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REVIEW

Lung inflammation caused by inhaled toxicants: a review

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Abstract: Exposure of the lungs to airborne toxicants from different sources in the environment may lead to acute and chronic pulmonary or even systemic inflammation. Cigarette smoke is the leading cause of chronic obstructive pulmonary disease, although wood smoke in urban areas of underdeveloped countries is now recognized as a leading cause of respiratory disease. Mycotoxins from fungal spores pose an occupational risk for respiratory illness and also present a health hazard to those living in damp buildings. Microscopic airborne particulates of asbestos and silica (from building materials) and those of heavy metals (from paint) are additional sources of indoor air pollution that contributes to respiratory illness and is known to cause respiratory illness in experimental animals. Ricin in aerosolized form is a potential bioweapon that is extremely toxic yet relatively easy to produce. Although the aforementioned agents belong to different classes of toxic chemicals, their pathogenicity is similar. They induce the recruitment and activation of macrophages, activation of mitogen-activated protein kinases, inhibition of protein synthesis, and production of interleukin-1 beta. Targeting either macrophages (using nanoparticles) or the production of interleukin-1 beta (using inhibitors against protein kinases, NOD-like receptor protein-3, or P2X7) may potentially be employed to treat these types of lung inflammation without affecting the natural immune response to bacterial infections.

Keywords: cigarette, mycotoxin, trichothecene, ricin, inflammasome, macrophage, inhibitors

Introduction

Inflammation is a complex biological process that occurs in response to harmful stimuli and whose function is to eliminate the cause of cell injury and initiate the repair process. Lung inflammation occurs in response to bacterial and viral pathogens and environmental pollutants. The sources of indoor pollution include cigarette smoke, mycotoxins, and airborne particulates of asbestos, silica, and heavy metals. Sustained inflammation of the lung, as occurs in response to cigarette smoke, may lead to chronic obstructive pulmonary disease (COPD), which is the third leading cause of death globally and whose prevalence is still rising.[1,2] Current therapies for COPD focus on long-acting bronchodilators and do not sufficiently target pulmonary inflammation that underlies the pathogenesis of the disease.[3] There exists a critical need to understand the mechanisms that lead to lung inflammation and develop novel strategies to treat COPD. In addition to cigarette smoke, other inhaled toxicants are known to produce lung inflammation. Recent epidemiologic evidence has recognized the importance of air pollution from traffic worldwide and domestic fires that burn biomass fuels in underdeveloped countries.[4] In cases of exposure to sublethal amounts of inhaled toxicants, such as mycotoxins and ricin, inflammation is usually resolved when the cause of the cell injury has been eliminated. Although these toxicants belong to the different classes of chemicals, they nevertheless may activate similar biochemical

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pathways. Elucidating these pathways may serve to identify potential therapeutic targets susceptible to anti-inflammatory treatments.

Several types of cells are involved in lung inflammation, including the epithelial cells that line the airways and alveoli and the immune cells in the blood. Airway epithelial cells are important in the host defense system by acting as a physical barrier and secreting mucus that traps inhaled particles.[5] These cells also secrete antimicrobial peptides and proteases that neutralize the danger,[6–8] cytokines and chemokines that serve as inflammatory mediators,[9–12] and growth factors that promote tissue repair and fibrosis.[13] During the acute phase of inflammation, neutrophils rapidly migrate to the lung as first responders, producing reactive oxygen species and secreting serine proteases, matrix metalloproteinases, and other enzymes during degranulation. These products not only degrade invading dangers but also contribute to alveolar destruction.[14,15] Resident and recruited macrophages engulf invading particles and secrete inflammatory mediators and various enzymes.[16–18] The number of T lymphocytes also increases and may contribute to the pathophysiology of lung inflammation.[19,20] The decreased effector function and increased regulatory function of these lymphocytes may account for the reduced host immunity to bacterial infections in COPD patients.[21]

Produced by epithelial and inflammatory cells, cytokines and chemokines play a central role in the inflammatory process. In particular, tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) act as initiator cytokines by inducing the increased production of themselves and the synthesis of other cytokines, chemokines, and adhesion molecules, thereby attracting and activating immune cells at the site of inflammation.[22–24] TNF-α is initially synthesized as a membrane-bound precursor and proteolytically released from cell surfaces.[25] Soluble TNF-α then binds to the TNF receptor and activates the mitogen-activated protein kinase (MAPK) cascade and the nuclear factor-kappa B (NF-κB) pathway after the ligand-bound receptor forms a protein complex with TNF receptor 1-associated death domain protein and TNF receptor-associated factor-2.[26,27] MAPKs are phosphorylated and activated by MAPK kinases, which in turn are activated by MAPK kinase kinases.[28–30] MAPKs directly phosphorylate and activate transcription factors or they phosphorylate other kinases, which in turn activate transcription factors that lead to the expression of response genes; MAPKs also phosphorylate other substrates that are involved in many biological processes, including inflammation.[28,31]

Like TNF-α, IL-1β is initially synthesized as pro-IL-1β, an inactive precursor. Pro-IL-1β is then cleaved inside the cell by a protein complex called the inflammasome, which is composed of apoptosis-associated speck-like protein containing caspase recruitment domain, caspase-1, and a member of the nucleotide-binding oligomerization domain (NOD)-like receptor family.[32–34] Different NOD-like receptor members respond to different signals. One of these members, NOD-like receptor protein-3 (NLRP3), is recruited in response to tissue damage, metabolic stress, and infection.[35,36] Once pro-IL-1β is processed, the mature IL-1β product is secreted and binds to the IL-1 receptor. The ligand-bound receptor forms a complex with myeloid differentiation primary response 88, IL-1 receptor-associated kinase, and TNF receptor-associated factor-6, thereby activating the MAPK cascade and the NF-κB pathway.[37–39] Different mechanisms have been proposed for the activation of the inflammasome, including potassium efflux and the generation of reactive oxygen species, but both hypotheses have been challenged.[40,41] Other researchers have demonstrated the importance of autophagy and the P2X7 receptor in mediating the processing of IL-1β by the inflammasome.[42–44]

There is currently no cure for COPD or effective treatment for severe lung inflammation caused by toxicants, such as fungal toxins and ricin. This review article summarizes current research on lung inflammation following exposure to cigarette smoke, mycotoxins, and ricin. The goal of comparing these studies is to determine whether common pathways exist and to identify potential targets for the future development of therapeutics. Indeed, although these toxicants belong to different classes of chemicals that exhibit a variety of pathological effects, some of the biochemical pathways they activate are identical, including the IL-1β pathway, which is increasingly recognized for its importance in lung inflammation.[45,46] Elucidation of these mechanisms is facilitated by reviewing the research that has been performed on these different toxicants, and such understanding may facilitate the development of therapeutics that would be useful in treating acute and chronic lung inflammation. Effective strategies that block inflammation may ultimately lead to successful treatment of COPD.

Lung inflammation by cigarette smoke

Cigarette smoking is the major risk factor for COPD and has been estimated to account for more than 50% of cases of COPD worldwide.[47] Interestingly, there is no consensus on the mechanisms by which cigarette smoke causes COPD. One reason for this difficulty is the presence of additional environmental factors that may contribute to the development of lung inflammation. These factors include occupational and environmental exposures to dusts and fumes,[48] infections

in early life,[49] genetic predisposition,[50–52] and asthma.[53,54] Another factor is the frequent contamination of tobacco by toxins from other sources and the presence of microbes that activate toll-like receptors.[55,56] Moreover, cigarette smoke contains several thousand distinct compounds,[57] further complicating an understanding of their individual contribution to lung disease. In the gas phase of smoke, these chemicals include acetaldehyde, methane, hydrogen cyanide, nitric acid, acetone, acrolein, ammonia, methanol, hydrogen sulfide, hydrocarbons, gas phase nitrosamines, and carbonyl compounds. In the particulate phase, they include carboxylic acids, phenols, humectants, nicotine, terpenoids, paraffin waxes, tobacco-specific nitrosamines, polycyclic aromatic hydrocarbons, catechols, metals, and other inorganic substances. Many of these chemicals are irritants, suspected carcinogens, and agents that promote inflammation.[58]

Despite these challenges, and in view of the millions of tobacco-related deaths and the accompanying billions of dollars in estimated health care cost each year, extensive research has been conducted to study the biochemical and health effects of cigarette smoking. Exposure to cigarette smoke in vitro induces the release of IL-1β from human airway epithelial cells[59] and chemokines from both epithelial cells and neutrophils.[59,60] However, there are conflicting data on whether macrophages produce a similar inflammatory response in vivo.[61] Components in cigarette smoke also block protein synthesis in macrophages.[62–64]

COPD is thought to be associated with an innate immune response by macrophages, neutrophils, and epithelial cells and an adaptive immune response by lymphocytes. Because lung inflammation persists after smoking cessation, autoimmunity has been proposed as a mechanism that drives disease progression. Th17 cells are a subset of $CD4^+$ T lymphocytes associated with autoimmune conditions, and these cells increase in numbers in COPD patients. Interestingly, levels of regulatory T-cells, which normally control the proliferation of Th17 cells, are also elevated, suggesting that an imbalance of Th17 and regulatory T subsets may be important.[65] However, the presence of autoantibodies remains controversial.[66,67]

In rodents, cigarette smoke causes activation of MAPKs in the lungs,[68] increased numbers of neutrophils, lymphocytes, and macrophages,[20,69] and apoptosis of airway epithelial cells.[70] Pulmonary inflammation by cigarette smoke is dependent on IL-1 receptor/myeloid differentiation primary response 88 signaling,[71] and the release of IL-1β induced by cigarette smoke into the bronchoalveolar lavage fluid is mediated by the P2X7 receptor and the NLRP3-inflammasome.[59,72,73] Blocking the NLRP3-inflammasome by knocking out apoptosis-associated speck-like protein containing caspase recruitment domain, caspase 1, or NLRP3 also reduces neutrophilia, providing evidence that the inflammasome is involved in mediating pulmonary inflammation.[72] Similarly, knocking out the mitochondrial antiviral signaling molecule, which may play a role in the activation of the inflammasome by some agents by regulating autophagy and the mitochondrial production of reactive oxygen species,[74] leads to reduced levels of IL-1β and neutrophilia following exposure to cigarette smoke.[75]

Consistent with data from animal models, smokers have a fourfold increase in the number of macrophages and other leukocytes into the bronchoalveolar lavage fluid; this increase is positively correlated with smoking history.[76] The levels of IL-1β and many biomarkers, such as chemokines, are elevated in the serum of smokers and are believed to play a key role in the development of the chronic inflammation associated with COPD.[77] These mediators are mainly produced by macrophages,[16,18] which also show an impaired ability to clear apoptotic epithelial cells.[70] In contrast, even though cigarette smoke induces the expression of IL-1β by bronchial epithelial cells in vitro,[59] IL-1β and components of the inflammasome are not detected in the bronchial biopsies of COPD patients,[78] suggesting either that the inflammasome may not play a major role in the central airway of certain COPD patients or their levels may fall below detection levels. IL-33, a member of the IL-1 cytokine family, has also been recently found to be associated with COPD.[79,80] Unlike IL-1β, however, IL-33 is processed by neutrophil-derived proteases[81,82] rather than the inflammasome.[83]

The inflammatory response even persists in those who have quit smoking for years,[84] probably as a result of autoimmunity or continued microbial infection.[55,85,86] Effective anti-inflammatory treatment for COPD is currently lacking, in part because macrophages become resistant to the anti-inflammatory effects of corticosteroids as a result of dysregulated NF-κB activity.[87] Intensive research is currently being undertaken to develop potent protease inhibitors in an attempt to improve symptoms.[88,89]

Lung inflammation by mycotoxins

Fungal spores are ubiquitous in the environment. Containing allergens and mycotoxins, these spores are especially hazardous to those living inside damp buildings or to farmers, malt workers, and wood workers whose occupations include handling of moldy materials.[90] Different fungi produce mycotoxins as secondary metabolites, which include various trichothecenes that are synthesized by several species of *Fusarium*, *Myrothecium*, *Trichoderma*, *Trichothecium*, *Cephalosporium*, *Verticimonosporium*, and *Stachybotrys*.[91] Readily absorbed

through the skin, gut, and airways, trichothecenes are chemically stable and are neither degraded by elevated heat nor hydrolyzed in the stomach.[92] One such trichothecene, the T2 toxin, has been used in aerosolized form in biological warfare because of its toxicity, heat stability, and chemical stability.[93]

Trichothecenes cause immunosuppression in lymphocytes[94] and stimulate the production of IL-1β by macrophages in an NLRP3-inflammasome-dependent manner, mediated by the P2X7 receptor.[95,96] In addition, these toxins inhibit protein synthesis by targeting the ribosome, impair mitochondrial function, activate MAPKs, and induce apoptosis in mammalian cells.[92,97–99] They also stimulate the expression of genes that are upregulated in response to other ribosome-damaging agents, including many inflammatory cytokines.[100–105]

Deoxynivalenol, a trichothecene that commonly contaminates cereal grains, inhibits TNF-α signaling,[106] activates MAPKs through a unique MAPK kinase kinase called zipper sterile-alpha-motif kinase (ZAK) (Wong, unpublished data, 2011), and induces cytotoxicity and inflammation synergistically with particulates[107] and lipopolysaccharide[108] to induce cytotoxicity and inflammation. Because similar studies have not been conducted on other trichothecenes, it remains unknown whether these properties are common to other members of this family of compounds.

Following intranasal delivery in animals, mycotoxins are not only localized in the lung but are also distributed to the liver, kidney, and spleen.[105] These toxins elicit recruitment of alveolar macrophages and neutrophils, pulmonary hemorrhage, cytokine production, and damage to multiple organs.[109,110] In fact, it has been reported that toxicity following inhalation of a toxic dose of mycotoxin leads to systemic effects exclusive of lung injury,[111] but the systemic effects of a sublethal dose of mycotoxins were not addressed by these authors. Even when mycotoxins are ingested, they can cause chronic inflammation of the lungs.[112,113] Mycotoxins may also trigger COPD in farm animals.[114] Unfortunately, no effective treatment is currently available for exposure to mycotoxin.[91]

Lung inflammation by ricin

Found in the beans of the castor plant *Ricinus communis*, ricin is a ribosome-inactivating protein that is relatively easy to purify using simple procedures. Although ricin aerosols are not naturally occurring, the inhalation of ricin is the subject of many studies because of its high toxicity and potential to be exploited as an agent of bioterrorism. Ricin is listed as a biological select agent by the Centers of Disease Control and a category B priority pathogen for the study of the biodefense strategic plan of the US National Institutes of Health. In addition, ricin is being engineered as a component of immunotoxins to target and destroy cancer cells.[115,116]

Similar to lung inflammation caused by cigarette smoke and mycotoxins, effective treatment for ricin intoxication is lacking. Ricin is poorly absorbed through intact skin but can readily enter the body by ingestion, injection, or inhalation. In the case of ricin poisoning caused by inhalation, symptoms include fever, dyspnea, tightness in the chest, cough, and nausea.[117,118] Ricin intoxication induces an early massive migration of inflammatory cells (especially neutrophils) to the lungs and causes apoptosis and necrosis of airway epithelial cells.[119] In addition, and unlike cigarette smoke and mycotoxins, ricin causes apoptosis of alveolar macrophages.[119] Severe poisoning following inhalation of ricin causes interstitial pneumonia, alveolar edema, and respiratory failure, leading to death within days.[120] Exposure to a sublethal dose of ricin results in fibrosis and hemorrhage restricted to the lung tissue.[121]

The tissue distribution of ricin following pulmonary delivery in animal studies can be measured by several methods. Using enzyme-linked immunosorbent assay, ricin is localized to the lungs.[122] More sensitive methods, such as protein radiolabeling[123,124] and detection of ricin-specific damage in the ribosomal RNA,[125] show that inhaled ricin is also distributed to the kidney, heart, spleen, and blood. The spread of ricin to extrapulmonary tissues, likely the result of destruction of the barrier function of epithelial cells, may contribute to its systemic effects and lethality.

The lethality of ricin is caused by its ability to kill cells rapidly at low concentrations and induce extensive inflammation. Because ricin inhibits protein synthesis by damaging ribosomes, it causes cells to undergo apoptosis.[126] Similar to cigarette smoke and mycotoxins, ricin activates the NF-κB and MAPK pathways and increases the expression of inflammatory genes in airway epithelial cells[121] and macrophages.[127] Like deoxynivalenol and several other ribosome-damaging agents, including anisomycin, Shiga toxin, and ultraviolet radiation, ricin activates the MAPK cascade through ZAK.[128,129]

In animal studies, ricin causes alveolar macrophages to undergo apoptosis[119] and induces the expression of genes involved with the immune response, inflammation (including cytokine signaling), and wound healing.[125,130,131] Depletion of macrophages from mice prior to administration of pulmonary ricin reduces the expression of pulmonary IL-1β and subsequent inflammatory responses, demonstrating a central

role for both macrophages and IL-1β in the inflammatory process.[132] Similar results were obtained following administration of ricin into lungs of IL-1β-deficient mice.[132]

A causal relationship may exist between the apoptosis of macrophages and the inflammatory response when cells are exposed to ricin. Exposure of murine macrophages in vitro to zVAD, a chemical inhibitor of apoptosis, blocks the expression of inflammatory genes in macrophages,[127] suggesting that caspase activity is required for ricin-mediated gene expression. Because ricin and other inhibitors of protein translation are capable of activating the NLRP3-mediated inflammasome,[41,133] the ability of zVAD to block the production of IL-1β may result from inhibition of caspase-1.

When inhaled, chemicals that are not biologically derived can also lead to lung inflammation. Volatile organic compounds that can be produced from household items, office supplies, and craft materials (such as formaldehyde, benzene, and perchloroethylene) affect the lung by various mechanisms. One of these, toluene diisocyanate, is capable of activating the inflammasome in a mouse model.[134] Asbestos, crystalline silica, alloy particles, and carbon nanotubes can also activate MAPKs[135–139] and the inflammasome.[140–144] Macrophages may play an important role in the inflammatory response to the inhalation of these particulates.[145,146]

Summary

Despite extensive research that has been conducted to study lung inflammation induced by toxicants, effective treatment is lacking. Although cigarette smoke, mycotoxins, and ricin represent different classes of agents, they nevertheless induce similar gene expression profiles, produce a similar list of biomarkers, damage the airway epithelium, and involve macrophages in their pathogenesis. Recent advances in the targeting of macrophages using nanoparticle-based delivery of small interfering RNA[147] or simvastatin have been reported,[148] but the therapeutic value of these strategies has not been tested on lung inflammatory diseases.

The inhaled toxicants described in this review all activate the MAPK cascade, inhibit protein synthesis, and utilize the NLRP3-inflammasome to process IL-1β (Figure 1). Because MAPK and IL-1β are known to play important roles in toxicant-induced lung inflammation, inhibitors of MAPKs and the inflammasome may be effective in blocking the harmful effects of these agents. In recent years, several MAPK inhibitors have been developed to treat many human inflammatory diseases. These agents produce fewer side effects, such as severe infection, compared with therapeutics that directly inhibit cytokines, such as IL-1β.[149] However, many of these inhibitors are either still too toxic or ineffective in clinical settings,[149,150] probably as a result of complex positive and negative feedback from different members of the MAPK cascade and the presence of broad effects on downstream targets. Similarly, although hundreds of potential inhibitors against NF-κB have been identified, their toxicities are well known.[151,152] As a result, MAPK kinase kinases are an attractive therapeutic target because specific members of this family are activated by selective stimuli.[153] As discussed

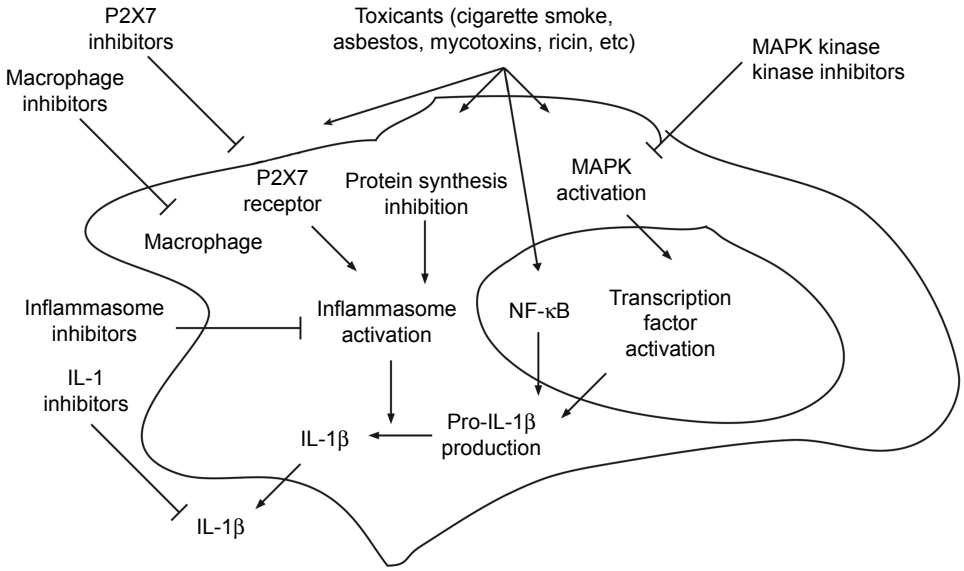

Figure 1 Common pathways involved in the production of IL-1β by inhaled toxicants.
Abbreviations: IL, interleukin; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B.

earlier, ricin acts exclusively through ZAK, a MAPK kinase kinase. Whether cigarette smoke and mycotoxins other than deoxynivalenol have specificity for activation of ZAK is unknown. Kinase profiling has identified small-molecule kinase inhibitors, such as nilotinib and sorafenib, which have strong affinity for ZAK.[154–156] Sorafenib has been shown to inhibit ZAK activity in vitro.[157] These agents have been successfully employed to block the inflammatory effects of ricin.[133] Another novel compound, INNO-406, is a ZAK inhibitor[158] that may prove effective against ZAK-mediated toxicants. Identifying the MAPK kinase kinases that signal lung inflammation in response to cigarette smoke and mycotoxins may facilitate the development of effective therapeutics. For example, researchers have identified transforming growth factor beta-activated kinase-1, another MAPK kinase kinase, which is involved in the cigarette smoke-induced inflammatory response of airway smooth muscle cells in vitro. Further research into the potential role of transforming growth factor beta-activated kinase-1 would be warranted.[159] Similarly, several P2X7 antagonists are currently being explored for the treatment of various inflammatory diseases.[160] The possible role of P2X7 in ricin intoxication has not yet been reported.

Inhalation of toxicants leads to the production of multiple cytokines and other mediators, which in turn produce multiple downstream inflammatory effects. Potential therapeutics is likely to have higher success when directed at upstream, rather than downstream, targets. Like IL-1β, TNF-α is also widely recognized as an initiator cytokine, and both IL-1β and TNF-α are produced after the inhalation of many toxicants (Table 1) and seem to be important in cigarette smoke-induced emphysema and small airway remodeling in mice.[161] However, anti-TNF-α therapy is ineffective in reducing symptoms of COPD in patients,[162] and TNF-α does not seem to play an important role in ricin intoxication.[132] Because several translation inhibitors, including deoxynivalenol, inhibit TNF-α signaling,[106] further research is warranted to investigate whether other ribosome-targeting toxicants share the same mechanism that could explain the lack of involvement of TNF-α.

Table 1 Expression of cytokines and chemokines induced by inhaled toxicants in vivo

Toxicant	Cytokines and chemokines	References
Cigarette smoke	IL-1β, IL-4, IL-5, IL-13, TNF-α, CCL11, CCL17	84, 167, 168
Trichothecene (mycotoxin)	IL-1β, IL-6, TNF-α	105, 169
Ricin	IL-1β, IL-6, TNF-α, CXCL1, CCL2	125, 130
Toluene diisocyanate (VOC)	IL-1β, IL-4, TNF-α	170, 171
Asbestos	IL-1β, IL-6, TNF-α, CCL4, CCL6, CCL10	172, 173
Crystalline silica	IL-1β, IL-6, IL-12, IFN-γ, TNF-α, CXCL1, CXCL2, CCL2	140, 174–176
Nanotubes	IL-1β, IL-6, IL-10, IL-33, TNF-α, CCL2, CCL7, CCL17	177–180

Abbreviations: IL, interleukin; TNF-α, tumor necrosis factor-alpha; VOC, volatile organic compound.

While it is still unknown whether cigarette smoke and other mycotoxins act through ZAK, it is clear that, like ricin, they stimulate the processing of IL-1β using NLRP3. By selective targeting of NLRP3, the production of IL-1β via other members of the inflammasome family may remain normal, thereby reducing the chance of immunosuppression. Several NLRP3 inhibitors, including parthenolide,[163] glyburide,[164] 5-chloro-2-methoxy-*N*-[2-(4-sulfamoylphenyl) ethyl]benzamide,[165] and isoliquiritigenin,[166] are currently under investigation. The selective targeting of toxicant-mediated production of IL-1β by MAPK kinase kinase inhibitors and inhibitors against specific NOD-like receptor members may thus lead to the development of novel therapeutic strategies that may be employed for treatment of lung inflammatory disease.

In conclusion, although acute and chronic lung inflammation is known to contribute to the serious effects of cigarette smoke, mycotoxins, ricin, and other inhaled toxicants, effective anti-inflammatory treatments are lacking. By looking beyond cigarette smoke and reviewing the current understanding of how different toxicants induce the inflammatory response, this paper has identified several promising targets to treat COPD and lung inflammation. In particular, ZAK, P2X7, and NLRP3 are unique targets that foster the production of IL-1β by specific stimuli that inhibits protein translation. Selective targeting may interrupt respiratory inflammation while simultaneously permitting a normal immune response to respiratory tract infections that frequently accompany COPD, thereby reducing the risk of severe pneumonia.

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Disclosure

The authors report no conflicts of interest in this work.

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