The mosaic of autoimmunity: the role of environmental factors

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1. ABSTRACT

The "mosaic of autoimmunity" describes the multifactorial origin and diversity of expression of autoimmune diseases in humans. The term implies that different combinations of the many factors that are involved in auto-immunity produce varying and unique clinical pictures in a wide spectrum of autoimmune diseases. Most of the factors involved in autoimmunity can be categorized into four groups: genetic, immune defects, hormonal and environmental factors. In this communication, only the environmental factors are reviewed such as: infectious agents (represented by Epstein-Barr virus and cytomegalovirus), vaccines as triggers of autoimmunity, smoking and its relationship with rheumatoid arthritis, systemic lupus erythematosus, thyroid disease, multiple sclerosis and inflammatory bowel diseases. Some aspects of stress as implicated in causing autoimmunity and the processes leading to autoimmunity are reviewed as well.

2. INTRODUCTION

"Mosaic of autoimmunity" is a term created over a decade ago; it describes the multifactorial origin and diversity of expression of autoimmune diseases. The term implies that different combinations of factors involved in autoimmunity produce varying and unique clinical pictures that represent a wide spectrum of autoimmune diseases. Most of the factors involved in autoimmunity can be categorized into four groups: genetic, immune defects, hormonal and environmental (1-3).

Environmental factors have been implicated in autoimmune diseases including infectious agents, vaccines, drugs, smoking, stress, etc (4-6).

In this article we review the major environmental factors that are associated in the initiation and development of autoimmunity.

3. INFECTIONS AND AUTOIMMUNITY

3.1. Epstein-Barr virus and cytomegalovirus infections in autoimmune diseases

The association between autoimmune diseases and several infections (*i.e.* viruses, bacteria, fungi, spirochetes and parasites) has been well established in the medical literature. Several mechanisms can contribute to the pathogenesis of an autoimmune disease by infectious agents:

- by molecular mimicry. When the infecting agent incorporates an epitope that is structurally similar to a self antigen (ag). The induction of an immune response to the microbial ag results in cross-reactivity with a self ag and induces an autoimmune state (7). Although epitope-specific cross-reactivity, between microbes and self-tissue ags, has been shown to occur in some animal models, molecular mimicry causing an autoimmune disease has not been clearly demonstrated in humans (8).

- by epitope spreading. When an exaggerated local activation of ag-presenting cells, due to an inflammatory state, may cause overprocessing and overpresentation of an ag. Such an exaggerated activation may cause the priming of large numbers of T cells with broad specificities, thus encouraging the development of an autoimmune disease (9). Viral and bacterial agents possess the ability to bind to the variable domain of the T cell receptor beta chain along with the ability to connect to a wide variety of MHC class II molecules. These capabilities allow them to bind to a wide variety of T cells, irrespective of their specificity, and therefore induce an autoimmune reaction.

- by bystander effect. When enhanced cytokine production, induced by infectious agents or their products, generates an expansion of auto-reactive T cells whose previous numbers were insufficient to produce the disease (10).

Activation of the innate immune system is essential for a protective adaptive immune response to develop; and vaccines that lack intrinsic activation of innate immunity require microbial adjuvants to be immunogenic. Although innate immune cells do not respond to specific ag epitopes on pathogens, they do produce restricted responses to particular classes of pathogens through pattern-recognition receptors (PRR), such as Toll-like receptors (TLR) (11). Interaction of the microorganism component of adjuvants with PRR on innate immune cells results in activation of ag-presenting cells and upregulation of molecules essential for ag presentation, such as major histocompatibility complex (MHC) class II and B7-1/2, as well as production of proinflammatory cytokines. This activation of PRR by the microbial components of adjuvants stimulates the immune response in a manner similar to pathogens, such as bacteria or viruses (11,12).

Several infecting agents have been associated with various autoimmune diseases and often many different microorganisms are involved in the development of a single autoimmune disease indicating that more than one infection can induce the same disease through similar mechanisms (13). Herein, we discuss two of these infectors: Epstein-Barr virus (EBV) and cytomegalovirus (CMV).

EBV is a common virus of the herpes family that causes infectious mononucleosis and is associated with Burkitt´s lymphoma and nasopharyngeal carcinoma. EBV is associated with autoimmune diseases since 1971, when a high prevalence of EBV was observed in the sera of Systemic lupus erythematosus (SLE) patients (14). This finding was recently confirmed by our group (15). McClain *et al* demonstrated that nearly 100% of pediatric SLE patients had serologic evidence of EBV infection compared to less than three-quarters of controls (16).

It is suggested that EBV infection may contribute to the pathogenesis of SLE – via molecular mimicry mechanism – by its nuclear ag 1 (EBVNA-1) initiating lupus-associated autoantibodies (aabs), such as anti-Sm anti-Ro (17,18).

As of interest, EBV DNA has been recovered in anti-nuclear antibody (ANA)-positive adult patients and high titre serum antibodies (abs) have been shown to precede SLE onset by years (18,19). Elevated anti-EBV ab titres have also been linked prospectively to the development of SLE: *i.e.* titres of anti-EBNA-1 and anti-Epstein-Barr viral capsid ag (VCA) abs were significantly higher in US military recruits who later developed SLE compared to normal individuals (a find not observed with CMV infection). Ab titres rose gradually from their detectable levels – years prior to the first symptoms of SLE – until the time of diagnosis of SLE, paralleling and in some cases preceding the development of SLE-specific abs, implicating EBV-specific immune responses in the pathogenesis of SLE (20). In the Carolina Lupus Study, the association between serologic responses to EBV and SLE was modified by a polymorphism in the cytotoxic T lymphocyte-associated ag-4 gene, age and gender; and EBV-IgA seroprevalence was more strongly associated with SLE among older and African-American participants (21).

CMV is another common viral infection that has been associated with autoimmune diseases (15), including SLE, inflammatory bowel disease and systemic sclerosis (22-24). Case reports have suggested an association between CMV and SLE symptoms including thrombocytopenia and vasculitis (22); and animal models have demonstrated aab production, polyclonal B-cell activation and hypergammaglobulinemia with CMV infection. Moreover, in the Carolina Lupus Study (21), the authors also found a potential association between African-American SLE patients and CMV seropositivity (21).

Recently, Barzilai *et al* 2007 (25) had analyzed a cohort of 1,595 serum samples of 23 different autoimmune disease groups and screened for possible evidence of prior infection with EBV and CMV. The authors found a new association between EBV and polymyositis and confirmed previous findings that suggested relationships between

EBV and multiple autoimmune disease developments, including SLE, antiphospholipid syndrome, rheumatoid arthritis (RA), multiple sclerosis (MS), pemphigus vulgaris, giant cell arteritis, Wegener´s granulomatosis and polyarteritis nodosa. Elevated CMV IgG titers were observed in sera of SLE patients. The authors concluded that EBV infection is notoriously associated with the occurance of many autoimmune diseases (25).

4. VACCINATION AND AUTOIMMUNITY

Since 1796, when Edward Jenner inoculated cowpox material and prevented smallpox in 12 people, vaccination has been used as a strong tool for the control of infectious diseases. In fact, vaccination has been the greatest medical discovery to date; it successfully eradicated some dreaded diseases of the world's population, such as plague and smallpox, and improved the survival and quality of life (26,27).

However, several adverse effects can follow vaccination: local reactions, systemic side effects, fever, flu-like symptoms, gastrointestinal disorders etc and in the last 20 years or so the most serious reported complications include autoimmune diseases (28,29).

Recently, considerable data have been gathered regarding post vaccination involvement of the immune system, though its precise role in relation to autoimmune disease development has not been completely defined (6,29).

Several authors have postulated that autoimmune processes could be triggered or enhanced by vaccine immunogens and also by adjuvants used to increase the immune response (27).

A common target, for autoimmune complications to occur, is the central nervous system, with the appearance of demyelinating disorders, such as MS and other neurological conditions, e.g. Guillain-Barre syndrome and autism. Aabs associated with MS have also been described (30).

Other autoimmune diseases can also occur after vaccination, such as: arthritis, RA, reactive arthritis, SLE, diabetes mellitus, thrombocytopenia, vasculitis, Reiter's syndrome, dermatomyositis and polyarteritis nodosa (6).

Rubella, mumps, measles, influenza, diphtheria, pertussis and tetanus (DPT), typhoid, hepatitis A and B , meningococcal, BCG, rabies, smallpox, poliovirus vaccines etc; practically all types of inoculates have been described to be associated occasionally with the onset of autoimmune disorders (6,29,31).

Similarly to vaccine agents, adjuvants that are used in vaccines to raise immunogenicity, may trigger autoimmune diseases in susceptible humans (28). In this regard, the induction of lupus aabs and clinical manifestations (*i.e.* arthritis and nephritis) by hydrocarbon adjuvants has been described in animal models (29).

The relationship between vaccines and autoimmunity is bi-directional. On one hand, vaccines prevent infectious conditions and thus in turn prevent the development of an autoimmune disease. On the other hand, various case reports strongly suggest that post-vaccination may trigger autoimmunity (6, 29).

It is important to emphasize that a temporal relationship of a specific vaccine does not always contribute to autoimmunity. This matter is complicated by the fact that one vaccine may cause more than one autoimmune phenomenon, and similarly a particular immune process may be caused by more than one vaccine (28).

Appropriate epidemiological studies should be done to confirm several case reports or series, where familial or genetic risk factors have been found in patients who developed autoimmune disturbs after vaccination (6).

Vaccination should be considered as part of the mosaic of autoimmunity, where abrogation of an infectious disease could concomitantly induce an autoimmune disease.

5. SMOKING AND AUTOIMMUNITY

Cigarette smoke is made up of a complex mixture of compounds, among them: tars, nicotine, carbon monoxide and polycyclic aromatic hydrocarbons. There are two components of cigarette smoke: a tar or particulate phase and a gaseous phase, both of which contain extremely high concentrations of free radicals. In addition, cigarette smoke activates endogenous sources of free radicals (32). These toxins and free radicals can interact with DNA (33) and could cause genetic mutations and gene activation responsible for development of an autoimmune disease. Cigarette smoke has also been shown to increase the expression of Fas on B and T lymphocyte cell surfaces (34).

The pro-inflammatory effects of cigarette smoke have been studied in relation to the risk of emphysema and atherosclerosis (35). It is associated with higher markers of systemic inflammation, including C-reactive protein, interleukin-6, fibrinogen, soluble-intercellular adhesion molecule type 1 and selectins (36,37). Moreover, abnormalities in T-cell function, reduction in natural killer cells, and impairment of both humoral and cell-mediated immunity have been observed among smokers (38,39). In addition, cigarette smoking has anti-estrogenic effects which may be relevant in autoimmune disease pathogenesis (40).

5.1. Autoimmune disease associated with cigarette smoking

Several autoimmune diseases have been associated with cigarette smoke: RA, SLE, MS, Graves' disease, Crohn´s disease (CD). In contrast, ulcerative colitis (UC) does not have similar association with smoking.

5.1.1. Rheumatoid arthritis

Smoking was recognized as an environmental risk factor for RA by Vessey *et al* in 1987 (41) as an unexpected finding from an epidemiological investigation on the effects of sex hormones in RA (41). Since then, several case-control studies as well as cohort studies confirmed the association between cigarette smoking and development of RA (42,43). The risk of developing RA is higher in both current and former smokers and, in fact, remains high for up to 20 years after smoking cessation (43). Epidemiological studies have demonstrated that the risk is higher in men compared to women. Intensity and duration of smoke are predictors of RA risk, although smoking duration may be the more important predictor of the two (44). Furthermore, among RA patients with first degree relatives with RA, the onset of the disease in smokers is at a younger age than in non-smokers (45).

Cigarette smoking may be associated with the severity of RA as well, including rheumatoid nodule formation, increased joint destruction, increased pulmonary disease and decreased functional abilities (46,47).

A gene-environment interaction may also be responsible for increased severity of RA in smokers. Glutatione-S-transferase (GST) enzymes are involved in hepatic detoxification of cigarette smoke. Mattey *et al* (48) have shown that women with RA who had a null polymorphism in GSTM1 gene (associated with absence of GST enzyme activity) and smoked, had more pronounced radiographic damage, decreased functional outcomes and higher rheumatoid factor (RF) levels than women with RA either but not with both risk factors (48).

RA has been associated with anti-cyclic citrullinated protein (anti-CCP) abs (49). Cigarette smoking is most closely associated with seropositive RA: RF and anti-CCP ab seropositivity. Work from the Epidemiological Investigation of Rheumatoid Arthritis (EIRA) cohort study in Sweden helped to elucidate an interesting gene-environment interaction that exists between cigarette smoking and the HLA-DRB1 'shared epitope' (SE). A group of HLA-DRB1 alleles strongly associated with susceptibility to RA share a region of sequence similarity or SE at amino acid positions 70-74 in the third hypervariable region of the HLA-DRB1 molecule (50,51). The authors have found that current smokers carrying 2 copies of the SE are at a 21-fold increased risk of developing anti-CCP+ RA (95% CI 11.0-40.2) and at a 16-fold increased risk of developing RF+ RA (95% CI 7.2-34.2) (51). Moreover, the EIRA group has demonstrated that the major association of cigarette smoking is with anti-CCP+ RA rather than with RF+ RA and proposed a model for the pathogenesis of anti-CCP+ RA (51). They showed that smoking and pulmonary inflammation both lead to increased numbers of citrullinated peptides in the lungs. They also suggested that cigarette smoking promotes citrullination and the subsequent generation of abs to citrullinated proteins (anti-CCP abs) that preferentially occurs in individuals carrying the SE genotypes (51).

5.1.2. Systemic lupus erythematosus

An association between smoking and development of SLE has been suggested from several case-control studies (52,53), although the data are less convincing than for RA. Some authors (54), but not all, have reported significant increased odds of SLE in smokers (55,56). Important methodological differences might explain the conflicting findings; e.g. exposure definitions varied across studies, as did controlling for potential confounders, selection of controls and the timing of exposure data ascertainment. Costenbader *et al* (52), in a meta-analysis that examined current smoking, found it to be an increased risk factor for SLE (RR= 1.5, 95% CI:1.09-2.08) (52). Furthermore, a recent study showed an association between current smoking and the presence of anti-dsDNA abs and smokers and non-smokers with SLE with an odds radio of 4.0 (95% CI: 1.6-10.4) (53). These results were not seen among former smokers and the authors have suggested that current smoking could induce adducts with half-life of 9-13 days, potentially explaining the association of the current, but not past smoking with increased risk of SLE. Alternatively, as cigarette smoke promotes an influx of short-lived inflammatory cells into lungs and impairs the capability of resident macrophages to clear inflammatory debris, anti-dsDNA abs may be the result of ineffective clearance of apoptotic pulmonary material (57).

5.1.3. Multiple sclerosis

The etiology of MS is unknown, but it is thought that it is mediated by autoreactive T-cells directed against components of myelin (58). MS affects approximately twice as many women than men associating with HLA class II alleles. Several case-control studies have explored a link between cigarette smoking and subsequent development of MS. Recently, metanalysis of six informative studies showed significantly elevated odds or rate ratios ranging from 1.22 to 1.5 (depending on the method of analysis) confirming that the risk of MS is increased for those who smoked prior to disease onset, as measured by the appearance of symptoms (59). A variety of mechanisms have been suggested to explain the association, e.g. by immune stimulation or suppression. Nicotine may increase blood-brain permeability to allow entry of abnormal T cells and tobacco smoke may poison the central myelin by elevated blood levels of its metabolite, thiocyanate. Another possible mechanism might be through axonal exposure to nitric oxide (NO). Physiologically active or demyelinated neurons are particularly susceptible to NO exposure and could result in axonal degeneration or conduction block (60). This theory provides a mechanism for both initiation of MS and claimed accelerated progression of disability. Smoking might increase a subject's vulnerability to respiratory infection allowing possible entry of causative agents such as viruses and/or bacteria.

5.1.4. Graves' hyperthyroidism

Graves' disease is one of the most common autoimmune diseases characterized by hyperthyroidism, ophthalmopathy, goiter and pretibial myxedema. Graves' is mediated by aabs to the thyrotropin (TSH) receptor that

stimulate thyroid hormone synthesis and secretion and thyroid growth. Genetics are important with a concordance rate of 17-35% in monozygotic twins. The onset of Graves' has also been associated with environmental risk factors, such as cigarette smoking. The association of thyroid disease and smoking was investigated in 25 meta-analysis studies of which 8 was limited to Graves' disease and showed the odds ratio for current smoking was 3.30 (95%CI 2.09-5.22) and 1.41 (95%CI 0.77-2.58) for past smokers (61). Similarly, cigarette smoking was confirmed to be a strong and time-dependent risk factor for the development of Graves' disease in the Nurses' Health Study II, where 543 incident cases of a cohort of 115,109 women were identified (62). The risk was associated with smoking intensity and was highest in women who smoked over 25 cigarettes a day. Smoking also appears to be an important risk factor for thyroid eye disease (63). Several mechanisms of smoking's effect on Graves' disease have been proposed, including increased production of aabs, increased concentrations of soluble adhesion molecules and enhanced generation of reactive oxygen species (64).

5.1.5. Ulcerative colitis and Crohn's disease

The inflammatory bowel disease, UC, is one of the few inflammatory diseases for which data exist on the protective effect of cigarette smoking on the onset of disease (65). UC affects predominantly non-smokers and former smokers. The percentage of current smokers (smoking more than seven cigarettes per week) in a group of patients with UC is about 10-15% (66). These percentages are significantly lower than those observed in a control population matched for sex and age (25-40%). The effect of smoking seems only to postpone the development of UC. In recent metanalysis by Mahid *et al* (67) current smoking decreased the risk for UC (OR: 0.58; 95% CI: 0.45-0.75), while former smoking was associated with an increased risk (OR: 1.79; 95% CI:1.37-2.34). It is noteworthy that patients who stopped smoking, 52% developed UC in the first three years, as reported by Motley *et al* (68).

Alternatively, the incidence of CD in a group of current smokers was significantly higher than in a control population of patients matched for sex and age (45-55% vs. 30-40%) (69). In concordance, an increased life–time risk for CD to occur was reported in current smokers compared to non-smokers in recent meta-analysis by Mahid *et al* (OR: 1.76; CI:1.40-2.22) (67). Compared to those who never-smoked, former smokers were reported to have an increased risk of developing CD (70). This risk decreased four years after smoking cessation.

The reason for the opposite effect of smoking in CD and UC remains obscure. Smoking has numerous specific and non-specific effects. Nicotine has been shown to decrease the synthesis of proinflammatory molecules, e.g. interleukin (IL)-1-beta and TNF-alpha by mouse colonic mucosa; as well as the production of mucosal eicosanoids and some proinflammatory cytokines by human mononuclear cells (*i.e.* IL-2, IL-8 and TNF-alpha). Macrophages from smokers express a selective functional deficiency in their ability to kill intracellular bacteria.

Moreover, chronic exposure of rats to nicotine inhibits ab-forming cell response, impairs ag-mediated signaling in T-cells and induces T-cell anergy. Other effects of smoking on the intestine include: alterations of gut motility, reductions of smooth muscle tone and contractility (modulated by nitric oxide), decreased permeability, alterations in microcirculation and increased lipid peroxidation (71).

6. STRESS AND AUTOIMMUNITY

Physical and psychological stresses have also been implicated in the development of autoimmune diseases, as evidenced in numerous animal and human studies, demonstrating the effect of various stressors on immune function. E.g. in several retrospective studies, 86% of patients reported uncommon emotional stresses before disease onset. Several studies suggest that stress is not only a participating factor but it is also a causative element in disease exacerbation that in turn may provoke additional stress in patients (6).

Stress may be related to work, community, or family; it may be cumulative or evoked by a critical incident. It is presumed that neuroendocrine hormones, triggered during stress, may lead to immune dysregulation by an alteration or an amplification of cytokine production, resulting in autoimmune diseases. Various types of neuroendocrine transmitters of the neuroendocrine-immune network that can initiate autoimmunity include: epinephrine, norepinephrine, acetylcholine, substance P, vasoactive intestinal peptide, glucagon, insulin, cytokines, growth factors, and many other substances. Stress response and dysregulation of cytokine balance can trigger the hypothalamic-pituitary-adrenal axis and sympathetic nervous system. In addition, the multiple roles of Th2 cells in maintaining allergic inflammation and altering the balance between Th1 and Th2 responses are important mechanisms for allergic inflammation and tissue damage (6).

These new concepts of neuroendocrine immunology are necessary to better understand the role of stress in the pathogenesis and treatment of autoimmune diseases. The treatment for autoimmune diseases should include stress management and behavioral intervention to prevent stress-related immune imbalances. Different stress reactions should be discussed with patients with autoimmune diseases and questionnaires on trigger factors must be answered by patients on psychological stress, in addition to the other components of the mosaic of autoimmunity. Both optimistic and confronting strategies are effective, and patients are encouraged to use whatever technique is most helpful in achieving a better quality of life (6).

Several studies suggest that stress is not only a participating factor but can be a cause for disease exacerbations as well (72). Unfortunately, not only does stress cause disease, but the disease itself causes a lot of stress in patients, and thus a vicious circle is created. The stress level and sociopsychological factors in general have

a great impact on the severity of pain and social functioning. The quality of relationship between the patient and his/her family and other social factors were found to be useful prognostic factors in patients with RA. And as with any chronic disease, the patients' perception of himself/herself, the disease and the support he/she can get from family and friends has no less effect on the overall quality of life then proper medical treatment. Coping strategies are important for daily routine and psychological well being of patients. The strategies enable the patient to adapt to problems and stressors arising from the disease – mostly pain, fatigue, limitations in mobility, difficulties in activities of daily life, threats to self-esteem and other stressors (72,73).

Patients with fibromyalgia have a central nervous system dysfunction resulting in amplification of pain transmission and interpretation. Some evidence also suggests that genetic and environmental factors play a role in the pathogenesis of this disorder (74) as well as in the establishment of chronic fatigue syndrome (75).

7. THE MULTIFACTORIAL BALANCE OF AUTOIMMUNITY

It is believed that autoimmune conditions develop after an environmental stimulus upsets a resilient immune equilibrium in a genetically susceptible host; often this dysregulation evolves into additional pathological entities. An alteration of the immune system in one patient will lead to one clinical condition, whereas in another subject (with the same disease), whose immune system is constituted differently, the autoimmune process may involve a different pathologic response and affect different organs. We have referred to this phenomenon as the *mosaic of autoimmunity* (1,2).

This definition implies that by reassembling the same pieces of the mosaic in a different manner, another image will appear. This metaphor suits the immune system; hence, by rearranging components of the immune system, diverse patterns of autoimmunity become evident. The integration of many genetic, environmental and hormonal factors into the etiology of autoimmune responses often merges into overlapping autoimmune diseases (76). In such instances, the presence of aabs in the circulation are good predictors of autoimmune disorders (77).

In summary, throughout lifetime a normally functioning immune system walks a fine line avoiding the occurance of autoimmune diseases.

The mortar of the autoimmune mosaic never dries and the tiles regularly shift in response to genetic, hormonal and environmental factors; the latter factor is described in the present communication.

Genetically resistant hosts who under normal circumstances would not develop autoimmune disorders can occasionally be transformed into susceptible ones; e.g. by exposure to uncommon agents *i.e.* ultraviolet radiation,

associated with ozone induced antiphospholipid syndrome, as reported in two cases (78).

We have described that the autoimmunity mosaic is composed of numerous pieces, all coexisting and maintaining a certain balance. Environmental factors in this network may be one of the triggering factors driving a predisposed host to an autoimmune disease with its clinical expressions.

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Abbreviations: aab: autoantibody, ab: antibody, ag: antigen, anti-CCP: anti-cyclic citrullinated protein, CD: Crohn's disease, CMV: cytomegalovirus, EBV: Epstein-Barr virus, EIRA: Epidemiological Investigation of Rheumatoid Arthritis, GST: Glutathione S-transferase, MS: multiple sclerosis, PRR: pattern recognition receptors, RA: rheumatoid arthritis, RF: rheumatoid factor, SE: shared epitope, SLE: systemic lupus erythematosus, TLR: toll-like receptors, UC: ulcerative colitis, VCA: viral capsid antigen, BCG: Bacillus of Calmette and Guérin, MHC: Major histocompatibility complex

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