAIV only permitting viral replication in the nose and limiting our ability to study effects that may differ in the lower airway.[79-81] Despite these limitations, this experimental design does allow for the examination of the effects of pollutants and viral infection in a model with immediate public health relevance. Controlled *in vivo* and *in vitro* exposure models have allowed us to begin to explore these mechanisms, yet as new viruses and pollutants continue to emerge, further study is needed. The current coronavirus disease 2019 pandemic has illustrated that better understanding of potential interactions between pollutants or toxicant exposures and effects on antiviral host defense responses is needed.

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