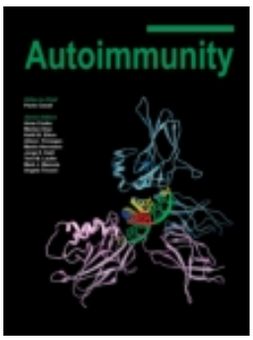

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Occupational exposures and risk of systemic lupus erythematosus

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Abstract
This review summarizes the growing body of epidemiologic and experimental research pertaining to the relationship between SLE and occupational exposures, such as crystalline silica, solvents, and pesticides. Epidemiologic studies, using different designs in different settings, have demonstrated moderate to strong associations between occupational silica exposure and SLE. Recent experimental studies of silica in lupus-prone mice provide support for the idea that, in addition to its known adjuvant effect, silica exposure increases the generation of apoptotic material, an important source of self-antigen. Despite compelling experimental studies of the organic solvent trichloroethylene (TCE) in lupus-prone mice, there is little evidence of an overall association of SLE and occupational exposure to a broad classification of solvents in humans. However, there is a lack of data on SLE in occupational cohorts with exposures to TCE or other specific solvents. One epidemiologic study reported an association of pesticide mixing and SLE, while a recent experimental study reported accelerated disease in pesticide-treated lupus-prone mice. Other occupational exposures worth investigating include asbestos, metals, and UV radiation. Attention should also be given to the role of gene-environment interactions, which may require large, multi-site studies that collect both genetic material and occupational exposure data. The quality of exposure assessment is an important consideration in designing and evaluating these studies. The use of pre-clinical endpoints (e.g. high-titer autoantibodies) in occupational cohorts with well-characterized exposure histories may reveal occupational risk factors for autoimmunity, and may also provide baseline data for studies of determinants of progression to SLE.

Keywords: *Crystalline silica, solvents, pesticides, SLE, occupational exposures*

Introduction

There is growing evidence of the influence of occupational exposures in risk of systemic lupus erythematosus (SLE). Exogenous influences on the development of SLE may include a diversity of workplace chemical exposures or other factors that modulate immune response. On the pathway leading to autoimmunity and the development of autoimmune diseases there are several points at which occupational exposures may act, including altered regulation of auto-reactive T cells and production of autoantibodies, secretion of pro- and anti-inflammatory cytokines, and other factors contributing to the pathogenesis of end organ damage. In the present review, we summarize the growing body of epidemiologic and experimental research pertaining to the relationship between SLE and selected occupational exposures, including recent studies on crystalline silica, solvents, and pesticides. We also discuss other occupational exposures that merit further investigation, the importance of considering gene-environment interactions and issues related to study design and exposure assessment, and the use of pre-clinical endpoints (e.g. high-titer autoantibodies) in occupational cohorts studies.

Crystalline silica

Epidemiologic studies

Crystalline silica, or quartz, is an abundant mineral found in sand, rock, and soil and is chemically distinct from the polymer, silicone or amorphous silica,

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Table I. Studies of occupational exposures in relation to development of SLE in humans.*

Exposure	Setting and Design (*N*)	References	Results†
Silica	Koeger, 1995 France, case-series ($N = 87$ SLE patients) Work history (structured interview; 3 or more years)	[4]	Prevalence of exposure = 5% among SLE patients (no comparison group)
	Sanchez-Roman, 1993 Spain, cohort ($N = 50$) Scouring powder manufacturing plant	[78]	3 SLE and 5 SLE/scleroderma overlap cases (more than 10 times the expected prevalence)
	Conrad, 1996 Germany, cohort ($N = 28{,}000$) Uranium miners	[5]	28 definite and 15 possible SLE cases (more than 10 times the expected prevalence)
	Brown, 1997 Sweden, registry linkage silicosis patients ($N = 1052$) Hospital discharge diagnosis of SLE	[6]	Strong association RR = 23.8 (10.3, 47.0)
	Rosenman, 1999 Michigan, registry linkage Silicosis patients ($N = 463$)	[7]	Highly imprecise estimate (small sample size) OR = 11.4 (0.2, 63.2)
	Parks, 2002 North and South Carolina, Case-control ($N = 265$ cases, 355 controls) Work history (structured interview, any duration)	[8]	Dose response across exposure groups Medium OR = 1.7 (1.0, 3.2) High OR = 3.8 (1.2, 11.6)
Solvents	Cooper, 2004 North and South Carolina, Case-control ($N = 265$ cases, 355 controls) Work history (structured interview, any duration)	[26]	No association across exposure groups Possible OR = 1.0 (0.57, 1.9) Likely OR = 1.0 (0.60, 1.6)
Pesticides	Balluz, 2001 Nogales, Texas Case-control ($N = 20$ cases, 36 controls)	[40]	No difference in DDE or organophosphate measures in blood
	Cooper, 2004 North and South Carolina, Case-control ($N = 265$ cases, 355 controls) Work history (structured interview, any duration)	[26]	Strong (but imprecise, based on small numbers) association with mixing pesticides, no association with applying pesticides Mixing: OR = 7.4 (1.4, 40.0) Applying: OR = 0.77 (0.34, 1.8)
Mercury	Cooper, 2004 North and South Carolina, Case-control ($N = 265$ cases, 355 controls) Work history (structured interview, any duration)	[26]	Moderate association with self-reported mercury exposure and work in dental environment OR Mercury = 3.6 (1.3, 10.0) OR Dental workers = 7.1 (2.2, 23.4)

*Adapted from Cooper and Parks, 2004 [3]. †Measures of association where given—OR = odds ratio; RR = risk ratio, followed by 95% confidence interval.

e.g. diatomaceous earth. High-level exposure to respirable silica dust (particles $<5\,\mu m$) can cause chronic inflammation and fibrosis in the lung and other organs, and can lead to the progressive lung disease, silicosis. Silicosis is a known occupational hazard of the "dusty trades" such as pottery and china manufacturing, quarry work, masonry, other work involving abrasive grinding, and mining [1]. Research linking silica dust exposure (or silicosis) to autoimmune diseases arose from case reports and small case series describing the occurrence of autoimmune disease in specific occupational settings (stone masons and miners) and focusing on scleroderma (systemic sclerosis) and rheumatoid arthritis. Since 1985 the research pertaining to occupational silica exposure and autoimmune diseases has grown substantially, with several new epidemiologic studies using a variety of study designs, conducted in different settings, and involving a spectrum of systemic diseases (rheumatoid arthritis, primary systemic vasculitis, scleroderma, and SLE). The literature was reviewed by Parks et al. in 1999 [2] and updated in 2004 [3]. The studies generally report relatively strong and consistent associations of silica with these diseases (relative risks of 3.0 and higher, with some studies reporting more than a 10-fold increased risk). Although specific problems (e.g. recall bias, exposure misclassification, confounding) could theoretically affect any single study, the observation of an association between silica exposure and autoimmune diseases in this collection of studies using different designs (clinic based, occupation-based, population-based, and registry-linkage), different exposure assessment techniques, and in different populations makes it unlikely that the results are due to bias.

Epidemiologic studies published since 1990 on occupational silica exposure and SLE are described in Table I. These studies include a clinic-based case-series of SLE patients in France [4], a study of 50 scouring powder factory workers in Spain, and a large study of male uranium miners [5]. The prevalence of SLE in the latter two occupational groups was more than 10 times higher than expected based on sex-specific prevalence rates in the general population. Two other studies examined SLE in silicosis patients using hospitalization registry data [6,7]. In the larger of these studies, the risk ratio for SLE-related hospitalization among patients with silicosis compared to all other hospitalized patients was 23.8 [6]. The most recent study was a case-control study in the southeastern United States in which a dose-response association with silica dust exposure (odds ratios = 2 to 4 for medium and high level exposure groups) was consistently seen across subgroups divided by sex, race, and education level [8].

Most (90%) SLE patients are female [9], while men comprise the majority of workers in the industries with high-level silica exposure (i.e. the dusty trades). Various aspects of women's work patterns (for example, duration of employment in specific jobs) are important to consider when designing exposure assessment techniques for studies that include women. Exposure assessment techniques that are based solely on relatively long periods of employment in the dusty trades may have low sensitivity for identifying individuals with a history of silica exposure in the general population, resulting in an attenuated estimate of association. In a comparison of the effect of different exposure assessment techniques in a population-based study of SLE, standardized coding of silica-related job histories was less likely to identify silica exposure than specific task-based questions [10]. In some settings, it may also be relevant to consider exposure from agricultural work [11]. One indicator of the sensitivity of an exposure assessment method is frequency of exposure among controls, which should be similar to studies in comparable populations. A lower than expected frequency of silica exposure suggests that the assessment method may be an insensitive indicator of exposure.

Other considerations in evaluating the role of silica in SLE are the relevant time window for exposure, and the dose required for autoimmune effects. Because silica is not metabolized or destroyed by the action of macrophages, it may have a long-lasting immune-modulating effect. Thus exposure assessment techniques should include experiences that occur years before disease onset. Data from some studies of silica-related autoimmune disease suggests that exposure intensity may be of equal or greater importance than cumulative life-time exposure levels, but other studies have not demonstrated an effect of duration or of intensity [2]. Studies may need to consider short-term work in jobs with high-intensity exposures that could overwhelm lung clearance mechanisms for silica, leading to higher doses in the lung-associated lymph nodes and other internal organs that have been seen to be responsible for systemic immunological effects in animal models (see below).

Experimental studies

Silica's inflammatory effects clearly play a role in the etiology of silicosis in experimental models [12,13]. Silica can act as an immune stimulant or adjuvant, resulting in the increased production of pro-inflammatory cytokines including tumor necrosis factor and interleukin-1 (reviewed by Parks [2]). This is a non-specific effect, but may be quite relevant given the association of silica exposure with several different autoimmune diseases [2]. An adjuvant effect is not sufficient to produce an autoimmune disease: other events or processes are necessary in the generation of autoimmunity and loss of self-tolerance. Silica may also result in increased exposure to self-antigens through generation of apoptotic material

(silica is toxic to macrophages, resulting in both apoptosis and necrosis). In a study of the New Zealand mixed lupus mouse strain, silica exposure exacerbated disease development (i.e. increased autoantibody production, immune complexes, proteinuria, and glomerulonephritis) [14], and autoantibodies from these mice recognized specific epitopes on apoptotic macrophages [15]. Changes were also seen in cervical lymph nodes including elevated B1a B cells, CD4 T-cell count, and the ratio of regulatory T-cell to helper T-cells in silica exposed versus non-exposed animals [16]. The increase in B1a B cells, implicated in the development of autoimmune disease pathology in lupus-prone mice [17], suggests another mechanism by which silica could be related to SLE.

Recent experimental studies also highlight the importance of dose or intensity of silica exposure with respect to clearance from the lung and subsequent effects on other organs and on immune response. If normal clearance mechanisms are overwhelmed, as is the case with the doses required for experimental silicosis, silica-containing macrophages can be translocated to pulmonary lymph nodes and possibly more widespread throughout the lymphatic system. A study in silica-exposed rats demonstrated profound, pathological changes in the pulmonary lymph nodes after silica dust exposure [18]. Other animal models of silicosis have shown that increased systemic immunoglobulin production is primarily due to the accumulation and effects of silica in the lymph nodes [19]. Another study showed that even peritoneal macrophages can be primed by respiratory silica exposure, showing significantly stronger responses to *in vitro* stimulation with lippopolysaccharide than those from non-silica exposed controls [20]. Recent studies also suggest that lymphocyte-derived interferon-gamma, which can activate macrophages and is expressed at elevated levels by lymphocytes in silicotic lymph nodes, may be responsible for the long-lasting expression of inducible nitric oxide synthase and maintenance of a chronic inflammatory state in silica-containing lymph nodes [21,22].

Solvents

Solvents are liquid compounds with a variety of chemical properties, and include alcohols, glycols, aromatic hydrocarbons (e.g. benzene, toluene, xylene) and chlorinated products (e.g. carbon tetrachloride, trichloroethylene [TCE]) [23]. Solvents are used extensively as degreasers and cleansers in machine shops, the aircraft and automobile industries, and many other settings. The specific type of solvent used varies across workplaces, has changed over time and even varies among workplaces involved in similar activities. Assessment of solvent exposure in population-based studies is very difficult since many workers do not know which specific products were or are used at their workplace. Solvents are usually metabolized quickly so biologic measurements (e.g. in blood or urine) generally reflect short-term rather than long-term or cumulative exposures.

Epidemiologic studies

Most of the epidemiologic studies pertaining to solvents and systemic autoimmune diseases have focused on systemic sclerosis and undifferentiated connective tissue disease [24,25]. The literature is consistent with a modest association (odds ratios between 1.5 and 3.0) with the broad classification of exposure to solvents, but less is known about associations with specific solvents. Associations between trichloroethylene, mineral spirits, and petroleum-based products and systemic sclerosis or undifferentiated connective tissue disease were seen in some, but not all, studies. Only one study has examined occupational exposure to solvents and SLE (Table I); no association was seen with the general category of solvents in this case-control study [26]. In our review of the literature, we identified no published studies or case reports linking solvent exposure and SLE in occupational settings. Given the diverse and widespread opportunities for workplace solvent exposure, further investigation in occupational cohorts is warranted, especially given the findings with respect to other autoimmune diseases and from experimental models. Exposures are not uncommon, and there is a substantial body of studies, for example, describing increased risk of cancer (e.g. non-Hodgkin's lymphoma) in large occupational cohorts with exposure to TCE [27,28].

Experimental studies

Several studies have examined the effect of trichloroethylene exposure in MRL +/+ mice, one of the strains of lupus-prone mice commonly used in experimental studies [29–32]. Exposure to trichloroethylene or some of its metabolites (in drinking water or by intraperitoneal injection) resulted in increased autoantibody and immunoglobulin production, activation of CD4+ T cells, and production of interferon gamma [29,30,33]. Blocking the cytochrome P450 CYP2E1 metabolic pathway with diallyl sulfide reduced the CD4+ T cell activation [31]. It is not yet known whether these results apply to other types of solvents since there have been no experimental studies using other compounds.

Given the relative paucity of data on occupational solvent exposure and SLE in humans, the experimental research on solvents in animal models could be expanded to include other solvents that may or may not share mechanisms with TCE. Some solvents, such as benzene, are known immunotoxicants [34], and

have documented effects on the human immune system in occupational settings (e.g. decreased white blood counts in solvent-exposed rubber-workers) [35]. It may be important to consider potential mechanisms when identifying which agents to investigate, as well as the route of exposure of solvent exposure (e.g. inhaled versus dermal) and other factors affecting toxicokinetics [36]. Inhaled solvents, for instance, can stimulate cells in lung-associated lymph nodes [37], even in the absence of notable effects on the spleen. Depending on the local context, such stimulation may be relevant. Experimental studies should also address the potential effects of solvents in the context of other chemical exposures, which will also help to reflect realistic human exposure scenarios. Many workers are exposed to more than one agent, for example, welders and housepainters may be exposed to different mixtures of solvents (e.g. cleaning fluids), metals (metal fumes, leaded paint dust), or silica [38,39].

Pesticides

Pesticides include a variety of agents with different chemical and biological properties. Pesticides can be classified based on function (e.g. herbicide, insecticide, fungicide, fumigant) or class (e.g. triazines, organophosphates, organochlorines). Recent exposure to specific pesticides can be measured using serum or urine samples, but for non-lipophilic compounds, assessment based on occupational history may provide a more accurate estimate of past exposure since most pesticides currently available have relatively short half-lives (compared with the lipophilipic organochlorinated pesticides such as 1,1,1-Trichloro-2,2'bis(p-chlorophenyl) ethane (DDT).

Epidemiologic studies

Only two epidemiologic studies have examined pesticide exposure in relation to SLE (Table I). There was little difference between SLE cases and controls in blood levels of DDE (the long-lasting metabolite of DDT) or other metabolites of organophosphate pesticides in a small case-control study in Nogales, Texas [40]. A larger case-control study examined self-reported use (mixing or applying) of pesticides in farmwork in a rural area of the southeastern United States [26]. Mixing pesticides was relatively uncommon (reported by 8% of cases and 1% of controls), resulting in a strong, but imprecise association (OR = 7.4, 95%CI 1.4, 40). In contrast, no association was seen with the more common activity of pesticide application (11% of cases and 15% of controls).

High-titer antinuclear antibodies (1:160 or higher) are seen in 95% of SLE patients. Low titer antinuclear antibodies (1:40) may reflect recent infections, and are fairly common in the general population (20–30%). One study examined the prevalence of low titer ($\geq$1:40) antinuclear antibodies in 322 residents of Saskatchewan, a rural province in Canada [41]. There was a two-fold increased prevalence with history of exposure to insecticides and herbicides (including specific organochlorines), but not with fungicides or algicides. These associations were not seen with higher-titer ($\geq$1:160) antinuclear antibodies. In another small study of African–American farmers, anti-nuclear antibody prevalence was somewhat elevated in those with the highest level of plasma DDE levels, though the difference was not statistically significant [42].

Experimental studies

Much of the experimental research concerning immunotoxicologic effects of pesticides has focused on immunosuppression and hypersensitivity [43]. A combination of immunosuppressive properties in conjunction with enhanced production of immunoglobulins and autoantibodies has been seen in some experimental studies of hexachlorobenzene and malathion (reviewed by Cooper [24]).

Some pesticides are endocrine-disruptors. Specific pesticides may have agonist and antagonist effects on steroidal hormones (estrogens, androgens, and progesterone), gonadotropin hormones or thyroid hormones [44]. The (NZB × NZM)F_1 mouse is an SLE model in which estrogen clearly influences the rate of disease progression. A recent experimental study in ovarectomized female (NZB × NZM)F_1 mice showed acceleration of the primary disease endpoint (renal disease) from exposure to three organochlorine pesticides with estrogen-like effects: *o,p′*-dichlorodiphenyltrichloroethane (*o,p′*-DDT), methoxychlor, and chlordecone [45]. This included a dose-dependent effect of chlordecone on the early development of elevated anti-dsDNA antibody titers, with subsequent development of glomerulonephritis. Upon investigation of the estrogenic hypothesis, however, autoimmune effects were not highly correlated with a non-immune marker of estrogenicity (uterine hypertrophy). Further investigation is needed to understand the mechanisms by which these pesticides might act in autoimmunity, including their possible estrogenic effects on the immune system. It should be noted that, although estrogen exposure clearly influences the onset of disease in some experimental models, human data on variation in estrogen exposure among women has shown inconsistent associations with risk of SLE [46].

Implications for future research

Other exposures

Crystalline silica is the agent with the most human data supporting an association with SLE. There are other silicates with similar properties that have been

related to the development of pneumoconiosis (e.g. talc) [47], including those described in case-reports of possible exposures linked to autoimmunity in dental technicians [48,49]. Other recent data in humans is emerging on an asbestos-exposed community in Libby, Montana [50], in which both occupational and environmental asbestos exposures have occurred. Analyses of serum from Libby residents compared with age and sex-matched controls from a comparison community revealed that low-titre positive ANAs were significantly more common in Libby residents, and that 22% of Libby residents compared with 6% of controls showed high-titer ($\geq$1:320) ANAs. Significantly higher levels of other autoantibodies were observed including RNP, Scl-70, Sm, SS-A, and SSB, though the number of individuals represented were relatively small. The exposure metric (including both occupational and environmental exposure to asbestos) was significantly correlated with both ANA titers and with the diagnosis of asbestos-related disease. None of the subjects, however, had a diagnosis of systemic autoimmune disease. Asbestos is a fibrous mineral dust that clearly has a different toxicological profile than crystalline silica. However, like other insoluble particles, asbestos inhalation may also lead to the persistent generation of reactive oxygen species and inflammation [51].

Heavy metals have been associated with exacerbating or accelerating disease in experimental models of lupus. These include lead (Pb), which can exacerbate lupus in NZM mice, but to differing extent and phenotype depending on gender and other strain-specific factors [52]. Cadmium exposure through drinking water also influenced development of disease in the NZBW mouse strain, even at very low doses [53]. Mercury exposure has also been shown to exacerbate disease development in the NZBW and MLR-mouse strains, though differences in effect were seen depending on genetic background of the model [54], and even very low-dose mercury accelerated development of disease in the a lupus-like chronic graft-versus-host disease model [55]. The mechanisms by which heavy metals might influence development of lupus are diverse [56]. However, observational data in humans examining the relationship between heavy metal exposure and SLE are sparse. One case-control study has described an association of SLE and self-reported occupational mercury exposure (OR = 3.6, 95% CI 1.3, 10.0), but exposure was uncommon and the finding bears replicating [26]. Occupational lead and cadmium exposure have not been directly linked with SLE, though mixed exposure to silica and metal dusts are not uncommon, as illustrated by a case-report of a steel worker with pulmonary fibrosis and lupus-like features [57]. Another difficulty in studying the role of occupational exposure to heavy metals is that, in the general population, especially in women, who comprise the majority of lupus patients but a minority of heavy industrial workers, environmental exposures to metals (e.g. diet, smoking) may be important contributors to body burden. This may be a particular problem if the autoimmune-related effects of low level exposure are relevant or if they differ from the effects of higher level exposures.

Exposure to ultraviolet (UV) radiation is known to exacerbate disease in both experimental and human studies [58,59], but there is little evidence from human studies that occupational exposure to sunlight is related to risk of SLE. One case-control study showed no overall association of SLE with duration of work in jobs with regular sunlight exposure, but identified a significant gene-environment interaction with gene polymorphisms in Glutathione S-transferease (GST) [60]. The gene products GSTM1, GSTT1, and GSTP1 may play a role in excretion of reactive oxygen species generated by cellular oxidative stress presumably induced by ultraviolet radiation in sunlight. Other mechanisms suggested by work in experimental models include the induction of DNA damage and apoptosis, differences in the production of vitamin D, or cytokine expression profiles [58,61,62]. In the skin of patients with cutaneous lupus erythematosus, research suggests disease develops due to a cycle of UV-induced apoptosis and necrosis in concert with chemokine production [63]. Given the experimental studies and evidence of UV-induced damage in SLE and cutaneous lupus, more investigation is warranted. In the construction of human studies, assessment of occupational sunlight exposure should be rigorous and studies should also attempt to identify residential latitude, race or skin color, personal behavior characteristics related to sunlight exposure, and take into account other occupational sources of UV exposure (e.g. Welding arcs) [64,65].

Gene-environment interactions

Genetic susceptibility clearly plays a role in the etiology of systemic lupus erythematosus (SLE). The concordance rate for SLE among monozygotic twins is thought to range from 25 to 35% [66,67], which is much higher than that seen in dizygotic twins ($<$ 5%), and is among the highest rates seen in any autoimmune disease [68]. However, the lack of concordance in the majority of twin pairs provides support for the idea that other factors, in addition to genetics, are involved in the etiology of SLE.

Variation in genes affecting the metabolism of or physiological response to occupational exposures deserves further attention. Stratifying analyses by genetic polymorphisms may reveal associations hidden in overall analyses: For example, in the previously described study of occupational sunlight exposure, an association with SLE was only seen in whites with the GSTM-1 null genotype [60]. Other gene-

environment interactions are plausible: For example, silicosis severity has been associated with differences in cytokine gene polymorphisms [69]. Given that cytokine polymorphisms have been associated with SLE, interactions with silica would be consistent with potential mechanisms proposed for silica in SLE.

Studies of gene-environment interactions in SLE are, however, limited by a number of factors, including the typical small sample size of case-control studies, identifying an appropriate source population for control sampling, and the lack of representation of diverse genetic populations. In order to conduct studies of gene-environment interactions in a rare disease such as SLE, there is a need for much larger (e.g. multi-site) studies of SLE patients that collect both genetic material as well as detailed occupational history data.

Intermediate endpoints

The development of autoimmune diseases likely involves many steps, including the loss of tolerance and development of autoimmunity. Autoimmunity, unlike autoimmune diseases, may be widespread and somewhat limited in duration. Nonetheless, it offers the opportunity to study exposures that could influence the early stages of disease development. The use of autoantibodies as an endpoint in observational human studies might increase statistical efficiency, given the relative low frequency of disease endpoints available in most occupational cohorts. Again, it is important to differentiate between low and high-titer ANAs, and to consider a diversity of antibodies specific to SLE. It is also worth noting in the extrapolation from animal models to the development of SLE in humans, exposures that accelerate disease in animal models may or may not be relevant to exposures that would trigger loss of tolerance and onset of human disease.

Several studies included in this review have examined exposures in relation to autoantibodies, including pesticides [41] and asbestos [50]. Studies have also described elevated autoantibody titers in relation to crystalline silica exposure [70–72]. In the Uranium Miner's cohort, a higher frequency of several SLE-related autoantibodies (e.g. anti-dsDNA, anti-Ro/SSA, anti-La/SSB) was observed relative to gender and age-matched controls [71]. In two miners with anti-dsDNA antibodies, progression to SLE was also described [72]. Inclusion of such markers in longitudinal cohorts, in particular, may also provide baseline data for studies of the determinants of disease development in individuals who are autoantibody positive.

Other covariates

Studies of occupational exposures and SLE should consider potential for confounding or effect modification by other non-occupational exposures. For example, smoking rates vary substantially by occupation [73]. A recent meta-analysis examined the association between smoking history and risk of SLE in seven case-control and two cohort studies [74]. The combined estimate showed a weak association with current smoking (i.e. smoking around the time of diagnosis, odds ratio, OR, 1.5, 95% confidence interval, CI, 1.1, 2.1), but no association with past smoking (OR 0.98, 95% CI 0.75, 1.3). Tobacco smoke has many different effects on immune function [75], including activation of alveolar macrophages, with increased myeloperoxidase activity and free-radical production. On the other hand, long-term smoking may impair secretion of pro-inflammatory cytokines and decrease activity of natural killer cells, which may contribute to an immunosuppressive effect of smoking and increased susceptibility to infections. Smoking has also been associated with indicators of systemic inflammation (e.g. leukocyte number, C-reactive protein) [76].

In addition to being a potential confounder, smoking may modify the effects of occupational exposures: In a study of silica and SLE, the effects of silica were significantly higher among smokers than among non-smokers [8]. A similar effect modification between silica and smoking has also recently been reported for rheumatoid arthritis [77]. Tobacco contains a variety of compounds with potentially immunomodulatory effects, including benzene and cadmium, as well as nicotine, which can influence neuroendocrine pathways. Thus, studies of occupational exposures and SLE should consider the potential of smoking to interact with or even to directly contribute to exposure burden.

Other potential confounders or effect modifiers might operate in studies of occupational exposures on SLE, but may be difficult to identify, given the relative scarcity of data on non-genetic risk factors. Occupational and non-occupational stress might be worth considering, given the widespread effects of stress on the immune system and the known role of stress in triggering flares in SLE and other autoimmune diseases. It should be noted, however, that in order to act as a confounder in epidemiologic models, a factor needs to be independently associated with both SLE and the occupational exposure of interest. Effect modification seems a more probable scenario for exposures that act along similar physiologic pathways, e.g. factors associated with a pro-inflammatory state.

Conclusions

Recent developments in epidemiologic and experimental research suggest the importance of investigating the role of occupational exposures in SLE. Silica is an example of a substance that is persistent in the body and may lead to increased apoptosis material

in a pro-inflammatory environment [78]. Although respirable silica exposure is unlikely to be a major cause of SLE in the general population, understanding the mechanisms by which silica acts in SLE may help to us better understand the potential contribution of environmental exposures in SLE and reveal opportunities for investigating other occupational risk factors. As the majority of evidence on silica and SLE stems from human studies, more experimental research is also needed to identify mechanisms involved in autoimmune response to silica.

Although an elegant body of research has examined the effects of trichloroethylene exposure in lupus prone mice, there have been very few epidemiologic studies of occupational solvent exposure in relation to SLE and no studies of other types of solvents in lupus-prone mice. Little is known about specific pesticides in relation to SLE, and there is limited data pertaining to a variety of other occupational exposures, including other silicates, asbestos, metals, and UV exposure. Metals, asbestos, and silicates may share some features with silica, including their persistence in the body and pro-inflammatory effects. Other occupational exposures (e.g. UV radiation) demonstrate both immune-stimulating and immunosuppressive qualities, and their impact on SLE may depend on dose, timing, and the context of other occupational and environmental exposures. Given the known importance of genetic susceptibility in SLE, and the growing experimental and epidemiologic evidence of occupational and environmental risk factors, understanding the etiology of SLE will likely require large, multidisciplinary studies to analyze the interactions between environmental exposures and genetic factors. Occupational cohort studies may also be used to study risk factors for autoimmunity in the pathway to SLE.

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