

## OCCUPATIONAL MINERAL DUST INDUCED TOXICITY AND CYTOKINES

İlker ATEŞ

Ankara University, Faculty of Pharmacy, Department of Toxicology, 06100, Tandogan, Ankara, TURKEY

### Abstract

*Mineral dusts can be produced naturally by wind erosion or by human activities such as mining or land use for agriculture. Some mineral dusts such as silica, coal and asbestos can lead to adverse respiratory health effects. The inhalation of these dusts can cause several different diseases like silicosis, coal workers' pneumoconiosis, (CWP) asbestosis and lung cancer. The pathogenesis of fibrotic lung diseases involve activation of inflammatory cells, fibroblast cell proliferation and the enhanced synthesis and/or breakdown of extracellular matrix components. Cytokines, chemokines, and growth factors play a crucial role in the onset, progression and termination of these reactions. Cytokines are playing role in inflammation and immune response, that are important mediators of the toxic effects in humans mineral dusts exposure. Existence of persistent stimulus and chronic release of cytokines may result in autoimmune and inflammatory diseases such as silicosis and CWP. Polymorphisms in cytokine genes have been reported to contribute with the inflammatory diseases. Epidemiological studies have pointed out that single nucleotide polymorphisms (SNPs) occurring in cytokine genes are associated with chronic inflammatory or immune-mediated diseases*

**Key words:** Mineral dusts, Cytokines, Cytokine gene polymorphisms

### Mesleki Mineral Toz Toksisitesi ve Sitokinler

*Mineral tozlar, maden veya tarım alanlarında insan aktiviteleri ile veya toz erozyonu ile doğal olarak oluşurlar. Silika, kömür ve asbest tozları solunum ile ilgili çeşitli zıt etkiler oluştururlar. Bu tozların solunması ile silikozis, kömür işçileri pnömokonyozu (KİP), asbestozis ve akciğer kanseri gibi hastalıklar meydana gelmektedir. Fibrotik akciğer hastalıklarının temelinde inflamasyon hücrelerinin aktivasyonu, fibroblast hücre çoğalması ile ekstraselüler matriksin aşırı sentezi ve/veya parçalanması yatmaktadır. Bu reaksiyonların başlaması, gelişimi ve sonlandırılmasında sitokinler, kemokinler ve büyüme hücreleri rol almaktadırlar. Sitokinler inflamasyon ve immün cevapta rol oynarlar ayrıca insanlarda mineral toz maruziyetinin toksik etkilerinde önemli araçlardır. Uyarının devamlılığı ve sitokinlerin kronik salınımı ile silikozis veya KİP gibi inflamatuvar hastalıklar ile otoimmün rahatsızlıklar oluşmaktadır. Sitokin genlerindeki polimorfizmlerin inflamatuvar hastalıklarla ilişkili olduğu rapor edilirken, yapılan epidemiyolojik çalışmalar ile sitokin genlerinde oluşan tek nükleotid polimorfizmlerinin kronik inflamatuvar hastalıklar ve immün aracılı hastalıklar ile ilişkileri net olarak gösterilmiştir.*

**Anahtar kelimeler:** Mineral tozlar, Sitokinler, Sitokin gen polimorfizmleri

\* **Correspondence:** Phone : +903122033121 ; Fax : +903122131081  
E-mail: iates@pharmacy.ankara.edu.tr

## Occurrence and Composition of Mineral Dusts

The earth's surface is covered by approximately 29% land area. Most of this surface area consists of soils, whose composition is changing over time. Soil is a mixture of organic and inorganic material and thus can contain a lot of mineral particles (1). Soil dust can be composed of minerals like feldspars, quartz, phyllosilicates in various crystalline forms, carbonates, sulfates, phosphates, salts, heavy minerals like pyroxenes and also special minerals with regard to human health like asbestos and erionite. But globally, the main constituents of mineral dust are clay minerals and quartz (2).

Mineral dusts can be produced naturally by wind erosion or by human activities such as mining or land use for agriculture. And those that originated naturally from the land surface is the major section. Mineral particles of atmospheric dust can be of distinct size range. Particles with the size of 500-1000  $\mu\text{m}$  get dislodged from the soil surface, but only with an aerodynamic diameter less than 75  $\mu\text{m}$  they will get suspended in the atmosphere and follow air currents (1). The median size of the far travelled dust is even smaller, around 2  $\mu\text{m}$  (3). Hence soil dust also includes so-called nanoparticles. The term nanoparticle is used for particles in the size range of 1- 100 nm which makes their possible reaction potential unclear and unexpected reactions may be caused (4). The atmospheric dust loading has been increasing over the last years due to global warming, increasing desertification, and especially human activities (5).

## Health Risks of Mineral Dusts

Some minerals in the atmospheric dust cause health problems for humans. Silicates represent the soil minerals with the highest health risks (1). Atmospheric soil dust of crystalline silica and coal, asbestos and erionite (a fibrous sodium-rich zeolite) can lead to adverse respiratory health effects. Silica, coal and asbestos have unique toxic features and almost no other mineral can be compared to them (6-8). Other minerals like metal oxides, talc, kaolinite, smectites and mica can also do some harm, but only if the exposure is for a certain time period and a certain intensity (9). Best known minerals with regard to human health effects are silica, coal, asbestos and erionite.

Mineral dusts can affect humans by several ways of action. Dust particles get in or on the human body especially by inhalation, or ingestion and touching. While some mineral dust is toxic by itself, other dust particles can carry toxic substances, which get in the human body together (1). Humans get exposed to mineral dust at several places, mostly depending on the origin of the mineral dust. People who live or work close to one of the big dust source regions, agricultural operations zones, construction activity zones or mines are at higher risk of health effects of mineral dust. Mostly affected are therefore agriculture workers, construction workers and miners. The health risk of inhaled mineral dust depends on the exposure level, the duration of the exposure, the frequency of the exposure and the chemical and mineralogical composition of an inhaled particle (1,5). Inhaled mineral dust with an aerodynamic diameter bigger than 10  $\mu\text{m}$ , stops in the upper respiratory tract where the particles get trapped in the mucous lining of the nasopharyngeal tract. They are normally of an only small health concern, unless the particles are of toxic mineralogy. If the dust particles have an aerodynamic diameter smaller than 10  $\mu\text{m}$ , they can penetrate more deeply into the lung passages to the tracheobronchial regions, where they also get trapped in a layer of mucus (9). Particles  $\leq 4.0 \mu\text{m}$  are defined as respirable dust and those particles are small enough to even reach the gas-exchange region of the lung, the alveoli (10). Depending on several factors like shape, size, chemical composition, surface state of the particle, length of exposure and certain lung functions different body responses can be triggered (5,8). The inhalation of mineral dusts can lead to several different diseases, some severer ones are silicosis, fibrosis, lung cancer and cancer of the pleura (serous membrane that surrounds the lung) (10).

## Mechanisms of Toxicity

Figure 1 shows the fate of inhaled mineral dust particles in the human body. Foreign substances in the human body lead to the activation of macrophages, in the case of particles in the alveoli, to the activation of alveolar macrophages (mononuclear phagocytes in the lung alveoli) (Fig.1, 1). The activated macrophages ingest the particles. As they contain lysosomes with acidic pH and digestive enzymes, they can degrade and clear the particles (Fig.1, 2). They also release chemicals (Fig.1, 3) to activate other macrophages (Fig.1, 4). When alveolar macrophages eventually die (Fig.1, 5), they release their contents, to recruit new macrophages (Fig.1, 6). Those then again reingest by the dying macrophages released particles. This cycle of cell death and newly recruited cells in the alveoli can lead to increased inflammation (11).

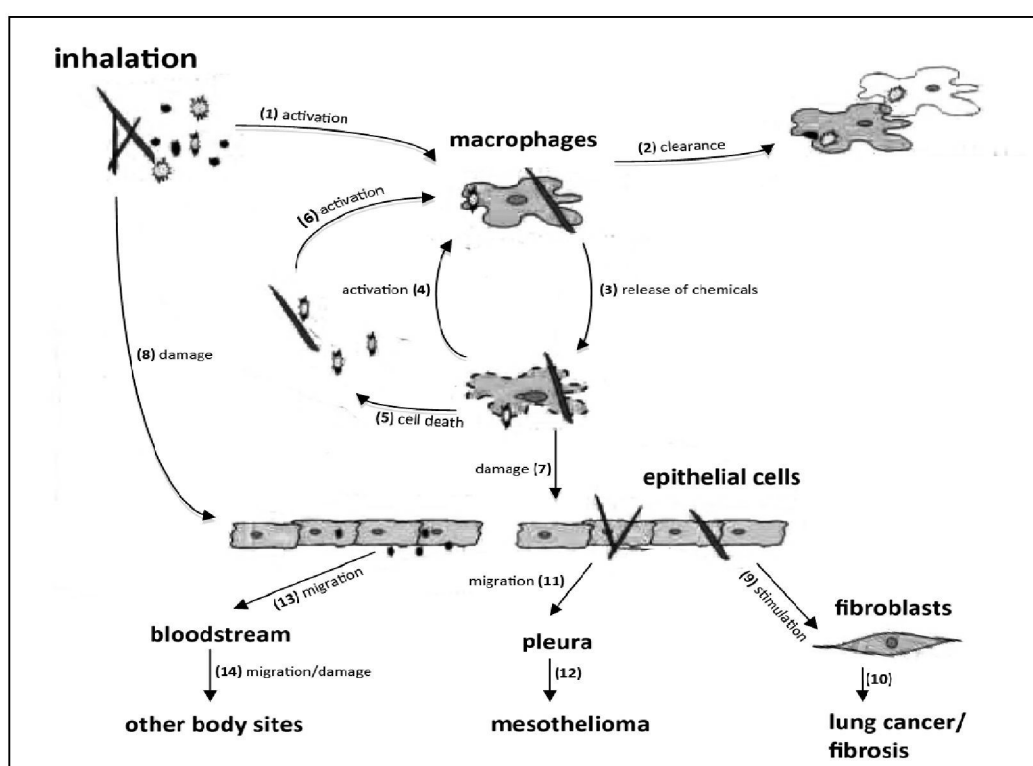


Figure 1. The fate of inhaled mineral dust particles (12).

The cytokines, growth factors, and reactive oxygen species (ROS), which are released by the dying macrophages (Fig.1, 7), can directly damage the cells in the alveoli. Not all of the particles in the alveoli get degraded by the macrophages or dissolved, but some remain as free mineral particles in the alveoli. While some of the remaining mineral particles induce no harm, others can damage the epithelial cells (Fig.1, 8) and by this stimulate fibroblastic cells (Fig.1, 9). Fibroblastic cells can lead to the deposition of a protein called collagen. If those processes go on for some time, it might result in the development of lung cancer or fibrosis (Fig.1, 10). The mineral fibers can damage the surrounding cells and macrophages and they are even able to cause mesothelioma (Fig.1, 12), a fatal neoplasia (abnormal proliferation of cells) of pleural mesothelial cells (membrane that covers the lung), because they may migrate to the pleura

(Fig.1, 11) (8,13). The nanoparticles are able to migrate through the alveolar membrane and get into the interstitial lung tissue. They can remain there or migrate further on, to the lymphatic system. Normally, most of those particles get filtered in the lymph nodes and remain there. Still some get via the lymph into the bloodstream (Fig.1, 13). On this way they can get away from the lung, reach other organs (Fig.1, 14) and possibly cause some harm at other sites in the body than the lung (8,13).

Silicosis, asbestosis and coal workers' pneumoconiosis (CWP) are the best known diseases caused by the mineral dusts.

## Mineral Dusts-Induced Fibrotic Lung Diseases

### a) *Silicosis*

Silicosis, the most ancient recognized occupational disease, is caused exclusively by exposure to crystalline silica (14). However, silicosis occurs frequently even in developed countries, particularly in certain occupations such as mining, sandblasting, surface drilling, stone cutting, construction, pottery making, silica flour mill operations, and other occupations in which silica dust exposures occur (15). Lung fibrosis and pulmonary changes associated with environmental silica and mixed dust exposures have been observed in the lungs of farm animals and humans. Exposure to crystalline silica can result in adverse pulmonary responses such as acute, accelerated, chronic and conglomerate silicosis (16). In addition, silica exposure may also be associated with systemic and autoimmune diseases such as scleroderma, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), nephropathy, proliferative glomerulonephritis (17), tuberculosis and lung cancer (18,19).

### b) *Asbestosis*

Asbestos is the general industrial term encompassing six different natural fibrous silicates. Amosite, crocidolite, tremolite, anthophyllite and actinolite all belong to the amphibole mineral group, while chrysotile is a serpentine. These minerals were exploited largely in the past century in industrial applications because of their versatile and unique properties. Nowadays, asbestos is associated with its potency to cause asbestosis, a debilitating and often fatal lung disease, and malignancies such as lung cancer and pleural mesothelioma, which may appear several decades after exposure.

Asbestos refinement and use is being restricted progressively or banned by several countries, including the entire European Union, which banned asbestos use in 2005. Conversely, in several developing countries, asbestos is still widely produced and used (20). Chronic inhalation of asbestos can lead to asbestosis, a degenerative fibrosis of the lung, mesothelioma, a cancerous tumor of the lung lining or pleural cavity or lung cancer (5). All asbestos minerals contain iron ions, hence the fibers can also release substances like reactive iron, which may trigger free-radical production. Those radical can lead to the damage of the DNA (8,9).

### c) *Coal Workers' Pneumoconiosis (CWP)*

Coal workers' pneumoconiosis (CWP) is an occupational lung disease characterized by fibrotic nodular lesions that result from the inhalation of coal. The severity of the disease is related to the total dose and intensity of dust exposure. Coal is a fossil fuel mine throughout the world. The generation of coal mine dust during underground coal mining is the most significant source of coal dust exposure. There are two basic types of coal mining operations, surface mining and underground mining, producing distinctively different exposure variables and disease entities. Underground coal miners are at greater risk of developing CWP than strip or surface miners because of the higher dust levels in the underground environment. CWP is

defined as the accumulation of the coal dust in the lungs and the tissue's reaction to its presence (21) and divided into two stages: simple pneumoconiosis (SP) and progressive massive fibrosis (PMF) according to the size and profusion of the lesions (22). Cytokines play a role in a wide spectrum of biological processes, especially in inflammation and immune response, and are important mediators of the toxic and pathogenic effects observed in humans exposed to mineral dusts as in CWP (23). Inhalation of coal mine dust can also lead to the development bronchitis, emphysema, Caplan syndrome, and silicosis (17).

Interstitial lung disease caused by exposure to silica and/or coal dust is the consequence of damage to lung cells and the resultant lung scarring associated with activation of the fibrotic process. The following mechanisms have been proposed to characterize this cycle of damage and scarring (15,24):

- \* Direct cytotoxicity: Chemical features of silica or coal dust result in reaction with lung cells, leading to peroxidation of membrane lipids and damage to cell membranes. Damaged cells may release intracellular enzymes, which would cause further tissue damage, leading to scarring or destruction of alveolar septa.

- \* Activation of oxidant generation by alveolar macrophages: Silica or coal dust stimulates the generation of ROS from alveolar macrophages, which overwhelms antioxidant defenses of the lung and causes lipid peroxidation and cell damage leading to scarring or destruction of alveolar septa.

- \* Stimulation of the secretion of inflammatory cytokines and chemokines from alveolar macrophages and/or alveolar epithelial cells: These inflammatory mediators act as chemoattractants to recruit polymorphonuclear leukocytes (PMNs) and macrophages from pulmonary capillaries to the air spaces. These cytokines also activate pulmonary phagocytic generation of oxidant species, leading to tissue damage and scarring.

- \* Stimulation of secretion of fibrogenic factors from alveolar macrophages and/or alveolar epithelial cells: Release of fibrogenic factors results in induction of fibroblast proliferation and/or the stimulation of collagen synthesis, leading to fibrosis.

## **Genetic Factors**

Multifactorial diseases involve complex interactions among multiple genes and environmental factors. Susceptibility depends on both intrinsic features of the host and the influence of environmental factors (25). Genetic factors such as polymorphisms are usually not, by themselves, sufficient for most diseases but modify the extent or severity of the disease after it has been initiated. In contrast to mutations, common allelic variants are present in high frequencies (>1%) in the general population. Among these variants, the most represented type of variations is single nucleotide substitutions, referred to as single nucleotide polymorphisms (SNPs). Although genetic association studies help to uncover the contribution of genetic background in disease susceptibility and severity, complex interplay between genetic and environmental factors creates a challenge in understanding the etiology of complex diseases. Environmental epidemiology using genetic information has focused primarily on examining hypothesis-driven associations between environmental/occupational diseases and specific polymorphisms such as silicosis and CWP. Genetic modifiers are known for a number of common complex diseases where immune/inflammatory mediators and environmental factors play a role. The pathogenesis of fibrotic lung diseases involve activation of inflammatory cells, fibroblast cell proliferation and the enhanced synthesis and/or breakdown of extracellular matrix components (26). Cytokines, chemokines, and growth factors play a crucial role in the onset, progression and termination of these reactions so that the SNPs occurred in these will effect the initiation and progression of the diseases.

## Cytokines

Cytokines are small cell-signaling protein molecules that are secreted by the glial cells of the nervous system and by numerous cells of the immune system and are a category of signaling molecules used extensively in intercellular communication. Cytokines can be divided into six groups: interleukins (IL), colony-stimulating factors, interferons, tumor necrosis factor (TNF), growth factors (GF), and chemokines. They are playing role in a wide spectrum of biological processes, especially in inflammation and immune response, are important mediators of the toxic and pathogenic effects observed in humans exposed to mineral dusts such as silica and coal dust. Macrophage-derived cytokines such as TNF- $\alpha$  and IL-1 play an important role in coal dust-induced inflammation. Existence of persistent stimulus and chronic release of cytokines may result in autoimmune and inflammatory diseases such as silicosis and CWP.

As cytokines are key regulators of homeostatic mechanisms, possible variations in their levels or their structures may be associated with the disease process (27). Polymorphisms in cytokine genes have been reported to contribute to the recognized stable inter-individual variation in the level of cytokine production rates (28-30). Inter-individual differences in spontaneous as well as stimulated production of IL-1 and TNF- $\alpha$  support the possibility that silicosis and pneumoconiosis severity are related to the genetic propensity of the host to produce these proteins. At the IL-1 and TNF loci, some allelic variants have been found to be significantly over-represented in inflammatory diseases. These variations affect the level of TNF- $\alpha$  expression in response to various stimuli. Epidemiological studies have pointed out that cytokine SNPs occurring in both pro- and anti-inflammatory cytokine genes are associated with chronic inflammatory or immune-mediated diseases (31-42).

We carried on a study in our laboratory about the evaluation of association of some TNF- $\alpha$ , IL-1, TGF- $\beta$  and IL-6 cytokines gene polymorphisms in CWP and its severity in Turkish coal workers and found that TNF- $\alpha$  (-238) variant may be a risk factor in both development and the severity of CWP, while TNF- $\alpha$  (-308) variant seems to be important only in disease severity. On the other hand, IL-6 variant may have a protective effect on the development and disease severity (43) and the secretion of TNF- $\alpha$  from the blood monocytes of the coal workers having variant allele is significantly higher than those of the controls (44).

## CONCLUSION

Mineral dusts such as silica dust and coal mine still cause significant respiratory diseases in spite of modern dust control regulations. Recent reports of researchers about the health effects of dusts are cause for concern. Due to the complexity, the underlying mechanisms of these diseases are not yet clarified clearly so further mechanistic studies are needed to evaluate and clarify the black holes in the occurrence and progression of dust-induced health problems.

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Received: 27.01.2011

Accepted: 24.02.2011