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Association of Immune-Related Genetic and Epigenetic Alterations with Lupus Nephritis

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Abstract
Background: The familial clustering phenomenon together with environmental influences indicates the presence of a genetic and epigenetic predisposition to systematic lupus erythematosus (SLE). Interestingly, regarding lupus nephritis (LN), the worst complication of SLE, mortality, and morbidity were not consistent with SLE in relation to sexuality and ethnicity. ***Summary:*** Genetic and epigenetic alterations in LN include genes and noncoding RNAs that are involved in antigen-presenting, complements, immune cell infiltration, interferon pathways, and so on. Once genetic or epigenetic change occurs alone or simultaneously, they will promote the formation of immune complexes with autoantibodies that target various autoantigens, which results in inflammatory cytokines and autoreactive immune cells colonizing renal tissues and contributing to LN. ***Key Messages:*** Making additional checks for immunopathology-related heredity and epigenetic factors may lead to a more holistic perspective of LN.

Introduction

The onset of systematic lupus erythematosus (SLE) is insidious, and the etiology is complex. As one of the most common complications, lupus nephritis (LN) can be manifested by proteinuria, hematuria, hypertension, edema, etc. Eugeniu et al. [1] reported that up to 6.3% of patients died within 5 years after their diagnosis of LN, a percentage which has remained stable over the last three decades despite the reduction of clinical severity in recent years [2]. In detail, according to a 2003 histological classification made by the International Society of Nephrology/Renal Pathology Society (ISN/RPS) based on microscopic lesions and immune complexes (ICs) observed in a kidney biopsy, Class III and IV LN (proliferative LN) now account for 50% and 25% of the prevalence, respectively, with the worst prognosis to end-stage renal disease (ESRD) and in urgent need of immunosuppressive treatment [3].

The progression of LN is associated with pregnancy, aging, and drug-induced nephrotoxicity. It is worth noting that the incidence of SLE across gender is approximately 9:1 (female: male). However, the incidence of LN is somewhere between 1.1:1 and 1.7:1 by male to female ratio [4]. In addition, younger people, as well as ethni-

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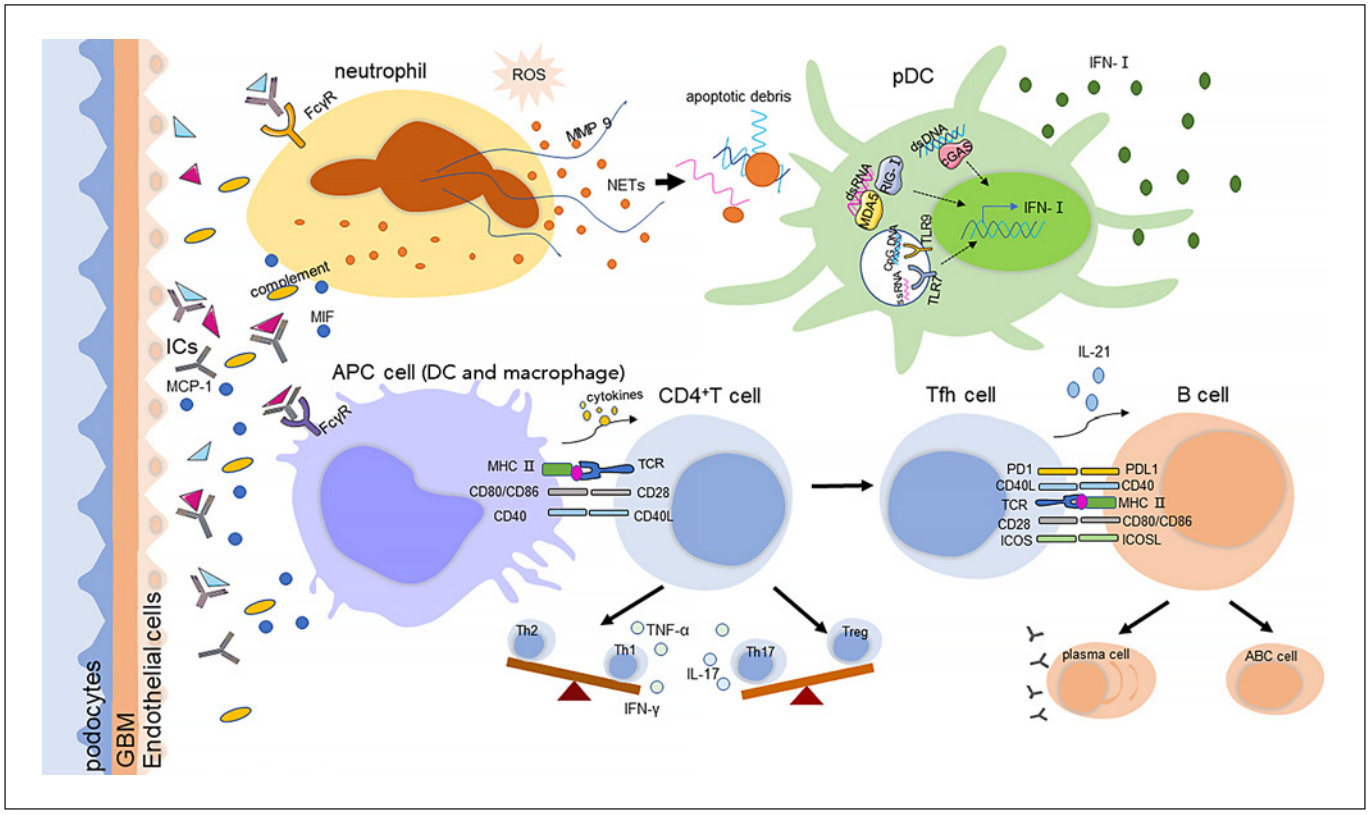

Fig. 1. The immune microenvironment of LN. Deposition of ICs in GBM triggers a series of immune responses. (1) ICs attract complements and innate immune cells which bear FcγRs to clear themselves, whereas (2) excessive neutrophils release NETs to activate pDC through IFN-I pathways; (3) excessive APCs recruit proinflammatory T and further B cells, primarily plasma B and ABCs, to form an inflammatory milieu. GBM, glomerular basement membrane; NET, neutrophil extracellular trap; ABC, age-associated B-cell; APC, antigen-representing cell, pDC, plasmacytoid dendritic cell.

cally Asian, African, or Hispanic patients, seem to have a higher probability of developing LN compared with white individuals, indicating that genetic and epigenetic alterations in LN patients may vary from those of SLE patients.

With an increasing number of targeted therapy drugs approved by the FDA, immune cell-targeting agents such as belimumab have become the new hope for SLE patients who have poor responses to glucocorticosteroids, cyclophosphamide, and other immunosuppressive agents, whereas none for LN to date [5]. In this regard, we hope to dig more possible immunotargets which are responsible for this lethal outcome of SLE instead of angiogenesis and fibrosis, which are the common targets for other kidney diseases. Moreover, we have summarized the aberrant genetic and epigenetic changes in LN immunopathology, which may pave the way for monitoring and management in the future.

Immune Mechanisms in the Pathogenesis of LN

As for the mechanism of SLE onset, much of the previous research has shown that the increase of autoreactive T and B cells as well as apoptotic debris in circulation are indispensable. We therefore see no need to discuss these processes at length here. However, due to the difference in cell components, target organ damage in lupus has a different pathophysiology and pathogenesis. Key points relating to immune mechanisms in LN flares are listed below and compiled in Figure 1.

Autoantibodies, ICs, and Complements

Although not all of the observed lupus patients had LN, almost all patients had deposition of ICs in the mesangial region [6], primarily IgG derived. In the past, ds-DNA antibodies in serums have served as a strong indicator of renal damage for lupus. Some ICs originate from

circulation, while planted [7] and locally distributed autoantigens such as α-enolase and annexin AI attract anti-DNA antibodies to form IC and deposits further in the glomerular basement membrane, which constitute another part of kidney IC. Complements and cells expressing Fc receptors (FcγRs), a receptor for IgG, will then be activated to clear ICs. Excessive myeloid cells [6, 8] and platelets [9] bearing stimulatory FcγRs in LN, which can also be potentiated by a complement, will degranulate and release reactive oxygen species. Finally, immune cells are recruited leading to damage of the endothelial and epithelial cells and renal fibrosis.

The Infiltration of Innate Immune Cells

Macrophages are the dominant immune cells in the kidney and include the resident cells in the renal interstitium as well as the infiltrating cells around the glomeruli [10]. Macrophage migration-related cytokines such as monocyte chemotactic protein 1 and macrophage migration inhibitory factor are secreted by damaging tubular cells and have been deemed one of the markers of LN. Trajectory analysis of monocytes/macrophages within the kidney suggested that patrolling, phagocytic, and activated monocytes were present in the progressive stages of monocyte differentiation in situ [10]. Generally, macrophages are thought to play different roles in their inflammation and repair states, M1 and M2, respectively. M1 secretes inflammatory cytokines and is skewed by Toll-like receptors (TLRs) and danger-associated molecular patterns [11]. A noteworthy observation is that TLRs not only directly influence macrophages but also facilitate the renal endothelium to recruit monocytes [12]. Previous studies have observed increasing expression of TLR 3, 7/8, 9, both in the mouse model and in human renal biopsies of LN [13].

After neutrophils are activated by FcγRs and produce reactive oxygen species, neutrophil extracellular traps containing DNA, histone, MMP9, and other nuclear materials release and promote type I interferons (IFN-I) produced mainly by plasmacytoid dendritic cells (pDCs) [14]. Apoptotic debris taken up by DCs can be further lysed into single-stranded or double-stranded DNA/RNA (ssDNA/RNA, dsDNA/RNA). Unrestricted DNA and RNA in the cytosol is a dangerous signal and can be sensed by specific sensors such as TLRs, cyclic GMP-AMP synthetase (cGAS), or melanoma differentiation associated gene 5 (MDA5), which results in activation of downstream IFN-regulatory factor 3 (IRF3)–IRF7 to produce IFN-I [15, 16]. Multiple articles have illustrated that abnormal expression of interferon-stimulated genes in SLE such as MX1 [17] and IFI44L [15, 18, 19] is related to the severity of LN flares. More importantly, a high IFN-response signature in tubular cells is even associated with poor treatment efficacy [20].

The Infiltration of Adaptive Immune Cells

T and B cells are often present in crescentic glomerulonephritis. Aggregations of T and B cells are tightly associated with low levels of estimated glomerular filtration rate and renal tubular function [21]. With the advent of single-cell techniques, the transcriptome of immune cells in lupus-affected kidneys has been shown to be distinct from those of the peripheral circulatory system. Recent research reveals that compared to excessive plasma cells in the peripheral blood, not only B cells in the kidneys are differentiated to plasma cells but also that activation of local B cells is more likely to correlate with the expression of the BCR/TLR signaling-mediated age-associated B-cell (ABC) signature [10]. In terms of T cells and follicular helper T cells (Tfh), a B-cell helper, which are all differentiated from naïve $CD4^+$ T cells, is believed to contribute to the severity of LN [10, 22]. Interestingly, markers of Tfh and Treg cells like PDCD1 and FOXP3 were found to be co-clustered in situ, suggesting T follicular regulatory cells (Tfr) may also be present and protect the kidney from damage [10].

Genetic Risk of LN

It is postulated that the risk of SLE is determined by the amount of risk-associated single nucleotide polymorphisms (SNPs) and their log odds ratios, which can be summarized by a genetic risk score (GRS) [23]. Studies have been increasingly devoted to research on the relationship of GRS with SLE's occurrence, manifestation, severity, and prognosis. Among the many SLE clinical phenotypes, only LN has been specially designated as being genetically associated and observed to have significant differences in outcome based on a patient's racial background. Chen et al. [23] recently reported that GRS could predict SLE in both European and Chinese populations and correlates with a younger age-of-onset, LN, and poorer prognosis, consistent with findings of Reid et al. [24] and Dominguez et al. [25]. In Europeans, the associations between high GRS and LN even increased when narrowing cases to adult-onset, proliferative LN, or ESRD [25].

Major Histocompatibility Complex Loci

The present evidence indicates a super-hot spot, the human major histocompatibility complex (MHC) region, which is located on a segment of chromosome 6 (6p21.3). This region, about 25–32 Mb and responsible for encoding more than 200 genes many of them with a specific immunological role, participates in the development of autoimmunity, infection, and transplantation [26]. Previous studies have demonstrated that the heterogeneity in this region is its most established characteristic and it exists in almost all SLE and LN patients regardless of ethnicity [27, 28]. Among several MHC haplotypes, HLA DR2 (HLADRB1*1501, DQA1*0102, and DQB1*0602) and HLA DR3 (DRB1*0301, DQA1*0501, and DQB1*0201) which are primarily located in MHC class II, were the most frequently reported [29–31]. Prithvi et al. [30] showed that the risk haplotype of HLA-D induces higher surface expression of HLA II after activation of TLR pathways and the differentiation of DCs. Meanwhile, to lessen linkage disequilibrium influence, the GWAS study also showed that HCG27, located in the MHC class I region, which is independent of HLA-DR2 and HLA-DR3, is associated with LN [29]. In addition, HLA-DR4 and DR11 alleles were identified as protective factors for LN [32]. Several studies also revealed that polymorphism in the tumor necrosis factor (TNF) gene in this region is linked to LN susceptibility [33, 34].

Non-MHC Loci

As an initial factor in complement activation, C1q plays an important role in LN. C1q-deficient mice could develop LN-like phenotypes [35], while anti-C1q IgG2 can be detected in renal biopsies of up to 70% LN patients [7]. C1q-encoded genes, C1QA, C1QB, and C1QC, are located at chromosome 1p34.1–36. According to the genotype of C1QA polymorphism, the G allele for rs665691 and A allele for rs172378 were protective against nephritis [36, 37], while the A allele of rs292001 seems to be the risk factor for juvenile LN in Egypt [38].

APOL1 risk variants, the G1 (rs73885319 and rs60910145) and G2 (rs71785313) alleles, are tightly correlated only with LN and not with SLE patients, especially for African Americans and ESRD [39]. Notably, the time to ESRD progression is even shorter in those with 2 risk alleles [39]. APOL1 encodes apolipoprotein L-1, which is an abundant component in high-density lipoproteins. Apart from LN, SNPs are also represented in patients with virus-associated collapsing focal segmental glomerulosclerosis [40]. Furthermore, TLR3, IFN, and related cellular sensors such as RIG-I and cGAS could possibly upregulate APOL1 expression. This indicates APOL1's role in innate immunity and antiviral activities. Functional studies also show that APOL1 risk variants confer autophagic deficiency but increased pyroptosis in podocytes [41].

Other findings have also revealed the significance of non-MHC loci (shown in Table 1). Most of them are related to the following vital pathways of LN [6, 42]: complements, phagocytosis, the clearing of ICs (FCGR2B [43], FCGR3B [43], FCGR2A [43], FCGR3A [44], PADI4 [45]), interferon pathways (IRF5 [46], STAT4 [24, 47, 48], IFN3/4 [49], etc.), T and B cell development and signaling (TNFSF4 [42], TL1A [50], IKZF1 [51]), etc. There were also some protective haplotypes in non-MHC regions, such as ACA of P2X7R gene [52] and GTTCTAA of CD40 gene [53]. In a research study conducted with a sample of 109 Korean LN patients (classes III–V), poor responses to cyclophosphamide were related to polymorphisms in the FCGR2B-FCRLA (1q23) locus [54]. Chung et al. [29] integrated 3 large GWAS studies and reported the prevalence of several independent susceptibility genes, such as chemotaxis-related HAS2 and apoptosis-related SLC5A11, which provide even stronger directionality to LN patients compared to lupus patients without nephritis in unrelated European women than the MHC region.

TLRs express both in immune (antigen-representing cells and B cells) and nonimmune cells (endothelial cells, renal mesangial cells). They function by sensing different pathogen-associated molecular patterns and activating downstream JAK/STAT and NF-κB pathways to release cytokines. TLR3, TLR7/8, and TLR9 are the receptors of dsRNA, ssRNA, and unmethylated ssDNA, respectively. SNPs located at TLR3 rs3775291 and rs3775294 [55], TLR7 rs3853839 [55, 56], TLR9 rs352139 [57], and rs352140 [57, 58]. However, some studies also pointed out that the genetic change among TLRs correlates with SLE but not with LN [59–61]. The occurrence of genetic alterations in TLRs with LN is still controversial.

Epigenetic Risk of LN

The environment-gene interaction is usually linked by a bridge, epigenetics. Epigenetics refers to an alteration that occurs on a chromosome without altering the DNA sequence. DNA methylation, chromatin remodeling through histone modifications, and noncoding RNAs (ncRNAs) are the three most extensively studied and

Table 1. Immunogenetics of LN

Locus	Location	SNP	Method	Ancestry	Reference
(A) MHC region					
C6orf10, NOTCH4	6p21.32	rs9267972	GWAS	European women	[29]
HLA-DRB1*1501	6p21.32	rs9271366	GWAS	European women	[29]
HLA-DRB1*0301	6p21.32	rs2187668	GWAS	European women	[29]
			GWAS	European	[27]
HCG27	6p21.33	rs9263871	GWAS	European women	[29]
TNF	6p21.33	rs1800629	TaqMan SNP genotyping	Chinese	[34]
		rs1800750	TaqMan SNP genotyping	Mexican	[33]
(B) Complements, ICs, and phagocytosis					
FCGR2B-FCRLA	1q23.3	rs6697139, rs10917686, rs10917688	GWAS	Korean	[54]
FCGR3A	1q23.3	rs115866423	Pyrosequencing	African American	[44]
FCGR2B	1q23.3	Haplotype 2B.4 (negative association)	Multiplex ligation-dependent probe amplification	Caucasian	[43]
C1QA	1p36.12	rs292001	RFLP SNP genotyping	Egyptian children	[38]
		rs172378	TaqMan SNP genotyping	Bulgarian	[37]
ITGAM	16p11.2	rs1143679	Illumina custom bead system	European	[42]
		rs1143679, rs1143683	GWAS	Chinese and Thai	[111]
(C) Monocytes, T-, and B-cell development and signaling					
HAS2	8q24.12	rs7834765	GWAS	European women	[29]
TNFSF4	1q25.1	rs2205960	Illumina custom bead system	European	[42]
MCP-1	17q12	A-2518G	RFLP SNP genotyping	Brazilian	[100]
IKZF1	7p12.2	rs1456896	TaqMan SNP genotyping	Chinese	[51]
		rs4917014	GWAS	Chinese	[101]
(D) Interferon pathways					
IFNL3/4	19q13.2	rs8099917, rs12979860, rs4803217, ss469415590	TaqMan SNP genotyping	Chinese	[49]
STAT4	2q32.2-q32.3	rs7574865	GoldenGate SNP genotyping	Japanese women	[47]
			GWAS	European	[48]
IRF3	19q13.33	rs7251	GWAS	Chinese	[102]
APOL1	22q12.3	rs73885319, rs60910145, rs71785313	GWAS	African American	[39]
(E) Neutrophil activation					
PADI4	1p36.13	rs1635564, rs11203366, rs11203367, rs874881, rs2240340, rs11203368	In-house multiplex luminex assay	Danish	[45]
IL-8	4q13.3	T-845C	RFLP SNP genotyping	African American	[103]
(F) Cell apoptosis					
SLC5A11	16p12.1	rs274068	GWAS	European women	[29]
P2X7R	12q24	rs2230911	TaqMan SNP genotyping	Chinese	[52]

MCP-1, monocyte chemotactic protein 1.

best-characterized epigenetic processes, while our understanding of RNA methylation (RNAm) is emerging only now. Epigenetic changes could happen in PBMCs, serum/plasma, urine, renal tissues, etc. Different stages of disease progress represent different epigenetic changes. For example, hypermethylation was observed in pDCs of severe LN patients, while H3K4me3 and H3K27me3 were markedly decreased in the early stage of LN [62], indicating the possible roles of epigenetics in the precise diagnosis and treatment of lupus.

DNA and RNA Methylation

Global levels of DNA hypomethylation in the T cells have long been recognized as characteristics of lupus and other autoimmune diseases. Among all the targeted genes, interferon-stimulated genes were the most frequently reported. More importantly, our group reported the hypomethylation of two CpG sites located in the promoter region of IFI44L as biomarkers for diagnosing SLE with high sensitivity and specificity (both above 95%) [19]. We found that the methylation levels of IFI44L pro-

moters were significantly lower in SLE patients with renal damage than in those without renal damage, indicating the potential for phenotype-specific differentially methylated CpG sites (DMCs). The canonical hypomethylated genes in lupus T cells also include CD40L, CD70, CD11a, etc. Specifically, inhibiting DNA methyltransferases in T cells [63], or administering CD40 antagonist [64], ameliorates proteinuria and restores glomerular morphology in lupus-like mice. The therapeutics used to target immune-related epigenetics in preclinical studies of LN are summarized in Table 2.

Like the GWASs, epigenome-wide association studies (EWASs) aim to identify epigenetic variation mainly in DMCs across the whole genome [65]. An EWAS associated with LN identified 19 DMCs in 18 genomic regions (mainly located in genes regulating the response to tissue hypoxia and IFN-mediated signaling); four sites in HIF3A, IFI44, and PRR4 were replicated from $CD4^+$ T cells [66]. Patrick et al. [67] also observed similar results with more significant hypomethylation in the naïve T cells of lupus patients with renal involvement, especially for the IFN transcription factor IRF7. In addition to T cells, a 4-year longitudinal and trans-ancestral analysis of lupus patients reported that demethylation of a CpG site of GALNT18 gene in neutrophils was especially relevant to the development of LN [68].

RNAm has gained increasing importance in recent years, which includes N^6-methyladenosine (m^6A), N^1-methyladenosine, N^5-methylcytosine, pseudouridine (Ψ), etc. Similar to DNA methylation, it also requires a writer, eraser, and reader protein to guarantee this reversible process. The latest m^6A study revealed that compared to the tubulointerstitium and whole kidney tissue, significant downregulation of m^6A-related proteins was most obviously observed in glomeruli. METTL3, WTAP, YTHDC2, YTHDF1, FMR1, and FTO even comprised an m^6A regulator signature to diagnose LN [69]. Pathway analysis demonstrated the involvement of activated NK cells, MHC-I-mediated antigen processing, cytokinesis, inflammation pathways, and interferon pathways. Mining the exact interplay between different RNAm proteins and immune responses may even develop into a productive direction for LN research.

Histone Modification

Histone modification is a covalent modification of small protein "tails" from the nucleosomes (containing two of each of the core histones: H2A, H2B, H3, and H4), thereby leading to chromatin compaction or decompaction and transcription alteration. In general, H3 and H4

Table 2. Immune-related epigenetic therapies in preclinical studies of LN

Model	Target	Method	Tool	Phenotype	Effect on immunity	Reference
(A) DNA methylation						
MRL/lpr mice	DNMT	DNMT inhibitor	Nanolipogel delivery of 5-azacytidine into $CD4^+$ T cells	↓Skin and renal injury, autoantibodies	↑Tregs and cytotoxic $CD8^+$ T, ↓double-negative T cell	[63]
(B) Histone modification						
MRL/lpr mice	HDACI/II	HDAC inhibitor	Trichostatin A (TSA)	↓Spleen weight, renal function	↓Th1 and Th2 cytokines	[104]
NZB/W_{F1} mice	HDACII	HDAC inhibitor	ACY-738	↓Renal pathology	↓Plasma cell and germinal center formation	[74]
MRL/lpr mice	HDACIII	HDAC agonist	Resveratrol	↓Autoantibody, renal function, renal fibrosis	↓B cell, GC B cell	[73]
MRL/lpr mice	HDACI	HDAC agonist	Sodium valproate (VPA)	↓Skin and renal injury, autoantibodies	↓Plasma cell	[105]
(C) NcRNAs						
$Fcgr2b^{-/-}$ mice	miR-150	Knockdown miR-150	Locked nucleic acid (LNA)-anti-miR-150	↓anti-dsDNA antibody, renal function, renal fibrosis, macrophage infiltration	↓Macrophage infiltration in kidney	[84]
NZB/W_{F1} mice	miR-130b	miR-130b overexpression	miR-130b agomir	↓Renal function, renal fibrosis	↓Type I IFN pathway	[106]
MRL/lpr mice	miR-10a-3p	miR-10a-3p overexpression	miR-10a-3p agomir	↓Renal function, renal fibrosis	↓Th17/Treg ratio	[107]
$Fcgr2b^{-/-}$ mice	miR-16	miR-16 overexpression	miR-16 agomir	↓Renal injury and fibrosis	↓TLR4 signaling pathway	[82]
MRL/lpr mice	MiR-223	Knockout Mir223	$Mir223^{-/-}$ mice	↓Renal function, renal pathology	↑T cell migration and survival	[108]
BALB/c mice injected with pristane		miR-654, miR-152 overexpression	miR-654/miR-152 mimics	↓Renal function, renal pathology	↓MIF	[81, 83]

MIF, migration inhibitory factor; DNMT, DNA methyltransferase.

Table 3. NcRNAs involved in the immunopathology of LN

NcRNA	Sample	Target	Function	Reference
miR-150, circHLA-C	Renal biopsies	–	Fibrosis, inflammation, macrophages infiltration	[84, 88]
lncRNA RP11-2B6.2	Renal biopsies	SOCS1	IFN pathway	[87]
miR-130b	Renal biopsies	IRF1	IFN pathway	[106]
miR-181a, lincRNA-p21	PBMCs, urine cells	p21	Apoptosis	[109]
miR-10a-3p	PBMCs	REG3A	Th17/Treg ratio, JAK2/STAT3 pathway	[107]
miR-16	Plasma	DEC2	TLR4 signaling pathway	[82]
miR-654	PBMCs	MIF	AKT pathway	[81]
miR-155	HRMCs	CXCR5	CXCR5-ERK pathway	[110]
miR-223	Human plasma, $CD4^+$ T in MRL/lpr mice	S1PR1	T-cell migration and survival	[108]
miR-148a	B cells	BACH1,BACH2,PAX5	B lymphocyte homeostasis	[80]

MIF, migration inhibitory factor; HRMC, human renal mesangial cell.

acetylation (H3ac, H4ac) and H3 lysine4 di- or tri-methylation (H3K4me2/3) mediate chromatin decompaction and increased transcription, while H3 lysine9 di- or trimethylation (H3K9me2/3) and H3 lysine27 trimethylation (H3K27me3) lead to chromatin compaction and transcriptional repression [70, 71]. Studies of histone modification contributing to phenotypes of LN are rare. Urinary levels of histone deacetylase sirtuin-1 (Sirt1) were reported to be positively associated with disease activity in LN [72]. An inhibitor of Sirt1, resveratrol, was shown to ameliorate LN in MPL/lpr mice by deacetylating p65 NF-κB and increasing binding phosphor-p65 NF-κB to the Fcgr2b promoter, which results in the clearance of autoreactive B cells [73]. Alternatively, inhibitors of histone deacetylase 6 (HDAC6) and enhancers of zeste homolog 2, a histone-lysine N-methyltransferase, also performed well in treating LN in mice by modulating B cell and IFN-I pathways, individually, in lupus-like models [74, 75].

Noncoding RNAs

The human genome is widely transcribed, and most transcripts are ncRNAs. An ncRNA is a functional molecule that could not be translated into a protein. There are several subtypes of ncRNAs, such as microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs). Abundant research has revealed the crucial roles of ncRNAs in autoimmune and inflammatory diseases, indicating that ncRNAs may not only serve as biomarkers but also as therapeutic agents or targets [70, 71, 76, 77].

iRNAs are ncRNAs with 21–23 bases, which function by binding to the messenger RNA 3′ untranslated region. Dicer, Argonaute-2, and other cellular factors such as RNA-induced silencing complexes are also observed to degrade messenger RNA [78]. Numerous studies have revealed that dysregulated miRNAs are involved in almost all the immune mechanisms mentioned above (shown in Table 3). Zhang et al. [79] found that B cell-related miR-15b in plasma can predict disease activity and low estimated glomerular filtration rate in SLE. Apart from miR-15b, elevated miR-148a significantly relates to renal relapses by influencing B-cell homeostasis [80]. Supplementation of miRNA analogs such as miR-654 [81], miR-16 [82], and miR-152 [83] or antagonists such as LNA-anti-miR-150 [84] reduced glomerulonephritis, IC deposition, and proteinuria in lupus-prone mice. LncRNA and circRNA are two types of newly defined ncRNAs that can function as a miRNA sponge or directly influence gene transcription and translation. Some researchers have found that aberrant levels of those ncRNAs serve as novel predictors of LN, such as Lnc-FOSB-1:1 in neutrophils [85] and circRNA_002453 in plasma [86]. Mechanically, ATAC sequencing identified lncRNA RP11-2B6.2 in renal biopsies can decrease the chromatin accessibility of SOCS1 of LN, which leads to positive feedback in IFN-I production [87]. In addition, circHLA-C [88]and hsa_circ_0123190 [89] can sponge fibrotic-related miRNA, miR150, and hsa-miR-483-3p, respectively. To date, their roles in the immune pathogenesis of LN have not yet been well studied.

Crosstalk between Genetics and Epigenetics

Notably, although linkages between genetics and epigenetics are involved in lupus, most are aggregated in studies of SLE. Protein kinase C δ (PKCδ) is a crucial mol-

ecule in the pathogenesis of lupus, as its coding gene, PRKCD, is a susceptible locus for lupus. Mice lacking protein kinase C δ in T cells were shown to have lupus-like symptoms including renal damage with IgG deposition and decreased expression of DNA methyltransferase 1, possibly through its downstream ERK pathway signaling cascade [90]. In addition, genetics can also affect epigenetics directly. Several key enzymes in epigenetics [91], such as TET3 (encodes DNA demethylase), SMYD3 (encodes histone methyltransferase), and ncRNAs, such as lncRNA SLEAR [92], miR-146a [93, 94], have been reported to have SLE-associated SNPs, while miR-146a and miR-155 [95] were found to have LN-associated SNPs. Mechanically, take the miR-146a for example, with 3D chromatin structure and analysis, Hou et al. [93] demonstrated that the risk variant rs2431697, which is localized in the miR-146a enhancer, could resist to NF-κB binding, lower miR-146a expression, and eventually activate downstream IFN pathway in a monocyte-specific pathway.

Conclusion

In summary, genetic and epigenetic alterations are present in almost all aspects of the immunopathology behind LN. Currently, there are still limitations to studies of LN. For example, the genetic characteristics that may be associated with specific clinical manifestations of SLE are still understudied. Sanchez et al. [42] found that risk alleles in ITGAM and TNFSF4 were relevant to LN, FCGR2A was relevant to malar rash, and IL21 was relevant to hematological disorders. Therefore, more attention should be paid to the restricting characteristics of the enrolled SLE and LN patients to reduce false conclusions. In addition, besides aberrant immune responses, genetic alterations such as polymorphisms in adipokines [96], epigenetic alterations such as miR-422a [97], miR-26a, and miR-30b [98] in angiogenesis, lipid metabolism, fibrosis, and proliferation could also change the function of renal mesangial cells and tubular epithelial cells, influencing the progress of LN. Furthermore, in the case of LN, epigenetic research mostly focuses on ncRNAs, while studies of DNA and RNA modification and chromatin remodeling are lacking, even if lupus-related studies are abundant. Finally and perhaps most importantly, as So et al. [99] revealed that few references clarified miRNAs among different LN subclasses, the same was true with other immune-related genetic and epigenetic alterations. Hence, future studies that feature different LN subclasses or conversion between different subclasses seem necessary to elucidate the exact mechanism behind this challenging complication of SLE and to provide novel opinions for precision medicine.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Xiaole Mei and Hui Jin drafted the manuscript; Qianjin Lu and Ming Zhao revised the manuscript.

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