RESEARCH PAPER

GENETIC AND ENVIRONMENTAL FACTORS IN SYSTEMIC SCLEROSIS: A COMPREHENSIVE REVIEW

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Abstract
Systemic sclerosis (SSc) is a rare, multisystem autoimmune disease of connective tissue characterized by vascular disease, immune dysregulation, and progressive fibrosis of the skin and viscera. Despite its low prevalence—approximately 100–250 cases per million—the disease is associated with significant morbidity and mortality, disproportionately affects women, and poses a significant therapeutic challenge. The etiology of SSc remains poorly understood; however, increasing evidence supports a multifactorial model in which genetic predisposition and environmental factors interact to initiate and maintain a pathogenic cascade. This review summarizes current knowledge about the genetic architecture of SSc, including associations with human leukocyte antigens (HLA), non-HLA susceptibility loci identified in genome-wide association studies (GWAS), and emerging epigenetic mechanisms. Environmental and occupational factors influencing the pathogenesis of systemic sclerosis are also considered, including silica, organic solvents, and infectious agents. The complex interplay of these factors is explored through the lens of the "exposome" concept, which integrates external influences with internal biological responses. Finally, this review considers the clinical implications of these findings and outlines future research directions, including multi-omics approaches and the potential for personalized medicine in systemic sclerosis
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1. Introduction

Systemic sclerosis (SSc), often used synonymously with scleroderma due to its characteristic cutaneous fibrosis, is a chronic autoimmune disease of unknown etiology. The disease involves dysregulated immune activity, vascular injury with subsequent defective neovascularization and vascular remodeling, and progressive fibrosis of the skin and viscera, including the lungs, heart, gastrointestinal tract, and kidneys [1]. Clinically, SSc is classified into two main subtypes based on the extent of skin involvement: limited cutaneous SSc (lcSSc), in which skin thickening is limited to the extremities, face, and neck, and diffuse cutaneous SSc (dcSSc), in which skin thickening progresses proximally to the elbows and/or knees or involves the chest and abdomen. lcSSc typically occurs more chronically and progresses more slowly than dcSSc, and generally has a more severe prognosis [2]. Furthermore, classification based on serum autoantibody profiles—specifically, anticentromere antibodies (ACA) and topoisomerase I antibodies (ATA)—provides additional prognostic stratification: ACA is associated with a limited form of systemic sclerosis (lcSSc) and a more favorable prognosis, while ATA is a marker of the diffuse form of systemic sclerosis (dcSSc) and the mechanism of new pulmonary fibrosis [3].

The pathogenesis of systemic sclerosis involves a complex and self-sustaining cascade of events. Vascular damage is considered an early and primary event, leading to endothelial cell dysfunction, vascular obliteration, and, according to theory, tissue hypoxia. These factors arise from both the innate and adaptive immune systems, leading to the development of specific disease processes, autoantibodies, and chronic inflammation [4]. In genetically predisposed individuals, uncontrolled fibroblast activation leads to increased accumulation of collagen and extracellular matrix molecules, ultimately leading to tissue and organ fibrosis failure. The progressive and difficult-to-treat nature of the disease's pathogenetic processes contributes to the poor prognosis associated with systemic sclerosis [5].

Understanding the etiology of SSc is essential for monitoring, diagnosis, and treatment. Current data indicate that no single genetic or environmental factor

contributes to the development of the disease. SSc is likely a multigenic disorder with significant gene-environment interactions, with environmental factors likely initiating the disease in genetically predisposed individuals [6]. The aim of this review is to provide a comprehensive overview of the current state of knowledge on genetic and environmental factors in SSc, general results from epidemiological studies, genetic analysis and new multi-omics studies.

2. Genetic Factors in Systemic Sclerosis

2.1 Evidence for Genetic Susceptibility

The contribution of genetic factors to the predisposition to systemic sclerosis (SSc) is supported by extensive data. Familial clustering studies consistently demonstrate an increased risk among relatives of affected individuals [7]. One study reported that first-degree relatives of patients with SSc have a 13-fold higher risk of developing the disease than the general population, while siblings have a 15-fold higher risk [8]. Furthermore, first-degree relatives of patients with SSc also have an increased risk of other autoimmune diseases, including hypothyroidism, hyperthyroidism, and systemic lupus erythematosus (SLE), suggesting common genetic components among autoimmune diseases [9].

Population-based studies further support the presence of a genetic component. Notably, among the Choctaw Native Americans of Oklahoma, the prevalence of SSc is approximately 20 times higher than the general population. In this population, certain HLA haplotypes were strongly associated with disease susceptibility and the presence of topoisomerase I antibodies [10]. However, twin studies have yielded more nuanced results. Classic twin studies have found similar concordance rates between monozygotic (4.2%) and dizygotic (5.6%) twins for clinically confirmed systemic sclerosis, suggesting lower heritability compared to other autoimmune diseases [11]. However, an important finding from these studies is that the concordance for positive autoantibody results is significantly higher in monozygotic twins (95%) compared to dizygotic twins (60%), indicating that genetic factors strongly influence autoimmunity but are insufficient for the development of clinically evident systemic sclerosis [12]. These observations highlight the need for environmental factors to translate genetic predisposition into clinical disease.

2.2 HLA Associations

The human leukocyte antigen (HLA) region on chromosome 6p21 encodes proteins necessary for antigen presentation and immune recognition [13]. Numerous autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, ankylosing spondylitis, and type 1 diabetes mellitus, are strongly associated with allelic variations in this region. Similarly, susceptibility to systemic sclerosis (SSc) has been consistently linked to polymorphisms in the HLA region, with class II alleles representing the strongest genetic risk factor for the disease. These associations are strongly influenced by race and clinical subgroups of the disease, highlighting the complexity of HLA-mediated susceptibility [14].

Early large case-control studies laid the foundation for understanding HLA associations in systemic sclerosis. A seminal study of 1,300 patients with systemic sclerosis (SSc) demonstrated that HLA-DRB1*11:04 alleles and specific DQB1 alleles (DQB1*26 epi) are associated with a high susceptibility to SSc in Caucasians and Hispanics [15]. Conversely, the HLA-DRB1*07:01, DQA1*02:01, DQB1*02:02, and DRB1*15:01 haplotypes demonstrated a protective role in these populations [16]. Notably, distinct haplotype associations were observed in African Americans: HLA-DRB1*08:04, DQA1*05:01, and DQB1*03:01 haplotypes conferred susceptibility, highlighting the importance of ancestry in shaping HLA-mediated risk profiles [17].

Subsequent studies using the Genome Research in African American Scleroderma Patients (GRASP) cohort and European-American populations refined these observations [18]. Confirming previous reports, the HLA-DRB1*08:04 allele was reproducibly associated with susceptibility to systemic sclerosis in African-American patients. Additionally, a novel association with HLA-DRB1*11:02 was identified in this population [19]. In European-American subjects, associations with HLA-DQB1*02:02 (a protective factor), HLA-DPB1*13:01, and HLA-DRB1*11:04 further confirmed and strengthened previously established risk associations [20]. These results highlight the value of including diverse populations in genetic studies to identify population-specific risk variants.

Studies in smaller, ethnically diverse patient groups have expanded on these observations. In a cohort of patients with systemic sclerosis from India, the association of HLA-DRB1*11 with susceptibility was confirmed and a potentially novel protective association with HLA-DRB1*12 was identified [21]. Similarly, in Thai patients with systemic sclerosis, multiple alleles, including HLA-DRB1*15:02:01, DRB5*01:02:01, DQB1*05:01:24, DPB1*13:01:01, DQA1*01:01:01, and DPA1*02:01:01, were associated with susceptibility, with DPB1*13:01:01 carrying the highest risk [22]. The DPB1*13:01:01 association was also observed in a cohort of African Americans, suggesting that this allele may represent a common risk factor across populations, although confirmation in future studies is needed [19].

Recent GWAS have enabled comprehensive examination of the HLA region using significantly larger cohorts (9,846 patients with systemic sclerosis and 18,333 healthy controls) [23]. A global meta-analysis identified two synonymous single nucleotide polymorphisms in the HLA-DQA1 gene associated with the risk of developing systemic sclerosis: rs1048372 (protective) and rs1142338 (positive risk) [24]. Classical HLA allele analysis identified 21 alleles associated with risk, with HLA-DRB1*11:04 demonstrating the strongest association, followed by HLA-DQB1*02:02 and HLA-DPB1*13:01, consistent with previous observations [25].

A novel and potentially paradigm-changing finding of these GWAS was the identification of associations of HLA class I alleles with SSc risk, including HLA-

B08:01 and MHC class I haplotypes (HLA-B44:03, HLA-C*16:01) [14]. Associations of MHC class I with susceptibility to systemic sclerosis have not been previously reported and, if confirmed, may have important implications for understanding the pathogenesis of SS. These observations require confirmation in independent cohorts but suggest that CD8+ T-cell-mediated immune mechanisms may contribute to disease development [26].

The clinical utility of SSc-associated autoantibodies for stratifying patients into different clinical subgroups is well established. Given this heterogeneity, it is likely that genetic associations differ depending on the subgroups defined by the presence of autoantibodies [27]. Indeed, stratification by autoantibody status revealed distinct HLA associations [28]. In Caucasian populations, HLA-DPB1*13:01 and HLA-DRB1*11:04 are strongly associated with susceptibility to SSc with positive results for topoisomerase I antibodies (ATA), whereas in African Americans, HLA-DPB1*13:01, HLA-DQB1*02:01, and HLA-DQA1*05:01 are associated with ATA-positive disease. An association of HLA-DPB1*13:01 with ATA-positive SSc was also noted in a Thai cohort, suggesting potential cross-population consistency of this particular allele-autoantibody relationship [14].

For anticentromere antibody (ACA)-positive SSc, the epi-alleles HLA-DQB1*05:01, HLA-DQB1*07:01, and DQB1*26 showed a strong association in Caucasians, although not in African-American patients, suggesting population-specific effects [29]. Risk alleles in RNA polymerase III antibody (ARA)-positive patients also differed by race: HLA-DRB1*04:04, DRB1*11, and DQB1*03 were associated with SSc in Caucasians, while DRB1*08 was associated with SSc in African-Americans [30]. Notably, these associations were not confirmed in subsequent studies, highlighting the need for larger, well-designed analyses. Finally, HLA typing analysis in patients with fibrillarin antibodies revealed associations with HLA-DRB1*08:04 and HLA-DQB1*06:09 in African Americans, although this observation requires confirmation due to the limited sample size [31]. Taken together, these data indicate multiple, strong effects of HLA class II in systemic sclerosis, with distinct associations across autoantibody subsets and racial groups, highlighting the complex interplay between genetic variation, immune responses, and clinical phenotype in the pathogenesis of systemic sclerosis. The HLA associations across different ethnic groups and autoantibody subsets are summarized in Table 1.

Table 1. Summary of HLA risk and protective alleles associated with systemic sclerosis (SSc), stratified by ethnic background and serological autoantibody profiles (anti-topoisomerase I [ATA], anti-centromere [ACA], and anti-RNA polymerase III [ARA]).

Population / Ethnicity	**Risk Alleles**	**Protective Alleles**	**Autoantibody-Specific Associations**
European-Caucasian	**DRB1*11:04**, DPB1*13:01, DQB1*26 (epi)	DRB1*07:01, DQA1*02:01, DQB1*02:02, DRB1*15:01	**ATA+:** DPB1*13:01, DRB1*11:04; **ACA+:** DQB1*05:01, DQB1*07:01, DQB1*26; **ARA+:** DRB1*04:04, DRB1*11, DQB1*03
African Americans	**DRB1*08:04** (reproducible), DRB1*11:02, DQA1*05:01, DQB1*03:01	Not established	**ATA+:** DPB1*13:01, DQB1*02:01, DQA1*05:01; **ARA+:** DRB1*08; **Anti-fibrillarin+:** DRB1*08:04, DQB1*06:09
South Asian (Indian)	DRB1*11	DRB1*12 (potentially novel)	Insufficient data
Southeast Asian (Thai)	**DPB1*13:01:01** (highest risk), DRB1*15:02:01, DRB5*01:02:01	Not established	**ATA+:** DPB1*13:01 (confirmed)
Global Meta-analysis (trans-ethnic)	**rs1142338** (SNP in HLA-DQA1), DRB1*11:04, DQB1*02:02, DPB1*13:01,	**rs1048372** (SNP in HLA-DQA1)	Requires further stratification

Population / Ethnicity	Risk Alleles	Protective Alleles	Autoantibody-Specific Associations
	plus **HLA-B08:01**& **B44:03** (Class I)		

2.3 Non-HLA Susceptibility Loci

GWAS have significantly expanded our understanding of the genetic architecture of SSc, identifying numerous non-HLA-linked susceptibility loci. To date, large-scale GWAS in European and East Asian populations have identified more than 30 risk loci. Importantly, most of these loci encode proteins involved in immune regulation and inflammation, highlighting the strong autoimmune component underlying the pathogenesis of SSc [32].

The largest GWAS conducted in European populations identified several key susceptibility loci, including the HLA region and gene regions for CD247, interferon regulatory factor 5 (IRF5), and signal transducer and activator of transcription 4 (STAT4). These genes are involved in critical immune pathways: CD247 encodes a T-cell receptor subunit involved in regulating the immune response; IRF5 is a transcription factor involved in type I interferon signaling; and STAT4 is a transcription factor involved in inflammatory signaling [33]. Notably, most of these gene variants associated with SSc have also been associated with other autoimmune diseases, particularly systemic lupus erythematosus (SLE), supporting the concept of common genetic factors influencing the development of autoimmune diseases. Additional non-HLA genes implicated in SSc susceptibility through GWAS and candidate gene studies include angiotensin-converting enzyme (ACE), endothelial nitric oxide synthase (eNOS), CD19, PTPN22, BANK1, IRF8, TNFAIP3 (A20), IL-23 receptor, and TNIP1 [34]. PTPN22, a polymorphism associated with anticentromere and antitopoisomerase antibodies in SSc, has also been linked to type 1 diabetes, rheumatoid arthritis, systemic lupus erythematosus, and other autoimmune diseases, further highlighting shared genetic risks [35]. The TNFAIP3 gene, encoding the immunomodulatory enzyme A20, is associated with diffuse systemic sclerosis (dcSSc) and interstitial lung disease. Furthermore, a combination of BANK1, STAT4, and IRF5 alleles exhibits a stronger association with dcSSc, suggesting a role for B-cell biology in this severe subtype [36].

Importantly, recent GWAS studies in East Asia have identified new risk variants that were not as highly represented in European populations, highlighting the importance of population diversity for understanding the genetics of complex traits [37]. This finding underscores the need for genetic studies in diverse ethnic groups to fully characterize the genetic component of systemic sclerosis globally.

2.4 Epigenetic Mechanisms

Epigenetics is defined as the study of heritable changes in gene expression that occur without changes in the underlying DNA sequence. These modifications—primarily DNA methylation, histone modifications, and noncoding RNAs—can have profound effects on cellular function and are dynamic and reversible [38]. In SSc, epigenetic aberrations have been identified in all three major cell types involved in the pathogenesis of the disease: immune cells, endothelial cells, and fibroblasts. The growing understanding that epigenetic mechanisms link genetic predisposition and environmental factors makes them central to understanding the etiology of SSc and promising therapeutic targets [39].

2.4.1 DNA Methylation

DNA methylation, the best-studied epigenetic mechanism, involves the addition of a methyl group to the fifth carbon of cytosine to form 5-methylcytosine, predominantly in CpG dinucleotides. This modification allows the binding of proteins with a methyl-CpG-binding domain, which subsequently recruit enzymes that modify histones and remodel chromatin, ultimately leading to transcriptional silencing [40]. The enzymes responsible for catalyzing DNA methylation—DNA methyltransferases (DNMTs)—include DNMT1, which maintains existing methylation patterns, and DNMT3A and DNMT3B, which catalyze de novo methylation. Importantly, the discovery of ten-eleven translocation (TET) enzymes, which convert 5-methylcytosine to 5-hydroxymethylcytosine and further oxidation products, demonstrated that DNA demethylation can occur through active enzymatic processes, challenging the previously held belief that DNA methylation is irreversible [41].

DNA methylation abnormalities have been documented in various cell types in SSc. Global hypomethylation with reduced DNMT1 expression was observed in $CD4^+$ T cells compared to healthy individuals. A genetically specific study revealed hypomethylation of CD40L, CD70, and ITGAL in $CD4^+$ T cells in SSc, coinciding with increased protein expression and enhanced inflammatory and migratory functions [42]. Whole-genome bisulfite sequencing further identified differentially methylated regions encompassing genes involved in the Wnt and Hippo signaling pathways, which are known to play a critical role in fibrosis. In fibroblasts, whole-genome methylation analysis revealed distinct patterns between the diffuse and limited cutaneous subtypes of SSc [43]. Notably, hypermethylation of the SOCS3 promoter, encoding a suppressor of cytokine signaling that inhibits STAT3, lowers the threshold for STAT3 activation, thereby promoting profibrotic transcriptional programs [44]. This epigenetic silencing persists even after multiple passages in culture, explaining the persistent activated phenotype of fibroblasts in systemic sclerosis. Similarly, hypermethylation of the FLI1 promoter, leading to reduced FLI1 expression, has been associated with the

activation of immune cells, endothelial cells, and fibroblasts. Methyl-CpG-binding protein 2 (MeCP2) has been shown to mediate profibrotic effects by binding to the hypermethylated promoter of the Wnt inhibitor secreted frizzled-related protein 1 (sFRP1), enhancing Wnt signaling and fibrosis [45].

2.4.2 Histone Modifications

Histone modifications represent a second important category of epigenetic regulation. Histone tails surrounding the nucleosome core can be chemically modified through acetylation, methylation, ubiquitination, sumoylation, and the recently described lactylation [46]. These post-translational modifications are carried out by "writing" enzymes and removed by "erasing" enzymes, affecting chromatin accessibility and gene expression. Lysine acetylation, mediated by histone acetyltransferases (HATs) and removed by histone deacetylases (HDACs), typically leads to chromatin relaxation and permissive gene expression. Conversely, histone methylation can lead to either activation or repression depending on the specific lysine residue modified and the degree of methylation [47]. In systemic sclerosis, histone modifications have been extensively studied in fibroblasts and endothelial cells. In dermal fibroblasts, the histone methyltransferase EZH2, which deposits the repressive H3K27me3 mark, has been shown to promote fibrosis via Notch signaling and GLI2 expression. Inhibition of EZH2 with pharmacological agents such as DZNeP or GSK126 attenuates fibrosis in vitro and in animal models [48]. Conversely, inhibition of the H3K27me3 demethylase JMJD3 with GSKJ4 also reduces fibroblast activation, highlighting the complexity of histone methylation dynamics in SSc [49]. Bromodomain and extraterminal domain (BET) proteins, which function as epigenetic "readers" by binding acetylated lysines, have emerged as promising therapeutic targets. The BET inhibitor JQ1 effectively blocks fibrosis in SSc fibroblasts and bleomycin-induced skin fibrosis by suppressing the expression of fibrotic genes. In endothelial cells, increased expression of HDAC5 and EZH2 contributes to the antiangiogenic state characteristic of SSc, with EZH2-mediated suppression of angiogenesis mediated by the Notch ligand DLL4 [50]. Genome-wide chromatin accessibility analysis revealed a global decrease in chromatin accessibility in both endothelial cells and fibroblasts in SSc, with genes involved in nervous system pathways and transcriptional regulation enriched in differentially accessible regions [51].

2.4.3 Non-Coding RNAs

MicroRNAs (miRNAs) are small, single-stranded RNA molecules approximately 22 nucleotides long that negatively regulate gene expression by binding to the 3'-untranslated region of target mRNAs, leading to translational inhibition or mRNA degradation [52]. In SSc fibroblasts, miR-27a-3p has been shown to target sFRP1, enhancing Wnt signaling and extracellular matrix deposition. miR-16-5p, which targets NOTCH2, is downregulated in SSc fibroblasts, while miR-326 is downregulated in SSc lung fibroblasts, leading to increased IL-31 receptor expression [53]. In monocytes, miR-26a-2-3p negatively correlates with interferon signatures, and exogenous administration of miRNA mimics reduces TLR-mediated interferon gene activation. Plasmacytoid dendritic cells from patients with systemic sclerosis exhibit increased expression of miR-618, miR-126, and miR-139-5p, the latter two potentially targeting ubiquitin-carboxyl-terminal hydrolase 24, thereby prolonging interferon release [54].

Long noncoding RNAs (lncRNAs), defined as transcripts longer than 200 nucleotides, have also been implicated in the pathogenesis of systemic sclerosis. The lncRNA HOTAIR is elevated in fibroblasts from systemic sclerosis and promotes myofibroblast differentiation through EZH2-dependent downregulation of miR-34a, leading to increased Notch activity and GLI2 expression [55]. H19X, another lncRNA elevated in systemic sclerosis skin, regulates extracellular matrix production through genomic conformational changes that influence DDIT4L expression. In monocytes, the lncRNA NRIR correlates with the interferon gene signature and regulates TLR-mediated expression of proinflammatory genes [56]. These results highlight the diverse roles of noncoding RNAs in the pathogenesis of systemic sclerosis and their potential as therapeutic targets, although challenges remain regarding delivery and in vivo stability [57]. The reversibility of epigenetic modifications makes them highly attractive for therapeutic intervention, and several epigenetic drugs are already in clinical use for other indications, suggesting potential for their repurposing in systemic sclerosis.

3. Environmental Factors in Systemic Sclerosis

Geographic variations in the prevalence of systemic sclerosis (SSc) strongly suggest the importance of environmental factors in the development of the disease. SSc is more common in North America and Australia than in Europe or Japan, and more common in southern Europe than in northern Europe [58]. Cases of SSc have been reported on Indigenous reservations, among miners, and in London neighborhoods located near international airports. Several theories suggest that environmental factors trigger the development of SSc by affecting the cellular, innate, and adaptive immune systems, or even by remodeling epigenetic methylation and histone modifications [59]. Numerous hypotheses have been put forward regarding the influence of environmental factors, including occupational exposures, chemicals, silicone implants, microorganisms, medications, and smoking.

3.1 Occupational Exposures

Silicon

Silicon is the second most abundant mineral in the Earth's crust and is often used as a building material. Two early seminal papers drew worldwide attention to the potential link between silicon exposure and SSc [60]. In a study of gold miners in South Africa, cumulative lifetime silicon exposure was significantly higher in patients compared to controls [61]. A correlation was reported between SSc and silica dust exposure among miners. Subsequent case-control and

cohort studies have shown that individuals exposed to silicon, such as miners, are predisposed to developing SSc compared to unexposed groups [62]. It was found that the odds of developing SSc are 25 times higher in workplaces with silicon exposure [63]. Two meta-analyses and one systematic review provide compelling epidemiological evidence. McCormick and colleagues reported an overall relative risk estimate of 3.2, and for cohort studies, the relative risk was 15.49 [64]. Rubio-Rivas and colleagues found an odds ratio of 2.81 and a hazard ratio of 17.52 for cohort studies [65]. Occupations associated with silica exposure include miners, stonemasons, sandblasters, sandstone sculptors, glass grinders, cast polishers, construction workers, foundry workers, and jewelers, among others.

The temporal relationship between exposure and disease onset varies across studies. Silica exposure may predict myositis and is a poor prognostic factor for progressive pulmonary fibrosis. Antibodies to topoisomerase I are detected at an increased frequency in patients exposed to silica, suggesting that silica particles may induce specific changes in the immune system [66]. From a pathogenetic perspective, in vivo and in vitro studies show that silica dust stimulates inflammation caused by the activation of interleukin-1β mediated by the NALP3 inflammasome. Silicon dioxide binding to scavenger receptors also leads to apoptosis of alveolar macrophages and the release of proinflammatory cytokines, causing pulmonary inflammation and fibrosis [67].

Organic Solvents

Solvents are chemicals used for dissolution and extraction, commonly used in many industries, including spray painting, building painting, printing, dry cleaning, and electronics manufacturing. Several meta-analyses demonstrate a correlation between solvent exposure and the risk of developing SSc. Aryal and colleagues reported a pooled relative risk estimate of 3.14 for case-control studies [68]. Kettaneh and colleagues found an odds ratio of 1.76, noting that men were at higher risk of developing the disease after solvent exposure than women [69]. Zhao and colleagues reported a pooled odds ratio of 2.07, with men having an odds ratio of 5.2 compared with women [70]. Analysis of individual solvents revealed significant associations with aromatic solvents, trichloroethylene (TCE), halogenated solvents, and ketones [71]. In subjects exposed to solvents for three months or more, the risk was higher, with an odds ratio of 2.40. Exposure to trichloroethylene has been observed in male patients with antibodies to topoisomerase I, suggesting its potential to induce a specific autoimmune response in genetically predisposed individuals [71].

Evaluating solvent exposure is difficult because commercial products often mix specific solvents or have multiple product names. Assessing the dose-response relationship is also difficult, and data are often based on self-reporting, which may under- or overreport exposure. The proposed pathogenesis is supported by experimental studies showing that the formation of large amounts of reactive oxygen species can trigger cellular inflammation, induce DNA fragmentation and DNA hypomethylation, followed by transcriptional changes in genes responsible for fibrosis and the production of profibrotic cytokines.

Epoxy Resin, Welding Fumes, and Pesticides

Epoxy resin is a chemical material used as an adhesive, widely used in the manufacture of automobiles, bicycles, wood products, and glass. Following the first case series reported in 1980, case-control studies were conducted to evaluate the association between epoxy resin exposure and the risk of developing the disease [72]. A meta-analysis of four case-control studies showed an association between epoxy resin and SSc with an odds ratio of 2.97. Bis(4-amino-3-methylcyclohexyl)methane is suspected as a potential causative factor for SSc [73].

Welding fumes, a product of welding, may contain several metals, including aluminum, arsenic, beryllium, lead, and manganese. The risk of exposure to welding fumes as a trigger for SSc has been suggested by two case-control studies [74]; However, a meta-analysis of four case-control studies found no association, with an odds ratio of 1.29. Similarly, three case-control studies suggested a role for pesticides as a potential causal factor, but a meta-analysis did not support this association, showing an odds ratio of 1.02 [65].

Asbestos

Asbestos is a naturally occurring fibrous silicate mineral that is resistant to high temperatures and widely used as a building material. Growing evidence links asbestos exposure to autoimmune diseases [75]. In Montana, USA, among 6,603 individuals screened at the Asbestos Disease Center, 13.8% were diagnosed with an autoimmune disease (including 10 cases of systemic sclerosis), a prevalence seven times higher than expected. Gold and colleagues reported an increased risk of mortality from systemic sclerosis after asbestos exposure, with a hazard ratio of 1.2 [76].

Heavy Metals

A large case-control study by Marie and colleagues assessed the association of heavy metal exposure with SSc [77]. Hair samples from 100 SSc patients and 300 controls were analyzed to quantify trace levels of heavy metals. Higher levels of seven heavy metals were detected in SSc patients: antimony, cadmium, lead, mercury, molybdenum, palladium, and zinc. Heavy metals can release oxygen radicals, causing DNA damage, impaired phagocytosis, T- and B-cell activation, and vascular damage due to oxidative stress. Heavy metals can alter transcription factors responsible for fibrosis by increasing the expression of microRNAs involved in oxidative stress and inflammation, altering epigenesis and hypomethylation of profibrotic genes, and increasing the expression of ICAM-1 and VCAM-1 [78]. Occupations potentially associated with heavy metal exposure include work in gold and diamond mines, semiconductor manufacturing, lead-acid battery manufacturing, soldering, metal alloy work, and electronics manufacturing. Table 2 summarizes the key occupational exposures and their respective risk estimates from published meta-analyses [79].

Table 2. Summary of environmental and occupational risk factors for systemic sclerosis (SSc), including pooled odds ratios (OR) and hazard ratios (HR) from published meta-analyses, high-risk occupations, and the suspected molecular mechanisms driving fibrosis and immune dysregulation.

Exposure Agent	Risk Estimate (OR / RR)	High-Risk Occupations	Proposed Pathogenic Mechanism
Silica / Crystalline Silicon	**OR = 2.81** (Rubio-Rivas); **RR = 15.49** (Cohort studies); 25-fold increased risk (German study)	Miners, stonemasons, sandblasters, foundry workers, jewelers, construction	NLRP3 inflammasome activation → IL-1β release; alveolar macrophage apoptosis; induction of anti-topoisomerase I (ATA) antibodies
Organic Solvents (incl. Trichloroethylene)	**Overall OR = 2.07** (Zhao); **OR = 5.2** (males); **OR = 2.40** (exposure > 3 months)	Painters, printers, dry cleaners, electronics manufacturing, degreasers	Oxidative stress & DNA fragmentation; **DNA hypomethylation**; transcriptional upregulation of profibrotic genes
Epoxy Resins	**OR = 2.97** (Meta-analysis of 4 case-controls)	Automobile, bicycle, and boat manufacturing; woodworking	Suspected immunotoxicity (mechanism under investigation)
Asbestos	**HR = 1.2** (mortality);	Construction workers,	Chronic granulomatous inflammation; oxidative damage to mesothelium
	Prevalence 7x higher than expected (Montana cohort)	shipyard workers, insulation installers	
Heavy Metals (Pb, Hg, Cd, Zn, Pd)	Significantly higher hair levels detected in SSc patients (Mari et al.)	Gold/diamond mining, battery manufacturing, soldering, semiconductor industry	ROS production; dysregulation of microRNAs; oxidative stress-induced endothelial dysfunction
Welding Fumes / Pesticides	**Not statistically significant** (OR = 1.29 and 1.02 respectively)	Welders, agricultural workers	No confirmed association in meta-analyses

3.2 Medications

Case reports and case series suggest that a number of medications are potentially associated with skin changes resembling SSc or with the onset of SSc. Taxanes induce the production of IL-2, IL-6, and GM-SCF. Halogenated anesthetics have physicochemical and toxicological properties similar to solvents [80]. Bleomycin increases the synthesis of type I procollagen in cultured human skin and lung fibroblasts. In a patient receiving paclitaxel, Fli1 (friend leukemia integration 1) protein levels in dermal fibroblasts were undetectable. Fli1 is a protein that suppresses the type I collagen gene in dermal fibroblasts [81]. Whether discontinuing the suspected

drug improves skin sclerosis varies from patient to patient. With taxane-based medications, reversible changes were observed in two cases after drug discontinuation, and in one patient, after discontinuation of methysergide. Drugs associated with scleroderma-like changes include gemcitabine, doxorubicin, tryptophan, appetite suppressants, pentazocine, bromocriptine, methylphenidate, checkpoint inhibitors, interferon-alpha, and cocaine [82].

3.3 Infectious Triggers

Growing evidence suggests potential infectious triggers for SSc. Although these data are primarily derived from isolated case reports and case series, viral detection in tissue samples, cell lines, and animal models has led to the suggestion of a pathogenic role for these organisms. Particular attention has been paid to the herpesvirus family [83]. Several studies have demonstrated high levels of Epstein-Barr virus (EBV) viral load in endothelial and fibroblast cells. In EBV-infected monocytes, EBV induces immunogenicity by upregulating Toll-like receptor 8 expression and enhancing interferon signaling [84]. Human cytomegalovirus (HCMV) has been proposed as a potential causative agent; CMV gene transcripts have been detected in endothelial cells from skin samples of women with SSc [85]. In vitro models demonstrated molecular mimicry between the human CMV UL94 peptide and endothelial/fibroblast cell peptides, causing endothelial damage with inflammatory and fibrotic cascades. Higher levels of HHV-6 A/B DNA were detected in peripheral blood cells from patients with SSc compared to controls [86]. In vitro studies showed that endothelial cells loaded with HHV-6 released large amounts of profibrotic cytokines and impaired endothelial angiogenesis. High viral load correlated with the presence of topoisomerase antibodies and extensive skin fibrosis [87].

Parvovirus B19 (PVB-19) infection is considered a potential trigger for autoimmune diseases, including SSc. PVB-19 DNA or the viral transactivator protein NS1 were detected in the bone marrow, serum, and skin of patients with SSc [88]. The level of PVB-19 RNA expression correlated with endothelial inflammation and TNF-α expression. Several theories suggest that PVB-19 may enhance disease progression through molecular mimicry, followed by autoantigen expression on endothelial cells, and by stimulating the NLRP3 inflammasome pathway in monocytes [89]. Antibodies to retroviral proteins have been detected in serum samples from patients with systemic sclerosis (SSc), and when normal human skin fibroblasts are induced with the retroviral protein, they produce extracellular matrix proteins, acquiring a phenotype similar to SSc [90]. Other potential infectious triggers include hepatitis B and C viruses, Coxiella burnetii, Toxoplasma gondii, and Rhodotorula glutinis. Helicobacter pylori infection has been extensively studied, and a meta-analysis showed an increased incidence of H. pylori infection in patients with SSc compared with healthy controls (odds ratio 2.10) [91]. However, the direction of causality remains uncertain; impaired gastrointestinal motility in SSc may enhance the association with Helicobacter pylori or increase mucosal permeability, allowing bacteria to be released and trigger an immune response. Eradication of H. pylori may improve primary Raynaud's phenomenon.

3.4 Microbiome and Dysbiosis

Emerging evidence suggests a role for microbial flora changes in autoimmune diseases, with an increase in pathobiont organisms and a decrease in commensal microorganisms in gastrointestinal samples. Gastrointestinal dysbiosis has been found to correlate with the severity of gastrointestinal dysmotility and pulmonary fibrosis, but not with skin fibrosis [92]. In systemic sclerosis, dysbiosis of the skin flora has been observed, with colonization by unexpected species and an altered molecular signature characterized by a decrease in lipophilic organisms and an increase in Gram-negative organisms in the skin [93]. A causal relationship is difficult to establish, as changes in the skin or gastrointestinal tract may contribute to increased susceptibility to microbial imbalances. It remains unclear whether dietary changes can improve gastrointestinal dysmotility or indigestion by altering the balance of gastrointestinal microbiota.

3.5 The Exposome Paradigm

The new exposome concept provides a comprehensive framework for understanding the influence of environmental factors on the development of SSc [94]. The exposome is defined as the significance of all exposures to an individual from all sources—including environmental and occupational—over the lifespan, and how these exposures influence health. This concept underpins classical epidemiology, integrating environmental factors (general environmental factors such as social capital, education, and psychological stress; and key environmental factors such as chemical pollutants, infectious agents, and lifestyle exposome factors) with the exposome (metabolism, endogenous hormones, gut microbiota, stress, oxidative stress, and aging) [95].

It is proposed that the cascade of SSc development is triggered by environmental events in a genetically predisposed individual, leading to a chronic and self-sustaining multifocal process [96]. While traditional epidemiological studies have often focused on individual exposures, the exposome-based approach aims to examine the exposure-disease continuum as a whole, identifying relationships between different exposures and their biological processes. New studies are beginning to integrate exogenous exposome data with clinical records, medical imaging, and diagnostic data to improve understanding of the environmental and occupational causes of systemic scleroderma [97]. However, most studies measuring key exposome markers (such as epigenetics, transcriptomics, and metabolomics) have not been supplemented with exogenous exposome data, representing a significant gap in the field.

4. Gene-Environment Interactions

The concept of gene-environment interaction is central to understanding the ethos of SSc. The remarkable pathogenesis of the disease, involving vascular, fibrotic, inflammatory, and immunological processes,

suggests that no single gene or environmental factor alone causes the development of SSc [98]. Rather, exposure to an environmental factor is likely to trigger the disease in genetically predisposed carriers, resulting in a variable form of the disease.

Multiple data support this model. First, the discrepancy in the clinical presentation of SSc in monozygotic twins who develop autoantibodies suggests that genetic predisposition must be linked to environmental factors for the development of the disease [99]. Second, the ethnic clustering of SSc, such as in the Choctaw population, suggests a population-specific genetic predisposition that is likely influenced by environmental factors [100]. Third, the temporal sequence observed in Klf5+/−; The Fli1+/- mouse model, in which symptoms and autoimmunity initially develop, followed by vasculopathy and fibrosis, represents a proposed human pathogenesis, where environmental factors initiate immune activation in a genetically predisposed individual, leading to subsequent vascular injury and fibrosis [101].

Several mechanisms have been proposed for the interaction of environmental factors with genetic predisposition. In the case of silicon, the mechanism may involve inflammasome activation, leading to the production of IL-1β and IL-18 and subsequent fibrosis [102]. For viruses such as CMV, molecular mimicry may trigger autoimmunity through cross-reactivity between viral and host proteins. Epigenetic modifications may be particularly important mediators of gene-environment interactions, as environmental exposures can alter DNA methylation, histone modification, and microRNA expression, leading to persistent changes in gene expression in several important cell types [103]. This concept is supported by the fact that the FLI1 promoter produces pink methylation in fibroblasts from systemic sclerosis, and by the fact that decreased FLI1 expression is associated with both genetic variations and epigenetic modification.

5. Clinical Implications and Future Directions

5.1 Clinical Applications

Current understanding of genetic and environmental factors in SSc has several clinical implications. Although the association of specific HLA alleles with disease subtypes and autoantibody profiles is not perfect, as there are affected individuals without the putative genes and healthy individuals with these genes [104]. HLA typing may still be clinically valuable for identifying patients at increased risk of complications, such as pulmonary fibrosis or rapidly progressive skin disease. This information could potentially aid in disease monitoring and the development of early intervention strategies [105].

Identification of environmental risk factors, particularly silica dust exposure, offers opportunities for primary prevention. Public health measures aimed at reducing occupational silica dust exposure have the potential to reduce the incidence of SSc in at-risk groups [106]. However, the relative rarity of SSc and the multifactorial nature of its etiology make population-based prevention challenging. From a therapeutic perspective, identifying specific genetic and molecular pathways involved in the pathogenesis of SS opens up new avenues for targeted therapy. The discovery that many systemic sclerosis susceptibility genes encode proteins involved in immune signaling suggests that immunomodulatory therapy may be beneficial [107]. Indeed, understanding the genetic basis of systemic sclerosis may ultimately enable genotypic stratification of patients for clinical trials and personalized therapeutic approaches.

5.2 Future Research Directions

Based on current knowledge, several promising areas for future research can be identified. First, there is a pressing need for comprehensive studies combining genetic, epigenetic, transcriptomic, proteomic, and metabolomic data with detailed assessment of environmental exposures (the exposome) to fully characterize the etiology of SSc [108]. Single-cell RNA sequencing studies, which have already identified cell-type-specific transcriptomic changes in peripheral blood, skin, and lungs, should be integrated with genetic and environmental data to identify disease-relevant cell populations and their responses to various factors [109].

Second, identifying causal variants remains a priority. Although GWAS have identified numerous risk loci, most associated variants are located in intergenic (non-coding) regions of the genome, and their functional contribution to disease susceptibility is largely unknown [110]. To identify causal variants and understand their mechanisms, detailed mapping using statistical methods and functional characterization of regulatory elements, particularly enhancers, are necessary. Integrative multi-omics approaches combined with in-depth phenotyping of study cohorts are crucial for fully characterizing the genetic component of SSc [111].

Third, diversity in genetic studies is essential. The observed differences between European and East Asian GWAS highlight the importance of including diverse populations in studies to identify population-specific risk variants and ensure the generalizability of results to other ethnic groups [112]. Future research should focus on underrepresented populations, including Southeast Asia, South Asia, Latin America, and sub-Saharan Africa, where SSc datasets are currently incomplete.

Fourth, further research is needed on the biological pathways linking environmental exposures to SSc. The mechanisms by which silicon, solvents, and infectious agents induce disease in susceptible individuals remain poorly understood. Understanding these pathways may help identify new therapeutic targets and preventive strategies [113]. The exposome concept, which seeks to integrate all exposures across the lifespan, provides a valuable conceptual approach for studying these complex interactions.

Finally, the potential for personalized medicine in SSc should be explored. As our understanding of the genetic, epigenetic, and environmental heterogeneity of SSc deepens, it may become possible to stratify patients based on molecular signatures for prognosis and treatment selection [114]. Identifying molecular subgroups of SSc based on gene expression patterns

suggests that such stratification is feasible and may ultimately improve clinical outcomes.

6. Conclusion

Systemic sclerosis is a complex, multifactorial disease resulting from the interaction of genetic predisposition, epigenetic modifications, and environmental factors. Genetic studies have identified both HLA and non-HLA susceptibility loci, with the strongest associations observed with genes involved in immune regulation and inflammation. Epigenetic mechanisms, particularly DNA methylation and histone modifications, provide a link between environmental exposure and stable changes in gene expression in critically important cell types. Environmental factors, including exposure to silica dust, organic solvents, and viral infections such as CMV, are considered triggers for disease onset in genetically predisposed individuals.

An emerging model of systemic sclerosis pathogenesis proposes that environmental exposure initiates a cascade of events—beginning with immune activation and autoimmunity, followed by vascular damage, and culminating in fibrosis—in individuals with a favorable genetic background. This model has important clinical implications, including potential for prevention (particularly by reducing occupational exposure to silica dust) and the potential for personalized medicine approaches based on genetic and molecular profiling.

Despite significant advances, many questions remain. The mechanisms by which environmental factors interact with genetic predisposition to shape the systemic sclerosis phenotype require further investigation. The functional consequences of most non-HLA risk variants are unknown. The role of epigenetic modifications in maintaining pathological phenotypes and their potential as therapeutic targets merit further investigation. Future studies integrating genetics, epigenetics, transcriptomics, and exposome data in diverse populations promise to advance our understanding of systemic sclerosis and ultimately improve treatment outcomes for patients suffering from this devastating disease.

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