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Silica, Immunological Effects

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Without Abstract

Synonyms

Autoimmune diseases as the complication of silicosis; Environmental dysregulation of autoimmunity

Definition

Patients with silicosis suffer from lung fibrosis causing respiratory dyspnea, complicated chronic bronchitis, pulmonary tuberculosis, emphysema, and other pulmonary diseases and are often complicated by autoimmune/collagen diseases such as RA (rheumatoid arthritis, well known as Caplan syndrome), SLE (systemic lupus erythematosus), SSc (systemic sclerosis), and ANCA (anti-neutrophil cytoplasmic autoantibody)-related vasculitis/nephritis. It had previously been considered that dysregulation of autoimmunity caused by silica exposure was induced by an adjuvant effect of silica. However, recent developments in immunology have provided new concepts such as recognition of the danger signal by the NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin-domain-containing 3, Nalp3) inflammasome in antigen-presenting cells, alteration of the CD95/Fas molecule in autoimmune diseases, and the importance of functional and/or changes in the number of CD4 + 25+ FoxP3 (Forkhead box p3, Scurfin) positive regulatory T cells.

Silica-Induced Dysregulation of Autoimmunity

Epidemiology

The complication of autoimmune diseases with silicosis was first reported more than half a century ago. Caplan syndrome, which describes silicosis with rheumatoid arthritis, was initially reported in 1953 (Caplan 1953). Since then, many reports and reviews have been published regarding the accompaniment of silicosis with autoimmune diseases, such as RA, SLE, and SSc. These three types of autoimmune connective tissue diseases are typical forms of silica-induced autoimmune diseases (Haustein and Anderegg 1998; Steenland and Goldsmith 1995). However, other forms of these diseases have also been reported such as Wegener's granulomatosis, ANCA (anti-neutrophil cytoplasmic autoantibody)-related vasculitis/nephritis, Sjögren syndrome, and pemphigus vulgaris. Furthermore, many autoantibodies are detected in silicosis patients even in the absence of typical clinical manifestations. In addition to autoantibodies related to the aforementioned autoimmune diseases, antinuclear, ANCA, rheumatoid factor, and anti-topoisomerase I, anti-Fas, anti-caspase-8, and anti-desmoglein antibodies have been reported. These findings indicate that silica possesses immunological effects to induce dysregulation of autoimmunity, in addition to having immunological effects on local immunocompetent cells located at the lung, which can lead to pulmonary fibrosis.

Although several reports have indicated that the incidence of Caplan syndrome is between 20% and 30% in all silicosis patients, the prevalence seemed to differ depending on the report. However, the odds ratio or RA-defined cases with silicosis in South African gold miners indicated a value of 3.79 ($p = 0.0006$) (Sluis-Cremer et al. 1986). Regarding mortality, the SMR (standardized mortality ratio) for RA was reported as 2.01 and 2.29 (Steenland and Goldsmith 1995). While the SMR for SSc was 2.45, the SMR for renal disease with silicosis was 2.22–2.77.

Overall, it is clear that silica can induce immunological effects and cause dysregulation of autoimmunity.

Role of Inflammasome in the First Signal for the Biological Body

Silica enters the body through the pulmonary region. Following entry, alveolar macrophages acting as antigen-presenting cells are mainly responsible for recognizing silica particles and attempt to exclude it. Although it is known that these alveolar macrophages produce interleukin (IL)-1β as a consequence of processing foreign danger signals such as those associated with the presence of silica, the detailed cellular and molecular mechanisms involved have yet to be clarified. However, a recent discovery concerning the role of the NLRP3 inflammasome has assisted in clarifying the cellular response (Dostert et al. 2008). When silica, asbestos fibers, uric acid crystals, or cholesterol encounter antigen-presenting cells, the resulting extrinsic and intrinsic danger signals lead to activation of NLRP3 and recruitment of apoptosis-associated speck-like protein (ASC) with CARD (Caspase activation and recruitment domains)/pyrin-containing adaptor. This complex cleaves pro-caspase-1 to generate active caspase-1. Subsequent caspase-1 activity leads to the production of pro-inflammatory cytokines, and in particular IL-1β and IL-18. These cytokines function to serve fibroblasts to form lung fibrosis. This represents the latest scenario to account for the initial response of a body to silica, although it remains undetermined whether these cascaded reactions are closely related to the subsequent dysregulation of autoimmunity.

Moreover, details of the interaction between silica particles and alveolar macrophages have been reported. Based on experimental results, silica particles are toxic to alveolar macrophages as a result of the production of ROS (reactive oxygen species) directly from the particle surface, and indirectly from the cellular response following an encounter with silica. During this encounter, the important role of surface class A scavenger molecules, such as SR-A1/2 (scavenger receptors type 1 and 2), which are trimers with a molecular weight of about 220–250 kDa and preferentially bind modified LDL (Low-density lipoprotein) via acetic acid and oxidized LDL, and MARCO to induce binding and internalization of silica particles has been reported (Hamilton et al. 2008). Thereafter, as a result of interactions with the aforementioned inflammasome, the locus where silica

particles first meet with human immunocompetent cells such as alveolar macrophages participate in alternative cytokine production and formation of chronic inflammation, which leads to lung fibrosis and chronic retention of silica particles with subsequent induction of autoimmune dysregulation.

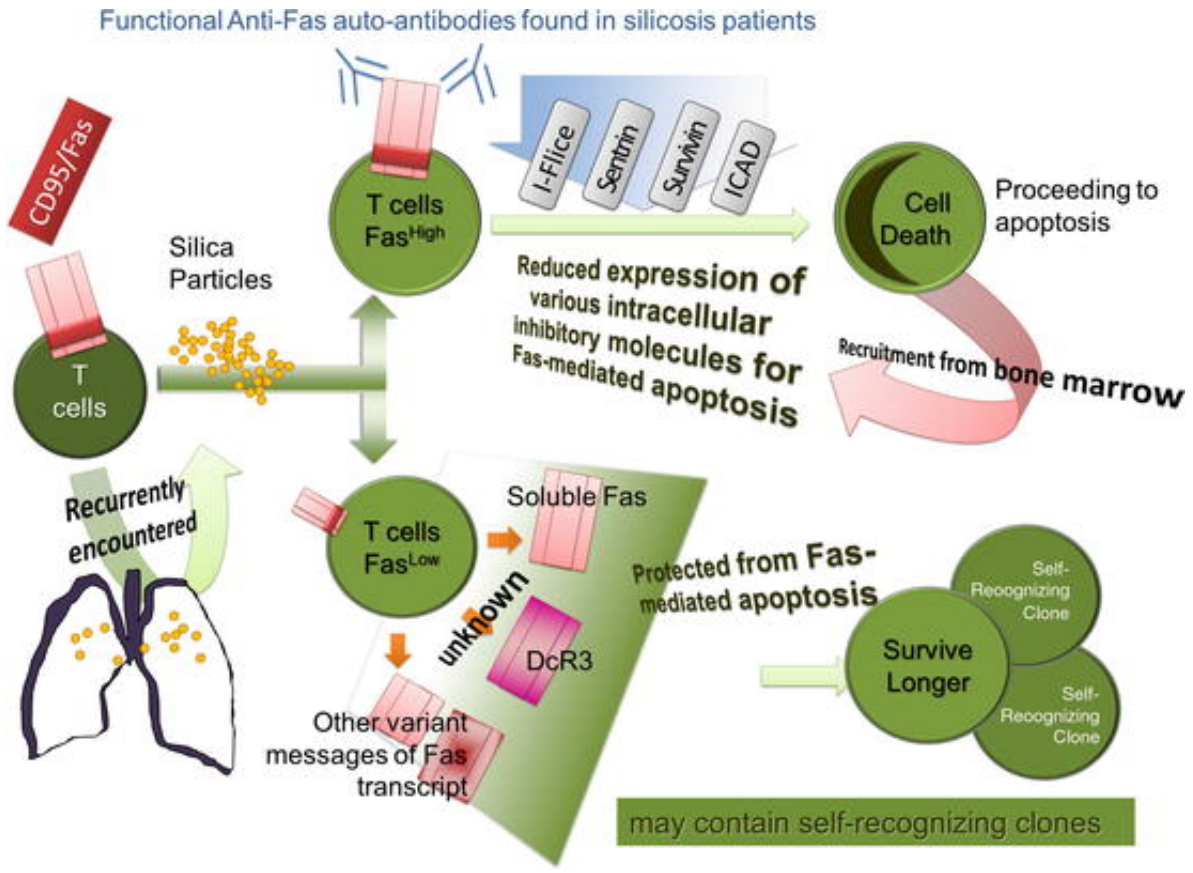
Status of CD95/Fas and Related Molecules in Silicosis

The CD95/Fas death receptor possesses an important role in the apoptosis of lymphocytes. Furthermore, the molecular alteration of CD95/Fas causes the pathological enhancement of autoimmunity. For example, the genetic mutation of Fas or Fas-ligand in mouse (lpr and gld genes, respectively) manifests a SLE-like pathological status and genetic mutation of the Fas gene in humans causes ALPS (autoimmune lymphoproliferative syndrome). Furthermore, Fas-mediated apoptosis is inhibited by the soluble form (alternatively spliced form lacking the membrane-bound domain) (sFas), DcR3 (decoy receptor 3), and splicing variants other than sFas, which contain the Fas-ligand-binding domain but lack the membrane-bound domain. Serum sFas and soluble DcR3 are detected in the serum of individuals covering a variety of autoimmune diseases. When silicosis is positioned as a pre-autoimmune disease, this may result in dysregulation and/or altered Fas and Fas-ligand apoptosis system in immunocompetent cells such as lymphocytes and macrophages in peripheral blood or pulmonary lesions. The following findings have been reported in the last decade.

1. In the lung, silicosis progression is related to the expression of Fas-ligand, mast cells, and extracellular matrix remodeling.
2. Fas and Fas-ligand systems may regulate apoptosis in alveolar macrophages and the occurrence of Fas-mediated apoptosis may be a biomarker of silicosis development.
3. Genetic polymorphism of the Fas gene is related to the development of silicosis.
4. Serum sFas and messenger transcript expression of sFas, DcR3, and alternatively spliced variant messenger transcripts of the Fas gene in peripheral blood mononuclear cells derived from silicosis are elevated.
5. Parameters related to Fas-mediated apoptosis are independent of the respiratory parameters in silicosis.
6. Autoantibodies against Fas-related molecules such as Fas and caspase-8 are detected in serum from silicosis.
7. In the animal model, mutation of Fas-ligand prevents the development of acute silicosis.

From aforementioned findings 1–3, it seems that Fas and Fas-ligand apoptosis is related to lung fibrosis caused by silica exposure via apoptosis of alveolar macrophages. The important role of Fas-mediated apoptosis is not restricted to silicosis. Fibrotic interstitial lung diseases such as interstitial pneumonitis, asbestosis, and experimental models of bleomycin-induced lung fibrosis show altered Fas and/or Fas-ligand expression in lung parenchyma or bronchoalveolar lavage.

Furthermore, exposure to silica may influence circulating immunocompetent cells associated with aforementioned findings 4–7 (Otsuki et al. 2006). Additionally, anti-Fas autoantibodies detected in silicosis can induce Fas-mediated apoptosis and mRNA expression of several genes such as I-Flice, sentrin, survivin, and ICAD (inhibitor of caspase-3-activated DNase), all of which can act as inhibitors of Fas-mediated apoptosis, and are reduced in peripheral blood mononuclear cells from silicosis. These findings indicate that Fas-mediated apoptosis is enhanced in circulating lymphocytes under conditions of silicosis. On the other hand, aforementioned findings 4–7 suggest that Fas-mediated apoptosis is protected by extracellular inhibitory molecules such as sFas and DcR3 to facilitate earlier binding with Fas-ligand. From these results, it may be that two populations of circulating T cells are present in silicosis (Otsuki et al. 2006; Lee et al. 2011). One population may comprise T cells which express high levels of membrane Fas, are sensitive to anti-Fas autoantibodies, and undergo Fas-mediated apoptosis with recruitment from bone marrow. The other population of T cells may express lower levels of membrane Fas, produce sFas and DcR3 to escape from Fas-mediated apoptosis, and survive longer. The latter population may contain self-recognizing clones which generate autoimmune diseases. This idea is schematically summarized in Fig. 1, and may account for the role of the Fas and Fas-ligand apoptotic pathway in circulating T cells with respect to the occurrence of autoimmune dysregulation with silicosis, aside from the biological role of this apoptotic pathway in the development of lung fibrosis from local pulmonary lesions resulting from silica exposure.



Silica, Immunological Effects, Fig. 1

Summary of the alteration of Fas and related molecules in silicosis patients. There are two populations of Cd4+ lymphocytes, with one population possessing higher expression of membrane Fas compared with the other. The cell population with higher membrane Fas expression is sensitive to functional anti-Fas autoantibodies found in silicosis (approximately 25%) and progresses to Fas-mediated apoptosis as represented by the reduced expression of various inhibitory molecules for apoptosis. This population may be repeating cell death and involve recruitment from bone marrow. The cell population with lower Fas membrane expression secretes soluble Fas, Decoy Receptor 3, and other variant Fas messenger transcripts, all of which inhibit Fas-mediated apoptosis by binding Fas-ligand at the extracellular area. Avoiding apoptosis, this cell population survives longer and may include self-recognizing clones

Activation of Responder and Regulatory T Cells by Silica Exposure

The recent discovery of CD4 + 25 + FoxP3 (Forkhead box protein P3) positive regulatory T cells (Tregs) and Th17 cells has contributed toward investigations concerning the cellular and biological development of autoimmune diseases. Tregs comprise a subpopulation of T cells which downregulate the immune system, maintain tolerance to self–antigens, and suppress autoimmune disease. Several autoimmune diseases show reduced function and/or a lower population of peripheral Tregs. Interestingly, manifestation of the CD4+25+ phenotype is also found in antigen–activated responder T cells. Thus, if the T cell population in silicosis is being chronically activated by auto-antigen, the peripheral CD4+25+ fraction may be contaminated by activated responder T cells together with a reduced true Treg (FoxP3 positive) population. This condition may result in reduced inhibitory function of the peripheral CD4+25+ fraction which has been reported. Moreover, several reports have detailed the silica–induced activation of

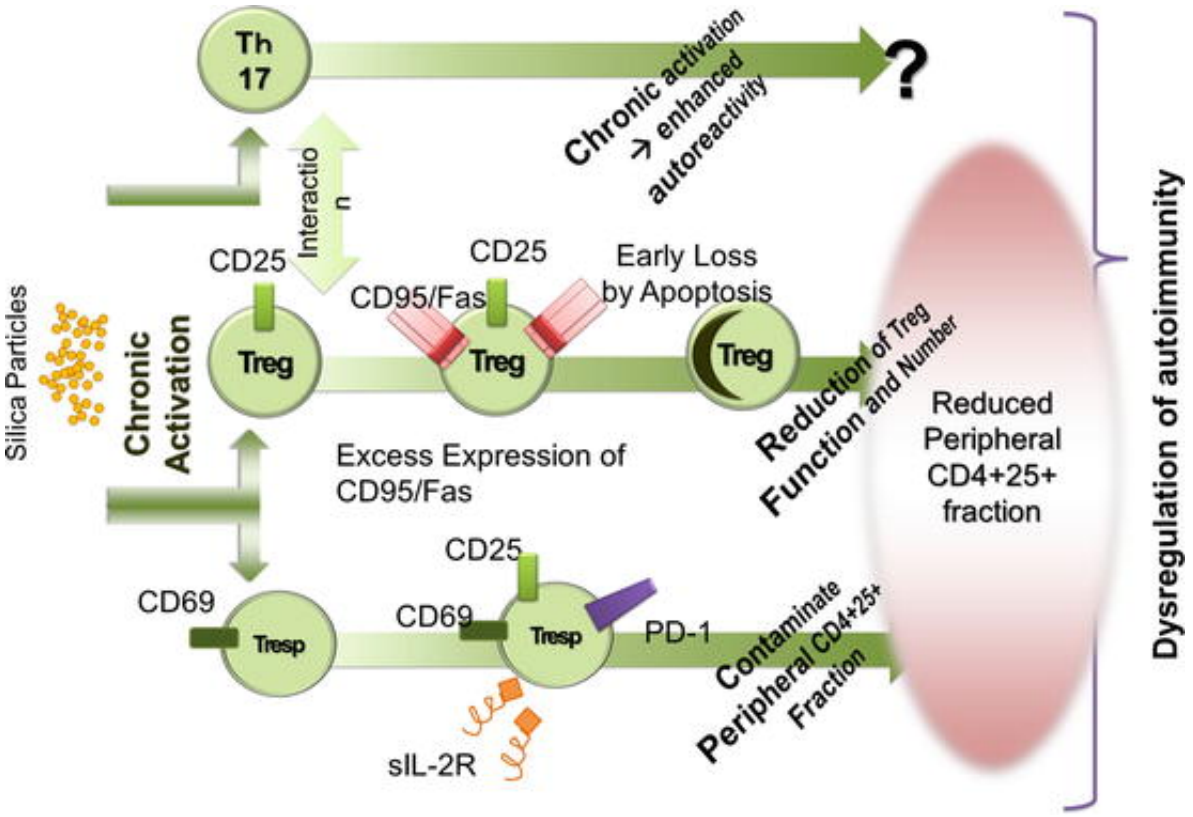
responder T cells.

1. Silica slowly and gradually activates peripheral T cells in vitro as determined by monitoring CD69 surface expression as a marker of early T cell activation.
2. Gene expression of CD69 is higher in the peripheral CD4+25+ fraction of silicosis patients compared with healthy donors.
3. Gene expression of PD-1 (Programmed cell death 1, as an activation marker of T cells) is higher in CD4+25- and CD4+25+ fractions of silicosis patients compared with healthy donors.
4. The serum level of soluble IIL-2 receptor (sIL-2R) is higher in silicosis patients compared with healthy donors, and the level of sIL-2R is higher in silicosis patients compared with healthy donors, with the highest levels being detected in patients with systemic sclerosis according to a positive correlation.

On the other hand, exposure to silica also activates Tregs. When Tregs are activated, the expression of surface CD95/Fas is enhanced.

1. Expression of surface Fas in peripheral FoxP3 Tregs is higher in silicosis patients compared with health donors.
2. Tregs derived from silicosis patients are sensitive to Fas-mediated apoptosis-inducing antibodies.
3. In vitro exposure of peripheral blood mononuclear cells to silica caused a reduction in FoxP3 expressing cells, but had no effect on the CD25 expressing cell population. These findings indicate that in vitro cultivation facilitates the processing of Tregs toward apoptosis and the activation of originally CD25 negative responder T cells.

Taken together and summarized in Fig. 2, silica exposure chronically activates both responder and regulatory T cells (Hayashi et al. 2010). The development of early loss of Tregs by Fas-mediated apoptosis with contamination of chronically activated responder T cells into the peripheral CD4+25+ fraction results in reduced inhibitory function of this fraction. Chronically activated responder T cells may include self-antigen recognizing clones, and activation of these cells may not be reduced by Tregs (Lee et al. 2011). These conditions may further lead to the dysregulation of autoimmunity.



Silica, Immunological Effects, Fig. 2

Model showing the activating effects of silica on responder and regulatory T cells. Silica can activate both cell types. Activated responder T cells (CD4 + 25- fraction) can express CD69, PD-1 (programmed cell death1), and CD25. Activated regulatory T cells (CD4 + 25+ and FoxP3 positive) can express CD95/Fas death receptor and are sensitive to Fas-mediated apoptosis. Since chronically activated Tregs progress to apoptosis, the inhibitory effects involving the termination of activated responder T cells has been reduced. As a result, chronically activated responder T cells may avoid termination caused by the suppressive function of regulatory T cells, and prolonged activation is manifested. These conditions may result in the longer survival of self-recognizing responder T cell clones and reaction with self-antigens. Furthermore, the inhibitory function of the peripheral CD4 + 25+ fraction is reduced given the earlier loss of regulatory T cells and contamination of activated responder T cells expressing CD4 + 25+

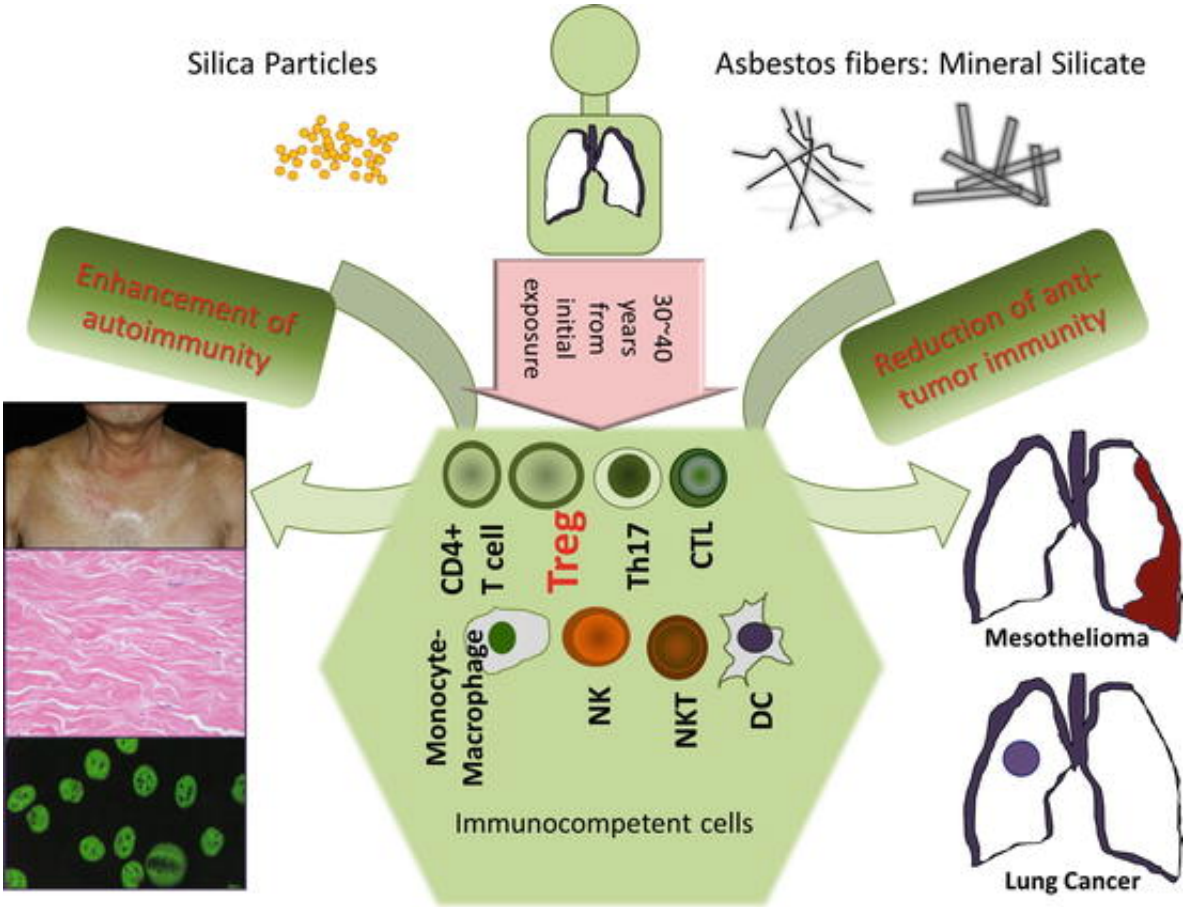
Immunological Effects of Asbestos, Mineral Silicate

Although the physical form of asbestos is rigid and linear compared with particulate silica, asbestos is chemically composed of silicon and oxygen, and additional minerals such as magnesium, sodium, and iron. Regarding initiation of the fibrogenicity of asbestos which leads to asbestosis, the important role of forming the inflammasome, as mentioned above, has been well recognized. The physical differences between asbestos fibers and silica particles may influence the pathological features of fibrosis which manifest in silicosis and asbestosis. The former forms middle to upper pulmonary areas with small rounded silicotic nodules, while the latter forms middle to lower lesions with linear and irregular progression of fibrosis, which finally develops a honeycomb lung.

Investigations concerning in vitro exposure of immunocompetent cell lines to asbestos, ex vivo exposure of freshly isolated lymphoid cells derived from healthy donors, and circulating peripheral blood lymphoid cells have revealed evidence of reduced antitumor

immunity. For example, the functional activation of NK (natural killer) cell receptors such as 2B4, NKG2D, and NKp46 with suppressed intracellular signaling such as the MAPK (mitogen-activated protein kinase) cascade. Additionally, the surface expression of CXCR3 (chemokine (C-X-C motif) receptor 3) on CD4+ T cells was reduced, together with the capacity to produce IFN (interferon)-γ, both processes being important in the development of antitumor immunity. Moreover, marked secretion of IL-10 and TGF-β occurs when the human CD4+ T cell line is continuously exposed to asbestos, with both cytokines possessing immune suppressive effects and also typical soluble factors for the function of Tregs.

Taken together, the immunological effects of asbestos tend to reduce antitumor immunity. This is reasonable according to the complications which arise in patients exposed to asbestos, such as the occurrence of malignant mesothelioma and lung cancers, as summarized in Fig. 3. In particular, if Tregs are placed at the center of the immunological effects of these environmental substances, silica can reduce Treg function and population, although asbestos seemed to enhance Treg function at least from the results pertaining to cytokine production in asbestos-exposed cell lines and patients (Matsuzaki et al. 2012).



Silica, Immunological Effects, Fig. 3

Comparison of the immunological effects of silica and mineral silicate (asbestos). If Treg function is placed at the center of these reactions, silica and asbestos are assumed to induce opposite effects. A detailed analysis of the immunological effects of silica and asbestos should be performed to better

understand the biological effects of these environmental substances

Further Perspectives

The effects of silica on Th17 cells and the role of Th17 cells in silica-induced dysregulation of autoimmunity have yet to be delineated. One report has indicated that IL-17A-producing $\gamma\delta$ T and Th17 lymphocytes mediate lung inflammation but not fibrosis in experimental silicosis. However, further clarification is required concerning cytokine alterations in silicosis and the induction of Th17, the status of Th17 and related cytokines such as IL-17A, IL-21, IL-22, Il-23, IL-6, and TGF (transforming growth factor)-β, and the effects of silica on generalized antigen-presenting cells such as dendritic cells not located at the local pulmonary area. The difficulties associated with an analysis of the immunological effects of silica relate to the need to consider these effects on the local processing of lung fibrosis and the development of general autoimmune dysregulation. The important players may be similar, such as CD95/Fas and its ligand, Th17, Tregs, and others. The need to distinguish the immunological effects of silica in terms of the local pulmonary area and general immune system is important in contributing toward an understanding of the total effects of silica on the human body. Furthermore, a comparison of the immunological effects of particulate silica and asbestos fibers is also needed to better understand the biological effects of these environmental substances.

Cross-References

Chromium(III) and Immune System

Gallium Nitrate, Apoptotic Effects

Lead and Immune Function

Mercury and Immune Function

Thallium, Cell Apoptosis Inducement

Zinc and Immunity

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