Chapter 8

Immunological Risks Caused by Fibrous and Particulate Substances

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Abstract

The immunological risks caused by fibrous and particulate substances, especially the effects caused by asbestos fibers and silica particles, are discussed in this chapter. Patients with silicosis often suffer from autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis, and antineutrophil cytoplasmic antibody–related vasculitis. Silica particles, SiO_2, may influence directly various immune cells resulting in the production of many autoantibodies and imbalance between responder and regulatory T cells. The core chemical content of asbestos fibers is Si and O, although the physical feature is different. Considering the complications in asbestos-exposed patients, malignant tumors, such as lung cancer and malignant mesothelioma, are the most important. To think about these situations, asbestos fibers may cause the reduction of antitumor immunity. The experimental findings and measurements of various immunological parameters in silicosis patients, as well as asbestos-exposed population, such as patients with pleural plaque and mesothelioma, are demonstrated and discussed in this chapter.

Keywords: asbestos, silica, autoimmune diseases, antitumor immunity, regulatory T cell

1. Introduction

Regarding environmental factors that cause health risks, exposure to fibrous and particulate substances, such as asbestos fibers and silica particles, represent classic examples, and the investigation of other materials that lead to health impairment following exposure is ongoing [1–10]. In addition to pulmonary effects, such as fibrosis, chronic inflammations, and cancers, such as lung malignancies and pleural mesothelioma, in asbestos-exposed patients, there may be certain effects on immunological cells [11–16]. Among people who have been exposed to asbestos fibers or silica particles, people exposed to silica and have developed silicosis often suffer from complicated autoimmune diseases, such as rheumatoid arthritis, systemic sclerosis, and antineutrophil cytoplasmic antigen (ANCA)–related vasculitis [17–20]. The core chemical components of asbestos fibers are Si and O_2, and although the physical makeup of fibrous and particulate matter differs, asbestos fibers may affect the immune system. Therefore, we have been investigating the immunological effects of silica and asbestos [11–16].

Regarding silica particles, the mechanism of silica-induced dysregulation of autoimmunity is thought to involve silica acting as an adjuvant [21–24]. However, silica particles may also act by directly stimulating on circulating peripheral immune cells, which cause certain alterations in the cellular or molecular functions of these cells, since silica particles may remain in pulmonary lesions and lymph nodes after inhalation [11–16]. Since these direct effects may change the characteristics of immune cells and consequently facilitate the dysregulation of immune tolerance, clarification of these cellular and molecular mechanisms may be useful in the prevention of immune disorders that occur in silicosis patients (SIL), in addition to contributing toward an understanding of the etiology of various autoimmune diseases.

We have been focusing on the immunological effects of silica using human peripheral blood immune cells derived from healthy donors (HD) and SIL [11–14]. We will summarize our findings which indicate that silica is an environmental immune stimulator, and chronic activation of immune cells induced by recurrent and chronic exposure to silica causes an imbalance in the regulation of T cell responses.

Regarding asbestos fibers, asbestos-related cancers, such as malignant mesothelioma (MM) and lung cancer, have been a major global concern in Japan [25–29]. Given the conflict that has arisen due to economic considerations and the medical evidence, there is a confusion concerning the pathological mechanisms of asbestos-induced cancers, and in particular, an uncertainty concerning the dangers of iron-absent chrysotile (white) asbestos compared with iron-present crocidolite (blue) and amosite (brown) asbestos [30–33]. However, regarding the poor prognosis of MM, novel medical approaches to investigate the biological effects of asbestos and pathological mechanisms of asbestos-induced carcinogenesis, as well as clinical trials to detect early stages of MM, should be implemented to assist in the development of improved prevention strategies and cure of asbestos-related malignancies [34–36]. From this standpoint, our group has been investigating the immunological effects of asbestos with respect to the reduction of tumor immunity [11, 12, 15, 16]. In this chapter, cellular and molecular approaches to clarify the immunological effects of asbestos are described, and all findings indicate that a reduction of tumor immunity is caused by asbestos exposure and is involved in asbestos-induced cancers. In addition to confirming the well-known biological effects of asbestos, these investigations provide a basis for the development of a novel procedure for the early detection of previous asbestos exposure, mesothelioma and the chemoprevention of asbestos-related cancers.

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As shown in **Figure 1**, both silica particles and asbestos fibers cause pulmonary fibrosis known as pneumoconiosis, silicosis, and asbestosis. Additionally, both can affect various immune cells, such as B cells, CD4 T helper (Th1), regulatory T (Treg), cytotoxic T lymphocyte (CTL), natural killer (NK) cells, and other immune cells [11, 12, 15, 16].

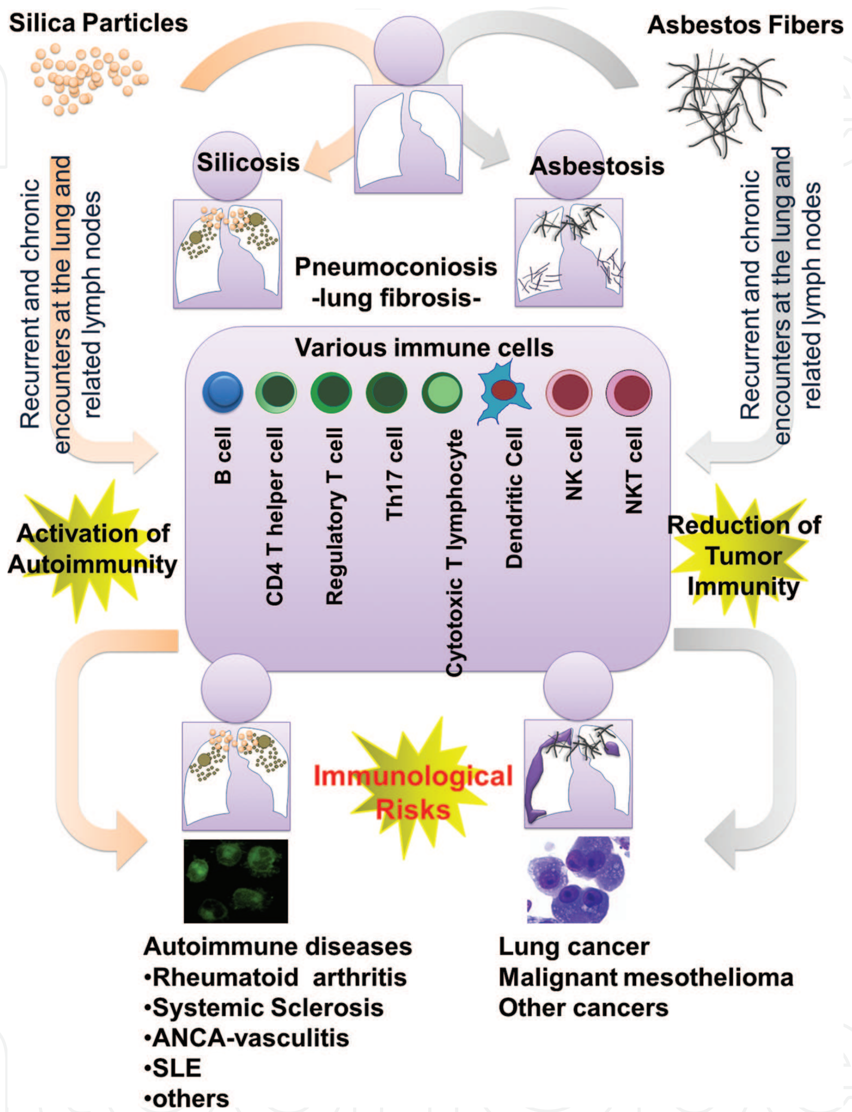

Figure 1. Schematic representation of immunological risks caused by exposure to silica particles and asbestos fibers. The immunological risks induced crucial complications, such as autoimmune diseases, in silicosis patients, as well as malignant tumors, such as lung cancer and malignant mesothelioma, in asbestos-exposed populations.

In this chapter, the immunological effects on various immune cells caused by silica particles and asbestos fibers as investigated in our laboratory will be presented and discussed with respect to the detection of immunological risks of particulate and fibrous environmental factors [11–16]. These summarized findings may be helpful in the development of future risk management strategies, including cases related to newly developed fibrous and particulate matter, such as nanoparticles and nanotubes.

2. Immunological risks caused by silica particles

As shown in **Table 1**, there are various immunological risks associated with exposure to silica particles. These findings were established by in vitro assays using peripheral blood mononuclear cells (PBMC) derived from HD cultured with silica particles as well as freshly isolated immune cells derived from SIL. Additionally, various autoantibodies (aAbs) were detected from SIL [11–14]. All SIL comprised Japanese workers of a firebrick factory located at Bizen City, Okayama Prefecture, Japan, diagnosed with silicosis according to the International Labor Organization (ILO) 2000 guidelines for pneumoconiosis and monitored at Kusaka Hospital or Hinase Urakami Iin/Clinic at Bizen City. All SIL showed no symptoms related to autoimmune diseases or cancers.

Risk manifestation	Target cells/molecules	Findings	References
Unusual autoantibody	B cell	Detection of autoantibodies against	
		➢ Fas/CD95	61
		➢ Caspase 8	62
		➢ Scl-70/Topoisomerase I	56–58
		◆ Specific HLA type	
		➢CENP-B/centromere	64
		➢Desmoglein	65
Dysregulated apoptosis	T cell	Increased level of molecules against	
		Fas-mediated apoptosis	
		➢ Soluble Fas	
		◆ Serum soluble Fas	69
		◆ mRNA expression in PBMC	70
		➢ Variant Fas, alternatively spliced variants	71
		➢ Decoy receptor 3	74
		◆ mRNA expression in PBMC	
		Chronic activation	80
		➢ Soluble IL-2 receptor	78
		➢ PD-1 expression	79
		➢ CD69 surface expression	
		Increase in Fas-mediated apoptosis	61
		➢ Autoantibody for Fas	75
		➢ Decreased expression of physiological inhibitors of Fas-mediated apoptosis	

Risk manifestation	Target cells/molecules	Findings	References
	Regulatory T cell	Chronic activation	
		➢ Excess expression of Fas/CD95	>78

IL, interleukin; PBMC, peripheral blood mononuclear cells; and PD-1, program death protein 1

Table 1. Immunological risks caused by silica particles.

2.1. aAbs detected in SIL

First, the risk of dysregulated autoimmunity assessed by the detection of particular aAbs will be discussed. Various aAbs have been detected in SIL, such as antinuclear antibody (ANA) [37–40], antismooth muscle aAb [41], antiglomerular basement membrane (GBM) aAb [41], antineutrophil cytoplasmic aAb (MPO-ANCA) [37, 42–48], rheumatoid factor (RF) [37–39, 49–53], anti-Scl-70/topoisomerase I aAb [37, 54–60], anti-Fas/CD95 aAb [61], anticaspase 8 aAb [62], anticentromere/CENP-B (centromere protein B) aAb [63], antidesmoglein aAb [64], anti-PL 12 (aminoacyl tRNA synthetase) aAb [65], and anticollagen aAb [39], as found in publications located via PubMed.

Of these aAbs, we investigated several Abs of interest, such as anti-Fas/CD95 Ab [61], anti-caspase 8 Ab [62], anti-Scl-70 Ab with respect to specific human leukocyte antigen (HLA) types [56–58], and anti-CENP-B Ab [63] and reported the case of antidesmoglein Ab-positive SIL [64].

We detected anti-Fas/CD95 aAb in approximately one-fourth of SIL [61]. Since T cells in SIL tend to be categorized into two classes, Fas/CD95-mediated apoptosis prone and resistant groups as described later in this chapter, it is important to determine whether the detected anti-Fas/CD95 aAb is functional in terms of the induction of Fas/CD95-mediated apoptosis. To examine this issue, we employed our established human sister myeloma cell lines, KMS-12PE and KMS-12BM. The former cell line was established from the pleural effusion of a myeloma patient, which showed high expression of Fas/CD95 on its surface as a result of apoptosis and growth inhibition caused by anti-Fas/CD95 agonistic antibody. The latter cell line was derived from bone marrow obtained from the same patients, who showed very low expression of Fas/CD95 and no apoptosis caused by Fas/CD95 agonistic antibody [66]. Following cultivation of both cell lines with anti-Fas/CD95 aAb-positive serum from SIL, the growth of KMS-12PE was reduced by apoptosis, whereas the growth of KMS-12BM was unaffected [61]. These results indicated that anti-Fas/CD95 aAb is functional. Additionally, epitope mapping employing 12-amino acid polypeptides with the SPOT system of anti-Fas/CD95 aAb was analyzed. As a result, a minimum of four and a maximum of ten epitopes were found, and several amino acid residues involved in binding Fas ligand, such as C66, R87, L90 E93, and H126, were identified [61].

As in the case of anti-Fas/CD95 aAb, anticaspase 8 aAb was investigated in terms of the dysregulation of Fas/CD95-mediated apoptosis of lymphocytes in SIL [62]. The association of anticaspase 8 aAb with HLA types was examined. As a result, the frequencies of HLA-DRB1*0406 were significantly higher in aAb-positive SIL (16.7%) compared with control individuals (3.0%, $p<0.001$). Additionally, HLA-DR4; DQB1*0302 was found in one-fourth of positive SIL, and DPB1*0601 was also higher in positive SIL (5.9%) compared with controls (0.6%, $p<0.05$), whereas DQB1*0401 was lower in positive SIL (0%) compared with controls (13.3%, $p<0.001$). Furthermore, epitope mapping showed that a minimum of four and a maximum of thirteen polypeptides seemed to be involved. Among these, two important catalytic cysteine residues were found, cysteine Cys287 and Cys360, located in the unique pentapeptide motif QACQG [62].

Regarding the relationship between aAb and specific HLA type, we reported HLA types among anti-Scl70/topoisomerase I aAb-positive SIL [56–58]. Results indicated that the allelic frequency of HLA-DQB1*0402 was significantly higher in aAb-positive SIL (28.6%) than in aAb-negative SIL (1.5%, $p<0.001$), as well as in controls (0.8%, $p<0.001$). Additionally, DQDB1*0301, DQB1*0601, and DPB1*1801 were higher in aAb-positive SIL than in aAb-negative SIL, whereas no significant differences were found compared with controls [56–58].

In terms of anti-CENP-B/centromere aAb, the titer index (Log10) of anti-CENP-B autoantibody in SIL was higher than that of HV, and patients with systemic sclerosis (SSc) was higher than those of HV and SIL. This titer index was positively correlated with an assumed immune status for HV as 1, SIL as 2, and SSc as 3. Moreover, although the titer index of anti-CENP-B autoantibody formed the same factor with anti-Scl-70 autoantibody, the Ig G value, and age of SIL, the property of other factors extracted indicated that anti-Scl-70 antibody was positively related with the Ig A value, while the converse was true for anti-CENP-B from the results of factor analysis. Those results indicated that the titer index of anti-CENP-B autoantibody may be employed as a biomarker in identifying dysregulation in SIL cases.

Taken together, various aAbs found in SIL have indicated that dysregulation of autoimmunity was caused by chronic and recurrent exposure to silica particles that remained in lung and related lymph nodes of various human cells, especially B cells. Some of these aAbs may be related to Fas/CD95-mediated apoptosis of lymphocytes and cause further dysregulation of autoimmunity such as in the case of long-surviving self-antigen recognizing clones in T cells [11–14].

Furthermore, examination of HLA types seemed to be important in revealing several aAbs in SIL. Although it can be mentioned that repeated and continuous screening of aAbs as well as the initial screening of HLA types seems to be necessary among workers in contact with silica-related substances for the detection of dysregulation of autoimmunity, the use of genotyping, such as determining HLA types, is not permitted during employee selection procedures. However, a consideration of particular occupational health risks together with individual sensitivities is required in an effort to prevent occupational health hazards and associated future hardships.

2.2. Fas/CD95-mediated apoptosis–related molecules in SIL

Fas/CD95-related molecules analyzed in SIL are shown in **Table 1** [11–14, 67]. Regarding molecules that inhibit Fas/CD95-mediated apoptosis, the level of soluble Fas/CD95 was higher in the serum of SIL compared with HD, and similar to the level in systemic lupus erythematosus (SLE) [68], while higher mRNA expression, determined as the ratio of soluble to wildtype Fas/CD95, was present in SIL compared with HD in PBMC [69]. Additionally, higher amounts of various alternatively spliced variant messages of the Fas/CD95 gene were detected in PBMC from SIL compared with HD [70]. All of these variant messages, including soluble Fas/CD95, possess a Fas ligand-binding domain but lack a membrane-binding domain. Hence all of these translation products are secreted into the extracellular space and bind with Fas ligand, thereby protecting cells against membrane Fas-mediated apoptosis [70]. Furthermore, the expression of the protective molecule decoy receptor 3 (DcR3), which acts against the Trail molecule and similarly induces apoptosis via a Trail receptor and the same intracellular signaling molecules for apoptosis, such as caspase 8 and 10 [71, 72], was higher in SIL PBMC compared with HD [73]. These findings indicated that some types of T cells in PBMC from SIL provide protection against Fas/CD95- and Trail-induced apoptosis, which leads to long survival of these T cells and self-antigen recognizing clones [67].

However, several findings that showed accelerated Fas/CD95- and Trail-mediated apoptosis in PBMC of SIL were investigated. Messenger RNA expression in PBMC of several genes which act as physiological inhibitors of Fas/CD95- and Trail-mediated apoptosis, such as I-Flice (inhibitor of FADD-like interleukin-1β–converting enzyme), surviving, sentrin, and inhibitor of caspase-activated DNase (ICAD) was lower in SIL compared with HD [67, 74]. In addition to the aforementioned detection of functional anti-Fas/CD95 autoantibody, some types of T cells in PBMC from SIL possess enhanced Fas/CD95-mediated apoptosis [61]. Further studies revealed that this fraction may include Treg cells [13, 14]. Thus, a decrease in the number of Treg cells by apoptosis and an increase in the number of responder T cells caused by silica exposure may be the cellular biological mechanisms at work in SIL, which consequently impart susceptibility to autoimmune diseases in SIL.

We found higher expression of Fas/CD95 in Treg (CD4+, CD25+, and forkhead box P3 (FoxP3) +) [75, 76] and sensitivity to Fas-agonistic antibody–induced apoptosis in Treg cells from SIL [77]. Furthermore, when PBMC from HD were cultured with silica particles in vitro, Treg cell numbers were selectively reduced by apoptosis and the population of responder T cells was enhanced [77]. Thus, the aforementioned T cell population prone to Fas/CD95-mediated apoptosis seems to comprise Treg cells, and the imbalance that occurs as a result of a decreased Treg and surviving responder T cell population in SIL induces dysregulation of autoimmunity [13, 14, 77].

Moreover, there is evidence showing chronic activation of responder T cells. For example, CD69, an early activating marker of T cells, was gradually expressed in T cells when PBMC from HD were cultured in vitro with silica particles [78]. Expression of the program death protein 1 (PD-1) gene, another activation marker of T cells, in CD4+ CD25+ as well as in CD4+ CD25− T cell populations was higher in SIL compared with HD, which showed negligible expression [78]. Expression of serum soluble interleukin (IL)-2 receptor (sIL-2R) was also higher in SIL compared with HD [79].

Taken together, SIL possess a risk of developing dysregulation of autoimmunity. This risk can be detected using various markers mentioned above, such as serum soluble Fas, sIL-2R, and serum DcR3 (recently, the enzyme-linked immunosorbent assay (ELISA) kit is available for laboratory use), in SIL during their early clinical phases.

3. Immunological risks caused by asbestos fibers

As shown in **Figure 1**, the most important and critical complications that arise in asbestos-exposed patients concern the development of malignancies, such as lung cancer and MM [25–29]. Of course, asbestos fibers possess carcinogenic-related activities, such as oxygen stress caused by iron in the asbestos fibers, frustrated macrophages incapable of phagocytosing asbestos fibers, chromosome tangling, and the absorption of other carcinogenic substances inhaled in the lung, such as materials from tobacco smoke and other air pollutants [34–36]. However, given the long latency period that precedes the onset of MM following initial exposure to asbestos, it was considered that asbestos fibers cause alterations in antitumor immunity by recurrent and chronic encounters with various immune cells at the lung and related lymph nodes.

As shown in **Table 2**, our findings show altered immune cell function and manifestations from experimental settings as well as PBMC derived from pleural plaque and MM [11, 12, 15, 16, 80, 81].

Risk manifestation	Target cells	Findings	References
Innate Immune system	NK cells	Reduction of cytotoxicity	
		➢ Freshly isolated NK cells	
		◆ NK cells from asbestos-exposed patients (PP and MM)	83–84
		◆ NK cells from HD stimulated in vitro with	83
		asbestos	83
		➢ Human cell line cultured with asbestos	
		Reduced expression of NK cell activation receptor	83
		➢ Human cell line cultured with asbestos: NKG2D, 2B4	83,84
		➢ Freshly isolated NK cells	
		◆ NK cells from asbestos-exposed patients (PP and MM): NKp46	83,84
		◆ NK cells from HD stimulated in vitro with asbestos: NKp46	84
		Reduction of phosphorylation of ERK 1/2	
		➢ Human cell line cultured with asbestos	
MHC class I restricted killing System	CTLs	Suppressed differentiation and proliferation	
		➢ In vitro assay using MLR with asbestos	85
		Alteration of killing molecules (granzyme B, IFNγ, perforin)	
		➢ In vitro assay using MLR with asbestos	86
		➢ Freshly isolated and in vitro stimulated peripheral	

Risk manifestation	Target cells	Findings	References
		CD8+ cells from PP	86
		➢ Freshly isolated and in vitro stimulated peripheral CD8+ cells from MM	
MHC class II restricted killing system	Th1 cells	Decrease in CXCR3 expression, IFNγ	
		➢ Cell line model continuously cultured with asbestos	87
		➢ Freshly isolated and cultured in vitro with asbestos from HD	88
		➢ Freshly isolated CD4+ T cells from PP and MM	88
Regulation of T cell response	Regulatory T (Treg) cells	Enhanced function	
		➢ Cell line model continuously cultured with asbestos	
		◆ Increased suppressive function via cell-cell contacts	91
		◆ Excess production of soluble factors	
		✓ IL-10	91
		× Enhanced suppressive function	89
		× Phosphorylation of STAT3 with over-expression of Bcl-2 causing resistance against asbestos-induced apoptosis	
		✓ TGFβ	91
		× Enhanced suppressive function	90
		× Increased phosphorylation of p38 and SMAD3 causing resistance against TGFβ-induced growth inhibition	

CXCR3, CXC chemokine receptor 3; HD, healthy donor; IFN, interferon; IL, interleukin; MLR, mixed lymphocyte reaction; MM, malignant mesothelioma; NK, natural killer; PP, pleural plaque; TGF, transforming growth factor; SMAD, vertebrate homologues of *Sma* and *Mad* [Drosophila protein; mothers against decapentaplegic (MAD) and the Caenorhabditis elegans protein SMA (from the sma gene for small body size)]; and Th1, T helper.

Table 2. Immunological risks caused by asbestos fibers.

3.1. NK cells

Regarding NK cells, cytotoxicity was reduced in peripheral NK cells from pleural plaque (PP) and MM, in NK cells from HD cultured in vitro with asbestos fiber, and in a human NK cell line continuously exposed to asbestos [82]. Additionally, the expression of various NK cell activating receptors, such as NKG2D, 2B4, and NKp46, was reduced in a human NK cell line cultured continuously with asbestos, in freshly isolated NK cells from HD cultured in vitro with asbestos, and in fresh NK cells from PP and MM [82, 83]. Among these receptors, NKp46 was thought to be an important marker for impaired function of NK cells exposed to asbestos. Moreover, reduced cytotoxicity in NK cells exposed to asbestos was accompanied with reduced phosphorylation of extracellularly regulated kinases (ERK) 1 and 2 and reduced degranulation of perforin and granzyme B, which are the killing small molecules secreted from NK cells [82, 83].

3.2. Cytotoxic T lymphocytes

Other types of cytokilling immune cells, CTLs, are also involved and have their functional and cellular properties altered by asbestos exposure. From in vitro analyses using peripheral CTLs in a mixed lymphocyte reaction (MLR), it was found that differentiation and proliferation of CD8+ naïve T cells were disturbed by the presence of cocultured asbestos fibers with decreased expression of killing small molecules, such as granzyme B and interferon γ (IFNγ) [84]. Moreover, alteration of killing molecules, as well as the phenotype of CD8+ cells, was manifested by CD45RA as the marker of effector/memory T cells. Freshly isolated CD8+ cells derived from asbestos-exposed patients, such as PP and MM, showed a higher predominance of CD45RA-negative cells compared with HD [85]. However, the cytokilling activity differed between isolated and in vitro-stimulated CD8+ cells. CD8+ cells from PP and MM revealed an increase in the number of perforin-positive cells; however, after in vitro stimulation, only CD8+ cells from MM showed a decrease in the perforin-positive cell population when subtracted from the unstimulated base line [85].

These findings indicated that asbestos exposure caused dysfunction of CTLs, while specific cell functions differed depending on disease status, for example, PP patients do not carry any malignant tumors, whereas MM patients suffer from mesothelioma. However, the impact of asbestos fibers on CTLs is considered to involve a reduction of tumor immunity, as we showed in NK cells mentioned above [84, 85].

3.3. Th 1 cells

Asbestos fibers are also known to modify Th1 cells. We developed continuously exposed sublines using a cell line model. The cDNA microarray data were examined of the original cell line, which has had no contact with asbestos fibers, and six independently established sublines, which were continuously exposed to asbestos fibers for more than 8 months using an asbestos concentration that did not induce apoptosis in more than half of the cells by transient exposure. The microarray showed a decrease in IFNγ and related molecules, such as IFN regulatory factor 9 (IRF9) and IFN-stimulating gene factor-3 (ISGF3), in addition to a decrease in CXC chemokine receptor 3 (CXCR3), which is regulated by IRF9 [86].

CXCR3 is important in antitumor immunity to summon IFNγ-positive tumor antigen recognizing Th1 cells to the tumor. Thus, the asbestos-induced reduction of CXCR3 and IFNγ seems to cause a reduction of antitumor immunity in asbestos-exposed patients. As we assumed, examination of freshly isolated CD4+ cells from HD stimulated in vitro and cocultured with

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asbestos fibers as well as peripheral CD4+ cells from PP and MM revealed a decrease in the cell surface expression of CXCR3 in addition to a decrease in the number of intracellular IFNγ-positive cells [87].

Taken together, one of the immunological risks resulting from asbestos exposure concerns a reduction of Th1-type T cell–derived antitumor immunity.

3.4. Treg cells

Treg cells are important in antitumor immunity. If the function and number of Treg cells are enhanced, immune cells responding to tumor antigen show suppressed function, which causes a reduction of antitumor immunity [75, 76].

Our cell line model continuously exposed to asbestos fibers using MT-2, a human T-lymphotropic virus type 1, which causes adult T cell leukemia/lymphoma, showed excess production of transforming growth factor (TGF) β and IL-10, typical soluble factors examined to reveal the function of Treg cells [88, 89]. Overproduction of IL-10 is regulated by the Src-family receptor and is used by the IL-10 receptor via autocrine mechanisms, which then causes activation of the signal transducer and activator of transcription 3 (STAT 3) and upregulation of antiapoptotic molecule Bcl-2 located downstream of STAT3 [88]. Continuously exposed sublines acquire resistance to apoptosis induced via transient exposure to asbestos [88]. Furthermore, overproduction of TGFβ induces resistance to TGFβ-induced growth inhibition in continuously exposed sublines with phosphorylation of p38, one of the signaling molecules in the mitogen-activated protein kinase (MAPK) signaling pathway, as well as phosphorylation of SMAD3 [SMAD; vertebrate homologues of *Sma* and *Mad* [Drosophila protein, mothers against decapentaplegic (MAD) and the Caenorhabditis elegans protein SMA (from the sma gene for small body size)] [89].

In addition to the two aforementioned typical soluble factors, continuous exposure of MT-2 sublines to asbestos resulted in markedly higher suppressive activity when mixed with cultures of CD4+ responder cells activated with anti-CD3 antibody and autologous peripheral blood monocyte-derived dendritic cells compared with the original MT-2 cell line, which has had no contact with asbestos [90].

Taken together, exposure to asbestos results in enhanced Treg function, which is manifested by a reduction of antitumor immunity [11, 12, 15, 16, 80, 81].

3.5. Risks of asbestos on antitumor immunity

As mentioned above and shown in **Table 2**, all of the examined effects of asbestos on NK cells, CTLs, Th1, and Treg cells indicate that asbestos exposure can cause a reduction of antitumor immunity. These findings are considerable and the risks associated with asbestos exposure may be used as early detection markers for the occurrence of asbestos-induced malignancies. Additionally, the ability to mitigate the observed reduction of antitumor immunity through the use of chemopreventive substances derived from foods or plants may be an important strategy in the treatment of high-risk groups exposed to asbestos, such as residents who have a history of living near factories handling asbestos and workers in the building demolition and rubble processing fields.

4. Conclusion

Risks associated with exposure to fibers, such as asbestos, and particulates, such as silica, were discussed based on our experimental findings and analyzed using cell lines, freshly isolated peripheral immune cells from HD, as well as patients exposed to silica particles, exposed to asbestos fibers, and patients with silicosis, PP, and MM. The immunological risks manifested in different directions, in that silica caused dysregulation of autoimmunity, whereas asbestos induced a reduction of antitumor immunity. Both cellular and molecular alterations contributed to the complications of silica exposure, the occurrence of autoimmune diseases and asbestos exposure, and the development of malignant tumors.

These risks may be detected using findings described in this chapter, and early detection of these risks may assist workers, as well as other exposed populations, in avoiding further exposure and therefore prevent the onset of various pathological states caused by exposure to fibrous and particulate substances. Recently, although exposure to silica and asbestos has been reduced through the improvement of work-related environments as well as banning the use of asbestos, new substances, such as nanomaterials, which are widely used in the industrial fields, are now feared to cause health risks. It should be reiterated that risks, and particularly immunological ones which hitherto have not received a great deal of attention, caused by classical types of particulate and fibrous substances, such as silica and asbestos, require continued and greater consideration in an effort to further prevent the health impairment caused by environmental substances.

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