Published in final edited form as:
Transl Res. 2009 April ; 153(4): 143–152. doi:10.1016/j.trsl.2009.01.004.

Asbestos-induced lung diseases: an update

DAVID W. KAMP
Department of Medicine, Division of Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine and Jesse Brown VA Medical Center, Chicago, Ill

Abstract

Asbestos causes asbestosis (pulmonary fibrosis caused by asbestos inhalation) and malignancies (bronchogenic carcinoma and mesothelioma) by mechanisms that are not fully elucidated. Despite a dramatic reduction in asbestos use worldwide, asbestos-induced lung diseases remain a substantial health concern primarily because of the vast amounts of fibers that have been mined, processed, and used during the 20th century combined with the long latency period of up to 40 years between exposure and disease presentation. This review summarizes the important new epidemiologic and pathogenic information that has emerged over the past several years. Whereas the development of asbestosis is directly associated with the magnitude and duration of asbestos exposure, the development of a malignant clone of cells can occur in the setting of low-level asbestos exposure. Emphasis is placed on the recent epidemiologic investigations that explore the malignancy risk that occurs from nonoccupational, environmental asbestos exposure. Accumulating studies are shedding light on novel mechanistic pathways by which asbestos damages the lung. Attention is focused on the importance of alveolar epithelial cell (AEC) injury and repair, the role of iron-derived reactive oxygen species (ROS), and apoptosis by the p53- and mitochondria-regulated death pathways. Furthermore, recent evidence underscores crucial roles for specific cellular signaling pathways that regulate the production of cytokines and growth factors. An evolving role for epithelial-mesenchymal transition (EMT) is also reviewed. The translational significance of these studies is evident in providing the molecular basis for developing novel therapeutic strategies for asbestos-related lung diseases and, importantly, other pulmonary diseases, such as interstitial pulmonary fibrosis and lung cancer.

Asbestos is a term for a group of naturally occurring hydrated silicate fibers whose tensile strength and resilience are ideal for a variety of construction and insulation purposes. The word “asbestos” is derived from the Greek word for “inextinguishable” or “unquenchable.”1 Industrial production of asbestos began in the 1850s, but by the middle of the 20th century, it was evident that asbestos exposure increased the risk for non-malignant inflammatory (pleural effusions, pleural plaques, rounded atelectasis, and asbestosis) and malignant (mesothelioma and bronchogenic carcinoma) pulmonary diseases.2–4 The first cases of asbestos-associated fibrosis were described in the early 1900s, and the term “asbestosis” was coined by Cooke in 1927.5 Asbestos-associated bronchogenic carcinoma was established by the mid-1950s, whereas the association between asbestos and malignant mesothelioma (MM) was recognized by the 1960s. In the early 1970s, the United States placed a moratorium on asbestos use, and at least 40 other countries have banned or severely restricted asbestos use.6 However, asbestos continues to challenge health care providers and the medico-legal system such that the translational aspects of new studies in this field are urgently needed. The purpose of this review is to summarize the important information

Reprint requests: David W. Kamp, MD, Pulmonary and Critical Care Medicine, Northwestern University Feinberg School of Medicine, McGaw M-330, 240 E. Huron St., Chicago, IL 60611-3010; d-kamp@northwestern.edu.

reported over the last several years that has increased our understanding of the epidemiology and scientific basis for asbestos-induced lung diseases.

EPIDEMIOLOGY

Despite a dramatic decline in asbestos use in industrialized countries since the 1970s, asbestos-induced lung diseases remain a significant health concern for several reasons. First, more than 30 million tons of asbestos have been mined, processed, and used in the United States since the early 1900s.2 An estimated 27 million workers in the United States were exposed to aerosolized asbestos fibers between 1940 and 1979.7 Globally, Lin et al8 recently demonstrated a direct relationship between the national consumption of asbestos (kg per person per year; 1960–1969) in 33 countries and the number of deaths caused by mesothelioma and asbestosis in 2000–2004. Second, a long interval (latency period) exists between fiber exposure and the development of asbestos-induced lung diseases (30 to 40 years). This requires long-term, careful follow-up of people who were exposed both occupationally and nonoccupationally. A recent study of 18,211 sheet metal workers examined between 1986 and 2004 showed that 9.6% had asbestosis and that 21% had pleural disease; the strongest predictor of both was the calendar year in which the worker began sheet metal work (1940s > 1950s > 1960s > 1970s).9 Third, asbestos exposure from consumer products and from fibers released during structural renovation is a source of morbidity and mortality, especially for occupationally exposed workers.3,10 In the year 2000 in the United States, an estimated 20,000 hospital discharges listed “asbestosis,” and of these discharges, asbestosis was the primary or contributing cause of death in 2000 of them. 10 It is estimated that the total number of asbestos-related deaths in the United States may exceed 200,000 by the year 2030.11 Worldwide, asbestos accounts for an estimated 100,000–140,000 lung cancer deaths per year and contributes to nearly 5% to 7% of all lung cancers.12,13 Surveys in Europe and the United States have shown a doubling of the prevalence of asbestos-associated pleural disease, which includes MM, from the early 1970s until 2000.1 The incidence of MM is expected to peak sometime between 2010 and 2020 because of the long latency period.1,14 The prevalence of MM is nearly 2% in asbestos textile workers exposed to approximately 1 fiber/cm^3 over 50 years and accounts for approximately 8% of the deaths in asbestos workers.15 In industrial countries, the yearly incidence of MM is 2 cases per million person-years among women and 10 to 30 cases per million person-years among men, but the rate is as high as 270 to 366 cases per million person-years among men exposed to crocidolite asbestos (see below).14,16 Given the above, it is not surprising that asbestos-related diseases have inundated our legal system, which resulted in very large class-action lawsuits—68,000 individual claims in the year 2000 alone—and the bankruptcy of many old-line industrial companies.1 Collectively, these data support the worldwide severe restriction or ban on asbestos importation and use advocated by the World Health Organization in 2005 and the International Labour Organization in 2006.17,18

It is unclear whether a safe threshold level of asbestos exposure exists that does not increase the risk of malignancy. The Occupational Safety and Health Administration (OSHA) established a permissible exposure limit (PEL) for fibers more than 5 μm long with a 3:1 aspect ratio assessed by phase-contrast light microscopy of 0.1 fibers/cm^3 over an 8-h period for all fiber types. Two classes of asbestos fibers are serpentine and amphibole fibers. Serpentine fibers (eg, chrysotile) are curly stranded structures, whereas amphiboles (eg, crocidolite, amosite, tremolite, and others) are straight, rod-like fibers. As reviewed elsewhere,3,6,19–22 considerable controversy exists regarding the malignant risks associated with chrysotile exposure, which accounts for more than 95% of asbestos consumption in the United States. It is estimated that chrysotile levels several hundred times those of amphiboles are necessary to induce a similar risk of malignancy.21,22 Well-

designed epidemiologic studies that have directly assessed the malignant risk from low-dose asbestos exposure are lacking. However, 1 large-scale, retrospective population study of 405 hospital-based patients and control subjects concluded that 5 years of exposure to the current OSHA PEL would produce a 4-fold excess of pleural MM.23

An important public health issue concerns the risks of developing pulmonary diseases from environmental asbestos exposure from asbestos-containing materials in buildings or materials that affect residents who live near asbestos mines or processing plants. Pleural plaques occur in 20% to 60% of occupationally exposed workers24,25 but in 2% to 6% of nonoccupationally exposed individuals.26 Importantly, no firm evidence suggests that pleural plaques increase the risk of developing an MM or lung cancer. In a review of 13 studies of the relationship between pleural plaques and risk for lung cancer, 10 were deemed appropriate to address this issue, and none of the 10 demonstrated a direct relationship.27 In 1997, an international expert meeting concluded that parietal pleural plaques alone were insufficient for attributing lung cancer to asbestos.28 Although a well-documented case of asbestosis caused by brief inhalation of asbestos has been described, most patients have had significant occupational asbestos exposure over a prolonged period.2,7,29 The development of asbestosis is directly associated with both the magnitude and the duration of asbestos exposure, but low-level asbestos exposure has been linked with the development of a malignant clone of cells.2,6,30 Airborne asbestos levels in public buildings are generally several orders of magnitude below the current OSHA standard, but higher levels occur during renovation and demolition. A recent survey of 3978 indoor samples from 752 buildings that were the subject of litigation stemming from alleged asbestos exposure noted the following: (1) the average concentration of airborne asbestos 5 μm long or longer was 0.00012 fibers/cm^3, (2) 99.9% of all samples contained less than 0.01 fibers/cm^3, and (3) no asbestos was detected in 90% of the buildings when the analysis was restricted to optically detected fibers (≥5 μm long; ≥0.25 μm wide).31 These findings suggest that intact asbestos-containing materials in buildings pose a negligible risk to occupants being exposed to airborne asbestos levels above the OSHA PEL.

Several recent studies have documented more precisely the risks from environmental asbestos exposure. In 2007, Reid et al32 reported 67 cases of MM among 4,768 residents of Wittenoom, Western Australia, who never worked in the crocidolite asbestos mines or mills that operated between 1943 and 1966. Notably, Wittenoom crocidolite asbestos doubled the risk of MM at a cumulative level of 0.015 fibers/cm^3/year, which is about 2 months exposure to OSHA PEL of 0.1 fibers/cm^3.32 An increased standardized mortality ratio from MM was also reported in residents who lived as far as 2200 m downwind of an asbestos cement plant in Amagasaki, Japan.33 In the United States, residents of Libby, Montana, have an increased risk of developing asbestos-related lung diseases after exposure to vermiculite that is contaminated with up to 26% amphibole asbestos from a nearby mine that was active between 1920 and 1990.34 A cross-sectional radiographic screening of residents living in Libby conducted on 6668 subjects for the Agency for Toxic Substances and Disease Registry showed the following: (1) 1186 (17.8%) had pleural abnormalities, (2) the prevalence of pleural abnormalities was highest in WR Grace workers in the Libby vermiculite mine (51%) and lowest in residents who reported neither occupational nor domestic asbestos exposure (6.7%), and (3) some risk factors for pleural abnormalities included being a WR Grace worker, having household contact with a WR Grace worker, increasing age, duration of residence in Libby, and recreational contact with the vermiculite piles.35,36 Furthermore, 31 reported cases of MM resulted from nonoccupational exposure while residing in Libby with a latency period ranging from 13 to 67 years.37 A recent study evaluating data from 70 sites in 23 states where Libby vermiculite was used reported no significant increases in asbestosis mortality but detected 11 sites that had excess rates of MM.38 The latter findings represent a challenge because, as noted by Putnam et al,39 the

Environmental Protection Agency estimates there are currently nearly 30 million homes in the United States with asbestos-containing vermiculite insulation. Collectively, these data show that environmental asbestos exposure is associated with an excess of asbestos-induced lung diseases, but this finding is about 10 times lower than that observed with occupational asbestos exposure.

Asbestos-induced bronchogenic lung cancer, which is similar to that caused by cigarette smoke, can occur in any lobe of the lung with a comparable distribution of the major histopathologic lung cancer types.40 Currently, no genetic test or biologic marker distinguishes lung cancer caused by asbestos or tobacco smoke. Asbestos is generally attributed as the cause of lung cancer in the setting of asbestosis with the appropriate latency period. A review of 23 studies exploring the causal relationship between asbestos and cigarette smoke in lung cancer concluded that asbestos causes lung cancer in nonsmokers despite the small numbers of such workers available for study.41 Moreover, a multiplicative or synergistic interaction rather than an additive model better described the association between asbestos and cigarette smoke in causing lung cancer. This synergistic interaction, which is not observed with MM, implies that the combined attributable lung cancer risk exceeds the sum of the risk of each agent. The mechanisms underlying this synergistic effect are not established, but implicated mechanisms include impaired lung fiber clearance and enhanced DNA damage.30,42

Controversy persists whether the excess lung cancer risk is limited to asbestos workers with asbestosis.43–47 It is generally agreed that the presence of asbestosis significantly increases the risk of lung cancer in a manner that is similar in patients with other forms of pulmonary fibrosis, especially idiopathic pulmonary fibrosis (IPF). Only 6.5% of 234 patients with lung cancer and asbestos exposure had pleural plaques without histologic asbestosis.40 A review of 34 asbestos cohort studies reported a direct correlation between the rate of asbestosis and lung cancer, which suggests that asbestosis is a better predictor of excess lung cancer risk than measures of asbestos exposure.46 Others have challenged this conclusion, arguing that asbestos exposure, and not asbestosis, causes lung cancer.47 These investigators point out that the presence of emphysema is not required to implicate cigarette smoke as a cause of lung cancer. Asbestos, which is a well-recognized carcinogen, can act on all the critical steps in the formation of a malignant clone of cells (eg, initiation, promotion, and progression) and, as such, is not dependent on the presence of fibrosis. Asbestos-exposed workers can have mutations in the k-ras gene at codon 12 in lung cancers without radiographic asbestosis, which suggests that these 2 events are not necessarily linked.3 Oksa et al48 showed that 11 of 24 patients with progressive asbestosis (46%) developed lung cancer, whereas only 5 of 54 patients with stable asbestosis (9%) developed lung cancer. They postulated that the progression of asbestosis is an independent predictor of lung cancer risk in patients with asbestosis. Thus, it remains unclear whether asbestosis is simply a marker of high-dose asbestos exposure or a necessary requirement for attributing an individual's lung cancer to asbestos. This controversy is not likely to be resolved soon because of the nonuniform definition of asbestosis used in the various studies (eg, clinical–radiographic vs histopathologic) and the uncertain biologic scenario whereby the molecular mechanisms underlying interstitial fibrosis are required to develop a malignancy. Until more definitive studies have clarified these issues, lung cancer attribution should be based on the merits of each patient's carcinogen exposure history combined with the appropriate clinical history and radiographic findings.

PATHOPHYSIOLOGY—WHAT'S NEW?

It is well established that the toxic effects of asbestos inhalation depend on the cumulative dose, the elapsed time since the initial exposure, and the physical-chemical properties of the

different asbestos fibers.1–3,30 Amphibole fibers, as compared with chrysotile, are generally more toxic in part because amphibole fibers accumulate more readily in the distal lung parenchyma, are not cleared as effectively, and are more durable (estimated half-life in the lungs on the order of decades vs months, respectively).30 The “amphibole hypothesis” implicating that fiber structural characteristics (length, diameter, aspect ratio) are crucial for promoting asbestos-induced lung diseases has been challenged because fiber physical properties alone appear insufficient to account fully for asbestos toxicity.3,30 One confounder that has not been well controlled for is the presence of tremolite amphibole fibers frequently mixed with chrysotile. Although as noted above, chrysotile-induced malignancies are associated with at least a hundred-fold higher lung fiber concentration as compared with amphiboles, chrysotile can promote iron-derived free radical formation *in vitro*, can injure lung target cells, and can induce asbestosis, lung cancer, and mesothelioma in humans.4,21,22,30 As reviewed in detail elsewhere49–51, numerous studies over the past several years have examined whether biomarkers in asbestos-exposed workers are useful indicators of increased MM risk (eg, mesothelin, megokaryocyte potentiating factor, osteopontin, soluble mesothelin-related protein, and others). To date, none of the biomarkers studied haven proven useful as a screening test for MM because of a significant number of false-positive and false-negative tests. The translational utility of these biomarkers awaits the outcome of ongoing large prospective studies investigating the diagnostic accuracy and the relationship between biomarker levels and mortality.

After asbestos inhalation, alveolar epithelial cells (AEC), and alveolar macrophages (AM) rapidly internalize the fibers that result in an oxidative stress to the lungs. In lung epithelial cells, $\alpha v\beta 5$ integrin receptor-mediated endocytosis seems crucial for fiber uptake and subsequent toxicity.52 Accumulating evidence has established that reactive oxygen species (ROS) and reactive nitrogen species (RNS) are important 2nd messengers of asbestos toxicity.3,30,42 The mechanisms underlying free radical generation by asbestos are in part caused by reactions occurring at the surface of mineral dusts, by activation of AMs or neutrophils attempting to take up the fibers and by mitochondrial dysfunction in target cells. Asbestos bodies are formed when the fibers are coated with a mucopolysaccharide as well as iron that can be redox active. Not surprisingly, asbestos-exposed individuals have altered iron homeostasis in the lungs as manifested by increased levels of bronchoalveolar lavage fluid (BALF), iron, transferrin, transferrin receptors, lactoferrin, and ferritin.53 Asbestos fibers induce the expression of ferritin heavy chain (FHC), a core subunit of ferritin, and an iron binding protein in human mesothelial cells and MM cell lines.54 FHC acts as an antiapoptotic protein against oxidative stress. Interestingly, the silencing of FHC using small interfering RNA promotes apoptosis in MM cells. Given the dismal response of MM to chemotherapy, these findings may have an important translational significance. Extracellular superoxide dismutase (EC-SOD), which is expressed in high levels in the lungs and limits the toxic effects of $O2^{-}$, has recently been shown to be important for preventing both bleomycin- and asbestos-induced murine pulmonary fibrosis.55 More recently, the protective effects of EC-SOD against asbestos were shown to involve inhibiting oxidative fragmentation of hyaluronan in the extracellular matrix and the subsequent inflammatory response.56 Taken together, these studies suggest several novel strategies for limiting the toxic effects of oxidative stress in lungs exposed to asbestos.

DNA damage and apoptosis are important downstream deleterious effects of the ROS and RNS generated by asbestos and occur in all the major lung target cells studied to date. 3,30,42 AEC apoptosis is an important early event implicated in the pathogenesis of pulmonary fibrosis from a variety of agents, which include asbestos, as well as in IPF and chronic obstructive pulmonary disease.3,42,57,58 These findings highlight the importance of understanding precisely how AEC apoptosis occurs. Several groups have shown that mitochondria-derived ROS mediate asbestos-induced AEC DNA damage and apoptosis via

the mitochondria-regulated (intrinsic) death pathway.59–62 Although the molecular mechanisms are not fully established, 1 implicated mechanism involves protein kinase C-δ (PKC-δ). PKC-δ, which is 1 of at least 12 PKC isozymes, is specifically activated by asbestos, migrates to the mitochondria, and induces AEC intrinsic apoptosis.62 Notably, PKC-δ knockout mice are protected against asbestos-induced peribronchiolar epithelial cell proliferation and cytokine (eg, interleukin-1β(IL-1β), KC, IL-4, IL-6, IL-13, and others) production.63 These findings suggest that the targeted disruption of PKC-δ activation may have a role in the management of asbestos-induced lung diseases.

Another important mechanism that regulates AEC mitochondria-regulated apoptosis after asbestos exposure involves p53 activation.64 p53 is a tumor suppressor protein that is critically involved in the DNA damage cellular response by acting as a transcriptional factor to affect numerous genes that inhibit cell growth to allow time for DNA repair and, if DNA damage is extensive, augment apoptosis in part by the mitochondria-regulated death pathway (see references 65 and 66 for reviews). A normal-functioning p53 response after exposure to DNA damaging agents prevents mutations from accumulating. Not surprisingly, the most common mutations in human tumors involve the p53 gene family members.65,66 The precise mechanisms by which p53 regulates apoptosis are complex and not fully established despite extensive investigation. p53 induces apoptosis in part by activating the mitochondria-regulated death pathway by increasing gene expression of proapoptotic stimuli (eg, BAX, NOXA, PUMA, and others) while inhibiting the expression of antiapoptotic Bcl-2 family members.65,66 DNA damaging agents, which include asbestos, also induce a p53 transcriptional-independent mechanism of apoptosis by stabilizing p53 and promoting rapid mitochondrial p53 translocation.64–66 The DNA binding domain of wild-type p53 protein interacts with the Bcl-xl, which is an antiapoptotic protein, in the cytoplasm to trigger Bax/Bak-induced outer mitochondrial membrane permeabilization. Tumor-derived p53 mutants that block the interaction between p53 and Bcl-xl cause a “double hit” on the mitochondria-regulated apoptotic pathway by preventing both the transcriptional-dependent and direct mitochondrial effects of p53.65,66 A mechanistic link among mitochondria-derived ROS, altered iron homeostasis, and p53-induced apoptosis has been suggested after exposure to various agents including asbestos.64,67 Notably, phytic acid, which is an iron chelator, attenuates asbestos-induced p53 expression in distal alveolar cells and lung fibrosis in a rat model of asbestosis.64

Several lines of evidence support the translational significance of future studies exploring how p53 regulates asbestos-induced AEC apoptosis. First, altered p53 expression is implicated in the pathophysiology of pulmonary fibrosis, which includes that caused by asbestos exposure as well as asbestos-associated malignancies. Increased p53 protein expression occurs in the bronchiolar and alveolar epithelium of humans with IPF as well as rodents exposed to asbestos.64,68–70 p53 levels accumulate in lung cancers of patients with asbestosis.71,72 Second, crocidolite asbestos promotes p53 gene mutations predominantly in exons 9 through 11 in BALB/c-3T3 cells.73 Third, asbestos induces p53 and p21CIP1/WAF1/SD11 (p21) expression in lung epithelial and mesothelial cells that can result in cell cycle arrest.74–76 p21 is a downstream family of proteins (p21, p27, and p57) expressed during a p53 genotoxic stress response that results in cell cycle arrest to allow time for DNA repair.77 The importance of targeting p21 has recently been suggested by studies showing that p21 regulates lifespan in telomerase-deficient mice prone to premature aging, augments pulmonary inflammation caused by oxidative stress, and mediates transforming growth factor-β (TGF-β)–induced pulmonary inflammation and fibrosis that occurs via tumor necrosis factor-α (TNF-α) signaling.78–80 Finally, using microarrays, hierarchical clustering analyses, and a systems biology approach to examine asbestos-induced AEC whole genome expression profiling (~54,000 genes), a crucial role for p53 activation was confirmed along with the activation of nearly 2500 other genes involved with regulating

tumor suppression, cell cycle arrest, apoptosis/antiproliferation, and cell survival/antiapoptosis.81 In another gene expression profile study, asbestos-exposed epithelial and mesothelial lung cell lines had increased expression of p53 as well as PKC-δ, thioredoxin, and many other intriguing genes that warrant more investigation.82 Some important targets identified from these and other studies mentioned in this review are shown in Fig 1. Collectively, these data firmly implicate a prominent role for p53 in mediating asbestos-induced AEC mitochondrial dysfunction and apoptosis; these data also suggest that iron-derived ROS from the mitochondria have an important role in activating p53. Studies exploring the genetics of the p53 pathway and its negative regulator MDM2 are identifying novel targeted therapies that may prove useful for managing various cancers.83 Future studies are warranted to define the crucial downstream p53 targets important for mediating the apoptotic effects of p53 after asbestos exposure that, ideally, would not alter the multiple beneficial roles of p53 in DNA repair and cell survival.

It is well known that asbestos-induced mitogen activated protein kinase (MAPK) pathway members are important 2nd messengers crucial for mediating cell surface signals to the nucleus. Recent studies using human monocytes show that increased TNF-α gene expression in patients with asbestosis is caused by constitutively activated p38 and decreased phosphorylated extracellular signal-regulated kinase (ERK) MAPK when compared with normal subjects.84 Furthermore, the reduced ERK signaling was caused by increased lung MAPK phosphatase (MKP)-3 activity. In murine lung epithelium, the disruption of MAPK-1 using a dominant-negative transgene targeted to the bronchiolar epithelium with the CC10 promoter inhibits asbestos-induced proliferation and procollagen gene expression.85 Inactivation of the Akt and MAPK pathways mediates asbestos-induced AEC apoptosis, which is a potentially crucial step for promoting a fibrotic response.86 However, the Akt/mammalian target of rapamycin (mTOR) signaling pathways augment tumor formation in part by promoting the formation of cells that are resistant to apoptosis.87,88 A provocative recent study showed that mTOR increases survival of MM cells and that rapamycin (a mTOR inhibitor) or silencing p–S6K (a major downstream target of mTOR), can each augment cell death of these otherwise apoptosis-resistant MM cells.89 Thus, the targeted disruption of MKP-3 or activated p38 in macrophages to limit TNF-α gene expression or regulating Akt/MAPK/mTOR signaling in the lung epithelium or in MM cells are novel approaches that merit additional study.

A murine laser capture microdissection study has recently documented that asbestos induces gene expression (TNF-α, TGF-β, and others) at the bronchiolar-alveolar duct junctions and first alveolar duct bifurcation; this location is precisely where fiber deposition is greatest.90 In animal models of asbestosis, the development of fibrosis directly correlates with TNF-α levels, and TNF-α receptor knockout mice are protected against asbestosis.91,92 TNF-α is also prominently implicated in the direct association between inflammation and malignancy because it is crucial for mediating tumor promotion and cell transformation in various model systems.93,94 In human mesothelial cells, TNF-α prevents asbestos-induced cell death via a nuclear factor-κB (NF-κB)-dependent mechanism despite the presence of cytogenetic abnormalities.95 Using transgenic (Tg) mice expressing an inhibitory κB (IκB) mutant resistant to phosphorylation-induced degradation and targeted to the bronchiolar epithelium via the CC10 promoter in a murine model of asbestosis, Tg(+) mice exposed to asbestos had less BALF inflammatory cytokine levels (eg, KC, IL-6, and IL-1β) and reduced levels of bronchiolar and distal epithelial proliferation as compared with Tg(−) mice.96 Two groups have recently shown that bone marrow progenitor cells contribute to the inflammatory and fibrogenic effects of asbestos.97,98 These studies underscore the importance of TNF-α, the NF-κB–dependent pathway, and bone marrow progenitor cells in the pathogenesis of asbestos-induced lung disease that may lead to novel therapeutic strategies.

Another recently described mechanism by which asbestos and silica, but not inert particulates, activate pulmonary inflammation and fibrosis is via Nalp3 inflammasome sensing.99,100 Nalp3, which can activate caspase-1 in response to diverse stimuli, is a member of the NLR family of over 20 proteins that contain an N-terminal protein-protein interaction domain that consists of a caspase activation and recruitment domain (CARD), a central nucleotide-binding NACHT, and a C-terminal leucine-rich repeat domain.101 The Nalp3 inflammasome is formed when Nalp3 activation recruits the adaptor molecule apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain (ASC) and then caspase-1 by CARD–CARD interactions. Notably, asbestos-induced inflammatory cell lung recruitment, cytokine production (IL-1β and KC), and silicosis are all reduced in mice deficient in Nalp3, ASC, or caspase-1.99,100 Furthermore, using specific inhibitors and select knockout mice, an important role for fiber uptake, an intact actin cytoskeleton, and ROS generated by nicotinamide adenine dinucleotide phosphate oxidase during phagocytosis were shown to be necessary. Thus, asbestos-induced Nalp3 inflammasome activation is an innovative therapeutic target with clear translational significance.

As reviewed in detail elsewhere, increased TGF-β expression and decreased expression of bone morphogenetic proteins (BMPs) are associated with the development of epithelial-mesenchymal transition (EMT) important in the pathogenesis of cancer and fibrosis, which includes IPF.102 A recent study has shown that gremlin, which is a BMP antagonist that is overexpressed in patients with IPF,103 is also overexpressed in patients with asbestosis as well as in a murine model of asbestosis.104 Notably, asbestos-induced gremlin expression could be blocked by inhibitors of the TGF-β receptor or the MAPK pathway as well as by exogenously administered BMP-7, which is known to prevent TGF-β-induced EMT and fibrosis in the kidney and liver.105,106 Collectively, these findings emphasize the importance of the balance between TGF-β and BMP signaling in the development of asbestosis as well as other fibrotic disorders. Also, restoration of lung BMP signaling activity is a novel therapeutic approach worthy of additional investigation.

CONCLUSIONS

Asbestos-related lung diseases remain a significant challenge to health care providers as well as to investigators studying the basic mechanisms that underlie asbestos-induced pulmonary toxicity. Given the long latency between asbestos exposure and disease as well as the direct relationship between asbestos consumption and mortality from asbestos-related lung diseases, a total worldwide asbestos ban is strongly supported.6,8,17,18 If asbestos use continues in countries where it is less regulated, we can expect the asbestos-induced lung disease crisis to continue for most of the 21st century.6 Studies published in the last several years have yielded unique insights into the epidemiologic significance of asbestos exposure as well as the basic mechanisms that account for asbestos-induced pulmonary toxicity. The significance of these investigations is that they provide the molecular basis for developing novel treatment strategies for asbestos-related lung diseases. Importantly, these studies demonstrate that the asbestos paradigm has broad translational implications for our understanding of other pulmonary diseases where comparable mechanistic pathways are implicated and for which innovative management approaches are urgently required.

Acknowledgments

The author acknowledges the helpful comments provided by Dr. David W. Cugell.

Supported by a Merit Review grant from the Department of Veterans Affairs.

Abbreviations

AEC	alveolar epithelial cell
AM	alveolar macrophages
ASC	apoptosis-associated speck-like protein containing a C-terminal caspase activation and recruitment domain
BALF	bronchoalveolar lavage fluid
BMP	bone morphogenetic protein
CARD	caspase activation and recruitment domain
EC-SOD	extracellular superoxide dismutase
EMT	epithelial-mesenchymal transition
ERK	extracellular signal-related kinase
FHC	ferritin heavy chain
IL	interleukin
iκB	inhibitory κB
IPF	idiopathic pulmonary fibrosis
MAPK	mitogen actvated protein kinase
MKP-3	MAPK phosphatase-3
MM	malignant mesothelioma
mTOR	mammalian target of rapamycin
NF-κB	nuclear factor-κB
OSHA	Occupational Safety and Health Administration
PEL	permissive exposure limits
PKC-δ	protein kinase C-δ
RNS	reactive nitrogen species
ROS	reactive oxygen species
Tg	transgenic
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α

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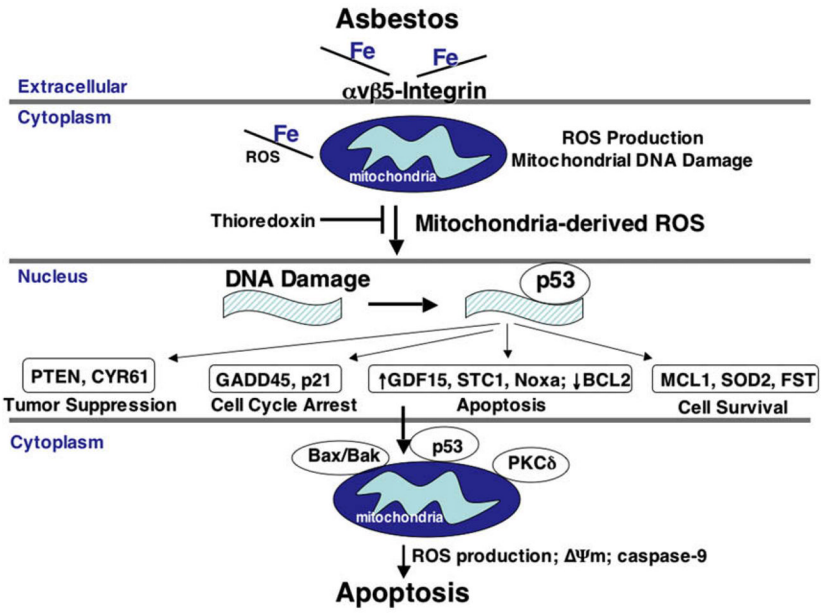

Fig 1.

Hypothetical model depicting some of the crucial events that lead to asbestos-induced alveolar epithelial cell mitochondria-regulated apoptosis. Asbestos, which is an iron containing fiber, is rapidly internalized via the $\alpha v\beta 5$ integrin receptor and induces mitochondria-derived ROS production. By mechanisms that are still uncertain, mitochondrial ROS signaling that results from asbestos exposure stabilizes p53 and promotes p53-dependent transcription of a variety of important proteins involved with tumor suppression, cell cycle arrest, apoptosis, and cell survival. Asbestos-induced AEC intrinsic apoptosis is augmented by mitochondrial translocation of proapoptotic Bcl-2 family members (eg, Bax and Bak) p53 and PKCδ. The model is a modified version of one initially developed by Hevel et al81 that incorporates their findings as well as the work of others. 52,59–62,64,81,82 (Color version of figure is available online.)