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Research Article

Cytokines:Their Relation with Mineral Dust Induced Diseases

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Abstract

Mineral dusts naturally can be generated via wind erosion or via human activities such as agricultural land use or mining. Some types of mineral dusts for instance asbestos, coal and silica can evoke several respiratory diseases. Inhalation of these dusts can lead to asbestosis, Coal Workers' Pneumoconiosis (CWP), silicosis and lung cancer. Inflammatory cell activation, fibroblast cell proliferation and the increased synthesis and/or disruption of extracellular matrix components are the underlying facts of the fibrotic lung diseases pathogenesis. Several mediators such as cytokines, chemokines and growth factors play a major role in the onset, progression and termination of these reactions. Cytokines have major role in inflammation and immune response that are important mediators in humans related with mineral dusts exposure and toxicity. Presence of permanent stimulus and chronic release of cytokines may end in some autoimmune and inflammatory diseases such as silicosis and CWP. Cytokine genes polymorphisms have been reported to assist in the inflammatory diseases. Epidemiological studies have indicated that Single Nucleotide Polymorphisms (SNPs) arose in cytokine genes are related with chronic inflammatory or autoimmune illnesses. Due to the data of recent studies it's obviously shown that the inflammatory cytokines TNF-α and IL-1 are related with the occurrence and development of the CWP, silicosis and asbestosis. In this article, the toxic potentials of most common mineral dusts, the relationship and the roles of cytokines and their possible genetic variations in the development of these dust-induced diseases were highlighted.

Keywords: Cytokines; Inflammatory diseases; Mineral dusts

The surface of Earth is coated by approximately 29% land area and most of this surface area comprised of soils whose composition is changing over time by several biological, chemical and physical factors [1]. Soil is a mixture of organic and inorganic materials and thus can contain lots of mineral particles including feldspars, quartz, phyllosilicates in various crystalline forms, carbonates, sulfates, phosphates, salts, heavy minerals like pyroxenes and also special ones with regard to human health like asbestos and erionite. However, the world-wide main constituents of mineral dust are clay minerals and quartz [2].

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Mineral dusts naturally can be generated via wind erosion or via human activities such as agricultural land use or mining. The naturally originated ones from the land surface is the major fragment. Atmospheric dust's mineral particles can be of prominent size range. 500-1000 μm sized particles get dislodged from the soil surface, but the ones with a diameter less than 75 μm can get suspended in the atmosphere and follow air currents [1]. The median size of the far travelled dust is even smaller, around 2 μm [3]. Therefore soil dust also includes 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 enhancing over the last years depending on global warming, increasing desertification and especially human activities [5]. As a result, air pollution is a big threat for people living in mega cities. It is an important health problem causing several diseases including respiratory diseases, cardiovascular disorders, conjunctivitis and skin irritations [6].

Several minerals in the composition of atmospheric dust culminate in health problems for humans. Silicates represent the soil minerals with the highest health risks [1]. Atmospheric soil dust of crystalline silica, coal, asbestos and erionite (a fibrous sodium-rich zeolite) can induce adverse respiratory health effects. Silica, coal and asbestos have unique toxic features and almost no other mineral can be compared to them [7-9]. Other minerals like metal oxides, talc, kaolinite, smectites and mica can also give harm, but only if the exposure is for a definite time period and certain intensity [10].

Some aerosol particles with large sizes can be formed in the atmosphere under special atmospheric conditions. Pinkish mineral microspherulites defined as iberulites are spherical mineral aggregates with a large size (50-300 μm) that can be found at the highest levels of solid additions in summer. Diaz-Hernandez and Parraga (2008) collected samples of iberulites in Southern Spain [11]. Iberulites are formed and structured in the troposphere after transport of the dust from far places like Sahara Desert and composed of complex mineral associations whose phases have diverse hygroscopic properties including mainly silicates, carbonates, sulphates, halides, oxides and phosphates [12]. It is clearly seen that particles > 10 μm have attracted little attention but they can be transported over long distances directly from their sources and may play major roles in regional circulation of materials [13]. Long-range transport of giant particles have been reported in Saharan dust across the Atlantic Ocean and the Mediterranean Sea [11,14].

Common and iberulite-rich aerosols from the Sahara include mainly quartz, feldspars, carbonates and clays (illite, smectite and kaolinite). The texture of iberulites consists of large mineral particles embedded in a matrix of clay minerals also surrounding the entire spheroidal aggregate. Clays play a major role in their formation and providing a mechanical strength to the aggregates. The clay mineralogy has been addressed in several occasions and pointed out to depend on sources and sampling location [14,15]. Due to the data from the recent studies clay minerals are essential for their formation of these large mineral aggregates within water droplets in the atmosphere. They also influence the fabric and porosity of aggregates [11,16,17].

The best known minerals due to their human health effects are silica, coal, asbestos and erionite. Mineral dusts can affect humans by

several ways of action. Dust particles penetrate the human body especially by inhalation or ingestion and through the skin. While some mineral dust is toxic by itself, others can carry toxic substances entering the human body together [1]. Exposure risk can be increased at places mostly related with the origin of the mineral dust. People living or working closer to dust sources are at higher risk of health problems of mineral dust. Therefore, mostly affected individuals are agriculture workers, construction workers and miners. The health risk of inhaled mineral dust depends on the exposure level the duration and the frequency of the exposure the chemical and mineralogical composition of the particle [1,5]. If the aerodynamic diameters of the inhaled mineral dusts are bigger than 10 μm, they are stuck in the upper respiratory tract where they get trapped in the mucous lining of the nasopharyngeal tract. If their aerodynamic diameters are smaller than 10 μm (PM_{10}), they can easily penetrate more deeply into the lung passages to the tracheobronchial regions, where they also get trapped in a layer of mucus [10]. Due to WHO limits and EPA standards, particles ≤ 2.5 μm ($PM_{2.5}$) are accepted as unhealthy to humans and defined as respirable dust and those particles can easily reach the alveoli region of the lung where gas-exchange is performed [18]. According to WHO (accessed 29th June, 2013) the acceptable annual mean value of PM_{10} is 20 μg/m^3 and the acceptable 24 h mean value is 50 μg/m^3 [19]. The EU (accessed 29th June 2013) has 1 year mean $PM_{2.5}$ values of 25 μg/m^3, 1 year PM_{10} mean values of 40 and 24 h mean PM_{10} values of 50 [20]. On Dec 14, 2012, the US Environmental Protection Agency (EPA) strengthened the nation's air quality standards for fine particle pollution to improve public health protection by revising the primary annual $PM_{2.5}$ standard to 12 micrograms per cubic meter (μg/m^3). The EPA also has a 24 h $PM_{2.5}$ standard of 35 μg/m^3 and a 24 h standard of 150 g/m^3 for PM_{10} (accessed 29th June, 2013) [21]. The dust deposition adds exogenous mineral and organic materials to terrestrial surfaces, having a significant impact on ecosystems, biogeochemical cycles [22,23] and also on health [24-26].

Subject to shape, size, chemical composition, surface state of the particle, length of exposure and certain lung functions, different responses can be triggered [5,9]. Mineral dust inhalation can lead to severe diseases such as silicosis, asbestosis, coal workers' pneumoconiosis (termed as pneumoconiosis) lung and pleura cancer [18].

Figure 1 demonsatrates the fate of inhaled mineral dust particles in the human body. Xenobiotics cause the activation of macrophages [1]. The activated macrophages ingest the particles and due to the acidic pH and digestive enzymes found in their lysosomes they can degrade and clear the particles [2]. They also release chemicals [3] to activate other macrophages [4]. Depending on their death [5], they release their contents, to recruit new macrophages [6]. This cycle of cell death and newly recruited cells in the alveoli can give rise to enhanced inflammation [27].

The cytokines, growth factors and Reactive Oxygen Species (ROS) released following the death of macrophages [7], can directly harm the alveoli cells. Not all of the particles in the alveoli get degraded by the macrophages or dissolved but some remain as free. While some of the remaining ones give no harm others can damage the epithelial cells [8] and stimulate fibroblastic cells relatively [9]. Fibroblastic cells can make a way for the deposition of a protein called collagen. If those processes become permanent, it may end in the development of lung cancer or fibrosis [10].

The mineral fibers can give harm to the surrounding cells and macrophages and they are even able to cause mesothelioma [12] a

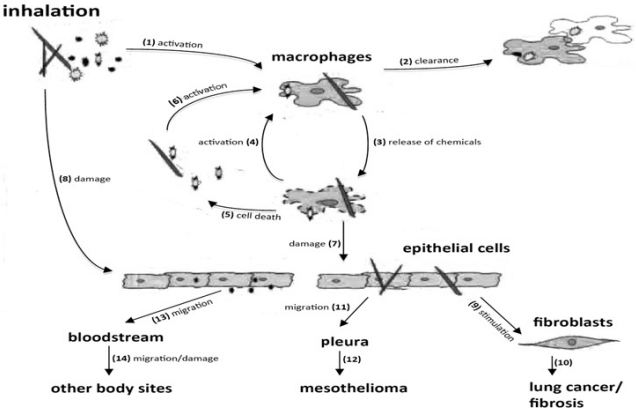

Figure 1: The fate of inhaled mineral dust particles [28].

fatal neoplasia of pleural mesothelial cells (membrane that covers the lung) because of their possible migration to the pleura [9,11,29]. The nanoparticles are capable of migrating through the alveolar membrane to enter the interstitial lung tissue. They can abide there or furthermore migrate to the lymphatic system. Generally, most of those filtered particles in the lymph nodes stay there. Nevertheless some entered into the bloodstream via the lymph [13]. By this way, they can easily arrive other organs and tissues [14] to give harm at other regions of the body [9,29].

Silicosis, asbestosis and Coal Workers Pneumoconiosis (CWP) are the well known mineral dust induced diseases.

Silicosis

Silicosis, the most ancient recognized occupational disease, exclusively occurs by crystalline silica exposure [30]. At the same time, it appears frequently even in developed countries, particularly in certain occupations such as mining, sandblasting, surface drilling, stone cutting, construction, pottery making and silica flour mill operations [31]. Due to environmental silica and mixed dust exposures, lung fibrosis and pulmonary alterations have been observed in the lungs of humans and farm animals. Exposure to crystalline silica can culminate in adverse pulmonary responses such as acute, accelerated, chronic and conglomerate silicosis [32]. In addition, silica exposure can also be associated with systemic and autoimmune diseases such as Rheumatoid Arthritis (RA), Systemic Lupus Erythematosis (SLE), nephropathy, proliferative glomerulonephritis [33], tuberculosis and lung cancer [34,35].

Asbestosis

Asbestos is the common industrial term covering six different natural fibrous silicates. Amosite, crocidolite, tremolite, anthophyllite and actinolite all pertain to the amphibole mineral group, chrysotile is a serpentine exceptionally. These were exploited largely for industrial processes in the past century because of their unique and versatile properties. Nowadays, asbestos is taken into account because of its potency to develop asbestosis (a debilitating and often fatal lung disease) and malignancies such as lung cancer and pleural mesothelioma, occurring many time later after exposure.

Asbestos refinement and its usage have been restricted progressively or banned by several countries. The European Union banned asbestos in 2005. On the contrary, asbestos is yet widely produced and used in developing countries [36]. 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, as a result the fibers can also release substances like reactive iron, triggering free-radical production. Those radicals give harm to the DNA [9,10].

Coal Workers' Pneumoconiosis (CWP)

Coal Workers' Pneumoconiosis (CWP) is an occupational lung disease characterized by fibrotic nodular lesions following inhalation of coal dusts. The severity of the disease is associated with the total dose and exposure intensity. Coal is a fossil fuel that have been mining throughout the world. The formation of coal mine dust during underground mining is the most important source of exposure. Surface mining and underground mining are the two basic types of coal mining processes. Underground miners are at higher risk of developing CWP than strip or surface miners because of the higher ambient dust levels. CWP is defined as the accumulation of the coal dust in the lungs and the tissue's reaction to its presence [37] and divided into two stages: Simple Pneumoconiosis (SP) and Progressive Massive Fibrosis (PMF) according to the size and profusion of the lesions [38]. Cytokines play a major role in a wide spectrum of biological processes such as inflammation and immune response and are important mediators of the toxic and pathogenic effects observed in exposed individuals [39]. Inhalation of coal dust can also cause bronchitis, emphysema, caplan syndrome and silicosis [33].

For many years, it has been thought that within the coal components quartz was the active agent leading the development of CWP but due to the data of recent studies, it has not an important role in the prevalence of CWP as thought [40]. Following Heppleston's report [40], Ghio and Quigley [41], addressed the role of iron in CWP. They indicated certain types of transition metals including iron tend to be concentrated in the lungs of miners with CWP. They suggested that humic-like substances in coal dust with iron clad-ions catalyze the oxidation generation and the accumulation of iron in tissues of CWP. The level of iron in coal is termed as Bio Available Iron (BAI) is related with the development of the disease. Several studies have been done to see whether there is a relationship between BAI in coal account for regional differences in both the prevalence and severity of CWP or not and according to their results, they found positive relationship [42-47]. Interstitial lung disease caused by silica and/or coal dust exposure is the outcome of lung cells damage and lung scarring related with fibrotic process activation. The under mentioned mechanisms have been proposed to characterize this damage and scars [31,48]; Direct cytotoxicity: Chemical features of silica or coal dust reacted with lung cells, causes damage to cell membranes following membrane lipid peroxidation. Damaged cells may release intracellular enzymes, able to provoke further tissue damage, resulting in scarring or alveolar septa destruction.

Activation of oxidant formation by alveolar macrophages: Silica or coal dust stimulates the formation of ROS from alveolar macrophages, destructing the antioxidant lung defense leading to lipid peroxidation and cell injury. This kind of injury may result in scarring or alveolar septa destruction.

Stimulation of the inflammatory cytokine and chemokine secretion from alveolar macrophages and/or alveolar epithelial cells: These inflammatory mediators act as chemoattractants in order to recruit Polymorphonuclear leukocytes (PMNs) and macrophages from pulmonary capillaries to the air gaps. These cytokines also activate pulmonary phagocytic formation of oxidant species, ending up with tissue injury and scarring.

Stimulation of fibrogenic factor secretion from alveolar macrophages and/or alveolar epithelial cells: Fibrogenic factor release leads to induction of fibroblast proliferation and/or the stimulation of collagen synthesis, resulting in fibrosis.

Genetic Factors

Multifactorial diseases include complex interactions among multiple genes and environmental factors. Susceptibility attaches to both intrinsic features of the host and the influence of environmental factors [49]. Genetic factors like polymorphisms are not usually sufficient for most diseases by themselves but important for modifying the extent or severity of the disease after initiation. Counter to mutations, common allelic variants are present in high frequencies (>1%) in the general population. Among these, the most represented type of variations is single nucleotide substitutions, defined as Single Nucleotide Polymorphisms (SNPs). Even though genetic association studies assist to reveal the contribution of genetic background in disease susceptibility and severity complex interactions between genetic and environmental factors create a challenge in understanding the aetiology of complicated diseases. Environmental epidemiology using genetic information has focused primarily on investigating hypothesis-driven relations between specific polymorphisms and environmental/occupational diseases such as silicosis and CWP. The pathogenesis of fibrotic lung diseases contain activation of inflammatory cells, fibroblast cell proliferation and the increased synthesis and/or breakdown of extracellular matrix components [50]. Cytokines, chemokines and growth factors play a major role in the onset, progression and termination of these reactions so that the appeared SNPs will affect all the processes of the diseases.

Cytokines

Cytokines are small cell-signaling protein molecules excreted from the glial cells of the nervous system and numerous cells of the immune system. They are a set of molecules used as signalling extensively in intercellular communication and can be classified into six groups: Interleukins (IL), colony-stimulating factors, interferons, Tumor Necrosis Factor (TNF), Growth Factors (GF), and chemokines. They are playing important role in a wide spectrum of biological procedures such as inflammation and immune response and they are crucial mediators of the toxic and pathogenic effects observed in human mineral dust exposure. Macrophage-derived cytokines such as TNF-α and IL-1 are involved in coal dust-induced inflammation as proinflammatory cytokines. Presence of permanent 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 processes, possible variations in their levels or their structures may be associated with the disease development [51]. Polymorphisms in cytokine genes have been demonstrated to contribute to the recognized stable inter-individual variation in the level of cytokine production rates [52-54]. Inter-individual differences in spontaneous as well as stimulated production of IL-1 and TNF-α encourage the possibility that silicosis and pneumoconiosis severity are associated with the genetic propensity of the host to produce these proteins. At the IL-1 and TNF loci, several allelic variants have been found to be significantly over-represented in inflammatory diseases. These variations affect the level of TNF-α expression in response to various stimuli. Epidemiological studies

have indicated that cytokine SNPs occurring in both pro- and anti-inflammatory cytokine genes are related with chronic inflammatory or immune-mediated diseases [55-66].

We also carried out a study in our laboratory aimed to evaluate possible association of some TNF-α, IL-1, TGF-β and IL-6 cytokines gene polymorphisms in CWP and its severity in Turkish coal workers [67,68]. According to the results we found that TNF-α (-238) variant may be a risk factor in both development and the severity of CWP, while TNF-α (-308) variant seems to be important only in disease severity. On the contrary, IL-6 variant may have a protective effect on the development and disease severity [67] and the secretion of TNF-α from the blood monocytes of the coal workers having variant allele is significantly higher than those of the controls [68]. According to the data of recent studies, it's obviously shown that the inflammatory cytokines TNF-α and IL-1 are related with the occurrence and development of the CWP, silicosis and asbestosis [69-74].

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