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Review

Effects of atmospheric suspended particulate matter on the immune system

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Abstract: Atmospheric pollution causes enormous damage to public health worldwide resulting in millions of deaths annually, and reducing both life expectancy and quality of life. Suspended particulate matter (SPM) in the air triggers immune system responses, which in turn determines a wide range of diseases based on chronic inflammation. However, many issues regarding the relationship between air pollution and the development and course of pathologies remain unresolved. The present review summarizes the data of domestic and foreign publications regarding the effect of atmospheric SPM on the immune system. The article reveals the effect of SPM on immunocompetent cells and investigates cellular and molecular response mechanisms of the body. The data presented in the review imply the need for further studies of immune system response mechanisms under the impact of atmospheric SPM.

Keywords: suspended particulate matter, immune system, oxidative stress, inflammation.

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Introduction

According to the World Health Organization (WHO), air pollution causes enormous damage to public health worldwide resulting in millions of deaths annually, and reduces life expectancy and quality of life [1]. Suspended particulate matter (SPM) is a heterogeneous mixture of solid particles of different sizes, qualitative traits and quantitative characteristics. The chemical composition of SPM can be represented by nitrates, sulfates, carbon, organic and biological compounds, along with various metals (iron, copper, nickel, zinc, etc.) [2, 3]. The main area of exposure to SPM when inhaling ambient air is the respiratory tract from the nasal passages to the lungs, where direct interaction between particles and cells of the respiratory tract occurs. Microtoxicants in the ambient air activate immune system responses, which, in turn, determines a wide range of diseases with underlying chronic inflammation [4-8]. SPM triggers signaling pathways leading to the activation of a complex response of the immune system, including the participation of various types of cells [9-12]. This field of study is of great interest to researchers. Numerous publications are presented in foreign and, to a lesser extent, Russian scientific journals. They are usually devoted to identifying the response of immunocompetent cells and cytokines to SPM. Our review summarizes ideas about response mechanisms at several hierarchical levels: from cellular to molecular. The interaction of the immune system with thiol-disulfide homeostasis in the formation of a response to air microtoxicants are shown. Abnormalities in subpopulations of immune cells that signal dust particles are described in detail. The features of the immune system's response to different qualitative compositions of SPM are presented.

Impact of SPM on immunocompetent cells

Airway epithelial cells (ECs) are the most important target for inhaled SPM because they are the first barrier to xenobiotics, capable of releasing various mediators [13]. In response to the detection of microtoxicants, human bronchial epithelial cells produce a variety of cytokines, chemokines, and other signaling molecules, including interleukins (IL-1α, IL-1β, IL-6, IL-8) and granulocyte-macrophage colony-stimulating factor (GM-CSF), which contribute to the activation of airway inflammation (*Figure 1*) [9, 14]. IL-6 content are of particular importance when exposed to SPM. Increased SPM contamination has been shown to result in a concomitant increase in IL-6 levels in airway epithelial cells, macrophages and bronchoalveolar lavage fluid, as well as in the systemic circulation [9, 15, 16]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) promotes the maturation of myeloid dendritic cells (DCs) and the differentiation of monocytes into DCs, and is required for the survival of granulocytes [9, 17]. The functions of these cells are cross-linked: ECs can control DC function by secreting cytokines that stimulate a Th2 response [18].

Dendritic cells of the human respiratory tract form complex adaptive immune responses when interacting with SPM. DCs form the link between innate and adaptive immunity by recognizing antigens through the expression of innate receptors, such as toll-like receptors (TLRs). Next, DCs process fragments of these antigens for T lymphocytes, which causes an effector immune response. Dendritic cells also express a number of co-stimulatory molecules and secrete soluble mediators. The nature of the lymphocyte response (Th1 or Th2) largely depends on the quantity of peptides, co-stimulatory molecules and cytokines that DCs present to T lymphocytes [9, 19, 20].

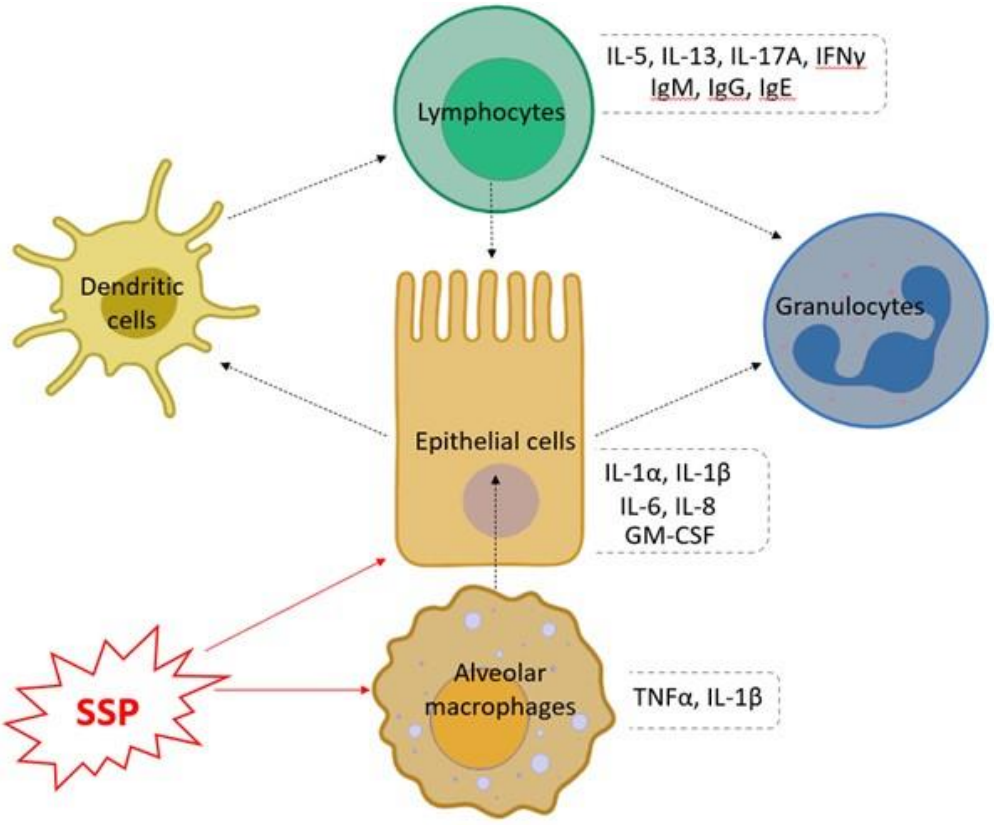

Figure 1. Effects of SPM on immunocompetent cells.

The SPM influences antigen-presenting cells and increases antigen immunogenicity. Numerous studies have shown that stimulation of SPM accelerates maturation of DCs, as well as increases CD80+ expression and proinflammatory cytokine release [9, 21, 22]. Active maturation of DCs triggers the T lymphocyte response and enhances cytokine production by T-cells [21, 23]. Under the impact of SPM, DCs trigger CD4+ and CD8+ cell responses characterized by increased production of IFN-γ and IL-17A [9, 22]. Furthermore, amount of natural killer cells in peripheral blood decreases [11, 25]. B lymphocytes also represent an important link in forming the immune response to SPM exposure. There are data showing the relationship between the action of SPM and a decrease in the production of immunoglobulin (Ig)A and an increase in the levels of IgM, IgG and IgE [9, 26-28].

Alveolar macrophages (AMs) are the major immune cell population of the airways. One of their main functions is the phagocytosis of SPM and certain types of microorganisms in the lungs, which is the initial stage of their removal. AMs are also capable of phagocytosing carbon-containing particles [9, 29, 30]. When exposed to SPM, AMs experience a decrease in motility and mucociliary clearance, which leads to the development of ROS-mediated oxidative stress, especially during chronic inhalation of microparticles [9, 31]. Exposure to SPM may induce a Th2-type immune response and reduce the phagocytic ability of AMs, which may be associated with TLR2 and TLR4 [11]. SPM can stimulate the production of proinflammatory cytokines by macrophages [9, 14, 31]. Cytokines, especially TNF-α and IL-1β produced by macrophages, can also stimulate epithelial cells and trigger an enhanced response to microtoxicants.

Exposure to SPM leads to a significant increase in the numbers of neutrophils and eosinophils [32]. Eosinophils are effector cells that secrete cytokines involved in the activation of Th2-type T helper cells. Currently, the effect of SPM on eosinophilic inflammation is poorly studied [9]. However, there is evidence that in patients with respiratory diseases, oxidative stress induced by SPM can cause eosinophilic airway inflammation, enhance atopic allergic sensitization and increase susceptibility to infections [33, 34]. Neutrophils are particularly important granulocytes when considering the effects of SPM on the body, as they are the most abundant leukocyte cells in the blood and are rapidly transported to sites of inflammation. Published studies confirmed that when exposed to microtoxicants, neutrophils infiltrate into the bronchial mucosa activating and increasing the production of IL-8 [35]. At the same time, neutrophils express the enzymes NADPH oxidase and myeloperoxidase, which produce superoxide anions and hypochlorite anions [36].

The role of oxidative stress induced by SPM in the formation of the immune response

SPM can penetrate not only into the respiratory tract and lungs, but also into the circulatory system. The main mechanism of this action is the induction of oxidative stress in cells. Mechanisms of oxidative stress may involve the formation of oxidants on the surface of SPM, the release of metals or organic components from particles and the initiation of an inflammatory response. Activation of epithelial cells and resident macrophages, recruitment and activation of neutrophils, eosinophils, monocytes and lymphocytes are also mechanisms of response to the effects of SPM [37]. SPMs are known to stimulate cells to produce proinflammatory

cytokines and chemokines. The ability of T-cells to produce a specific set of cytokines and differentiate T-cells is programmed by transcription factors. E.g., the main factors for Th1 and Th2 are T-bet and Runx3, and GATA3, respectively. SPM causes airway inflammation by regulating the expression of transcription factors. Exposure to SPM has been shown to disrupt the balance between Th1/Th2 cells, with a decrease in the percentage of Th1 cells due to the suppression of Runx3 and an increase in the number of Th2 cells due to the activation of GATA3 expression [33, 38, 39]. Therefore, exposure to SPM can trigger a cascade of immune dysfunction, which can lead to the development or progression of SPM-related pathologies [8, 9].

Oxidative stress products trigger the mitogen-activated protein kinase (MAPK) signaling cascade that leads to the activation of the redox-sensitive transcription factor (NF-κB), which regulates the expression of many proinflammatory genes, including cytokine genes and their receptors (*Figure 2*) [40]. Moreover, SPM is capable of generating reactive oxygen species (ROS), promoting oxidative stress and reducing the level of endogenous antioxidants. Organic compounds present in SPM can donate electrons to O2 molecules to form superoxide free radicals. SPM metals similarly donate electrons to form superoxide and hydrogen peroxide and can directly deplete endogenous thiol antioxidants [8, 9, 41, 42]. Oxidative stress stimulates the generation of intracellular signals that can induce inflammatory reactions, including the production of interleukins [9]. Exposure to microtoxicants leads to the synthesis of IL-1β, IL-6 and tumor necrosis factor (TNF-α) by T lymphocytes. Activation of this pathway also determines the production of C-reactive protein and serum amyloid A [7, 32, 43, 44]. In addition to activating proinflammatory pathways, ROS can cause damage to cellular proteins. The inflammatory response to airborne microtoxicants is also driven by mechanisms of alteration and damage to both microRNA and DNA, which may involve various genes and processes [45].

The development of oxidative stress and ROS production leads to mitochondrial damage, which is characterized by three key processes: damage to mitochondrial DNA (mtDNA), protein oxidation and activation of lipid peroxidation processes. SPM can cause a decrease in mitochondrial membrane potential and activate mitochondria-mediated apoptosis [8, 46-49]. MtDNA and ROS are involved in the transcriptional regulation of immune cells. During the development of SPM-mediated mitochondrial dysfunction, molecular patterns associated with damage are released into the cytoplasm and detected by pattern recognition receptors, which triggers the formation of an immune response. Signaling mechanisms are generated in immune cells leading to the activation of NF-κB, MAPK and interferon regulatory factor, which control the expression of proinflammatory chemokines and cytokines [8, 50-52].

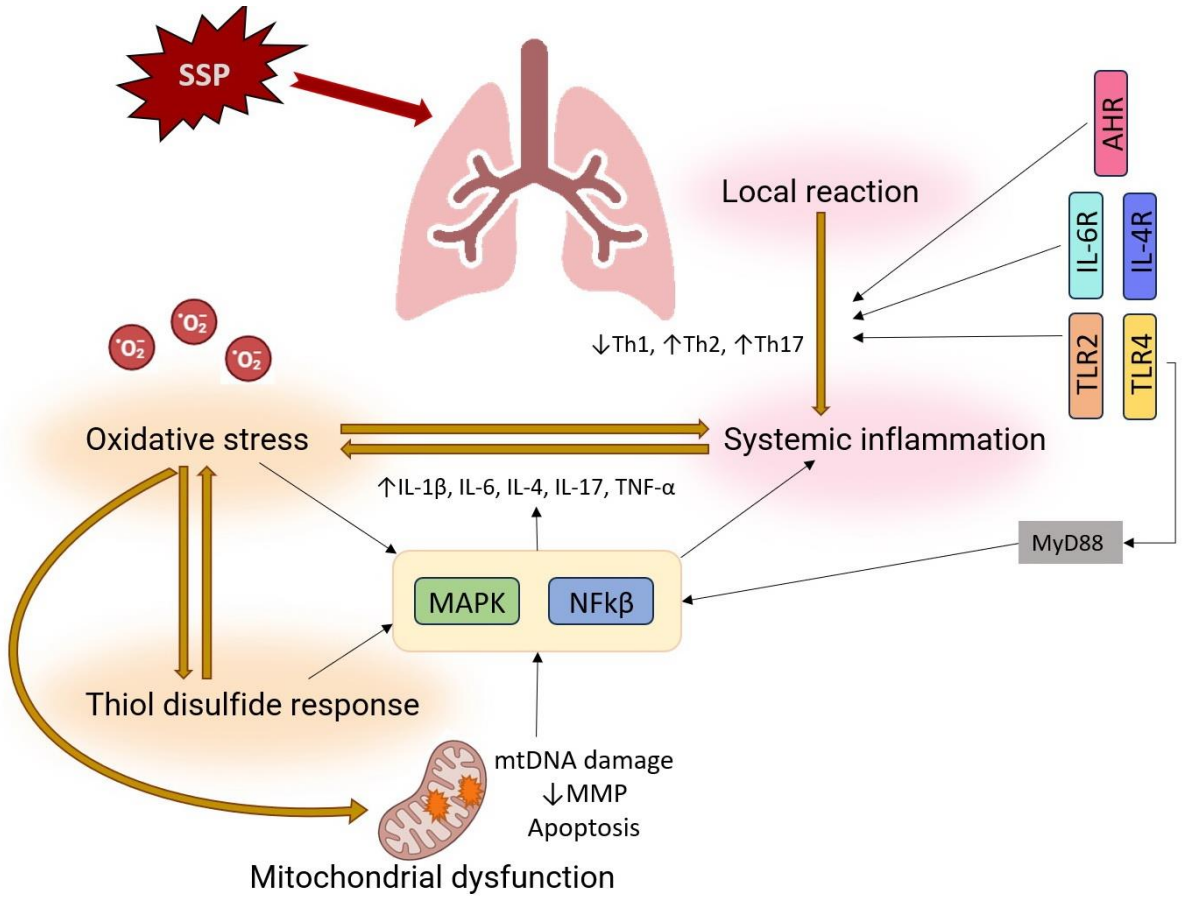

Figure 2. Mechanisms of immune response during exposure to SPM.

The maintenance of thiol-disulfide homeostasis ensured by the activity of the thioredoxin and glutathione systems, plays a significant role in the regulation of the redox balance in cells and in protecting the body from oxidative stress. Reversible post-translational disulfide modifications of proteins and their subsequent reduction by thiol-disulfide-dependent antioxidant enzymes constitute the most significant mechanism of intracellular redox signaling. The thioredoxin system plays an important role in immune responses and regulation of inflammation. Under stress conditions, thioredoxin protects immune cells from oxidative stress and apoptosis. The thioredoxin system ensures the restoration of disulfide bonds in proteins damaged by oxidation. Another example of redox regulation is the activation of the transcription factor NF-κB by cytosolic thioredoxin, which regulates the immune response, apoptosis and the cell cycle [53-57].

The glutathione system maintains a reduced intracellular environment ensuring the formation of the correct tertiary structure of proteins and regulating key intracellular processes, including the activity of the thioredoxin system. As an antioxidant, glutathione directly neutralizes ROS generated by atmospheric SPM and inhibits lipid peroxidation. It is involved in the detoxification of hydrogen peroxide by various glutathione peroxidases, helping to protect cell membranes from oxidative stress. Glutathione activates a number of signaling pathways, including those associated with the transcription factor NF-κB and MAPKs [53-56].

Immune response mechanisms during exposure to SPM

Stimulation of cells by SPM involves a variety of mechanisms including TLRs, ROS, and polycyclic aromatic hydrocarbon (PAH) pathways, such as the aryl hydrocarbon receptor. These, in turn, activate proinflammatory intracellular signaling cascades, such as nuclear factor (NF-κB) and MAPK pathways [9, 58].

Production of ROS by SPM and formation of oxidative stress induce transmission of NF-κB and MAPK signals. Although both signaling pathways are activated upon exposure to SPM, the NF-κB pathway has been found to play a crucial role [57, 59-62]. Active oxygen species can directly affect cellular calcium channels, thereby disrupting the transmission of intracellular ionic signals. Intracellular Ca2+ is an important signaling system that can affect the NF-κB pathway [9, 63]. Lung oxidant/antioxidant imbalance also leads to NF-κB activation [62]. SPM induces nuclear translocation of NF-κB and production of inflammatory cytokines in human bronchial epithelial cells [61, 64].

TLRs play a significant role in the activation of inflammatory pathways mediated by exposure to SPM [32, 61, 65]. A dose-dependent increase in TLR2, TLR4, and MyD88 levels occurs under the impact of microtoxicants, leading to the development of systemic inflammation [32, 66-71]. TLR4 also activates the TIR base containing adaptor-inducing interferon-β (TRIF) located on the endosome [70]. There is evidence that upon exposure to SPM, activation of TLR4 triggers a signal transduction cascade and activates NF-κB phosphorylation, which leads to increased expression of proinflammatory cytokines, such as TNF-α, IL-6 and IL-1β [72]. Thus, TLR2 and TLR4 play a key role in the development of the inflammatory process when exposed to SPM. Once a TLR binds to a ligand, molecular adapters, including MyD88, trigger a cascade of signaling reactions [32, 61, 73].

SPM influences the release of proinflammatory cytokines, which is regulated by aryl hydrocarbon receptor (AHR) signaling [9, 74, 75]. In addition to the activation of transcription enzymes, AHRs are associated with the differentiation of Th17 lymphocytes [76, 77]. AHR is expressed in various T-cells: maximally in Th17 cells and minimally in naïve Th0 cells [77]. AHR is critical for the balance of TReg7 and Th17 cells. The degree and duration of AHR activation changes the balance between these effector and regulatory responses. Th17 cells produce IL-17 responsible for the development of inflammation when exposed to AHR [77-79].

Important participants in the cytokine regulation under the influence of SPM are IL-4 and IL-6. It has been shown that both short-term and long-term exposures to SPM lead to a dose-dependent increase in IL-6 production [14, 53, 80-82]. Under the influence of SPM, the increase in IL-6 expression is regulated by the TLR2 and TLR4/NADPH oxidase/ROS/NF-κB signaling pathways. We emphasize that activation of the NF-κB pathway is the key process initiating the cascade of reactions [54, 67, 68]. There is evidence that in patients with COPD, SPM of micro-sized fractions contributes to the modulation of the IL-6 signaling pathway in the direction of conventional signal transduction to T helper blood cells to regulate the inflammatory process and compensate for apoptotic changes [53]. Exposure to air microtoxicants also leads to a significant increase in IL-4 levels [83]. An experimental study on mice showed an increase in IL-4 production in response to exposure to SPM in bronchial asthma [84]. Another study showed that as COPD worsened under conditions of high anthropogenic load, circulating T helper cells experienced a decrease in the expression of IL-4R and an increase in the synthesis of IL-6R, thereby indicating inhibition of the anti-inflammatory activity of IL-4 and activation of the anti-inflammatory and anti-apoptotic effects of IL-6 on these cells [53].

Effect of qualitative SPM composition on the immune response

The formation of the response is influenced by various components of SPM, including adsorbed metals, and organic substances such as PAHs (benzo[α]pyrene, benzo[β]fluoranthene, pyrene), PAH-like compounds, quinolines, etc., which may cause oxidative stress.

Binding of PAH ligand triggers nuclear translocation and induction of xenobiotic metabolic enzymes, such as cytochrome P450 genes (CYP1A1, CYP1B1, CYP5), which in turn produce more cytotoxic and genotoxic products [65]. When exposed to PAHs, inflammasome activation occurs through the aryl hydrocarbon receptor pathway. Cells have a specific mechanism (AHR) for the perception of PAHs that is a cytosolic receptor sensitive to environmental factors [9, 77, 85].

Metals adsorbed on SPM, when interacting with enzymes expressed by neutrophils (NADPH oxidase, myeloperoxidase), are capable of catalyzing a further redox cycle and causing oxidative damage [9]. There is evidence that heavy metal-rich SPM can stimulate Th2 and Th17 inflammation, which is accompanied by airway hyperresponsiveness and the release of cytokines (IL-5, IL-13, IFN-γ and IL-17A) [86].

SPM may contain lipopolysaccharides (LPS) and fungal spores, which are natural ligands of TLRs, as well as oxidized phospholipids and nucleic acids that act as alternative TLR agonists [9, 19]. LPS stimulate cells through TLR4; however, LPS can also stimulate airway epithelial cells through TLR2 [9, 65, 87]. Moreover, the ratio

of these two pathways varies depending on different cell types and size ranges, as well as on the qualitative composition of SPM [9, 65]. Hence, studying the composition of SPM in different regions is a key issue in examining the impact of airborne SPM on human health.

Conclusion

Hence, immunological responses associated with exposure to SPM are considered to be the result of a synergistic effect of systemic and local inflammation. Under the influence of SPM, a complex of cellular and molecular processes is triggered, causing the launch of specific signaling pathways that determine the outcome of the formation of environmentally dependent pathology. Despite the available evidence, some response mechanisms remain poorly understood. The immune response may depend on the qualitative, quantitative and dimensional nature of the microtoxicants, the physiological state of the body and the duration of exposure. Therefore, studying the parameters of the SPM of specific zones, their impact on the human body, and identifying subtle cellular mechanisms can help in the development of new strategies for the prevention of environmentally dependent pathologies.

Conflict of interest

The authors declare no conflicts of interest.

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