〈Review〉

Silica and mineral silicates causing autoimmune diseases

Suni LEE, Hidenori MATSUZAKI, Naoko KUMAGA-TAKEI,
Shoko YAMAMOTO, Tamayo HATAYAMA, Kei YOSHITOME,
Yasumitsu NISHIMURA, Takemi OTSUKI

Department of Hygiene, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan

ABSTRACT There are many environmental, occupational and medical substances that cause dysregulation of autoimmunity. Among these substances, the effects and causative mechanisms of silica particles and asbestos fibers are discussed in this review. Many epidemiological studies have shown a significant association between silica exposure and the occurrence of autoimmune diseases such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systemic lupus erythematosus (SLE), and anti-neutrophil cytoplasm antibody (ANCA)-related vasculitis. Although the importance of NALP3 inflammasome as the initial immune reaction against silica particles has been recognized, the processes that form the various autoimmune diseases in silica-exposed patients remain unclear. Silica can activate various immune cells and cause an unbalance of regulatory T cells, responder T cells and T helper 17 cells, which might be key factors in understanding the silica-induced autoimmune alteration. In contrast, asbestos exposure shows a smaller association with autoimmune diseases. However, interesting findings have been reported regarding anti-endothelial and mesothelial cell antibodies detected in asbestos-exposed patients. Further investigations may contribute to elucidation of the mechanisms involved in environmental factor-induced modification of autoimmunity.

doi:10.11482/KMJ-E42(1)15 *(Accepted on May 11, 2016)*

Key words: Silica, Asbestos, Autoimmune diseases, Autoantibody

INTRODUCTION

It is well known that various environmental factors such as chemical agents, including silica, asbestos, metals, pesticides and solvents, physical agents such as ionizing radiation, ultraviolet radiation (sunlight), electric and magnetic fields, and biological agents that include infectious microorganisms, foods, molds, mycotoxins, and other toxins may influence the human immune system, particularly in regard to dysregulation of autoimmunity[1-7]. Many epidemiological investigations and experimental studies have evaluated environmental factors that induce autoimmune diseases[1-7]. In order to investigate the biological mechanisms by which these environmental factors cause autoimmune diseases, it is important to conduct risk and hazard

Corresponding author
Takemi Otsuki
Department of Hygiene, Kawasaki Medical School, 577 Matsushima, Kurashiki, 701-0192, Japan
Phone : 81 86 462 1111
Fax : 81 86 464 1125
E-mail: takemi@med.kawasaki-m.ac.jp

analyses of environmental and occupational substances, as well as safeguard the health of workers in various occupational situations and people living in hazardous residential areas[1-7]. In addition to these aims, these investigations may be useful in determining the causative mechanisms of various autoimmune diseases, among which the pathophysiological and immunological aspects are well known, but the causative mechanisms remain unclear[8-10].

In this review, we investigate silica and mineral silicate, a form of asbestos, by evaluating and discussing epidemiological and experimental findings in an effort to better understand environmental factor-induced autoimmune disorders.

SILICA

Epidemiological studies

There are many reports describing the epidemiological significance of silica exposure and complicated autoimmune diseases. Caplan syndrome, complicated pneumoconiosis, and rheumatoid arthritis (RA) were initially reported in 1953 by Caplan[11]. Although it was thought that the causes of pneumoconiosis were not confined to silica, and included coal and asbestos, subsequent reports suggested that silica is the most common cause of this syndrome[12-17]. Another important syndrome involves complications of silicosis and systemic sclerosis, and is known as Erasmus syndrome. In 1957 Erasmus described an apparently high prevalence of progressive systemic sclerosis (PSS) / systemic sclerosis (SSc) in Witwatersrand gold miners exposed to dust containing free silica[18].

Recent epidemiological investigations involving meta-analysis of factors associated with exposure to silica indicate that the relative risk for RA in the silica-exposed population is more than three times higher than that of non-exposed people[19-22]. Meta-analysis has also been used to investigate the association between silica and SSc[22-23]. All of these studies indicate the significant high risk of SSc in the silica-exposed population[22-23]. Studies have also been performed regarding the association between silica exposure and systemic lupus erythematosus (SLE)[22, 24-28]. A positive association was reported in each of these studies and a high risk was indicated. In addition, case reports and case-control studies have been conducted concerning complications of anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis[29-40]. These investigations revealed a higher prevalence of ANCA in silicosis patients [29-40].

The overall findings of these epidemiological studies indicate with certainty that silica exposure alters human autoimmune tolerance and causes various autoimmune diseases.

Mechanistic investigations

Investigations concerning the mechanisms by which silica exposure affects the regulation of autoimmunity suggest that inflammasomes are very important[41-45]. They contribute toward the innate immunity against various external factors (including silica, asbestos, bacteria and their toxins) and internal factors (including crystalline derived from uric acid and cholesterol) that represent danger signals which need to be handled as the first step in a series of successive phenomena. The inflammasomes are large multi-molecular complexes composed of caspase-1, PYCARD/ASC (apoptosis-associated speck-like protein containing caspase recruitment domain), and NALPs (a type of NOD-like receptors) that induce the secretion of mature interleukin (IL)-1β and IL-18 (pro-inflammatory cytokines) from antigen-presenting cells (APC)[46-50]. Although the activation of inflammasomes can contribute to the formation of lung fibrosis in silicosis and asbestosis, two typical forms of pneumoconiosis[51-53], the long-term and gradual development of dysregulation of autoimmunity

may require additional cellular and molecular mechanisms involving various cell-to-cell, cytokine-to-cytokine, and molecule-to-molecule interactions.

There are many players in the development of autoimmune diseases when considering cell-to-cell interactions, such as APCs to present self-antigens, T cells to recognize them, B cells to produce antibodies, regulatory T cells (Treg) to control / inhibit the self-reactivity, and T helper (Th) 17 cells to promote hyper-reactivity to self-antigens[54-58]. The cytokine network plays a key role during any alteration or disturbance of the control of immune tolerance[59-63]. As mentioned above, IL-1β and IL-18 are produced from APC[46-50]. IL-1α is also secreted from monocyte-macrophage-APC cells and has various biological effects on immune, neurological and hematological conditions. IL-1α can expand Th1 cells to produce interferon (IFN)-γ. IFN-γ stimulates genes such as interferon regulatory factor 1 (IRF1) as the transcription factor to activate immune reactions[64, 65]. The networks then enlist nuclear factor-κB (NFκB) to activate self-antigen reacting immune cells such as B cells and T cells.

Unfortunately, it is not fully understood how the silica particles activate these networks through cell, cytokine and molecular interactions. The activation of inflammasomes is only the initial step of a series of cascading events that induce dysregulation of autoimmunity[46-50].

Silica-induced chronic activation of T cells

In addition to the adjuvant effects of silica that present various self-antigens to APCs with sufficient size as antigens, silica particles can also activate responder Th1 cells and Treg as we reported previously[66-70]. Evidence of silica-induced activation was found with the expression of CD69, an early activation T-cell marker, when T cells were cultured with silica particles *in vitro* and resulted in a remarkably higher expression of Programed Death-1 (PD-1) genes in peripheral blood T cells compared to those derived from healthy donors (HD), as well as higher soluble IL-2 receptor (R) in the serum of silicosis patients compared to HD[66-70].

Silica also changes activation-induced cell death in stimulated helper T cells by altering transcription of the Fas/CD95 cell death receptor gene, and results in the longer survival of these T cells[71-75]. Soluble Fas (sFas), an alternative spliced variant of the Fas gene, was more highly expressed relative to the wild-type Fas transcript in T cells from silicosis patients compared to those from HD[72-74]. In addition, sFas was elevated in the serum of silicosis patients[75]. sFas prevents activation-induced cell death in stimulated T cells, resulting in the long-term survival of these T cells in which self-recognizing clones may be present[72, 76-79].

In contrast to results obtained for responder T cells, Treg expressed Fas/CD95 to a much higher level when it was chronically activated, and Fas/CD95 expression was higher in Treg derived from the peripheral blood of silicosis patients compared to HD[70]. Furthermore, peripheral blood mononuclear cells from HD were cultured with silica particles and results indicated that forkhead box P3 (FoxP3) gene positive Treg was decreased[70]. The overall findings indicate an unbalance, increase of responder T cells, and decrease of Treg that may form the base condition in silicosis patients for the development of dysregulation of autoimmunity[76-79].

Th17 and silicosis

A consideration of autoimmune diseases indicates that another T-cell type, Th17, plays an important role. The balance between Treg and Th17 is critical for the development of autoimmune diseases; Treg can be induced by transforming growth factor (TGF) β and IL-2, and if IL-6 is also present, T cells are polarized to Th17 rather than Treg. The decrease of Treg and increase of Th17 may be the important factors that induce autoimmune diseases[80-85].

However, the relationship between silica exposure and alteration of Th17 cells remains unclear. It has been reported that Th17 can regulate silica-induced lung inflammation through an IL-1β-dependent mechanism[80-85]. As mentioned above, pulmonary inflammation and development of fibrosis in the lung may initially be induced by activation of the NALP3 inflammasome, and the previous findings therefore seem reasonable. This would ensure direct and recurrent contact between Th17 cells and inhaled remaining silica particles in the lung, as well as in lymph nodes, and may alter the features of Th17 cells. Additionally, chronic inflammation and progression of lung fibrosis may alter cytokine conditions toward an IL-6-dominant state in silicosis patients to result in a Th17-dominant and Treg-reduced situation in these patients[80-85]. Factor-analysis of our preliminary data indicated that the serum IL-6 level is included in the same factor with the titer of anti-nuclear antibody (ANA) and serum level of ANCA when the levels of various cytokines and titers of auto-antigens were analyzed in silicosis patients. This may suggest that the level of IL-6 (as well as TGF-β) is a key factor for the detection of silicosis patients prone to dysregulation of autoimmunity[80-85].

MINERAL SILICATE, ASBESTOS

We would like to turn our attention now to the mineral silicate, a form of asbestos. The core molecule of asbestos comprises Si and O, and is therefore similar to silica. The physical features of asbestos differ completely from those of silica, and partly result from the fact that silica comprises particulate matter, whereas asbestos is fibrous and includes various other minerals such as magnesium and iron. Silica and asbestos exposure causes pneumoconiosis, i.e., lung fibrosis, and both are categorized as a Group 1 carcinogen by the International Agency for Cancer Research (IARC)[86, 87]. However, evidence that asbestos causes dysregulation of autoimmunity is insufficient, and contrasts with the affirmative evidence found for silica[88-95]. Several case-control studies have shown a positive concern for the role of asbestos exposure in the development of RA[88-95]. Furthermore, some studies have shown immune enhancement or activation of autoimmunity defined by elevated immunoglobulins, rheumatoid factors, and ANA or ANCA following asbestos exposure without any confirmed symptoms of autoimmune diseases[88-95].

Some interesting investigations have been published regarding the impact of asbestos exposure[96-100]. These reports indicated that asbestos exposure induces production of autoantibodies against specific cell types, and complement previous reports showing the presence of anti-endothelial cell antibodies in vasculitis, SSc and SLE[101-103]. Similar to findings concerning these antibodies, reports indicate that anti-fibroblast antibodies (AFAs) and anti-mesothelial cell antibodies (MCAAs) are present respectively in the serum of mice and humans that have been exposed to "Libby Amphibole (LA)"[96-100]. LA is a mixture of amphibole fibers that contaminated the vermiculite that was mined outside of Libby, Montana, U.S.A. The interesting aspects of these antibodies include collagen production caused by binding with target cells such as AFAs to fibroblasts, and MCAAs to mesothelial cells[96-100]. The overall results suggest that asbestos exposure and production of these antibodies may play causative roles in asbestos-induced fibrosis formation in the lungs and pleura[96-100].

Although these findings were not consistent with systemic autoimmune diseases, it is very interesting that antibodies against these specific cell types may contribute to asbestos-induced disease formation such as fibrosis[96-100].

CONCLUSION

There are many reviews of environmental

substances, drugs and chemicals that cause dysregulation of autoimmunity[1-7]. Various drugs including hydralazine, quinidine and procainamide are associated with the development of SLE[1-7]. Silica and silicone (breast augmentation) are known to be related to SSc[1-7]. In addition, certain organic chemicals such as aromatic hydrocarbons, including toluene, benzene and xylene, aliphatic chlorinated hydrocarbons such as vinyl chloride, trichloroethylene and perchloroethylene, epoxy resins, and metaphenylenediamine are known to cause SSc following environmental or occupational exposure[1-7].

In this review, we only focused on silica and silicate, a form of asbestos, since silica is known as the most frequent environmental factor causing dysregulation of autoimmunity[1-7]. The summarized findings detailed in this review are presented in Fig. 1. New cases of pneumoconiosis, including silicosis and asbestosis, have been rapidly decreasing in the previous two to three decades because of improvement in occupational environments

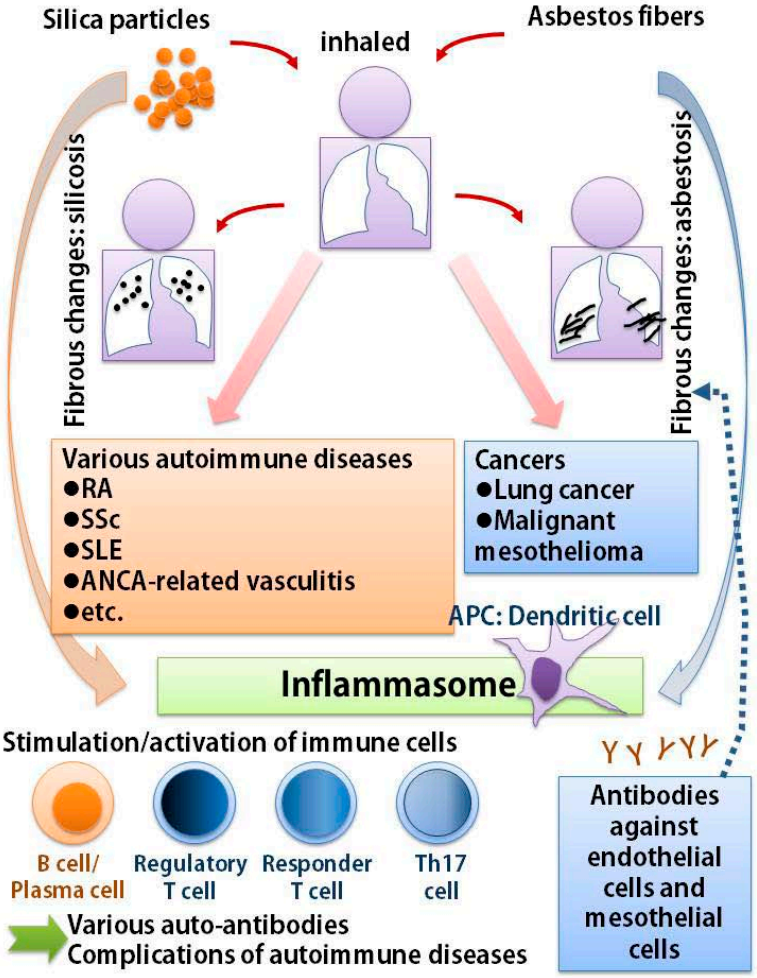

Fig. 1. Schematic presentation of the biological effects of silica and mineral silicate, a form of asbestos, detailing fibrous changes in the lung, autoimmune diseases in silica-exposed patients, cancer in asbestos-exposed patients, immune stimulation and activation to yield various auto-antibodies, complications of autoimmune diseases in silica-exposed patients, and production of antibodies against endothelial and mesothelial cells in asbestos-exposed patients through activation of inflammasomes.

and material handling procedures. However, we now have to consider low-level exposure to environmental factors causing autoimmune diseases, as well as individual factors such as HLA types and single nucleotide polymorphism (SNP) in certain genes, including the epigenetic status of various genes, since these situations may influence the occurrence of systemic autoimmune diseases due to the relationship between exposure to environmental factors and individual situations.

Further studies are required to elucidate the detailed pathogenic mechanisms involved in environmental factor-induced dysregulation of autoimmunity. These investigations may contribute to the development of tools for the prevention and treatment of various autoimmune disorders.

CONFLICT OF INTEREST

All authors have nothing to declare conflict of interest regarding this study.

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