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Review

Diseases caused by asbestos: mechanisms of injury and disease development

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Abstract

Asbestos is a ubiquitous, naturally occurring fiber that has been linked to the development of malignant and fibrotic diseases of the lung and pleura. These diseases may be initiated by injury to epithelial cells and mesothelial cells by asbestos fibers through the formation of reactive oxygen intermediates. Elaboration of oxidants are also a consequence of inflammation, a hallmark of exposure to asbestos after inhalation or injection of asbestos fibers into animals. The type, size, and durability of asbestos fibers may be important in toxicity and pathogenicity of asbestos types. This review discusses the pathways of oxidant generation by asbestos fibers, cell–cell interaction that may initiate and perpetuate inflammation, cytokine release and proliferative responses to asbestos, and cell signaling pathways implicated in these events. © 2002 Published by Elsevier Science B.V.

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1. Introduction

Epidemiologic and animal studies indicate that inhalation of asbestos can result in pulmonary fibrosis, lung cancer, and mesothelioma. Occupational exposure to asbestos has been associated with the development of pulmonary fibrosis (asbestosis), lung cancer, malignant mesothelioma, and other pleuropulmonary disorders [1–3a,b]. The National Institutes of Health in 1978 estimated that approximately 11 million individuals had been exposed to asbestos in the United States since 1940 [4]. The Work-Related Lung Disease Surveillance Report, published by the National Institute for Occupational Safety and Health (NIOSH) in 1999, determined that between 1987 and 1996, the total number of deaths associated with asbestosis was 9614, of which 5207 were from malignant neoplasms of the pleura [5]. Due to these health concerns, the use of asbestos has been limited or prohibited in the United States and in several other countries, but in developing countries, the use of asbestos continues to increase [6].

The mechanisms of injury and disease development caused by asbestos fibers are presumed to be related to the greater fibrogenic and carcinogenic properties in comparison to other minerals. The exact mechanisms of injury by asbestos fibers to cells of

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the lung and pleura are unclear, but generation of oxidants by fibers due to their surface redox properties or upon interaction and uptake of fibers by cells has been shown to be an important factor in many cellular responses to asbestos [7–10]. Inflammation observed both in animal models and in the lungs of patients with asbestos-related lung disease may be another source of reactive oxygen and nitrogen species (ROS/RNS). In this article, we first describe briefly the diseases caused by asbestos, their chemical and physical properties, pathways of oxidant generation by fibers in vivo and in vitro, and how these may relate to the development of asbestos-associated pathologies. We then discuss the role of asbestos and oxidants in the stimulation of cytokines and pro-inflammatory mediators, describing how cell–cell interactions may be important to the initiation of diseases and/or repair of lung injury. Lastly, we provide an overview of cell signaling pathways, activation of transcription factors, and gene expression implicated in the development of inflammation, fibroproliferative diseases, and cancers induced by asbestos.

2. Diseases caused by asbestos

2.1. Asbestosis

Development of bilateral diffuse interstitial pulmonary fibrosis is caused by the inhalation of asbestos fibers [1,11]. The most common clinical symptoms of asbestosis are dyspnea on exertion with progression over time leading to restrictive impairment and decreased diffusing capacity. Radiographically, the disease is usually confined to the lower zones of the lungs as reticulonodular infiltrates with the presence of calcified pleural plaques suggestive of exposure of asbestos. High resolution computer tomography (CT) scans are sometimes helpful in the diagnosis of subtle parenchymal changes, although the results are often debatable.

Gross pathology reveals bilateral interstitial fibrosis involving the lower zones of the lungs with severe disease closer to the pleura. In advanced asbestosis, honeycombing is common [1]. Moderate or initial subtle stages of asbestosis can only be identified by critical light microscopic evaluation of the lung by several representative sections of the lung. For the pathologic diagnosis of asbestosis, it is mandatory to demonstrate discrete foci of fibrosis in the walls of respiratory bronchioles associated with the presence of asbestos bodies or fibers which are coated with iron and protein. A history of exposure to asbestos is supportive evidence to document disease with an etiologic association of a specific fiber type in the lung tissue and in an air sample from the work site.

2.2. Pleural plaques

Pleural plaques appear as white or yellow smooth surfaced lesions on parietal, visceral and diaphragmatic pleura. They are often considered hallmarks of exposure to asbestos or other fibrous materials [12]. They can become extensive with calcification and encase the lungs. Pleural thickening and or plaques can impair lung function [13]. Microscopically, pleural plaques are acellular, nonvascular dense strands of hyalinized collagen showing a ''basket-weave'' pattern of mesh appearance. On the pleural surface, it is covered by a single layer of mesothelial cells. Asbestos bodies are very uncommon, and occasional fibers can be found by critical evaluation.

2.3. Bronchogenic carcinoma

An increased risk for developing lung cancer in workers with heavy occupational exposure to asbestos and a dose–response relationship between asbestos exposure and cancer incidence has been well documented [14,15]. However, the presence of asbestosis and the severity and extent of exposure required for an excess lung cancer risk are disputed especially when cancer risk is not observed for 10 or more years from initial exposure, whereas with longer exposures, increased risk is evident. On the other hand, it was shown that radiographic asbestosis is not a prerequisite for asbestos-associated increased lung cancer risk [16,17]. In a consensus report by the Helsinki Criteria for Diagnosis and Attribution on Asbestos, Asbestosis, and Cancer, it was stated that it is not necessary to demonstrate asbestosis on the chest X-ray or in biopsied tissue in order to attribute a causal role to asbestos in cases of lung cancer [18].

Cigarette smoking and asbestos exposure have additive or synergistic interactions in inducing cancer of the lung [2,19]. Compared to cigarette smokers with

no asbestos exposure, there is a substantial increase in mortality rate in cigarette-smoking asbestos workers [19,20].

Histological cell types associated with lung cancer in asbestos workers are similar in cellular features to other primary cancers of the lung. In a number of studies, a predominant incidence of adenocarcinomas has been reported with an increased frequency of occurrence in the peripheral and lower lung zones [21–24]. However, there is no consistent reliable evidence on the association of asbestos exposure and genesis of a specific cell type and site or lobe of tumor origin. Recent studies have shown no difference between cancers associated with asbestos exposure and those associated with cigarette smoking [25].

2.4. Mesothelioma

Diffuse malignant mesotheliomas of the pleura and peritoneum are well associated with asbestos exposure. However, in addition to asbestos, there are idiopathic and other accepted causes of mesothelioma including fibrous minerals such as erionite, radiation, pleural scarring, and SV 40 virus. Overall, there is an increased prevalence of pleural mesothelioma and lower prevalence of peritoneal mesothelioma in asbestos-exposed workers [1]. Peritoneal mesotheliomas are predominantly found in heavily exposed asbestos workers. Asbestos-induced mesothelioma has a long latency period, usually 30 or more years, and the latency increases with lower levels of exposure [26]. Unlike carcinoma associated with asbestos exposure, mesothelioma is not associated with cigarette smoking [3b,14].

The disease potential to induce malignant mesothelioma varies significantly between amphiboles and chrysotile. Commercial amphiboles like amosite, crocidolite, or tremolite have the greatest potential and chrysotile the least potential to induce mesothelioma. In millers and miners with heavy chrysotile exposure, pleural mesotheliomas were reported [3b,24]. However, the potential to induce mesothelioma by chrysotile is debated because there is lung fiber analysis evidence suggesting that tremolite, a component of the ore, is the actual etiologic agent [27].

Malignant mesothelioma rapidly spreads over the surfaces of the lung, thoracic, and abdominal cavities. Metastasis to other organs is very rare. There are three types of cellular features observed in mesotheliomas such as epithelial, sarcomatous, and mixed types showing different cellular patterns. Definitive diagnosis of mesothelioma is made on the basis of gross appearance, histological examination, and with the aid of special immunohistochemical stains and/or electron microscopy.

There are a number of other disorders presumed to be associated with or implicated to asbestos exposure. These include benign pleural effusions, generalized pleural thickening, carcinoma of the larynx, carcinomas of the gastrointestinal tract, small airway disease, Caplan's syndrome, honeycombing, and bronchiectasis. These topics are outside the scope and purpose of this review.

2.4.1. Physical and chemical characteristics of asbestos

Asbestos is a group of naturally occurring crystalline fibrous silicate minerals used extensively in the past due to their valuable insulating and electrical properties, and in other uses requiring high tensile strength and/or chemical and heat resistance. Its extensive use in over 3000 commercial products, including roofing materials, floor tiles, cement pipes, and textiles, has resulted in wide distribution of asbestos in public places and the environment. There are six commercially used types of asbestos derived from two groups: serpentines (curly fibers) and amphiboles (straight fibers). Chrysotile, a serpentine asbestos, is the only serpentine asbestos commercially used and has many industrial applications worldwide. It is very flexible, curly and heat resistant, but is damaged in acid environments. Chrysotile fibers are made of fibrils with a layered silicate structure formed of cylindrical tubes. It was estimated that more than 95% of commercially used asbestos in North America in the past was chrysotile, and most of it was derived from Canadian and Russian mines [1,28].

Amphiboles (amosite, crocidolite, tremolite, actinolite, and anthophyllite) on the other hand are straight, needle-shaped, not pliable, relatively acid-resistant fibers. These types of asbestos were used extensively as insulation against seawater corrosion and as a fire retardant in ships and other applications. The basic subunit of amphibole asbestos is a silicon dioxide tetrahedron arranged in parallel chains and linked laterally by cations. Among the five amphiboles, amosite

and crocidolite were used extensively in North America and the United Kingdom and were imported from South Africa. In North America, amosite was used extensively in shipyards, while in the United Kingdom, crocidolite was preferentially used in several commercial applications. Other amphiboles (actinolite, anthophyllite, and tremolite) are not extensively used commercially due to the lack of huge deposits, except for anthophyllite in Finland.

The most commonly used two amphiboles, amosite and crocidolite, have chemical and physical compositions, shapes, sizes, durability, and pulmonary penetration abilities disparate from that of chrysotile. The higher potency of these two types of asbestos to increase health risk is correlated with the fiber gradient or amphibole hypothesis for disease development [8].

2.4.2. Surface properties and oxidant generation by asbestos

Toxicity, fibrogenicity, and carcinogenicity of asbestos fibers are dependent on many chemical and physical properties of the fibers. Biopersistence as well as chemical and physical characteristics play important roles in toxicity, pathogenicity, and carcinogenicity. Durability of asbestos fibers has a direct correlation to toxicity and pathogenicity. Clearance and dissolution kinetics of amphibole fibers in animal studies and occupationally exposed populations are slower than chrysotile fibers [29]. Elements, such as magnesium and iron are known to leach from inhaled fibers mediating toxicity through redox reactions. Leaching of elements from chrysotile asbestos changes its surface charge from positive to negative and reduces potential toxicity [30]. Because of the leaching of elements from chrysotile fibers, the relative toxicity and pathogenicity of these fibers has been suggested to be relatively low compared to that for amphiboles.

Several studies have suggested the presence of transition metals on the fiber surface is associated with the ability of fibers to generate ROS and induce injury [31–34]. The generation of ROS by different types of asbestos and cellular interactions have been well documented [33,35–38]. The results show that generation of ROS, from the interaction of phagocytes with target cells, correlates with toxicity and pathogenicity of asbestos types. In general, asbestos fibers, which contain more iron and longer fibers, have been shown to generate more ROS. Iron-dependent ROS generation from fibers results in the generation of hydroxyl radicals through the Fenton reaction and the Haber–Weiss cycle. In addition, fiber length and biopersistence are important in ROS generation and the resulting toxicity and pathogenicity. Experimental studies suggest that "frustrated phagocytosis" appears to have a dramatic influence on the sustained generation of ROS [33,38]. Repeated "frustrated phagocytosis" would be expected to attract more phagocytes, resulting in an enhanced generation of ROS.

3. Oxidant release and pro-inflammatory mediators

The pathogenesis of asbestos-associated diseases is associated with a persistent inflammatory response initiated directly or indirectly by ROS, cytokines, chemokines, growth factors, and pro-inflammatory factors. These secretions trigger activation of transcription factors and mitogen-activated protein kinases (MAPK), which are linked to early response genes. Pro-inflammatory gene responses appear to be regulated at the transcriptional level by DNA binding proteins that are under the influence of ROS. Modulation of several transcription factor-mediated, pro-inflammatory responses has been shown in cell systems and animal models. Time and dose-responsive increases in nuclear factor-kappa B (NF-κB) activation following exposure of cells to different types of asbestos have been demonstrated (see below). The increases in NF-κB activation can be accompanied by increases in tumor necrosis factor-alpha (TNF-α) production by the exposed cells. TNF is reported to be an important mediator of pulmonary fibrogenesis [29]. Asbestos fibers induce release of TNF-α from macrophages and cultured cells, which is mediated by ROS and dependent on fiber length [39,40]. Increased release of TNF has also been shown in animals exposed to crocidolite asbestos [41,42] and in humans exposed in the workplace [43].

The ROS production initiated by inhalation of asbestos contributes to the inflammatory response that is thought to play a key role in the development of fibrosis. TNF, a cytokine agonist for chemotactic chemokine production, is upregulated in alveolar ma-

crophages exposed in vitro to crocidolite or chrysotile asbestos [44]. The mechanism of TNF induction in macrophages following asbestos exposure involves the activation of NF-κB by ROS [39]. While TNF is not by itself chemotactic for neutrophils or macrophages, at least three TNF-inducible chemotactic chemokines are thought to play a role in the recruitment of inflammatory cells to the site of asbestos exposure: macrophage inflammatory protein-2 (MIP-2), interleukin-8 (IL-8), and cytokine-induced neutrophil chemoattractant (CINC) [45]. Additionally, asbestos exposure induces production of IL-1 and IL-6, in alveolar macrophages (AMs) [46]. Though both of these cytokines are involved in the recruitment of inflammatory cells, IL-6 also encourages fibroblast proliferation [45]. While TNF encourages the production of IL-6, there is also evidence that the cellular redox state plays a direct role in the induction of IL-6 [47]. The demonstration, using antibodies directed at TNF and employing IL-1 receptor antagonists, that the neutralization of these mediators abrogates the development of asbestos-induced fibrosis in mice provides convincing evidence for a critical role for these mediators in initiating the inflammatory response involved in asbestos-induced pathology [48,49]. Other evidence strongly implicating TNF in the pathogenesis of asbestosis comes from in vivo models utilizing transgenic mice. Mice overexpressing TNF in type II alveolar epithelial cells spontaneously develop fibrosis similar to that seen in asbestosis [50]. Furthermore, knockout mice lacking the TNF receptor produce increased levels of TNF when exposed to chrysotile asbestos, but do not develop the fibrotic lesions seen in wild-type mice [51].

In vivo studies have also suggested a role for transforming growth factor (TGF) in the development of asbestosis. Both TGF-β and TGF-α are produced in bronchoalveolar duct regions of developing asbestotic lesions [52,53]. The spontaneous development of fibrotic lesions resembling those found in asbestosis in transgenic mice overexpressing TGF-α in the lungs further implicates TGF in the pathogenesis of asbestosis [54]. There are a number of other cytokines proposed as putative mediators in the inflammatory response to asbestos; however, more research is needed to characterize what part, if any, these mediators play in the pathogenesis of asbestos-related disease [29].

4. Activation of cell signaling pathways in inflammation and fibroproliferative responses

In vitro experiments have shown that the mitogen-activated protein kinase (MAPK) cascade is involved in both apoptotic and proliferative responses to asbestos. The extracellular signal-regulated kinases (ERKs), c-Jun N-terminal kinases (JNKs), and p38 kinases are all important components of the MAPK cascade, which plays a role in cellular responses to a variety of stimuli [55]. Activation of MAPK pathways can lead to a number of outcomes including cell proliferation, cell survival, or apoptosis. Western blots performed on rat pleural mesothelial cells (RPMs) have shown that treatment with crocidolite asbestos stimulates the phosphorylation of the ERK isoforms designated as ERK1 and ERK2, enzymes that play a role in cellular proliferation under some circumstances [56,57]. Kinase assays performed on crocidolite-treated cells confirmed that the phosphorylation of ERK1 and ERK2 corresponded with an increase in ERK activity. Further work showed that the compound tyrphostin AG1478, a specific inhibitor of the tyrosine kinase activity of EGFR, blocked phosphorylation and activation of these enzymes by both EGF and crocidolite. Treatment with AG1478 has also been shown to prevent the induction of the early response proto-oncogene c-*fos*, thought to be important in asbestos toxicity, thus providing further evidence that EGFR is involved in responses to asbestos [58]. In vitro experiments, using alveolar type II epithelial cells (C10), have established that EGFR and ERK also play a role in initiating cell cycle alterations in lung epithelial cells [55].

The exact nature of the interaction between asbestos and EGFR is unknown, but a variety of methods have provided some clues. Using fluorescence microscopy, it has been shown that crocidolite blocks the interaction of EGF and its receptor [58]. While both crocidolite treatment and EGF cause increased levels of EGFR protein and mRNA, EGF causes an increase in degradation of EGFR whereas crocidolite does not. It has also been found that the increase in EGFR protein expression correlates with the carcinogenicity of various mineral fibers [59]. Experiments using confocal scanning laser microscopy demonstrated that immunoreactivity to EGFR in cells exposed to crocidolite asbestos is concentrated around the contact area

between the fiber and the cell [60]. The same technique has also demonstrated that crocidolite fibers longer than 60 μm are associated with immunoreactivity to EGFR much more often than smaller fibers.

In vivo studies have also suggested a role for ERK in asbestos-induced damage. Immunoperoxidase staining of lung sections from animals exposed to chrysotile asbestos in inhalation experiments have demonstrated that immunoreactivity to phospho-ERK is concentrated within pulmonary epithelial cells at sites of developing fibrotic lesions after both 14 and 30 days of asbestos exposure [57]. These studies are the first to demonstrate activation of the MAPK cascade in key cell types of fibrosis and carcinogenesis.

5. Activation of transcription factors and early response genes

The cell signaling pathways activated by asbestos are of importance as they initiate the transactivation of genes that may be critical to the development of inflammation and/or fibroproliferative diseases of the lung and pleura, including fibrosis, mesothelioma, and lung cancer. Thus, knowledge of these signaling pathways and their relationship to the activation or inactivation of transcription factors and gene expression critical to changes in cell phenotype and function are critical to the design of strategies for prevention and intervention of asbestos-related diseases. Thus far, two classical transcription factors, activator protein-1 (AP-1) and NF-κB, have been studied in our laboratories in both cells and rodent models after exposures to asbestos.

5.1. Activator protein-1 (AP-1)

AP-1 is a family of transcription factors comprised of homo- and heterodimers of the Jun and Fos family of proteins. As summarized above, these proteins are phosphorylated and activated by MAPK signaling cascades [61,62]. We first showed in both rodent tracheal epithelial and mesothelial cells that asbestos and erionite, a type of fiber that morphologically resembles crocidolite asbestos and causes mesothelioma in both rodents and humans, induced increased mRNA levels of the early response proto-oncogenes, c-*fos* and c-*jun*, in contrast to a number of nonpathogenic fibers and particles (glass, polystyrene beads, riebeckite, and antigorite) [63–65]. Since complexes of Jun and Fos family members interact with regulatory DNA sequences known as TPA (12-*O*-tetradecanoylphorbol 12-myristate 13-acetate) response elements (TREs), we explored, using electrophoretic mobility shift analyses (EMSAs), the formation of AP-1 complexes in these cells by asbestos, TPA, and H_2O_2 [63,64]. Studies revealed that asbestos fibers, particularly crocidolite, in contrast to other stresses, caused delayed and protracted expression of early response genes and AP-1 binding to DNA. In mesothelial cells, inhibition of protein kinase C or its down modulation by phorbol ester dibutyrate inhibited crocidolite asbestos-induced elevations in c-*fos* and c-*jun* mRNA levels, whereas tyrosine kinase inhibitors were effective in decreasing c-*fos*, but not c-*jun*, levels in these cells [66]. We also demonstrated AP-1-dependent gene transactivation by H_2O_2 and crocidolite asbestos in tracheal epithelial cells as well as a functional role for c-*jun* in cell proliferation and transformation using transient transfection techniques [67]. Induction of c-*jun* and c-*fos* by asbestos is oxidant-related and ameliorated when stores of intracellular glutathione are increased [64]. A murine AP-1 luciferase stable type II epithelial cell line developed in this laboratory has recently allowed confirmation of elevated AP-1-dependent gene expression by silica and asbestos, and revealed other members of the Fos/Jun family, i.e. Fra-1, which are oxidant-inducible and important in AP-1 complex formation governing cell cycle alterations [68].

A critical question is whether in vitro increases in Fos/Jun expression and AP-1 transactivation occur in rodent lungs after in vivo exposures to asbestos. In comparative studies using rats exposed to crocidolite or chrysotile asbestos by inhalation, increased c-*jun* in lung homogenates was observed by Northern blot analyses in crocidolite-exposed rats which subsequently developed pulmonary fibrosis [69,70]. We subsequently showed, in a murine inhalation model using AP-1 luciferase reporter transgenic mice [71] and anti-luciferase antibody, that exposures to crocidolite caused increases in AP-1-dependent gene expression in bronchiolar and alveolar type II epithelial cells [62].

Further studies at the National Institute for Occupational Safety and Health, on a well characterized

mouse epidermal JB6+ cell line system for studying tumor promotion and neoplastic transformation responses, and in mice carrying the TRE-luciferase transgene mice with AP-1 luciferase reporter, showed that crocidolite asbestos activates AP-1 through the generation of ROS [72,73]. Asbestos exposure caused a time- and dose-dependent activation of AP-1 in cultured JB6+ cells and transgenic mice, which was inhibited by OH radical scavengers. These studies suggest that the carcinogenic effect of asbestos may be mediated through the generation of OH leading to the induction of AP-1 activation. Studies using transgenic animals further support this hypothesis because when the AP-1 activation increased 10-fold in lung tissue, the corresponding increase in the bronchial tissue was significantly higher (22-fold), suggesting that AP-1 activation may play a pivotal role in cancer development. The induction of AP-1 activation appears to be mediated through MAPK family members such as ERK 1 and ERK 2 [72,73]. Thus, increases in AP-1-dependent gene expression by asbestos in epithelial cells of the lung are likely to be important in the epithelial cell proliferation observed after inhalation of asbestos [74]. A key area of future investigation is to determine the causal relationship of AP-1-dependent gene expression to asbestos-induced cell proliferation, fibrosis, and cancers. In addition, identification of AP-1 regulated genes that are critical to these processes is vital to understanding the pathogenesis of cell injury, proliferation, and repair after exposures to asbestos.

6. NF-κB

The NF-κB transcription factor family is activated in response to physical and oxidative stress, mitogens, microbial products such as endotoxin, and inflammatory cytokines [75,76]. Like AP-1, NF-κB is comprised of protein dimers, including the transcription-activating heterodimer consisting of p50 and p65 (RelA) subunits. NF-κB activity is controlled by members of the IκB family which bind directly to NF-κB dimers in the cytoplasm, preventing its nuclear localization which is required for DNA binding. Upon stimulation by oxidants, IκB family members are phosphorylated at specific serine residues, causing the dissociation of IκB, which is subsequently ubiquitinated and degraded. Thus, the NF-κB nuclear localization sequence enters the nucleus and interacts at specific sites, i.e. κB motifs. DNA binding then leads to recruitment of essential components allowing transcription and enhanced expression of genes proximal to the κB motif. These include a number of inflammatory chemokines and cytokines that are causally related to inflammation and asbestosis [29], as well as cell adhesion molecules, growth factors, etc. that are associated with fibrogenesis and carcinogenesis. In addition, NF-κB activation causes increased cell survival and anti-apoptosis in a number of cell types [76].

We first showed that crocidolite asbestos caused protracted and dose-related increases in proteins binding to nuclear NF-κB binding DNA elements in tracheal epithelial cells. NF-κB binding to DNA was decreased by elevation of intracellular glutathione levels [77]. Transient transfection assays with a construct containing NF-κB-binding sequences linked to a luciferase reporter gene showed that asbestos induced transcriptional activation of NF-κB regulated genes. Some of these have subsequently been identified as c-*myc* [77] and iNOS [78]. After inhalation of crocidolite asbestos, increases in immunolocalization of the p65 transcriptionally active subunit were initially observed in the epithelial cells of rats in both the distal bronchioles and at sites of developing inflammatory and fibrotic lesions [79]. With increasing time of exposure to asbestos, immunostaining increased in fibrotic lesions. This indicated a gradual pattern of increased NF-κB activation occurring first in proliferating epithelial cells, and later identified as key to the initiation of inflammatory responses after inhalation of asbestos or silica [29].

7. Summary and relationship to the development of asbestos-associated fibroproliferation and cancers

An overall hypothetical schema relating the cellular signaling events and outcomes of asbestos-induced exposures to inflammation and the development of asbestos-related diseases is provided in Fig. 1. Studies in our laboratories have shown that multiple signaling pathways and transcription factors are activated by asbestos fibers through oxidant-dependent pathways involving the elaboration of oxidants from redox

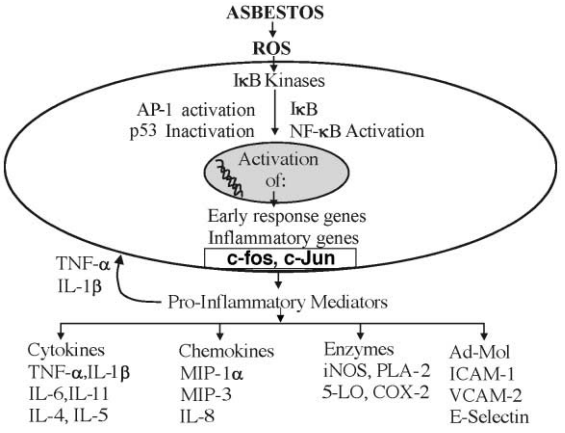

Fig. 1. Activation of transcription factors and related gene expression by asbestos. ROS have been shown to be important mediators of asbestos-induced cellular events in a number of cell types.

reactions on the fiber surface driven primarily by iron. In addition, production of oxidants from cells after interaction with and phagocytosis of fibers during the respiratory burst is a likely source of oxidant production, particularly after "frustrated phagocytosis" of long (>5 μm) fibers that may cause chronic oxidant elaboration from both epithelial cells and macrophages. Oxidants are known to interact with macromolecules, such as proteins and DNA, and the precise alterations in signaling molecules by asbestos and other oxidant stresses are fields ripe for investigation. From the complex interactions illustrated in Fig. 1, it is likely that a number of signaling pathways cooperate in cellular responses to asbestos. Moreover, these pathways may have different roles in various cell types in different phases of the cell cycle. The ability to study these cascades in transgenic mouse models after inhalation of asbestos and other particulates will allow dissection of the key components of these pathways as well as genes that contribute to inflammation and the pathogenesis of asbestos-associated diseases.

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