Environment and Autoimmunity: Facts and Gaps

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Angela Ceribelli, Elena Generali, and Carlo Selmi

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13.1 Introduction

The etiology of autoimmune diseases remains unknown; even if many studies have investigated it in the past and are still exploring it, until now no unique genetic or environmental risk factor has been identified to be responsible for the onset of

A. Ceribelli
Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Milan, Italy

BIOMETRA Department, University of Milan, Milan, Italy

E. Generali
Division of Rheumatology and Clinical Immunology, Humanitas Research Hospital, Rozzano, Milan, Italy

C. Selmi, MD, PhD (✉)
Division of Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center, via A. Manzoni 56, Rozzano, Milan 20089, Italy

BIOMETRA Department, University of Milan, Milan, Italy
e-mail: carlo.selmi@unimi.it

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autoimmune diseases. We now consider autoimmune diseases to be induced by multiple factors, genetic and environmental, and this is well supported by the fact that no direct genetic transmission of the same autoimmune disease has yet been found in a familiar group, even if different expressions of autoimmunity (organ specific or systemic) are found in families with affected individuals. An important observation comes from the incomplete concordance rate for autoimmune diseases in couples of monozygotic twins, in which only one twin expresses the rheumatic disease, despite the identical genomic sequences (Miller et al. 2012b; Selmi et al. 2012a). Twin studies are indicated in the study of autoimmune diseases as these allow also the possibility to calculate the genetic heritability of each condition, i.e., the proportion of observable differences in a phenotype between individuals that is due to genetic differences (Bogdanos et al. 2012; Christensen et al. 2011; De Santis and Selmi 2012). Since heritability is a proportion, its value ranges from 0 (when genes do not contribute to phenotypic differences) to 1 (when the environment does not contribute to phenotypic differences). This estimate depends on numerous variables, including the prevalence of the disease in the general population, and does not reflect the risk of getting a disease but the variance between twins. The term "heritability" defines the proportion of the phenotypic variance attributable to genetics (A + D), while the less known term "environmentability" represents the proportion of phenotypic variance attributable to environmental features (or 1-heritability). Of particular importance in the discussion of environmental factors is the fact that "environmentability" includes environmental influences that are the sum of common/shared environmental factors and individual environmental variance, while also including the differences due to measurement errors or observation bias. In specific autoimmune diseases, genetic heritability estimates are summarized in Table 13.1 and demonstrate that the weight of genetic influences is mostly observed in some conditions (as for Crohn's disease or ankylosing spondylitis) while being almost negligible in others (as for systemic sclerosis) (Selmi et al. 2004, 2011). To tackle this complex view in which causality is difficult to prove, the National Institute of Environmental Health Sciences (NIEHS) organized an expert workshop in September 2010 to provide a consensus on the definition of environmentally induced autoimmune diseases (Parks et al. 2014). The results of the expert panel were reported in three comprehensive articles on the mechanisms, epidemiology, and animal models, while a consensus statement was later reported (Miller et al. 2012a, b; Parks et al. 2014; Selmi et al. 2012a). The Delphi exercise results are summarized for immune or other mechanisms (Table 13.2), animal studies (Table 13.3), and factor-specific mechanisms (Table 13.4).

Based on these observations, it is now commonly accepted that multiple genetic predisposition factors must interact with epigenetic and environmental triggers to induce the clinical expression of autoimmune diseases, such as rheumatic ones (Ehrenfeld 2010). This could explain why some diseases develop mainly in some geographic areas (usually industrial zones), and they seem to have a seasonal concentration, maybe related to viral infections, as in the case of dermatomyositis (Tanaka and Takikawa 2013; Invernizzi 2010; Shapira et al. 2010; Chandran and

Table 13.1 Genetic heritability based on twin concordance rates for specific autoimmune diseases (Selmi et al. 2012b)

	Genetic heritability	Reference
Acute rheumatic fever	0.60 (0.41–0.81)	Engel et al. (2011)
Ankylosing spondylitis	0.97 (0.92–0.99)	Brown et al. (1997)
Celiac disease	0.57 (0.32–0.93) *if 1/1000 prevalence* 0.87 (0.49–1.00) *if 1/91 prevalence*	Nistico et al. (2006)
Crohn's disease	1.00 (0.34–1.00) 0.55 (*)	Tysk et al. (1988) So et al. (2011)
Multiple sclerosis	0.25 (0–0.88) 0.76 (0.33–0.88)	Hawkes and Macgregor (2009)
Psoriasis	0.66 (0.52–0.77)	Grjibovski et al. (2007)
Psoriatic arthritis	0.65 (0.22–1.00)	Pedersen et al. (2008)
Rheumatoid arthritis	0.68 (0.55–0.79) *ACPA positive* 0.66 (0.21–0.82) *ACPA negative*	van der Woude et al. (2009)
Sarcoidosis	0.66 (0.52–0.80)	Sverrild et al. (2008)
Systemic lupus erythematosus	0.66 (*)	So et al. (2011)
Systemic sclerosis	0.008	Feghali-Bostwick et al. (2003)
Type 1 diabetes	0.88 (0.78–0.94) 0.80 (*)	Hyttinen et al. (2003) So et al. (2011)

* prospective longitudinal study
When available, 95 % confidence intervals are provided

Raychaudhuri 2010; Zeki et al. 2010; Moroni et al. 2012; Selmi and Tsuneyama 2010; Prieto and Grau 2010). Despite the increasing interest about environmental risk factors, the recommendations and the ongoing growth of pathophysiological data about autoimmune diseases, there are still numerous gaps in our knowledge. The aim of this chapter is to describe the environmental factors and the general and specific mechanisms that are considered to play a role in the onset of autoimmune diseases.

13.2 Environment and Autoimmune Diseases: The Role of Chemicals, Xenobiotics, and Adjuvants

Every day an increasing number of factors responsible for autoimmune diseases are under evaluation, and in particular growing evidence for a pathogenic role is associated to chemicals, xenobiotics, and adjuvants (Chandran and Raychaudhuri 2010; Costenbader et al. 2012; Hemminki et al. 2010; Miller et al. 2012a, b). In the case of chemicals, some studies have demonstrated that aryl hydrocarbon receptor (AhR) can induce Th17 cell to differentiate with their activity exacerbating autoimmune diseases in animal models (Veldhoen et al. 2008), while others have shown that AhR promotes the expansion of regulatory T-cell (Treg) populations, decreases Th17

Table 13.2 The 2010 NIEHS expert workshop and panel findings on mechanisms involved in the role of environmental factors and development of autoimmune disease (Parks et al. 2014)

We are confident of the following	We consider the following likely, but requiring confirmation	Broad themes to be pursued in future investigations
B cells		
Dysfunctions of B-cell tolerance checkpoints are directly correlated with autoimmune disease in murine models B cells modulate autoimmunity positively and negatively as secretors of antibodies and inflammatory cytokines, as antigen-presenting cells to autoreactive T cells, and secretors of anti-inflammatory cytokines such as IL-10 Follicular B cells (B2) are a major source of autoreactive pathogenic antibodies B cells secreting pathogenic autoantibodies can emerge when somatic hypermutation occurs outside of germinal centers Sex hormones like estrogen and prolactin can differentially activate autoreactive B-cell populations from different subsets (e.g., B2)	B1 cells and marginal zone B cells can modulate autoimmunity by exacerbating it through secretion of autoreactive antibodies and/or by down-modulating it through secretion of anti-inflammatory cytokines B10 cells secrete IL-10 may be functionally specialized to carry out a negative regulatory role in inflammation and autoimmunity	The roles of B1 and marginal zone B cells in autoimmunity The role of the recently discovered B10 cell population in autoimmunity The survival/apoptotic pathways that when deregulated lead to expansion and survival of autoreactive B cells (such as the BAFF/BlyS receptor system and CD40) Tolerance checkpoint mechanisms regulating the formation of high-affinity autoreactive B2 cells both in and outside the germinal center Environmental agents with the potential to disrupt B-cell function
T-helper 17 (TH17) cells		
Deregulated Th17 cell activity can lead to pathology, as in chronic inflammatory diseases such as asthma or inflammatory bowel disease Th17 cells are involved in MS, RA, Crohn's disease, and psoriasis, where they seem to be involved in disease development and relapse	Smoking is an important risk factor for RA; and nicotine exerts effects via Th17 cells Aryl-hydrocarbon receptor (AhR) binding by aromatic hydrocarbons and non-halogenated polycyclic aromatic hydrocarbons favors differentiation of Th17 cells and can exacerbate autoimmunity	The involvement of environmental agents and exacerbation of autoimmune disease through Th17 cells Therapeutic modulation of Th17 cells

Innate immunity		
1. The interaction between xenobiotics and TLR is a major mechanism involved in the interaction of environmental factors with autoimmunity development 2. Innate immune activation TLR predisposes to toxic-induced inflammation 3. Adjuvants activate both innate and adaptive immunities, inducing the release of chemokines and inflammatory cytokines 4. Immunization must be accompanied by a strong adjuvant, such as complete Freund's adjuvant, including the mycobacterium component 5. Incomplete Freund's adjuvant results in production of antibodies, but without the occurrence of autoimmune diseases	Altered innate immune responses and deregulated TLR signaling are a key step in triggering autoimmune diseases, as in virus-induced animal models of type I diabetes TLR activation in macrophages may predispose cells to toxin-induced inflammatory cytokine production Active infection or microbial products of infection can provide the adjuvant effect necessary for the induction of many autoimmune disorders	Allergenicity, functional mimicry of environmental contaminants, and physical/chemical elements resembling TLR ligands Deregulation of the regulatory B cell (IL-10 producing, CD5+ B cells) through modulation of TLR signaling Molecular motifs of adjuvants and their physiological receptors that are associated with clinical manifestation of autoimmunity Genomic predisposition to innate immunity dysfunctions
T regulatory (Treg) cells		
Quantitative and qualitative Treg changes are culprit for tolerance breakdown The AhR ligand dioxin TCDD induces immunosuppressive T cells expressing specific Treg markers AhR ligands also affect skewing of the T-cell repertoire toward Treg cells indirectly via antigen-presenting cells TCDD induces IDO transcription to skew the T-cell repertoire toward FoxP3+ Tregs Activation of PPAR promotes Treg induction from naive cells	Most studies suggest that AhR activation in T cells or in antigen-presenting cells may increase Treg production and therefore decrease autoimmunity, but the opposite outcome is also likely and possibly ligand specific Context-specific activation of the AhR by specific ligands may result in either increased or decreased Treg activity Sex hormones play an important role in Treg development and may underlie female predominance of autoimmune diseases	Specific chemical, infectious, or physical agents capable of modulating Tregs Environmental modulators of AhR stimulation Mechanisms of sex-specific Treg changes

(continued)

Table 13.2 (continued)

We are confident of the following	We consider the following likely, but requiring confirmation	Broad themes to be pursued in future investigations
Modification of self-antigens		
The majority of human proteins undergo posttranslational modification (PTM), and these modifications or lack thereof may lead to tolerance breakdown PTM may explain the tissue specificity of autoimmune diseases MS pathogenesis includes PTM that increase the complexity of myelin proteins through the autoimmune response or neurodegenerative processes In RA, citrullination is an apoptotic PTM that seems to be helpful in opening protein conformation and favoring cleavage processes In PBC, cholangiocytes do not covalently link glutathione to lysine-lipoyl groups during apoptosis leading to accumulation and exposure to potentially self-reactive antigens, accounting for bile duct-specific pathology	Multiple self-protein modifications (phosphorylation, glycosylation, acetylation, deamidation) can lead to either T- or B-cell responses to self-antigens Serum autoantibodies to modified self-antigens may bind either modified or unmodified forms and thus be crucial to effector immune reaction in target tissues Mercury-induced cell death results in the formation of a unique and more immunogenic 19 kDa cleavage fragment of fibrillarin	Mechanisms by which citrullination and glutathionylation lead to tolerance breakdown in susceptible individuals The role of glucosylation in MS and other autoimmune diseases Experimental models to prove that autoantigens can be modified to increase their immunogenicity Technologies to reverse or induce PTM in animal models of autoimmunity
Modification of DNA methylation		
DNA methylation profiles are associated with environmental factors including prenatal tobacco smoke, alcohol, and environmental pollutants The importance of DNA methylation in regulating immune function is suggested by two rare congenital diseases, Silver-Russell and Beckwith-Wiedemann syndromes Changes in DNA methylation in specific peripheral immune cell types are associated with autoimmune diseases	Phenotypic differences are increased with age in twins in a trend coined as “epigenetic drift,” due to different environmental exposures, and may explain late-onset autoimmunity Specific impairments in epigenetic regulation in immune cells may be responsible for immune-tolerance breakdown through hypo-methylation of genes or involvement of transcription repressors Recent genome-wide association studies demonstrate that genomics significantly predispose to SLE onset, but experimental studies indicate that epigenetic mechanisms, especially impaired T- and B-cell DNA methylation, may be one of these factors	The functional effects in vivo of DNA methylation changes under different environmental and genomic conditions The development of new therapeutic molecules capable to prevent or counteract DNA methylation changes in a cell-specific manner The DNA methylation changes in the target cells and not only in the rapidly accessible effector immune cells

Table 13.3 The 2010 NIEHS expert workshop and panel finding studies of animal models in the role of environmental factors and development of autoimmune disease (Parks et al. 2014)

We are confident of the following	We consider the following likely, but requiring confirmation	Broad themes to be pursued in future investigations
Chemical factors		
1. Autoimmune responses are influenced by species and strain of animal model 2. There is no preferred species or strain, but studies with rats and mice predominate 3. Forms of inorganic mercury (HgCl2, vapor, amalgam) induce systemic autoimmune disease in rats (transient) and mice 4. Inorganic mercury (HgCl2) exacerbates or accelerates systemic autoimmune disease in lupus-prone mice 5. Gold causes (transient) nephropathy in rats 6. Several mineral oil components and certain other hydrocarbons can induced an acute inflammatory arthritis in some rat strains 7. The mineral oil component 2,6,10,14-tetra-methylpentadecane (TMPD or pristane) induces lupus-like disease and inflammatory arthritis in several strains of mice 8. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) suppresses models of autoimmune disease in adult mice	Gold and silver cause autoimmune responses in mice; effects of other metals (e.g., organic mercury, cadmium, lead, arsenic) require additional studies Silica/asbestos (at lower doses) stimulate autoimmune disease, but more studies are needed using more species/strains and a wider range of doses and exposure routes High-dose silica (≥100 mg) suppresses organ-specific autoimmune disease, but mechanisms are not known Trichloroethylene (TCE) exacerbates systemic autoimmunity although responses are often limited and transient. Studies of autoimmune liver disease are needed with additional species/strains and in developmental studies Dimethyl sulfoxide (DMSO) reduces some aspects of autoimmunity, but effectiveness depends on timing and mode of exposure. Mechanisms and side effects are not known Hydrocarbons may induce lupus-like disease in mice or inflammatory arthritis in rats Silicon may enhance autoimmunity in strains of mice susceptible to arthritis or lupus PBC-like disease can be induced by immunization with xenobiotically modified lipoyl hapten-carrier conjugates TCDD exposure during fetal or early neonatal development may promote autoimmunity Hexachlorobenzene (an organochlorine pesticide) suppresses adjuvant arthritis and exacerbates EAE Organochlorine pesticides may enhance lupus-like disease in a predisposed mouse strain	Epidemiological and clinical studies should be "shaped by what is observed in humans, not by what is possible in mice" Studies should not be restricted to a "gold standard" animal model Multiple models should be investigated to reflect human genetic heterogeneity When using spontaneous disease models, it is important to consider whether environmental exposures exacerbate/accelerate idiopathic autoimmunity or reflect environmental factor-specific autoimmunity Genetic and biological markers should be sought in easily obtained biological fluids to enhance comparison with human studies Biomarkers of stress exposure are needed to identify contributing or confounding roles of stress in autoimmune disease outcomes Determining whether an environmental agent or compound affects autoimmune diseases should include screening autoimmune-prone and non-autoimmune species and strains If necessary, animal models should be tailored (e.g., humanized) to verify findings from human epidemiological data of suspected modifiers of autoimmune disease More studies on the effects of environmental factor exposure on expression of autoimmunity during different stages of life (gestational to adulthood) are needed

(continued)

Table 13.3 (continued)

We are confident of the following	We consider the following likely, but requiring confirmation	Broad themes to be pursued in future investigations
Physical factors		
Sunlight/UV exposure exacerbates lupus in genetically prone mice Emotional stress (e.g., noise) can modify disease incidence, onset, or severity	Stressful life events interact with other risk factors (e.g., chemicals, infections), thereby confounding indices of autoimmune diseases Common underlying mechanisms of chemical, biological, and physical stressor effects on autoimmune disease are likely and may provide a better framework for predicting the role of oxidative stress and cytotoxicity and cell clearance in autoimmune disease	
Biological factors		
For a limited number of pathogens (i.e., Streptococcal group A, coxsackie B virus), there is a clear association with development of autoimmune diseases Caloric restriction in adults protects against a wide range of autoimmune diseases Restricting various dietary components, such as protein and especially fats, can be more protective than limiting calories Excess iodine increases the incidence of autoimmune thyroiditis in genetically predisposed animal models	For many pathogens, evidence from animal models suggests associations with specific autoimmune diseases, but corroborative human data is not always available Data on their mode of action and strong evidence in animal models suggest at least some vaccine additives are capable of inducing autoimmunity Infections may protect (hygiene hypothesis) against some types of autoimmune diseases, as animal models show reduced exposure to infections increases autoimmune disease risk Some dietary and nutritional supplements (vitamin D and antioxidants) protect against specific autoimmune diseases	

Table 13.4 The 2010 NIEHS expert workshop and panel findings on mechanisms involved in the role of environmental factors and development of autoimmune disease (Parks et al. 2014)

We are confident of the following	We consider the following likely, but requiring confirmation	Broad themes to be pursued in future investigations
Chemicals		
Crystalline silica (quartz) contributes to the development of several systemic autoimmune diseases, including RA, SSc, SLE, and antineutrophil cytoplasmic antibody (ANCA)-related vasculitis Solvents contribute to the development SSc Smoking contributes to the development of ACPA-positive and antirheumatoid factor (RF)-positive RA (with an interaction with the shared epitope genetic susceptibility factor)	Solvents contribute to the development of MS Smoking contributes to the development of seronegative rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus, Hashimoto's (HT) thyroiditis, Graves' disease (GD), Crohn's disease (CD) Current smoking protects against the development of ulcerative colitis	There is insufficient evidence on the role of metals, including those associated with animal models of autoimmunity, e.g., mercury The identification of single causal agents within groups of exposures is needed (e.g., specific solvents or pesticides contributing to increased risk for the group) Studies are needed on plasticizers (e.g., phthalates and bisphenol A), some of which may be endocrine or immune disruptors, and have been associated with other immune-mediated diseases There is insufficient evidence on the role of cosmetics in autoimmune diseases
Physical factors		
An inverse association exists between increased ultraviolet radiation exposure and risk of developing MS	Ionizing radiation contributes to the development of HT and GD	There is insufficient evidence on a possible protective role of ultraviolet radiation on TID Prospective data are needed on sun exposure as a risk factor for SLE (prior to early clinical symptoms) and dermatomyositis
Biological agents		
Ingestion of gluten contributes to the development of gluten-sensitive enteropathy (GSE) Ingestion of certain lots of L-tryptophan contributes to the development of eosinophilia-myalgia syndrome Dietary intake of 1,2-di-oleyl ester (DEPAP) and oleic anilide-contaminated rapeseed oil contributes to the development of toxic oil syndrome	EBV infection contributes to MS development Early introduction of complex foods contributes to the development of T1D and GSE Low dietary vitamin D intake and blood levels contribute to the development of MS	Studies are needed on MS and vitamin D in racial/ethnic groups with darker skin (associated with UV-associated vitamin D deficiency) and examining dose effects Prospective data are needed on vitamin D and other autoimmune diseases Additional studies are needed on associations of food chemicals, dyes, or additives Prospective studies are needed on nitrates/nitrosamines and T1D

frequency, and limits the clinical symptoms of disease (Quintana et al. 2008). Mechanisms linking nicotine, inflammation, and interleukin-17 (IL-17) production were studied in a rat adjuvant-induced arthritis model of human rheumatoid arthritis (RA). In this model, nicotine pretreatment aggravates arthritis increasing interferon (IFN) and IL-17 production, whereas posttreatment nicotine suppressed the disease (Yu et al. 2011).

Moreover, toxicological factors, such as silica, have been recently considered as triggering factors for autoimmune diseases based on both epidemiological and experimental evidences. The observation of a possible link between chemicals and disease onset is based on epidemiological studies that associate chemical exposure with biological markers of autoimmunity and also by laboratory studies that identify plausible biological mechanisms through which environmental agents can influence autoimmunity (Miller et al. 2012a, b). As for the role of xenobiotics in autoimmune diseases, recent works showed that the activation of toll-like receptors (TLR) in macrophages predisposes the cells to produce toxin-induced inflammatory cytokines. In fact, co-exposure to nickel and TLR2 agonists induces the release of IL-6 by lung fibroblasts in a protein kinase-dependent pathway (Gao et al. 2010). Because TLR signaling and IL-6 production are key elements in autoimmune diseases, they may be involved in the onset and perpetuation of an autoimmune response in the long term. In mouse models undergoing mercury exposure later developing an autoimmune disease, lipopolysaccharide (LPS) exposure has been shown to trigger the disease onset. Similarly, studies performed in vitro on human peripheral blood mononuclear cells stimulated with mercuric chloride showed that proinflammatory cytokines were induced only when the cells were co-exposed to LPS (Gardner et al. 2009). Similarly to chemicals and xenobiotics, adjuvants can stimulate the immune system even without having an antigenic effect per se. Adjuvants such as pristane, squalene, and mineral oil are capable of activating the immune response and can induce the release of chemokines and proinflammatory cytokines. Some studies, mainly performed on animal models, showed that adjuvants can activate the innate immune system mainly by binding to TLR and inducing dendritic cells or macrophage function, and moreover, they can modulate the release of chemokines and the recruitment of immune cells. Based on these data, we assume that environmental adjuvants can stimulate the innate immune response and then activate the adaptive response, which finally leads to chronic arthritis and production of autoantibodies such as lupus-related anti-Sm/RNP or Su antibodies (Rose 2008; Meroni 2011). Beside adjuvants that can be traced because of their use in experimental models, no specific autoimmune-associated biomarker of adjuvant exposure is currently used to identify and design studies of specific biomarkers of adjuvant exposure.

Another mechanism through which dietary components and environmental toxins can influence autoimmune disease onset is through the modification of the Th17 response in susceptible individuals. This has been evaluated and supported by scientific evidence in autoimmune diseases such as RA, Crohn's disease, and psoriasis, where Th17 cells seem to be involved in the development and in the relapse of the diseases (Di Cesare et al. 2009; Sarkar and Fox 2010; Segal 2010). In the last

decade, several reports showed that vitamin A and vitamin D can exert an immune modulatory effect by controlling the Th17 and Treg balance, and also they play a hormonal role linked not only to bone health but also to immune homeostasis (Quintana and Weiner 2009).

Several studies have indicated that mercury-induced cell death leads to the formation of a unique 19 kDa cleavage fragment of fibrillarin, which cannot be detected in cells died from other causes. These mercury modifications of fibrillarin appear to increase its immunogenicity, and it is unclear whether this process is limited to fibrillarin itself or whether nontargeted cellular proteins are left intact following mercury exposure (Havarinasab and Hultman 2005; Pollard et al. 1997).

Recent reports suggest that environmental chemicals could influence the autoimmune response through the alteration of Treg production or function mediated by multiple intracellular receptors. But new studies are necessary to analyze the assumption that exposure to environmental chemicals, capable of modulating intracellular receptor signaling, is associated with the risk or severity of autoimmune diseases in humans.

13.3 Environment and Autoimmune Diseases: The Role of Physical Elements

Among many environmental factors that can play a role in autoimmune diseases, receptor-independent stressor-mediated environmental effects have been reported. Among these factors, ultraviolet B (UVB) light is able to induce Treg cell differentiation to produce IL-10 for antigen-specific immunosuppression (Maeda et al. 2008; Shintani et al. 2008). This process mediated by UV light may represent an immunosuppressive response to UV-mediated epithelial cell death and autoantigen presentation by Langerhans cells (Lehmann and Homey 2009). Ionizing radiations are also likely to contribute to the onset of autoimmune diseases, especially thyroid diseases, such as Hashimoto thyroiditis and Graves' disease, even if research bias (i.e., few studies of medical radiation therapy and inconsistency in findings from nuclear testing fallout and accidental radiation contamination) is still present. Another important field of investigation that deserves further development is the role of UV exposure as risk factor for dermatomyositis and systemic lupus erythematosus (SLE), as suggested by prospectively collected and preclinical data on sun sensitivity.

13.4 Environment and Autoimmune Disease: The Role of Infectious Agents

Infectious agents are one of the most studied environmental factors in the etiopathogenesis of autoimmune diseases. A well-known example is represented by rheumatic fever, caused by streptococcal antigens that can induce systemic symptoms such as fever, arthritis, and also heart disease (Malkiel et al. 2000). Other infections,

mainly mediated by viruses such as Epstein-Barr virus (EBV), are linked to the development of autoimmune diseases such as SLE (Barzilai et al. 2007) but also RA (Balandraud et al. 2004), and Sjögren's syndrome (Padalko and Bossuyt 2001). Besides EBV, a potential role for cytomegalovirus (CMV) in the development of SLE has been suggested (Su et al. 2007), similarly to antiphospholipid syndrome (Blank et al. 2004; Blank and Shoenfeld 2004; Shoenfeld and Blank 2004).

The mainly accepted hypothesis assumes that genetically predisposed individuals with a normal immune system who develop a viral infection (probably with other concomitant environmental factors) activate autoimmunity through the action of viral superantigens, molecular mimicry, polyclonal activation, epitope spreading, and bystander activation (Barzilai et al. 2007). This uncontrolled activation leads to autoimmunity, which we can detect through sera autoantibodies, even before the onset of the clinical symptoms of the disease. Whether these are stochastic associations or significant pathogenetic links remains to be clarified in most cases; however, the time lapse between induction of infection and clinical manifestations will make a direct proof poorly feasible in humans, maybe in animal models.

13.5 Conclusions

The data reported in this chapter show that multiple agents are under investigation for their capacity to lead to multiple modifications (i.e., phosphorylation, glycosylation, acetylation, deamidation) in response to self-antigens, with the breakdown of tolerance and the onset of autoimmune reactions and diseases. Beside cellular mechanisms of innate and adaptive immunity, also autoantibodies to modified self-antigens can be crucial to the effector immune reaction against target tissues, as well represented in RA.

The lack of epidemiological data reflects that main difficulties and gaps are still present in this field, such as quantifying the exposure to environmental chemicals and analyzing multiple cellular subsets and their functions in human populations. A few recommendations for future research include (i) analysis of multiple chemical mixtures, reflecting the real-life complexity of human life in contact with the environment; (ii) exposure-related risks within specific disease phenotypes and in the context of genetic risk factors, such as the smoking associated with RA-defined anti-citrullinated peptide antibody positivity; and (iii) the definition of critical "windows of opportunity" in the timing of exposure and latency relative to age/developmental stage, understanding dose-response relationship, and identifying mechanisms that lead to autoimmunity.

More "translational" epidemiological studies of environmental autoimmunity are needed and should be guided by mechanisms defined in animal model systems and vice versa. An integrated, multidisciplinary approach is critical, and programs should be established to provide opportunities for collaboration and improve communication between epidemiologists, exposure scientists, and basic cellular/molecular biologists, i.e., fostering of interdisciplinary research through forums, funding,

and training. Moreover, funding opportunities need to be specifically addressed toward autoimmunity and environmental factor research studies. In fact, a better coordination across the different disciplines and agencies conducting autoimmune research may help to encourage collaborations. Such coordinated efforts may also promote a more cohesive body of knowledge through studies of multiple autoimmune diseases with similar underlying mechanisms and shared genetic or environmental risk factors.

An important need for human autoimmune research is, for example, the availability of high-quality, validated measurement tools. As to the efforts to characterize the genome, new technologies should be harnessed to address the critical need to characterize human environmental exposures. An environment-wide association (exposure/EWAS) study database (complementing PHENX) would facilitate future epidemiological studies. More data are also needed to establish the contribution of psychosocial factors, infections, complex mixtures, and susceptibility factors to the development and severity of autoimmune diseases. Biomarkers identified by mechanistic studies should be applied to epidemiological research in the context of relevant exposure measures. Investments in high-quality exposure measures and biological markers will increase the ability to identify environmental contributions to the etiopathogenesis of autoimmune diseases.

Finally, a consensus-based approach should be established to define autoimmune phenotypes (rather than diseases), which may improve comparability between human studies and animal models. The focus on studying diseases defined by classification criteria may limit interpretation of animal model data and the ability to identify human exposure cohorts using the broadest disease definitions. Conversely, there is a need for animal models to better represent phenotypes that occur in human diseases (e.g., CNS-SLE). Some environmental exposures may cause diseases characterized by a mixture of outcomes or multiple phenotypes that do not fit the standard diagnostic criteria. Outbreak investigations should collect data to characterize the emerging phenotypes and include the preservation and archiving of biological specimens. Long-term follow-up of affected individuals is critical to assess phenotypes that might develop with long latency.

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