



Chemical exposure and alveolar macrophages responses: 'the role of pulmonary defense mechanism in inhalation injuries'

Mahtab Tapak,^{1,2} Somaye Sadeghi,³ Tooba Ghazanfari,^{4,5} Nariman Mosaffa ¹

To cite: Tapak M, Sadeghi S, Ghazanfari T, *et al.* Chemical exposure and alveolar macrophages responses: 'the role of pulmonary defense mechanism in inhalation injuries'. *BMJ Open Respir Res* 2023;**10**:e001589. doi:10.1136/bmjresp-2022-001589

Received 15 December 2022
Accepted 28 April 2023



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¹Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

²Alinasab Hospital, Laboratory Department, Iranian Social Security Organization (ISSO), Tabriz, Iran

³Advanced Therapy Medicinal Product (ATMP) Department, Breast Cancer Research Center, Motamed Cancer Institute, ACECR, Tehran, Iran

⁴Immunoregulation Research Centre, Shahed University, Tehran, Iran

⁵Department of Immunology, Shahed University, Tehran, Iran

Correspondence to
Dr Nariman Mosaffa;
mosaffan@sbmu.ac.ir

ABSTRACT

Epidemiological and clinical studies have indicated an association between particulate matter (PM) exposure and acute and chronic pulmonary inflammation, which may be registered as increased mortality and morbidity. Despite the increasing evidence, the pathophysiology mechanism of these PMs is still not fully characterised. Pulmonary alveolar macrophages (PAMs), as a predominant cell in the lung, play a critically important role in these pathological mechanisms. Toxin exposure triggers events associated with macrophage activation, including oxidative stress, acute damage, tissue disruption, remodelling and fibrosis. Targeting macrophage may potentially be employed to treat these types of lung inflammation without affecting the natural immune response to bacterial infections. Biological toxins, their sources of exposure, physical and other properties, and their effects on the individuals are summarised in this article. Inhaled particulates from air pollution and toxic gases containing chemicals can interact with alveolar epithelial cells and immune cells in the airways. PAMs can sense ambient pollutants and be stimulated, triggering cellular signalling pathways. These cells are highly adaptable and can change their function and phenotype in response to inhaled agents. PAMs also have the ability to polarise and undergo plasticity in response to tissue damage, while maintaining resistance to exposure to inhaled agents.

INTRODUCTION

Undoubtedly, the inhalation of airborne toxicants is a significant international health issue.¹ According to the WHO, air pollution exposure is responsible for over seven million deaths annually throughout the world.² Rising air pollution levels are associated with increased mortality/hospital admissions in individuals suffering from respiratory diseases.³ Toxicity of air pollution includes not only gaseous components, but also particulate matter (PM). PM is the main cause of air pollution exposure's adverse effects that composes of suspended solid fragments and a fluid droplet of biological compounds, organic chemicals, metals, acids and airborne

dust.⁴ The origins of PM typically include road construction, farming, smokestacks and forest fires. However, most particles are formed from the conversion of gaseous precursors, like SO₂ and NO_x, generated by industries, solid fuels, combustion and automobile traffic.¹⁵

The human respiratory tract is continuously challenged by infectious and non-infectious stimuli including PM.⁶ Components of pollutants, stimulate cells through a vast array of recognising mechanisms including Toll-like receptors, and polyaromatic hydrocarbon (PAH) sensing pathways such as the aryl hydrocarbon receptor (AhR) and reactive oxygen species (ROS) sensing pathways.⁷ NF-κB and MAPK pathways as a proinflammatory intracellular signalling cascade are in turn activated.⁸ Exposure to toxins through skin/eye contact, and/or swallowing particularly inhalation in the form of aerosols or dust (in occupation and environments) can lead to severe destruction of the airways, even death, and compromise the respiratory system's function^{9 10}; hence, a coordinated and fast-acting lung immune system is required to control detrimental microbial and environmental pollutants and maintenance of homeostasis.⁶ Understanding and extracting biochemical pathways activated through exposure to various inhaled toxicants, such as ricin, silica and cannabis, may help us identify potential therapeutic targets that are susceptible to anti-inflammatory treatments.

Lung inflammation is caused by various cell types, including alveolar macrophages (AMs), in response to airborne stimuli and inhaled toxins. AMs act as the first line of defence and play a vital role in coordinating the initiation and resolution of the inflammatory response in the lungs.^{11–13} Long-term exposure to external stimulation induces a severe immune response, leading to the release of cytokines



and chemokines and the recruitment of inflammatory cells. Exposure to PM leads to the production of ROS and enzymes, indicating oxidative stress as a common mechanism of damage. Both oxidative stress and inflammation contribute to respiratory diseases by causing alveolar destruction.^{14–16}

At present, there is no definite cure or effective treatment for severe lung inflammation caused by biotoxins. Some studies have summarised the lung inflammation following exposure to cigarette smoke, mycotoxins and ricin.¹¹ However, to fully understand the effective mechanism of biotoxins on lung inflammation, more investigations are needed. The current review aimed to summarise the current state of knowledge regarding biological toxins. Investigating the effects of chemical exposures on the immune system's response through AMs can help find solutions for treating damages caused by toxic exposure. This approach can help identify common pathways, enabling the identification of therapeutic targets for anti-inflammatory treatments. Ultimately, this will lead to the design of effective strategies for successfully treating acute and chronic lung inflammation.

Inhalation toxins

Toxins, as defined in modern terms, are the metabolic products of poisons from bacteria, plants, animals and fungi that can be found in nature or produced through chemical/biotechnological means. Gases and vapours are commonly inhaled substances, while liquids and solids can be inhaled in the form of fine mist, airborne particles or dusts. This may cause irritated lung damage, suffocation or other systemic effects and acute inhalation damage.¹⁰ In this section, the absorption process of toxins, that cause lung damage through inhalation, was summarised.

Diesel exhaust particles

Inadequate combustion of fossil fuel from diesel vehicles leads to generate DE particles (DEP) which is a combination of three gases (NO, CO, NO₂) and DEP.¹⁷ DEP is composed of halogenated aromatic hydrocarbons, PAHs and quinones with active oxidation, metals such as Fe and Ca, and many other organic components.¹⁸ After inhalation, DEP is deposited in the lungs and absorbed by AM and pulmonary epithelial cells.^{19,20}

PAH binds to the cytosolic AhR,²¹ which leads to the induction of cytochrome-P450, a metabolising enzyme that transforms toxicants into intermediates with greater toxicity. This induction results in the generation of excessive ROS and oxidative stress,²² which stimulates the release of CCL2 and CXCL8 by AMs. This, in turn, leads to the recruitment of cytotoxic-T-lymphocytes and neutrophils, with an enhancement in the generation of oxygen-free radicals that intensify the destruction of the AMs and ultimately result in chronic lung disorders.²¹

Ricin

Ricin, derived from the castor bean plant *Ricinus Communis*, is the most toxic phytotoxin and category B agent under the Biological and Toxins Weapons Convention (BTWC). Ricin is a type II protein that can inactivate ribosomes.²² It comprises two subunits: Ricin's A subunit (RTA) and Ricin's B subunit (RTB). RTA, with toxic moiety, cleaves 28S-rRNA and hinders the binding of elongation factor 2, leading to cessation of protein synthesising and triggering apoptosis. RTB, also, with a lectin moiety, transports ricin into cells via glycolipids/glycoproteins.²³ A single RTA can inactivate nearly 1500 ribosomes per minute, preventing the cell from compensating for the loss.²⁴

The first cells to encounter ricin in the pulmonary system are AMs, which attach to the mannosylated B-chain of ricin via a mannose receptor (MR;CD206) on its surface.²⁵ As soon as ricin is up-taken by AMs, they undergo apoptosis, which leads to invocation of inflammatory cells to the lungs.²⁶ Cells undergo mitochondrial changes after exposure to ricin, because of production of ROS, leading to activation of the internal apoptotic pathway or mitochondrial pathway.^{27,28} So, inhalation of aerosolised ricin can lead to acute lung injuries (ALIs) and symptoms resembling acute respiratory distress syndrome (ARDS).²⁹

Cannabis

Cannabis oil extract or other cannabinoids are highly lipophilic molecules taken from marijuana plant (one of the most popularly smoked materials after tobacco).^{30,31} Marijuana smoke contains many suspended particles including phenols, aldehydes, acrolein, benzpyrene, benzanthracene and the major psychoactive ingredient named delta-9-tetrahydrocannabinol (THC) that all are so harmful for pulmonary system.³²

Cannabinoid receptors-1 and 2 (CB1,2) are the main receptors that are connected to cognate cannabinoid, which activate the Gi/o α subunit to inhibit adenylate-cyclase activity. This, in turn, reduces cAMP and Protein Kinase A activity.³³ THC, as a major psychoactive-immunosuppressive ingredient in marijuana, acts via CB2 receptors that expressed on thymus, tonsils and immune cells.³¹ CB1 and CB2 regulate macrophages' activity in different ways. So, ROS, generated by CB1 via the pathway of p38-MAPK, produces proinflammatory cytokines consecutively, whereas CB1-induced ROS are negatively regulated through the activation of Rap1 mediated by CB2.³⁴

Silica

Two forms of silica include: (1) crystalline silica (CS), which is available in substances derived from Earth's crust; and (2) amorphous silica, which is used in semiconductor circuits.³⁵ Industrial workers who are exposed for long durations to excessive inhalation of CS are at an

increased risk of respiratory diseases, which is associated with lung inflammation and fibrosis.³⁶

As the first intrinsic cell in the lung, AMs bind to inhaled CS via collagen-structured macrophage receptor (MARCO) and scavenger receptors (SR)-AI and SR-AII.^{37 38} They undergo phagosome interactions with the endolysosome system and activation of the inflammasome cascade.^{37 38}

AMs that survive after encountering silica migrate out of the pulmonary via either the proximal lymph nodes or mucociliary escalator. However, if they stay in the lung, AMs are recruited to the tissue space and shift to activated interstitial macrophage (IM) that are responsible for pathogenesis.³⁹

If AMs, which have ingested silica particles through scavenger receptors, are not cleared from the lung, then ROS are induced and cause damage to AM lysosomes. This damage results in the leaking of the contents of the lysosome into the cytoplasm, which leads to the formation of a multiprotein complex, called the active inflammasome. This complex then leads to the release of IL-1 β and the recruitment of more inflammatory cells, initiating an inflammatory response that results in lung damage.⁴⁰

Smoke

Elemental carbon components are found in smoke resulting from burning materials such as tobacco.⁴¹ The toxic compounds of smoke include irritants with solubility in water such as CO, HCN, acrylonitrile and Phosgene (which is slightly soluble in water).^{42 43}

Smoke inhalation leads to thermal/chemical damages to cilia and airway epithelial cells and release of proinflammatory cytokines from activated neutrophils, lung capillary endothelial cells and macrophages, and consequently results in the synthesis of ROS and the production of a large amount of NO and finally an inflammatory response.⁴⁴

Hydrogen chloride (HCl) and chlorine

Cl₂ and hydrogen (H₂) gases can combine directly to form HCl, a toxic light yellow gas with harsh odour. Because of its acidity and water solubility, HCl extremely irritates the mucosa of the nose, throat and respiratory tract.^{42 45 46} The characteristic of lung damage caused by HCl and Cl₂ is reactive airways dysfunction syndrome.^{46 47}

Further oxidative damage of Cl₂ and hypochlorous acid to airways occur by recruitment and activation of macrophages, granulocytes, epithelial cells and subsequent induction of iNOS, ROS and a high quantity of fibrinogen, adiponectin, SAP (serum-amyloid-P) and sVCAM-1 (soluble-vascular cell adhesion molecule-1) in bronchoalveolar lavage fluid (BALF) and airway epithelium.⁴⁷⁻⁴⁹

Chlorine exposure can lead to mitochondrial dysfunction, resulting in the excessive production of ROS, which is the main cause of cellular and organ injury, including damage to mitochondrial DNA, the formation of MPT

pore and apoptosis.^{50 51} Myeloperoxidase increases the formation of reactive oxygen mediators and exacerbates chlorine-induced damages. Therefore, MPO is an important therapeutic target for diseases with inflammation manifestations.⁴⁷

Phosgene (carbonyl chloride)

Phosgene (COCl₂) has a sweetish and pleasant odour of mown grass with lipophilic properties.^{52 53} Because of its low water solubility, its reaction rate with mucus layer and irritation in the upper airway is low, while its lipophilic properties cause a rapid inhibition by surfactant nucleophiles.^{52 53} Nonetheless, the absence of quick sign and recognisable odour aggravates its toxicity.⁵⁴ The source of phosgene is chlorinated hydrocarbons combustion (like welding and fires) and the synthesis of solvents (such as degreasers, cleaners).⁵⁵

Once phosgene penetrates to pulmonary, it interacts with surfactant and then nucleophilic groups like amino, hydroxyl, sulfhydryl part of proteins, lipids and nucleic acids are acrylated. This causes the disruption of the surfactants which in turn leads to pulmonary oedema.⁵⁴ Moreover, heterolytic/homolytic segregation of phosgene produces extreme reactive carbamoyl-monochloride-radicals, which are responsible for transformation and impairment of phospholipids and proteins, as well as the increased production of lethal ROS.⁵⁵

Therefore, phosgene evacuates glutathione of lung tissue that is the principal antioxidant for neutralising ROS. Additionally, peroxyxynitrite is biosynthesised from NO and superoxide-radical (O₂^{•-}) by inducible NOS₂ in the lung environment. Overall, peroxyxynitrite and ROS cause caspase cascades activation that eventually result in apoptosis.^{56 57} Oxidative stress triggers release of intracellular molecular chaperones such as high mobility group box-1 (HMGB-1) and heat shock proteins, which causes sterile inflammation through heterolytic and hemolytic mechanisms.⁵⁸

Hydrogen sulfide (H₂S)

H₂S gas with spoiled eggs odour is a toxic environmental pollutant, obtained from waste water treatment, petrochemical, agricultural, industries of natural gas and factories of asphalt and rubber.⁵⁹ Inhalation of H₂S initially irritates the airways, and inhibits oxidative phosphorylation, leading to haemorrhagic pulmonary oedema.⁶⁰ The toxicity mechanism of H₂S is disruption of complex IV of electron transport chain via inhibition of cytochrome-c during aerobic glucose metabolism, which then changes to anaerobic metabolism, causing cellular toxicity via diminished ATP. This, leads to lactate accumulation due to metabolic acidosis.^{61 62} Overall, H₂S toxicity impels oxidative stress and attenuates antioxidant system.⁶³

The levels of antioxidants and inflammatory response are closely linked. Inflammation and oxidative stress are both significant factors that can induce apoptosis, which,

in turn, plays a crucial role in regulating the immune response and contributes to various pathologies.⁶⁴

Excessive exposure to atmospheric H₂S can cause inflammation, oxidative stress and dysfunction of energy metabolism. H₂S in the atmosphere can increase the expression of COX-2 and iNOS, which are downstream signals of NF-κB. This, in turn, stimulates the production of ROS and impairs gene expressions that are involved in energy metabolism.^{63 65}

Ammonia (NH₃)

Ammonia is a colourless gas with a sharp, pungent smell that is transported under pressure at subzero temperatures in a liquid form.⁶⁶ Besides its natural origins, including the decomposition of animal excretes, decay of organic materials, soil and volcanic eruptions, ammonia is also a common agent that is released by industrial processes such as plastic and explosive synthesis and household chemical, fertiliser, refrigerant, cleaning agent.^{66 67} Furthermore, it plays an essential role in PM_{2.5} aerosol constitution via reaction with acid species in the air, that leads to air pollution.^{68 69}

Ammonia induces oxidative stress, the release of [Ca²⁺], cytochrome-c and ROS from mitochondria, as well as increases mRNA levels of glutathione peroxidase, COX-2, iNOS, TNF-α and TGF-β, which are genes related to apoptosis and NF-κB protein levels. As a result, it ultimately induces mitochondrial inflammation and apoptosis.^{70 71} The release of cytochrome-c is accompanied by the formation of large quantities of mitochondrial ROS, which activate caspase proteins and trigger apoptosis.⁷² Taken together, inhalation of NH₃ causes loss of mitochondrial integrity, an increase in oxidative stress, and release of calcium, ROS and cytochrome-c from mitochondria, which in turn induces apoptosis through the intrinsic pathway. Therefore, the mechanism of ammonia toxicity involves the induction of mitochondrial apoptosis and the NF-κB pathway.⁷³

Oxides of nitrogen (NO_x)

The most toxic chemical pollutant found in DE gases, produced from the combustion of fuel, is NO and NO₂. These nitric oxides are non-flammable and range in colour from colourless to brown at room temperature. They also have little solubility in water.⁷⁴

NO_x consists of photochemical oxidants and ozone.⁷⁵ Ozone reaches to an equilibration concentration, depending on solar severity, environment temperature and concentration ratio of NO₂ to NO, in lack or small quantity of volatile organic compounds (VOCs) or CO. Then, NO₂ is converted into O₃ and NO via photolysis, and ozone is used to regenerate a NO₂ molecule. These reactions cause ozone to accumulate.⁷⁶ NO_x in the distal airways changes to nitrous (HNO₂) acids and nitric (HNO₃) that lead to generating free radicals as well as oxidation of protein and peroxidation of plasma membrane lipids.¹⁰

Ozone can react with airway cells membrane such as AMs, alveolar epithelial cells (AECs) and lining fluids of airways and induces oxidative damages. This leads to inflammatory responses and bronchial hyperactivity in humans underlined by a neutrophilic inflammation.⁷⁷ Recruitment of immune cells results in oxidative stress and inflammatory mediators production, for instance cytokines and free arachidonic acid, platelet activating factor and prostaglandin E₂.⁷⁸

Ozone exposure activates innate immune cells such as neutrophils, NK and innate lymphoid type 2 cells, which are involved in inflammatory responses Th1 and Th2.⁷⁹ Exposure to ozone leads to surfactant protein D to be released, which stimulates INF-γ. Also, oxidative stress response induced by ozone can activate NLRP3 inflammasome.⁸⁰ Efferocytosis and phagocytic function of AMs with exposure to ozone is impaired.⁷⁸ Also, it is directly cytotoxic to macrophages.⁸¹

Cyanide (CN)

Hydrogen cyanide (HCN), also known as 'prussic acid' (chemical warfare agents), is a pale blue fluid/gas with a poor bitter almond-like smell which is nearly 35 times more toxic than CO. This toxicant is released from fire and ignition of chemicals or artificial substances, used in construction of synthetic products, extraction of metals, biocides and in chemical laboratories.^{82 83} Because of its small size, HCN is mildly soluble in lipid and can penetrate the extracellular fluid of tissues, through binding to the iron inhibits mitochondrial cytochrome-c oxidase and blocking electron transport.^{42 83}

The main mechanism of HCN's toxicity, after inactivation of cytochrome-c oxidase, is uncoupling mitochondrial oxidative phosphorylation and in turn cellular respiration inhibition, although adequate oxygen is available. As a result, cellular metabolism converses from aerobic to anaerobic.⁸⁴ Energy crisis occurs due to the decrease in ATP production, lactic acidosis and increased ROS formation in mitochondria.⁸⁵

Carbon Monoxide (CO)

Carbon monoxide (CO) is an odourless and colourless gaseous molecule produced by the burning of carbon-containing materials in ignition engines/fireplaces in enclosed areas. It can penetrate the alveolar membrane and has an affinity for iron ions in heme that is 230–300 times greater than that of oxygen, which leads to the formation of carboxyhemoglobin. CO also reacts with cytochrome-c oxidase, cytochrome P-450, soluble guanylate cyclase, inducible nitric oxide synthase and other cellular cytochromes.^{86 87}

By binding to iron A3 in the active site of cytochrome-c oxidase, CO inhibits oxidative phosphorylation and thus reduces ATP production in tissues. Electron transfer continues in other complexes of the electron transport chain and excessive production of ROS continues, leading to oxidative stress and cell damage.^{87 88}



Nitrogen mustard and sulfur mustard

Both sulphur mustard, a yellow-brown oily liquid, and nitrogen mustard (a related analogue), are harmful agents. They cause pulmonary toxicity⁸⁹ and acute/chronic effects which comprise dysfunction of alveolar-epithelial barrier, accumulation of activated AM, oedema, emphysema which progress to fibrosis.^{90 91}

The main cytotoxic effects of mustards are alkylation of DNA and cross-linked nucleophilic sites in DNA, lipids and proteins, which ultimately induce poly ADP-ribose polymerase-1 (PARP-1) pathways for DNA repair.⁹²⁻⁹⁴ PARP-1 overactivation depletes the NAD⁺ reservoir.⁹⁵ This depletion interrupts catabolic processes such as glycolysis, resulting in ATP exhaustion.^{92 94 96} The intense ATP evacuation leads to inhibition of PARP cleavage by caspase-3, and this overactivation results in cellular necrosis PARP resulting in cellular necrosis.⁹⁷

The other cytotoxic mechanism is oxidative stress induced by ROS and antioxidants inactivation. Recruitment of leucocytes to the lung, overexpression of ROS-producing enzymes and mitochondrial deficiency cause massive production of ROS.^{98 99} Overproduction of ROS leads to oxidative damage of cellular DNA, proteins and lipids, which can subsequently be associated with cell death, inflammation and damage to respiratory system.¹⁰⁰

Lung immune response

A pulmonary immune system consists of innate and adaptive system. It comprises non-specific parts that recognise and inactivate external agents, often without causing inflammation. The adaptive immune system includes

both secreted antibodies and T cells. It can be said, the innate and adaptive immunity are interlaced.⁹³

Two main types of lung macrophages based on location, property and function include: (1) AMs, which are in the vicinity of alveoli type I and II epithelial cells via integrins on their surface and are responsible for sampling, responding and clearing pathogens^{101 102} and (2) IMs, reside in the lung interstitium between the blood compartment and alveolar epithelium.¹⁰³

The role of AMs

AMs have a deterministic role in the lung microenvironment that has a relative immunologic benefit and play an important role in defending against organisms that infiltrate the lower respiratory tract, because they are extremely phagocytic and release countless mediators. Keeping the lung alveoli clear, without inducing inflammatory responses that might disrupt gas exchange in the lung, is a critical function of AMs.^{104 105}

AMs in homeostasis condition

AMs are critical for maintenance of lung homeostasis condition, immune defence, surfactant and debris purging, pathogen recognition, onset and elimination of lung inflammation and tissue regeneration.^{12 106-108}

In homeostatic conditions, AMs are kept in a relatively steady state through surface protein interaction (eg, CD200, SIRP α , MARCO, programme death-ligand-1 and CD47) or paracrine factors secreted by IMs and AECs to avoid unnecessary responses to inhaled particles and damage to the lungs.¹⁰⁹ On the other hand, AMs retain

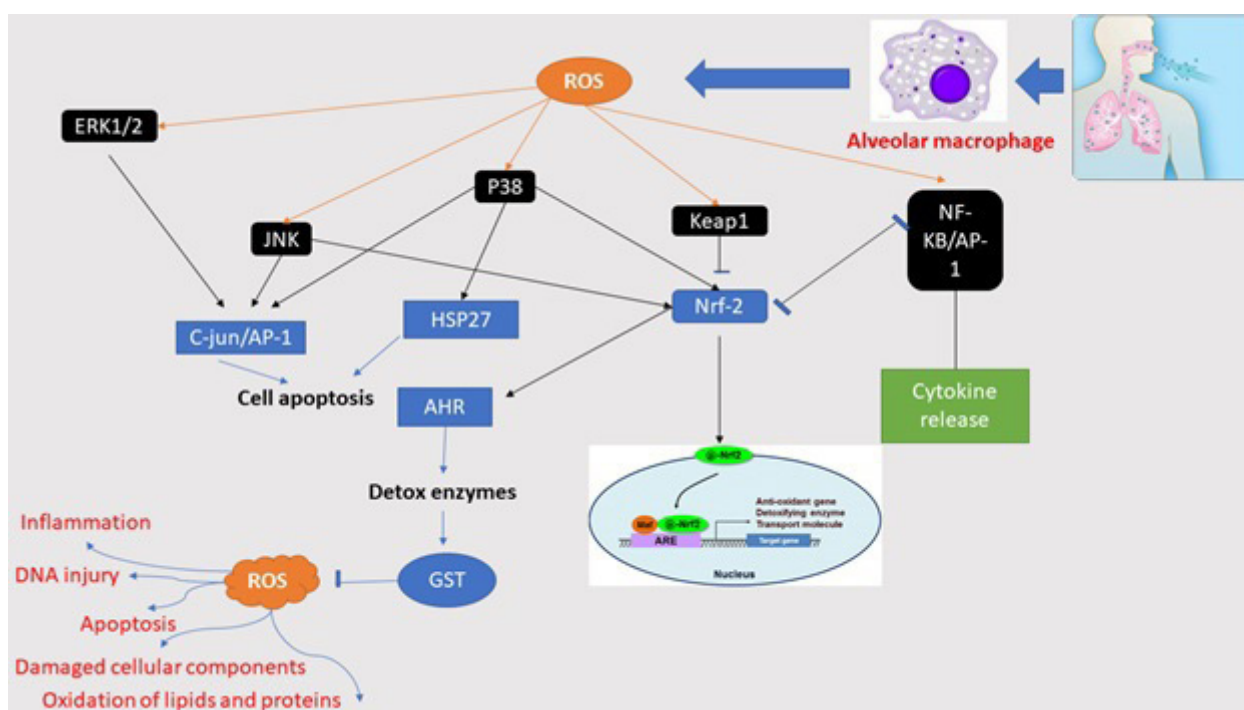


Figure 1 The role of alveolar macrophages response to chemical exposure. ROS, reactive oxygen species.



a high phagocytic activity to clear particulate antigens from the respiratory system.¹¹⁰ Biological activity based on the microenvironment around the macrophage is carried out by two separate subpopulations including M1 and M2.¹¹¹ M1 macrophages produce proinflammatory mediators and ROS that exacerbate lung injury, but M2 phenotypes have an anti-inflammatory effect that inhibits inflammation and initiates wound repair.¹¹²

Role of AMs in pulmonary diseases

Exposure to toxins triggers a set of events associated with macrophage activation, such as oxidative stress, acute injury and fibrotic response to tissue remodelling.¹¹³ This indicates that ROS generation has fundamental role and common mechanism in progression of many inflammatory diseases. While physiological concentrations play regulatory roles in cell growth, cell adhesion to other cells, differentiation, senescence, and apoptosis, excessive concentrations of ROS kill pathogens and are destructive for cells and can lead to inflammatory tissue injury.^{114 115} The main point considered in inflammatory diseases is the prolonged and chronic production of ROS.^{116 117}

After the interaction of inhaled toxins with the lung surfactant, they are deposited on the alveoli, thereby preventing the metabolism of the surfactant. Also, these particles may be ingested by AMs or removed by mucociliary clearance. Prolonged stimulation of inhaled particles, phagocytosed by AMs without suppressing the immune response, causes AMs to be overactivated again and again, so that a variety of cytokines and chemokines are released which recruit inflammatory cells into the lungs, eventually triggering inflammatory response and resulting in acute lung damage or development of chronic lung disease.¹⁰⁵

ARDS is a clinical syndrome characterised by severe inflammatory reactions in the lung, usually is secondary to pneumonia, sepsis and trauma and induced the recruitment of neutrophils and AMs (predominant) into the BALF.¹¹⁸ Commonly, asthma, chronic obstructive pulmonary disease (COPD) and lung fibrosis depend on polarisation of macrophage in the context of M1 and M2, with various functions and metabolic states. In fact, macrophage polarisation shift is considered as a factor of respiratory diseases development.¹¹⁹

Conclusion

One of the most critical tissue-resident macrophages is the pulmonary alveolar macrophages (PAMs) (heterogeneous in size and cytoplasmic contents) due to their pivotal role in the complex mechanisms of host defence. Additionally, the kinetics of AMs in the air-liquid composition of the alveolar cavity need to contribute to the proper filtration of inhaled gases, including toxic components. The defence of macrophages against toxic gases can lead to structural and functional damage to lung. Exposure to PM_{2.5}, profoundly affects human health.

The inhaled particulates in air pollution and toxic gases can interact with AECs and immune cells within the airways stimulated when they sense ambient pollutants, as the constituents trigger cellular signalling pathways (figure 1). PAMs are highly capable of changing their function and phenotype, especially when exposed to inhaled agents. One of their abilities, compared with other resident macrophages in the body, is their power of polarisation and the occurrence of plasticity. This results from tissue damage and, at the same time, the cells' resistance to exposure to inhaled agents.

The effect of inhaling irritant gases depends on the quantity and duration of exposure. Although, the clinical effects correspond to the recognised experimental immunological actions of airborne pollutants, the relative importance of specific immunological actions and different ambient pollutants to clinical pathology remains uncertain. Moreover, ROS can increase the penetrance of the alveolar endothelial cells, and oxidative stress plays a significant role in the pathogenesis of ALI and ARDS. The origin of ROS is intricate, and multiple routes are implicated in its production. Therefore, avoiding the overproduction of ROS and the declined capacity of defence in ALI/ARDS may reveal a novel scope of approaches to therapy for this disease, which despite 50 years of investigation, has not made considerable advances. A profound understanding of the immune system's response can help develop new strategies to decrease the health damage caused by air pollution, such as using supplements, like vitamin D or antioxidants, in potentially susceptible individuals.^{7 120} The emphases on occupational respiratory diseases, which directly affect AMs, and the spread of urbanisation have given rise to a new wave of respiratory disorders. Special focus should be placed on the function of these cells and inhibiting the intensified reactions within them, which disrupt the hemostatic space in the alveolar region. Future studies will also aid in forming government policies to alleviate sources of air pollution with specific immunomodulatory features.

Acknowledgements This study was a part of comprehensive project carried out by the Immunoregulation Research Center of Shahed University.

Contributors MT and NM conceived the idea. All authors participated in designing, reviewing, interpreting and writing. All authors contributed to drafting and finalising the manuscript and approved the final version for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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ORCID iD

Nariman Mosaffa <http://orcid.org/0000-0003-1695-782X>

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