An Overview of the Role of Mineral Solubility in Silicosis and Asbestosis

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Asbestosis and silicosis are fibrotic diseases initiated by the inhalation of silica-containing dusts, asbestos and quartz. There are various approaches for explaining the causes of these diseases. At present, our knowledge on the matter indicates that silicic acid dissolved from these minerals, contact between macrophages and minerals, highly reactive and oxidative species formed on the mineral surface, and lysosomal enzymes released upon engulfment of particulate mineral of appropriate size all contribute to various extents to the initiation of fibrosis. Among these mineral solubility seems to have a substantial contribution as a causative factor.

Key Words: silicosis; asbestosis; PVNO; free radicals; oxidizing agents.

INTRODUCTION

The pneumoconioses are interstitial lung disorders resulting from the inhalation of inorganic dusts and are associated with chronic inflammatory processes in the lower respiratory tract. Chronic exposure to high concentrations of airborne asbestos leads to asbestosis, exposure to coal leads to coal workers pneumoconiosis, and exposure to quartz or silica leads to silicosis (Shi et al., 1989). Although each of them is well defined in terms of its associated symptomatology, physical findings, and physiological disfunction, the exact mechanism by which these particles induce these inflammatory and fibrogenic lung diseases remains to be elucidated.

Due to the similarities in the causative factors and the end result, silicosis and asbestosis deserve special attention.

STUDIES ON THE MECHANISM OF SILICOSIS

Silicosis is caused by the inhalation of excessive quantities of respirable silica-bearing dusts by miners, foundry and ceramic workers, etc. It has been reported that silicates or crystalline and amorphous quartz particles with diameters in the range of 0.5 to 2 μm are of great importance for the development of silicosis (Ghio et al., 1990; Shi et al., 1989). The duration of exposure and the amount of dust in the air inhaled effect the degree of fibrosis. Once initiated, the disease is irreversible and progressive (Rom et al., 1987).

Alveolar macrophages induced by the inorganic dust spontaneously release exaggerated amounts of fibronectin (a 440-kDa glycoprotein, which is a potent chemoattractant for lung fibroblasts) and alveolar macrophage-derived growth factor (AMDFG, an 18-kDa peptide, which is a progression factor). Fibronectin provides a mechanism for attaching the fibroblasts to the connective tissue matrix and plays a role as a competence signal to move fibroblasts into the early portion of G1 of the replication cycle. AMDFG acts later in the G1 of cell cycle signaling fibroblasts to synthesize DNA and replicate. The cellular parameters indicative of the disease are increased levels of procollagen mRNA (Vuorio et al., 1989), fibrogenic cytokines such as interleukin-1, tumor necrosis factor-α, platelet-derived factor (Dubois et al., 1989; Piguet et al., 1990), mRNA of superoxide dismutase and catalase (Jannsen et al., 1992), intracellular Ca2+ concentration, and LDH release.

Most of the increase in RNA levels could be explained by a concomitant increase in the number of cells in the silicotic lungs, and the lungs respond to silica by increasing the level of proαI (III) collagen mRNA more than the level of proαI (I) collagen mRNA. The increased procollagen mRNA levels indicate that fibrotic lungs acquired the potential to
produce higher amounts of collagen than normal lungs.

In the presence of chrysotile and silica, alveolar macrophages can produce both leukotriene (LTB4) and tumor necrosis factor (TNF), and the mechanism suggests that asbestos and silica may modulate the production of inflammatory and fibrogenic cytokines (Gossart et al., 1996).

Silica and chrysotile produce a 3- to 4-fold enhancement in TNF production and a 13- to 32-fold augmentation of LTB4 production in rats (Dubois et al., 1989). A single instillation of silica leads to a marked increase in the level of TNF mRNA in lung mice which lasts for 70 days (Jannsen et al., 1992; Piguet et al., 1990).

Although the exact mechanism by which the dusts cause these changes, exert their toxic actions, and lead to fibrogenesis is still poorly understood, some investigations provide evidence that the interaction of the silica surface with the cell membrane is the starting point of the silicotic process (Rom et al., 1987; Wiessner et al., 1990) (Fig. 1). Silica is known to be cytotoxic to the alveolar macrophages, and the death of macrophage has been suggested to be intimately related to the genesis of silicotic fibrosis (Bagchi, 1992). The reaction of macrophages, in combination with fibroblasts, may have evolved as a part of the defense mechanism of the body. When these cells are stimulated by phagocytosis, they are capable of secreting enzymes like collagenase and degrade the connective tissue (Bagchi, 1992). It is believed that inhaled silica particles become incorporated into secondary lysosomes via the phagosomes upon phagocytosis by alveolar macrophages (Allison, 1971). The toxic properties of the dusts are related to their capacity to damage lysosomal membranes through hydrogen bonding. Upon lysis of lysosomal membranes, lysosomal enzymes cause extensive damage to the cell membrane leading to silicosis after a number of steps. The continuation of the cycle of engulfment, unmasking of the surface with proteins called opsonins, and macrophage death, promotes the silicotic process. The initial interaction between silica dust and cell membrane was suggested to be through the hydrogen bonding or free-radical-mediated reaction or both (Shoemaker et al., 1995). It is suggested that the toxicity of quartz is due to the silanol groups that are formed on the surface of quartz particle which might act as sites for strong hydrogen bonding with a cell membrane (Ghio et al., 1990; Shi et al., 1989). Other researchers reported that the quartz surface is toxic due to the negative charge (Garofalini and Martin, 1994; Wiessner et al., 1990). A contrary report suggests that toxicity is due to the positive charge of the quartz surface (Bagchi, 1992). Whatever functional groups or charges are involved, the observation that quartz particles can react with proteins, phospholipids, and biological membrane systems emphasizes the contribution of quartz surface interaction with membranes to initiation of fibrosis (Bonner et al., 1974; Harley and Margolis, 1961; Heppleston and Styles, 1967; Marasas and Harington, 1960; Stalder and Stober, 1965).

The free radicals generated on the surface of the particles upon crushing the quartz (Si· and SiO·) and oxygenated reactive species originated from these (i.e., O₂-, H₂O₂, and OH·) are proposed to be involved in the interaction of the cell membrane with quartz dust (Ghio et al., 1990; Shi et al., 1989). The result of this reaction would be the peroxidation of unsaturated fatty acids, phospholipids glycolipids, sterols of the membrane, oxidizable amino acids, and sulfhydryl groups of the transmembrane proteins. The oxidation of transmembrane proteins may in turn cause the membrane permeability to increase, allowing more free ion migration and breaking down transmembrane ion gradients in the cell and resulting in cell death. Mediator-induced release of ROI (reactive oxygen intermediates) seems to be an important event in the development of lung fibrosis which was reported that the release of two soluble fragments, about 20 and 10 kDa, were responsible for a new mechanism of quartz dust and coal mine dust fibrogenicity (Maly, 1988).
A final causative factor reported is monosilicic acid that dissolves from the surface of quartz particles (Iller, 1955). It has been suggested that silicic acid interacts with the cell membranes in free form or after polymerization on the membrane leading to membrane damage (Garofalini and Martin, 1994; Janssen et al., 1992). It was earlier shown that polymerization of monosilicic acid could take place on templates (Hasirci, 1976; Erdogdu and Hasirci, 1994) and this could also if it take place on cell and lysosomal membranes. Agglutination of erythrocytes caused by monosilicic acid can be taken as poor of this (Hasirci, 1977).

It has been found that a number of substances reduce the toxic effects of quartz (Heppleston and Styles, 1967; Goldstein and Rendall, 1987; Wiessner et al., 1990; Bagchi, 1992). Treatment with a free-radical scavenger reversed lung histopathologic changes (Gossart et al., 1996) (Fig. 2). The N-oxide group of polyvinylpyridine N-oxide has a strong electronegative oxygen atom capable of forming strong bonds with the silanol groups on the quartz surface or silicic acid in solution (Nash et al., 1966; Holt and Nasrallah, 1968; Hasirci, 1976; Shi et al., 1989). This is known to reduce the hydrogen bonding between the silanol groups and the cell membrane (Nash et al., 1966) and because of the reduction in the quartz-membrane bonding, phagocytosis and the subsequent cell lysis by the quartz particles can be delayed or decreased. Another observation is that the interaction of monosilicic acid and erythrocytes caused agglutination, and treatment with polyvinyl N-oxide (PVNO) prevented this effect (Hasirci, 1977). Absence of an interaction between PVNO and the cell components lecithin and γ-globulin suggests that this could be a plausible mechanism for the prevention action of PVNO (Fig. 2).

It was also suggested that a kind of chelating activity might be required for silicosis prevention via the formation of complexes with monosilicic acid or with the membrane surface to prevent polymerization or membrane adsorption. Coating the surface of quartz with organic or inorganic cations decreased the hemolytic effect (Ghio et al., 1990). A nontoxic chelating agent (8-hydroxyquinoline-5-sulfonic acid) (Erdogdu and Hasirci, 1983) and a group of bisbenzylisoquinoline alkaloids (tetrandrine, fangchinoline, and methoxyadiantifoline (MA)) were tested as potential preventatives with a certain degree of success on liposomes and on alveolar macrophages, respectively (Ma et al., 1991).

Quartz pretreated with aluminum elicited a markedly reduced inflammatory response. The reduced activity of the treated quartz was also reflected in the attenuated change in the key functional parameters, oxidant production, and proteolysis of fibronectin (Brown et al., 1989).

**STUDIES ON THE MECHANISM OF ASBESTOSIS**

The term asbestos refers to a group of hydrated silicates that have a fibrous morphology. Serpentine and amphibole are recognized as two main asbestos groups. Asbestosis is a slowly progressive and
persistent interstitial fibrosis of the lung, associated with the inhalation of asbestos dust and characterized by asbestos fibers and bodies appearing in large numbers in the tissue (Erdogdu and Hasirci, 1994).

It is reported that the amount of silicic acid released by chrysotile is at least twice greater than that released by other asbestos samples (SiO$_2$ per 50 mg asbestos was in chrysotile 21.5 µg, in crocidolite 5.5 µg, in anthophyllite 7.6 µg, and in amosite 14.0 µg) and interaction with EDTA resulted in a 50% decrease in hemolysis by chrysotile (from 91.35 to 42%). Since silicon dioxide is the major constituent, it is highly likely that it is the hemolytic agent.

Fiber type and length appear to have a significant effect on the degree of fibrosis (Rom et al., 1987; Hiroshima et al., 1993; Roggli et al., 1993). There appear to be two hypothetical schemes which could explain how inhaled asbestos caused fibrosis. One suggests that as in the case of silicosis, toxic oxygen radicals generated on fiber surfaces and/or intracellularly are the central modulators of disease leading to lipid peroxidation and membrane damage (Rom et al., 1991) (Fig. 1). Total dismutase activity was significantly elevated in asbestos-exposed rats. mRNA levels were observed after 10 days of exposure, and expression of MnSOD 8.25 and CuZnSOD 47.4 were detected whereas expression of MnSOD 4.23 and CuZnSOD 33.8 was observed. The second view is a more advanced version of the first: The cellular injury induced by oxygen radicals further stimulates the elaboration of different growth factors and cytokines that mediate the pathogenesis of asbestosis (Rom et al., 1987). In both cases the generation of these oxidizing agents is explained by the presence of divalent cations Mg$^{2+}$ and Fe$^{2+}$, in the fiber structure. The decrease in cellular damage achieved by chelators is a further support for this approach (Kamp et al., 1992).

In vitro and in vivo experiments carried out reveal that phagocytosis is associated with release of several factors, including radicals by oxygen derivatives and clastogenic factors (Jaurand, 1991). The mechanism accounting for DNA damage is not clear but radicals and clastogenic factors are thought to be among the potential causative factors. A cellular response to exposure to asbestos is an increase in the mRNA levels for deoxidative enzymes (Janssen et al., 1992). There are reports that alveolar macrophages cultured in the presence of chrysotile or silica can produce both LTB and TNF (Dubois et al., 1989). TNF production induced by LTB$_4$ has a crucial importance in the process of lung inflammation and fibrogenic disease.

**CONCLUSION**

What becomes apparent is that these two types of silica-containing dusts have great similarities as well as distinct differences in the way they cause fibrosis. The profiles of antioxidant enzymes are dissimilar during the development of experimental asbestosis and silicosis, and different lung responses to these minerals are shown (Janssen et al., 1992). When all the criteria are investigated it becomes apparent that asbestosis and silicosis are caused not by the surface charge, functional groups, ions, oxidant species, etc.) alone but also by compounds that dissolve from these. In both asbestosis and silicosis one of the dissolved species that deserves significant attention is monosilicic acid. Monosilicic acid is known to polymerize under favorable conditions and membranes appear to be appropriate templates on which this can take place and lead to damage. That, with the combined effect of ions such as Mg$^{2+}$ and Fe$^{2+}$, seems to constitute a significant step in the initiation of fibrosis whether they come from asbestos or quartz. Figure 1 shows a presentation of the events underlying the initiation process and Fig. 2 shows the prevention by a number of compounds through several routes which are shown to exist. We believe these schemes also represent the processes involved in fibrogenesis induced by asbestos fibers.

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**REFERENCES**