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Review Article

Mechanistic insights into environmental and genetic risk factors for systemic lupus erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organ systems with diverse presentation, primarily affecting women of reproductive age. Various genetic and environmental risk factors are involved in the pathogenesis of SLE, and many SLE susceptibility genes have been identified recently; however, gene therapy is not a viable clinical option at this time. Thus, environmental risks factors, particularly regional characteristics that can be controlled, need to be further investigated. Here, we systematically explored these risk factors, including ultraviolet radiation, seasonal distribution, geographical distribution, and climate factors, and also summarized the mechanisms related to these risk factors. Probable mechanisms were explicated in at least four aspects including inflammatory mediators, apoptosis and autophagy in keratinocytes, epigenetic factors, and gene-environment interactions. This information is expected to provide practical insights into these risk factors in order to benefit patients with SLE and facilitate the development of potential therapeutic strategies.

Keywords: Risk factors, systemic lupus erythematosus, ultraviolet radiation, season distribution, geographical distribution, climate factors

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organ systems with diverse presentation, primarily affecting women of reproductive age. SLE can persist throughout the entire life of the patient, exhibiting possible frequent relapses. The etiology of SLE is not well understood, although the disease is known to be caused by genetic and environmental interactions. A study by Deapen *et al*. showed that the SLE concordance rate in monozygous twins was 24%, which was substantially lower than a prior estimation [1], indicating that environmental risk factors cannot be neglected. Environmental factors can work together to cause epigenetic changes, resulting in immune dysregulation, loss of tolerance, and autoimmunity and leading to onset or recurrence of SLE. Although many studies have evaluated susceptibility-related genes, research on environmental risk factors and the mechanisms through which these risk factors contribute to the development of SLE remains limited. Moreover, compared with the complexity and technical difficulties of genetherapy, changing environmental factors is much more practical.

In this review, we discuss environmental risk factors, including ultraviolet radiation (UVR), climate factors, and geographical distribution, in the pathogenesis of SLE and illustrate the underlying mechanisms with the goal of facilitating the development of new therapeutic strategies for the management of SLE.

Environmental risk factors for SLE

UVR is the most important environmental factor inducing SLE, as demonstrated in various studies of human populations and experimental studies [2-7]. UVR includes UVA, UVB, and UVC. UVA (wavelength range: 320-400 nm) is abundant in terrestrial sunlight, but is not strongly

Table 1. Association between natural factors and SLE

Definite		Probable	
UVR	Season distribution	Climate factors	Geographical distribution
UVB	Winter and spring	Temperature	Latitude
UVA		Atmospheric pressure	Longitude
		Mean humidity	Altitude
		Precipitation	
		Wind speed	

Abbreviation: UVR: ultraviolet radiation, UVB: ultraviolet B, UVA: ultraviolet A.

absorbed by proteins and nucleic acids and induces erythema; UVB (wavelength range: 290-320 nm) strongly induces erythema and is present in the terrestrial solar spectrum; and UVC (wavelength range: 200-290 nm) is absorbed by the earth's ozone layer and is germicidal, although its effects on the development of SLE appear negligible [8]. UVA exposure induces cutaneous lupus skin lesions, but requires nearly 1000 times more energy than UVB to induce erythema [8]. The role of UVA in the development of SLE remains controversial. McGrath showed that in a New Zealand White/New Zealand Black mouse model of lupus, low-dose UVA markedly decreased mortality, prolonged survival, improved immune function, and had significant therapeutic effects [9]. In a follow-up human study, McGrath *et al*. found that low-dose UVA with long-term therapy significantly decreased clinical disease activity in SLE, such as remission of joint pain and rashes, reversal of brain dysfunction, elimination of anticardiolipin antibodies, and cessation of cognitive decline [10-15].

In contrast, UVB is known to be involved in the pathogenesis of SLE development. UVB exposure is responsible for photosensitivity, skin rashes, and recurrence in patients with preexisting SLE. Additionally, Cheng *et al*. found that annual sunshine duration is related to disease activity [16]. Indeed, SLE has been shown to have seasonal variation, with higher incidence in the summer, during which UVR is the strongest [17]. However, a counter-season phenomenon has also been observed with regard to the seasonal distribution of SLE disease activity. For example, some studies have demonstrated that there are more cases of new onset and recurrence of SLE in winter and spring than in summer and autumn [18-25]. Moreover, different organs were shown to exhibit changes in seasonal variation patterns in a prospective longitudinal cohort study of 2102 patients with SLE; significantly more photosensitive rash and arthritis activity were observed in spring and summer, decrease in renal activity was found in the summer, higher serositis activity was found from August to October, and higher anti-double-stranded DNA levels were observed during October and November [26]. Additionally, some geographical environment factors, such as climate factors (temperature, atmospheric pressure, mean humidity, wind speed, and precipitation) and geographical distribution (latitude, longitude and altitudes), are also closely associated with UVR and have been studied in the context of susceptibility to SLE.

Based on hypotheses drawn from epidemiological or experimental animal studies, climate factors and geographical distribution maybe risk factors for the development of SLE [18, 22-25, 27, 28]. Climate factors, as an important part of the geographical environment, have been shown to be correlated with autoimmune diseases and may influence the progression of SLE. Several studies have reported that the activity and incidence of SLE are correlated with temperature, atmospheric pressure, mean humidity, wind speed, and precipitation [16, 18, 22-25]. In addition, Pan *et al*. showed that the proportion of lupus nephritis increased significantly with the decreasing geographic latitude from the northern to the southern part of China, although no significant correlation was found with the change in geographic longitude, potentially because most studies were performed within a particular longitudinal band in China [27]. Cheng *et al*. also showed that living in the southern part of China is a risk for disease activity in SLE [16]. This epidemiology of the geographical distribution of SLE suggests that latitude may be an important environmental factor contributing to the development of SLE. In contrast, Deng *et al*. found that there was no significant correlation between SLE activity and altitude; Generally speaking, in patients with active or inactive SLE, clinical features and organ activities had different patterns of altitudinal variations. The development of SLE can also be affected by specific environ-

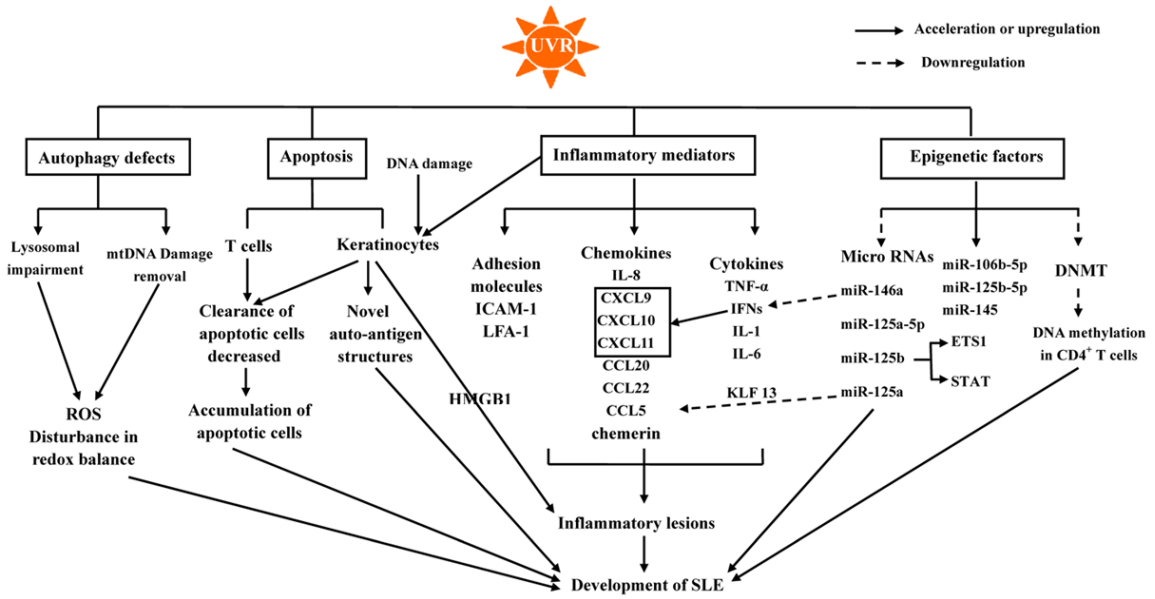

Figure 1. The role of UVR in the development of SLE. Abbreviation: SLE, systemic lupus erythematosus; UVR, ultraviolet radiation; IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CXCL, chemokine (C-X-C motif) ligand; CCL, chemokine (C-C motif) ligand; ICAM-1, intercellular adhesion molecule 1; HMGB1, high-mobility group protein B1; LFA-1, lymphocyte function-associated antigen; DNA methyl transferase 1, DNMT1.

Table 2. Inflammatory mediators in the development of SLE

Classification	Details of Inflammatory mediators
Cytokines	IFN-α, IL-1, IL-6, TNF-α, IL-12.
Chemokines	CXCL9, CXCL10, CXCL11, IL-8, CCL 5, CCL20, CCL22, chemerin.
Adhesion molecules	ICAM-1, LFA-1, e-selectin, vascular cell adhesion molecule-1.
Proteins	HMGB1.

Abbreviation: IFN, interferon; IL, interleukin; TNF, tumor necrosis factor; CXCL: chemokine (C-X-C motif) ligand; CCL, chemokine (C-C motif) ligand; ICAM-1, intercellular adhesion molecule 1; HMGB1, high-mobility group protein B1; LFA-1, lymphocyte function-associated antigen.

mental factors at high altitudes [28]. These findings are summarized in **Table 1**. Further studies on the season distribution (temporal distribution) and geographical distribution (spatial distribution) patterns in SLE will improve our understanding of these SLE-related climate factors and geographical distributions in order to establish seasonal treatment programs for vulnerable groups.

Pathogenic mechanisms

Inflammatory mediators

Inflammatory mediators regulated by UVR and climate factors may propagate inflammatory responses, recruit immune cells, suppress immune system tolerance, and promote B- and T-cell activation, giving rise to the development of SLE (**Figure 1**).

UVR

In genetically predisposed individuals, UVR, as a predisposing factor of SLE, has important roles in the pathogenesis of lupus by inducing a pro-inflammatory environment and leading to abnormal long-lasting photoreactivity *via* inflammatory mediators, such as pro-inflammatory cytokines, chemokines, and adhesion molecules (**Table 2**). UVR exposure upregulates pro-inflammatory cytokines expression, such as interferon (IFN)-α, interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α [4, 5, 29-35]. In particular, IFNs, which have important roles in the early activation of the immune system, are involved in the development of UVB-induced inflammatory skin lesions in patients with SLE [36].

UVR and neutrophil extracellular traps induce oxidative modifications in DNA, which can result in resistance to degradation by the intra-

cellular nuclease three prime repair exonuclease 1. Subsequently, oxidized DNA produces various type I IFNs, which are involve in the pathogenesis of SLE [37, 38]. Additionally, type I/III IFNs increase the expression of pro-inflammatory chemokines, including chemokine (C-X-C motif) ligand (CXCL) 9, CXCL10, and CXCL11, which recruit chemokine (C-X-C motif) receptor 3 effector cells and induce keratinocyte apoptosis [5, 39, 40]. However, another study in IFN-α receptor-knockout mouse considered type I IFNs protective against skin inflammation induced by UVB irradiation [41].

UVR also upregulates intracellular adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and lymphocyte function-associated antigen 1 [32, 36, 42-44], and increase the secretion of chemokines, including IL-8, chemokine (C-C motif) ligand (CCL) 5, CCL20, CCL22, and chemerin [3, 34, 45], which are important for recruiting immune cells to areas of inflammation. Yin et al. reported that chemerin, which was found to be elevated in UVB-irradiated skin, was chemotactic for plasmacytoid dendritic cells (pDCs) *via* its functional receptor chemR23 and recruited PDCs to areas of inflammation [45]. PDCs contribute to the pathogenesis of SLE by producing type I IFNs. Additionally, Abdulahad *et al*. revealed that UVB exposure induced high-mobility group protein B1 (HMGB1) release, which is related to the number of apoptotic cells in patients with SLE. HMGB1 released from apoptotic keratinocytes exerts inflammatory effects through binding to its receptors, resulting in the development of inflammatory lesions in the skin of patients with SLE upon UVB exposure [46].

Low temperature

Low temperature also plays an important role in the occurrence, development and recurrence of SLE. Pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-12, which are produced by monocytes, can be upregulated by low temperature. The proportions of pro-inflammatory cytokines (IL-12/IL-10 and TNF-α/IL-10) may then increase [47-50]. In parallel, cold stimulation induces the expression of the inflammatory adhesion molecules e-selectin, ICAM-1, and vascular cell adhesion molecule-1 [51], and complement is activated at low temperature [52-54]. Also, cold exposure can induce cell apoptosis [55, 56]. These factors may lead to the development of SLE.

Pressure

Extracellular pressure may alter some aspects of macrophage and monocyte functions. Singhal *et al*. showed that pressure increases monocytes migration in a dose-dependent manner when compared with normal atmospheric pressure [57], and Hironosuke *et al*. revealed that pressure enhances the expression of scavenger receptors in macrophages [58]. Interestingly, extracellular pressure regulates the production of TNF-α and IL-1β, which are involved in the development of SLE, by regulating monocytes and macrophages [59].

Humidity

Ye *et al*. demonstrated that humidity may be a risk factor for SLE and may decrease the body's resistance to bacterial infections [60]. Zhang *et al*. also showed that a damp environment may reduce cellular immune function and alter some aspects of the ultra structure, resulting in pathological changes in the joints, lungs, and kidneys and causing function damage to multiple systems and organs in rats [61]. In particular, they also demonstrated that dampness and wind may increase the production of TNF-α and IL-6, resulting in organ damage in rats [62].

Apoptosis and autophagy in keratinocytes

Apoptosis

UVR, particularly UVB, is a strong inducer of apoptosis [6] and has dose-dependent effects on the rate of apoptosis in keratinocytes. Low doses induce apoptosis without inflammation, intermediate doses induce apoptosis and IL-1α production, and high doses induced necrosis and dramatic increases in IL-α production [63]. The DNA of keratinocytes absorbs UVR, leading to strand breaks or cyclobutan pyrimidine dimmers [64]. Pro-inflammatory mediators and DNA damage, which are influenced by UVR, jointly results inkeratinocyte death [65]. Moreover, UVR can upregulate the Fas antigen on peripheral T cells in patients with SLE, resulting in apoptosis in T cells [66]. Furthermore, decreased clearance of apoptotic cells has been observed. Some studies have shown that UV exposure can induce accumulation of ap-

optotic cells due to impaired clearance of apoptotic cells in the skin of patients with cutaneous lupus [6, 67-69]. In contrast, Reefman *et al*. reported that UVB exposure did not induce apoptosis in the skin of patients with SLE compared with that in controls [70], and *in vivo*, there were no significant differences in clearance rates of apoptotic cells after UVB irradiation between patients with SLE and controls [71]. However, the skin of patients with SLE after UVB irradiation can induce infiltrates and inflammatory lesions due to an altered, inflammatory clearance of apoptotic cells; this may have a crucial role in the development of lupus-related skin lesions [71]. Many studies have also shown that UVB radiation can lead to a redistribution of nuclear antigens, including Ro, La, nuclear RNP, and Sm, which are related to cutaneous forms of lupus, to the cell surface in human keratinocytes [72-74]. Additionally, UVB radiation upregulates Ro52 expression in keratinocytes in inflammatory skin, which may generate auto-antibodies for Ro52 and disrupt-tolerance [75, 76]. Also, UVB irradiation can generate novel auto-antigen structures in apoptotic keratinocytes after UVB irradiation, e.g., covalent RNA-protein complexes involved in antigen capture and processing [77]. Overall, these effects, which promote an autoimmune state, are thought to be involved in SLE pathogenesis.

Autophagy

Studies of receiver biases have suggested that autophagy is involved in UVR-induced damage. Moreover, exposure to UVA, UVB, and UVC induces autophagy, which may be a protective response to UVR [78-84]. Exposure to UVA and UVA-oxidized phospholipids, which leads to oxidative stress, such as accumulation of protein aggregates and elevated levels of reactive oxidized phospholipids, induce autophagy to promote the removal of oxidized phospholipids and protein aggregates in epidermal keratinocytes [82]. Additionally, autophagy reduces reactive oxygen species and maintains the redox balance upon UVA-induced oxidative damage in limbal stem cells [84]. Chronic UVA has also been shown to inhibit the enzymatic activities of cathepsin B (CB) and cathepsin L (CL) and to impair autophagic flux; downstream CB and CL inactivation results in UVA-induced lysosomal impairment in human skin fibroblasts, consequently causing skin damage in patients with SLE [85, 86]. Notably, however, UVB exposure activates autophagy, which may be a protective response to UVB-induced damage, such as DNA damage and apoptosis, in epidermal cells. Studies have also shown that UVB-induced autophagy is mediated by inhibition of glycogen synthase kinase 3β and activation of AMP-activated protein kinase (AMPK) [79]. UVC exposure induces irreparable mitochondrial DNA (mtDNA) damage, and mitochondrial autophagy, which is increased after UVC exposure, can remove mtDNA damage in primary human fibroblasts [78, 81]. Overall, autophagy may play a protective role in UVR-induced damage, and autophagy defects may promote the development of SLE.

Epigenetic factors

DNA methylation

Previously evidence has shown that DNA hypomethylation is implicated in the pathogenesis of SLE. Normal $CD4^+$ T cells develop auto-reactivity when inhibiting DNA methylation, and these auto-reactive cells promote autoantibody production [43, 87-90]. Recent studies have shown that UVB exacerbates the development of SLE by decreasing the levels of DNA methylation in $CD4^+$ T cells in a dose-dependent manner [91-94]. Additionally, methylation-related molecules, such as DNA methyl transferase 1 (DNMT1) and methyl CpG binding domain protein 2 (MBD2), which maintain methylation and demethylation, respectively, may be involved in UVB-induced DNA hypomethylation in $CD4^+$ T cells [95]. Zhu *et al*. demonstrated that UVB exposure decreases the levels of *DNMT1* mRNA at higher dosages in patients with active SLE and but not affect *MBD2* mRNA expression [92]. Wu *et al.* also found that UVB can inhibit DNMT1 activity in $CD4^+$ T cells from patients with SLE [96]. However, Wang *et al*. and Wu *et al*. found that UVB exposure did not affect mRNA and protein expression of DNMT1 in $CD4^+$ T cells from patients with SLE [91, 93]. Moreover, Wu *et al*. suggested that UVB enhances global DNA hypomethylation in $CD4^+$ T cells by inhibiting DNMT1 catalytic activity in patients with SLE [93]. Another study concluded that loss of DNMT1 catalytic activity resulted in aberrant DNA methylation [97]. However,

Table 3. Expression levels of MicroRNAs in SLE patients

Expression levels	Details of Micro RNA
Upregulation	*miR-145, miR-106b-5p, miR-125b-5p.*
Downregulation	*miR-146a, miR-125a-5p, miR-125a, miR-125b.*

the exact roles of DNMT1 in the pathogenesis of SLE are still unclear.

Overall, these findings demonstrated that the process through which DNA hypomethylation occurs in patients with SLE is complicated and that further studies are needed to evaluate the multiple factors involved in DNA methylation and demethylation.

MicroRNAs

UVB exposure induces microRNA-mediated gene regulation earlier than most transcriptional responses [98] and can cause variations in the expression of microRNAs (**Table 3**) [99, 100], which modulate the UVR-induced DNA-damage response [101]. These deregulated microRNAs may be potentially involved in the pathogenesis of SLE. Xu *et al*. found that *miR-146a and miR-125a-5p* were downregulated after UVB exposure in mouse skin [102]. When *miR-146a*, which negatively regulates the IFN pathway, is expressed at low levels, the expression of type I IFNs is increased by targeting key signaling proteins in patients with lupus [103]. Indeed, *miR-146a* expression is negatively correlated with SLE activity [104]. Moreover, overexpression of *miR-125a* markedly reduces the levels of its target gene kruppel-like factor 13 (KLF 13) [105] and may induce CCL5 expression in late-activated T cells [106]. The level of CCL5 [105] modulates the recruitment of T cells to inflammatory sites, leading to tissue and organ inflammation [107-109]. In contrast, UVB exposure decreases the level of *miR-125a*, which can result in elevated levels of inflammatory chemokines, such as CCL5, and promote the development of SLE [105]. Dong *et al*. showed that *miR-145* is overexpressed and contributes to IL-6-induced increases insensitivity to UVB irradiation by decreasing the levels of MyD88 [110].

In a study of UVB-mediated microRNA expression in peripheral blood T cells from patients with SLE, UVB was found to induce significant upregulation of *miR-106b-5p and miR-125b-5p* [111]. However, few studies have evaluated the associations of *miR-106b-5p* and *miR-125b-5p* with SLE. Luo *et al*. reported that *miR-125b* levels were reduced, showing a negative association with lupus nephritis, in T cells from patients with active SLE. Additionally, downregulation of *miR-125b* regulates the expression of *ETS1* and *STAT3* genes, triggering the development of SLE [112]. Gao *et al*. also demonstrated that the level of *miR-125b-5p* is decreased in peripheral blood mononuclear cells from patients with SLE and that *miR-125b* inhibits autophagy in Jurkat cells by targeting UVR resistance-associated gene protein, indicating that *miR-125b* maybe a therapeutic target for SLE [113]. Further studies are needed to determine the complex processes through which microRNAs are deregulated in patients with SLE.

Gene-environmental interactions

As external factors, climate factors, which have been shown to affect various polymorphic loci related to the immune response, can influence the roles of these polymorphic loci in disease processes by altering the allele frequency distribution. Many studies have shown that multiple polymorphic loci are strongly correlated with climate factors, such as UVR, humidity, temperature, and latitude [114, 115]. For example, two human-specific polymorphisms, p53 codon 72 (rs1042522) and MDM2 single nucleotide polymorphism (SNP) 309 (rs2279744), which influence the activities of p53, have strong correlations with minimum winter temperature, latitude, and summer downward solar radiation [114]. Some findings of the gene-environment interaction hypothesis have shown that climate factors may alter the allele frequency distributions of multiple polymorphic loci involved the development of SLE [114, 115]. Interestingly, a study in a Korean population showed an association of the p53 codon 72 polymorphism with SLE susceptibility, and individuals with the Pro allele were found to be more susceptible to SLE than those carrying the Arg allele [116]. Furthermore, two case-control studies from Anhui province in China and Shiraz in Iran also revealed that p53 codon 72 (rs1042522) may be associated with susceptibility of SLE in Chinese and Iranian populations [117, 118].

Recent findings have shown that p53 may be a crucial factor in the pathogenesis of SLE. The tumor suppressor p53 has been shown to play central roles in apoptosis, cell proliferation, and DNA repair [119-121]. In addition, p53 suppresses autoimmunity. Indeed, overexpression of p53 and the presence of autoantibodies to the C-terminal domain of p53 inhibit the functions of p53 in patients with SLE and murine lupus [122-127]. Moreover, mutations in the *TP53* tumor-suppressor gene are prognostic factors for the development of lymph proliferative disorders in patients with autoimmune diseases, including rheumatoid arthritis, SLE, dermatomyositis, progressive systemic sclerosis, and autoimmune hemolytic anemia [128]. p53 reduces regulatory T cells, consequently suppressing the development of autoimmunity [129, 130]. However, the roles of genetic polymorphisms in p53 in SLE remain unclear. The p53 codon 72 polymorphism was not associated with SLE in Spanish and Polish populations [131, 132]. Moreover, a study in Caucasian, African American, and Asian children and adults also demonstrated a lack of association of the *TP53* Arg72Pro SNP and the MDM2 SNP309 with SLE [133]. However, a meta-analysis of associations between p53 codon 72 polymorphisms and SLE demonstrated that p53 codon 72 may explain why Asians but not Europeans are susceptible to SLE [134]. In contrast, MDM2 SNP309 may promote the expression of the *MDM2* gene by increasing the affinity of transcriptional activator of nuclear hormone receptors (Sp1), leading to the higher levels of MDM2 RNA and protein and attenuating the p53 pathway [135, 136]. The SNP309 may also affect the roles of hormones, such as estrogen, in tumorigenesis because the G-allele of SNP309 increases the affinity of the protein for Sp1 [137]. Activation of MDM2 may also reduce the numbers of plasma cells and $CD3^{+}CD4^{-}CD8^{-}$ T cells, leading to the production of autoantibodies and immune complexes and aggravating the development of SLE and lupus nephritis in a mouse model of lupus [138].

Taken together, these findings demonstrate that polymorphisms in both p53 codon 72 (rs1042522) and MDM2 SNP309 (rs2279744) are involved in the pathogenesis of SLE and that climate factors, such as minimum winter temperature, latitude, and summer downward solar radiation, may affect SLE by modulating the allele frequency distributions of p53 codon 72 and MDM2 SNP309.

Hancock *et al*. showed that the SNP rs2313132, located in the upstream promoter region of *PCDH18*, was strongly correlated with summer UVR from a worldwide analysis. Additionally, the SNP rs2187668, located in the region of the first intron of *HLA-DQA1*, was strongly correlated with relative humidity in Africa and Western Eurasia. Both polymorphic loci were confirmed to be related to SLE genetic susceptibility [115]. However, a case-control study from Anhui province in China found a lack of association of *PCDH18* (SNP rs2313132), *HLA-C* (SNP rs10484554), and *TLR6* (SNP rs5743810) with susceptibility to SLE in Asians, although these polymorphic loci were strongly correlated with climate factors [117]. Despite these findings, these SNPs were found to be correlated with the clinical symptoms of patients with SLE. For example, *PCDH18* (SNPs rs2313132), which was strongly correlated with summer UVR, was correlated with leucopenia; *TP53* (rs1042522), which was strongly correlated with minimum winter temperature, latitude, and summer shortwave radiation, was correlated with discoid erythema; *HLA-C* (rs10484554), which was strongly correlated with summer precipitation rate, was correlated with leucopenia, alopecia, and fever; and *TLR6* (rs5743810), which was strongly correlated with winter UVR, was correlated with pericarditis, oral ulcers, and photosensitivity. These SNPs may be associated with the geographical distribution of patients with SLE in China [117].

Sun *et al*. suggested that the SNP rs11868112 in the *RPTOR* gene was strongly correlated with latitude and winter temperature and hypothesized that the frequency of the derived T allele may increase with decreasing temperature and increasing latitude. These changes may promote regulation of the immune response through mammalian target of rapamycincomplex 1, consequently reducing the expression of *RPTOR* to maintain the balance between pathogen pressure and immune response. Conversely, low latitudes and high temperatures, under which conditions pathogen diversity is increased [139], induce the production of *RPTOR* to enhance the immune response; this can result in increased risk of susceptibility to autoimmune diseases, such as

Table 4. SLE susceptibility genes

SLE susceptibility genes	Induction factors	Symptoms
p53 codon 72 (rs1042522)	Minimum winter, temperature, latitude, summer downward solar radiation.	Rheumatoidarthritis, SLE.
MDM2 SNP 309 (rs2279744)	Minimum winter, temperature, latitude, summer downward solar radiation.	Aggravating the development of SLE and lupus nephritis in a mouse model of lupus.
PCDH18 (SNP rs2313132)	Summer UVR.	SLE genetic susceptibility.
HLA-DQA1 SNP rs2187668	Humidity.	SLE genetic susceptibility.
TP53 (rs1042522)	Latitude, minimum winter temperature, summer shortwave radiation.	Discoid erythema.
HLA-C (rs10484554)	Summer precipitation rate.	Leucopenia, alopecia, fever.
TLR6 (rs5743810)	Winter UVR.	Pericarditis, oralulcers photosensitivity.
RPTOR (SNP rs11868112)	Latitude, winter Temperature.	Susceptibility to Autoimmune diseases.

SLE [140]. Further studies of the association of *RPTOR* (SNP rs11868112) with SLE are required.

Overall, differentiation between polymorphic loci and ethnic groups may explain why different populations exhibit differences in racial compositions when exposed to distinct environmental factors, such as UVR, temperature, and latitude (**Table 4**). These factors can affect the roles of these polymorphic loci in the development of SLE by changing the allele frequency distribution.

Conclusion

In this review, we summarized environmental risk factors, including UVR, season distribution, climate factors, and geographical distributions, affecting the development of SLE. The probable mechanism was assessed based on inflammatory mediators, apoptosis, autophagy in keratinocytes, epigenetic factors, and gene-environment interactions. This information is expected to facilitate the development of new strategies for preventing the occurrence and progression of SLE. Susceptible individuals should avoid environmental risk factors if possible. However, the effects of some environmental factors, particularly seasonal distribution, climate factors, and geographical distributions, on SLE are still controversial, and the information is limited. Accordingly, further studies are required to clarify the environmental determinants of SLE.

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Disclosure of conflict of interest

None.

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