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Alteration of Various Lymphocytes by Particulate and Fibrous Substances

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<http://dx.doi.org/10.5772/intechopen.79054>

Abstract

Various occupational and environmental substances alter the cellular and molecular function of the human lymphoid system. For example, silicosis patients who have been chronically exposed to silica particles often complicate with autoimmune diseases such as rheumatoid arthritis and systemic sclerosis. From our investigations, silica particles affect CD4⁺ responder T cells and regulatory T cells (Tregs), which results in the disruption of autoimmunity. Asbestos fibers are a type of mineral silicate, and patients exposed to asbestos fibers revealed cancers such as mesothelioma and lung cancer. In these cases, asbestos fibers may reduce antitumor immunity. Our results investigating the effect of asbestos on cytotoxic T lymphocyte, natural killer (NK) cells, CD4⁺ cells, and Tregs revealed a reduction in antitumor immunity. To date, the effects of silica and asbestos on Th17 cells and antigen-presenting cells such as dendritic cells and macrophages remain unclear. Based on these findings, it will be possible to generate earlier detection methods to identify the occurrence of immune alterations in silicosis as well as the appearance of a decreased antitumor immunity in asbestos-exposed populations. Additionally, research efforts should also be directed at discovering and identifying physiological substances from foods, plants, and other sources that can restore the immune status in people exposed to particulate and fibrous substances.

Keywords: silica, asbestos, responder T cell, regulatory T cell, cytotoxic T lymphocyte, NK cell

1. Introduction

There are a variety of lymphocytes including T cells, B cells, and natural killer (NK) cells [1–4]. Additionally, there are other smaller populations of lymphocytes such as natural killer T (NKT) cells. T cells are further divided depending on their surface molecules as well as function and cytokine production in CD4⁺ and CD8⁺ T cells. CD8⁺ cells are designated as cytotoxic T lymphocytes (CTLs), which express T cell receptors (TcRs) and recognize a specific antigen. TcRs on CTLs can bind to the complex of the class I major histocompatibility complex (MHC) molecule and antigen. Thereafter, CTLs can destroy the cells using granzymes and perforins as the attacking molecules. CD4⁺ T cells include various subpopulations [1–4]. Although CD4⁺ cells are referred to as T helper (Th) cells, depending on the kind of stimulation, cytokine circumstances surrounding Th cells, naïve Th cells are skewed to Th1, Th2, Th17, and Treg (regulatory T) cells. Th1 and Th2 cells are balanced subpopulations. The proliferation of Th1 cells is triggered by interleukin (IL)-12 and produces IL-2 and interferon (IFN)- γ . The key transcription factors are T-bet and the signal transducer and activator of transcription 4 (STAT4). Th1 cells act against intracellular bacteria by activating macrophages. On the other hand, Th2 cells are activated by IL-4 and IL-2, and results in the secretion of IL-4, IL-5, IL-9, IL-10, IL-13 and IL-25 cytokines. The key transcription factors for Th2 are STAT6 and GATA3. IL-4 produced by Th2 cells acts as a positive feedback to restimulate Th2 cells and stimulate B cells to produce immunoglobulin (Ig) E. Therefore, Th2 cells play an important role in the context of allergies and hypersensitivity such as atopic dermatitis and bronchial asthma [1–4].

Additionally, Th17 and Treg cells are also balanced according to the skewing cytokine circumstances surrounding Th naïve cells. Initially, transforming growth factor (TGF)- β stimulates naïve Th cells to express two transcription factors, ROR γ t and forkhead box (Fox) P3. Although IL-6 together with TGF- β causes activation of the STAT3 signaling pathway to suppress FoxP3, IL-2 together with TGF- β facilitates the movement of cells toward the Th17 phenotype. Tregs produce IL-10, TGF- β and IL-35 and act to inhibit effector T cell reactions against foreign as well as non-self/self-antigens. On the other hand, Th17 cells produce IL-17, IL-21 and IL-22 and play an important role in pathogen clearance at the mucosal surface and are implicated to play a role in autoimmune and inflammatory disorders [1–4].

B cells act in humoral immunity to produce Ig/antibodies to attack foreign antigens. Additionally, B cells express B cell receptors (BcRs), which allow for the binding of B cells to a specific antigen in the process involving innate immunity [1–4].

NK cells also act in innate immunity by quickly attacking virally infected cells, as well as tumor cells, after recognition. NK cells do not need MHC presentation. These cells can kill virally infected cells and tumor cells *via* lytic reactions and apoptosis by releasing granzymes and perforins [1–4].

When the immune system recognizes the presence of foreign substances such as bacteria and viruses, as well as transformed cells derived from self, the human immune system works to attack these non-self substances and facilitates the curtailment of alterations in the human body such as various symptoms resulting from bacterial and viral infections and cancers.

These reactions are physiological. Additionally, certain alterations of the immune system may recognize self-antigens and subsequently cause various autoimmune diseases [1–4].

2. Occupational and environmental substances that affect the human immune system

There are many environmental and occupational substances which induce alterations of the immune system. For example, isocyanate latex, cement including chromium, and whitening agents including persulfates and other substances cause occupational hypersensitivity (allergy). Sometimes, patients exposed to these reagents reveal respiratory asthma and contact dermatitis. However, these allergic reactions may be categorized as a range of physiological reactions against foreign antigens [5–11]. On the other hand, some occupational and environmental substances cause autoimmune diseases. For example, vinyl chloride, silica dust, and chemicals including trichloroethene and epoxy resins can cause systemic sclerosis, one of the typical generalized autoimmune diseases that occur with certain frequencies in exposed populations. Unlike occupational allergies, autoimmune diseases caused by occupational and environmental substances seem to be the result of disruption of the human immune system caused by these substances [12–15]. Additionally, there are many cancers caused by occupational and environmental substances such as lung cancers due to asbestos, tobacco smoke, certain metals including arsenic, chromium, nickel and beryllium, bladder cancer caused by benzidine, β -naphthylamine and other aromatic hydrocarbons, and others [16–22]. Of course, there are many mechanisms involved in the genesis of these occupational cancers when triggered by certain substances, such as DNA damage caused by reactive oxygen species (ROS), formation of DNA adducts, and others. However, it is also possible that certain substances that cause cancers may also affect the human immune system by reducing antitumor immunity. If so, it is understandable that a relatively long latency period may exist prior to the occurrence of occupational cancers following initial exposure to carcinogenic agents.

Taken together, it is important to assess how these occupational and environmental substances alter the human immune system. Unlike standardized toxicological investigations, people or workers are usually exposed to these substances in low-dose, chronic, and continuous ways. Thus, it is important to assess the cellular and molecular alterations in immune cells derived from exposed populations, as well as to establish continuous and low-dose exposure models using human lymphoid cells exposed *in vitro* to substances that may cause alterations in autoimmunity or act as carcinogens.

From this viewpoint, we have been investigating the immunological effects of silica particles or asbestos fibers since certain silica-exposed populations such as silicosis patients (SIL) are often complicated with various autoimmune diseases such as rheumatoid arthritis (known as Caplan syndrome) [23], systemic sclerosis (known as Erasmus syndrome) [24], systemic lupus erythematosus (SLE) [25], and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis/glomerulonephritis [26–29]. Asbestos fibers are a type of mineral

silicate, while silica is particulate in nature. Additionally, asbestos can cause cancers such as malignant mesothelioma (MM) and lung cancer [30–33]. Silica particles can act to disrupt the regulation of autoimmune tolerance while asbestos fibers can facilitate a decline in antitumor immunity.

3. Silica and disruption of lymphoid cells

Silica exposure causes disruption of autoimmune tolerance. Thus, silicosis patients are often complicated with autoimmune diseases [34, 35].

When considering the effects of B cells and plasma cells, various autoantibodies have been detected in sera derived from silicosis patients. For example, some autoantibodies (AAB) are typically detected in autoimmune diseases such as anti-nuclear antibodies (ANA), anti-topoisomerase I (Sck-70) AAB [36], and anti-CENP-B (centromere) AAB [37]. In addition to these typical AABs, we found anticaspase-8 AAB [38, 39], anti-Fas-AAB [40], and antidesmoglein AAB [41], which is usually detected in skin bullous autoimmune diseases such as pemphigus vulgaris. However, we have not investigated alterations of B cells caused by silica exposure. The production of various AABs from B cells/plasma cells may be caused by alterations of B cells or be dependent on T cells which produce AABs to B cells.

What about effector T cells? There are many alterations that have been detected in effector T cells. CD4⁺ responder T cells showed an increase in activation markers and an excess of survival markers. For the former, the expression of CD69, a typical early activation cell surface marker for T cells, increased at 5–10 days when peripheral blood mononuclear cells (PBMCs) derived from healthy donors (HD) were cultured *in vitro* with silica particles [42]. Additionally, soluble IL-2 receptor (sIL-2R) levels in serum derived from silicosis patients showed an increasing tendency compared with those of HD. Then, if we set 1, 2, and 3 as sequential numbering for HD, silicosis, and SSc for autoimmune disruption, this number and the level of serum sIL-2R in these three categories showed a significant positive correlation [43]. Although sIL-2R is considered as a tumor marker for T cell acute lymphoblastic leukemia and T cell malignant lymphoma, the elevation of serum sIL-2R was recently detected in various autoimmune diseases. This increase in serum sIL-2R is the evidence of chronic activation of T cells in certain pathological situations such as autoimmune diseases. Thus, silicosis is also considered as a condition whereby peripheral T cells are activated chronically, and the degree of activation was higher than that in HD, although less than that in autoimmune diseases such as SSc. Moreover, programmed death-1 (PD-1) gene expression in peripheral CD4⁺ cells derived from silicosis patients was significantly higher than that in HD [44]. Although PD-1 is one of the most important molecules that act in the immune checkpoint system, PD-1 is also a marker of T cell activation. Thus, upregulation of PD-1 in T cells derived from silicosis patients also indicates that T cells in silicosis are chronically activated (due to long-term and continuous exposure to silica particles in the body, such as lung fields and related lymph nodes).

Considering survival factors, we found that serum from silicosis patients showed significantly higher levels of soluble Fas (sFas) compared with HD and similar levels with SLE patients [45].

Additionally, since sFas is a product due to alternative splicing of the Fas gene, losing 63 bp of the transmembrane domain, mRNA expression of wild-type membrane Fas and sFas transcripts were examined. As a result, the ratio of wild-type Fas message divided by soluble-type alternatively spliced message decreased in PBMCs from silicosis patients compared with HD [46]. These findings indicated that T cells in silicosis patients are protected against Fas-ligand-induced apoptosis by increasing the binding of Fas ligand and sFas at extracellular spaces, thereby resulting in the extended survival of T cells in silicosis patients. Additionally, the scenario of Fas, sFas, and Fas ligand was employed for tumor necrosis factor-related apoptosis-inducing ligand (Trail) receptor, decoy receptor 3 (DcR3), and Trail. DcR3 mRNA expression levels in PBMCs derived from silicosis patients were higher compared with HD [47]. Furthermore, serum DcR3 levels were higher in silicosis patients compared with HD. Hence, in both Fas and Trail systems, T cells in silicosis patients were protected from apoptosis. Taken together, T cells in silicosis patients are chronically activated as well as continuously protected from apoptosis, thereby resulting in the circulation of longer surviving T cells in the peripheral blood of silicosis patients. If so, rare self-antigen acting T cell clones may also survive longer and be chronically activated. Thus, antigen (non-self or self)-activated T cells increase their volume in silicosis patients.

What about Tregs? It is known that Fas/CD95 expression on the cell surface of Tregs is one marker of Treg activation. Thereafter, Tregs proceed to apoptosis when its role is ceased. Thus, we examined Fas expression in peripheral Treg (CD4⁺ and FoxP3⁺) as well as CD4⁺ + FoxP3⁻ T cells derived from HD and silicosis patients. As a result, Fas expression was significantly higher in Tregs from silicosis patients compared with HD [44, 48]. Of course, CD4⁺ + FoxP3⁻ T cells did not express sufficient amounts of Fas in HD or silicosis patients. Then, PBMCs derived from HD or silicosis patients were cultured with agonistic antibody. Tregs from silicosis patients showed earlier and higher apoptosis compared with HD because of a greater expression of Fas. Thereafter, PBMCs from HD were cultured with silica particles for 4 days. As a result, CD4⁺ + FoxP3⁺ cell levels were significantly reduced. However, CD25⁺ + FoxP3⁻ cell levels were not altered, translating Tregs were reduced, and initial CD4⁺ + CD25⁻ cells were activated to reveal CD25 as an activation marker.

Taking together the results of responder T cells and Tregs, an imbalance between responder CD4 cells and Tregs was found, in that the increase of responder T cell levels increased, while Treg cell levels decreased. This tendency is well known in the area of dysregulation of autoimmunity which leads to the occurrence of autoimmune diseases. Thus, silica exposure affects the immune system to create an imbalance between responder T cells and Tregs and sets the foundation for the appearance of autoimmune diseases in silicosis patients.

What about Th17? Unfortunately, we have not investigated the Th17 status in silicosis patients. It was reported that Th17/I-17 is involved in silicosis to facilitate the progression of lung fibrosis found in silicosis [49, 50]. As mentioned earlier, Tregs in silicosis seem to progress toward apoptosis. This may induce an increase in Th17 levels in the peripheral blood of silicosis patients and consequently make these patients more susceptible to autoimmune diseases. Thus, further investigation of Th17 in silicosis is necessary from the viewpoint of efforts to delineate the early processes involved in the disruption of autoimmunity.

4. Asbestos and antitumor immunity

As mentioned earlier, carcinogenic factors among occupational and environmental substances may facilitate a decline in antitumor immunity. We chose asbestos since it is a mineral silicate and possesses the potential to disrupt human lymphocytes in such a way as to make the human body prone to autoimmune diseases.

For the CTLs, we used a mixed lymphocyte reaction (MLR) to assess the asbestos fibers with respect to clonal expansion of the cells examined. The use of chrysotile asbestos resulted in a decreased differentiation and proliferation of CD8⁺ cells and a decreased production of cytotoxic granules such as granzyme B and perforin [51–53]. These findings were confirmed using peripheral blood CD8⁺ cells derived from MM patients considered to have a history of exposure to asbestos even though the patients did not remember the exposure. Interestingly, the status of intracellular perforin expression in CD8⁺ cells from patients with pleural plaque (PP) differed from that of HD and MM patients [51–53]. Perforin expression in CD8⁺ cells increased somewhat in PP patients. These findings indicated that immunological alterations, especially in CTLs, differed depending on the disease status when examining PP and MM patients exposed to asbestos. This may be dependent on the occurrence of cancer in the body [51–53].

What about NK cells? We tried to expose a human NK cell line, freshly isolated peripheral NK cells derived from HD, as well as NK cells from PP and MM patients to asbestos fibers. The killing activity was reduced in a cell line model subjected to continuous exposure to asbestos, *ex vivo* activated and expanded freshly isolated NK cells cultured with asbestos fibers, and NK cells derived from patients. Additionally, the most correlated marker of killing activity was the cell surface expression level of NKp46 [54–58]. NKp46 is an NK cell activating receptor that belongs to the natural cytotoxicity receptor (NCR) family. In addition to a reduction in NKp46 expression, phosphorylation was induced of extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) which are involved in the mitogen-activated protein kinase (MAP-K) signaling pathway [54–58]. Moreover, degranulation to produce cytotoxic molecules such as granzyme and perforin was also suppressed by asbestos exposure. These results were obtained from a cell line model, an *ex vivo* culture model, and from the investigation of freshly isolated NK cells derived from PP and MM patients exposed to asbestos [54–58].

Next, the continuous and low-dose exposure of human CD4⁺ T cells to asbestos fibers was investigated. We employed the human T cell leukemia virus (HTLV)-1 immortalized human polyclonal T cell line MT-2 as the cell line model, an *ex vivo* clonal expansion model using freshly isolated peripheral blood CD4⁺ cells derived from HD, and peripheral CD4⁺ cells derived from PP and MM patients exposed to asbestos. As a result, all models showed that continuous and low-dose exposure to asbestos induced a decline in chemokine receptor CXCR3, a G α_i protein-coupled receptor of the CXC chemokine receptor family [59, 60]. The reduction in CXCR3 resulted in diminished trafficking of T cells which produce IFN γ to attack tumor cells. In addition to this, CD4⁺ T cells exposed to asbestos showed potential to produce IFN γ . Both findings suggest a reduction in antitumor immunity [59, 60].

The MT-2 cell line was reported to possess Treg functionality. Thus, Treg suppressive functionality in MT-2 cell sublines continuously exposed to asbestos fibers was compared with the original MT-2 cell line not exposed to asbestos. As a result, sublines showed enhanced suppressive function by cell-cell contact in addition to excess production of typical soluble factors such as IL-10 and TGF β [61]. In addition to these enhanced functions in MT-2 (a model of Tregs) caused by continuous exposure to asbestos, these sublines showed decreased levels of FoxO1 transcription factor [62]. FoxO1 regulates cell cycle progression in a negative fashion by inhibiting various cyclins as well as in a positive fashion by regulating many cyclin-dependent kinase inhibitors (CDK-Is) such as Cip1/p21, Kip1/p27, Kip2/p57, and CDKN2A to 2D such as p16, p15, p18, and p19. As a result of decreased levels of FoxO1, MT-2 sublines showed an enhanced expression of cyclins, especially cyclin D1, and a reduced expression of CDK-Is. Additionally, cell cycle progression was also enhanced compared with the original MT-2 line not exposed to asbestos [63]. Thus, both function and proliferation were enhanced with continuous and low-dose exposure of Tregs to asbestos, which suggest that the antitumor immunity controlled by Tregs was reduced [61–63].

Taken together, continuous and low-dose exposure to asbestos caused a reduction in antitumor immunity in CTLs, NK cells, CD4⁺ T cells, and Tregs [64–66]. Thus, it could be considered that people subjected to continuous, low-dose exposure to asbestos are susceptible to the onset of cancers because of a gradual reduction in antitumor immunity. Thereafter, certain localized areas such as lung fields or the pleural cavity may become the locus where fibers remain in the body and chronic stimulations may occur at these locations on the basis of reduced antitumor immunity [64–66]. This may represent the mechanism by which asbestos-induced cancers occur in the long term, after a latency period of approximately 30–40 years, following initial exposure to asbestos fibers.

5. Conclusion

All findings described in this chapter are summarized in **Figure 1**. In this review, the effects of silica [67–69] and asbestos [64–66] are introduced and discussed. However, people are exposed to many more potentially hazardous occupational and environmental substances, such as various materials in air pollutants and a variety of metals in work environments. Thus, any immunological alterations induced in cells by these and many other substances should be investigated utilizing the methods described earlier to further our understanding of immune responses and cancer.

Additionally, as described earlier, the identification of certain physiologically active materials among various foods, plants, and other sources, which modify and repair the immune state following disruption by various occupational and environmental substances such as silica and asbestos, should lead to the establishment of effective preventive and treatment measures. So far, we have examined immune-neutralizing effects of some extracts from bamboo and some carbohydrates made from starch such as corn. However, we have not obtained enough results yet. In the future, these approaches should be continued to find some substances.

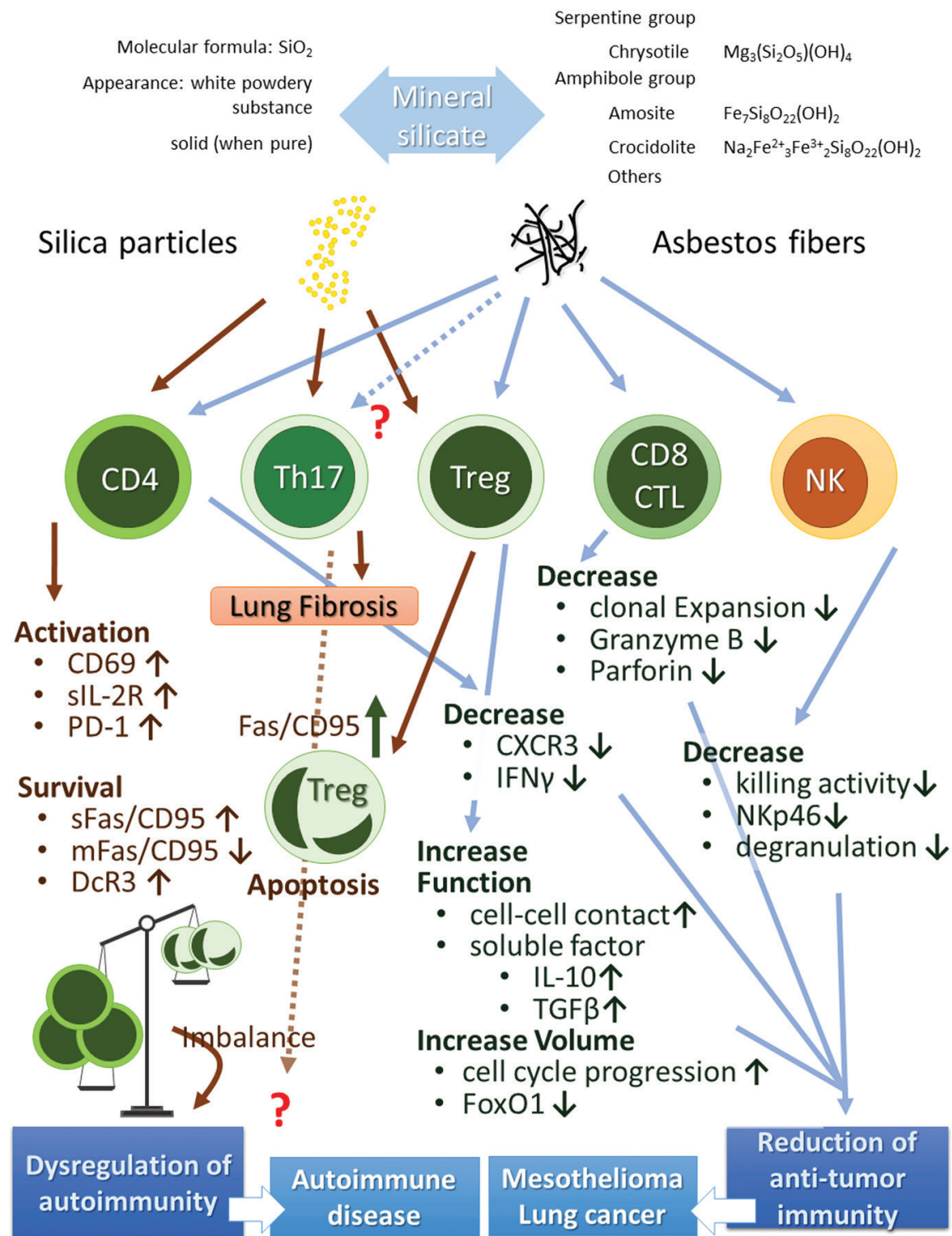


Figure 1. Summary of effects of silica and asbestos on various lymphocytes. Silica exposure induces the disruption of autoimmunity resulting in frequent complications such as autoimmune diseases in silicosis patients. Additionally, asbestos exposure causes a reduction in antitumor immunity in CD4+ T cells, Tregs, CTLs, and NK cells. These result in the onset of cancers such as mesothelioma and lung cancer in the long term after a latency period following initial exposure.

Acknowledgements

The authors thank Ms. Tamayo Hatayama, Shoko Yamamoto, Miho Ikeda, and Mikiko Fukuda for their valuable technical assistance.

Conflicts of interest

All authors declare that there are no conflicts of interest.

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