Section V
Chapter 3

POTENTIAL MECHANISMS OF SILICA-INDUCED CANCER

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CONTENTS

I. INTRODUCTION

Although the last 20 years have led to considerable advances in cancer research, a complete understanding of the mechanism of action for any given carcinogen, including silica, as a lung cancer inducer is still lacking. Currently, the generally accepted concept is that carcinogenesis is a long-lasting, multistage, multigenic, and multicausal process. As such, both genetic and epigenetic factors are probably important. In other words, cancer is regarded as the end point of a connected series of changes and/or actions. A three-stage theory of initiation, promotion, and progression has been proposed on the basis of experimental induction of mouse skin cancer by the application of a polycyclic aromatic hydrocarbon (PAH).[1] More recently, the multistage nature of carcinogenesis has been demonstrated with various chemical compounds for other tissues such as liver, urinary bladder, thyroid, mammary gland, and lung.[1] Further experiments have shown that initiation is an irreversible process, while promotion is reversible and can be further divided into several substages.[1] It is now believed that initiation is related to DNA damage, or genotoxic effects, but promotion is considered to be an epigenetic process. During the promotion stage, initiated cells expand clonally over surrounding normal cells. Recent studies suggest

that the activation of cellular proto-oncogenes or the deactivation of tumor suppressor genes may be responsible for certain cancers, and that the crucial targets for chemical carcinogens inside cells are specific proto-oncogenes.[2] The normal physiological role of some cellular proto-oncogenes is in the control of cell proliferation and cell differentiation. Alteration of their normal function by chemical carcinogens may therefore change the differentiation pathway and lead to tumor formation.[2]

Silica, a group of minerals including many occupationally important dusts, is polymorphic. Various forms of silica, including α- and β-quartz, display diverse physical properties such as particle size, surface properties, and crystallinity. Different varieties also contain different impurities, some of which are thought to reduce the biological activity of "free silica."[3] The differences in physical and chemical properties of silica varieties do influence their pathogenic effects, including carcinogenicity.[4] This makes the carcinogenesis of silica more complex. Moreover, it is believed that the multistage process of carcinogenesis can be influenced by a variety of exogenous and endogenous factors. Human beings are surrounded by chemical, physical, and biological factors which may be mutagenic and/or carcinogenic. Simultaneous or sequential combinations of these factors may modify the reaction of the exposed human body, resulting in a response different from the response that any single factor could induce. It is especially important to note that, in addition to silica dust, workers often are simultaneously exposed to many chemical compounds in their living environment and workplaces; therefore, combination effects in silica carcinogenesis should be considered.

Here, we review the genotoxic and epigenetic activities of silica and the combination effects of known carcinogens with silica dust. To some extent, the reason that our understanding of the mechanisms of chemical carcinogenesis in general, and of silica carcinogenesis in particular, is rather limited is that there is no obvious approach to such mechanistic studies. Therefore, based on recent developments in understanding the role of oncogene activation in chemical carcinogenesis, some possible mechanisms of silica carcinogenesis are discussed.

II. SILICA AS A GENOTOXICANT

The term genotoxicant is a general description, distinguishing chemicals that have an affinity for direct DNA/chromosome interaction from those that do not. Genotoxicants produce alterations or damage in the genetic material at subtoxic exposure levels. Silica has not been studied extensively as a genotoxicant. The genotoxicity data for silica from available literature and some results from our laboratory are summarized below.

A. GENE MUTATION

The Ames Salmonella/microsome assay measures mutation in histidine-requiring auxotrophs of *Salmonella typhimurium*. Mutant strains are used to detect agents which cause base pair substitution or frameshift mutations. One study has shown that silica is not mutagenic in tester strains TA98, TA100, TA1535, TA1537, and TA1538.[5] The rec-assay in *Bacillus subtilis* is also negative.[6] Data are not available for mutagenesis assays using mammalian cells.

B. CLASTOGENICITY

Min-U-Sil, a type of α-quartz, at the concentration of 1 μg/cm^2 caused no change in the number of binucleated and micronucleated Syrian hamster embryo (SHE) cells, nor was there evidence of a change in the percentage of tetraploid or near-tetraploid cells compared to untreated controls. However, when cells were treated with a dose of Min-U-Sil (20 μg/cm^2) similar in transforming potency to 1 μg/cm^2 of chrysotile asbestos, an increase in the incidence of cells with micronuclei was observed.[7] Micronuclei are formed either by acentric chromosomal fragments due to chromosomal breakage or by centric chromosomes lagging behind in mitosis due to spindle damage. Therefore, the increase in the incidence of micronuclei following treatment of cells is an indication of clastogenic and/or aneuploidogenic activity of silica. The number of binucleated cells also increased relative to controls, but not to the same degree as in asbestos-treated cells. The incidence of tetraploid cells was not significantly increased in the Min-U-Sil-treated cells. This contrasts with the effects observed following chrysotile asbestos treatment.

A nonfibrous mineral dust, α-quartz, at the concentration of 2 μg/cm^2 did not induce chromosomal aberrations, micronucleus formation, or binucleated cells in SHE cells following 48-h exposure.[8] Positive results were found in other experiments.[9] The *in vivo* studies of Vanchugova et al.[10] demonstrated that

quartz did not induce micronuclei in mice following one intraperitoneal injection at a dose of 500 mg/kg b.w. Price-Jones et al.[11] found no increase in the number of aneuploidies and polyploidies or in the frequency of sister chromatid exchanges (SCE) in Chinese hamster lung fibroblasts (V79) cells treated with Min-U-Sil at concentrations ranging from 1 to 15 μg/ml.

Recently, Pairon et al.[12] tested samples of Min-U-Sil <5 and tridymite 118 using the SCE assay in human monocytes and lymphocytes. The results showed that the level of SCE was increased after combined cultures of lymphocytes and monocytes were treated with tridymite and Min-U-Sil <5 separately at a concentration of 100 μg/ml. The increase, however, was not observed in purified lymphocytes. There was no increase in the SCE levels with tridymite filtrates. These tests indicate that the induction of SCE in lymphocytes results from an interaction of lymphocytes and monocytes with tridymite particles, not from soluble compounds released in the culture medium by tridymite.

C. DNA DAMAGE AND REPAIR

Silicic acid leached from silica is considered to be responsible for some of the pathological alterations associated with silica toxicity. DNA strand breaks, after exposure of cells to silicic acid, have been detected by the alkaline unwinding assay, which is considered to be a sensitive technique for the quantitation of strand breaks in cellular DNA induced by various chemical and physical agents. This effect is temperature dependent. Relative to room temperature, higher temperatures cause the formation of a larger number of strand breaks, indicating an increased rate of reaction of silicic acid with DNA.[13] Silicic acid has also been shown to cause a disruption of the secondary structure of DNA *in vitro*.[14] Such disruption may be due to single-strand breaks.[13]

D. CELL TRANSFORMATION

Unlike other short-term assays, *in vitro* cell transformation systems have been developed to simulate the *in vivo* process of carcinogenesis. Under normal conditions, the mammalian cells used for *in vitro* transformation assays will grow in a monolayer until they reach confluency. However, due to genetic and/or epigenetic changes induced by carcinogens, some of the cells may lose control and continue to divide. The dividing cells will pile up and form transformed foci. Thus, these systems have been used to detect potential carcinogens regardless of their mechanisms of action, i.e., genotoxic or nongenotoxic.[15]

Using SHE cells, Hesterberg and Barrett[9] have shown that at concentrations comparable to transforming concentrations of chrysotile asbestos (0.25–1 μg/cm^2), Min-U-Sil and another α-quartz sample were neither cytotoxic nor transforming in SHE cells. However, at 10 μg/cm^2, both quartz dusts reproducibly enhanced the colony-forming efficiency of cells, although further increases in concentration resulted in decreases in relative survival. Both types of dust induced a dose-dependent increase in transformation frequency at concentrations greater than 2 and 10 μg/cm^2, respectively. Min-U-Sil was more potent than the other α-quartz at all concentrations tested. The slopes of the dose-response curves for these quartz dusts were 0.7 and 0.5, respectively. Electron microscopic examination of both quartz dusts revealed the presence of only nonfibrous particulates in these samples. However, Oshimura et al.[8] reported that nonfibrous α-quartz induced neither cell transformation nor cytogenetic effects in SHE cells at the concentration of 2 μg/cm^2.

Saffiotti and co-workers[15a] have found that four silica dust samples including Min-U-Sil <5 induced cell transformation in BALB/c-3T3 cells. The response was dose dependent up to 25–50 μg/cm^2 followed by plateau. In our laboratory, Min-U-Sil <5 silica dust particles were examined using the BALB/c-3T3 cell transformation system. Positive results were found for concentrations of 90 μg/cm^2 and higher. The data are presented in Table 1.

E. CONCLUDING REMARKS

Studies of Hesterberg and co-workers[7] have shown that silica can be taken up by mammalian cells and can accumulate in the perinuclear region. These findings, as indicated by the authors, suggest that mineral particulates might indeed gain access to the genetic material of the cell, especially during mitosis when the nuclear membrane disappears. It is not known, however, whether silica per se, chemicals associated with silica, or mediators and free radicals generated directly or indirectly by silica are responsible for the genotoxicity described in the previous sections.

It should be noted that some of the results in genotoxicity studies are conflicting. It is not known whether the nongenotoxic response in some reports is due to the low concentration of silica, the different

TABLE 1
Induction of Cell Transformation in BALB/c-3T3 Cells Treated with Min-U-Sil <5 for 72 h

Treatment	Concentration	Relative cloning efficiency (%)	Transformation frequency[a]	
			No. foci per total flasks	Foci per flask (mean ± S.D.)
DMSO	2 µl/ml	100	5/19	0.26 ± 0.10
Min-U-Sil <5	23 µg/cm²	69.7	18/19	0.95 ± 0.24
	45 µg/cm²	36.4	21/20	1.05 ± 0.24
	90 µg/cm²	20.5	23/20	1.15 ± 0.24*
	180 µg/cm²	14.2	22/20	1.10 ± 0.28**
Benzo(a)-pyrene	2 µg/ml	—	38/20	1.90 ± 0.31

[a] Only Type III foci scored.
* $p < 0.05$,
** $p < 0.01$.

assay systems, or the different test protocols used. The concentration of silica used in the experiments varies highly from study to study.

An hypothesis has been formulated to explain the role of monocytes in the induction of SCE in lymphocytes by silica particles. Phagocytosis of silica particles by monocytes could be followed by release of mediators from monocytes, some of which may be responsible for inducing SCE in lymphocytes.[12] Monocytes are known to release interleukin 1, prostaglandins, leukotrienes, oxygen derivatives, arachidonic acid, and growth factors after stimulation.[16,17]

Grinding of silica produces $\dot{S}i$ and $Si\dot{O}$ radicals. These silicon and silicon-oxygen-based radicals react with metal ions in silica-containing aqueous media to produce highly reactive species such as the hydroxyl radical, $\dot{O}H$.[18] Hydroxyl radicals react with DNA and generate a series of modified purine and pyrimidine bases which could lead to gene mutations and other genetic damage.[19] Daniel et al.[20] found that freshly ground crystalline silica caused detectable changes in phage λ DNA due to formation of crystalline silica-derived superoxide free radicals in aqueous solution. Silica also has been found to affect lipid peroxidation. Peroxy radicals, cytotoxic aldehydes, and alkoxy radicals, generated by decomposition of lipid peroxides, may also cause DNA damage.[19]

III. EPIGENETIC ACTIVITIES

Any activities which influence the phenotype without damaging and/or altering DNA/chromosomes are epigenetic activities. Induction of cell proliferation, for instance, is considered to be an epigenetic activity. It is known that macrophages release substances that stimulate fibroblasts and induce fibrosis.[21] Several studies have suggested that silica interacts with macrophages, leading to production of a factor or factors that, in turn, alter fibroblast proliferation. *In vitro* studies have also shown that silica has a direct effect on fibroblasts. Absher and Sylvester[22] found a variable proliferative response to silica that appeared to be related to the age and type of fibroblast cultures. Thus, some fibroblast cultures are stimulated to proliferate in the presence of silica, while others are not. Pathological studies indicate that epithelial proliferative lesions in rats exposed to dusts appear to be located near fibrotic reactions.[17] In mice, silica was reported to penetrate Type 1 alveolar epithelial cells, causing cell injury and cell death, but this was rapidly repaired by induced proliferation of Type 2 alveolar epithelial cells.[17] Mediators such as interleukins, prostaglandins, and tumor necrosis factor released by monocytes after phagocytosis of silica particles are related to the inflammatory process, cell proliferation, and differentiation.[23]

IV. SYNERGISTIC OR COMBINATIONAL EFFECTS

In addition to silica, workers may also be exposed, intentionally or unintentionally, to other agents such as cigarette smoke, other chemicals, and radiation. Limited evidence indicates that there are synergistic or combinational effects.

A. CIGARETTE SMOKE

The available information indicates that dusty trade workers who smoke are at greater risk of lung cancer than either smokers unexposed to silica or nonsmokers exposed to silica. As indicated by Goldsmith and Guidotti[24] in their review of the literature, cigarette smoking plays a prominent role in the development of lung cancer in dusty trade workers and in silicotics.

It has been reported that smoking underground gold miners[25] and smoking silicotics[26] have a high relative risk for lung cancer compared to nonsmoking miners, dust-exposed nonsmokers without fibrosis, or unexposed nonsmokers. These reports support the synergistic effects of the combination of silica exposure and smoking.[24–26] However, in most epidemiological studies, cigarette smoking, though a major confounding factor, was not adjusted for in the findings. This factor must be included in future risk assessment studies of silica-exposed workers, and the synergistic or combinational effect of silica exposure and cigarette smoke needs further investigation.

B. CHEMICALS

PAH include hundreds of compounds which have attracted much attention because many of them are carcinogenic, especially those containing four to six aromatic rings. PAH are formed by pyrolysis or incomplete combustion of organic materials containing carbon and hydrogen. In the air, PAH are emitted as vapors from the zone of burning. Due to their low vapor pressures, most PAH will immediately condense as particles on soot or form very small particulates themselves. Those entering the atmosphere as vapor will be adsorbed by existing particles, including silica dusts. The most important source of PAH in the occupational environment is coal tar, formed by pyrolysis of coal in gas and coke works where emission of fumes from the hot tar occurs. Tar preparations are used in furnaces and ingot molds.[27] Many steel and foundry workers who are chronically exposed to silica also inhale carcinogenic pyrolysis products of hydrocarbons such as PAH adsorbed by silica dusts.

Stenbäck and Rowland[28] showed that intratracheal instillation of benzo(a)pyrene (BaP), a PAH, in combination with silica results in a high incidence of lung tumors. When instilled alone, the silica dusts induced nonspecific bronchial epithelial alterations, interstitial cell proliferation, and a few granulomatous changes in the lung. No respiratory tract tumors were seen. BaP alone induced only tracheal epithelial alterations, desquamation and metaplasia, and a few papillomas or squamous cell carcinomas. Silica with BaP was highly effective in inducing papillomas; squamous cell carcinomas; adenomas; and adenocarcinomas of the larynx, trachea, and lung. The tumors were preceded by epithelial proliferative dysplastic alterations not seen in animals treated with BaP plus MnO_2 or dibenzanthracene plus Fe_2O_3.[28,29]

Niemeier et al.[30] used Syrian hamsters to test ten silica compounds or silica substitutes and iron oxide administered in saline by intratracheal instillation. The respirable particle dosage was based on surface area standardized to Min-U-Sil 5. Each group receiving silica was matched to a group receiving silica plus BaP. There were no tumors in saline-treated control and very few in silica-treated animals, but silica plus BaP-treated animals showed significantly more tumors than saline plus BaP control animals.[30]

A high incidence of respiratory disease among hematite miners in the northwest of Britain has been noted. Pathological studies suggest that lung cancer is a relatively common cause of death, apparently related to the presence of siderosilicosis.[31] While it is possible that a combination of iron and silica is carcinogenic to the lung, an alternative cause was suggested when a survey of radon in British mines revealed high levels of radiation in these same hematite mines.

C. RADIATION

An excess of lung cancer among underground miners has been observed.[32,33] The question of whether or not silica and radon daughters are both involved in the induction of lung cancer has been investigated. Silica is one of the most abundant minerals in the crust of the earth, and it is found in the air of most underground mines. On the other hand, any hole in the ground will contain higher levels of radon and radon daughters than those which occur on the ground surface, due to the small amounts of uranium and radium occurring in all soils, which are constantly emitting radon. This means that most miners are exposed to both silica dust and higher than normal levels of radon and radon daughters. However, the quantitative relationship between the two agents often differs. This difference has been used to assess the role of the two agents in the development of lung cancer in miners. Archer et al.,[33] in their review paper, indicated that lung cancer incidence is a function of radon daughter exposure in hard rock mines where a variety of ores from iron to uranium have been excavated. A similar relationship between radon daughter exposure and lung cancer has been demonstrated in rat experiments where there was no

accompanying silica exposure. In uranium mines, there is no correlation between levels of airborne quartz dust and radon daughters. The rates of silicosis and lung cancer were compared among five mining or milling groups selected on the basis of their exposure to silica dust and radon daughters. When quartz dust levels were high, pneumoconiosis rates were high. However, lung cancer rates were high only when radon daughter levels were also elevated. This comparison demonstrates that the two effects of mine exposures are basically independent, although there may be some minor interaction between the two disease-producing agents. The independent action is supported by the Swedish mining experience with different ventilation rates of the air through old mines to warm the air. Large volumes of air greatly lowered the airborne quartz concentrations, but tended to increase radon daughter levels. As a result, the frequency of silicosis was markedly reduced in the cohorts, whereas lung cancer rates rose or remained unchanged.[33]

In contrast, miners with very low exposures to radon and decay products have had little or no excess of lung cancer (i.e., in coal, potash, and iron mines). It seems therefore that radioactivity rather than other factors in the mine atmosphere is mainly responsible for the lung cancer risk, even if some other agents may be contributors. In some mining situations, other factors such as diesel exhaust or heavy metals in respirable particles may contribute to a carcinogenic hazard. It has become clear in recent years, however, that certain silica dust exposure is associated with lung cancer risk, and some contribution to lung cancer in miners cannot be ruled out.[34]

D. CONCLUDING REMARKS

Occupational exposures to mineral dusts, including silica dusts, are particularly complex. The mineral mixture to which workers are exposed may differ according to geological source. Workers in different processes, such as mining, milling, production, and use, may be exposed to different mineral phases and components. Workers are exposed to additional agents in the occupational environment and in daily life. Therefore, a combinational effect of silica with other known carcinogens or suspected causative agents should be considered when silica-induced lung cancer is investigated. Other agents may potentiate the induction of lung cancer by silica, or may act as confounding factors. In most investigations conducted in an effort to assess the role of silica exposure in the pathogenesis of lung cancer, confounding factors, such as cigarette smoking and nonsiliceous environmental pollutants, have not been considered. It is important to determine the contribution of other factors to the incidence of lung cancer among silica-exposed workers. In addition to epidemiologic studies, animal experiments (for example, the intratracheal instillation of BaP in combination with silica results in a high incidence of lung tumors) and *in vitro* assays may be of great help in solving this problem. The combination and/or synergistic effect of the factors mentioned in this section should be considered with respect to the role of silica in the pathogenesis of bronchogenic carcinoma in humans.

V. POTENTIAL MECHANISM OF CARCINOGENESIS

As described in the other chapters and according to the International Agency for Research on Cancer, there is sufficient and limited evidence for the carcinogenicity of crystalline silica in experimental animals and humans, respectively.[4] However, the mechanism of cancer induction by silica in either animals or humans has not been elucidated. Based on a knowledge of chemical carcinogenesis in general and genotoxic as well as epigenetic activities, it may be construed that silica may act as initiator and/or promotor in multistage carcinogenesis and/or may act as a cocarcinogen.

A. AS AN INITIATOR

The somatic mutation theory for the etiology of cancer was proposed in the 1920s. This theory receives support from the observations that

1. Cancer originates from a single cell or a clone.
2. Cancer cells possess heritable phenotypes.
3. There is a correlation between mutagenicity and carcinogenicity of certain groups of chemicals.
4. Certain chromosomal aberrations and gene mutations are related to cancer incidence.
5. Defective DNA repair increases cancer risk.

Researchers generally agree that alteration of genetic material plays an important role in the initiation and progression of chemical carcinogenesis.

Recent studies in the area of molecular biology have found that more than 50 and possibly as many as 100 genes in the eukaryotic organism are involved in the governance of cell growth and/or differentiation.[35] These genes generally are referred to as proto-oncogenes and tumor suppressor genes. Indeed, genetic alteration or damage in these genes, the *ras* proto-oncogene and p53 tumor suppressor gene in particular, has been shown to be present in a variety of human cancers. Proto-oncogenes can be activated and tumor suppressor genes can be deactivated by gene amplification, gene rearrangement, or point mutation.[35]

The mechanism of gene amplification is not yet clear. Different models including replication, unequal exchange, episome excision, double rolling circle, and chromosome breakage have been proposed as possible mechanisms for mammalian gene amplification. A recent review regarding these models has been provided by Windle and Wahl.[36] Using SV40 as a model, Aladjem and Lavi[37] have shown that amplification of viral sequences may be induced by chemical carcinogens in a replication-dependent manner which involves overactivation of the origin region and the generation of inverted repeats. In a variety of tumors, one or another proto-oncogene is known to be expressed abundantly because it resides within an amplified region of DNA.[38] Chromosomal translocation, inversion, and deletion can lead to gene rearrangement.[39] If the rearrangement moves a proto-oncogene from where it is usually dormant or suppressed to a location adjacent to an active region of chromosome, the proto-oncogene may be activated. Deletion of certain chromosomal fragments may result in loss of tumor suppressor genes and result in deregulation of cell division and differentiation. Chromosomal translocations and inversions have been reported to be the most common and diverse of the karyotypic abnormalities found in human cancer cells.[40] A point mutation such as a change of a single base at specific sites has been shown to result in expression of the transforming activity of proto-oncogenes. Different point mutations have been associated with different cancer types.[41,42]

Induction of micronuclei in mammalian cells by silica indicates that silica is clastogenic and/or aneuploidogenic. Induction of chromosomal or DNA breaks may lead to translocation, deletion, or inversion. Free radicals generated directly or indirectly by silica dusts may induce point mutations. Therefore, silica may act as an initiator in multistep carcinogenesis. Genetic alteration or damage caused by silica may also be involved in the progression stage of carcinogenesis. A recent study reported by Ahmed and Saffiotti[43] shows that the transformed BALB/3T3 cells induced by quartz are tumorigenic in nude mice and have new chromosomal translocations as well as elevated expression of several proto-oncogenes including *ras* and p53.

B. AS A PROMOTER

Chemical carcinogens can be broadly grouped into genotoxic carcinogens and nongenotoxic or epigenetic carcinogens. An epigenetic carcinogen is operationally defined by the absence of genotoxicity as demonstrated by short-term assays. The carcinogenic mechanism of epigenetic carcinogens is not well understood. They are believed, however, to act by altering gene expression without permanent damage to the genetic material, leading to cell proliferation. Epigenetic carcinogens therefore may act as promoters. For instance, the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA), an epigenetic carcinogen, is a known promoter. Its promoting action is accompanied by inhibition of cell differentiation and enhancement of proliferation and by alteration of enzymes and cell surface properties. Induction of cell proliferation by chemical agents, either by direct mitogenesis of the target cell population or by cytotoxicity and consequent regenerative proliferation, has been suggested to play an important role in chemical carcinogenesis.[44] It may be involved in the fixation and/or expression of oncogenic changes.

Epidemiological studies show that the incidence of lung cancer is higher in silicotics than in exposed workers without silicosis.[45] A mortality study of South African gold miners showed no association between lung cancer and silicosis of the parenchyma or pleura, but a positive association existed between silicosis of the hilary glands and lung cancer.[46] Experimental foreign body tumorigenesis has demonstrated a role of chronic fibrosis in the induction of tumors.[21] Hepatitis B virus can cause chronic hepatitis and cirrhosis, characterized by persistent necrosis and regenerative hyperplasia, and is also associated with an increased incidence of hepatoma.[47] The common element in these observations is the presence of chronic fibrosis. Fibrosis is causally linked to preneoplastic promotion. This role appears plausible in

view of the structural disorder inflicted on tissues and organs. Intercellular communication and, consequently, homeostatic growth regulation are impaired as evidenced by the frequent development of epithelial dysplasias adjacent to fibrotic areas.[20]

Concerning the relationship of cell proliferation to silica-induced lung cancer, the following hypothesis has been proposed: one or more of the cell mediators released by macrophages and other reticuloendothelial cells during the complex process of fibrogenesis acts upon the adjacent epithelial cells of the distal airways throughout the duration of the fibrogenic response to induce cell damage and/or stimulate cell proliferation. These effects act in combination with direct genetic damage, possibly at the chromosomal level, induced by silica particles upon the epithelial cells in the early phases of the pulmonary response. In so doing, they provide a combined mechanism sufficient to account for the full carcinogenic activity of silica on the epithelia of susceptible species.[17]

The role of silica in the synergistic or combinational effects on carcinogenesis is not known. Radiation, many PAH, and chemicals associated with cigarette smoke are known to be genotoxic and carcinogenic. These agents are capable of altering or damaging genes, including proto-oncogenes and tumor suppressor genes. It is possible therefore that silica may act as a promoter, causing the damaged cells to proliferate and leading to cancer development. This may account for the results discussed above in the section on Synergistic or Combinational Effects.

C. AS A COCARCINOGEN

Silica may act as a cocarcinogen by functioning as a vehicle for an adsorbed carcinogen such as BaP, and also may act as a carcinogen through specific physiological and biochemical activities and through interference with respiratory function.[48] One of the main effects of the vehicle is to increase the retention time of BaP in the lungs. Chemicals which are adsorbed by particles, such as silica, are more rapidly transported to target cells. In addition, silica has been shown to facilitate membrane uptake of BaP.[49]

D. CONCLUDING REMARKS

The possible mechanisms regarding the carcinogenesis of silica discussed in this section are based on conjecture. More studies such as that reported by Ahmed and Saffiotti[43] on the molecular aspects of functional and structural changes caused by silica need to be pursued to more clearly understand the mechanism of silica carcinogenesis.

VI. SUMMARY

Results of animal and epidemiological studies indicate that silica, at least in the crystalline form, may be carcinogenic. The process and mechanism by which silica may induce carcinogenesis are not known. It is known, however, that silica is genotoxic and can cause fibroblast proliferation. Genotoxic and mitogenic effects of silica, its metabolites, free radicals produced, or the mediators released by damaged macrophages and other reticuloendothelial cells may lead to the activation of proto-oncogenes or inactivation of tumor suppressor genes. Such activation and/or inactivation may play an important role in the initiation, promotion, and/or progression of cancer in silica-exposed animal and human populations. More work is needed to better understand the mechanism of silica carcinogenesis.

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