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Silicosis: biomarkers and pathogenesis

Abstract

Ramazzini first described this disease, namely " Pneumonoultra-microscopicsili-covolcanokoniosis" and then was changed according to the types of exposed dust. No reliable figures on the silica-inhalation exposed individuals is officially documented. How silica particles stimulate pulmonary response and the exact pathophysiology of silicosis are still not known and urgently require further research. Nevertheless, many researchers hypothesized that pulmonary alveolar macrophages play a major role by secreting fibroblast-stimulating factor and re-ingesting these ingested silica particles by the pulmonary alveolar macrophage with progressive magnification. Finally, ending up of the death of the pulmonary alveolar macrophages and the development of pulmonary fibrosis appear. A hypothesis of silicosis-associated abnormal immunoglobulins has been postulated. In conclusion, novel studies on pathogenesis and biomarkers of silicosis are urgently needed for precise prevention and control of this silently threaten disease of the world.

Objective of the study: The objective of this study is to review the new ideas of pathogenesis of silicosis and possibly practical novel biomarkers for silicosis.

Keywords: silicosis, biomarkers, pathogenesis

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Abbreviations: ACE, angiotensin converting enzyme; BAL, bronchoalveolar lavage; FasL, fas ligand; FEV1, forced expiratory volume in one second; IL, interleukin; L-BAL, bronchoalveolar lavage lymphocyte; mRNA, messenger ribonucleic acid; MIP, macrophage inflammatory protein; TNF, tumor necrosis f actor; MCP, monocyte chemotactic factor; RA, receptor antagonist; VC, vital capacity

Introduction

The name of this disease "Pneumonoultra-microscopicsili-covolcanokoniosis", first description by Ramazzini[1] was changed due to the types of exposed dust.[2] There are no reliable figures on the silica-inhalation exposed populations. Nevertheless, in 2000, the CAREX registry recorded 3.2 million silica-exposed people in the European Union.[3] Silicosis is histologically characterized by hyalinized and fibrotic pulmonary nodules, accumulation of lymphocytes and alveolar macrophages, and thickening of pulmonary alveolar interstitium.[4] The disease is caused by continuous inhalation of the silica dust (crystalline silica, SiO_2 (Silicon dioxide)) with marked inflammation and irreversible scarring of the lungs with nodules in the upper lobes.[5,6] Oxygen and silicon, together amount for 74.32% weight and 83.77% of crustal rocks are the two most occurring common elements on the surface of the earth.[7] Silicon dioxide or silica is formed under the conditions of increased pressure and heat that exists in amorphous and crystalline (quartz, a typical component of rocks) form. The risk of developing silicosis is closely associated with the accumulated exposure of a person to respirable crystalline silica during his or her working lifetime. The intensity of accumulated respirable silica exposure can be calculated as the following: Accumulated silica dose = fraction of respirable dust X percentage of free silica in mg/m^3 X number of years of exposure.[8] Silicosis is the most frequently occurring pneumoconiosis due to wide prevalence in the atmosphere and more common than the other types of dust.[1,9,10] Both in Developing and developed world, silicosis is an occupational hazard with greater risk for workers engaged in stone crushing, stone cutting, cement industries, glass manufacturing, mining, agriculture, and construction.

Pathogenesis

When the silica particles of 0.5 to 5microns in diameter are inspired into the lungs, these particles get embedded into the alveolar sacs and ducts and cause inflammation. The inflammation and scarring damage the pulmonary alveolar sacs, prevent gas exchange in the lungs, and contribute to abnormal breathing. The damage to the lung tissue leads to reduction of oxygen supply to the blood. Silicosis is an irreversible medical condition without cure. Degree of silica-dust exposure is directly associated with occurrence of silicosis. Through the process of inhalation, different size of the silica particles deposit in the different parts of the human respiratory system. For examples, 10-5microns in size particles reach up to upper respiratory tract causing rhinitis and laryngitis, 5-3microns in size particles reach up to the mid-respiratory system and may cause tracheaitis, bronchitis and bronchiolitis, and 3-1microns in size particles directly are deposited in the alveoli causing asthma, chronic obstructive pulmonary disease, and other pulmonary interstitial diseases including silicosis.[11] How silica particles stimulate pulmonary response and the precise pathophysiology of silicosis are still research questions. Nevertheless, several studies indicated interactions between respirable silica particles and pulmonary alveolar macrophages and this interaction plays major role in the development of the silicosis disease. The intensity of the inhaled silica particles influence on the nature and extent of the pulmonary alveolar response that provides explanation to some silicosis extension why rock drillers and sandblasters who are intensively exposed to freshy fractured silica dust develop silicosis disease.[12]

Several studies revealed that silica promote macrophage activation. The affected macrophages release inflammatory mediators and chemotactic factors that trigger cellular responses of the leukocytes and lymphocytes and then release the fibroblast stimulating factor (Figure 1). Hyalinization and collagen deposition are promoted by the fibroblast stimulating factor and resulting in pathologically pulmonary nodular lesion. This pulmonary nodule composes of a central acellular zone with free silica and surrounding spirals of collagen and fibroblasts.[13] After ingestion of silica particles, pulmonary alveolar

macrophages secrete fibroblast-stimulating factor. Then macrophages die due to the toxicity of the ingested silica and these silica particles are re-ingested by macrophages and this process is progressively magnified. Lysosomal enzymes are then released rapidly into the cytosol and contributing breakdown of the intracellular organelles with irreversible injury to the affected pulmonary alveolar cells. Intracellular lysosomal rupture circumstantially results in cell death. It seems that damage of the plasma membrane results in macrophage death. Nevertheless, pathogenesis of silicosis may be associated with immunological mechanism due to identification of abnormal serum immunoglobulins and immunoglobulins in the silicotic nodules.[12]

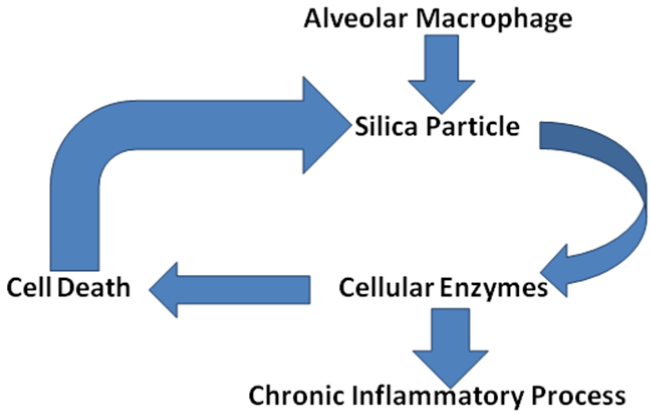

Figure 1 Impact of silica particle on pulmonary tissues.

Source: Elcosh-electronic library, 2016.

Biomarkers

In the development of silicosis, the pulmonary alveolar macrophages play a dominant role by releasing host mediators, such as chemok ines and cytokines, that result in the onset of pulmonary injury, inflammation, and potentially pulmonary fibrosis. These mediators regulate the development immune effector cells. In a murine study, cristobalite-induced macrophage inflammatory protein (MIP)-2 messenger ribonucleic acid (mRNA) level were reduced by 57, 52 and 38% with N-acetyl-L-cysteine, dimethyl sulfoxide, or extracellular glutathione, respectively.[14] Reduction of both MIP-1alpha and MIP-1beta mRNA levels were at the same magnitude as the reduction of tumor necrosis factor (TNF)-alpha mRNA levels, while MIP-2 mRNA levels were reduced at a magnitude similar to the reduction of monocyte chemotactic protein (MCP)-1 mRNA levels after antioxidant treatment.[14] Increased TNF-alpha, interleukin (IL)-1beta, IL-6, IL-8 levels were identified in bronchoalveolar lavage (BAL) fluid in patients with silicosis,[15] whereas decreased cristobalite-induced TNF-alpha mRNA levels were found in a murine study.[14] Human IL1 family consist of three genes located on long arm of chromosome 2 that code for IL1-a, IL1-b, and IL1 receptor antagonist (RA).[16]

Several studies revealed that serum angiotensin converting enzyme (ACE) levels were elevated in granulomatous diseases, such as silicosis and sarcoidosis.[17] Because of its principal localization in the large capillary bed of the lungs, the serum activity of ACE in pulmonary diseases is of much interest. Elevation of serum copper or ceruloplasmin could be possible associated with primary pathologic changes including fibrosis and the proliferation of collagen tissue in the lungs of patients with silicosis.[18,19] In silica dust-exposed persons without developing the disease, the serum copper levels as biomarker is uncertain.[20] A experimental study in rats demonstrated a decrease in *FAS-L* expression and silica-induced apoptosis in old macrophages,[21] whereas a study in 11 patients with silicosis revealed that bronchoalveolar lavage lymphocytes (L-BAL) apoptosis was inversely correlated with FEV1/VC value (r = -0.26, p < 0.05).[22] Dysregulation of apoptosis in the Fas/FasL pathway play a role in the pathogenesis of autoimmune diseases.[23]

Discussion

Respirable silica particles with 3-1 microns in diameter are directly deposited in the pulmonary alveoli[11] and interact with pulmonary alveolar macrophages causing the silicosis disease.[12] The nature and extent of the lung response depend on the intensity of inspired silica particles.[12] Silica particles that deposit in the pulmonary alveoli promote pulmonary alveolar macrophage activation by releasing several chemotactic factors and inflammatory mediators. These factors and mediators cause releasing of the fibroblast stimulating factor via the cellular response of the lymphocytes and leukocytes. Fibroblast-stimulating factor promote collagen deposition and hyalinization in the pulmonary tissues resulting in pulmonary nodule that composes of a central acellular zone with containing free silica.[13] Crystalline silica-laden macrophages cause cell death, fibrous proliferation, and finally pulmonary fibrosis. Pulmonary fibrosis is progressively magnified by re-ingestion of silica particles by macrophages. However, pathogenesis of silicosis may due to abnormal immunological mechanism.[12] Several prospect biomarkers, such as MIP-1beta mRNA, MIP-2 mRNA, MCP-1 mRNA, TNF-alpha mRNA, IL-1beta, IL-6, IL-8, ACE could be the prognostic indicators for silicosis.[14–17]

Conclusion

Further studies are urgently needed to identify suitable biomarkers for silicosis, including associated mechanism of immunoglobulins.

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Conflict of Interest

No conflict of interest is declared.

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