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# Environmental Basis of Autoimmunity

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**Abstract** The three common themes that underlie the induction and perpetuation of autoimmunity are genetic predisposition, environmental factors, and immune regulation. Environmental factors have gained much attention for their role in triggering autoimmunity, with increasing evidence of their influence as demonstrated by epidemiological studies, laboratory research, and animal studies. Environmental factors known to trigger and perpetuate autoimmunity include infections, gut microbiota, as well as physical and environmental agents. To address these issues, we will review major potential mechanisms that underlie autoimmunity including molecular mimicry, epitope spreading, bystander activation, polyclonal activation of B and T cells, infections, and autoinflammatory activation of innate immunity. The association of the gut microbiota on autoimmunity will be particularly highlighted by their interaction with pharmaceutical agents that may lead to organ-specific autoimmunity. Nonetheless, and we will emphasize this point, the precise mechanism of environmental influence on disease pathogenesis remains elusive.

**Keywords** Autoimmunity · Environmental factors · Infections · Microbiota · Chemicals · Solvents · Pollution

**Abbreviations**

| | |
|---|---|
| AIDs | Autoinflammatory diseases |
| AIH | Autoimmune hepatitis |
| APCs | Antigen-presenting cells |
| ASGPR | Asialo glycoprotein receptor |
| DIA | Drug-induced autoimmunity |
| EBV | Epstein-Barr Virus |
| HAV | Hepatitis A virus |
| HCV | Hepatitis C Virus |
| HLA | Human leukocyte antigen |
| IFN | Interferon |
| IUL | Interleukin |
| LSE | Systemic lupus erythematosus |
| NLRs | Nucleotide-binding oligomerization domain-like receptors |
| NLRC4 | NLR family CARD domain-containing protein 4 |
| Oss | Organic solvents |
| PAMPs | Pathogen-associated molecular patterns |
| PBC | Primary biliary cirrhosis |
| PDC | Pyruvate dehydrogenase complex |
| PRRs | Pattern recognition receptor |
| RA | Rheumatoid arthritis |
| TACE | TNF-a-converting enzyme |
| TLRs | Toll-like receptors |
| TNF | Tumor necrosis factor |

## Introduction

Autoimmune disease can occur in any site, but the three common themes that underlie induction and perpetuation include: genetic predisposition, environmental factors, and immune regulation (1–4) (Fig. 1). Current data suggests that environmental factors, i.e., infections, gut microbiota, toxic chemicals, and dietary components have up to a 70 % contribution to loss of tolerance (5, 6). The number of peer-reviewed papers in PubMed identified with "autoimmune disease" increased from 8890 in 1997 to 67,229 in 2015. Clearly, knowledge on the interaction between environmental factors and the architecture of the immune system is critical is critical to

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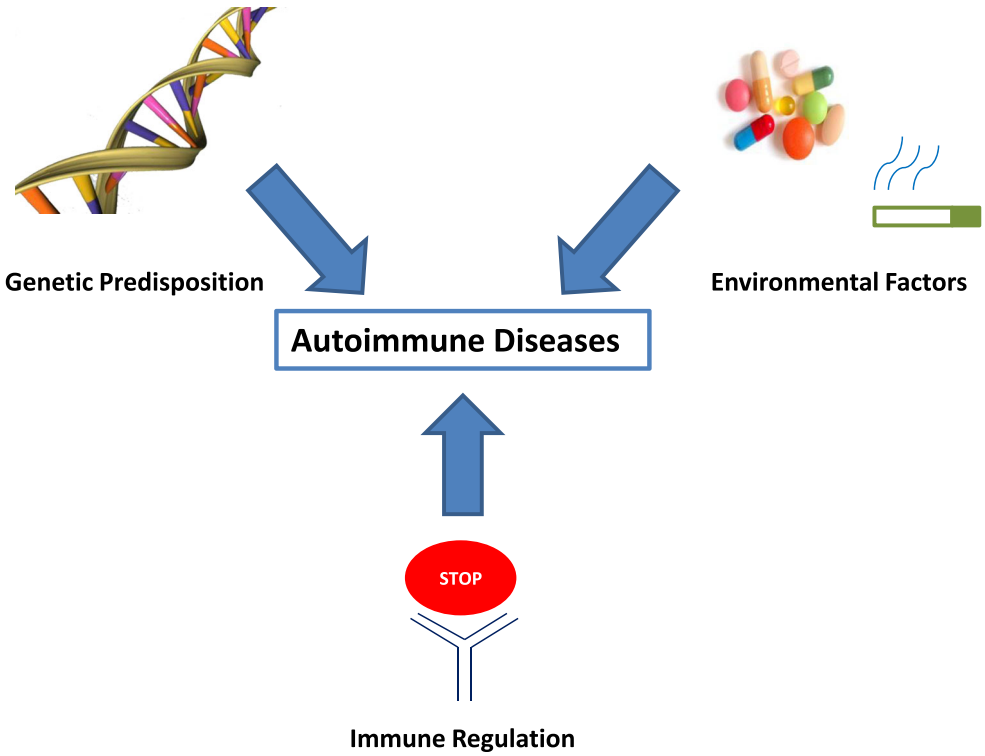


**Fig. 1** Three common themes that underlie induction and perpetuation of autoimmune diseases

unveil the mechanisms of autoimmunity and future design of treatment modalities. In this review, we will describe current perspectives on environment and autoimmune diseases. Specific examples on selected autoimmune diseases are included to illustrate the significance of environmental agents on the development of autoimmunity. Many of these principles are illustrated in the methods by which autoimmune diseases are classified (7–11). Finally, we will discuss lessons, we learned in our recent studies on the role of environmental etiology on primary biliary cirrhosis (PBC), a prototypic organ-specific autoimmune disease.

## Infections

An autoimmune disease may be induced or triggered by infectious agents including viruses, bacteria, fungi, and parasites (12). The levels of evidence are determined using three criteria, in particular: (i) epidemiological studies, (ii) laboratory studies, and (iii) experimental models (13). Examples of virus-induced autoimmune diseases are shown in Table 1 (14–27). Autoimmune diseases which have been reported to be triggered by viruses include rheumatoid arthritis (RA), thyroid diseases, primary biliary cirrhosis (PBC), type I diabetes, and autoimmune hepatitis (AIH). Interestingly, hepatitis A virus (HAV) has been reported to be associated to a fulminant type I diabetes in a 38-year-old man who suffered acute hepatitis A before the onset of diabetes (16). In this case, pancreatic involvement was attributed to an immune response, rather than to a direct cytotoxic effect of HAV. Moreover, additional cases of AIH have been reported to be triggered by HAV (25, 26). Another possible trigger for AIH is the Epstein-Barr virus (EBV); some cases of AIH have been described in strict temporal sequence after an acute EBV infection (25). In two cases, a defect in suppressor/inducer T cells controlling the response to the asialoglycoprotein receptor (ASGPR) had been identified prior to the viral infection, and anti-ASGPR antibodies

**Table 1** Examples of virus-induced autoimmune diseases

| Virus | Disease |
|---|---|
| Parvovirus | RA (18) |
| | Thyroid disease (21) |
| Epstein-Barr virus | RA (23) |
| | Thyroid disease (200) |
| | AIH (25) |
| HCV | Thyroid disease (15) |
| Mumps | Thyroid disease (22) |
| Rubella | Thyroid disease (27) |
| Coxsackie virus | Thyroid disease (14) |
| HTLV-1 | Thyroid disease (17) |
| Herpes virus type 7 | Thyroiditis (19) |
| Beta retrovirus | PBC (20) |
| HAV | Type I diabetes (16) |
| | AIH (25, 26) |

*RA* rheumatoid arthritis, *AIH* autoimmune hepatitis, *PBC* primary biliary cirrhosis

persisted and increased after the viral illness (26). Examples of bacteria-induced autoimmune disease are shown in Table 2 (28–44). An early report on the presence of an immunological response to *Candida albicans* in the synovial fluid and peripheral blood lymphocytes suggests that even fungi may induce autoimmune disease (45). However, in many cases, it is not a single infection but rather the "burden of infections" from childhood that is responsible for the induction of autoimmunity (46). The mechanisms and cell types responsible for the onset and progression of these multifactorial diseases remain unclear. Both autoimmune pathogenic and protective immune responses require the cooperative function of the innate, humoral, and cellular arms of the immune system. Thus, B and T lymphocytes and innate antigen-presenting cells (APCs) all contribute to these responses.

Infectious agents are known to trigger an autoimmune disease through several mechanisms: (1) molecular mimicry, (2) epitope spreading, (3) bystander activation and stimulation of pattern recognition receptors, (4) viral persistence and polyclonal activation of B cells, (5) autoinflammatory activation of innate immunity.

## Molecular Mimicry

Molecular mimicry, a mechanism by which infections can induce autoimmunity, occurs when foreign antigens share sequence or structural similarities with self-antigens (47). This is due to the fact that immune responses can be directed against peptides with similar charge distribution and overall shape (48). Immune response to microbial antigens could then result in activation of T cells that are cross-reactive with self-antigens. For example, molecular mimicry and cross-reactivity involving *Escherichia coli* and human subunit E2 epitopes of the pyruvate dehydrogenase complex (PDC) have been considered to trigger of the initiation of *E. coli*-associated anti-mitochondrial immune response in PBC (49–52). Strong evidence regarding CD4-T cell cross-recognition of *E. coli* and human mitochondrial autoantigens has been obtained over the past 20 years (53–56), further supporting the concept of molecular mimicry as the driving force of the immunological breakdown characteristic of PBC.

**Table 2** Examples of bacteria-induced autoimmune disease

| Bacterium | Disease |
|---|---|
| *Porphiromonas gingivalis* | RA (28) |
| Segmented filamentous bacteria | RA (29) |
| *Yersinia enterocolitica* | RA (30) |
| | Thyroid disease 21 |
| *Salmonella typhi* | RA (32) |
| *Shigella flexneri* | RA (33) |
| *Proteus mirabilis* | RA24 |
| *Campylobacter jejuni* | RA (35) |
| *Klebsiella pneumoniae* | RA (36) |
| *Clostridium difficile* | RA (37) |
| *Staphylococcus aureus* | RA (38) |
| *Streptococcus pyogenes* | RA (39) |
| *Leptospira pomona* | RA (40) |
| *Chlamydia* | RA (41) |
| *Mycoplasma arthritidis* | RA32 |
| *Mycobacterium tuberculosis* | RA (42) |
| *Borrelia burgdorferi* | RA (43) |
| *E. coli* | PBC (44, 213) |

*RA* rheumatoid arthritis, *PBC* primary biliary cirrhosis

## Epitope Spreading

Epitope spreading consists of the development of autoimmune responses to endogenous epitopes secondary to the release of self-antigens during a chronic autoimmune or inflammatory response (57). Epitope spreading can result from a change in protein structure, i.e., changing of an amino acid residue from arginine to citrulline. This may result in an immune reaction not only against the original protein or in its citrullinated form but also against other citrullinated proteins; this is a characteristic of rheumatoid arthritis. Systemic lupus erythematosus (SLE), multiple sclerosis, pemphigus bullous, pemphigoid, and other autoimmune diseases are all influenced by intermolecular and intramolecular B cell epitope spreading. Endocytic processing, antigen presentation, and somatic hypermutation are just some of the molecular mechanisms that assist in driving epitope spreading and broadening the immune response in autoimmune diseases (58). An example is type I diabetes in which autoimmunity first may be triggered against the B9–23 region of insulin (59), and progression to overt disease is mediated by epitope spreading to an array of beta cell antigens.

Epitope spreading is a crucial point for therapeutic strategies. Due to the unknown biological pathways and changes in antigen specificity, it is difficult to design drugs directed at epitope spreading. Instead, historically, the use of several drugs to control and inhibit both B and T cell activities has been the most commonly used approach to autoimmune diseases (60–62).

## Bystander Activation and Stimulation of Pattern Recognition Receptors

Bystander activation occurs when microbial infection stimulates toll-like receptors (TLRs) and other pattern recognition receptors on antigen-presenting cells (APCs), leading to the production of pro-inflammatory mediators, which in turn may lead to tissue damage (63). The release of both tissue antigens and bacterial antigens could result in autoreactive T cells and

bacterial-specific T cells in the process called bystander activation, a process contributing to autoimmunity. Additionally, virally infected APCs and concomitantly released mediators activate autoreactive Th1 or Th17 cells in a bystander manner (64). It has been shown that gut-derived antigens stimulate liver cells and result in a distinctive immune response via TLRs. TLRs are expressed on Kupffer cells, dendritic cells, hepatic stellate cells, endothelial cells, and hepatocytes. The cross-talk between gut-derived antigens and TLRs on immune cells trigger a distinctive set of mechanisms to induce immunity, contributing to various acute and chronic liver diseases including liver cirrhosis and hepatocellular carcinoma (65).

### Viral Persistence and Polyclonal Activation of B Cells

Prolonged infection with a virus, such as EBV, can lead to constant activation and proliferation of T cells, resulting in the production of monoclonal and polyclonal antibodies as well as immune complexes, leading to loss of tolerance (48). Patients with several autoimmune diseases have a high prevalence of anti-hepatitis C virus (HCV) serum antibodies suggesting a pervasive role for HCV in tolerance breakdown (66).

### Autoinflammatory Activation of Innate Immunity

Autoinflammatory diseases (AIDs) and autoimmune diseases are characterized by an aberrant chronic activation of the immune system, leading to tissue inflammation and damage. In AIDs, the innate immune system is directly responsible for tissue inflammation, while in autoimmune diseases, the adaptive immunity becomes the main effector of the inflammatory process (67). The immune system is constituted by immune sensors, i.e., soluble and cellular receptors and effector mechanisms, including different cell types. The sensors of innate immunity are named pattern recognition receptors (PRRs). They bind to highly conserved structures of pathogen-associated molecular patterns (PAMPs) or damaged cells (67) and include three classes of receptors: TLRs, nucleotide-binding oligomerization domain-like receptors (NLRs), and retinoic acid-inducible gene-I-like receptors (68). Activation of NLRs and NLR family CARD domain-containing protein 4 (NLRC4) leads to the formation of large protein complexes termed inflammasomes. Inflammasomes play a role in the defense against pathogens through activation of pro-caspase-1 and cleavage of the pro-forms of interleukin (IL)-1β and IL-18 to their respective active forms (68). A dysregulation of an inflammasome complex, in some cases, may lead to the development of autoimmune responses (69). Infections can trigger autoinflammatory processes in genetically predisposed individuals by various mechanisms, including induction of innate immune responses through binding to TLRs and activation of the intracellular inflammasome system. The effector cells of innate immunity include macrophages, dendritic cells, and other APCs. Moreover, vaccinations in genetically susceptible hosts have been found to trigger autoimmune diseases or AIDs in different animal models and to induce autoimmune/autoinflammatory symptoms in humans (70).

## The Gut Microbiota

There is growing evidence that the commensal bacteria in the gastrointestinal tract (the gut microbiota) influence the development of autoimmunity (71, 72). This evidence has been reinforced by studies in neonatal subjects. This is illustrated by a study (73) of microbiomes of 33 HLA-matched infants from monthly samples collected from birth until 3 years of age. Study participants were selected on the basis of having HLA risk alleles associated with type 1 diabetes mellitus (73). Of the 33 infants, 11 seroconverted to serum autoantibody positivity during the course of the study, and 4 of them developed type 1 diabetes. The taxonomic composition of the microbiomes varied widely within the same individual; more importantly, unique changes to the microbiomes were shared among the individuals who developed autoantibodies, including an increase in pathobionts and a decrease in bacteria that produce short-chain fatty acids (73).

Gut microbiota can be influenced by several factors: the motility of the gastrointestinal tract and the intake of pharmaceutical medications, including antibiotics, nonsteroidal anti-inflammatory drugs, smoking, and alcohol. These factors can lead to inappropriate gut-brain axis signaling and associated consequences for central nervous system function and ultimately resulting in disease (71). Most interestingly, a recent study showed that an oral bacteria-derived lipopeptide, lipid 654, which is produced by commensal bacteria, is present at significantly lower levels in the serum of patients with multiple sclerosis compared to levels observed in the serum samples of both healthy individuals and patients with Alzheimer's disease (74). This result identified for the first time a potential mechanism relating gastrointestinal and oral commensal microbiome to a human systemic autoimmune disease.

Several experimental models of autoimmune diseases associated to gut microbiota have been developed, particularly focusing on inflammatory arthritis (75). Naïve RA patients carry high levels of *Prevotella copri*, a Gram-negative anaerobe relevant in many inflammatory and autoimmune conditions (75). However, the gut microbiome interacts not only with the host but also with other organisms and environmental factors. Indeed, exogenous viruses and the virome, the genomes of all viruses that inhabit a host, interact with the gut microbiota (76, 77) and live within commensal bacteria. Furthermore, the microbiota and immune systems interact: malnutrition affects the innate and adaptive immune systems as well as the microbiota (78). The

microbiota acts as a barrier to enteropathogen infection; this barrier function may be disrupted by malnutrition or perturbations in immune system function (79). Finally, there is clear and increasing evidence that changes in the microbiota are associated with autoimmune diseases involving the gastrointestinal mucosa that lies in close contact with luminal contents as exemplified by celiac disease and also autoimmunity targeted toward distant sites, such as type 1 diabetes and RA (80–83). Clearly, much work remains to be done (84).

## Environmental Agents

Both physical and chemical environmental agents, because of their ubiquitous nature, have been the subject of active investigations. Of particular significance, change in lifestyle that have led to an increase in exposure to environmental chemicals over several decades has been considered as a putative reason for the increase in autoimmune diseases.

### Ultraviolet Light

Exposure to ultraviolet light (UV) light is a factor associated with SLE (85). UV-B induces apoptosis of keratinocytes and other dermal cells, thus releasing self molecules and pro-inflammatory cytokines, triggering systemic inflammation (86). Despite experimental studies showing a significant immunomodulatory role for UV radiation (87, 88), strong epidemiologic data regarding its role in triggering SLE is lacking.

### Vitamin D Deficiency

1,25-dihydroxyvitamin D (1,25 $OH_2$ vit D) is a steroid hormone derived from vitamin D which plays an important role in maintaining an adequate levels of serum calcium and phosphorus. Recent findings that several human tissues and cells express the vitamin D receptor (VDR) and 1α-hydroxylase have led to growing interest in extra-skeletal functions of vitamin D (89). Vitamin D plays an essential role in a variety of acute and chronic illness, including autoimmune diseases (90, 91), and several genetic studies have demonstrated an association between thyroid autoimmunity susceptibility and gene polymorphisms of numerous proteins and enzymes associated with vitamin D function and the vitamin D receptor (92). It should be stressed, however, much of the data is still controversial (93–103). One of the reasons of this controversy is study design, particularly inadequate sample sizes (89).

### Smoking, Silica, Tropospheric Pollutants, and Solvent/Pesticides

A variety of chemicals have been associated with autoimmune diseases (104–130), including cigarette smoking, silica, and tropospheric pollutants (Table 3) (131). However, the precise mechanisms how chemicals can cause autoimmunity are still unknown and can vary greatly depending on the nature of the physiological interaction and exposure. SLE represents a paradigm for understanding how environmental agents convert normal antigen-specific "helper" T cells into autoreactive, cytotoxic, pro-inflammatory T cells causing lupus in animal models and similar changes in humans (132). An expert panel workshop of the National Institutes of Environmental Health Sciences demonstrated that an autoimmune response following exposure to environmental factors is dependent upon genetic background of the host and can vary widely among species and strains (133).

Accumulating data have implicated that exposure to industrial solvents is associated to the development of autoimmunity (134, 135). Industrials solvents can be classified into two categories: organic and inorganic. Organic solvents (Oss) contain carbon and can be broken down into aliphatic-chain compounds, such as n-hexane, and aromatic compounds, such as benzene or xylene. Common uses for OSs include dry cleaning (e.g., tetrachloroethylene), paint thinner (e.g., toluene, turpentine), nail polish removers, glue solvents (acetone, methyl acetate, ethyl acetate), spot removers (e.g., hexane, petrol ethers), detergents (citrus turpenes), and perfumes (ethanol) (136). A systematic review and meta-analysis including 33 articles found that exposure to OSs is associated with systemic sclerosis, primary systemic vasculitis, and multiple sclerosis individually and also to several autoimmune diseases evaluated when taken together as a single trait (137).

**Table 3** Studies of chemicals in autoimmune diseases based on levels of evidence

| Chemical | Level of evidence (refs.) |
|---|---|
| Cigarette smoking | |
| RA | A (104–106); B (109, 114, 118, 119, 123) |
| SLE | C (107, 116) |
| | A (110, 124); B (111, 130) |
| Silica | |
| RA | A (117, 121, 127); B (120, 128, 129, 214) |
| SLE | A (108, 122, 126); B (112, 113, 186, 215, 216); C (217) |
| Tropospheric pollutants | |
| RA | A (218); B (219) |
| SLE | A (220) |
| Solvent/pesticides | |
| SLE | B (186, 216, 221–223) |

A: randomized controlled trial/meta-analysis/cohort studies; B: well-designed control study/non-randomized clinical trial/case reports; C: consensus/expert opinion

## Alcohol

Alcohol has been investigated for its potential role in triggering autoimmunity in several diseases with conflicting results. Interestingly, there are a number of studies suggesting a protective role in at least two autoimmune diseases: SLE and RA. The first report with a statistically significant inverse association and dose-response relationship between alcohol consumption and SLE came from the UK (138). Two further studies in Japan (139) and Sweden (140) corroborated these results. However, this association was only seen in light and moderate drinkers and not in heavy drinkers (140). Other studies, including two case-control studies and a prospective cohort analysis, failed to find any association between alcohol consumption and SLE susceptibility (141–143). These inconsistent findings have been explained on the basis of selection bias and different patterns of alcohol consumption (144). Nevertheless, in a meta-analysis assessing the relationship between alcohol and SLE risk in patients treated for less than 10 years (including six case-control studies and one cohort study), Wang et al. found a significant protective effect of alcohol (145).

A beneficial effect of alcohol has also been found for patients with RA associated with antibodies to citrullinated protein antigen in a meta-analysis comprising six case-control studies (3564 cases, 8477 controls, and three cohort studies (444 RA cases, 84,421 individuals) (146)).

Psoriasis seems to be the only common autoimmune disease for which excess alcohol is a risk factor for its onset (147). This finding has been shown in population studies (148, 149). Moreover, an epidemiological study based on the Finnish nationwide Hospital Discharge Register and Cause of Death over a 22-year period demonstrated that the cause of death in women was due to liver disease and in men was due to both liver disease and alcohol-related psoriasis (150). Alcohol and its metabolites have been shown in experimental studies in vivo to increase critical markers involved in systemic immunoregulation in active psoriasis such as tumor necrosis factor (TNF)-α-converting enzyme (TACE) and TNF-receptor type 1 (151). In theory, alcohol may have a potential risk in triggering autoimmunity in the liver since it involves a complex array of derangements in cellular signaling of hepatic parenchymal and non-parenchymal cells as well as cells of the immune system. Chronic ethanol renders Kupffer cells hyperresponsive to endotoxins, which results in production of cytokines and TNFα via a TLR 4-dependent pathway, leading to inflammation and hepatic necrosis (152).

## Drugs

To date more than 100 drugs spanning over ten drug categories have been associated with drug-induced autoimmunity (153). In general, there are two ways to classify these reactions: (i) drug-induced autoimmunity (DIA), an immune-related drug reaction temporally related to continuous drug exposure, which resolves after withdrawal of the offending drug and (ii) autoimmune disease triggered by a drug and perpetuating over time. The difficulty in distinguishing the two conditions is rooted in the understanding of the pathophysiologic mechanisms of drug reactions and the chronological criteria in a long period observation after the drug withdrawal. Two drugs are considered as a paradigm for DIA: procainamide and hydralazine. The incidence of procainamide-induced lupus was approximately 20 % during the first year of therapy (154), and the incidence of hydralazine-induced lupus was approximately 5–8 % (155). Procainamide, an antiarrhythmic agent, can induce lupus-like disease in susceptible individuals by inhibiting cellular DNA methylation (156). Hydralazine, an antihypertensive agent as well as an anti-heart failure agent, when used in combination with nitrates, reduces DNA methylation and protein levels in T cells by deactivating the ERK pathway (157). Interestingly, the new biological drugs especially the inhibitors of TNFα (etanercept, infliximab, adalimumab, certolizumab pegol, golibumab) have been associated with DIA. Biological modulators have been developed for a number of autoimmune diseases including Crohn's disease, rheumatoid arthritis, Sjogren's syndrome, and multiple sclerosis (158, 159). In contrast to lupus-like syndrome induced by hydralazine and procainamide, the occurrences of anti-dsDNA antibodies and hypocomplementemia are more common in anti-TNF-induced lupus, although the mechanism is not fully understood (160).

Autoimmune hepatitis (AIH) is an example of an autoimmune disease, which can be triggered by a number of drugs (161, 162). Table 4 includes examples of drugs and toxins implicated in DIA-like hepatitis (163). Minocycline and nitrofurantoin are such examples. Minocycline, an antibiotic commonly used for acne, can induce AIH within 2 years after starting drug (range 3 days–6 years) with the typical hallmarks of autoimmunity (non-organ-specific autoantibodies, hypogammaglobulinemia, and characteristic histologic changes (lymphoplasmacytic inflammation and necrosis) (164, 165)). Nitrofurantoin, an antibiotic used in the treatment of urinary tract infections can cause an acute hepatocellular reaction, which can progress in chronic hepatitis in one third of cases with the classical histological changes of AIH (166, 167). The clinical characteristics at presentation of both DIA-like hepatitis and classical AIH are similar; however, there is a higher prevalence of cirrhosis in classical AIH compared to DIA-like hepatitis, but it primarily differs by the absence of relapse after corticosteroid withdrawal (163).

## Hormones

Sex hormones, particularly estrogens, have been shown to play a role in autoimmunity through supporting survival of

**Table 4** Drugs associated to DIA-like hepatitis (from Czaja A, modified, ref. (163))

| Drugs proposed for DIA-like hepatitis: definite association | Drugs proposed for DIA-like hepatitis: probable or possible association | Toxins proposed for DIA-like hepatitis: possible association |
|---|---|---|
| Dihydralazine | Atorvastatin | Black cohosh |
| Halothane | Clometacin | Dai-saiko-to |
| Methyldopa | Diclofenac | Germander |
| Minocycline | Infliximab | Hydroxycut |
| Nitrofurantoin | Isoniazid | Ma huang |
| Oxiphenisatin | Propylthiouracil | Trichloroethylene |
| Tienilic acid | Adalimumab | |
| | Benzarone | |
| | Cephalexin | |
| | Fenofibrate | |
| | Indometacin | |
| | Imatinib | |
| | Meloxicam | |
| | Methylphenidate | |
| | Papaverine | |
| | Pemoline | |
| | Phenprocoumon | |
| | Prometrium | |
| | Rovusastin | |
| | Terbinafine | |

autoreactive T cells and influencing cytokine profile in the natural killer T cells (168, 169). A marked beneficial effect of pregnancy has been observed in RA, whereas several other rheumatic diseases such as ankylosing spondylitis and SLE demonstrated either no protective effect or an aggravation of symptoms during pregnancy (170). Differences emerging in regard to modulation of disease symptoms during pregnancy appear to be related to response to hormones, cytokine profile and immune responses, and downstream interactions of molecular pathways associated with inflammation (170). Patients with some autoimmune diseases such as PBC or systemic sclerosis have significantly higher numbers of pregnancies compared to controls (171–173). Interestingly, there is an increased susceptibility of RA in the first-year postpartum (174, 175), suggesting also a possible effect of fetal microchimerism.

Progesterone, an immunomodulatory sex steroid, is also important in autoimmune diseases. For example, SLE is associated with early menarche where there is an increased exposure to endogenous sex steroids, and exogenous sex steroids (contraceptive pill or hormone replace therapy) are associated with an approximately 1.5- to 3.0-fold increased risk of SLE (176). Data from animal studies also support a role of progesterone and estrogens in SLE models (177, 178). Sex hormones can potentially modulate the expression of autoimmunity, with androgens suppressing and estrogens accelerating disease.

In the collagen-induced arthritis model, pretreatment with progesterone had little effect on joint swelling or serum TNFα and prostaglandin E2 but appeared to reduce the beneficial effect of estrogen treatment on these parameters (179, 180). Interestingly, neither progesterone nor estrogen treatment altered anti-collagen autoantibody responses, suggesting that hormones were not modulating autoimmunity but rather acting primarily at the level of joint inflammation (181). Finally, sex hormones, particularly estrogens, can be found in a variety of foods (182). Examples include daidzein in soybeans, genistein in vegetables, zearalenone in corn, or 17β-estradiol in poultry meat. Moreover, estrogen-mimicking chemicals are found in many household items such as detergents, surfactants, and plastics (182). Several estrogen-containing pesticides (methoxychlor, chlordane, hexachlorbenzene, pentachlorphenol, aldicarb) may act as triggers for autoimmune diseases.

## Personal Care Products and Cosmetics

Personal care products such as shampoo, hair dyes, and cosmetics contain natural and synthetic chemicals. The interest in hair dyes and other hair products in induction of autoimmunity is based on similarities of some constituents of these products (acrylamides) to medications involved in drug-induced lupus. However, hair dyes failed to demonstrate an association with the development of SLE in two case-control studies (139, 183) and in a cohort study (184) (Table 5). Nail polish emerged as a risk factor for PBC and for SLE (185, 186). In a study by Gershwin et al. (185), 1032 patients with PBC and 1041 controls matched for sex, age, race, and geographical location were administered a modified version of the US

**Table 5** Case-control study in populations with autoimmune diseases exposed to cosmetics; refs. (139, 181–183, 185)

| Autoimmune disease | Cosmetic | Author | Country | Type of study | Association |
|---|---|---|---|---|---|
| SLE | Hair day | Petri, 1992 | USA | Case-control | No |
| SLE | Hair day | Bengtsson, 2002 | Sweden | Case-control | No |
| PBC | Nail polish | Gershwin, 2005 | USA | Case-control | Yes |
| SLE | Nail polish | Cooper GS | Canada | Case-control | Yes |
| SLE | Lipstick | Wang J, 2008 | USA | Case-control | Yes |

National Health and Nutrition Examination Study questionnaire including 180 questions and 300 subquestions regarding demographics, lifestyle, personal and familial medical history, and reproductive and occupational history. Family history of PBC, history of urinary tract infections, past smoking, use of hormone replacement therapies, and frequent use of nail polish emerged as risk factors significantly associated with PBC. Although the odds ratio for increased frequency of nail polish use was not impressive, this finding is intriguing in view of the xenobiotic hypothesis proposed for the development PBC with specific halogenated compounds that could increase the immunogenicity of mitochondrial proteins and induce AMA in animal models (187, 188). A study by Cooper et al. (186) was conducted in Canada using 258 cases with SLE and 263 controls matched for sex, age, and area of residence. Relatively strong, but imprecise associations were observed in people who worked with paints, dyes or film developing, and work that included applying nail polish or nail applications.

Interestingly, lipstick contains some components which have been associated to autoimmune phenomena: eosin, phthalate, and 2-octynoic acid. Eosin is a red dye implicated in both photosensitivity and lupus flares (189). Phthalate can induce anti-DNA antibody responses and SLE-like syndrome in an experimental model (190–192). 2-Octynoic acid is a xenobiotic that can modify the immunodominant E2 component of pyruvate dehydrogenase complex (PDC-E2) and induce AMA responses in PBC (193). A more recent work extending from our 2-octynoic acid data suggests that a broad class of electrophilic drugs including acetaminophen and other commonly used nonsteroidal anti-inflammatory drugs may contribute to xenobiotic-induced mimicry and loss of tolerance to PDC-E2 seen in PBC (194–196).

### Pristane and Naturally Occurring Hydrocarbons

Tetramethylpentadecane is a naturally occurring hydrocarbon oil commonly known as pristane which is found in small quantities in many plants and thought to be derived primarily from the metabolism of phytol, a ubiquitous ester of chlorophyll (197). Relatively high levels are also found in various marine organisms, including algae and zooplanktonic copepods, and pristane is strongly concentrated in the livers of sharks (197). Pristane occurs also in crude oils and is a common constituent of mineral oil, a byproduct of the fractional distillation of petroleum containing straight- and branched-chain paraffinic, naphthenic, and aromatic hydrocarbons. Medicinal (pharmaceutical or food grade) mineral oils, which are free of aromatic and unsaturated compounds, are used as laxatives, protective coatings for food, and cosmetics (198). For instance, canned sardines contain up to 370 mg/kg and white bread up to 550 mg/kg of mineral oil (197). Pristane-induced lupus is a murine model of SLE. Renal disease and autoantibody production depend on signaling through the interferon (IFN)-I receptor (198). The major source of IFN-I is immature monocytes bearing high levels of the surface marker Ly6C. Interferon production is mediated exclusively by signaling through TLR7 and the adapter protein MyD88. It is likely that endogenous TLR7 ligands such as components of small nuclear ribonucleoprotein complexes are involved in triggering disease (199).

### The PBC Lesson

There is extensive literature on primary biliary cirrhosis, including animal models, that illustrate the importance of genetics and environment, and indeed, PBC is considered the model autoimmune disease {Beuers, 2015 #336; Chang, 2015 #337; Floreani, 2015 #334; Katsumi, 2015 #338; Kurth, 2014 #331; Lleo, 2014 #332; Sun, 2015 #335; Wang, 2015 #339; Ando, 2013 #342; Deng, 2013 #340; Floreani, 2015 #333; Tanaka, 2014 #329; Wang, 2015 #328; Lleo, 2013 #343; Leung, 2013 #344; Hudspeth, 2013 #345; Kawata, 2013 #346; Ridgway, 2014 #347; (173)}.

Epidemiological studies support the hypothesis that environmental factors play a role in the etiology and pathogenesis of PBC in genetically susceptible individuals (185). Numerous microbial agents, mainly bacteria, but also viruses, parasites, and fungi, have been investigated as possible agents involved in PBC (200), but most studies have failed to demonstrate a clear association of a microbial agent with disease and report only circumstantial evidence that could not be independently recapitulated. Indeed, most studies supporting the role of infectious agents in the pathogenesis of PBC are based on the linear or conformational mimicry between microbial proteins and human mitochondrial antigens (201–203). Notwithstanding a substantial shared sequence homology, in a fewer cases, a cross reactivity by 2OADC-specific autoantibodies and/or T cells has been also demonstrated (56). This is the case for *Escherichia coli*, *Novosphingobium aromaticivorans*, *Salmonella minnesota*, *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Yersinia enterocolitica*, *Streptococcus intermedius*, *Lactobacillus delbrueckii*, *Paracoccus denitrificans*, *Mycoplasm*, *Mycobacterium gordonae*, *Borrelia burgdorferi*, *Trypanosoma*, and *Ascaridia galli* (200). Moreover, microbial antigens or DNA have been found in liver specimens, gallbladder bile, and fecal samples of patients with PBC as for *N. aromaticivorans*, *Propionibacterium acnes*, and the Epstein-Barr virus (200).

PBC is also the first autoimmune cholangitis studied with different spatial analysis since cluster distribution has been observed (204). A 3-year study was conducted in the city of Sheffield (1977–1979), and a closer inspection demonstrated an apparent clustering of cases with a suspected relationship with one water reservoir (205). Nevertheless, analysis of the

water showed no significant relevant differences between the reservoir serving areas with a high prevalence of PBC and other reservoirs. Twenty-five years later, a spatial clustering was observed in the North-East England (206). A further study in the same region was performed during a defined period (1987–2003) (207). Space-time clustering was observed when excess of cases of a disease were found within limited geographical areas at limited period of time. This finding is suggestive of the involvement of one or more environmental components in the cause of a disease. When a more rigorous statistical method was applied, clustering was most marked for cases diagnosed within 1–4 months of one another, suggesting that transient environmental agents may play a role in the cause of PBC (204). The finding of a seasonal variation in the diagnosis of PBC provides evidence for the involvement of a seasonally varying environmental agent in the etiology of PBC (208). Seasonal variation in PBC is consistent with the involvement of at least one transient environmental agent in etiology: examples of such factors that may be implicated include infections, air pollution, and diet (208). Another interesting study evaluating the relationship between environmental factors and PBC was published in 2006 (209). This study suggested that the number of PBC patients requiring transplantation was increased near superfund toxic waste sites in New York state (210). Additionally, a statistical significant PBC patient cluster, including both patients not listed for transplantation or listed for transplantation, was identified in Staten Island near a superfund waste site contaminated with volatile aromatic hydrocarbons and trichloroethylene. This has led to suggest that inhalation of volatile organic compounds (e.g., benzene) and particle-bound chlorinated hydrocarbons released into the air from these sites is a plausible method of exposure. Although specific environmental compounds causing PBC have not been clearly identified, xenobiotics are now emerging as compounds that could possibly narrow the gap between environmental exposure and pathogenesis (125). The working hypothesis is that modifications of the lipoylated major mitochondrial autoantigen could trigger the production of autoantibodies (193, 211, 212).

## Conclusions

Several indirect lines of evidence support the role of environmental factors in triggering autoimmunity in genetically predisposed individuals. No single factor has been identified as prominent. Greater understanding of how different environmental exposures results in different disease phenotypes and varying degrees of severity will help identify the mechanisms and checkpoints that control development of autoimmunity and autoimmune disease (6). In addition, it should be noted that genome-wide association studies have proven extremely disappointing and have not pointed to any “smoking guns”. Indeed, such work has only further highlighted the role of environment and, in particular, specific epigenetic events that may contribute to loss of tolerance.

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