ОБЗОР ЛИТЕРАТУРЫ О ВЛИЯНИИ РАЗЛИЧНЫХ ГАЗОВ НА ЛЕГКИЕ ЧЕЛОВЕКА

Рахмонбердиев Муҳаммаджон Ахмаджон ўғли
Бухоро давлат тиббиёт институти
Tel : +998911329697
rahmonberdiyevM@gmail.com

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 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.

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 cells59 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 proteases81,82 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

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 lymphocytes94 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

ИСПОЛЬЗОВАННАЯ ЛИТЕРАТУРА

1. Uktamovich, K. O. CLINICAL AND THERAPEUTIC NUTRITION. // *EUROPEAN JOURNAL OF MODERN MEDICINE AND PRACTICE*, (2023). – P. 42–44.
2. Uktamovich, K. O. Diets of Altered Consistency. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2023). – P. 81–84.
3. Jumaeva A.A., Qodirov O.O`. HYGIENIC BASES OF THE ORGANIZATION OF CHILDREN'S NUTRITION. // CENTRAL ASIAN ACADEMIC JOURNAL OF SCIENTIFIC RESEARCH ISSN: 2181-2489 VOLUME 2 | ISSUE 6 | 2022. – P. 264-268
4. Uktamovich, K. O. Ecological Approaches to Human Nutrition. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2022). - P. 251–254.
5. Uktamovich, K. O. Impact of Ecology on Health. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2022). – P. 255–257.
6. Uktamovich, K. O., & Gafurovna, A. N. NUTRIENT RECOMMENDATIONS AND DIETARY GUIDELINES FOR PRAGNENT WOMEN. // *FAN, TA'LIM VA AMALIYOTNING INTEGRASIYASI*, *3*(6), . (2022). - P. 340-342
7. Uktamovich, K. O. Study of Health Indicators. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2023). – *P*. 91–92.
8. Kadyrov Oybek Uktamovich. Noise as a Harmful Production Factor. // *American Journal of Pediatric Medicine and Health Sciences, (2023).* - *P*.249–251.
9. Kadyrov Oybek Uktamovich. Industrial Poisons, Prevention of Occupational Poisoning. // *American Journal of Pediatric Medicine and Health Sciences, (2023).* – *P*. 246–248.
10. Uktamovich, K. O. Dental Care Rules. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2023). - P. 88–90.
11. Uktamovich, K. O. How to Properly Carebehind the Oral Cavity. // *AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI*, (2023). - P. 86–87.
12. Ibrohimov K. I. Features of Lobor in Agriculture //CENTRAL ASIAN JOURNAL OF MEDICAL AND NATURAL SCIENCES. Voleme. – 2022. – T. 2. – C. 87-91.
13. Ibrohimov KI. The Meal of Students //Indonesian Journal of Education Methods Development. - 2022. - T. 20. - S. 10.21070 / ijemd. v20i. 629-10.21070/ijemd. v20i. 629.

14. Ibrohimov K. I. Health State of Workers of Cotton Enterprises, Structure of Diseases, Influence of Age and Work Experience //AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI. – 2022. – C. 55-59.
15. Nurov.A.S. Current Problems in Providing the Population with Clean Drinking Water // AMERICAN Journal of Pediatric Medicine and Health Sciences. AMERICAN Journal of Pediatric Medicine and Health Sciences, (2023).-P.240-242
16. Nurov.A.S. The Role of Water in the Spread of Infectious and Non-Infectious Diseases // AMERICAN Journal of Pediatric Medicine and Health Sciences. AMERICAN Journal of Pediatric Medicine and Health Sciences, (2023).-P.243-245
17. Nurov.A.S. Existing Problems in Providing the Population With Drinking Water Through Underground Water Sources // AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI, (2023).-P.77-79
18. Nurov.A.S. Cleaning of Open Water Bodies From Waste Water From Production Enterprises // AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI, (2023).-P.80-82
19. Nurov.A.S. Sanitary Protection of Water Bodies and The Process of Natural Cleaning in Water Bodies// AMALIY VA TIBBIYOT FANLARI ILMIY JURNALI, (2023).-P.83-85