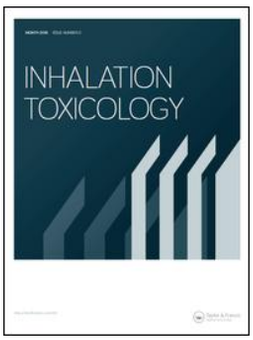

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FROM COAL MINE DUST TO QUARTZ: Mechanisms of Pulmonary Pathogenicity

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Exposure to coal mine dust or crystalline silica can result in the initiation and progression of interstitial lung disease. Pathogenesis is the consequence of damage to lung cells and resulting lung scarring associated with activation of fibrotic processes. This review presents the radiologic and histologic characteristics of simple and complicated coal workers' pneumoconiosis (CWP) as well as pathological indices of acute and chronic silicosis. This presentation also reviews the results of in vitro, animal, and human investigations that elucidate mechanisms involved in the development of these pneumoconioses. Results support the involvement of four basic mechanisms in the etiology of CWP and silicosis:

1. *Direct cytotoxicity of coal dust or silica, resulting in lung cell damage, release of lipases and proteases, and eventual lung scarring.*
2. *Activation of oxidant production by pulmonary phagocytes, such as alveolar macrophages. When oxidant production exceeds antioxidant defenses, lipid peroxidation and protein nitrosation occur, resulting in tissue injury and consequent scarring.*
3. *Activation of mediator release from alveolar macrophages and alveolar epithelial cells. Chemokines recruit polymorphonuclear leukocytes and macrophages from the pulmonary capillaries into the air spaces. Once within the air spaces, these leukocytes are activated by proinflammatory cytokines to produce reactive species, which increase oxidant injury and lung scarring.*
4. *Secretion of growth factors from alveolar macrophages and alveolar epithelial cells. Release of such mediators stimulates fibroblast proliferation and induces fibrosis.*

In conclusion, results of in vitro and animal studies have provided the basis for proposing mechanisms that may lead to the initiation and progression of CWP and silicosis. Data obtained from exposed workers has lent support to these proposals. The mechanistic understanding obtained for the development of CWP and silicosis should be useful in elucidating the possible pathogenicity of other inhaled particles.

Coal workers' pneumoconiosis (CWP) is a respiratory disease associated with the inhalation of coal mine dust (Castranova & Ducatman, 1997). CWP is categorized according to severity into simple and complicated CWP. The initial stage of simple CWP is characterized by macules concentrated in the upper lung lobes. Coal macules contain coal-laden macrophages with a fine network of reticulin and some collagen. These macules (1–5 mm in diameter) are typically found at the bifurcations of respiratory bronchioles and may be associated with focal emphysema. With increased exposures, coal nodules de-

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velop, which are areas of fibrous material detectable upon palpitation. As coal nodules converge and coalesce to ~2 cm in size, the disease progresses to complicated CWP, also known as progressive massive fibrosis (PMF). This histological progression of disease is also noted radiographically. In simple CWP, round opacities appear initially in the outer fields of the upper lung zones. As the disease progresses to PMF, the size (>1 cm) and number of opacities increase. Simple CWP is often symptomless in its early stages. However, as CWP progresses to its complicated form, irreversible airway obstruction and decreased gas exchange become evident.

Silicosis is a respiratory disease associated with the inhalation of crystalline silica (Driscoll & Guthrie, 1997). Acute silicosis can occur in sandblasting, rock drilling, and silica flour milling. The disease is associated with a rapid onset (1–3 yr). Morphologically, the disease is characterized by alveolar proteinosis, that is, edema, interstitial inflammation, and the accumulation of proteinaceous material in the alveolar spaces. Radiographically, acute silicosis exhibits diffuse lesions in the middle and lower lobes. Acute silicosis results in labored breathing, fatigue, cough, weight loss, decreased gas exchange, and decreased pulmonary function. It is often fatal. In contrast, chronic silicosis results from prolonged exposure to crystalline silica with an onset of 20–40 yr. Histologically, it is characterized by silicotic nodules, which are fibrotic lesions with collagen material arranged in a spiral or whorled pattern. Radiographically, chronic silicosis exhibits rounded opacities initially in the upper zones of the lung. Chronic silicosis is a restrictive lung disease in which pulmonary fibrosis may result in decreased gas exchange and shortness of breath.

PROPOSED MECHANISMS FOR THE INITIATION AND PROGRESSION OF CWP OR SILICOSIS

Interstitial lung disease due to inhalation of coal mine dust or crystalline silica is believed to be the consequence of pulmonary damage that results in inflammation, fibrosis, and lung scarring. In vitro and animal studies have contributed greatly to development of a mechanistic framework to understand the molecular and cellular processes that lead to initiation and progression of CWP and silicosis. Data obtained from exposed workers has lent support for these proposed mechanisms. The following framework has been proposed to describe events that result in a cycle of damage and scarring in response to exposure to coal mine dust or silica (Lapp & Castranova, 1993; Castranova & Vallyathan, 2000).

1. Direct cytotoxicity: Surface properties of silica or coal mine dust can result in damage to lung cells. Damaged cells can release enzymes or reactive products, which could lead to tissue destruction and/or lung scarring.
2. Stimulation of oxidant production by alveolar macrophages: Silica or coal mine dust interacts with alveolar macrophages and results in enhanced generation of reactive oxidant species by these phagocytes. If antioxidant

defenses are exceeded, lipid peroxidation and protein nitrosation occur, resulting in tissue injury and consequent scarring.

3. Activation of mediator release from alveolar macrophages and/or alveolar epithelial cells: Chemokines recruit polymorphonuclear leukocytes and macrophages from the pulmonary capillaries to the air spaces. Once within the air spaces, proinflammatory cytokines activate these leukocytes to produce reactive oxidant species, which lead to further tissue injury and lung scarring.
4. Secretion of growth factors from alveolar macrophages and/or alveolar epithelial cells: Release of fibrogenic factors can stimulate fibroblast proliferation and enhance collagen synthesis, resulting in fibrosis.

Direct Cytotoxicity

Both crystalline silica and coal mine dust have been shown to cause lipid peroxidation and cell damage in vitro. Markers of cellular damage are also elevated after pulmonary exposure in vivo. These toxic responses are summarized in Table 1. In general, silica-induced cytotoxicity and lung damage are more pronounced than for coal dust.

Nash et al. (1966) proposed that the unique toxicity of silica was due to the ability of surface SiOH groups to act as H donors and participate in forming hydrogen bonds with biological membranes. Nolan et al. (1981) suggested that it was the negative charge of the surface SiO^- groups that was critical to cytotoxicity. Evidence indicates that fracturing crystalline silica generates $Si^{\cdot}$ and $SiO^{\cdot}$ radicals on the cleavage planes, which can produce $^{\cdot}OH$ radicals in aqueous medium (Vallyathan et al., 1988). Freshly fractured silica has been shown to be more cytotoxic both in vitro and in vivo than aged silica (Castranova et al., 1996).

TABLE 1. Evidence that Silica and Coal Mine Dust Exhibit Direct Cytotoxicity

	In vitro		In vivo	
Toxic response	Silica	Coal dust	Silica	Coal dust
Lipid peroxidation	++	+	++	NR
Hemolysis	++	+	NR	NR
LDH release	++	+	++	NR
Lysosomal enzyme release	++	+	++	–
Inhibition of mammalian cell growth	NR	+	NR	NR
Increased permeability of T_{II} monolayers	++	NR	NR	NR
Apoptosis	++	NR	++	NR
Lavage protein	NR	NR	++	+
Lavage RBC	NR	NR	++	NR

Note. Key: – indicates no significant response; + indicates a significant increase; ++ indicates a greater increase than +; NR indicates that a response has not been reported. From Castranova and Vallyathan (2000), Lapp and Castranova (1993), Castranova (1998), Castranova and Ducatman (1997), and Driscoll and Guthrie (1997).

The cytotoxicity of coal mine dust has been related to the content of metals, such as nickel, in the dust (Christian & Nelson, 1978). As with silica, fracturing coal generates surface radicals. However, coal-based radicals seem less bioactive than those generated on freshly fractured silica (Vallyathan, 1994).

Stimulation of Oxidant Production by Alveolar Macrophages

Both silica and coal mine dust have been shown to increase the production of reactive oxygen and nitrogen species by alveolar phagocytes. These responses are summarized in Table 2. In general, in vitro and animal data agree well with data obtained from workers with silicosis or CWP. In animal models, a correlation exists between the pathogenicity of the dust, lung damage, and the ability to stimulate oxidant production (Blackford et al., 1997). Data, demonstrating a similar correlation in humans between oxidant production and disease severity have been reviewed previously (Lapp & Castranova, 1993). As with direct cytotoxicity, silica appears to be a more potent stimulant of oxidant production by alveolar macrophages than coal dust. In addition, freshly fractured silica is a more potent stimulant of oxidant production by alveolar phagocytes than aged silica (Castranova et al., 1996).

Activation of the Release of Proinflammatory Mediators

Following exposure to silica, marked inflammation characterized by recruitment of polymorphonuclear leukocytes has been reported in animal models and exposed workers (Lapp & Castranova, 1993). In general, the magnitude of pulmonary inflammation and the degree of PMN recruitment is less dramatic after coal mine dust exposure than silica exposure (Blackford et al., 1997). Pulmonary inflammation is substantially greater after exposure of rats to freshly fractured silica compared to exposure to silica that has been aged for 2 mo after fracturing (Castranova et al., 1996).

Recruitment of phagocytic cells into the alveolar air spaces is in response to the production of proinflammatory cytokines and chemokines by alveolar macrophages and/or alveolar type II epithelial cells (Driscoll & Guthrie,

TABLE 2. Evidence that Silica and Coal Mine Dust Stimulate Oxidant Release from Alveolar Macrophages

	In vitro		Animals		Humans	
Oxidant production	Silica	Coal dust	Silica	Coal dust	Silica	Coal dust
Superoxide anion	++	NR	NR	NR	++	+
Hydrogen peroxide	++	NR	++	NR	++	+
Chemiluminescence	++	NR	++	+	++	+
Nitric oxide	–	NR	++	+	+	+

Note. Key: – indicates no significant response; + indicates a significant increase; ++ indicates a greater increase than +; NR indicates that a response has not been reported. From Castranova and Vallyathan (2000), Lapp and Castranova (1993), Castranova (1998), Castranova and Ducatman (1997), and Driscoll and Guthrie (1997).

1997; Barrett et al., 1998, 1999). A list of inflammatory mediators whose production is stimulated by silica or coal mine dust exposure is given in Table 3. Leukotriene B_4, platelet activating factor (PAF), and interleukin-1 (IL-1) are reported chemoattractants for PMN (Driscoll & Guthrie, 1997; Lapp & Castranova, 1993). Tumor necrosis factor-α (TNFα) has been reported to be a chemoattractant for monocytes and PMN (Ming et al., 1987). It is also a potent stimulant of chemokines, such as macrophage inflammatory protein (MIP-1 and MIP-2) and cytokine-induced neutrophil chemoattractant (CINC) (Driscoll et al., 1995). Indeed, a direct relationship exists between TNFα production and PMN recruitment in silica-exposed rats (Driscoll & Guthrie, 1997). Once recruited into the air spaces, PMN release of oxidants can be stimulated by several proinflammatory cyokines, such as PAF, IL-1, and TNFα, thus adding to the oxidant burden in the lung (Lapp & Castranova, 1993). Data are most complete for in vitro exposure, where silica appears to be a more potent stimulant of proinflammatory mediators than coal mine dust.

Secretion of Growth Factors From Alveolar Pneumocytes

The stimulatory effects of dusts on the production of fibrogenic factors have been most extensively investigated in bronchoalveolar lavage cells harvested from miners with CWP. As shown in Table 4, the production of numerous fibrogenic mediators has been found to be elevated in CWP. Platelet-derived growth factor and fibronectin are competence factors, while alveolar macrophage-derived growth factor is a progression factor. TNFα is not only

TABLE 3. Evidence that Silica and Coal Mine Dust Stimulate the Release of Proinflammatory Mediators

	In vitro		Animals		Humans	
Mediator	Silica	Coal dust	Silica	Coal dust	Silica	Coal dust
Platelet activating factor	++	+	NR	NR	NR	NR
Leukotriene B_4	+	–	+	+	NR	–
Prostaglandin E_2	++	+	+	NR	NR	–
Thromboxane A_2	++	+	NR	+	NR	–
Tumor necrosis factor-α	++	+	++	NR	NR	+
Interleukin-1	++	+	+	NR	NR	+
Interleukin-6	++	+	NR	NR	NR	+
Interleukin-8	+	+	NR	NR	NR	+
Cytokine-induced neutrophil chemoattractant	NR	NR	++	NR	NR	NR
Macrophage inflammatory protein	+	NR	++	NR	NR	NR
Monocyte chemoattractant peptide	+	NR	NR	NR	NR	+

Note. Key: – indicates no significant response; + indicates a significant increase; ++ indicates a greater increase than +; NR indicates that a response has not been reported. From Castranova and Vallyathan (2000), Lapp and Castranova (1993), Castranova (1998), Castranova and Ducatman (1997), Driscoll and Guthrie (1997), Barrett et al. (1998, 1999), Steerenberg et al. (1998), Stringer et al. (1996), and Kim et al. (1999).

TABLE 4. Evidence that Silica and Coal Mine Dust Stimulate Growth Factor Secretion from Pneumocytes

	In vitro		Animals		Humans	
Growth factor	Silica	Coal dust	Silica	Coal dust	Silica	Coal dust
Tumor necrosis factor-α	++	+	++	NR	NR	+
Interleukin-1	++	+	+	NR	NR	+
Fibronectin	NR	NR	+	NR	+	+
Transforming growth factor β	+	NR	+	NR	NR	+
Alveolar macrophage-derived growth factor	NR	NR	NR	NR	+	+
Platelet-derived growth factor	NR	+	NR	NR	NR	+
Type I insulin-like growth factor	NR	NR	NR	NR	NR	+

Note. Key: – indicates no significant response; + indicates a significant increase; ++ indicates a greater increase than +; NR indicates that a response has not been reported. From Castranova and Vallyathan (2000), Lapp and Castranova (1993), Castranova (1998), Castranova and Ducatman (1997), Driscoll and Guthrie (1997), Absher et al. (1993), and Kim et al. (1999).

a direct proliferative agent for fibroblasts, but has been shown to simulate the secretion of platelet-derived growth factor in vitro (Hajjar et al., 1987). The critical role of TNFα in fibrogenesis is demonstrated by the report that treatment of silica-exposed mice with a TNFα antibody significantly decreases pulmonary fibrosis (Piquet et al., 1990).

Role of Oxidants in Control of Inflammatory and/or Fibrotic Mediators

Recent evidence indicates the binding of transcription factors to gene promoter sites on DNA is a step controlling the induction of mRNA levels for a number of proinflammatory cytokines and proliferative agents. Silica has been reported to activate nuclear factor kappa B (NFκB) binding to DNA in macrophages after in vitro exposure and in rat bronchoalveolar lavage cells harvested after in vivo exposure (Chen et al., 1998; Sacks et al., 1998). DNA binding of a second transcript factor, activator protein-1 (AP-1), is also stimulated by exposure of lung epithelial cells to silica (Ding et al., 1999). In addition, AP-1 has been reported to be activated by coal dust (Huang et al., 1998). Both silica-induced activation of N-FκB and AP-1 are inhibited by antioxidants or treatments that decrease the radical generating potential of silica. Indeed, freshly fractured silica is a more potent activator of AP-1 than aged silica (Ding et al., 1999).

CONCLUSION

In vitro and animal exposure investigations have been of great value in constructing a mechanistic model for the initiation and progression of CWP or silicosis (Figure 1). Data for workers exposed to coal mine dust or silica

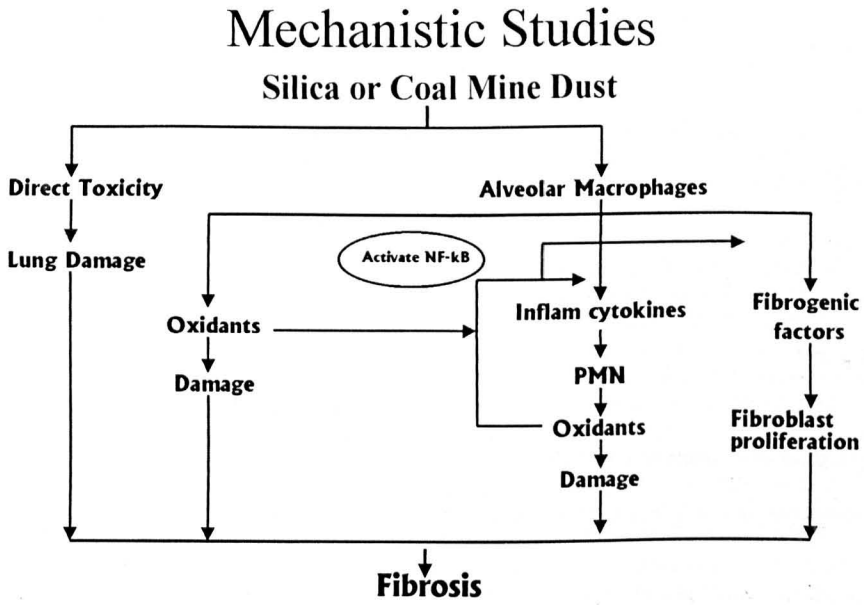

FIGURE 1. Mechanistic model for pathogenicity of silica or coal mine dust.

support the applicability of this model. This mechanistic model for CWP and silicosis should be useful for the elucidation of the pathogenicity of other occupational dust exposures (Castranova, 1998).

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