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REVIEW

Genetic and epigenetic influences on the loss of tolerance in autoimmunity

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Immunological tolerance loss is fundamental to the development of autoimmunity; however, the underlying mechanisms remain elusive. Immune tolerance consists of central and peripheral tolerance. Central tolerance, which occurs in the thymus for T cells and bone marrow for B cells, is the primary way that the immune system discriminates self from non-self. Peripheral tolerance, which occurs in tissues and lymph nodes after lymphocyte maturation, controls self-reactive immune cells and prevents over-reactive immune responses to various environment factors. Loss of tolerance results in autoimmune disorders, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D) and primary biliary cirrhosis (PBC). The etiology and pathogenesis of autoimmune diseases are highly complicated. Both genetic predisposition and epigenetic modifications are implicated in the loss of tolerance and autoimmunity. In this review, we will discuss the genetic and epigenetic influences on tolerance breakdown in autoimmunity. Genetic and epigenetic influences on autoimmune diseases, such as SLE, RA, T1D and PBC, will also be briefly discussed.
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INTRODUCTION

Immune tolerance refers to unresponsiveness of the immune system toward certain substances or tissues that are normally capable of stimulating an immune response. Self-tolerance is essential for normal immune balance, and failure or breakdown of that tolerance results in autoimmunity and autoimmune diseases.

Autoimmune diseases are a group of >80 chronic, relapsing, and sometimes lethal diseases, characterized by a defective immune system resulting in the loss of tolerance to self-antigens and over-expression of autoantibodies. More importantly, autoimmune disorders often occur during reproductive years, which may lead to pregnancy loss and infertility.[1] Although great progress has been made, particularly new gene loci discoveries with the advent of genome-wide association studies, the pathogenesis of autoimmune diseases remains elusive. The origins of autoimmune diseases cannot be explained by genetic factors alone because the occurrence of autoimmune diseases in identical twins is not always consistent.[2] Subsequent studies imply that epigenetic modifications also participate in the loss of immune tolerance and autoimmunity in genetically predisposed individuals.[3]

This article will review the current status of genetic and epigenetic contributions to the loss of immune tolerance in autoimmunity. Genetic and epigenetic influences on autoimmune diseases, such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), type 1 diabetes (T1D) and primary biliary cirrhosis (PBC), will also be briefly discussed.

LOSS OF TOLERANCE AND AUTOIMMUNITY

The immune system is responsible for identifying and executing proper responses to eliminate non self-antigens and prevent the harmful response to self-antigens, referred to as immune tolerance.[4] To maintain immune homeostasis in balance, the individual must be tolerant of their own potentially antigenic substances. Once self-tolerance is disrupted, autoimmunity will arise.

Based on where the state is originally induced, self-tolerance can be classified into two types: central and peripheral tolerance (Figure 1a). Central tolerance refers to eliminations of autoreactive lymphocyte clones before they become fully immunocompetent, of which the main mechanism is negative selection. This procedure occurs in the stage of lymphocyte development

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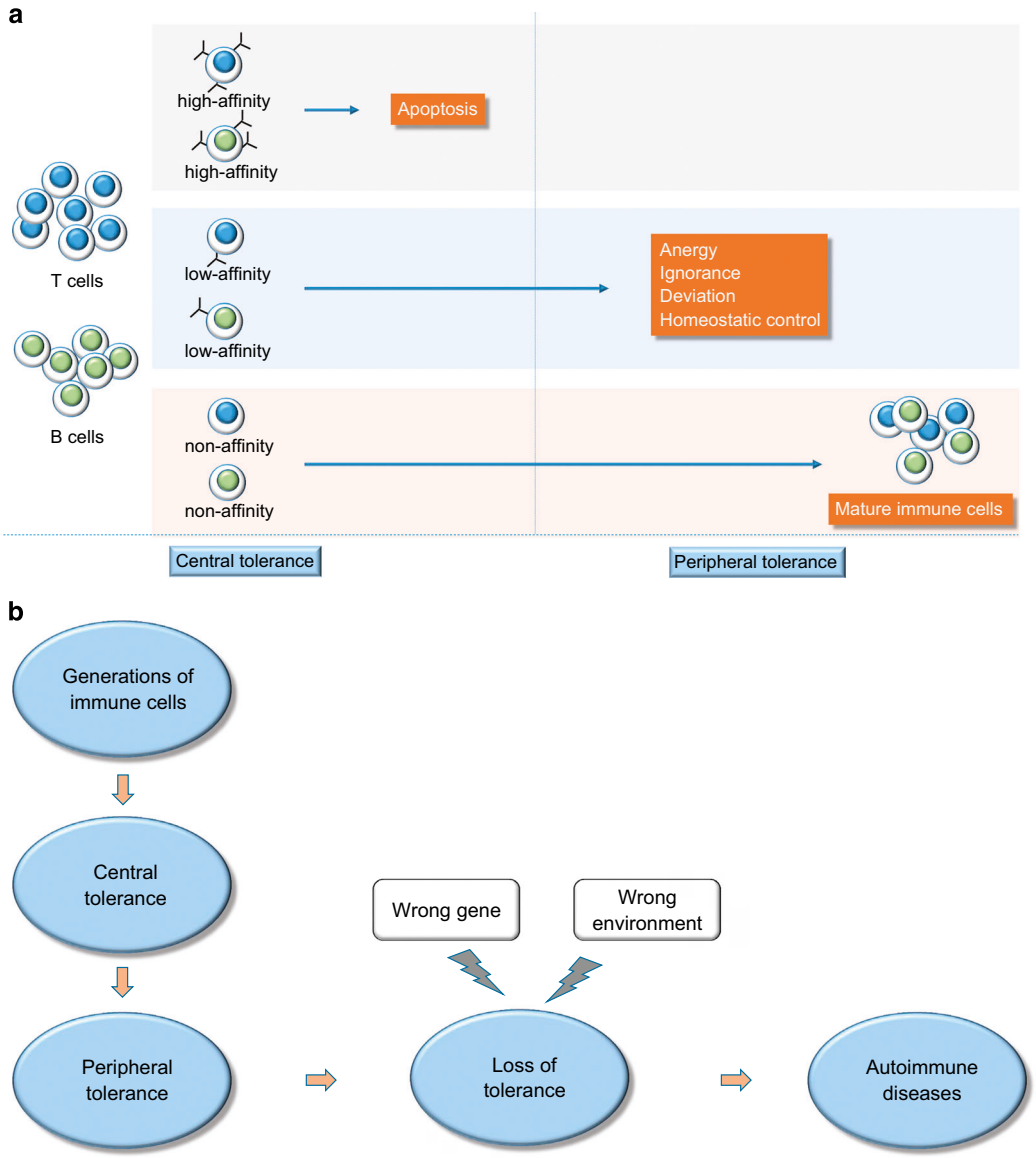

Figure 1 **(a)** Central and peripheral tolerance. In the thymus, T cells with high affinity for self-antigens undergo apoptosis, while B cells undergo a similar process in the bone marrow. Low-and non-afnity T and B cells enter peripheral tissues and lymph nodes, where non-affinity T and B cells mature into immune cells and low-affinity T and B cells are deleted by many mechanisms, such as anergy, ignorance, deviation and homeostatic control. **(b)** The process of loss of tolerance to autoimmune diseases. Immune cells generate and experience central and peripheral tolerance. Tolerance fails because of the interaction of the wrong environment with the wrong gene, resulting in autoimmune disease.

in the thymus and bone marrow for T and B lymphocytes, respectively. After T and B lymphocytes enter the peripheral tissues and lymph nodes, peripheral tolerance will occur to inhibit immune responses against the body's own tissues, which occurs primarily in the secondary lymphoid organs, such as spleens and lymph nodes. Mechanisms of peripheral tolerance include anergy (functional unresponsiveness), deletion (apoptotic cell death) and suppression by regulatory T cells.[5] As stated above, the tolerance is processed on two 'levels', in which the 'lower level' of peripheral tolerance functions as a back-up strategy of the 'upper level' of central tolerance. Autoimmune diseases may develop when self-reactive lymphocytes escape from tolerance and are thereby activated. However, the underlying exact mechanisms are not entirely known. Current knowledge suggests that autoimmunity stems from a combination of genetic variants and various acquired environmental triggers. Figure 1b illustrates the loss of tolerance and autoimmune diseases.

GENETIC INFLUENCES IN THE TOLERANCE BREAKDOWN IN AUTOIMMUNITY

The loss of tolerance is a complex process that poses a great challenge to investigate. Recent studies on monogenic forms of autoimmune diseases advance our understanding of the loss of tolerance (Table 1).[6]

AIRE and central tolerance

The transcription factor autoimmune regulator (*AIRE*) was originally identified as the mutated gene in patients with an autosomal recessive form of autoimmunity called autoimmune polyglandular syndrome Type 1 (APS1), featured by autoimmune attacks against multiple endocrine organs, skin and other tissues.[7,8] When the gene *AIRE* was knocked out in mice, the thymic expression of some antigens that are normally expressed at high levels in different peripheral tissues is influenced. Therefore, T cells specific for these antigens will escape from negative selection (central tolerance), entering the periphery and initiating damage to the self.[9]

Foxp3 and Treg cells in autoimmune diseases

Either protective or harmful immune responses are mainly regulated by T and B cells; however, firm evidence shows that the normal immune system also produces a sub-population of $CD4^+CD25^+$ regulatory T cells, namely Treg cells. Treg cells function to suppress the immune responses, and a deficiency of Treg cells is responsible for autoimmune and inflammatory diseases. Treg cells specifically express the transcription factor *Foxp3* (forkhead box P3), which is a key regulator of Treg cell development and function. Because of the absence of Treg cells, induced knockout or spontaneous mutation of the *Foxp3* gene in mice results in a systemic autoimmune disease.[10–12] Correspondingly, in humans, the *Foxp3* gene mutation also leads to a genetic disease called immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX syndrome), demonstrating the importance of *Foxp3* in the immune system.[13]

CTLA4 in T cell anergy

As an inhibitory receptor, cytotoxic T lymphocyte antigen 4 (*CTLA4*; *CD152*) is expressed by T cells and interacts with the costimulatory molecules B7-1 (CD80) and *B7-2* (*CD86*) and is capable of inhibiting T-cell responses and promoting long-lived anergy.[14] Knockout of germline *CTLA4* in mice represents a fatal syndrome with lymphocyte infiltration of multiple organs and severe enlargement of lymphoid organs.[15] Several autoimmune diseases, such as type 1 diabetes and Graves' diseases, are demonstrated to be associated with *CTLA4*, although the exact function has not been defined.[16]

FAS and lymphocyte apoptosis

Fas (CD95), the prototype of a death receptor of the tumor necrosis factor (TNF) receptor family, plays a role in the deletion of mature T and B cells that recognize self antigens.[17] The Fas ligand binding with its receptor induces apoptosis. Fas ligand/receptor interactions play a critical role in the process of the immune system. For example, activated T cells express the Fas ligand. During clonal expansion, activated T cells are initially resistant to Fas-mediated apoptosis and will become progressively sensitive, ultimately leading to activation-induced cell death (AICD). This process is vital to prevent an excessive immune response and eliminate autoreactive T cells. Mutations of Fas will lead to a childhood disorder of apoptosis called autoimmune lymphoproliferative syndrome (ALPS).[18]

EPIGENETIC INFLUENCE ON T AND B LYMPHOCYTE TOLERANCE TO SELF

Genetic background is essential to understand the onset of diseases, but it is insufficient for the full explanation. The incomplete concordance rates of autoimmune diseases in monozygotic twins also strongly suggest that other factors, such as environmental triggers, are involved in the pathogenesis of autoimmunity. Epigenetics refers to heritable genomic expression without alterations in the original DNA sequence, consisting of DNA methylation, histone modifications and microRNA (miRNA) regulations. Studies show that DNA methylation and the post-translational modification of histones are potentially responsible for the breakdown of immune tolerance and autoimmune disorders.

T and B lymphocytes are key players for immune responses, and during the T and B lymphocyte differentiation process, the regulation of each progression step is influenced by a potent network of transcription factors specific for each particular cellular state. Recent studies indicate that both T and B lymphocyte development are under epigenetic regulations.

DNA methylation

In naive $CD4^+$ and $CD8^+$ T cells, DNA hypermethylation in the promoter of IL-2 and IFN-γ was identified, suggesting that the defect in IL-2 and IFN- γ production is independent of clonal selection.[19] Similarly, CpG residues at the IL-2 promoter and enhancer are also methylated in tolerant T cells.[20] The loss of DNA methyltransferase Dnmt1 results in the overproduction of IL-2, Th1 and Th2 cytokines.[21]

Table 1 Genes related to loss of tolerance in autoimmunity

Gene	*Autoimmune disease*	*Function*	*Reference*
AIRE	APS-1	Downregulates self-antigens in the thymus, resulting in defective negative selection of self-reactive T cells	7,8
Foxp3	IPEX	suppresses $CD4^+$ $CD25^+$ regulatory T cells	13
CTLA4	Graves' disease type 1 diabetes	Inhibits T cell responses and promotes long-lived anergy	15
FAS	ALPS	Failure of apoptotic death of self-reactive B and T cells	17

During the process from lymphoid progenitors to the B cell lineage, transcription factors EBF and E2A contribute to the DNA demethylation and nucleosomal remodeling of the CD79a promoter, which is necessary for its transcriptional activation by Pax5 and is essential to the formation of pro-B cells.[22]

Histone modifications

Compared to naive T cells, when activated T cells were restimulated under anergic conditions, increased histone deacetylation was observed at the IL-2 promoter, which was associated with enhanced recruitment of HDAC1 and HDAC2.[23] Hypoacetylation at the IL-2 locus in anergic CD4 + T cells is caused by increased deacetylation and intact acetylation. The IFN-γ locus in anergic T cells is also hypoacetylated, resulting in a significant reduction of IFN-γ.[24,25] Therefore, histone hypoacetylation at the *IFN-γ* and *IL-2* gene loci function to sustain the closed chromatin structures and thus suppress transcriptional activities.

Unlike histone acetylation, histone methylation is more specific and complicated. For example, histone H3 trimethylation at lysine 27 (H3K27me3) is related to repressive chromatins whereas H3K4me3 is generally associated with permissive chromatins. In Th1 cells, H3K4me3 specifically marks IFN-γ and T-bet gene loci, whereas IL-4 and Gata-3 loci are imprinted with H3K27me3.[26]

During the stage from the pre–pro-B cell to pro-B cell, E2A-associated genes, such as EBF and FOXO1, are modified by H3K4me, a mark of gene enhancer elements. The activation of *EBF* and *FOXO1* will lead to histone modifications of H3K4me3 on Pax5.[27]

MicroRNAs

During B-cell development and differentiation, miR-181, miR--150, and miR34a help target and repress transcripts critical for genes involved in B-cell generation. Genome-wide miRNA scans during lymphopoiesis lead to the identification of miRNAs that are primed for expression at different stages of differentiation, including the repressive mark H3K27me3 associated with gene silencing of lineage-inappropriate miRNA and the presence of the epigenetically active mark H3K4me. During B cell lineage specification, miR-320, miR-191, miR-139 and miR28 act as potential regulators of B-cell progression.[28]

GENETIC AND EPIGENETIC INFLUENCES IN AUTOIMMUNE DISEASES

As stated above, both genetic and epigenetic factors play indispensable roles in the pathogenesis of autoimmune diseases, most of which have unknown etiology. Genetic background is a source of susceptibility for disease onset, but it is insufficient for disease development. Recent genome-wide association studies confirmed the strong genetic background for immune-related diseases, but they fail to illustrate the mechanisms underlying immune tolerance breakdown explained by genetic aspects alone.[29] Environmental factors, such as ultraviolet rays, infections, nutrition and chemicals, also participate in the pathogenesis of autoimmunity.[30] The advent of epigenetic research creates a bridge over genetics and the environment, providing a novel perspective to interpret these complex diseases. Tables 2 and 3 list epigenetic and genetic changes in autoimmune diseases.

Genetic and epigenetic influences on SLE

SLE is a systemic, multiple-organ involved autoimmune disease with a spectrum of clinical manifestations and outcomes, characterized by the production of pathogenic autoantibodies targeting nucleic acids and their binding proteins. It is a typical model of a global loss of tolerance with the activation of autoreactive T and B cells.[31]

Genetic factors of SLE. Genetic contributions to human lupus are well-established based on the fact that there is a significant difference in disease concordance between monozygotic twins (25–57%) and dizygotic twins (2–9%).[32] Chromosome 1 consists of some of the loci most consistently recognized in SLE. The linkage interval 1q23 encodes Fcγ receptors FCGR2A and FCGR3A. The variants of different affinities for IgG and its subclasses of FCGRs contribute to incomplete clearance of immune complexes, leading to deposition in the kidney and blood vessels.[33] Other disease-associated genes on chromosome 1 are *PTPN22*,[34] *IL10*[refs 35,36] and *C1Q*.[37]

Genes encoding the major histocompatibility complex (MHC) and components of the complement pathway (C2, C4) and TNFα and TNFβ reside in chromosome 6, and their polymorphisms have been demonstrated to be susceptible to SLE.[38,40] Programmed cell death 1 gene (*PDCD1*) is upregulated in T cells, inhibiting TCR signaling and T/B cell survival. It is implicated that one intronic SNP in *PDCD1* is associated with the development of SLE in Europeans. The SNP alteration on the associated allele affects the binding site for the runt-related transcription factor 1 (*RUNX1*), suggesting a contribution to the development of SLE in humans.[41] CTLA4, a negative costimulatory molecule, inhibits T cell activation and may limit T cell responses under inflammation. Genetic variability in *CTLA4* has also been linked to SLE development.[41,42]

Epigenetic factors of SLE. Global DNA hypomethylation in T cells is a characterized epigenetic feature in SLE, resulting in the activation of transcription and close correlations with disease activity.[43] Numerous studies have validated the critical roles of T cell DNA hypomethylation in the pathogenesis of SLE.[44,45] Hypomethylation at specific regulatory regions of DNA is the reason for the overexpression of autoimmune-associated genes in lupus CD4+ T cells, contributing to the pathogenesis and development of SLE. CD11a, CD40L and CD70 are well-known examples.[46–48] Lupus-associated inflammatory cytokines, such as interleukin (IL)-4 and IL-6, are epigenetically regulated by DNA demethylation.[49] During T cell activation and differentiation, DNA methylation of specific genes plays vital roles in the process. For example, *Foxp3*, a

Table 2 Epigenetic modifications in autoimmune diseases

Diseases	*Epigenetic modifications*	*Influence*	*Ref.*
SLE	Hypomethylation of CD11a (ITGAL), CD40L (TNFSF5) and CD70 (TNFSF7)	Contributes to the overexpression of CD11a, CD40L and CD70	31–33
	Hypomethylation of IL-4 and IL-6	Increases IL-4 and -6mRNA transcriptions	34
	Hypomethylation of Foxp3	Induction of Foxp3 expression	35
	H3 and H4 acetylation and H3K4 dimethylation of TNFSF7	Increases CD70 expression on T cells	36
	deacetylation of histone H3K18 of CREMα	silences IL2 gene expression	37
	Increased miR-21, miR-126 and miR148a	Inhibits DNMT1 expression	38,39
	Increased miR-142 and miR-31	Inhibits IL-4, IL-10, CD40L and ICOS expression and stimulates IL-2 production	40
	Overexpression of miR-30a	Reduction of Lyn	41
RA	Demethylation of the IL-6 promoter in PBMCs	Overexpression of IL-6 in serum, synovial tissue, and synovial fluid	42
	Hypomethylation of CXCL12 in synovial fibroblasts	Promotes matrix metalloproteinases and joint destruction	43
	Increased H3K4me3 in MMP-1, MMP-3, MMP-9 and MMP-13 and decreased H3K27me3 in MMP-1 and MMP-9	Regulates the transcription of MMPs in synovial fibroblasts	44
	Increased histone acetylation of MMP-1 and IL-6	Up-regulates MMP-1 and IL-6 in synovial fibroblasts	45,46
	Overexpressed miRNA-155 and 146a in synovial fibroblasts	miRNA-155 targets PU.1 and inhibits its expression; miRNA-146a targets IRAK1 and TRAF6 and suppresses their expression	47
	Decreased miRNA-124a	Targets MCP1 and CDK2 and increases their expression	48
	Increased miRNA-223	Suppresses IGF-1R-mediated IL-10	49
T1D	Increased global DNA methylation level in LADA	Accompanied by upregulated expression level of DNMT3b	50
	Hypermethylation of UNC13B	Indicated with the risk of diabetic nephropathy in T1D	51
	Genome-wide histone H3K9me2 in peripheral lymphocytes and monocytes	Increase in methylation level in H3K9me2 in several high-risk genes for T1D including the CTLA4 gene	52
	Increased miR-326 in PBMCs	Positively correlated with disease severity	53
	Downregulated miR-146	Upregulates the expressions of TNF receptor-associated factor 6 (TRAF6), B-cell CLL/lymphoma 11A (BCL11A), syntaxin 3 (STX3) and numb homolog (NUMB)	54
PBC	Hypermethylation of ATP12A, ATP5A1 and HOXD4	Involved in ion channel transport and transport of bile salts	55
	DNA demethylation of CD40L	Inversely correlated with IgM serum level	56
	Upregulated histone H4 acetylation in the promoter regions CD40L, LIGHT, IL17 and IFNG	Increased expression of these genes	57
	Downregulated histone H4 acetylation in the promoter regions of TRAIL, Apo2 and HDAC7A	Decreased expression of these genes	57
	Downregulation of miR-122a and miR-26a and increased expression of miR-328 and miR-299-5p	Affects cell proliferation, apoptosis, inflammation, oxidative stress, and metabolism	58
	Upregulated expression of miR-506	Decreases the level of InsP3R3	59

gene for maintaining Treg cell function, is also closely controlled by DNA methylation.[50] Additionally, transcription factors may participate in the regulation of DNA methylation. The down-regulation of RFX1 found in transcript factors screening in SLE CD4+ T cells inhibits the recruitment of DNMT1 and histone deacetylase 1 (*HDAC1*) to the promoter regions of *CD70* and *CD11a*, leading to DNA hypomethylation and histone H3 hyperacetylation at these promoters.[51] Growth arrest and DNA damage-induced 45alpha (*Gadd45a*) functions reduce the epigenetic silencing of genes via removing methylation marks. Upregulated Gadd45a in CD4+ T cells from SLE patients promotes DNA demethylation and stimulates the expression of methylation-sensitive genes including *CD70* and *CD11a*.[52] High mobility group box protein 1 (*HMGB1*) may also be involved in DNA demethylation by binding to Gadd45a.[53]

Histone modification is another important epigenetic mechanism for regulating gene expression. Global hypoacetylation of histone H3 and H4 has been discovered in lupus CD4+ T cells.[54] CD70 overexpression on T cells occurs partly because of aberrant histone modifications within the TNFSF7 promoter.[55] Transcription factor cAMP-responsive element modulator (CREMα) mediates silencing of the IL2 gene in SLE T cells though the deacetylation of histone H3K18 and DNA hypermethylation.[56] In addition to T cells, significant alterations of H3K4me3 in various key candidate genes was

Table 3 Genetics of autoimmune diseases

Diseases	*Genes*	*Chro.*	*Influences*	*Ref.*
SLE	*FCGRs*	1q23.3	Contributes to the incomplete clearance of immune complexes	60
	PTPN22	1p 13.3–13.1	Increases the formation and deposition of immune complexes	61
	IL10	1q 31–32	Suppresses expression of proinflammatory cytokines	62,63
	C1Q	4 D3	Associated with neuropsychiatric SLE	64
	TNFα	6p 21.33	Regulates inflammation and apoptosis	65
	TNFβ	6	Represents a risk factor in Korean SLE and nephritis in patients with SLE	66
	PDCD1	2q 37.3	Affects the binding affinity and activity of NFkB and RUNX1	64
	CTLA4	2 q33	Mediates antigen-specific apoptosis of T cells and suppresses autoreactive proliferation of T lymphocytes	67,68
RA	*PTPN22*	1p 13.3–13.1	Enhances neutrophil effector functions	69
	IL23R	1p31.3	Over-expression in the synovial fibroblasts and plasma	70
	TRAF1	9q33.2	Negatively regulates Toll-like receptor signaling	71
	CTLA4	2q33.2	Contributes to susceptibility	72
	IRF5	7q32.1	Mediates proinflammatory cytokine production	73
	STAT4	2q32	Overexpression in peripheral blood leukocytes and synovial fluid cells	74
	CCR6	6q27	Mutations in CCR6 result in either a gain or loss of receptor function	75
	PADI4	1p36.13	Protects fibroblast-like synoviocytes from apoptosis	76
T1D	*CTLA4*	2 q33	Involved in immune tolerance	77
	PTPN22	1p 13.3–13.1	Modulates intracellular signaling	78
	IL2RA	10p15.1	Involved in Treg cell suppressive function	48
	CLEC16A	16p13.13	Protective factor of T1D	48
	STAT4	2q32	Influences cytokine signaling	49
PBC	*IL12A*	3q25.33	Contributes to susceptibility	79
	IL12RB2	1p31.3	Contributes to susceptibility	79
	STAT4	2q32	Contributes to susceptibility and ANA status in the Japanese population	54
	DENND1B	1q31	Contributes to susceptibility	80
	CD80	3q13	Contributes to susceptibility	81
	IL7R	5p13	Contributes to susceptibility	81
	CXCR5	11q23	Contributes to susceptibility	82
	TNFRSF1A	12p13	Contributes to susceptibility	82
	CLEC16A	16q24	Contributes to T cell hyporeactivity	83
	NFKB1	4q24	Contributes to susceptibility	82

observed in lupus PBMCs,[57] and altered global H4 acetylation was found in lupus monocytes.[57]

miRNAs are a large group of small, non-coding RNAs that function as post-transcriptional and posttranslational regulators of gene expression by binding to the 3′-untranslated region (UTR) of the mRNA of a target gene. Based on the different cell types and tissues in lupus, aberrant expression of miRNA can be observed in T cells, B cells, dendritic cells and serum. For example, increased miR-21, miR-126 and miR148a were found in SLE T cells and DNMT1 is their target, contributing to DNA hypomethylation in SLE CD4+ T cells.[58,59] miR-142 and miR-31 are believed to regulate T cells by inhibiting *IL-4*, *IL-10*, *CD40L* and *ICOS* expression and stimulating IL-2 production, respectively.[60] A recent study on the pharmacological mechanisms of mycophenolic acid (MPA) on CD4+ T cells in SLE patients shows that miR-142 and miR-146a expression was increased after MPA activation through histone modification at the promoter region.[61] In SLE B cells, the over-expression of miR-30a is responsible for the reduction of Lyn, suggesting that miR-30a plays an important role in B cell hyperactivity.[62]

Genetic and epigenetic influences on RA

RA is a chronic and systemic autoimmune disease characterized by chronic inflammation and the destruction of peripheral joints. As discovered in other autoimmune diseases, such as SLE, the development of RA also requires the combination of genetic susceptibility factors and environmental influences.[63,64]

Genetic factors in RA. Genetic factors contribute to the development of at least 50% of RA patients based on the data of familial and twin studies, and the concordance rate in monozygotic twins is 12–30%. The prevalence of RA is also high in first-degree relatives.[65] HLA genes at 6p21 and HLA-DRB1 allele variants are closely associated to RA.[66] In addition to the HLA loci, many other genes related to RA have been recognized. Thanks to the development of GWAS and single-

nucleotide polymorphism (SNP) array genotyping, numerous candidate genes have been identified,[67] but few have been studied for their biological function. The most relevant non-HLA genes associated with RA include *PTPN22*,[68] *IL23R*,[69] *TRAF1*,[70] *CTLA4*,[71] *IRF5*,[72] *STAT4*,[73] *CCR6*[ref. 74] and *PADI4*.[71,75]

Epigenetic factors in RA. DNA methylation status in blood cells, synovium and synovial fibroblasts in RA has been investigated. Although a global hypomethylation in T cells from RA patients has been observed, there is no proof of the association between methylation levels and disease activity.[76] However, changes in DNA methylation in RA synovium and synovial fibroblasts have been reported. A genome-wide evaluation of DNA methylation loci in fibroblast-like synoviocytes (FLS) isolated from the area of the disease in RA was performed. Compared to osteoarthritis (OA), 1 859 differentially methylated loci, mostly associated with immune cell trafficking, cell adhesion, and extracellular matrix interactions, were revealed in the FLS of RA.[77] A global DNA hypomethylation in RA synovial fibroblasts has also been demonstrated.[78] Furthermore, methylation changes of a single gene also participate in the pathogenesis of RA. For example, demethylation of the IL-6 promoter in PBMCs from patients with RA results in the over-expression of IL-6,[79] which occurs in the serum, synovial tissue, and synovial fluid from patients with RA.[80] Hypomethylation of *CXCL12* in RA synovial fibroblasts promotes matrix metalloproteinases and joint destruction.[81]

The complexity of histone modifications gives rise to difficulties in investigating their exact mechanisms in RA, and studies were limited in the extent of the expression of histone-modifying enzymes. Conflicting data on the expression of HDACs in PBMCs and synovial tissues in RA patients were published, partly because of the diverse HDAC activities influenced by disease activity and therapy in patients enrolled in these studies.[82–85] In synovial fibroblasts, increased expression of H3K4me3 in the promoters of *MMP-1*, *MMP-3*, *MMP-9* and *MMP-13* and decreased expression of H3K27me3 in the promoters of *MMP-1* and *MMP-9* were obsevered.[86] Moreover, increased histone acetylation leads to up-regulations of *MMP-1* and *IL-6* in synovial fibroblasts.[87,88] These epigenetic changes provide a reasonable explanation for the over-expression of *MMPs* and *IL-6* in RA synovial fibroblasts.

In 2008, compared to OA patients, the first screening of differentially expressed miRNAs identified overexpressed miRNA-155 and 146a in synovial fibroblasts from RA patients.[89] A recent study revealed that the target of miRNA-155 is PU.1, a transcription factor in early B cell commitment, which is downregulated during B-cell maturation. The repression of endogenous miRNA-155 levels in B cells of RA patients results in the upregulation of PU.1 and the downregulation of the antibody production.[90] Components of the toll-like receptor pathway, IRAK1 and TRAF6, are targets of miRNA-146a, but there is no difference in their levels in PBMCs from RA patients and healthy controls,[91] indicating that increased miRNA-146a alone is insufficient to restrain inflammation. Compared to OA synovial fibroblasts, miRNA--124a, which targets monocyte chemoattractant protein 1 (MCP1) and cyclin-dependent kinase 2 (CDK2), was decreased in RA, leading to decreased proliferation of synovial fibroblasts.[92] The only deregulated miRNA in the peripheral T lymphocytes of RA patients was miRNA-223, which is positively correlated with rheumatoid factor (RF) titers.[93] Furthermore, increased miRNA-223 levels suppressed the insulin-like growth factor 1 receptor (IGF-1R)-mediated IL-10 production in T cells from RA patients.[94]

Genetic and epigenetic influences on T1D

T1D is an autoimmune disease resulting from T cell-mediated β cell destruction in genetically susceptible individuals with involvement of both genetic and environ-mental factors.[95]

Genetic factors in T1D. T1D is one of the most common heritable diseases, although a positive family history of T1D is confirmed in only 10 to 15% of newly diagnosed patients. To date, more than 50 susceptibility regions have been recognized to be linked with T1D. In T1D, the HLA class II alleles (primarily the HLA-DRB1, HLA-DQA1 and HLA-DQB1 loci) are the main susceptibility genes, and up to 50% of them have genetic risks.[96] HLA-DRB1 and DQB1 are consistently associated with T1D in almost all ethnic groups.[97] In addition to HLA class II, HLA class I genes have also been considered to be strongly associated with T1D. Among HLA class I genes, the HLA-B*39 allele, which significantly increases the risk of T1D, has one of the strongest associations with T1D.[95] Moreover, multiple non-HLA loci also contribute to disease risks, such as *CTLA4*,[98] *PTPN22*,[99] *IL2RA*,[100] *CLEC16A*,[100] *PTPN2*[ref. 99] and *STAT4*.[101–103]

Epigenetic factors in T1D. Compared to healthy controls, the global DNA methylation level is significantly increased in CD4 + T cells in patients with latent autoimmune diabetes of adults (LADA), accompanied by the upregulated expression level of DNMT3b.[104] The DNA methylation level of nineteen CpG sites correlated with the time of onset of nephropathy were identified in a genome-wide DNA methylation analysis of T1D patients with diabetic nephropathy, and one of the CpG sites located nearby gene *UNC13B* has been indicated to reflect a risk of diabetic nephropathy in T1D.[105]

Studies have revealed that HDAC expression was aberrant in T1D patients. Decreases in H3K9Ac at the upstream promoter regions of HLA-DRB1 and an increase in H3K9Ac at the upstream promoter/enhancer region of HLA-DQB1 were noted in patients with T1D and healthy controls, and both genes are highly associated with T1D.[106] Upregulated acetylated histone H4 levels were associated with T1D patients without vascular complications, suggesting a protective role against vascular injury in T1D.[107] Genome-wide histone H3K9me2 patterns in peripheral lymphocytes and monocytes from T1D patients and normal controls were compared, presenting a significant

increase in methylation levels of H3K9me2 in several high-risk genes for T1D, including the *CTLA4* gene.[108]

Accumulating data support a role for miRNA in the development of T1D. miR-326 was found to be significantly increased in PBMCs from patients with T1D and positively correlated with disease severity, playing important stimulatory effects toward the development of T1D by targeting important immune regulators.[109] Downregulated miR-21a and miR-93 were noticed in the PBMCs of T1D patients in the presence of incubation with glucose; however, no association with autoimmunity was observed.[110] Global miRNA profiles in PBMCs from newly diagnosed T1D patients revealed that the most downregulated miRNA, miR-146, was associated with the ongoing autoimmune imbalance in T1D.[111]

Genetic and epigenetic influences on PBC

PBC, which is associated with both genetic and environmental factors, is a chronic, cholestatic autoimmune liver disease and may progress to liver cirrhosis and eventually liver failure.[112,113]

Genetic factors in PBC. Growing evidence indicates that PBC is a genetic-related condition, which was supported by familial clustering, the monozygotic twin concordance and the high prevalence of other autoimmune disorders in PBC patients and their family members.[114] Similar to many other AIDs, the major genetic elements of PBC are found within the HLA region. The HLA class II DRB1*08 allele family shows the strongest association between specific HLA alleles and PBC susceptibility.[115] Other loci, such as HLA DRB1, DQB1, DPB1, DRA, and c6orf10, are also strongly related to PBC susceptibility, as implicated in a GWAS study.[116] Interestingly, specific class II HLA alleles function to protect against PBC, such as DQA1*0102, DQB1*0602, DRB1*13 and DRB1*11.[115,117–119] Moreover, many non-HLA risk loci associated with PBC susceptibility have been discovered in high-throughput genetic studies, such as interleukin 12A (*IL12A*),[116] *IL12RB2* loci,[116] *STAT4*,[120] *DENND1B*,[121] *CD80*,[122] *IL7R*,[122] *CXCR5*,[123] *TNFRSF1A*,[123] *CLEC16A*[124] and *NFKB1*.[116,123]

Epigenetic factors of PBC. Recently, DNA methylation profiles in 60 differentially methylated regions corresponding to 51 genes on the X chromosome and nine genes on autosomal chromosomes were identified in twins of PBC patients and normal twins. DNA hypermethylation was observed in specific gene families such as *ATP12A*, *ATP5A1* and *HOXD4*, suggesting DNA methylation as a regulator in the pathogenesis of PBC.[125] A significant DNA demethylation level at the *CD40L* promoter is inversely correlated with IgM serum levels in CD4 + T cells from PBC patients,[126] supporting the involvement of methylation modifications of *CD40L* in the development of PBC. Thus far, histone modification dysregulation in PBC remains under investigation.

Dysregulated histone modifications of genes demonstrated in autoreactive T cells with PBC patients include upregulated histone H4 acetylation in the promoter regions *CD40L*, *LIGHT*, *IL17* and *IFNG* and downregulated histone H4 acetylation in the promoter regions of *TRAIL*, *Apo2* and *HDAC7A*.[127]

A total of 35 independent miRNAs were found to be differentially expressed in the tissues from PBC patients, with predicted targets belonging to cell proliferation, apoptosis, inflammation, oxidative stress, and metabolism. The downregulation of microRNA-122a (miR-122a) and miR-26a and the increased expression of miR-328 and miR-299-5p were validated.[128] One example is miR26-a, contributing as a post-transcriptional regulator of the overexpression of a polycomb group protein EZH2 in PBC.[129,130] One miRNA for a PBC target cell (cholangiocytes) is miR-506,[131] which is capable of regulating pH homeostasis by decreasing the level of InsP3R3, an intracellular Ca channel.[132]

CONCLUSION

Great progress in understanding the development and pathogenesis of AIDs has been made in recent decades, particularly with the advent of epigenetic research, which has created a bridge between genetic and environmental factors. It is believed that both genetic and epigenetic factors influence the process and development of immune tolerance on different levels. However, an exact and full picture of the network related to gene expression and epigenetic modifications on the mechanisms of loss of tolerance is urged to provide new perspectives on autoimmunity.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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