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Review

Environmental factors involved in the pathogenesis of autoimmune diseases

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ABSTRACT

Autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) predominantly affect women and are characterized by widespread immunologic abnormalities. These diseases involve multiple organs including the skin, joints, lung and kidney, as well as the peripheral and central nervous systems. Significant progress has been made in elucidating the role of several loci and genes in the pathogenesis of autoimmune diseases. In addition to the studies of genetic factors involved in the pathogenesis of autoimmune diseases, progress has also been made in identifying environmental factors involved in their pathogenesis. Although the etiology of autoimmune diseases is not yet fully understood, both genetic and environmental factors have been identified and an interplay between predisposing genetic factors and environmental conditions has been suggested in the triggering of the disease manifestation. Therefore, an overview of the environmental factors involved in the pathogenesis of autoimmune diseases could be quite useful for all researchers in the world. In this review, we discuss the historical and recent findings on the possible role of environmental factors such as sex hormones, viral infections, microbiome, ultraviolet radiation, cigarette smoking and alcohol consumption in autoimmune diseases.

KEYWORDS: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjögren's syndrome (SjS), environmental factors

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1. Systemic lupus erythematosus (SLE)

SLE is an autoimmune disease that predominantly affects women (90% of patients are women) and is characterized by a complex set of immunological abnormalities that result in dysfunction of several organs, including the skin, joints, kidney, serosal membranes, and central nervous system [1]. In the recent decades, significant progress has been made in elucidating the role of several loci and genes in the pathogenesis of SLE [2]. Extensive studies have elucidated the roles of T cells and cytokines/chemokines in the pathogenesis of SLE and these findings have impacted the development of therapeutic targets and biomarkers [3, 4]. In addition to the studies of genetic factors involved in the pathogenesis of SLE, progress has also been made in understanding the environmental factors involved in the pathogenesis of this disorder.

1.1. Sex hormones

The predominance of females among the patients with SLE suggests a role of sex hormones in the immune system. It has been suggested that estrogens can enhance the immune response while androgens and progesterone suppress it. Many reports indicate that sex hormone receptors are expressed by various populations of immune cells. B cells have been shown to express both estrogen and androgen receptors while there is no evidence for progesterone receptor expression [5]. In T cells, only CD8+ T cells express estrogen receptors while CD4+ T cells do not express any of the steroid receptors [6]. Estrogen receptors were also found in monocytes and neutrophils [7, 8]. These data indicate that sex hormones can affect the

function of the immune cells by binding to steroid receptors. In addition, estrogen receptor-α signaling has been reported to regulate the development of dendritic cells (DCs), the antigen-presenting cells crucial for initiation of innate and adaptive immunity [9]. Sex hormones have been reported to affect T cell-mediated immunity. The Th1/Th2 shift is one of the most important immunologic changes during gestation. This shift is due to the progressive increase of estrogens, which reach a peak level in the third trimester of pregnancy. At these high levels, estrogens suppress the Th1-mediated responses and stimulate Th2-mediated immunologic responses [10]. Progesterone has been shown to increase the cytokines produced by Th2 cells which predominate over those produced by Th1 cells, resulting in the maintenance of pregnancy. Th2 cells are dominant within the decidua in early pregnancy in humans. Progesterone has been shown to stimulate the secretion of Th2 and reduce the secretion of Th1 cytokines [11]. This observation might explain why Th1-mediated autoimmune diseases such as RA tend to improve and Th2-mediated diseases such as SLE tend to worsen during pregnancy.

Interestingly, a significant number of men suffering from SLE have higher estradiol levels and lower testosterone levels compared to healthy individuals [12].

Several studies indicate that changes in sex hormone levels caused by castration of animals influences the severity and/or the onset of different autoimmune diseases such as SLE. In (NZBxNZW) F1 mice (a murine model of SLE), the onset of disease is significantly delayed in males compared to females, while castration of males makes the onset of the disease similar to that in untreated female mice of the same strain. Similarly, ovariectomy of female (NZBxNZW) F1 mice significantly delays the onset of disease, making it similar to that in untreated males of this strain [13]. These data suggest both protective roles for male hormones and disease accelerating properties of female hormones.

In vitro studies of human peripheral blood mononucleated cells (PBMCs) from SLE patients indicate that treatment of these cells with estrogen enhances total IgG production as well as anti-dsDNA autoantibody levels. This effect was partially interleukin (IL)-10-dependent and autoantibodies were not secreted by healthy control PBMCs treated in the same way. However, in a separate study, it was shown that estrogen induced total IgG and IgM production by PBMCs from healthy males and females while testosterone had the opposite effect [14]. These data suggest that sex hormones can directly affect the pathogenesis of autoimmune diseases by elevating the total level of immunoglobulins and enhancing autoantibody production, indicating that female hormones can influence the onset of autoimmune diseases.

1.2. Infections

1.2.1. Microbes

The mammalian gut harbors trillions of microorganisms known as the microbiota [15]. Increasing evidence in recent years suggests that host microbiota and the immune system interact to maintain tissue homeostasis in healthy individuals [16]. Perturbation of the host microbiota, especially in the gut, has been shown to be associated with many autoimmune disorders such as type 1 diabetes [17], rheumatoid arthritis [18] and multiple sclerosis [19]. There are some reports showing the role of gut microbiota in SLE. In the young female SLE mouse model MRL/Mp-*Faslpr* (MRL/lpr), the depletion of *Lactobacilli*, increase of Clostridial species (*Lachnospiraceae*) together with increased bacterial diversity has been reported. Importantly, dietary treatments that alleviated lupus symptoms in lupus mice also restored gut colonization of *Lactobacillus* and decreased that of *Lachnospiraceae* [20]. In human SLE, a recent cross-sectional study has shown that a lower *Firmicutes* to *Bacteroidetes* ratio was present in women with SLE even after disease remission [21]. Similarly, a higher level of *Bacteroidetes* was found in lupus-prone SNF1 mice with more severe disease [22]. These results suggest a potentially important role of gut microbiota, especially *Bacteroidetes*, in the pathogenesis of SLE.

1.2.2. Epstein-Barr virus (EBV)

EBV is a ubiquitous infectious agent, latently infecting approximately 95% of the world's population. Primary infection with EBV mostly occurs during childhood and causes a mild, usually

asymptomatic infection. However, primary infection in adolescence causes infectious mononucleosis in 30-70% of cases, where up to 20% of B cells are infected with EBV. Many studies have reported a link between EBV and the development of SLE. SLE patients have been shown to have a 10-40-fold increase in PBMC viral load compared to healthy controls [23]. The viral load was found to be associated with disease activity and to be independent of the intake of immunosuppressive medication. Furthermore, an elevated level of EBV DNA was found in the serum from 42% of SLE patients compared to only 3% of healthy controls [24]. The findings on increased EBV load suggest active EBV lytic replication in SLE patients. As the viral load was associated with disease activity, it could be speculated that the reactivation of EBV is associated with development of SLE and flares. EBV infection is mainly controlled by cell-mediated immunity. However, EBV-specific cytotoxic T cell reactivity has been observed to be reduced in SLE patients resulting in poor control of the EBV infection [25]. Less CD8+ cytotoxic T cells were found to produce IFNγ upon stimulation with EBV in SLE patients compared to healthy controls, which must be a consequence of either defective or fewer EBV-specific cytotoxic T cells [25]. Thus, SLE patients have an elevated viral load, increased EBV mRNA expression, elevated levels of EBV-directed antibodies and decreased EBV-directed cell-mediated immunity compared to healthy controls, indicating poor control of EBV with frequent reactivation.

1.2.3. Human cytomegalovirus (HCMV)

HCMV represents a human pathogenic herpes virus belonging to the subfamily of *Betaherpesvirinae*. Studies performed in European countries found an association between HCMV and SLE disease [26]. However, several other studies did not observe a direct association between HCMV seroprevalence and SLE [27]. In one of these studies HCMV seropositivity correlated significantly with Raynaud's phenomenon [28]. Another study reported significantly more frequent HCMV-specific IgM in SLE patients than in controls, but no difference in HCMV IgG prevalence was observed [29]. These findings indicate that more frequent HCMV reactivation occurs in SLE patients, which may occur as a result of immunosuppressive treatment. In addition, other studies found higher frequencies of HCMV infection in SLE patients or higher HCMV IgG titers [30]. Moreover, in SLE patients with higher HCMV-specific IgG titers, autoantibodies could be more frequently detected [31]. An interesting study reported that a patient group positive for anti-HCMV IgM (and IgG) showed lower levels of autoantibodies against U1RNP/Sm and U1-70k in comparison to the HCMV IgM(−)/IgG(+) group, suggesting a role for HCMV reactivation in regulation of autoantibodies. Altogether, these findings are compatible with the notion that genetic factors in combination with HCMV infection play an important role in SLE disease onset. Notably, antinuclear and anti-dsDNA antibodies were found in patients suspected to have an onset of SLE as a consequence of HCMV infection [32].

1.2.4. Parvovirus B19

Human parvovirus B19, a member of the *Parvoviridae* family, is a common human pathogen associated with a wide variety of diseases. The Ku80 DNA-binding protein has also been implicated in parvovirus B19 cell entry [33]. Interestingly, auto-antibodies against Ku antigen (anti-Ku) were originally described in patients with scleroderma-polymyositis overlap syndrome; several reports have shown that anti-Ku antibodies are also found in patients with SLE. Human parvovirus B19 infection is responsible for a wide range of human diseases such as mild erythema infectiosum in immunocompetent children, fetal loss in primary infected pregnant women, and aplastic anemia or lethal cytopenias in immunocompromised adult patients. Since parvovirus B19 infection presents with multi-systemic symptoms resembling SLE both clinically and serologically, parvovirus B19 is the object of intense efforts to clarify whether it is also able to trigger autoimmune diseases. Similarities have been so striking that patients have been initially misdiagnosed with SLE, having fulfilled 3-5 of the criteria of the American College of Rheumatology (ACR). There are some reports suggesting the possibility that parvovirus B19 triggers autoimmunity in SLE. Molecular mimicry between host and viral proteins seems to be one of the mechanisms involved in the induction of autoimmunity. By means of a random peptide library

approach, Lunardi C *et al.* have identified a peptide that shares homology with parvovirus VP1 protein and with human cytokeratin. Moreover the VP peptide shares similarity with the transcription factor GATA1, which plays an essential role in megakaryopoiesis and in erythropoiesis. These data support the role played by molecular mimicry in the induction of cross-reactive autoantibodies by parvovirus B19 infection [34]. As these studies have not fully proved the role of this virus in the pathogenesis of SLE, further studies are required to elucidate how parvovirus B19 infection is involved in the pathogenesis of SLE, as well as how molecular mimicry, association of Ku autoantigen and the triggering of anti-DNA antibodies are related.

1.2.5. Retroviruses

In recent years evidence has accumulated that supports a significant relationship between the so-called human endogenous retroviruses (HERVs) and the development of different autoimmune diseases [35, 36]. HERVs are polynucleotide sequences representing the complete structure of the virus [37]. Their structure consists of 2 long-terminal repeats (LTR). Between these repeats are the gene encoding the gag structural proteins, the genes encoding reverse transcriptase, protease, ribonuclease and integrase (pol), the gene encoding the envelope proteins (env) and also the starter tRNA binding region (the primer binding site-PBS) as well as the so-called packaging signal (Ψ), which is important for the function of the virus. HERVs were discovered in the 1980s. They represent about 8% of the human genome and are present in about 450,000 copies. They can be classified into 200 different groups and subgroups. HERVs were integrated into the germ-line cells of human ancestors. It is estimated that these insertions occurred 30 million years ago. A specific type of HERV can occur in the genome in a single copy, or can be repeated up to 1000 times. The greatest concentration of HERV sequences is found in chromosomes Y, X, 4 and 20. HERV is a member of the so-called retroelement family; these are nucleotide sequences that can move within the genome through a mechanism of "rewriting" their composition to RNA sequence and incorporation of its "DNA equivalent" in another location of the genome by the action of reverse transcriptase. The majority of HERVs are not expressed due to numerous inactivating mutations in the coding regions. These viruses are also frequently silenced by epigenetic mechanisms (DNA methylation). Some of the HERVs are active, however, and their expression is regulated by many different factors. Some types of HERVs are activated by X-rays and ultraviolet light. This occurs in patients with psoriasis. Pro-inflammatory cytokines, including interferon-α (IFN-α), tumor necrosis factor-α (TNF-α) and IL-1α and IL-1β, and glucocorticoids can act as factors inducing activity of HERVs. Their expression is highest in the placenta tissue and endocrine glands [38]. Krzysztalowska-Wawrzyniak *et al.* investigated the prevalence of HERV-K113 in patients with SLE and RA, and in healthy subjects in a Polish population. Their data revealed statistically significant differences in the insertion frequencies of HERV-K113 between the groups of SLE and RA patients *vs.* healthy controls [39]. Murine SLE is an autoimmune disorder characterized by B cell hyperactivity leading to the production of various autoantibodies and subsequent development of glomerulonephritis. Among the principal targets of autoantibodies produced in murine SLE are nucleic acid-protein complexes (e.g. chromatin) and the envelope glycoprotein gp70 of endogenous retroviruses [40]. In NZB/W F1 mice, we have observed high expression of endogenous retroviruses ahead of the development of glomerulonephritis (unpublished observation). Perl and Fernandez found that HRES-1 is a kind of HERV that encodes a 28-kD nuclear autoantigen and a 24-kD small GTP-ase, termed HRES-1/Rab4. HRES-1/p28 is a target of cross-reactive antiviral antibodies, whereas HRES-1/Rab4 regulates the surface expression of CD4 [41]. They concluded that HERVs can be considered as the molecular link between the human genome and environmental factors influencing the pathogenesis of SLE. HERV proteins may trigger lupus through structural and functional molecular mimicry, whereas the accumulation of HERV-derived polynucleotides stimulates interferon and anti-DNA antibody production. One example of cross-talk between retroviral proteins and human proteins is the human immunodeficiency virus-1 Tat protein. HIV-1 encodes a regulatory protein, Tat, which is required for efficient transcription of viral genes. It enhances the

processivity of RNA polymerase II by recruiting the positive elongation factor PTEF-b to the HIV-1 promoter through a Tat-TAR interaction. We have shown that the viral transactivator Tat inhibits the function of the class II transactivator CIITA, resulting in the suppression of expression of MHC class II genes in APC [42]. On the other hand, we also have shown that the over-expression of CIITA can block the activity of Tat and HIV-1 replication. The reciprocal modulations between Tat and CIITA could explain the functional impairment of APC in HIV [42]. Similar interactions between retroviral proteins and human molecules might be essential for proper control of the immune response.

1.3. Ultraviolet

Ultraviolet radiation (UVR) is a well-known exacerbating factor for SLE, with photosensitivity comprising one of the ACR diagnostic criteria for SLE. Cutaneous lupus erythematosus (CLE) has traditionally been sub-divided into acute, subacute and chronic forms, according to the 1981 Gilliam and Sontheimer classification [43]. Further distinctions have been made regarding chronic forms such as discoid lupus erythematosus (DLE), lupus tumidus (LET), lupus panniculitis/profundus and chilblain lupus, among others. For those with CLE, photosensitivity is a well-documented symptom in which UV radiation is a major exacerbating factor in cutaneous lesion development. The association of UV and cutaneous lesions in lupus has been studied extensively to clarify the possible pathophysiology behind this phenomenon. UV promotes development of cutaneous lesions by augmenting lymphocytic recruitment and antibody-mediated cytotoxicity. Assessment of both ultraviolet-A (UVA) (320-400 nm) and ultraviolet-B (UVB) (290-320 nm) radiation suggests that each contributes via different mechanisms towards promoting cutaneous lesion development. UVB causes keratinocyte apoptosis by damaging DNA strand breaks and pyrimidine dimer formation. Though prior results have shown some conflicting reports, enhanced keratinocyte apoptosis in SLE patients has been observed in skin biopsy samples and *in vitro* cultures after UVB radiation, suggesting an increased susceptibility of keratinocytes to UVB damage and defective clearance over healthy skin [44]. UVB is also thought to play other pathologic roles via modulation of immunologic function and recruitment and attraction of inflammatory proteins such as IL-1, TNF-α, intracellular adhesion molecule-1 and histocompatability class II molecules [45, 46]. Other studies have suggested the enhanced translocation of lupus autoantigens to the cell surface of apoptotic keratinocyte blebs, aiding autoantibody exposure to these autoantigens, which are normally sequestered intracellularly [47]. Nitric oxide (NO) is an important regulator of apoptosis and has an implication in the course of various autoimmune diseases. Interestingly, this molecule also has different effects on the various cell types within the skin, and it has been shown that NO can protect against UVA-induced apoptosis by increasing Bcl-2 expression and inhibiting UVA-induced over-expression of Bax protein in endothelial cells [48]. In addition, Weller *et al.* suggested an anti-apoptotic role for NO in keratinocytes after UVB irradiation [49]. Furthermore, UV exposure has also been shown to modulate local NO production through constitutive expression of neuronal nitric oxide synthase. In addition, several studies reported that another isotype of this family, the inducible nitric oxide synthase (iNOS), is expressed by epidermal keratinocytes after endogenous and/or exogenous stimuli. In 1998, it was demonstrated that iNOS is also expressed in human skin 48 h after exposure to UVA and UVB irradiation [50]. In striking contrast, an iNOS-specific signal appeared only 72 h after UV exposure and persisted in the evolving skin lesions of CLE patients for up to 25 days. These results suggest that the kinetics of iNOS induction and the time span of local iNOS expression might play an important role in the pathogenesis of this disease. It has further been reported that NO production is increased in patients with SLE, possibly due to up-regulated iNOS expression in activated endothelial cells and keratinocytes [51]. Other pro-inflammatory effects are seen with UVA-induced damage. Pro-inflammatory cytokines such as IL-1α/β and IL-6 are elevated following UVA exposure [52]. Similar to UVB, cyclobutane pyrimidine dimer formation is also seen following UVA exposure [53]. UVA augments the binding of autoantibodies to keratinocyte surfaces, though to a lesser degree compared to UVB sensitization. Photosensitivity

covers not only skin disease flares but also systemic symptoms such as fatigue and arthralgias [54]. Although the pathophysiological role of skin-infiltrating lymphocytes is clear, their recruitment and activation pathways in inflammatory skin diseases are still elusive. Recently, a superfamily of small chemotactic proteins has been shown to regulate lymphocyte trafficking under inflammatory conditions, and it has been demonstrated that UV exposure induces the expression of T-cell attracting chemokines [55]. Furthermore, the CXCR3 ligands CXCL9, CXCL10 and CXCL11 have been identified as the most abundantly expressed genes in patients with CLE. Additionally, it has been reported that the CCR4 ligand TARC/CCL17 is strongly expressed in skin lesions and elevated in the serum of patients with CLE [56]. The functional relevance of lymphocytic CCR4 expression could be confirmed by TARC/CCL17-specific *in vitro* migration assays, suggesting that CCR4 and TARC/CCL17 play a role in the pathophysiology of this disease. We have reported that plasma TARC/CCL17 levels are elevated in human lupus patients and a murine model of lupus [57, 58].

1.4. Cigarette smoking

Several epidemiologic studies have reported an increased risk of SLE among smokers. A meta-analysis of seven case-control studies and two cohort studies found that current smokers, but not former smokers, had a modest increased risk of SLE compared to nonsmokers (odds ratio (OR) 1.50, 95% confidence interval (CI) 1.09-2.08) [59]. The case-control studies included a heterogeneous group with varying definitions of smoking status, questionnaire response rates, adjustment for potential confounders and timing of the study questionnaire in relation to the onset of SLE. Strikingly, in the case of the Hispanic cohort from New Mexico, the authors found a strong correlation between smoking and the incidence of SLE: an OR of 6.7 for current smokers and 3.7 for former smokers, whereas in other populations the ORs ranged from 0.9 to 2.3 for current smokers and 0.6 to 1.2 for former smokers [60]. Taken together, these results suggest that smoking status may confer an immediate risk for SLE, and that, with time after the cessation of smoking, the risk of SLE returns to that observed in those who have never smoked. Notably, two large prospective cohort studies, the Nurses' Health Study and the Black Women's Health Study, did not observe an association between cigarette smoking and the development of SLE [61, 62]. Active smoking may also affect SLE disease severity. Ghaussy *et al.* studied the correlation of smoking status with disease activity (SLE disease activity index (SLEDAI) score) and cumulative organ damage (SLE international collaborating clinics (SLICC)/American college of rheumatology-damage index (ACR-DI) score). In a retrospective cohort analysis, investigators found that SLEDAI scores were significantly higher over a six-month period in current smokers compared to former and never smokers ($p < 0.001$). There was no significant difference in SLICC/ACR-DI scores [63]. Cigarette smoke contains numerous potentially toxic components including tars, nicotine, carbon monoxide and polycyclic aromatic hydrocarbons. Exposure to such toxins or their reactive metabolites can directly damage endogenous proteins and DNA. In fact, cigarette smoke contains 10^{14}-10^{16} free radicals per puff, including reactive aldehydes, quinones and benzo(a)pyrene, which induce oxidative stress implicated in the pathogenesis of SLE [64]. Cigarette smoke also induces epigenetic changes, some of which could modulate genes involved in pathways of inflammation and autoimmunity, perhaps triggering SLE [65]. Finally, exposure to cigarette smoke has harmful effects on both humoral and cell-mediated immunity. Cigarette smoke augments production of numerous pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, IL-8 and granulocyte macrophage colony-stimulating factor, while simultaneously decreasing the levels of anti-inflammatory cytokines such as IL-10 [66]. In a retrospective analysis of 140 ever-smokers and 270 nonsmokers with SLE, Freemer *et al.* found an association between current smoking and the presence of anti-double-stranded DNA (anti-dsDNA) antibodies. Compared to never-smokers, current smokers were more likely to have dsDNA antibody seropositivity (OR 4.0, 95% CI 1.6-10.4). Former smokers, however, were not at increased risk for these antibodies compared to nonsmokers [67].

1.5. Summary of environmental factors and SLE

Presented reports suggest that not only genetic factors, but also environmental factors such as sex hormones, infections, ultraviolet radiation and

cigarette smoking are important for the development of this disorder. Potential infections presented here include microbes, EBV, HCMV, parvovirus B19 and retroviruses.

2. Rheumatoid arthritis (RA)

RA is a chronic, destructive, inflammatory, polyarticular joint disease, characterized by infiltration of inflammatory cells, followed by the destruction of cartilage and bone [68]. Inflammatory cytokines such as TNF-α, IL-6 and IL-1 as well as chemokines such as pulmonary and activation-regulated chemokine/CCL18 and monocyte chemoattractant protein-4/CCL13 play important roles in the pathogenesis of RA. These cytokines have emerged as important pro-inflammatory mediators and dominant molecular targets for the therapeutic strategies [69]. The nuclear factor κB (NF-κB) family of transcriptional activators regulates the expression of a variety of cytokines involved in the pathology of RA, including TNF-α, IL-6 and IL-1 [70]. Thus, NF-κB is also an important target of RA treatment [71].

Although the etiology of RA is not yet completely understood, both genetic and environmental factors have been identified, and the interplay between predisposing genetic factors and environmental conditions has been suggested to trigger disease manifestation. One of the key findings to elucidate the pathogenesis of RA is the discovery of autoimmunity to citrullinated protein/peptide antigens (ACPA). This discovery has led to the concept that ACPA might be the essential link between disease genetic factors and the production of cytokines/chemokines.

To date, numerous genetic risk factors leading to RA have been identified including a group of MHC class II alleles such as HLA-DR4, -DR1 and -DR10 [72]. Shared epitopes (SEs) which share variants of the Q/R-K/R-R-A-A amino acid motif are present in the third hypervariable region of the DRβ1 chain of MHC class II molecule. This component constitutes the peptide binding groove [73]. Although the pathological role of SE has not yet been elucidated, SE is suggested to have roles in enhanced affinity and presentation of autoantigens, resulting in the activation of self-reactive T cells [74-77]. Another genetic risk factor for RA patients with ACPA positive is the susceptibility allele *620W* of *PTPN22*, a gene encoding a tyrosine phosphatase and a gene in the TNF receptor-associated factor 1-C5 (TRAF1-C5) region. Polymorphisms in the human *PADI4* gene were associated with RA in Asian cohorts [78].

In addition, a number of environmental factors have been reported to be linked to RA such as smoking and infections.

2.1. Cigarette smoking

The role of smoking in RA has been extensively studied and Sugiyama *et al.* used meta-analysis to conclude that smoking is a risk factor for RA, especially rheumatoid factor-positive RA men [79]. Klareskog *et al.* reported that both the SE positivity and smoking habits were risk factors for anti-CCP antibody positive RA but not anti-CCP negative. The presence of both factors was closely associated with the development of RA. They proposed that smoking activates an antigen-specific autoimmune response to citrullinated proteins in the presence of the HLA-DR SE alleles, resulting in the development of RA [80]. Mahdi *et al.* discovered that a SE, PTPN22 and smoking showed the strongest association with the anti-citrullinated α-enolase-positive subset and concluded that citrullinated alpha-enolase links smoking to genetic risk factors in the development of RA [81]. It seems that interaction between smoking and a SE induces immunological reactions to various citrullinated epitopes resulting in the autoimmune response associated with RA [82]. While the molecular mechanisms responsible for the influence of smoking in RA are not fully elucidated yet, some studies have shown an association between RA and toxic compounds found in cigarette smoke such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), nicotine and reactive oxygen species. We found that aryl hydrocarbon receptor (AhR) mRNA and protein levels were higher in RA synovial tissue than in OA tissue, and that TCDD enhanced the expression of IL-1β, IL-6 and IL-8 through binding to AhR, with this effect transmitted through the NF-κB and ERK signaling pathways. In addition, AhR expression in synovial cells was up-regulated by TNF-α. These data suggest that TNF-α activates AhR expression in RA synovial tissue, and that

cigarette smoking and exposure to TCDD enhances the RA inflammatory processes. In conclusion, TCDD exposure, such as during smoking, appears to exacerbate RA pathogenesis [83]. As tobacco smoke is a rich source of planar polycyclic aromatic hydrocarbons, many of which are AhR agonists, (e.g. benzo[a]pyrene) it is possible that activation of the AhR may play a significant role in disease progression [84]. Furthermore, smoking has been shown to modulate the immune system by altering Th-17 cell-mediated responses in a manner consistent with the ability of AhR activation to influence Th-17 cell differentiation [85, 86].

2.2. Sex hormones

Several lines of evidence indicate a role of sex hormones in the incidence and clinical expression of RA. Women are known to be three times more likely to develop RA than men. In women, RA often develops at times when sex steroid hormone levels are in flux, such as during the first 3 months postpartum and perimenopausal periods [87, 88]. In most studies, oral contraceptive use is protective against the development of RA [89]. However, there is a report showing that exogenous estrogen therapy among post-menopausal women did not reduce RA risk [90].

2.3. Epstein-Barr virus (EBV)

EBV has for long been suspected to have a role in the pathogenesis of RA. By the use of several methods including *in situ* hybridization and polymerase chain reaction (PCR), presence of EBV DNA/RNA has been demonstrated in synovial fluids and synovial membranes of RA patients [91]. Furthermore, 10-fold higher frequencies of EBV-infected B cells have been observed in RA patients compared to healthy controls [92]. Interestingly, EBV DNA was found in many of the plasma cells producing CCP antibodies localized in synovial tissues of RA patients. These results indicate widespread lytic EBV infection in RA patients, that also localizes in the joints, suggesting a role for EBV-infected cells in the synovial inflammation characteristic of RA patients [93].

2.4. Microbes

DNA sequence-based analyses of gut microbial flora and studies in the emerging field of mucosal immunology suggest that the microbiome represents an important environmental factor that can influence the development of autoimmune diseases [94]. The term microbiome defines the ecological communities of commensal, symbiotic and pathogenic microorganisms that share human body space. Intestinal epithelial cells expressing toll-like receptors (TLRs) in their cellular membrane recognize pathogen-associated molecular patterns of organisms comprising gut microbiome. This interaction activates the signaling adaptor molecule myeloid differentiation primary-response protein 88, ultimately resulting in the induction of downstream inflammatory responses. In addition, alteration of the microbiome may contribute to the disturbance of the delicate balance between type 1 T helper cells, type 2 T helper cells, type 17 T helper cells and regulatory T cells, thereby resulting in systemic autoimmune responses. Therefore, we can speculate that cross-talk between the microbiome and the human body in terms of genetic predisposing factors might contribute to the development of autoimmune diseases such as RA. Further studies are required to elucidate the role of the interaction between genetic and environmental factors in the development of RA.

2.5. Summary of environmental factors and RA

As presented above, environmental factors such as cigarette smoking, sex hormones and infectious agents are important for the development of this disorder. Other risk factors such as silica, air pollution and periodontitis have also been reported. On the other hand, several environmental factors have protective roles against the development of RA, including antioxidants, alcohol consumption and dietary intake of vitamin D, antioxidants, fish, protein and iron [95].

3. Sjögren's syndrome (SS)

Sjögren's syndrome (SS) is a chronic autoimmune disease that primarily involves salivary and lachrymal glands. This syndrome is clinically characterized by keratoconjunctivitis sicca and xerostomia, caused by inflammation – histologically identified as a focal lymphocytic infiltration of the affected glands. The syndrome may appear alone (designated as primary SS) or associated with other autoimmune diseases such as RA and SLE, traditionally designated as secondary SS.

3.1. Epstein-Barr virus (EBV)

EBV infection has also been associated with SS, with findings of increased viral load, high loads of EBV DNA and EBV-directed antibodies in SS patients [96-98]. There is a report showing that saliva from SS patients is able to activate EBV. Eight out of 12 SS saliva samples were found to have an activating effect on the *BZLF1* promoter in EBV-negative *BZLF1*-transfected salivary gland cells, indicating a possible frequent reactivation of EBV in the oropharynx of SS patients [99]. Furthermore, by the use of a monoclonal antibody directed against the lytic cycle antigen EA/D, a cytoplasmic staining of epithelial cells in salivary glands has been observed in 57% of SS patients compared to none of the healthy controls, suggesting that EBV reactivation of the epithelial cells in salivary glands of SS patients could initiate an immune response that damages the salivary glands of SS patients [96].

3.2. α-fodrin and apoptosis

Salivary glands of SS patients are characterized by abnormalities of proliferation/apoptosis regulation in glandular epithelial cells. Apoptosis is reported to be involved in the development of secretory dysfunction affecting the exocrine lachrymal and salivary glands [100]. Two factors associated with acinar tissue apoptosis include the proteolysis of α-fodrin and the Fas/Fas-ligand interaction [101]. Proteolysis of α-fodrin is pathogenic to cells due to the physiological involvement of the intact protein in the maintenance of the normal membrane structure and in the support of cell surface protein function [102]. Haneji N. *et al.* have identified α-fodrin as an important autoantigen in the development of SS both in an animal model and in SS patients [103]. Thus, this autoantibody might play an important role in the pathology of the destruction of salivary glands. There is a report showing the link between EBV and autoantibody against α-fodrin. Inoue *et al.* reported that ZEBRA (*Bam*H1-Z-DNA fragment of Epstein-Barr replication activator) mRNA expression, a marker for activation of the lytic cycle of EBV, was found in the salivary gland tissues from SS patients, but not in those from control individuals. They also found a significant link between production of antibodies against 120-kDa α-fodrin and reactivated EBV antigen in sera from patients with SS, but not in those from control individuals. In addition, they found EBV-activated lymphoid cells showed specific α-fodrin cleavage to the expected 120-kDa fragments *in vitro*. Therefore, it is speculated that apoptotic proteases activated with EBV activation might be involved in the progression of α-fodrin proteolysis and tissue destruction in SS pathology [104].

3.3. Summary of environmental factors and SS

As presented above, EBV is thought to be important for the development of this disorder. Other environmental factors such as hormone imbalance and hepatitis C virus infection have also been reported.

4. Conclusion

This review summarizes the involvement of environmental factors in the pathogenesis of autoimmune disorders such as SLE, RA and SS. Although various environmental factors may have direct roles in the pathogenesis of these disorders, these direct effects alone may not be sufficient to account for the development of autoimmune diseases. Indirect effects of environmental factors such as cytokines/chemokines, viral infection, molecular mimicry between host and pathogens also have roles in these autoimmune pathologies. Therefore, we can speculate that cross-talk between environmental factors and the human body in terms of genetic predisposing factors might contribute to the development of autoimmune diseases. Further studies are required to elucidate the role of the interaction between genetic and environmental factors in the development of autoimmune diseases.

CONFLICT OF INTEREST STATEMENT

There is no conflict of interest.

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