Journal of Translational Autoimmunity 5 (2022) 100176

Contents lists available at ScienceDirect

Journal of Translational Autoimmunity

journal homepage: www.sciencedirect.com/journal/journal-of-translational-autoimmunity

An update on epigenetic regulation in autoimmune diseases

Xiaole Mei [a,b,c,d,1], Bo Zhang [a,b,c,d,e,1], Ming Zhao [a,d,e,**], Qianjin Lu [a,b,c,d,e,*]

[a] Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China
[b] Key Laboratory of Basic and Translational Research on Immunological Dermatology, Chinese Academy of Medical Sciences, Nanjing, Jiangsu, China
[c] Institute of Dermatology, Jiangsu Key Laboratory of Molecular Biology for Skin Diseases and STIs, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China
[d] Research Unit of Key Technologies of Diagnosis and Treatment for Immune-related Skin Diseases, Chinese Academy of Medical Sciences, Changsha, Hunan, China
[e] Department of Dermatology, Second Xiangya Hospital, Central South University, Hunan Key Laboratory of Medical Epigenomics, Changsha, Hunan, China

ARTICLE INFO

Keywords:
Autoimmune disease
Epigenetics
Lupus
Rheumatoid arthritis
DNA methylation
Histone modification
Noncoding RNA

ABSTRACT

Autoimmune diseases (AIDs) generally manifest as chronic immune disorders characterized by significant heterogeneity and complex symptoms. The discordant incidence of AIDs between monozygotic twins guided people to attach importance to environmental factors. Epigenetics is one of the major ways to be influenced, some of them can even occur years before clinical diagnosis. With the advent of high-throughput omics times, the mysterious veil of epigenetic modification in AIDs has been gradually unraveled, and some progress has been made in utilizing it as indicators of diagnosis and disease activity. For example, the hypomethylated IFI44L promoter in diagnosing systematic lupus erythematosus (SLE). More recently, newly identified noncoding RNAs (ncRNAs), including long noncoding RNAs (lncRNAs) and circular RNAs (circRNAs), are also believed to be involved in the etiology of AIDs while the initial factor behind those epigenetic alterations can be diverse from metabolism to microbiota. Update and comprehensive insights into epigenetics in AIDs can help us understand the pathogenesis and further orchestrate it to benefit patients in the future. Therefore, we reviewed the latest epigenetic findings in SLE, rheumatoid arthritis (RA), Type 1 diabetes (T1D), systemic sclerosis (SSc) primarily from cellular levels.

1. Introduction

Epigenetics is considered a reversible and inheritable modification in gene expression while not affecting DNA sequence. Aberrant epigenetics is essential in the onset of autoimmune disease (AIDs). Among them, positive regulators of gene expression are DNA demethylation and histone acetylation, whereas DNA hypermethylation, microRNAs (miRNAs) usually suppress gene expression. The versatile roles of histone methylation are decided by its location as well as the level of methylation. For instance, histone H3 lysine 4 tri-methylation (H3K4me3) activates gene transcription, whereas H3K9me3, H3K27me3, H3K29me3 suppress gene transcription. Moreover, ncRNAs such as miRNAs, lncRNAs, and circRNAs function by either interacting between themselves [1] or binding to proteins (Fig. 1). Almost all the autoimmune susceptible genes, such as transcription factors, inflammatory cytokines, can be modified by epigenetics and account for the pathogenesis of AIDs. Accordingly, we focused on recent epigenetic findings in SLE, RA, and T1D, hoping to bring inspiration in novel diagnostic and therapeutic approaches.

2. Systematic lupus erythematosus

SLE features overproduction of autoantibodies and complements following multiple tissue damage, primarily attributed to dysregulated B and T-cell differentiation and loss of tolerance.

* Corresponding author. Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College, Nanjing, Jiangsu, China.
** Corresponding author. Research Unit of Key Technologies of Diagnosis and Treatment for Immune-related Skin Diseases, Chinese Academy of Medical Sciences, Changsha, Hunan, China.
E-mail addresses: pymeixiaole728@student.pumc.edu.cn (X. Mei), pyzhangboderm@student.pumc.edu.cn (B. Zhang), zhaoming307@csu.edu.cn (M. Zhao), qianlu5860@pumcderm.cams.cn (Q. Lu).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.jtauto.2022.100176
Received 13 April 2022; Received in revised form 9 October 2022; Accepted 25 November 2022
Available online 9 December 2022

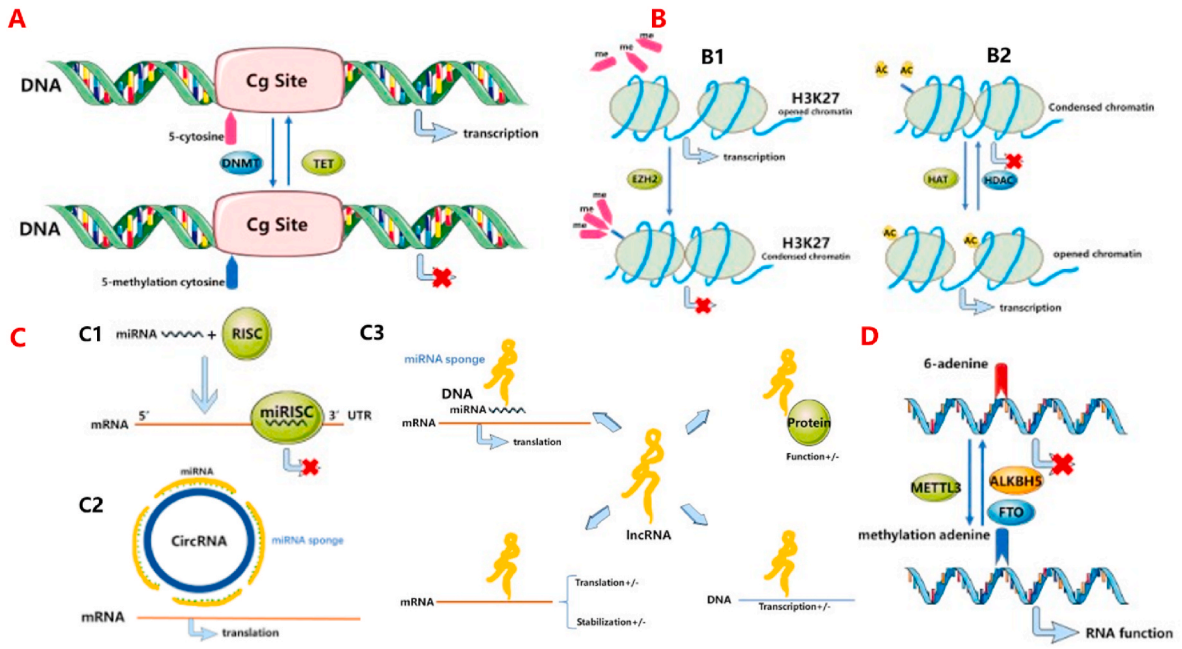

Fig. 1. The mechanism of epigenetic modification in autoimmune diseases. **(A)** DNMT and TET regulate gene transcription by mediating the hypermethylation and hypomethylation of cytosine in DNA. **(B)** H3K27 methylation promoted by EZH2 condenses chromatin, thereby inhibiting transcription. HAT and HDAC mediate histone acetylation to change the spatial structure of histones and thus regulate transcription. **(C)** miRNA and RISC form a complex to suppress mRNA transcription by binding mRNA 3′UTR. CircRNA acts as a miRNA sponge to influence mRNA transcription together with miRNAs. LncRNA may participate in modification by working as miRNA sponges, affecting the stability and transcription of mRNA, regulating the function of proteins, and directly regulating the transcription of DNA. **(D)** METTL3, FTO, ALKBH5 and other enzymes participate in the regulation of N6 position of adenosine methylation, regulating the function of RNA.

2.1. Emerging areas of epigenetics

To date, an increasing number of studies put an emphasis on lncRNAs and circRNAs in novel biomarkers for tissue damage in the diagnosis and prognosis of SLE. Latest studies have found that the increased expression of lncRNA ENST00000604411.1 and ENST00000501122.2 in monocyte-derived dendritic cells (moDCs) positively correlate to SLE-DAI score [2], circRNAs such as hsa_circ_0082688 and hsa_circ_0008675 in peripheral blood [3], circHLA-C in kidney tissues for lupus nephritis (LN) [4]. Mechanically, cell apoptosis seems to be a primary pathway. The A > G variation at rs13259960 in the enhancer of SLE-associated RNA (SLEAR) decreases its expression in SLE peripheral blood mononuclear cells (PBMCs), resulting in apoptosis of Jurkat cells in vitro as SLEAR activate antiapoptotic genes such as BCL2 and XIAP [5]. Higher expression of lincRNA-p21 in LN patients and mice was found to upregulate pro-apoptotic PUMA/BAX expression [6].

For circRNAs, the current understanding mainly focuses on the role of competitive endogenous RNAs (ceRNAs) to miRNAs [1]. Lower expressions of Hsa_circ_0045272 [7], circIBTK [8], hsa_circ_0012919 [9] were found in SLE patients. Hsa_circ_0045272 could be hsa-miR-6127 sponge to downregulate apoptosis and IL-2 [7], circIBTK could be miR-29 b sponge to affect DNA demethylation as well as AKT pathway [8], while hsa_circ_0012919 [9] could be miR-125a sponge to increase the expression of inflammatory cytokines, RANTES. Interestingly, the new role of circRNAs in the onset of SLE was reported recently. DsRNA-activated protein kinase (PKR) is a nucleic acid receptor with direct antiviral activity. The activation of PKR could contribute to the augmented type I IFN pathway. Liu et al. illustrated circRNAs to form 16–26 bp imperfect RNA duplexes and bind to PKR preferentially to inhibit its dsRNA-mediated activation. The decreasing numbers of global circRNAs and increased PKR phosphorylation were observed in SLE PBMCs [10].

Noteworthy, RNA modifications are crucial for the lifecycle of both mRNAs and noncoding RNAs. m^6A, a modification with the N^6 position of adenosine methylated, is the commonest mRNA modification of eukaryotes. In addition, RNA modification also includes N^1-methyladenosine (m^1A), N^5-methylcytosine (m^5C), pseudouridine (Ψ), etc. [11] RNA demethylase of m^6A, ALKBH5, was found to associate with anti-dsDNA, antinucleosome in peripheral blood of SLE patients, providing evidence that RNA modification participates in the pathogenesis of SLE [12]. Moreover, Guo et al. [13] suggested that hypermethylated m^5C genes relate to the inflammatory signaling while hypomethylated m^5C genes were involved in mRNA metabolism, eukaryotic translation elongation and termination in SLE $CD4^+$ T cells.

2.2. Epigenetics and immune cells

In a cohort that recruited discordant SLE monozygotic and dizygotic twins, B cells possessed the predominance of hypermethylation in gene promoters compared to other cell types [14]. The pre-antibody secreting cell termed $CD27^-CD11c^+$T-BET^+CXCR5^- B cell, which expanded in SLE and could be augmented by upregulated Toll-like receptor 7 (TLR7) and IL-21 stimulation [15], was shown to have increased chromatin accessibility in critical B-cell transcription factors AP-1, EGR and T-BET [16]. Of note, TLR7 also proved to regulate B-cell proliferation by increasing miR-15 b target CyclinD3 [17]. As for miRNAs in B cells, the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) pathway is the primarily affected signal in plasma cell differentiation and spontaneous germinal center (GC) formation in SLE. Accordingly, phosphatase and tensin homolog deleted on chromosome 10 (PTEN), a negative regulator of PI3K, suppressed by miR-7, miR-21, miR-22 [18], and miR-148a [19], play a vital role in the tolerance loss of B-cell. Besides, the activated AKT pathway downregulates miR-1246 to increase another critical B-cell transcription factor, EBF1 [20]. As one promoter could be targeted by multiple miRNAs and vice versa, miR-148a also suppresses the expression of the autoimmune suppressor GADD45A and the pro-apoptotic protein BIM [19]. Therefore, modulation on PI3K/AKT pathway and related miRNAs might reduce SLE autoantibodies. In addition, our previous study indicated that miR-152–3p is deleterious in SLE B cells as it upregulates B-cell activating factor (BAFF) expression [21]. Moreover,

elevated miR-155 [22,23] and miR-326 [24] were also found to be related to the autoactivate B cells.

In terms of T cells, the epigenetic alteration in SLE patients led to the balance breaking of T-cell differentiation and function. The upregulation of helper T 17(Th17)/regulatory T (Treg) ratio as well as T follicular helper (Tfh) cells have been well defined in various studies. Tfh cells produce IL-21 and IL-10 to facilitate memory B cells and plasma cells differentiation, while B cell lymphoma 6 (BCL6) is the key transcription factor for Tfh cells. Our previous study demonstrated that E4 promoter-binding protein 4 (E4BP4) suppresses Bcl6 expression by recruiting the histone deacetylase (HDAC)1 and histone methyltransferase, enhancer of zeste homolog 2 (EZH2), while E4BP4 phosphorylation site mutants were found in SLE patients [25]. Besides, the DNA methylation and H3K27me3 levels of BCL6 promoter also can be controlled by ubiquitin-like with PHD and RING finger domains 1 (UHRF1), which decreased in SLE Tfh cells [26]. Noticeably, interference on BCL6 increases overactive T-cell-related miR-142–3p/5p by inhibiting EZH2 and HDAC5 recruitment, thereby downregulating other Tfh-cell key regulators CD40L, ICOS, and IL-21 [27]. Another important transcription factor, STAT3, is important for Th17, Tfh cells, and B cells differentiation while detrimental for Treg cells, as it can be activated downstream to IL-6, IL-10, and IL-21 [28–31]. Our studies demonstrated that the IL-6/STAT3 axis could enhance Th17 cells differentiation by increasing histone H3 acetylation (H3Ac) and decreasing DNA methylation as well as H3K9me3 of IL-17 A by reducing regulatory factor X (RFX1) [29]. The histone modification of IL-17 A and IL-17 F in $CD4^+$ T cells also could be induced by TLR2 [32]. Moreover, STAT3 facilitates IL-10 expression by recruiting histone acetyltransferase (HAT) p300 to the IL-10 promoter and intronic enhancer [30]. MiR-125a was proved to decrease in SLE patients [33]. It can serve as a STAT3 inhibitor to stabilize Tregs while decreasing Tfh and Th17 number and function in the presence of IL-6. Consequently, MRL/lpr mice injected MiR-125a-loaded polymeric nanoparticles show an alleviation of lupus-like symptoms [28]. MiRNAs such as miR-7 [34], miR-410 [35], miR-155 [31], let-7f [36] also can influence STAT3 expression through direct or indirect actions that lead to SLE development. Other miRNAs such as miR-30e-5p [37], miR-101–3p [38], miR-200a-3p [39] in SLE patients also involved in the mess-up of Th17 and Treg cell differentiation.

In addition to cell differentiation, epigenetics also impairs immune cell function, including abnormal histone modification and DNA methylation on SLE susceptible genes [40] such as, CD11a, CD40L, CD70, perforin, etc. Since T cell adhesion, migration, and extravasation can also be mediated by EZH2, blockade of EZH2 might have therapeutic prospects for SLE patients [41].

2.3. Epigenetics and type I IFN pathway

Dysregulated Type I IFN pathway results in susceptibility to virus infection, cancer, and immunologic disorders. Type I IFN including IFN α/β, which were produced mainly by innate immune cells as long as their pattern-recognition receptors (PRRs) recognized different stimuli damage-associated molecular patterns (DAMPs) [42]. Increased IFN and IFN induced gene signature in the PBMCs and sera of patients correlated with SLEDAI and SLE patients of Asian and Hispanic ethnicity [42–44]. In terms of SLE, overproduction of apoptotic cells, endogenous self-nucleic acids, nucleic acid antibodies and immune complexes (ICs) could be deleterious stimuli sensed by sentinel receptors like TLR7, TLR9, retinoic acid-inducible gene I (RIG-I) and cyclic GMP-AMP synthase (cGAS) [42]. Valentina et al. [45] reported that IFN induction motif (IIM) containing microRNA miR574, let-7b, and miR21 in exosomes of SLE patient's plasma could be a novel self-ligand of TLR7 for plasmacytoid DCs (pDCs) activation. The signaling cascade of IFN downstream janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway finally led to the upregulation of a series of interferon stimulated genes (ISGs) like ISG15, MX dynamin-like GTPase 1 (MX1), IFN induced protein 44-like (IFI44L) and polymerase family member 9 (PARP9), etc. Our previous studies found that the methylation level of two CG pairs within IFI44L promoter was significantly decreased in SLE patients compared with healthy controls using Infinium Human Methylation 450 BeadChip arrays [46]. Next, we further established a simple and high-efficient method based on high-resolution melting-quantitative polymerase chain reaction (HRM-qPCR) to semi-quantitative analyze the methylation of IFI44L promoter for the diagnosis of SLE with relative high sensitivity and specificity [47]. IFI44L can be used not only to distinguish SLE from infectious diseases, inflammatory diseases, virus-associated cancers, but also to distinguish SLE from cutaneous lupus erythematosus such as discoid lupus erythematosus [48].

Abnormal expression of miR-146a was also found in SLE patients. Interestingly, it seems that miR-146a and type I IFN influence each other. On one hand, type I IFN reduces DICER1, an enzyme critical for miRNA maturation, to reduce miR-146a expression by upregulating MCPIP-1 [49]. On the other hand, increasing miR-146a expression by CRISPR activation of its functional enhancer, rs2431697 region, in the PBMCs from patients with SLE lower the level of ISGs such as IFI27, IFIT3, OAS1, and LY6E [50].

More recently, some lncRNAs have been shown to accelerate SLE symptoms through the IFN pathway. For example, the possible mechanism behind reduced LncRNA MALAT1 in PBMCs of SLE patients is that MALAT1 inhibited IFN key downstream factor IRF3 [51], while lncRNA NEAT1 in granulocyte (G)- myeloid-derived suppressor cells (MDSCs) from MRL/lpr mice could stimulate type I IFN signaling in B cells through BAFF secretion [52]. Positive regulators of this pathway also include LncRNA RP11-2B6.2 and linc00513 [53,54].

3. Rheumatoid arthritis

RA is a classic chromic autoimmune disease featured by damage of synovial membrane and degeneration of cartilage [55]. Numerous studies have suggested that epigenetics has good potential in diagnosing, treating, and prognosis on RA [56–58].

3.1. Emerging areas of epigenetics

LncRNA H19 promotes polarization of M1 macrophage by increasing KDM6A expression to increase RA activity [59]. It upregulates tumor necrosis factor (TNF)-α expression to aggravate the inflammatory response by activating the TGF-β-activated kinase 1 (TAK1) pathway [60]. LncRNA NEAT1 in exosomes derived by PBMCs promotes the incidence of RA by regulating miR-23a expression [61]. Meanwhile, lncRNA MEG3, MALAT1, and NEAT1 in peripheral PBMCs can be utilized to predict the clinical phenotype of RA [62]. However, some lncRNAs may relieve RA symptoms. For example, LncRNA GAS5 was downregulated in PBMC from RA, inhibiting IL-6 and IL-17 expression [63]. LncRNA 00197 regulated miR-150 to inactivate the TLR4/NF-κB pathway and reduce the activity of RA [64].

Studies also show circRNAs (0003353, 0005732, 0072428, 0091685, 0001200, 0001566, 0003972, 0008360) in PBMCs from RA patients have significant differences in expression compared with HCs, and circRNA_0003353 was supposed to be related to inflammation of RA, having the potential to be a diagnostic or prognostic biomarker [65,66]. Overexpression of circRNA_09505 in macrophages can work as a sponge for miR-6089, participating in the pathogenesis of RA and inducing inflammatory factors including IL-6 as well as TNF-α [67].

Furthermore, the peripheral blood global m^6A was upregulated in RA compared with healthy controls (HCs), accompanied by a low expression of FTO, which is crucial to m6A modification [68]. Besides, m^6A RNA Methyltransferase, METTL3, was proved to be upregulated in RA, which is positively related to C-reactive protein and erythrocyte sedimentation rate. METTL3 may relieve inflammation induced by lipopolysaccharide in macrophages through the NF-κB pathway [69]. All of this suggested that m^6A related enzymes can be used as biomarkers for

Table 1
Aberrant DNA methylation in SLE, RA, T1D, SSc.

Disease	Gene	Origin	Modification	Pathway	Reference
SLE	Global	B cells	Hypermethylation	–	[14,16]
	Global	T cells	Hypomethylation	–	[40]
	IFN regulated genes	$CD4^+$ T cells, $CD8^+$ T cells monocytes, granulocytes, and B cells, PBMCs	Hypomethylation	IFN pathway	[14,16,43,44,46, 148,149]
	PRDM1	B cells	Hypomethylation	plasma cell differentiation	[16]
	BCL6	$CD4^+$ T cells	Hypomethylation	Tfh differentiation	[26]
	IL-17 A	$CD4^+$ T cells	Hypomethylation	Th17/Treg imbalance	[29]
	F11R	$CD4^+$ T cells	Hypomethylation	T cell adhesion, migration, and extravasation	[41]
	CD70, CD11a, CD40L and perforin	$CD4^+$ T cells	Hypomethylation	T cell activation	[40,150,151]
	HLA-DRB1	$CD8^+$ T cells	hypomethylation	IFN, antigen presentation	[149]
RA	Foxp3	PBMCs	hypermethylation	Th17/Treg imbalance	[73]
	Global DNA	B cells	hypomethylation	–	[74]
	Global DNA	RASFs	hypomethylation	–	[94]
	TBX5	RASFs	hypomethylation	inflmmation	[96]
T1D	INS	Whole blood, serum, β cells	hypomethylation	β cell death	[120]
	GCK	whole blood	hypomethylation	β cell death	[121]
	CHTOP	Serum, β cells	hypomethylation	β cell death	[122]
	ITGB3BP, AFF3, CTSH, PTPN2, CTLA4	whole blood	SNP-CpGs dependent	Predicting T1D	[152]
SSc	CD11a	$CD4^+$ T cells	hypomethylation	T cell activation	[137]
	Foxp3	$CD4^+$ T cells	hypermethylation	Th17/Treg imbalance	[138]
	PARP-1	fibroblasts	hypermethylated	TGFβ signaling	[143]

Table 2
Aberrant histone modification in SLE, RA, T1D, SSc.

Disease	Gene	Origin	Histone modification (±)	Pathway	Reference
SLE	BCL6	$CD4^+$ T cells	H3Ac+, H3K27me3-	Tfh differentiation	[25,26]
	IL-17 A	$CD4^+$ T cells	H3Ac+,H4Ac+, H3K4me3+ H3K9me3-	Th17/Treg imbalance	[29,32]
	IL-17 F	$CD4^+$ T cells	H4Ac+, H3K9me3-	TLR2 pathway, Th17/Treg imbalance	[32]
	TNFAIP3	$CD4^+$ T cells	H3K4me3-	T cell activation	[153]
	IL-10	T cells	H3K18ac+	IL-10 contributes to the differentiation, activation and survival of B cells	[30]
	–	$CD4^+$ T cells	H3K27me3+	–	[41]
	AICDA	B cells	H3K9Ac/K14Ac+	CSR, SHM	[154]
RA	Foxp3	T cells	Tip60 -, EZH2 -	Th17/Treg imbalance	[76,77]
	–	RASFs	HDAC1+	–	[97]
	TBX5	RASFs	H3K4me3, H3Ac		[96]
T1D	HLA-DRB1, HLA-DQB1	monocytes	H3K9Ac	antigen presentation	[117]
	S100A9, S100A12	macrophages	H3Ac, H3K4me1, H3K4me3	inflammation	[118]
SSc	–	fibroblasts	H3K27me3+	Notch pathway	[141, 155]

+, Increased; –, Decreased.

diagnosing RA.

3.2. Epigenetics and immune cells

Immune cells, especially $CD4^+$ T cells, are crucial to the onset of RA. High-throughput sequencing of RA and HC $CD4^+$ T cells showed that differential methylated regions were mainly located in the T cell regulatory regions and regulated 548 differentially expressed genes [70]. Notably, the methylation level of $CD4^+$T cells was significantly different between newly diagnosed active RA and alleviated RA after methotrexate treatment, further proving the role of methylation of $CD4^+$T cells in the pathogenesis of RA [71]. The Th17/Treg ratio disruption directly led to the development of RA [72]. In a study of early active RA, abnormal methylation of crucial transcription factors of Treg and Th17 was observed [73]. Not only T cells, but B cells also show global hypomethylation in early RA, accompanied by a low level of DNMT1, which can be reversed after methotrexate treatment [74]. Aberrant DNA methylation was summarized in Table 1.

Abnormal histone acetylation and deacetylation were also crucial in the onset of RA [75]. In RA T cells, a low level of histone acetyltransferase Tip60, resulting in the insufficient acetylation of Foxp3, affect the function of Treg and break the balance of Th17/Treg [76]. Reduced EZH2 in $CD4^+$ T cells can also lead to abnormal differentiation of Treg by downregulating Foxp3 transcription [77]. Evidence showed HDACs in RA PBMCs were significantly downregulated compared with HCs [78]. Besides, the mice that knock out HDAC1 are more susceptible to the collagen-induced arthritis (CIA), with a low level of IL-17 and IL-6 in serum [79]. It demonstrated that histone modification is also a good therapeutic target. Animal experiments proved that HDAC6 inhibitor CKD-506 effectively inhibited the inflammatory response caused by macrophages and enhanced the function of Treg cells, thus alleviating clinical phenotypes [80]. CKD-L, another HDAC6 inhibitor, can also regulate Treg function by reducing the expression of cytotoxic T-lymphocyte associated protein (CTLA)-4 [81]. Aberrant histone modifications were summarized in Table 2.

Noncoding RNA is the most widely used in biomarkers and treatment in RA. The differentially expressed miRNAs in PBMCs in RA patients and healthy people, especially miR-99 b-5p, could inhibit T cell apoptosis and upregulate the inflammatory factors, including IL-6, TNF-α, and IFN-γ [82]. In addition, the overexpression of miR-126 in RA patients

Table 3
Aberrant ncRNAs in SLE, RA, T1D, SSc.

Disease	Modification (ncRNAs+/−)	Origin	Target	Pathway	Reference
SLE	Hsa_circ_0045272 -	T cells	hsa-miR-6127 sponge	Apoptosis, IL-2 secretion	[7]
	circIBTK -	PBMCs	miR-29 b sponge	AKT pathway	[8]
	hsa_circ_0012919 -	$CD4^+$ T cells	miR-125a sponge	DNA methylation, T cell activation	[9]
	global circRNAs-	PBMCs	PKR	Type I IFN pathway	[10]
	hsa_circ_0082688, hsa_circ_0008675+	peripheral blood	Predicting LN	–	[3]
	circHLA-C+	kidney tissues	Predicting L.N.	–	[4]
	hsa_circ_0123190-	kidney tissues	hsa-miR-483–3p sponge	renal fibrosis	[156]
	linc0949-	PBMCs	Predicting SLEDAI and LN	–	[157]
	GAS5-, lnc7074-, linc0597+, lnc0640+, lnc5150+	Plasma	Diagonosing SLE	–	[158]
	lncRNA ENST00000604411.1+, ENST00000501122.2+	moDCs	Predicting SLEDAI	–	[2]
	LncRNA SLEAR -	PBMCs	BCL2, XIAP	apoptosis	[5]
	linc-p21+	PBMCs, urine cells	miR-181a sponge	Apoptosis, IL2 secretion	[6]
	Lnc MALAT1-	PBMCs	TDP43	IFN	[51]
	Lnc 00513+	Kidney tissue	Promotes ISGs	IFN	[53]
	Lnc NEAT1+	PBMCs	–	IFN\BAFF	[52]
	lnc RP11-2B6.2+	Kidney tissue	SOCS1	IFN	[54]
	miR-15 b-	B cells	CCND3	TLR7 pathway, B-cell development	[17]
	miR-7, miR-21, miR-22	B cells	PTEN	PI3K/AKT pathway	[18,34]
	miR-148a	B cells	PTEN, GADD45A, BIM	PI3K/AKT pathway, apoptosis	[19]
	miR-1246	B cells	EBF1	B cell development	[20]
	miR-152–3p+	B cells	KLF5	BAFF secretion	[21]
	miR-155+	B cells, CD4+T cells	SHIP-1, CD1d in B cell, SOCS1 in T cell	TLR9 pathway, antigen-presention, IL-21 secretion	[22,23]
	miR-326+	B cells	Ets-1	B cell differentiation	[24]
	miR-142-	$CD4^+$ T cells	IL-10, CD84, SAP	T cell activation and B cell stimulation	[27]
	miR-125a-	$CD4^+$ T cells	STAT3	Th17/Treg balance	[33]
	miR-101-3p-	PBMCs	HDAC9	Th17/Treg balance	[38]
	miR-200a-	CD4+T cells, serum, urine	CTBP2	IL-2 secretion	[39]
	miR-let-7f-	BM-MSCs	Il6	Th17/Treg balance	[36]
	miR-26a-, miR-101-	$CD4^+$ T cells	EZH2	–	[41]
	miR574+, let-7b+, and miR21+	exosomes in plasma	Sensored by TLR7	TLR7 pathway	[45]
	miR-146a-	PBMCs	ISGs	IFN pathway, microRNA maturation	[49,50]
	miR-130 b-	Kidney tissue	IRF1	IFN pathway	[159]
	miR-30e-5p+	PBMCs	IFN negative regulators	IFN pathway	[160]
	miR-302 d-	PBMCs	IRF9	IFN pathway	[161]
	miR-26a, miR-125a, miR-155, miR-30c, and miR-182-	B cells	AICDA, PRDM1	plasma cell differentiation	[162]
	miR-21+	$CD4^+$ T cells	BDH2	iron metabolism	[150]
	hsa-miR-10 b-5p+	T cells	SRSF1	estrogen	[163]
RA	lnc GAS5-	RASFs	miR128–3p sponge	AKT/mTOR pathway	[102]
	miR-126+	CD4+T cell	DNMT1	DNA methylation	[83]
	miR155+	RASFs	MMP3	Inflammation	[164]
	miR-21+	RASFs	–	Inflmmation	[101]
	miR34a-5p+	RASFs	XBP1	RASF inflammation	[103]
	miR140-3p-, miR140-5p-	RASFs	SIRT-1 for miR140–3p, SDF-1 for miR140–5p	RASF inflmmation and activation	[105, 106]
	miR-17–5p+	RASFs	STAT3, JAK1	IL-6/STAT3 pathway	[106]
T1D	miR-26a+	activated Tregs	EZH2	Th17/Treg imbalance, predicting T1D	[110]
	miRNA181a+	CD4+T cells	NFAT5	PTEN/PI3K pathway	[111]
	miRNA92a+	CD4+T cell	KLF2	PTEN/PI3K pathway	[112]
	MiR-885-3p-	PBMCs	TLR4	TLR4/NF-κB pathway	[116]
	miR-204+	serum, β cell	Predicting T1D	β cell death	[123]
	miR-101–3p+	Serum	Predicting T1D	β cell death	[124]
	miR-23–27~24 clusters+	Plasma	prognosing T1D	C-peptide loss	[125]
	miR-375+	Plasma	prognosing T1D	Islet transplantation	[126]
	let-7c-5p-, miR-29a-3p-, let-7b-5p+, miR-21–5p+	Plasma	prognosing T1D	Renal function	[127]
	miR-150-	PBMCs, splenocytes and β cells	PUMA	NF-κB pathway	[128]
	miR-21+	β cells	PDCD4	Apoptosis, NF-κB pathway	[129]
	LncRNA SRA+	plasma, PBMCs, β cells	miR-146 b sponge	IRAK1/LDHA/Lactate Pathway	[130]
	Lnc13+	β-Cells	Promotes STAT1	Inflammation	[165]
SSc	miR-139-5+	pDCs	USP24	TLR9 pathway, IFN pathway	[140]
	miR-16-5p-	fibroblasts	NOTCH2	NOTCH signaling	[144]
	miR33a-3p+	fibroblasts	DKK-1	Wnt pathway	[145]
	Lnc RNA HOTAIR+	fibroblasts	miRNA-34a sponge	NOTCH signaling	[155]

+, Increased; –, Decreased.

affected CD4+T cell methylation by DNMT1 [83]. However, more miRNAs participated in RA by disrupting the balance of Treg/Th17 through interacting with transcription factors [84]. For DCs, the function of which can be regulated from the epigenetic level by miR-34a, and then the proliferation of Th17 was regulated to promote the incidence of RA [85]. Various miRNAs such as miR-146a, miR-155, miR let-7g-5p, miR-16, miR-17, miR-21, miR-34a, and miR-498 are all involved in regulating the Treg/Th17 axis of RA [86–92]. Aberrant ncRNAs were summarized in Table 3.

3.3. Epigenetics and RA synovial fibroblasts

The abnormal proliferation of RA synovial fibroblasts (RASFs) is a major cause of synovial inflammation and destruction of articular cartilage [93]. Epigenetics of RASFs has been further studied, providing a strategy for classification, diagnosis, prognosis, and precise treatment of RA. First, RASFs are global hypomethylated, which is associated with a range of disorders [94]. Hypomethylation of RASFs was accompanied by down-regulation of DNMT1 expression [95]. Compared with synovial fibroblast of osteoarthritis patients, it is proved that T-box transcription factor 5 (TBX5) in RASFs was hypomethylation [96] while HDAC1 in RASFs was significantly higher. In addition, animal experiments showed that inhibition of HDAC1 significantly alleviated CIA's joint swelling and other symptoms [97]. In addition, EZH2 was upregulated in RASFs, causing overexpression of TNF-α and increased disease activity [98].

miRNAs in RASF are also involved in the erosive effect of RASFs, which can affect multiple pathways, such as JAK/STAT and NF-κB, to regulate the inflammatory response. Some miRNAs can upregulate the expression of TNF-α and other inflammatory factors, while some miRNAs alleviate the inflammatory response of RA. Among them, miR155 and miR146a have the most related studies [99]. The upregulated miRNAs in RASFs included miR155, miR-21, miR128–3p, miR34a-5p, and miR574–5p, etc [100–104]. And the down-regulated miRNAs include miR140–3p, miR140–5p, miR17 [105–107], etc.

In addition to direct function in epigenetic regulation, miRNA can also indirectly influence the inflammatory response of RA exosomes. Some exosomal-derived microRNAs can protect against joint and cartilage destruction in RASF. For example, miR-146a in exosomes from mesenchymal stem cells (MSCs) can upregulate Foxp3 expression to enhance the function of Treg cells, while exosomal microRNA-320a from MSCs can suppress activation of RASFs by downregulating CXCL9 [108]. MiR-424 in exosomes from RASFs also plays a role in RA pathogenesis by affecting T cell differentiation and disrupting the balance of Th17/Treg [109]. Exosomal miR-17 can decrease the level of TGFBR II to suppress Treg induction, leading to the inflammation of RA [89]. The characteristics of stability and no immune rejection make exosomal miRNA a promising diagnostic biomarker and treatment method.

4. Type 1 diabetes

In contrast to insulin irresponsiveness in T2D, hyperglycemia in T1D patients was primarily caused by the disruption of islet β cells and T cells. Autoantibodies, including antibodies to insulin (IAA), glutamic acid decarboxylase (GADA) as well as islet antigen-2 (IA-2A), can even occur years before clinical T1D diagnosis. Those who are first-degree relatives of T1D patients with multiple islet autoantibodies were defined as T1D high-risk individuals [110].

4.1. Epigenetics and immune cells

As an AID, T1D is also charactered by T cell dysfunction. Multiple research suggested that aberrant miRNAs could affect Treg cells to impair T cell tolerance. Compared to HCs, upregulated miR-26a in activated Tregs in T1D high-risk groups by decreasing EZH2 [110], miRNA181a in $CD4^+$ T cells by regulating PTEN/PI3K/AKT pathway to reduce Foxp3 expression [111]. This pathway also involved in the increasing $CCR7^{low}PD1^{high}CXCR5^+$ Tfh precursor cells, which were modulated by miRNA92a [112]. Consequently, inhibiting miRNA181a and miRNA92a has been proved to ameliorate islet autoimmunity in murine and humanized models with antagomir applications [111,112]. In the course of T1D, $CD8^+$ T cells recognize C-peptide of preproinsulin to kill β cells. It is proved that the endoplasmic reticulum (ER) stress of β cells, induced by IFN-γ and IL-1β, could increase the generation of the autoantigenic peptide by decreasing miR-17–5p expression [113]. Interestingly, at the same time, β cell-specific $CD8^+$ T cell itself has a long-lived nature. Combining analysis of whole-genome bisulfite sequencing (WGBS) and single-cell ATAC-seq indicated that the epigenetic programs, especially DNA methylation atlas, of β cell-specific $CD8^+$ T cells are similar to stem-cell memory phenotype [114]. Moreover, HDAC was also hijacked in T1D $CD4^+$ T cells to promote $CD8^+$ T cells. With nonobese diabetic (NOD) mice models, Hsu et al. proved that enhanced IL-21 histone acetylation by HDAC2, induces extrafollicular helper T cell population and granzyme B-producing $CD8^+$ T cells further [115].

In the monocyte-macrophage system, aberrant epigenetic changes such as miR-885–3p [116], H3K9Ac status of HLA-DRB1 and HLA-DQB1 [117], H3Ac, H3K4me1, and H3K4me3 of inflammation regulator S100A9 and S100A12 [118], also have been revealed in the onset of T1D.

4.2. Epigenetics and islet β cells

Epigenetic alteration precedes loss of glucose homeostasis while correlates with autoantibodies production and β-cell death [119], indicating its potential in predicting the onset of T1D. The most intensive studied susceptible gene of epigenetic modulation in T1D was preproinsulin encoding gene INS [120]. Since β cell has increased unmethylated INS CpG sites, the elevation of unmethylated INS DNA in the circulation might represent β cell death. In addition, the unmethylated glucokinase (GCK) [121], chromatin target of PRMT1 (CHTOP) [122] were also proposed for the islet specificity. Increasing miRNAs such as miR-204 [123], miR-101–3p [124] also can be detected in the serum of high T1D risk subjects. After the onset of T1D, plasma circulating miR-23–27~24 clusters were suggested in predicting C-peptide loss [125], miR-375 in predicting early graft destruction and graft outcome [126], let-7c-5p, let-7b-5p, miR-29a-3p and miR-21–5p in predicting rapid progression to end-stage renal disease [127].

In the mechanical research of T1D pathogenesis, miR-150 [128], miR-21 [129] induced by NF-κB were found to prevent β cell inflammation and apoptosis by targeting p53 upregulated modulator of apoptosis (PUMA) and programmed cell death 4 (PDCD4), respectively. On the contrary, increasing LncRNA SRAs in T1D patients can cause apoptosis of β cells and Treg dysfunction by directly inhibiting miR-146 b through metabolic reprogramming [130]. In terms of biological therapy in T1D, miR-216a mimic nanodrug [131] were shown to promote β-cell proliferation by decreasing PTEN expression.

5. Systemtic sclerosis

SSc is an autoimmune disease of complicated scope. Patients have multiple organ damage such as vasculitis, fibrosis, and sclerosis, especially in skin. At the cellular level, it is usually manifested by abnormal function of vascular endothelial cells, fibroblasts, and immune cells. Severe disease may progress to death in five years [132]. Some advances have been made in the study of SSc epigenetics, mainly focusing on the above types of cells [133,134].

5.1. Epigenetics and immune cells

Immune cells, especially $CD4^+$ T cells, play a critical role in the onset and development of SSc [135]. Methylation microarray analysis of $CD4^+$ T cells from SSC patients and healthy controls revealed the presence of

differentially methylated CpG positions and differentially expressed genes that are associated with the inflammatory function of T cells [136]. CD11a methylation level regulatory region in $CD4^+$ T cells was significant decreased [137]. Similarly, Th17/Treg imbalance also participated in the pathogenesis of SSC. Patients with SSc were proved to have hypermethylation of the Foxp3 promoter region, affecting the differentiation and numbers of Treg, disrupting the balance of Th17/Treg and inducing the inflammatory response of SSc [138].

In addition, abnormal H3K4me3 and H3K27ac marks were found in SSc monocytes [139], upregulated miR-126 and miR-139-5 [140] were found in SSc pDCs. Both of them related to IFN pathway, which proves that the disruption of IFN is also involved in the pathogenesis of SSc.

5.2. *Epigenetics and fibroblasts*

Fibrosis is a prominent feature of SSc, in which the epigenetic regulation of fibroblasts plays an important role. Both EZH2 and H3K27 were upregulated in fibrolasts of SSc, which lead to the fibrosis and anti-angiogenesis. Moreover, EZH2 inhibitors was proved to regulate fibroblast activity and have the potential to be therapeutic agents [141].

Another methylation modification, methyl cap binding protein-2 (MeCP2), was crucial to SSc. The high expression of MeCP2 in fibroblasts in SSc patients can downregulate the expression of miR132 and mediate the occurrence and development of fibrosis by enhancing the Wnt pathway [142]. Zhang et al. found that the promoter region of the enzyme poly (ADP-ribose) polymerase-1 (PARP-1) was hypermethylated in fibroblasts of SSc patients, resulting in decreased expression of PARP-1. The low expression of PARP-1 may negatively regulate TGF-β signal transduction, thereby promoting the activity of SSc fibroblasts [143]. MicroRNAs also exert epigenetic regulation on fibroblasts. Low level of miR-16–5p activates fibrosis by positively regulating the NOTCH signaling [144]. In addition, miR33a-3p can downregulate level of DKK-1, an antagonist of Wnt pathway, and promote the fibrosis [145].

6. Conclusion

This review looks back on the emerging areas and cellular pathways of epigenetic modulation involved in AIDs. The strong link between dysregulated immune cells and epigenetics enables it as diagnostic and prognostic biomarkers and facilitates the therapeutic usage of reprogramming epigenetics both alone and in combination therapies [146]. However, to date, the side effect has limited epigenetics targeted drugs development in AIDs patients [147], although some DNMT inhibitors and HDAC inhibitors have been approved in anti-tumor immunity by the United States Food and Drug Administration (FDA) [146]. Thus, to obtain better management for AIDs patients and high-risk groups, there are broad prospects for exploring the etiological mechanism in-depth with advanced technologies.

Credit author statement

Xiaole Mei and Bo Zhang: Writing- Original draft preparation. **Qianjin Lu and Ming Zhao**: Writing- Reviewing and Editing.

Funding

This study was supported by the National Natural Science Foundation of China (No. 81874253), Natural Science Foundation of Hunan Province China (No. 2021JJ40837), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2020-RC320-003).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] C.Y. Tsai, C.Y. Shen, C.W. Liu, S.C. Hsieh, H.T. Liao, K.J. Li, C.S. Lu, H.T. Lee, C. S. Lin, C.H. Wu, et al., Aberrant non-coding RNA expression in patients with systemic lupus erythematosus: consequences for immune dysfunctions and tissue damage, Biomolecules 10 (2020), https://doi.org/10.3390/biom10121641.

[2] Y. Wang, S. Chen, S. Chen, J. Du, J. Lin, H. Qin, J. Wang, J. Liang, J. Xu, Long noncoding RNA expression profile and association with SLEDAI score in monocyte-derived dendritic cells from patients with systematic lupus erythematosus, Arthritis Res. Ther. 20 (2018) 138, https://doi.org/10.1186/s13075-018-1640-x.

[3] Q. Luo, L. Zhang, L. Xiong, B. Fu, Y. Guo, Z. Huang, J. Li, Peripheral blood circular RNA hsa_circ_0082688-hsa_circ_0008675 can be used as a candidate biomarker of systemic lupus erythematosus with renal involvement, Clin. Exp. Rheumatol. 38 (2020) 822–833.

[4] J. Luan, C. Jiao, W. Kong, J. Fu, W. Qu, Y. Chen, X. Zhu, Y. Zeng, G. Guo, H. Qi, et al., circHLA-C plays an important role in lupus nephritis by sponging miR-150, Mol. Ther. Nucleic Acids 10 (2018) 245–253, https://doi.org/10.1016/j.omtn.2017.12.006.

[5] Z. Fan, X. Chen, L. Liu, C. Zhu, J. Xu, X. Yin, Y. Sheng, Z. Zhu, L. Wen, X. Zuo, et al., Association of the polymorphism rs13259960 in SLEAR with predisposition to systemic lupus erythematosus, Arthritis Rheumatol. 72 (2020) 985–996, https://doi.org/10.1002/art.41200.

[6] Y.C. Chen, P.Y. Kuo, Y.C. Chou, H.E. Chong, Y.T. Hsieh, M.L. Yang, C.L. Wu, A. L. Shiau, C.R. Wang, Up-regulated expression of pro-apoptotic long noncoding RNA lincRNA-p21 with enhanced cell apoptosis in lupus nephritis, Int. J. Mol. Sci. (2020) 22, https://doi.org/10.3390/ijms22010301.

[7] L.J. Li, Z.W. Zhu, W. Zhao, S.S. Tao, B.Z. Li, S.Z. Xu, J.B. Wang, M.Y. Zhang, J. Wu, R.X. Leng, et al., Circular RNA expression profile and potential function of hsa_circ_0045272 in systemic lupus erythematosus, Immunology 155 (2018) 137–149, https://doi.org/10.1111/imm.12940.

[8] X. Wang, C. Zhang, Z. Wu, Y. Chen, W. Shi, CircIBTK inhibits DNA demethylation and activation of AKT signaling pathway via miR-29b in peripheral blood mononuclear cells in systemic lupus erythematosus, Arthritis Res. Ther. 20 (2018) 118, https://doi.org/10.1186/s13075-018-1618-8.

[9] C. Zhang, X. Wang, Y. Chen, Z. Wu, C. Zhang, W. Shi, The down-regulation of hsa_circ_0012919, the sponge for miR-125a-3p, contributes to DNA methylation of CD11a and CD70 in CD4(+) T cells of systemic lupus erythematous, Clin. Sci. (Lond.) 132 (2018) 2285–2298, https://doi.org/10.1042/CS20180403.

[10] C.X. Liu, X. Li, F. Nan, S. Jiang, X. Gao, S.K. Guo, W. Xue, Y. Cui, K. Dong, H. Ding, et al., Structure and degradation of circular RNAs regulate PKR activation in innate immunity, Cell 177 (2019) 865–880, https://doi.org/10.1016/j.cell.2019.03.046, e821.

[11] I.A. Roundtree, M.E. Evans, T. Pan, C. He, Dynamic RNA modifications in gene expression regulation, Cell 169 (2017) 1187–1200, https://doi.org/10.1016/j.cell.2017.05.045.

[12] Q. Luo, B. Fu, L. Zhang, Y. Guo, Z. Huang, J. Li, Decreased peripheral blood ALKBH5 correlates with markers of autoimmune response in systemic lupus erythematosus, Dis. Markers 2020 (2020), 8193895, https://doi.org/10.1155/2020/8193895.

[13] G. Guo, H. Wang, X. Shi, L. Ye, K. Yan, Z. Chen, H. Zhang, Z. Jin, X. Xue, Disease activity-associated alteration of mRNA m(5) C methylation in CD4(+) T cells of systemic lupus erythematosus, Front. Cell Dev. Biol. 8 (2020) 430, https://doi.org/10.3389/fcell.2020.00430.

[14] C.J. Ulff-Moller, F. Asmar, Y. Liu, A.J. Svendsen, F. Busato, K. Gronbaek, J. Tost, S. Jacobsen, Twin DNA methylation profiling reveals flare-dependent interferon signature and B cell promoter hypermethylation in systemic lupus erythematosus, Arthritis Rheumatol. 70 (2018) 878–890, https://doi.org/10.1002/art.40422.

[15] E. Zumaquero, S.L. Stone, C.D. Scharer, S.A. Jenks, A. Nellore, B. Mousseau, A. Rosal-Vela, D. Botta, J.E. Bradley, W. Wojciechowski, et al., IFNgamma induces epigenetic programming of human T-bet(hi) B cells and promotes TLR7/8 and IL-21 induced differentiation, Elife 8 (2019), https://doi.org/10.7554/eLife.41641.

[16] C.D. Scharer, E.L. Blalock, T. Mi, B.G. Barwick, S.A. Jenks, T. Deguchi, K. S. Cashman, B.E. Neary, D.G. Patterson, S.L. Hicks, et al., Epigenetic programming underpins B cell dysfunction in human SLE, Nat. Immunol. 20 (2019) 1071–1082, https://doi.org/10.1038/s41590-019-0419-9.

[17] D. Ren, F. Liu, G. Dong, M. You, J. Ji, Y. Huang, Y. Hou, H. Fan, Activation of TLR7 increases CCND3 expression via the downregulation of miR-15b in B cells of systemic lupus erythematosus, Cell. Mol. Immunol. 13 (2016) 764–775, https://doi.org/10.1038/cmi.2015.48.

[18] X.N. Wu, Y.X. Ye, J.W. Niu, Y. Li, X. Li, X. You, H. Chen, L.D. Zhao, X.F. Zeng, F. C. Zhang, et al., Defective PTEN regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus, Sci. Transl. Med. 6 (2014) 246ra299, https://doi.org/10.1126/scitranslmed.3009131.

[19] A. Gonzalez-Martin, B.D. Adams, M. Lai, J. Shepherd, M. Salvador-Bernaldez, J. M. Salvador, J. Lu, D. Nemazee, C. Xiao, The microRNA miR-148a functions as a

critical regulator of B cell tolerance and autoimmunity, Nat. Immunol. 17 (2016) 433–440, https://doi.org/10.1038/ni.3385.
[20] S. Luo, Y. Liu, G. Liang, M. Zhao, H. Wu, Y. Liang, X. Qiu, Y. Tan, Y. Dai, S. Yung, et al., The role of microRNA-1246 in the regulation of B cell activation and the pathogenesis of systemic lupus erythematosus, Clin. Epigenet. 7 (2015) 24, https://doi.org/10.1186/s13148-015-0063-7.
[21] S. Luo, S. Ding, J. Liao, P. Zhang, Y. Liu, M. Zhao, Q. Lu, Excessive miR-152-3p results in increased BAFF expression in SLE B-cells by inhibiting the KLF5 expression, Front. Immunol. 10 (2019) 1127, https://doi.org/10.3389/fimmu.2019.01127.
[22] T.H. Thai, H.C. Patterson, D.H. Pham, K. Kis-Toth, D.A. Kaminski, G.C. Tsokos, Deletion of microRNA-155 reduces autoantibody responses and alleviates lupus-like disease in the Fas(lpr) mouse, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 20194–20199, https://doi.org/10.1073/pnas.1317632110.
[23] F. Liu, H. Fan, D. Ren, G. Dong, E. Hu, J. Ji, Y. Hou, TLR9-induced miR-155 and Ets-1 decrease expression of CD1d on B cells in SLE, Eur. J. Immunol. 45 (2015) 1934–1945, https://doi.org/10.1002/eji.201445286.
[24] Y. Xia, J.H. Tao, X. Fang, N. Xiang, X.J. Dai, L. Jin, X.M. Li, Y.P. Wang, X.P. Li, MicroRNA-326 upregulates B cell activity and autoantibody production in lupus disease of MRL/lpr mice, Mol. Ther. Nucleic Acids 11 (2018) 284–291, https://doi.org/10.1016/j.omtn.2018.02.010.
[25] Z. Wang, M. Zhao, J. Yin, L. Liu, L. Hu, Y. Huang, A. Liu, J. Ouyang, X. Min, S. Rao, et al., E4BP4-mediated inhibition of T follicular helper cell differentiation is compromised in autoimmune diseases, J. Clin. Invest. (2020), https://doi.org/10.1172/JCI129018.
[26] L. Liu, L. Hu, L. Yang, S. Jia, P. Du, X. Min, J. Wu, H. Wu, H. Long, Q. Lu, et al., UHRF1 downregulation promotes T follicular helper cell differentiation by increasing BCL6 expression in SLE, Clin. Epigenet. 13 (2021) 31, https://doi.org/10.1186/s13148-021-01007-7.
[27] S. Ding, Q. Zhang, S. Luo, L. Gao, J. Huang, J. Lu, J. Chen, Q. Zeng, A. Guo, J. Zeng, et al., BCL-6 suppresses miR-142-3p/5p expression in SLE CD4(+) T cells by modulating histone methylation and acetylation of the miR-142 promoter, Cell. Mol. Immunol. 17 (2020) 474–482, https://doi.org/10.1038/s41423-019-0268-3.
[28] J. Zhang, C. Chen, H. Fu, J. Yu, Y. Sun, H. Huang, Y. Tang, N. Shen, Y. Duan, MicroRNA-125a-Loaded polymeric nanoparticles alleviate systemic lupus erythematosus by restoring effector/regulatory T cells balance, ACS Nano 14 (2020) 4414–4429, https://doi.org/10.1021/acsnano.9b09998.
[29] M. Zhao, Y. Tan, Q. Peng, C. Huang, Y. Guo, G. Liang, B. Zhu, Y. Huang, A. Liu, Z. Wang, et al., IL-6/STAT3 pathway induced deficiency of RFX1 contributes to Th17-dependent autoimmune diseases via epigenetic regulation, Nat. Commun. 9 (2018) 583, https://doi.org/10.1038/s41467-018-02890-0.
[30] C.M. Hedrich, T. Rauen, S.A. Apostolidis, A.P. Grammatikos, N. Rodriguez Rodriguez, C. Ioannidis, V.C. Kyttaris, J.C. Crispin, G.C. Tsokos, Stat3 promotes IL-10 expression in lupus T cells through trans-activation and chromatin remodeling, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 13457–13462, https://doi.org/10.1073/pnas.1408023111.
[31] T.K. Rasmussen, T. Andersen, R.O. Bak, G. Yiu, C.M. Sorensen, K. Stengaard-Pedersen, J.G. Mikkelsen, P.J. Utz, C.K. Holm, B. Deleuran, Overexpression of microRNA-155 increases IL-21 mediated STAT3 signaling and IL-21 production in systemic lupus erythematosus, Arthritis Res. Ther. 17 (2015) 154, https://doi.org/10.1186/s13075-015-0660-z.
[32] Y. Liu, J. Liao, M. Zhao, H. Wu, S. Yung, T.M. Chan, A. Yoshimura, Q. Lu, Increased expression of TLR2 in CD4(+) T cells from SLE patients enhances immune reactivity and promotes IL-17 expression through histone modifications, Eur. J. Immunol. 45 (2015) 2683–2693, https://doi.org/10.1002/eji.201445219.
[33] W. Pan, S. Zhu, D. Dai, Z. Liu, D. Li, B. Li, N. Gagliani, Y. Zheng, Y. Tang, M. T. Weirauch, et al., MiR-125a targets effector programs to stabilize Treg-mediated immune homeostasis, Nat. Commun. 6 (2015) 7096, https://doi.org/10.1038/ncomms8096.
[34] M. Wang, H. Chen, J. Qiu, H.X. Yang, C.Y. Zhang, Y.Y. Fei, L.D. Zhao, J.X. Zhou, L. Wang, Q.J. Wu, et al., Antagonizing miR-7 suppresses B cell hyperresponsiveness and inhibits lupus development, J. Autoimmun. 109 (2020), 102440, https://doi.org/10.1016/j.jaut.2020.102440.
[35] D. Liu, N. Zhang, X. Zhang, M. Qin, Y. Dong, L. Jin, MiR-410 down-regulates the expression of interleukin-10 by targeting STAT3 in the pathogenesis of systemic lupus erythematosus, Cell. Physiol. Biochem. 39 (2016) 303–315, https://doi.org/10.1159/000445625.
[36] L. Geng, X. Tang, S. Wang, Y. Sun, D. Wang, B.P. Tsao, X. Feng, L. Sun, Reduced let-7f in bone marrow-derived mesenchymal stem cells triggers Treg/Th17 imbalance in patients with systemic lupus erythematosus, Front. Immunol. 11 (2020) 233, https://doi.org/10.3389/fimmu.2020.00233.
[37] T. Cheng, S. Ding, S. Liu, X. Li, X. Tang, L. Sun, Resolvin D1 improves the Treg/Th17 imbalance in systemic lupus erythematosus through miR-30e-5p, Front. Immunol. 12 (2021), 668760, https://doi.org/10.3389/fimmu.2021.668760.
[38] H. Sun, F. Guo, L. Xu, Downregulation of microRNA-101-3p participates in systemic lupus erythematosus progression via negatively regulating HDAC9, J. Cell. Biochem. 121 (2020) 4310–4320, https://doi.org/10.1002/jcb.29624.
[39] E. Katsuyama, M. Yan, K.S. Watanabe, M. Narazaki, S. Matsushima, Y. Yamamura, S. Hiramatsu, K. Ohashi, H. Watanabe, T. Katsuyama, et al., Downregulation of miR-200a-3p, targeting CtBP2 complex, is involved in the hypoproduction of IL-2 in systemic lupus erythematosus-derived T cells, J. Immunol. 198 (2017) 4268–4276, https://doi.org/10.4049/jimmunol.1601705.
[40] Q. Lu, The critical importance of epigenetics in autoimmunity, J. Autoimmun. 41 (2013) 1–5, https://doi.org/10.1016/j.jaut.2013.01.010.
[41] P.S. Tsou, P. Coit, N.C. Kilian, A.H. Sawalha, EZH2 modulates the DNA methylome and controls T cell adhesion through junctional adhesion molecule A in lupus patients, Arthritis Rheumatol. 70 (2018) 98–108, https://doi.org/10.1002/art.40338.
[42] J. Jiang, M. Zhao, C. Chang, H. Wu, Q. Lu, Type I interferons in the pathogenesis and treatment of autoimmune diseases, Clin. Rev. Allergy Immunol. (2020), https://doi.org/10.1007/s12016-020-08798-2.
[43] S. Joseph, N. George, B. Green-Knox, E. Treadwell, B. Word, S. Yim, B. Lyn-Cook, Epigenome-wide association study of peripheral blood mononuclear cells in systemic lupus erythematosus: identifying DNA methylation signatures associated with interferon-related genes based on ethnicity and SLEDAI, J. Autoimmun. 96 (2019) 147–157, https://doi.org/10.1016/j.jaut.2018.09.007.
[44] C. Lanata, I. Paranjpe, J. Nititham, K. Taylor, M. Gianfrancesco, M. Paranjpe, S. Andrews, S. Chung, B. Rhead, L. Barcellos, et al., A phenotypic and genomics approach in a multi-ethnic cohort to subtype systemic lupus erythematosus, Nat. Commun. 10 (2019) 3902, https://doi.org/10.1038/s41467-019-11845-y.
[45] V. Salvi, V. Gianello, S. Busatto, P. Bergese, L. Andreoli, U. D'Oro, A. Zingoni, A. Tincani, S. Sozzani, D. Bosisio, Exosome-delivered microRNAs promote IFN-alpha secretion by human plasmacytoid DCs via TLR7, JCI Insight 3 (2018), https://doi.org/10.1172/jci.insight.98204.
[46] M. Zhao, Y. Zhou, B. Zhu, M. Wan, T. Jiang, Q. Tan, Y. Liu, J. Jiang, S. Luo, Y. Tan, et al., IFI44L promoter methylation as a blood biomarker for systemic lupus erythematosus, Ann. Rheum. Dis. 75 (2016) 1998–2006, https://doi.org/10.1136/annrheumdis-2015-208410.
[47] B. Zhang, L. Liu, T. Zhou, X. Shi, H. Wu, Z. Xiang, M. Zhao, Q. Lu, A simple and highly efficient method of IFI44L methylation detection for the diagnosis of systemic lupus erythematosus, Clin. Immunol. 221 (2020), 108612, https://doi.org/10.1016/j.clim.2020.108612.
[48] B. Zhang, T. Zhou, H. Wu, M. Zhao, Q. Lu, Difference of IFI44L methylation and serum IFN-a1 level among patients with discoid and systemic lupus erythematosus and healthy individuals, J Transl Autoimmun 4 (2021), 100092, https://doi.org/10.1016/j.jtauto.2021.100092.
[49] B. Qu, J. Cao, F. Zhang, H. Cui, J. Teng, J. Li, Z. Liu, C. Morehouse, B. Jallal, Y. Tang, et al., Type I interferon inhibition of MicroRNA-146a maturation through up-regulation of monocyte chemotactic protein-induced protein 1 in systemic lupus erythematosus, Arthritis Rheumatol. 67 (2015) 3209–3218, https://doi.org/10.1002/art.39398.
[50] G. Hou, I.T.W. Harley, X. Lu, T. Zhou, N. Xu, C. Yao, Y. Qin, Y. Ouyang, J. Ma, X. Zhu, et al., SLE non-coding genetic risk variant determines the epigenetic dysfunction of an immune cell specific enhancer that controls disease-critical microRNA expression, Nat. Commun. 12 (2021) 135, https://doi.org/10.1038/s41467-020-20460-1.
[51] W. Liu, Z. Wang, L. Liu, Z. Yang, S. Liu, Z. Ma, Y. Liu, Y. Ma, L. Zhang, X. Zhang, et al., LncRNA Malat1 inhibition of TDP43 cleavage suppresses IRF3-initiated antiviral innate immunity, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 23695–23706, https://doi.org/10.1073/pnas.2003932117.
[52] G. Dong, Y. Yang, X. Li, X. Yao, Y. Zhu, H. Zhang, H. Wang, Q. Ma, J. Zhang, H. Shi, et al., Granulocytic myeloid-derived suppressor cells contribute to IFN-I signaling activation of B cells and disease progression through the lncRNA NEAT1-BAFF axis in systemic lupus erythematosus, Biochim. Biophys. Acta, Mol. Basis Dis. 1866 (2020), 165554, https://doi.org/10.1016/j.bbadis.2019.165554.
[53] Z. Xue, C. Cui, Z. Liao, S. Xia, P. Zhang, J. Qin, Q. Guo, S. Chen, Q. Fu, Z. Yin, et al., Identification of LncRNA Linc00513 containing lupus-associated genetic variants as a novel regulator of interferon signaling pathway, Front. Immunol. 9 (2018) 2967, https://doi.org/10.3389/fimmu.2018.02967.
[54] Z. Liao, Z. Ye, Z. Xue, L. Wu, Y. Ouyang, C. Yao, C. Cui, N. Xu, J. Ma, G. Hou, et al., Identification of renal long non-coding RNA RP11-2B6.2 as a positive regulator of type I interferon signaling pathway in lupus nephritis, Front. Immunol. 10 (2019) 975, https://doi.org/10.3389/fimmu.2019.00975.
[55] G. Nygaard, G. Firestein, Restoring synovial homeostasis in rheumatoid arthritis by targeting fibroblast-like synoviocytes, Nat. Rev. Rheumatol. 16 (2020) 316–333, https://doi.org/10.1038/s41584-020-0413-5.
[56] J. Karami, S. Aslani, M. Tahmasebi, M. Mousavi, A. Sharafat Vaziri, A. Jamshidi, E. Farhadi, M. Mahmoudi, Epigenetics in rheumatoid arthritis; fibroblast-like synoviocytes as an emerging paradigm in the pathogenesis of the disease, Immunol. Cell Biol. 98 (2020) 171–186, https://doi.org/10.1111/imcb.12311.
[57] M. Ciechomska, L. Roszkowski, W. Maslinski, DNA methylation as a future therapeutic and diagnostic target in rheumatoid arthritis, Cells 8 (2019), https://doi.org/10.3390/cells8090953.
[58] N. Bottini, G. Firestein, Epigenetics in rheumatoid arthritis: a primer for rheumatologists, Curr. Rheumatol. Rep. 15 (2013) 372, https://doi.org/10.1007/s11926-013-0372-9.
[59] X. Zhu, Y. Zhu, C. Ding, W. Zhang, H. Guan, C. Li, X. Lin, Y. Zhang, C. Huang, L. Zhang, et al., LncRNA H19 regulates macrophage polarization and promotes Freund's complete adjuvant-induced arthritis by upregulating KDM6A, Int. Immunopharm. 93 (2021), 107402, https://doi.org/10.1016/j.intimp.2021.107402.
[60] J. Yang, Y. Li, L. Wang, Z. Zhang, Z. Li, Q. Jia, LncRNA H19 aggravates TNF-α-induced inflammatory injury via TAK1 pathway in MH7A cells, Biofactors 46 (2020) 813–820, https://doi.org/10.1002/biof.1659.
[61] Y. Rao, Y. Fang, W. Tan, D. Liu, Y. Pang, X. Wu, C. Zhang, G. Li, Delivery of long non-coding RNA NEAT1 by peripheral blood monouclear cells-derived exosomes promotes the occurrence of rheumatoid arthritis via the MicroRNA-23a/MDM2/SIRT6 Axis, Front. Cell Dev. Biol. 8 (2020), 551681, https://doi.org/10.3389/fcell.2020.551681.

[62] S. Chatterjee, D. Bhattcharjee, S. Misra, A. Saha, N. Bhattacharyya, A. Ghosh, MEG3, MALAT1, NEAT1Increase in significantly predicts the clinical parameters in patients with rheumatoid arthritis, Pers. Med. 17 (2020) 445–457, https://doi.org/10.2217/pme-2020-0009.

[63] J. Cao, X. Lv, Y. Zhang, A. Xu, T. Jiang, LncRNA GAS5 activates the AMPK pathway in peripheral blood mononuclear cells derived from rheumatoid arthritis patients, International journal of rheumatic diseases 23 (2020) 1318–1327, https://doi.org/10.1111/1756-185x.13930.

[64] F. Zhao, J. Dong, J. Guo, L. Bi, Inhibiting role of long non-coding RNA LINC01197 in inflammation in rheumatoid arthritis through the microRNA-150/THBS2 axis, Exp. Cell Res. 394 (2020), 112136, https://doi.org/10.1016/j.yexcr.2020.112136.

[65] J. Wen, J. Liu, X. Wang, J. Wang, Expression and clinical significance of circular RNAs related to immunity and inflammation in patients with rheumatoid arthritis, Int. Immunopharm. 92 (2021), 107366, https://doi.org/10.1016/j.intimp.2021.107366.

[66] J. Wen, J. Liu, P. Zhang, H. Jiang, L. Xin, L. Wan, Y. Sun, D. Huang, Y. Sun, Y. Long, et al., RNA-seq reveals the circular RNA and miRNA expression profile of peripheral blood mononuclear cells in patients with rheumatoid arthritis, Biosci. Rep. 40 (2020), https://doi.org/10.1042/bsr20193160.

[67] J. Yang, M. Cheng, B. Gu, J. Wang, S. Yan, D. Xu, CircRNA_09505 aggravates inflammation and joint damage in collagen-induced arthritis mice via miR-6089/AKT1/NF-κB axis, Cell Death Dis. 11 (2020) 833, https://doi.org/10.1038/s41419-020-03038-z.

[68] Q. Luo, Y. Gao, L. Zhang, J. Rao, Y. Guo, Z. Huang, J. Li, ALKBH5Decreased , , and in peripheral blood are as risk factors for rheumatoid arthritis, BioMed Res. Int. 2020 (2020), 5735279, https://doi.org/10.1155/2020/5735279.

[69] J. Wang, S. Yan, H. Lu, S. Wang, D. Xu, κMETTL3 attenuates LPS-induced inflammatory response in macrophages via NF-B signaling pathway, Mediat. Inflamm. 2019 (2019), 3120391, https://doi.org/10.1155/2019/3120391.

[70] E. Ha, S. Bang, J. Lim, J. Yun, J. Kim, J. Bae, H. Lee, B. Kim, K. Kim, S. Bae, Genetic variants shape rheumatoid arthritis-specific transcriptomic features in CD4 T cells through differential DNA methylation, explaining a substantial proportion of heritability, Ann. Rheum. Dis. (2021), https://doi.org/10.1136/annrheumdis-2020-219152.

[71] K. Guderud, L. Sunde, S. Flåm, M. Mæhlen, M. Mjaavatten, S. Lillegraven, A. Aga, I. Evenrød, E. Norli, B. Andreassen, et al., Rheumatoid arthritis patients, both newly diagnosed and methotrexate treated, show more DNA methylation differences in CD4 memory than in CD4 naïve T cells, Front. Immunol. 11 (2020) 194, https://doi.org/10.3389/fimmu.2020.00194.

[72] M. Lochner, Z. Wang, T. Sparwasser, The special relationship in the development and function of T helper 17 and regulatory T cells, Progress in molecular biology and translational science 136 (2015) 99–129, https://doi.org/10.1016/bs.pmbts.2015.07.013.

[73] Y. Huang, H. Wang, X. Ba, Z. Chen, Y. Wang, K. Qin, Y. Huang, P. Shen, S. Tu, Decipher manifestations and Treg/Th17 imbalance in multi-staging rheumatoid arthritis and correlation with TSDR/RORC methylation, Mol. Immunol. 127 (2020) 1–11, https://doi.org/10.1016/j.molimm.2020.08.002.

[74] M. de Andres, E. Perez-Pampin, M. Calaza, F. Santaclara, I. Ortea, J. Gomez-Reino, A. Gonzalez, Assessment of global DNA methylation in peripheral blood cell subpopulations of early rheumatoid arthritis before and after methotrexate, Arthritis Res. Ther. 17 (2015) 233, https://doi.org/10.1186/s13075-015-0748-5.

[75] C. Miao, Y. Yang, X. He, J. Li, New advances of DNA methylation and histone modifications in rheumatoid arthritis, with special emphasis on MeCP2, Cell. Signal. 25 (2013) 875–882, https://doi.org/10.1016/j.cellsig.2012.12.017.

[76] Q. Su, J. Jing, W. Li, J. Ma, X. Zhang, Z. Wang, Z. Zhou, L. Dai, L. Shao, Impaired Tip60-mediated Foxp3 acetylation attenuates regulatory T cell development in rheumatoid arthritis, J. Autoimmun. 100 (2019) 27–39, https://doi.org/10.1016/j.jaut.2019.02.007.

[77] X. Xiao, Y. Li, X. Jiang, X. Ji, X. Lu, B. Yang, L. Wu, X. Wang, J. Guo, L. Zhao, et al., EZH2 deficiency attenuates Treg differentiation in rheumatoid arthritis, J. Autoimmun. 108 (2020), 102404, https://doi.org/10.1016/j.jaut.2020.102404.

[78] Y. Li, M. Zhou, X. Lv, L. Song, D. Zhang, Y. He, M. Wang, X. Zhao, X. Yuan, G. Shi, et al., Reduced activity of HDAC3 and increased acetylation of histones H3 in peripheral blood mononuclear cells of patients with rheumatoid arthritis, Journal of immunology research 2018 (2018), 7313515, https://doi.org/10.1155/2018/7313515.

[79] L. Göschl, T. Preglej, N. Boucheron, V. Saferding, L. Müller, A. Platzer, K. Hirahara, H. Shih, J. Backlund, P. Matthias, et al., Histone deacetylase 1 (HDAC1): a key player of T cell-mediated arthritis, J. Autoimmun. 108 (2020), 102379, https://doi.org/10.1016/j.jaut.2019.102379.

[80] J.K. Park, Y.J. Jang, B.R. Oh, J. Shin, D. Bae, N. Ha, Y.I. Choi, G.S. Youn, J. Park, E.Y. Lee, et al., Therapeutic potential of CKD-506, a novel selective histone deacetylase 6 inhibitor, in a murine model of rheumatoid arthritis, Arthritis Res. Ther. 22 (2020) 176, https://doi.org/10.1186/s13075-020-02258-0.

[81] B.R. Oh, D.H. Suh, D. Bae, N. Ha, Y.I. Choi, H.J. Yoo, J.K. Park, E.Y. Lee, E.B. Lee, Y.W. Song, Therapeutic effect of a novel histone deacetylase 6 inhibitor, CKD-L, on collagen-induced arthritis in vivo and regulatory T cells in rheumatoid arthritis in vitro, Arthritis Res. Ther. 19 (2017) 154, https://doi.org/10.1186/s13075-017-1357-2.

[82] X. Zhu, L. Wu, X. Mo, W. Xia, Y. Guo, M. Wang, K. Zeng, J. Wu, Y. Qiu, X. Lin, et al., Identification of PBMC-expressed miRNAs for rheumatoid arthritis, Epigenetics 15 (2020) 386–397, https://doi.org/10.1080/15592294.2019.1676613.

[83] G. Yang, D. Wu, G. Zeng, O. Jiang, P. Yuan, S. Huang, J. Zhu, J. Tian, Y. Weng, Z. Rao, Correlation between miR-126 expression and DNA hypomethylation of CD4+ T cells in rheumatoid arthritis patients, Int. J. Clin. Exp. Pathol. 8 (2015) 8929–8936.

[84] T. Kmiołek, E. Rzeszotarska, A. Wajda, E. Walczuk, E. Kuca-Warnawin, K. Romanowska-Próchnicka, B. Stypinska, D. Majewski, P. Jagodzinski, A. Pawlik, et al., The interplay between transcriptional factors and MicroRNAs as an important factor for Th17/treg balance in RA patients, Int. J. Mol. Sci. 21 (2020), https://doi.org/10.3390/ijms21197169.

[85] M. Kurowska-Stolarska, S. Alivernini, E. Melchor, A. Elmesmari, B. Tolusso, C. Tange, L. Petricca, D. Gilchrist, G. Di Sante, C. Keijzer, et al., MicroRNA-34a dependent regulation of AXL controls the activation of dendritic cells in inflammatory arthritis, Nat. Commun. 8 (2017), 15877, https://doi.org/10.1038/ncomms15877.

[86] Q. Zhou, S. Haupt, J. Kreuzer, A. Hammitzsch, F. Proft, C. Neumann, J. Leipe, M. Witt, H. Schulze-Koops, A. Skapenko, Decreased expression of miR-146a and miR-155 contributes to an abnormal Treg phenotype in patients with rheumatoid arthritis, Ann. Rheum. Dis. 74 (2015) 1265–1274, https://doi.org/10.1136/annrheumdis-2013-204377.

[87] P. Yang, M. Zhang, X. Wang, A. Xu, M. Shen, B. Jiang, X. Zhou, L. Zhou, MicroRNA let-7g-5p alleviates murine collagen-induced arthritis by inhibiting Th17 cell differentiation, Biochem. Pharmacol. 174 (2020), 113822, https://doi.org/10.1016/j.bcp.2020.113822.

[88] Y. Wu, W. Liu, B. Xue, L. Zhang, X. Liu, B. Liu, Y. Wang, Y. Cai, R. Duan, Upregulated expression of microRNA-16 correlates with Th17/treg cell imbalance in patients with rheumatoid arthritis, DNA Cell Biol. 35 (2016) 853–860, https://doi.org/10.1089/dna.2016.3349.

[89] L. Wang, C. Wang, X. Jia, J. Yu, Circulating exosomal miR-17 inhibits the induction of regulatory T cells via suppressing TGFBR II expression in rheumatoid arthritis, Cell. Physiol. Biochem. : international journal of experimental cellular physiology, biochemistry, and pharmacology 50 (2018) 1754–1763, https://doi.org/10.1159/000494793.

[90] L. Dong, X. Wang, J. Tan, H. Li, W. Qian, J. Chen, Q. Chen, J. Wang, W. Xu, C. Tao, et al., Decreased expression of microRNA-21 correlates with the imbalance of Th17 and Treg cells in patients with rheumatoid arthritis, J. Cell Mol. Med. 18 (2014) 2213–2224, https://doi.org/10.1111/jcmm.12353.

[91] M. Xie, J. Wang, W. Gong, H. Xu, X. Pan, Y. Chen, S. Ru, H. Wang, X. Chen, Y. Zhao, et al., NF-κB-driven miR-34a impairs Treg/Th17 balance via targeting Foxp3, J. Autoimmun. 102 (2019) 96–113, https://doi.org/10.1016/j.jaut.2019.04.018.

[92] H. Xiang, F. Pan, J. Yan, L. Hong, L. Zhang, Y. Liu, X. Feng, C. Cai, [Upregulation of miR-498 suppresses Th17 cell differentiation by targeting STAT3 in rheumatoid arthritis patients], Sheng Li Xue Bao : Acta Physiol. Sin. 70 (2018) 167–174.

[93] S. Friday, D. Fox, Phospholipase D enzymes facilitate IL-17- and TNFα-induced expression of proinflammatory genes in rheumatoid arthritis synovial fibroblasts (RASF), Immunol. Lett. 174 (2016) 9–18, https://doi.org/10.1016/j.imlet.2016.04.001.

[94] N. Gaur, E. Karouzakis, S. Glück, E. Bagdonas, A. Jüngel, B. Michel, R. Gay, S. Gay, M. Frank-Bertoncelj, M. Neidhart, MicroRNAs interfere with DNA methylation in rheumatoid arthritis synovial fibroblasts, RMD Open 2 (2016), e000299, https://doi.org/10.1136/rmdopen-2016-000299.

[95] E. Karouzakis, R. Gay, B. Michel, S. Gay, M. Neidhart, DNA hypomethylation in rheumatoid arthritis synovial fibroblasts, Arthritis Rheum. 60 (2009) 3613–3622, https://doi.org/10.1002/art.25018.

[96] E. Karouzakis, M. Trenkmann, R. Gay, B. Michel, S. Gay, M. Neidhart, Epigenome analysis reveals TBX5 as a novel transcription factor involved in the activation of rheumatoid arthritis synovial fibroblasts, J. Immunol. 193 (2014) 4945–4951, https://doi.org/10.4049/jimmunol.1400066.

[97] S. Hawtree, M. Muthana, J. Wilkinson, M. Akil, A. Wilson, Histone deacetylase 1 regulates tissue destruction in rheumatoid arthritis, Hum. Mol. Genet. 24 (2015) 5367–5377, https://doi.org/10.1093/hmg/ddv258.

[98] T. Zhang, L. Yang, Y. Ke, J. Lei, S. Shen, S. Shao, C. Zhang, Z. Zhu, E. Dang, G. Wang, EZH2-dependent epigenetic modulation of histone H3 lysine-27 contributes to psoriasis by promoting keratinocyte proliferation, Cell Death Dis. 11 (2020) 826, https://doi.org/10.1038/s41419-020-03028-1.

[99] B. Zhang, M. Zhao, Q. Lu, Extracellular vesicles in rheumatoid arthritis and systemic lupus erythematosus: functions and applications, Front. Immunol. 11 (2020), 575712, https://doi.org/10.3389/fimmu.2020.575712.

[100] M. Kurowska-Stolarska, S. Alivernini, L. Ballantine, D. Asquith, N. Millar, D. Gilchrist, J. Reilly, M. Ierna, A. Fraser, B. Stolarski, et al., MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis, Proc. Natl. Acad. Sci. U. S. A 108 (2011) 11193–11198, https://doi.org/10.1073/pnas.1019536108.

[101] D. Sekar, Implications of microRNA 21 and its involvement in the treatment of different type of arthritis, Mol. Cell. Biochem. 476 (2021) 941–947, https://doi.org/10.1007/s11010-020-03960-y.

[102] T. Peng, D. Ji, Y. Jiang, Long non-coding RNA GAS5 suppresses rheumatoid arthritis progression via miR-128-3p/HDAC4 axis, Mol. Cell. Biochem. (2021), https://doi.org/10.1007/s11010-021-04098-1.

[103] A. Song, L. Kang, Y. Wang, M. Wang, MiR-34a-5p inhibits fibroblast-like synoviocytes proliferation via XBP1, Eur. Rev. Med. Pharmacol. Sci. 24 (2020) 11675–11682, https://doi.org/10.26355/eurrev_202011_23812.

[104] A. Hegewald, K. Breitwieser, S. Ottinger, F. Mobarrez, M. Korotkova, B. Rethi, P. Jakobsson, A. Catrina, H. Wähämaa, M. Saul, Extracellular miR-574-5p induces

osteoclast differentiation via TLR 7/8 in rheumatoid arthritis, Front. Immunol. 11 (2020), 585282, https://doi.org/10.3389/fimmu.2020.585282.
[105] J. Peng, S. Chen, C. Wu, H. Chong, Y. Ding, A. Shiau, C. Wang, Amelioration of experimental autoimmune arthritis through targeting of synovial fibroblasts by intraarticular delivery of MicroRNAs 140-3p and 140-5p, Arthritis Rheumatol. 68 (2016) 370–381, https://doi.org/10.1002/art.39446.
[106] A. Najm, F. Masson, P. Preuss, S. Georges, B. Ory, T. Quillard, S. Sood, C. Goodyear, D. Veale, U. Fearon, et al., MicroRNA-17-5p reduces inflammation and bone erosions in mice with collagen-induced arthritis and directly targets the JAK/STAT pathway in rheumatoid arthritis fibroblast-like synoviocytes, Arthritis Rheumatol. 72 (2020) 2030–2039, https://doi.org/10.1002/art.41441.
[107] J. Stanczyk, D. Pedrioli, F. Brentano, O. Sanchez-Pernaute, C. Kolling, R. Gay, M. Detmar, S. Gay, D. Kyburz, Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis, Arthritis Rheum. 58 (2008) 1001–1009, https://doi.org/10.1002/art.23386.
[108] Q. Meng, B. Qiu, Exosomal MicroRNA-320a derived from mesenchymal stem cells regulates rheumatoid arthritis fibroblast-like synoviocyte activation by suppressing CXCL9 expression, Front. Physiol. 11 (2020) 441, https://doi.org/10.3389/fphys.2020.00441.
[109] Y. Ding, L. Wang, H. Wu, Q. Zhao, S. Wu, Exosomes derived from synovial fibroblasts under hypoxia aggravate rheumatoid arthritis by regulating Treg/Th17 balance, Exp. Biol. Med. 245 (2020) 1177–1186, https://doi.org/10.1177/1535370220934736.
[110] Y. Zhang, Z.P. Feng, G. Naselli, F. Bell, J. Wettenhall, P. Auyeung, J.A. Ellis, A. L. Ponsonby, T.P. Speed, M.M. Chong, et al., MicroRNAs in CD4(+) T cell subsets are markers of disease risk and T cell dysfunction in individuals at risk for type 1 diabetes, J. Autoimmun. 68 (2016) 52–61, https://doi.org/10.1016/j.jaut.2015.12.006.
[111] I. Serr, M.G. Scherm, A.M. Zahm, J. Schug, V.K. Flynn, M. Hippich, S. Kalin, M. Becker, P. Achenbach, A. Nikolaev, et al., A miRNA181a/NFAT5 axis links impaired T cell tolerance induction with autoimmune type 1 diabetes, Sci. Transl. Med. 10 (2018), https://doi.org/10.1126/scitranslmed.aag1782.
[112] I. Serr, R.W. Furst, V.B. Ott, M.G. Scherm, A. Nikolaev, F. Gokmen, S. Kalin, S. Zillmer, M. Bunk, B. Weigmann, et al., miRNA92a targets KLF2 and the phosphatase PTEN signaling to promote human T follicular helper precursors in T1D islet autoimmunity, Proc. Natl. Acad. Sci. U. S. A. 113 (2016) E6659–E6668, https://doi.org/10.1073/pnas.1606646113.
[113] S. Thomaidou, M.J.L. Kracht, A. van der Slik, S. Laban, E.J. de Koning, F. Carlotti, R.C. Hoeben, B.O. Roep, A. Zaldumbide, Beta-cell stress shapes CTL immune recognition of preproinsulin signal peptide by posttranscriptional regulation of endoplasmic reticulum aminopeptidase 1, Diabetes 69 (2020) 670–680, https://doi.org/10.2337/db19-0984.
[114] H.A. Abdelsamed, C.C. Zebley, H. Nguyen, R.L. Rutishauser, Y. Fan, H. E. Ghoneim, J.C. Crawford, F. Alfei, S. Alli, S.P. Ribeiro, et al., Beta cell-specific CD8(+) T cells maintain stem cell memory-associated epigenetic programs during type 1 diabetes, Nat. Immunol. 21 (2020) 578–587, https://doi.org/10.1038/s41590-020-0633-5.
[115] C.Y. Hsu, L.T. Yeh, S.H. Fu, M.W. Chien, Y.W. Liu, S.C. Miaw, D.M. Chang, H. K. Sytwu, SUMO-defective c-Maf preferentially transactivates Il21 to exacerbate autoimmune diabetes, J. Clin. Invest. 128 (2018) 3779–3793, https://doi.org/10.1172/JCI98786.
[116] X. Zhang, H. Gu, L. Wang, F. Huang, J. Cai, MiR-885-3p is down-regulated in peripheral blood mononuclear cells from T1D patients and regulates the inflammatory response via targeting TLR4/NF-kappaB signaling, J. Gene Med. 22 (2020) e3145, https://doi.org/10.1002/jgm.3145.
[117] F. Miao, Z. Chen, L. Zhang, Z. Liu, X. Wu, Y.C. Yuan, R. Natarajan, Profiles of epigenetic histone post-translational modifications at type 1 diabetes susceptible genes, J. Biol. Chem. 287 (2012) 16335–16345, https://doi.org/10.1074/jbc.M111.330373.
[118] D.M. Mossel, K. Moganti, V. Riabov, C. Weiss, S. Kopf, J. Cordero, G. Dobreva, M. G. Rots, H. Kluter, M.C. Harmsen, et al., Epigenetic regulation of S100A9 and S100A12 expression in monocyte-macrophage system in hyperglycemic conditions, Front. Immunol. 11 (2020) 1071, https://doi.org/10.3389/fimmu.2020.01071.
[119] K.C. Herold, S. Usmani-Brown, T. Ghazi, J. Lebastchi, C.A. Beam, M.D. Bellin, M. Ledizet, J.M. Sosenko, J.P. Krischer, J.P. Palmer, et al., Beta cell death and dysfunction during type 1 diabetes development in at-risk individuals, J. Clin. Invest. 125 (2015) 1163–1173, https://doi.org/10.1172/JCI78142.
[120] Z. Wang, Z. Xie, Q. Lu, C. Chang, Z. Zhou, Beyond genetics: what causes type 1 diabetes, Clin. Rev. Allergy Immunol. 52 (2017) 273–286, https://doi.org/10.1007/s12016-016-8592-1.
[121] J. Sklenarova, L. Petruzelkova, S. Kolouskova, J. Lebl, Z. Sumnik, O. Cinek, Glucokinase gene may Be a more suitable target than the insulin gene for detection of beta cell death, Endocrinology 158 (2017) 2058–2065, https://doi.org/10.1210/en.2016-1923.
[122] F. Syed, S.A. Tersey, J.V. Turatsinze, J.L. Felton, N.J. Kang, J.B. Nelson, E.K. Sims, M. Defrance, M. Bizet, F. Fuks, et al., Circulating unmethylated CHTOP and INS DNA fragments provide evidence of possible islet cell death in youth with obesity and diabetes, Clin. Epigenet. 12 (2020) 116, https://doi.org/10.1186/s13148-020-00906-5.
[123] G. Xu, L.A. Thielen, J. Chen, T.B. Grayson, T. Grimes, S.L. Bridges Jr., H.M. Tse, B. Smith, R. Patel, P. Li, et al., Serum miR-204 is an early biomarker of type 1 diabetes-associated pancreatic beta-cell loss, Am. J. Physiol. Endocrinol. Metab. 317 (2019) E723–E730, https://doi.org/10.1152/ajpendo.00122.2019.
[124] A.S. Santos, E. Cunha Neto, R.T. Fukui, L.R.P. Ferreira, M.E.R. Silva, Increased expression of circulating microRNA 101-3p in type 1 diabetes patients: new insights into miRNA-regulated pathophysiological pathways for type 1 diabetes, Front. Immunol. 10 (2019) 1637, https://doi.org/10.3389/fimmu.2019.01637.
[125] S. Garavelli, S. Bruzzaniti, E. Tagliabue, D. Di Silvestre, F. Prattichizzo, E. Mozzillo, V. Fattorusso, L. La Sala, A. Ceriello, A.A. Puca, et al., Plasma circulating miR-23~27~24 clusters correlate with the immunometabolic derangement and predict C-peptide loss in children with type 1 diabetes, Diabetologia 63 (2020) 2699–2712, https://doi.org/10.1007/s00125-020-05237-x.
[126] S. Roels, O.R. Costa, S.A. Tersey, G. Stange, D. De Smet, E.V. Balti, P. Gillard, B. Keymeulen, Z. Ling, D.G. Pipeleers, et al., Combined analysis of GAD65, miR-375, and unmethylated insulin DNA following islet transplantation in patients with T1D, J. Clin. Endocrinol. Metab. 104 (2019) 451–460, https://doi.org/10.1210/jc.2017-02520.
[127] M.G. Pezzolesi, E. Satake, K.P. McDonnell, M. Major, A.M. Smiles, A.S. Krolewski, Circulating TGF-beta1-regulated miRNAs and the risk of rapid progression to ESRD in type 1 diabetes, Diabetes 64 (2015) 3285–3293, https://doi.org/10.2337/db15-0116.
[128] J. Tian, W. Pan, X. Xu, X. Tian, M. Zhang, Q. Hu, NF-kappaB inhibits the occurrence of type 1 diabetes through microRNA-150-dependent PUMA degradation, Life Sci. 255 (2020), 117724, https://doi.org/10.1016/j.lfs.2020.117724.
[129] Q. Ruan, T. Wang, V. Kameswaran, Q. Wei, D.S. Johnson, F. Matschinsky, W. Shi, Y.H. Chen, The microRNA-21-PDCD4 axis prevents type 1 diabetes by blocking pancreatic beta cell death, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 12030–12035, https://doi.org/10.1073/pnas.1101450108.
[130] Y.N. Huang, S.L. Chiang, Y.J. Lin, S.C. Liu, Y.H. Li, Y.C. Liao, M.R. Lee, P.H. Su, F. J. Tsai, H.C. Hung, et al., Long, noncoding RNA SRA induces apoptosis of beta-cells by promoting the IRAK1/LDHA/lactate pathway, Int. J. Mol. Sci. (2021) 22, https://doi.org/10.3390/ijms22041720.
[131] P. Wang, Q. Liu, H. Zhao, J.O. Bishop, G. Zhou, L.K. Olson, A. Moore, miR-216a-targeting theranostic nanoparticles promote proliferation of insulin-secreting cells in type 1 diabetes animal model, Sci. Rep. 10 (2020) 5302, https://doi.org/10.1038/s41598-020-62269-4.
[132] P. Tsou, Epigenetic control of scleroderma: current knowledge and future perspectives, Curr. Rheumatol. Rep. 21 (2019) 69, https://doi.org/10.1007/s11926-019-0877-y.
[133] C. Bergmann, J. Distler, Epigenetic factors as drivers of fibrosis in systemic sclerosis, Epigenomics 9 (2017) 463–477, https://doi.org/10.2217/epi-2016-0150.
[134] Y. Luo, Y. Wang, Y. Shu, Q. Lu, R. Xiao, Epigenetic mechanisms: an emerging role in pathogenesis and its therapeutic potential in systemic sclerosis, Int. J. Biochem. Cell Biol. 67 (2015) 92–100, https://doi.org/10.1016/j.biocel.2015.05.023.
[135] T. Maehara, N. Kaneko, C. Perugino, H. Mattoo, J. Kers, H. Allard-Chamard, V. Mahajan, H. Liu, S. Murphy, M. Ghebremichael, et al., Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis, J. Clin. Invest. 130 (2020) 2451–2464, https://doi.org/10.1172/jci131700.
[136] T. Li, L. Ortiz-Fernández, E. Andrés-León, L. Ciudad, B. Javierre, E. López-Isac, A. Guillén-Del-Castillo, C. Simeón-Aznar, E. Ballestar, J. Martin, Epigenomics and transcriptomics of systemic sclerosis CD4+ T cells reveal long-range dysregulation of key inflammatory pathways mediated by disease-associated susceptibility loci, Genome Med. 12 (2020) 81, https://doi.org/10.1186/s13073-020-00779-6.
[137] Y. Wang, Y. Shu, Y. Xiao, Q. Wang, T. Kanekura, Y. Li, J. Wang, M. Zhao, Q. Lu, R. Xiao, Hypomethylation and overexpression of ITGAL (CD11a) in CD4(+) T cells in systemic sclerosis, Clin. Epigenet. 6 (2014) 25, https://doi.org/10.1186/1868-7083-6-25.
[138] Y. Wang, Q. Wang, X. Sun, R. Liu, Y. Shu, T. Kanekura, J. Huang, Y. Li, J. Wang, M. Zhao, et al., DNA hypermethylation of the forkhead box protein 3 (FOXP3) promoter in CD4+ T cells of patients with systemic sclerosis, Br. J. Dermatol. 171 (2014) 39–47, https://doi.org/10.1111/bjd.12913.
[139] M. van der Kroef, M. Castellucci, M. Mokry, M. Cossu, M. Garonzi, L. Bossini-Castillo, E. Chouri, C. Wichers, L. Beretta, E. Trombetta, et al., Histone modifications underlie monocyte dysregulation in patients with systemic sclerosis, underlining the treatment potential of epigenetic targeting, Ann. Rheum. Dis. 78 (2019) 529–538, https://doi.org/10.1136/annrheumdis-2018-214295.
[140] E. Chouri, M. Wang, M. Hillen, C. Angiolilli, S. Silva-Cardoso, C. Wichers, M. van der Kroef, C. Bekker, M. Cossu, L. van Bon, et al., Implication of miR-126 and miR-139-5p in plasmacytoid dendritic cell dysregulation in systemic sclerosis, J. Clin. Med. 10 (2021), https://doi.org/10.3390/jcm10030491.
[141] P. Tsou, P. Campbell, M. Amin, P. Coit, S. Miller, D. Fox, D. Khanna, A. Sawalha, Inhibition of EZH2 prevents fibrosis and restores normal angiogenesis in scleroderma, Proc. Natl. Acad. Sci. U. S. A 116 (2019) 3695–3702, https://doi.org/10.1073/pnas.1813006116.
[142] J. Henderson, M. Brown, S. Horsburgh, L. Duffy, S. Wilkinson, J. Worrell, R. Stratton, S. O'Reilly, Methyl cap binding protein 2: a key epigenetic protein in systemic sclerosis, Rheumatology 58 (2019) 527–535, https://doi.org/10.1093/rheumatology/key327.
[143] Y. Zhang, S. Pötter, C. Chen, R. Liang, K. Gelse, I. Ludolph, R. Horch, O. Distler, G. Schett, J. Distler, et al., Poly(ADP-ribose) polymerase-1 regulates fibroblast activation in systemic sclerosis, Ann. Rheum. Dis. 77 (2018) 744–751, https://doi.org/10.1136/annrheumdis-2017-212265.
[144] Q. Yao, Y. Xing, Z. Wang, J. Liang, Q. Lin, M. Huang, Y. Chen, B. Lin, X. Xu, W. Chen, MiR-16-5p suppresses myofibroblast activation in systemic sclerosis by inhibiting NOTCH signaling, Aging 13 (2020) 2640–2654, https://doi.org/10.18632/aging.202308.

[145] J. Henderson, S. Pryzborski, R. Stratton, S. O'Reilly, Wnt antagonist DKK-1 levels in systemic sclerosis are lower in skin but not in blood and are regulated by microRNA33a-3p, Exp. Dermatol. 30 (2021) 162–168, https://doi.org/10.1111/exd.14136.

[146] S.J. Hogg, P.A. Beavis, M.A. Dawson, R.W. Johnstone, Targeting the epigenetic regulation of antitumour immunity, Nat. Rev. Drug Discov. 19 (2020) 776–800, https://doi.org/10.1038/s41573-020-0077-5.

[147] R. Mazzone, C. Zwergel, M. Artico, S. Taurone, M. Ralli, A. Greco, A. Mai, The emerging role of epigenetics in human autoimmune disorders, Clin. Epigenet. 11 (2019) 34, https://doi.org/10.1186/s13148-019-0632-2.

[148] M.E. Breitbach, R.C. Ramaker, K. Roberts, R.P. Kimberly, D. Absher, Population-specific patterns of epigenetic defects in the B cell lineage in patients with systemic lupus erythematosus, Arthritis Rheumatol. 72 (2020) 282–291, https://doi.org/10.1002/art.41083.

[149] S. Miller, P.S. Tsou, P. Coit, E. Gensterblum-Miller, P. Renauer, D.M. Rohraff, N. C. Kilian, M. Schonfeld, A.H. Sawalha, Hypomethylation of STAT1 and HLA-DRB1 is associated with type-I interferon-dependent HLA-DRB1 expression in lupus CD8 + T cells, Ann. Rheum. Dis. 78 (2019) 519–528, https://doi.org/10.1136/annrheumdis-2018-214323.

[150] M. Zhao, M.Y. Li, X.F. Gao, S.J. Jia, K.Q. Gao, Y. Zhou, H.H. Zhang, Y. Huang, J. Wang, H.J. Wu, et al., Downregulation of BDH2 modulates iron homeostasis and promotes DNA demethylation in CD4(+) T cells of systemic lupus erythematosus, Clin. Immunol. 187 (2018) 113–121, https://doi.org/10.1016/j.clim.2017.11.002.

[151] W. Liao, M. Li, H. Wu, S. Jia, N. Zhang, Y. Dai, M. Zhao, Q. Lu, Down-regulation of MBD4 contributes to hypomethylation and overexpression of CD70 in CD4(+) T cells in systemic lupus erythematosus, Clin. Epigenet. 9 (2017) 104, https://doi.org/10.1186/s13148-017-0405-8.

[152] J. Ye, T.G. Richardson, W.L. McArdle, C.L. Relton, K.M. Gillespie, M. Suderman, G. Hemani, Identification of loci where DNA methylation potentially mediates genetic risk of type 1 diabetes, J. Autoimmun. 93 (2018) 66–75, https://doi.org/10.1016/j.jaut.2018.06.005.

[153] H. Zhao, L. Wang, H. Luo, Q.Z. Li, X. Zuo, TNFAIP3 downregulation mediated by histone modification contributes to T-cell dysfunction in systemic lupus erythematosus, Rheumatology 56 (2017) 835–843, https://doi.org/10.1093/rheumatology/kew508.

[154] H. Gan, T. Shen, D.P. Chupp, J.R. Taylor, H.N. Sanchez, X. Li, Z. Xu, H. Zan, P. Casali, B cell Sirt1 deacetylates histone and non-histone proteins for epigenetic modulation of AID expression and the antibody response, Sci. Adv. 6 (2020), eaay2793, https://doi.org/10.1126/sciadv.aay2793.

[155] C. Wasson, R. Ross, R. Wells, C. Corinaldesi, I. Georgiou, N. Riobo-Del Galdo, F. Del Galdo, Long non-coding RNA HOTAIR induces GLI2 expression through Notch signalling in systemic sclerosis dermal fibroblasts, Arthritis Res. Ther. 22 (2020) 286, https://doi.org/10.1186/s13075-020-02376-9.

[156] C. Zhang, C. Gao, X. Di, S. Cui, W. Liang, W. Sun, M. Yao, S. Liu, Z. Zheng, Hsa_circ_0123190 acts as a competitive endogenous RNA to regulate APLNR expression by sponging hsa-miR-483-3p in lupus nephritis, Arthritis Res. Ther. (23) (2021) 24, https://doi.org/10.1186/s13075-020-02404-8.

[157] Y. Wu, F. Zhang, J. Ma, X. Zhang, L. Wu, B. Qu, S. Xia, S. Chen, Y. Tang, N. Shen, Association of large intergenic noncoding RNA expression with disease activity and organ damage in systemic lupus erythematosus, Arthritis Res. Ther. 17 (2015) 131, https://doi.org/10.1186/s13075-015-0632-3.

[158] G.C. Wu, Y. Hu, S.Y. Guan, D.Q. Ye, H.F. Pan, Differential plasma expression profiles of long non-coding RNAs reveal potential biomarkers for systemic lupus erythematosus, Biomolecules 9 (2019), https://doi.org/10.3390/biom9060206.

[159] X. Han, Y. Wang, X. Zhang, Y. Qin, B. Qu, L. Wu, J. Ma, Z. Zhou, J. Qian, M. Dai, et al., MicroRNA-130b ameliorates murine lupus nephritis through targeting the type I interferon pathway on renal mesangial cells, Arthritis Rheumatol. 68 (2016) 2232–2243, https://doi.org/10.1002/art.39725.

[160] R. Mishra, S. Bhattacharya, B.S. Rawat, A. Kumar, A. Kumar, K. Niraj, A. Chande, P. Gandhi, D. Khetan, A. Aggarwal, et al., MicroRNA-30e-5p has an integrated role in the regulation of the innate immune response during virus infection and systemic lupus erythematosus, iScience 23 (2020), 101322, https://doi.org/10.1016/j.isci.2020.101322.

[161] S. Smith, T. Fernando, P.W. Wu, J. Seo, J. Ni Gabhann, O. Piskareva, E. McCarthy, D. Howard, P. O'Connell, R. Conway, et al., MicroRNA-302d targets IRF9 to regulate the IFN-induced gene expression in SLE, J. Autoimmun. 79 (2017) 105–111, https://doi.org/10.1016/j.jaut.2017.03.003.

[162] H.N. Sanchez, J.B. Moroney, H. Gan, T. Shen, J.L. Im, T. Li, J.R. Taylor, H. Zan, P. Casali, B cell-intrinsic epigenetic modulation of antibody responses by dietary fiber-derived short-chain fatty acids, Nat. Commun. 11 (2020) 60, https://doi.org/10.1038/s41467-019-13603-6.

[163] S.A. Ramanujan, E.N. Cravens, S.M. Krishfield, V.C. Kyttaris, V.R. Moulton, Estrogen-induced hsa-miR-10b-5p is elevated in T cells from patients with systemic lupus erythematosus and downregulates splicing factor SRSF1, Arthritis Rheumatol. (2021), https://doi.org/10.1002/art.41787.

[164] J. Stanczyk, D.M. Pedrioli, F. Brentano, O. Sanchez-Pernaute, C. Kolling, R.E. Gay, M. Detmar, S. Gay, D. Kyburz, Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis, Arthritis Rheum. 58 (2008) 1001–1009, https://doi.org/10.1002/art.23386.

[165] I. Gonzalez-Moro, A. Olazagoitia-Garmendia, M.L. Colli, N. Cobo-Vuilleumier, T. S. Postler, L. Marselli, P. Marchetti, S. Ghosh, B.R. Gauthier, D.L. Eizirik, et al., The T1D-associated lncRNA Lnc13 modulates human pancreatic beta cell inflammation by allele-specific stabilization of STAT1 mRNA, Proc. Natl. Acad. Sci. U. S. A. 117 (2020) 9022–9031, https://doi.org/10.1073/pnas.1914353117.