MicroRNAs in the key events of systemic lupus erythematosus pathogenesis

Marketa Husakova

Background. Small non-coding RNA molecules (miRs) are involved in immune cell maturation and function and might influence immunopathological processes of systemic lupus erythematosus (SLE) pathogenesis.
Methods and Results. This paper presents the results of a literature search for publications dealing with the relationship between miRs and pathological factors related to SLE such as genetic background, immune dysregulation and gender-associated differences participating in SLE development. In SLE, distinct miRs are differentially expressed in SLE cells of innate and adaptive immunity. The miR-146a and miR-155 genes, among others, interfere with intracellular signalling pathways downstream of toll-like receptors 7 and 9 (TLR- 7, TLR-9) and influences interferon (IFN)-type I synthesis in plasmacytoid dendritic cells. In T and B cells, miR-126, miR-21, miR-146a, miR-155, miR-1246 and others might influence gene expression by epigenetic modifications, support abnormal cytosine release, differentiation of cell subsets, B cell hyperactivity and autoantibody production. Besides, estrogen might up- and downregulate immunologically active miRs, which are potential mediators of hormonal influences in SLE development. Moreover, SLE genetic basis included some polymorphisms of the miR-146a gene, which varies across populations.
Conclusion. Distinct miRs are differentially expressed in both SLE mice models and human patients and promote autoimmune features of immune processes. MiRs are important molecules modulating susceptibility to SLE as well as its onset, clinical diversity and progression.

Key words: microRNA, SLE, innate immunity, adaptive immunity, genetic predisposition, estrogen

Received: November 25, 2015; Accepted: January 22, 2016; Available online: March 21, 2016
http://dx.doi.org/10.5507/bp.2016.004

Institute of Rheumatology, Na Slupi 4, 12850 Prague 2, Czech Republic
Corresponding author: Marketa Husakova, e-mail: fojtikova05@gmail.com

INTRODUCTION

Systemic lupus erythematosus (SLE) is a severe autoimmune disease with various clinical manifestations including multiorgan involvement, an unpredictable course with alternation of flares and remissions requiring long-term treatment using glucocorticoids, immunosuppressive and biologic agents or both[1-3]. The worldwide overall incidence rates of SLE range from 1-10 per 100,000 person-years, and SLE affects predominantly females (the female to male ratio is 9:1) in reproductive age[4], although there appears to be a delay of the peak of disease onset after 40 years of age in the Caucasian population[5]. Interestingly, the severity of some organ manifestations, like lupus nephritis (LN) with consequences for morbidity and mortality[6], varies among populations. The clinical diversity of SLE is reflected in its complex pathogenesis. The risk conditions for SLE development, such as genetic predisposition, environmental and hormonal stimuli, dysregulation of innate as well as adaptive immunity, cumulate to cause the onset of the disease or influence its course[7].

MicroRNAs and SLE

The evolutionarily conserved small non-coding ribonucleic acid (microRNA) was discovered by Lee et al. in 1993 in the nematode *Caenorhabditis elegans* as a lin-4 transcript containing a complementary sequence to another protein-coding messenger RNA (mRNA), lin-14, whose function is regulated upon binding of these small molecules and causes disruption of larval development[8]. In subsequent years, small non-coding RNA became of key interest in many studies focused on the regulation of plant, animal and human gene expression, and the number of known microRNAs (miRNAs or miRs) increased gradually. Thus, a database of 218 miRs, miRBase (www.mirbase.org), comprising miRs sequences and annotations[9-11] was established in 2002 and has since been expending exponentially; it now contains more than 35,800 mature miRs products from 223 species including over 2500 human miRs (miRBase release 21, June 2014).

Due to their binding to complementary mRNA in the 3'-UTR region, 18-25 nucleotides long miRs alter protein expression, and are thus involved in almost all biological processes of the cell. In human medicine, the regulatory functions of miRs in cell metabolism, survival and apoptosis as well as cell proliferation and differentiation[12] have been supposed to participate in the pathogenesis of illnesses such as several types of cancer or degenerative, autoimmune and metabolic diseases[13-15]. MiRs are potent regulators of immune cell development and possibly interfere with several immunological processes[16]. In the pathogenesis of SLE, the central role belongs to dysregulation of adaptive immunity mechanisms, while pathological communication between T and B lymphocyte subsets leads to abnormal cytokine synthesis and production of autoantibodies, which are in some cases directly pathognomonic. Besides this, abnormalities in innate immunity, particularly in the early phases of the

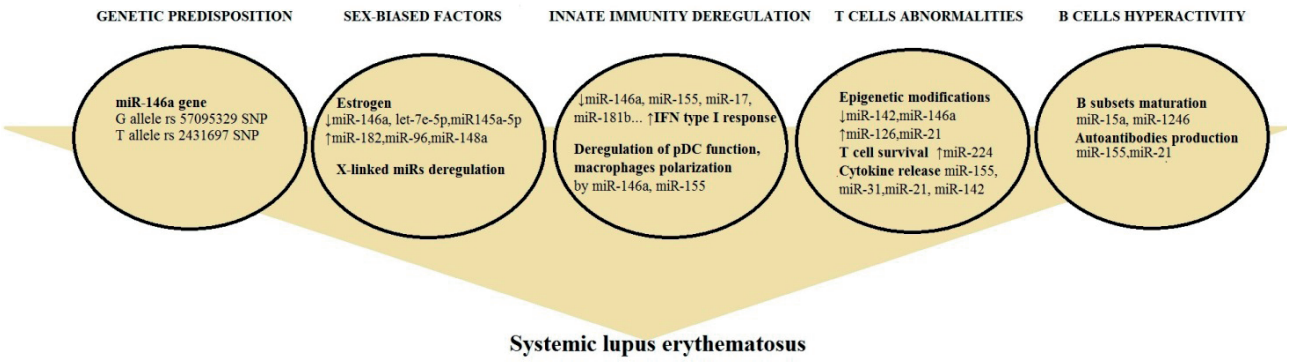

Fig. 1. List of key miRs in SLE pathogenetical events.
miR – microRNA, SNP – single nucleotide polymorphism, IFN – interferon, pDC – plasmacytoid dendritic cells, ↓downregulation, ↑upregulation.

inflammatory response during autoantigen presentation and processing by dendritic cells and phagocytes, are involved in SLE immunopathology[7]. MiRs are involved in the majority of immunopathological mechanisms in SLE. Furthermore, hormonal factors affect miRs expression particularly in immune cells, and the miR-146a gene is located within SLE-risk areas (see Fig. 1). Moreover, miRs are not located only intracelullarly, but their presence in tissues and body fluids, such as the plasma and the serum[17-23], makes them potential blood-based biomarkers of disease development and activity as well as for predicting therapeutic responses. In SLE, different patterns of miRs expression have been detected in the plasma[18-21], serum[22,23] and urine[22,23] as well as in peripheral mononuclear cells (PBMCs) (ref.[24-28]). Interestingly, underexpression of several miRs is more common in SLE (Table 1). A certain degree of variability in the SLE miRs pattern can be observed also in clinical manifestations such as renal involvement (e.g. miR-146a) (ref.[22,23]) or even SLE onset during childhood (miR-516a-3p, miR-629, miR-525-5p) (ref.[29]), and some miRs positively (e.g. miR-21) or inversely (e.g. miR-146a) correlate with the disease's activity[22,23,30]

Here we overview the genesis of miRs and potential approaches to treating SLE. Furthermore, we focus on potential links between miRs and SLE pathogenesis, in particular the distinct genetic association between miRs expression in SLE and hormonal influences on SLE and the connection to miRs dysregulation. We also review the role of miRs in immunopathological reactions linked to SLE, especially changes in innate immunity and the function of T and B cells.

MiRs biology and regulation

Biogenesis of miRs

The multistep process of miRs synthesis begins in the nucleus, and maturation is completed in the cytoplasm

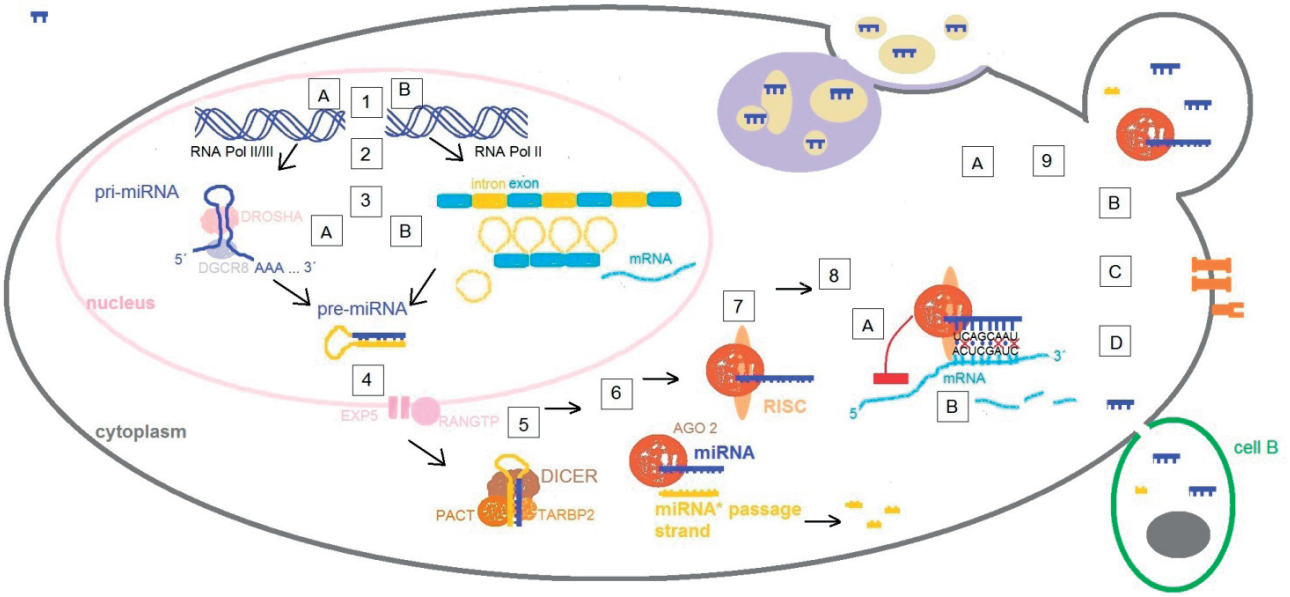

Fig. 2. MicroRNA biogenesis, function and excretion.
miRNA – microRNA, RNA – ribonucleic acid, RNA Pol – RNA polymerase, mRNA – messenger RNA, pri-miRNA – primary miRNA, DGCR8 – RNA-binding protein Pasha/DiGeorge syndrome critical region gene 8, Exp5 – Exportin 5, pre-miRNA – precursor miRNA, TARBP2 – transactivation-responsive RNA-binding protein 2, PACT – protein activator of double-stranded RNA dependent protein kinase, RISC – RNA induced silencing complex

Table 1. List of miRs differentially regulated in body fluids and peripheral mononuclear cells of Systemic lupus erythematosus.

Overexpression	Underexpression	Origin	Ref.
miR-223, miR-142-3p	miR-150	plasma	18
miR-21		plasma	20
miR-142-3p, miR-181a	miR-106a, miR-17, miR-20a, miR-203, miR-92a	plasma	19
miR-126, miR-21, miR-451, miR-16, miR-223	miR-125a-3p, miR-155, miR-146	plasma	21
	miR-200a,miR-200b,miR-429, miR-205, miR-192	serum	22
	miR-146,miR-155	serum	23
miR-189, miR-61, miR-78, miR-342, miR-142-3p, miR-299-3p	miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112	PBMC	24
	miR-127-3p, miR-1271-5p, miR-1301, miR-136-5p, miR-379-5p, miR-381-3p, miR-382-5p, miR-758-3p, miR-1466-5p, miR-154-3p, miR-154-5p, miR-31-5p, miR-409-5p, miR-410, miR-421, miR-543, miR431-5p, miR-432-5p, miR-654-3p, miR-181a-2-3p, miR-337-5p, miR-376-3p, miR-376b-3p, miR-376c-3p, miR-485-3p, miR-487b, miR-493-5p, miR-495-3p, miR-539-5p	PBMC	25
	miR-31, miR-95, miR-99a, miR-130b, miR-10a, miR-134, miR-146	PBMC	26
miR-21, miR-25, miR-148a, miR-214, miR-148b, miR-494, miR-198, miR-155, miR-324-3p, miR-342, miR-373, miR-106b, miR-544,	miR-296, miR-196c, let-17-5p, let-16, let-15a, miR-383, miR-184, miR-379, miR-150, miR-7a, miR-7d, miR-7g, miR-98, miR-832	PBMC	27
miR-157, miR-64, miR-147, miR-160, miR-65, miR-120, miR-100, miR-194, miR-217, miR-173	miR-41, miR-42, miR-27, miR-8, miR-21, miR-3, miR-40, miR-28,miR-9, miR-49	PBMC (only top ten novel dysregulated miRs)	28

The over- or underexpression to healthy controls. miR – microRNA, PBMC – peripheral mononuclear cells

(See Fig. 2, points 1-8). As described in the Fig. 2, the DNA template for miRs transcription is located either between independent transcription units (intergenic, see 1A) or intragenic (see 1B), mostly intronic regions (called mirtrons), or is deposited in repeats, in untranslated regions (UTRs), but also in coding regions of host genes in particular RNA (ref.[8,31,32]). Intergenic miRs have their own regulatory elements, but many are clustred in the genome, share promoters and are transcribed into polycistronic form, which is later divided. For example cluster miR17-92 consists of at least 6 mature miRs - miR-17, miR-18, miR-19a, miR-19b, miR-20a and miR-92. Some miRs share promoters with host genes, and intronic miRs are transcribed coincidentaly with host genes[32,33,34]. The transcription is usually guided by DNA-dependent RNA polymerase II to form a primary miR (pri-miR) (ref.[33-36]). However, if the miR sequences are interspersed within the Alu or other known repetitive elements the RNA Pol III is used for transcription[36] (see 2nd point, Fig. 2). In the nucleus, there are two independent pathways to process primary transcript to develop precursor miR (pre-miR). In canonical pathway (see Fig. 2, point 3A), the primary transcript pri-miR might be composed of one or several miR hairpins, it is a stem-loop structure containg 7-methylguanosine cap at the 5'end and a 3'polyadenylated tail and sometimes also introns. Pri-miR is captured by the RNA-binding protein Pasha/DiGeorge syndrome critical region gene 8 (DGCR8) and together with RNA III-type enzyme Drosha form a protein "microprocessor" complex, where is pri-miR cleaved into 60-70 nucleotides long pre-miR (ref.[37]). In the non-canonical pathway (see Fig. 2, point 3B) the primary transcript is processed in spliceosomes. Released spliced hairpins of pre-miR-sized introns are subsequently trimmed by debranching enzymes into pre-miR (ref.[34]). Pre-miR is transported from the nucleus to the cytoplasm by the Exportin-5 (Exp5) – RanGTP complex[38]. RanGTP structure stabilises the miRNA and facilitate the correct transport, see point 4 in the Fig. 2. In the cytoplasm, pre-miRs form protein complex consisting of transactivation-responsive RNA-binding protein 2 (TARBP2) and protein activator of double-stranded RNA dependent protein kinase (PACT) and undergoes final cleavage by RNA III endonuclease III Dicer[39,40] (see Fig. 2, 5th point). The resulting product, 22 nucleotides long miR-miR* strand duplex is attached to Argonaute (Ago)-2 protein and are separated into mature miR and miR* pas-

sanger strand (ref.[40,41]), see Fig. 2, 6th point. The miR star strand usually undergoes degradation[39], however, in some cases might keep regulatory function. Thus, according to sequence derived from 5'or 3' arms of pre-miR precursor can be miR/miR* also termed as -5 or -3p (ref.[10]). The single stranded mature miR –Ago2 becomes part of the RNA induced silencing complex (RISC) (ref.[40,41]), see Fig. 2, point 7. RISC complex bind to target mRNA (or other non coding RNAs) and causes its inhibition of translation (see Fig. 2, point 8A) or decay and degradation (see Fig. 2, point 8B). The target is located in the 3'UTR of mRNA and is recognized by the "seed region" of miR, complete complementarity is not essential [40-46].

Each step of miRs genesis can be controlled. Like other genes, promoters of miRs are under the regulation of multiple transcriptional factors, and alterations to their binding sites, be it by genetic variations or epigenetic modifications, may lead to aberrant expression. In SLE, the risk G allele of single nucleotide polymorphism (SNP) rs57095329 in the miR-146a promoter causes decreased binding of Ets-1 and subsequently decreased miR-146a expression[47]. Similarly, epigenetic modifications like histone acetylation[48] or CpG island hypomethylation may influence some miRs expression and increase the risk of diseases. Genetic variation in the miRs machinery (e.g. Dicer, Drosha, Ago proteins, Exp5) may cause global changes in miRs synthesis. On the other hand, miRs are able, through a feedback loop, to regulate the microprocesssor complex or other parts of the miRs machinery. The SNP rs3742330A>G in 3'UTR of the Dicer gene is located in the binding site for miRNA-5582-5p and miRNA-3622a-5p and is associated with survival of patients suffering from T cell lymphomas[49]. However, not only genetic variation, but also other regulatory molecules can affect expression or directly bind to the Ago or Dicer proteins and alter their functions. Estrogens and progesterone increase the expression of Exp5 and Dicer[50], and, interestingly, anti-Su antibodies occurring in SLE patients might have a role in miRNA biogenesis and RISC silencing because they recognize Ago proteins and Dicer[51]. The mechanisms and factors influencing expression of the miRNA machinery may depend on individual cells and organs and has been of immense research interest.

MiRs function in general

MiRs bind to the target miRNA-responsive element (MRE) of protein-coding mRNA, usually located in the 3'UTR region (ref.[32,40]), but occasionally in other regions such as 5'UTR (ref.[42]). Additional, miRs can bind to other regulatory RNAs or non-coding RNAs (ncRNAs) (ref.[43,44]). The miRs target is recognized by the "seed region", a 2-8 nucleotides long locus within the 5'terminal region of the miR (ref.[45,46]). For this reason, each miR can connect to hundreds of mRNAs, and mRNA might have multiple binding sites for miRs[46]. The potential interaction between mRNA and miR can be modelled and predicted by a range of different computational approaches (miRBase, DIANA-microT-CDS, miRanda-mirSVR and TargetScan) (ref.[52]). Matched miR-mRNA either causes mRNA destabilization, deadenylation and degradation or leads to inhibition of translation[41]. Although complete complementarity miR-mRNA is not essential, the functions of miRs are influenced by genetic variation either in miRs "seed regions" or in target regions of mRNA (ref.[53]). In addition, RNA editing can alter binding sites and affect the stability of miR (ref.[54]).

MiRs manipulate approximately of 60% of gene expression[41,46] and are important regulators in post-transcriptional modifications. Moreover, miRs can regulate not only the original cell, but are involved in intercellular communication. Between cells over short distances, miRs may be exchanged via the gap junction[55], but circulating miRs can influence intercellular communication of tumour, immune and healthy cells over long distances.

Extracellular miRs

Since mature miRs are found in the extracellular fluid, secretion outside the cell takes place by some as yet insufficiently known mechanisms, which is currently being studied. In the Fig 2 are described some known ways how miRs can leave viable cells – miRs become components of multivesicular body and by exocytose are secreted outside the cell[56] (point 9A), or are components of encapsulated cell membrane and leave the cell as microvesicles[57] (point 9B). Moreover, miR leaves the cell by transporter protein and is re-uptaked by receptor (point 9C, Fig 2). To date, there is only one example of this mechanism: HDL – miRs complexes are released from the cell by ABCA1 transporter and recipient cells use scavenger receptor class B type I (SR-B1) receptor for uptake[58]. Additionally, miR might leave the cell via gap junction during intercellular communication on short distance[55], see point 9D Fig 2.

Circulating miRs are highly stable in conditions, such as high and low pH, boiling or extracellular RNase activity, and are probably capable, by some unknown mechanism, to maintain stability outside the cell. Wang et al. demonstrated in experimental cell lines that the RNA-binding protein nucleophosmin 1 protects synthetic miR-122 from degradation[58], and in the human plasma, ribonucleoprotein Ago 2 maintains miRs stability[59]. MiRs in the whole blood, serum or plasma exist either as protein-bonded complexes or as microvesicles or exosomes[56,59,60]. Both these packages protect against extracellular RNase activity and allow the miRs to be accepted by other cells. The majority of circulating miRs are bound to proteins – the Argonaute family, particularly Ago 2 (ref.[59]), nucleoplasmin[60] or high density lipoproteins (HDL) (ref.[58]). The mechanism of cellular release and uptake requires a transporter and receptor system and is not yet definitely known. A minority of circulating miRs may be kept either by microvesicles or exosomes[56,57] from viable cells or are part of apoptotic bodies from cells undergoing apoptosis. Microvesicles are formed by encapsulation of the cell membrane, but exosomes are vesicles that are actively secreted by fusion of exocytic multivesicular bodies with the plasma membrane. Apoptotic bodies are large vesicles containing cytoplasmatic components, miRs and fragmented DNA. In general, host vesicles are

taken up by recipient cells via endocytosis, phagocytosis or fusion of plasma membranes. Microvesicles and apoptotic bodies are supposed to be involved in cell-to-cell communication over long distances and between organs. Recently, however, Chevillet et al. asked whether to revise this model in the case of exosomes. They demonstrated by quantitative and stoichiometric analysis that exosomes prepared from the plasma, seminal fluid, dendritic cells, mast cells and ovarian cancer cells do not carry biologically significant numbers of miRs (ref.[61]). On the other hand, exosomes containing miRs are involved in the formation of immunological synapsis of T cells and antigen-presenting cells (APC). The unidirectional transfer of exosomes containing miR-335 from T cells to APC is induced after antigen recognition[57]. The miRs in exosomes probably have a distinct role in the microenvironment of inflamed tissues, such as in the case of LN. Interestingly, in SLE, the majority of urine miRs are packaged in exosomes, especially in active LN. Exosomes in SLE contain miR335-5p, miR-302, miR-200c and in active LN the highest levels of miR-146a (ref.[62]). Mir-146a is highly expressed in the glomerulus and is involved in local inflammation. Similarly, miR-26a in urine exosomes reflects renal injury in LN (ref.[63]).

Genetic predisposition to SLE and miRs

Predisposing genetic factors are a prerequisite for the disease to manifest. Family studies indicate 66% heritability, and the concordance rate in monozygotic and dizygotic twins is in the range of 24-69% and only 2-5% (ref.[64]), respectively. Although genome-wide association studies (GWAS) reliably determine SLE risk locations, some genetic predisposing factors may differ between populations. The complex genetic background of SLE pathogenesis resides in variation of gene expression or in functional variants of members of multiple signalling pathways, immunologically active molecules or both[65]. Some association studies focused on particular SNPs of miRs genes and autoimmune diseases have already been performed, but failed to find any association with SLE. For example, miR-499 rs3746444 is associated with decreased risk of rheumatoid arthritis development[66], but there is no association with SLE (ref.[66,67]). The miR-146a gene, however, has become the centre of interest, as the novel genetic locus 5q33.3 has been ascertained in recent GWAS studies of SLE patients of European and Asian ancestry[68-70]. The miR-146a gene exhibits at least three functional SNPs important for autoimmunity.

Within the miR-146a promoter region, there is the A/G SNP rs57095329, and the G allele causes reduced promoter activity; furthermore, the GG genotype shows the lowest miR-146a mRNA levels compared to the AA genotype, $P = 0.019$ (ref.[47]). A meta-analysis of SLE in patients of Asian ethnicity (Hong Kong, Bangkok and the Chinese mainland) has demonstrated a significant association with the G allele ($P < 0.0001$, OR 1.29 [CI 95% 1.18-1.40]) (ref.[47]). In patients of European ancestry, however, the frequency of this allele of rs57095329/rs2277920 was found to be very low, so it cannot be presented as an SLE-associated genetic marker[71]. Future studies should examine whether differences in allele frequencies of miR-146a SNPs across ethnicities may be part of the explanation of population differences in SLE development and severity. The functionality of the rs57095329 SNP could be explained by an interaction with the Ets-1 transcription factor. Although rs57095329 is not located in the core sequence of Ets-1, the G allele, in particular, influences its binding affinity and reduces miR-146a transcription *in vitro*[47]. Interestingly, GWAS have established variations of Ets-1 (rs1128334 SNP) as a genetic factor in SLE (ref.[70]), and Luo et al. performed an interaction analysis of both risk SNPs (ref.[47]). No cumulative effect was found using a conditional logistic regression test with the interaction between the two variants treated as a covariate using PLINK. However, individuals carrying two or more risk alleles are at greater risk of developing SLE, and the OR increases in the process; for example, the combined risk for miR-146a homozygotes with no risk allele of Ets-1 (GG-GG) has an OR value of 1.75 (CI95%1.12-2.73), the risk for miR-146a homozygotes with one risk Ets-1 allele (GG-AG) has an OR value of 2.03 (CI 95% 1.35-3.05), and the combination of both risk homozygotes has an OR value of 4.79 (CI 95% 1.9-12.09) (ref.[47]). On the other hand, Leng et al. performed a gene-gene interaction analysis of miR-146a (rs57095329) and IL-21 (rs907715 and rs2221903), IRF-5, IKZF-1 and Ets-1 (rs6590330), using direct counting and a chi-square test with a 2×2 factorial design, and found no interaction of miR-146a, in particular with Ets-1[65]. The Ets-1 rs6590330 SNP is in high linkage disequilibrium with the rs1128334 SNP ($r^2 = 0.97$) (ref.[70]) and has been associated with earlier onset of the disease and certain SLE manifestations, including malar rash, photosensivity, arthritis, serositis and renal involvement[72]. The clinical diversity of SLE should probably be considered in further studies to elucidate genetic interactions, at least between Ets-1 and miR-146a.

The other miR-146a SNP, rs 24311697, is located between the pituitary tumour–transforming 1 (*PTTG1*) gene and the miR-146a gene, 15.3kb upstream of the miR-146a transcription starting site[68]. Löfgren SE et al. demonstrated a significant association of SLE with the T allele ($P < 0.001$, OR 1.23 [CI95% 1.10-1.38]) and the TT genotype ($P < 0.001$, OR 1.49 [CI 95% 1.17-1.90]) in patients of European ancestry[71]. Similarly, the T allele of rs2431697 has been established as a risk factor in the Chinese Han population, $P < 0.01$, OR 1.30 (CI 95% 1.08-1.56) (ref.[47]). This SNP seems to be functional whereas TT homozygotes, compared to the CC genotype, express in PBMC 1.6- and 2.2-fold lower mature and primary miR-146a levels (both $P < 0.01$) (ref.[71]), respectively. Interestingly, the association between the T allele and SLE in patients with anti-dsDNA antibodies ($P<0.001$, OR 2.510 [CI95% 1.545-4.077]), and in particular in SLE females ($P = 0.006$, OR 1.538 [CI95% 1.113-2.093]), has recently been proven (ref.[73]). The recent study of Tang et al., moreover, performed a meta-analysis of six studies involving 8642 SLE patients and 10947 healthy controls supporting the association of the T allele in patients

of both European Caucasian and Asian ethnicity ($P < 0.001$, OR 1.213[CI95% 1.145-1.284] and $P < 0.001$, OR 1.365[1.259-1.480], respectively) (ref.[73]).

The other SNP of miR-146a, rs2910164, influences its processing. The C allele of the rs2910164 SNP causes mispairing within the pri-miR hairpins and decreases the amount of pre- and mature miR-146a 1.9- and 1.8-fold[74], respectively. Although the miR-146a SNP rs2910164 has been supposed to be associated with autoimmune diseases[75], two recently performed meta-analyses of miR-146a SNP rs2910164 and SLE show different results[66,76]. The analysis of the miR-146a rs2910164 SNP in four studies comprised a total of 2505 SLE cases and 3248 controls and failed to confirm an association with SLE (OR 0.98, 95% CI 0.90-1.06) (ref.[76]). Additionally, no association was found in two ethnicities included in the studies, namely Caucasian – Mexican and European[66,71,77] and Asian – Chinese Han nationality[66,67].

MiRs and hormonal influences in SLE

The predominance of females over males suffering from SLE and the increased incidence of the disease during childbearing age apparently shows the role of sex hormones and other sex-biased factors in the disease's pathogenesis[4,78].

Estrogens, in contrast to testosterone, might support the development of autoimmune diseases and influence the immunopathological mechanisms of SLE-like autoreactive B cells selection, autoantibody production and aggravation of Th2 reactions[78]. Additionally, sex steroid hormones might influence miRs expression[79]. Recently, Dong G et al. found increased expression of interferon (IFN) type I inducible genes, including toll-like receptor (TLR)-7 and the signal transductor and activator of transcription (STAT)-1, but reduced levels of let-7e-5p, miR-98-5p and miR-145a-5p, in PBMCs of premenopausal females compared to age-matched men[80]. The effect of estrogens, in particular 17β-estradiol, on the development and function of cells of innate and adaptive immunity has already been well documented[4,78]. Estrogen enhances the innate immunity response of splenic lymphocytes to lipopolysaccharide (LPS) while at the same time it downregulates expression of miR-146a, which inhibits LPS-induced IFNγ and LPS-induced nitric oxide *in vivo*[81]. Interestingly, the effect of 17β-estradiol on miRs expression and enhanced activity of IFN type I in B cells has recently been elucidated[80]. 17B-Estradiol, via its estrogen receptor (ER) α, down-regulates expression of let-7e-5p, miR-98-5p and miR-145-5p *in vitro*, and all three miRs reduce the mRNA of inhibitor of kappa B kinase ε (IKKε, gene IKBKE), targeting it directly on 3'UTR (ref.[80]). IKKε is an essential factor for 17β-estradiol amplification of the IFN type I response in B cells, and gender differences of its expression have been found *in vivo*[80]. This finding supports the role of IKKε in SLE pathogenesis. In addition, the functional single nucleotide variant of the IKBKE gene (rs12142086) has been found to be associated with SLE (ref.[82]).

The influence of gender on the contribution of miRs to autoimmunity, SLE in particular, has been clarified in mice models. Female Dicer-deficient mice (CD19-Cre$^{ki/+}$Dicer$^{fl/fl}$) develop during ageing autoimmune features such as production of autoantibodies against cardiolipin, anti-dsDNA antibody production, and autoimmune kidney involvement, because lymphocyte infiltration and overall damage to the glomerulus architecture appears in 50% of them[83]. On the other hand, as demonstrated in orchiectomized lupus-prone NZB/W F1 mice, long-term estrogen treatment causes development of SLE and elevation of miR182-96-183 cluster, miR-379 and miR-148a levels, but no correlation between anti-dsDNA and these miRs was found after 26 weeks of estrogen treatment[84]. Female NZB/W F1 lupus mice typically express the disease earlier than males. Similarly, before the onset of SLE, the two genders do not differ in their expression of miRs (miR-182-96-183, miR-31 and miR-148a, miR-155) except miR-127 and miR-379. After SLE onset, however, the levels of miR-182-96-183, miR-31, miR-127, miR-379 and miR-148a are elevated in 30 weeks old females compared to age-matched males without SLE features[84]. Furthermore, estrogen-treated orchiectomized 32 weeks old mice express similar levels of these miRs as their female counterparts[84]. All these data explain the modulation of miRs by estrogen and support selected miRs as mediators of the alteration of immune reactions to autoimmunity by sex hormones.

To understand the differences of miRs expression between genders in relationship to SLE, it is necessary to keep in mind the potential role of other sex-biased factors. The sex-associated differences in miRs regulation have recently been robustly reviewed by Khan et al. (ref.[85]). The X sex chromosome comprises 113 miRs genes, in particular some that are involved in immune cells maturation and differentiation. Some of them are linked to the SLE, for example, miR-223, miR-222, miR-221, miR-98, miR-106a, the miR17-92 cluster, miR-503 and miR-542 (ref.[85]). Recently, Chen et al. found 46 dysregulated miRs located on chromosome X/Y in SLE compared to healthy controls, but when they considered fold changes of >1 or <-1 and $P \leq 0.01$, the number dropped to 11 up- and downregulated miRs (ref.[28]), respectively. In SLE, the dosage effect of chromosome X on disease development and severity has been found in an experiment on mice[79]. Similarly in humans, men with Klinefelter's syndrome (XXY) show an increased risk of disease development similar to women[86].

MiRs, the immune system and SLE

MiRs participate in immune cell life processes like survival, metabolism and apoptosis and are potent regulators of immune cell development, maintenance and functions. Both innate and adaptive immunity is influenced by these molecules, and moreover, due to intercellular communication during immune reactions, miRs might modulate the immune response. In the pathogenesis of SLE, modulation of immune processes leading to the perpetuation of a pathological inflammatory response, particularly the production of autoantibodies, might have a critical role.

Innate immunity and miRs and SLE

Humoral and cellular innate immunity jointly responds to foreign organisms, including viruses, either

directly, or by producing inflammatory cytokines and co-operating with the adaptive immune system, particularly B cells. The prolonged inflammatory answer, however, may crucially support the development of autoimmunity such as SLE, and SLE-associated miRs, particularly miR-146a and miR-155, are supposed to be involved in these processes. In experiments, mice deficient in miR-146a (*miR-146a*$^{-/-}$) respond hypersensitively to lipopolysaccharide (LPS) stimulation and produce large numbers of interleukins (IL), such as IL- 6, IL-1β, IL-10 and tumour necrosis factor (TNF)-α, and moreover, during aging develop an autoimmune disorder characterized as tissue damage by multiorgan lymphocytic and monocytic infiltrates and formation of anti-dsDNA autoantibodies[87]. Interestingly, Xing et al. demonstrated in a recent study of miR-155 knockdown lupus-prone Fas$^{lpr/lpr}$ mouse models a milder SLE phenotype than in wild-type strains[88].

Cells of the innate immune system are equipped with several families of pattern recognition receptors (PRRs) to recognized molecules derived from pathogens or damaged cells. Dendritic cells (DC), in particular plasmocytoid cells (pDCs), express endosomal toll-like receptors (TLR)-7 and TLR-9 recognizing host single stranded RNA and bacterial DNA, respectively, as well as endogenous complexes of nucleic acids derived from apoptotic or necrotic cells. After activation, pDCs become a source of interferon (IFN) type I and IL-6. Prolonged production these cytokines promotes processes essential for SLE development like B cell survival, antibodies production and T cell abnormalities[89]. Recently, the involvement of pDCs was observed in the inhibition of apoptotic cell clearance in marginal zone macrophages[90]. The pDCs, after TLR-7 and TLR-9 stimulation, express miR-146a, which through negative feedback accomplishes the survival of pDCs while down-regulating BCl2-A1 levels and causing apoptosis[91]. The next miR-146a target in pDCs, IL-1 receptor-associated kinase (IRAK)-1 of the MyD88/TRAF6/IRAK1 signalling pathway, inhibits the activation of NFκB (ref.[91]) and subsequently influences pDCs functions. Analogously, the pathway TLR9 – MyD88/IRAK1/IRF 7 of pDCs, originally from the umbilical cord, is suppressed by highly expressed miR-146a and miR-155 (ref.[92]). Both miR-155 and miR-155* formed after TLR 7 stimulation via the c-Jun N-terminal kinase (JNK) pathway are involved in IFN type I synthesis in human pDCs (ref.[93]). Zhou H. et al. demonstrated time differences during pDCs stimulation by miR-155/155*– in the early stage miRNA-155* rapidly augments IFN type I expression, but in a later stage miR-155 inhibits it by targeting the signalling molecule TGF-β-activated kinase 1/MAP3K7 binding protein 2 (TAB2) (ref.[93]). Disturbances in this negative feedback could cause dysbalance of IFN type I homeostasis. Recently, increased expression of IFN-α was observed in the PBMCs of SLE patients that inversely correlated with the levels of miR-155, miR-17 and miR-181b (ref.[94]). MiR-155 and miR-181b, moreover, directly regulate IFN-α secretion *in vitro*[94].

In PBMCs, miR-146a interfere in the IFN type I upstream and downstream signalling cascade by inhibiting either TNF receptor-associated factor 6 (TRAF-6) (ref.[95]) and interferon regulatory factor 5 (IRF-5) (ref.[26]) or even signal transductor and activator of transcription 1 (STAT-1) (ref.[26]). With PBMCs obtained from SLE patients, Tang et al. performed an *in vitro* study demonstrating reduced expression of three selected IFN inducible genes, namely Ly6E, OAS1 and MX1 after incorporation of the miR-146a plasmid[26]. Although the IFN type I response is also regulated, either indirectly by other PRRs like TLR-2 and TLR-4 (miR-19, let7e or miR-200 family) or directly by IFN-α mRNA suppression (miR-466l) (ref.[96]), all pathogenetic modes of miRs regulation of IFN type I expression require further study. Whereas IFN type I has been established as the main contributor to SLE pathogenesis[97], it is not surprising that the expression of miR-146a in PBMCs of SLE patients negatively correlates with disease activity and severity of renal involvement[94,98].

The other cells of innate immunity, macrophages, display deregulated phenotypes and functions in SLE patients. While the M2c subset together with the M2a subset are reduced in LN, the M2b subset matures after stimulation by immune complexes, and its amount correlates with LN relapse[99]. The experimental mouse model of induced lupus, following the administration of activated lymphocyte-derived DNA (ALD-DNA) to BALB/c mice, exhibits infiltration of macrophages, particularly of the M2b type, in the kidneys[100]. Xiao et al. recently demonstrated a critical role of miRs in M2b polarization in this model[101]. They performed miRs microarrays of bone marrow-derived macrophages (BMDMs) after ALD-DNA induction over time and found dynamic miRs expression corresponding with BMDMs polarization. The M2b subset expand after six hours of stimulation, but decreased after thirty-six hours, and 43 and 42 miRs, respectively, were found to be differentially expressed. However, expression of only six miRs was similar at both times, but the rest were up- or downregulated. Interestingly, miR-155, miR-29b and miR-30e were continuously up-regulated, while miR-129-5p, miR-466j, miR-222* or the miR-29 family showed transient up-regulation[101]. Early miRs are involved in the immune response, immune cell trafficking and cellular development whereas later miRs are associated with cell development, death and survival[101]. In light of these findings, it is necessary to keep in mind that the miRs network in the innate immune response is complex and time-dependent. Breakdown of this tight regulation may result in the perpetuation of pDC or macrophage activity and promote autoimmunity.

Pathologies in adaptive immunity in SLE and miRs

T cells, miRs and SLE

Abnormalities in T cell populations contribute intimately to SLE pathogenesis either by abnormal distribution of pro-inflammatory Th17 and anti-inflammatory T regulatory (Treg) cells or by abnormal production of cytokines such as IL-2 and IL-10 or even by abnormal communication with B cells leading to the production of autoantibodies[102]. MiRs are differentially expressed in SLE T cells[103] and contribute to their abnormalities by influencing several mechanisms (Table 2).

Firstly, miRs act as a modulator of epigenetic mecha-

Table 2. The selected T cells abnormalities influenced by miRs in systemic lupus erythematosus.

	Epigenetic Modifications	Ref.
DNA hypomethylation	miRNA-126, miRNA-29b, miRNA-21, miRNA-148a	30, 104-106
Histone acetylation	miRNA-142	48,107
	Intracellular signaling and trascription factor expression	
STAT-1	miRNA-145, miRNA-146a	26,108,115
SOCS-1	miRNA-155	112
KLF13	miRNA-125a	119
Jagged-1	miRNA-524-5p	114
NFκB	miRNA-146a	108
NFAT	miRNA-31	111
STAT-3	miRNA-125b	118
TRAF6,IRAK1	miRNA-146a	26,108
Ets-1	miRNA-125b	118
IRF-4	miRNA-224	103
	Abberation in cytokine and surface activation markers production	
IL-10	miRNA-21, miRNA-142-3p, miRNA-142-5p	27,107
IL-2	miRNA-155, miRNA-31	111,112
IL-17A	miRNA-146a	108
IFN-γ	miRNA-524-5p	114
CD40L	miRNA-21	27
RANTES	miRNA-125b	119
CD-84	miRNA-142-3p, miRNA-142-5p	107
CD-69	miRNA-146a	108
	Apoptosis, survival and proliferation	
	miRNA-224	115
	miRNA-146a	108
	miRNA-21	27
	CD4+ T cells differentiation	
	miRNA-31, miRNA-155	111,112
Treg	potential: miRNA-126 via PI3K/Akt	116
	potential: miRNA-125	109
TFH	potential: miRNA-10a, miRNA17-92 cluster	121,103
		120,122

STAT- Signal transductor and activator of transcription, SOCS- suppressor of cytokine signalling, KLF -Kruppel factor, NFκB- nuclear factor kappa B, NFAT-nuclear factor of activated T cells, TRAF- TNF receptor-associated factor, IRAK-IL-1 receptor-associated kinase, IL- interleukin, IFN- interferon, CD- cluster of differentiation, RANTES-regulated on activation, normal T cell expressed and secreted (Chemokine ligand 5), Treg-T regulatory cells, TFH- T follicular helper

nisms, yet changes in their expression correspond to epigenetic modifications. Whereas epigenetic modifications are among the key pathogenetic events in SLE, miRs are in the centre of interest. In SLE, decreased activity of the DNA methylation enzyme DNA methyltranferase 1(DNMT1) is associated with abnormal gene expression and disease development. MiRs alter DNMT1 activity in a direct or indirect manner. Two miRs, miR-126 and miR-148a, directly inhibit the translation of DNMT1 by binding to the 3'UTR of the transcript[30,104]. Both subsequently regulate the expression of CD11a and CD70 (ref.[30,104]), and moreover, experimentally over-expressed miR-126 instigates CD4 + cells to stimulate IgG production in co-cultured B cells[104]. On the other hand, DNMT1 levels are indirectly alleviated in SLE by two other miRs: MiR-29b reduces Sp1, the DNMT1 transactivator[105] and miR-21 reduce the activity of the Ras-MAPK-DNMT1 signalling pathway[30]. Although miRNA-21 is expressed equally in SLE with and without nephritis, it correlates with disease activity[30], and abnormalities in the "microRNA expression pattern" have been supposed to depend on the SLE phenotype. Zhao M. et al. recently demonstrated differences in methylation in CD4+ T cells within miRs as well as other genes in three SLE patients groups suffering from skin involvement only, both skin and renal involvement and involvement of all skin, kidneys and joints[106]. Although the study is limited by the number of SLE patients (n = 4 in each group), relevant data show differences not only in miRs target genes, but also in up-regulation and down-regulation of miRs genes, such as miR-126, miR-451 and miR-181b, and miR-142-3p, miR-505 and miR-324-5p (ref.[106]), respectively. Similarly, expression of some miRs such as miR-142 might be alleviated through another epigenetic mechanism, which is histone modification[107].

Recently, Tang Q et al. have shown escalated H4 acetylation contributing to increasing transcription of miR-142 in CD4+ T cells after treatment by mycophenolic acid (MPA), a drug commonly used for treating SLE (ref.[48]).

Secondly, abnormalities in the expression of cytokines or other signalling molecules are caused either by the regulatory effect of miRs on several intracellular signalling pathways or directly by binding to target molecules, see Table 1. The SLE-associated miR-146a is down-regulated in SLE CD4+ T cells[26,48], but MPA treatment restores its expression[48]. As demonstrated in *miR-146a*$^{-/-}$ mice, miR-146a plays multiple roles in T cells such as proliferation, apoptosis and cytokine production, for example, IL-17A (ref.[108]). The target pathway NFκB is modulated in a negative feedback manner via the T-cell receptor (TCR) pathway. TCR stimulation causes aggravation of miR-146a expression (ref.[108]). MiR-146a is involved in the differentiation of Th1 and Th17 cells, while Th1 cells show alleviated levels of miR-146a (ref.[109]).

In SLE, cytokines IL-2 and IFN-γ produced by T cells are down-regulated, but the levels of IL-10 are elevated and the ratio IL-10: IFN-γ determines the severity of SLE[110]. The regulation of IL-2 is complex, but miR-31 and miR-155 contributes to its expression. Fan et al. demonstrated that decreased miR-31 expression positively correlates with decreased IL-2 synthesis in SLE T cells[111]. Further experiments showed that miR-31 increases IL-2 promoter activity by altering the expression of the nuclear factor of activated T cells (NFAT) (ref.[111]). Similarly, miR-155 can bind directly to the suppressor of cytokine signalling 1 (SOCS1) and down-regulate IL-2 release[112]. In SLE CD4+ T cells, both elevated miR-21 and down-regulated miR-142-3p/5p contribute to enhanced expression of IL-10, either indirectly via suppression of programmed cell death-4 (PDCD4) or directly by inhibiting translation[27,107], respectively. Furthermore, an *in vivo* study of B6.Sle123 lupus mice with silencing of miR-21 found approximately 20% de-repression of PDCD4 in naïve CD4$^+$ T cells and amelioration of the disease[113]. On the contrary, in SLE, miR-524-5p over-expressed in T cells enhances IFN-γ production in the activated T cell line[114] and positively correlates with SLEDAI in SLE patients[114]. Since miR-524-5p affects the expression of the surface molecule Jagged-1 (ref.[114]), a ligand for the Notch-1 receptor and target for miR-21 with a function during maturation of monocyte-derived dendritic cells, the role of this miRNA in SLE pathogenesis should be clarified. Other signalling molecules, like surface activation markers (e.g. CD40L) or chemokines (e.g. RANTES), are regulated by miRs (Table 2).

Thirdly, miRs influence cell survival, proliferation and apoptosis. In SLE, the prolonged cell survival and persisting immune response promote immunopathological activity. Lu et al. demonstrated in CD4+ T cells increased miR-224 expression. *In vitro* miR-224 decreases its target apoptosis inhibitory protein 5 (API 5) at the protein level and could affect activated T cell survival[115]. Martinez-Ramoz recently confirmed elevated levels of miR-224 in CD4+ T cells obtained from inactive SLE patients[103].

Fourthly, differentiation of T cells, particularly into Treg cells or T folicular helpers (T_{FH}), which play an important role in SLE, might be influenced by several miRNAs. In short a nutshell, miR-150, miR-21 and miR-155 are involved in CD8+ genesis, but miR-150 or miR-146a and miR-147 or miR-155 and miR-326 in Th2, Th1 and Th17 (ref.[109]), respectively. We should, however, keep in mind that Th differentiation requires an extraordinarily managed orchestra of transcription factors and other regulatory molecules. For example, IRF-4 is involved in Th2 and Th17 differentiation and has been computationally identified as a target for miR-224, which is overexpressed in CD4+ T cells of inactive SLE (ref.[103]). The differentiation of Treg cells requires the transcription factor forkhead box protein 3 (Foxp3), which is the target of "SLE-associated" miR-126 (ref.[104,116]). As mentioned above, IL-2 – a cytokine that is essential for Treg survival – is down-regulated by miR-31 or miR-155 in SLE (ref.[111,112]). Moreover, miR-31 can suppress Foxp3 expression directly by binding to 3'UTR mRNA (ref.[117]). Elevated levels of miR-125 have been found in Treg cells and is involved in their development[109] whereas in SLE T cells both miR-125a and miR-125b are alleviated (ref.[118,119]). Another subset of CD4+ T cells, T_{FH}, is critical for cooperation with B cells and autoantibody production. T_{FH} cells are characterized by the transcription factor B cell lymphoma-6 (Bcl-6) and secretion of IL-21 and are supposed to interfere with SLE pathogenesis. SLE model mice depleted of miR-155, miRNA-155$^{-/-}$Fas$^{lpr/lpr}$ develop a phenotype with a reduced proportion of spleen T_{FH} and subsequent lower levels of IgG and IgM titres[88]. Similarly, reduced levels of Bcl-6 and IL-21 in mouse spleens and lower levels of IL-21 in the mouse serum are found in this model[88]. Recently, two miRNAs, cluster miR-17-92 and miR-10a, were described as modulators of T_{FH} genesis, Bcl-6 expression in particular (ref.[120,121]). Experimentally, the miR-17-92 transgenic mouse model develops spontaneous T_{FH} cell differentiation[120] and miR-10a directly suppresses Bcl-6 on 3'UTR (ref.[121]). Upregulation of miR-10a has been found in PBMC SLE cells[26,103] and miR-17 and miR-19a or miR-19b in PBMCs of SLE patients with anti-dsDNA or anti-ENA autoantibodies[122], respectively. Both these links to SLE should be elucidated in future studies. Recently, the miR-146a has been found to be highly expressed in T_{FH} cells and plays a role in T_{FH} cells development[123]. MiR-146a directly represses multiple T_{FH} cell mRNAs, including ICOS and STAT-1, and downregulates T_{FH} accumulation, while miR-146a$^{-/-}$ mice exhibited a 5-fold increase of T_{FH} cells compared to wild-type littermates[123].

B cells, miRs and SLE

Disturbances of B cells are a hallmark of SLE pathogenesis. They are manifested either as hyperactivity in autoantibody production, in the functioning of antigen-presenting cells or even as a source of inflammatory cytokines. Autoantibodies are involved in SLE immunopathological events and might serve as markers for monitoring SLE activity and organ manifestations[7]. The multistep process of B cells maturation in bone marrow

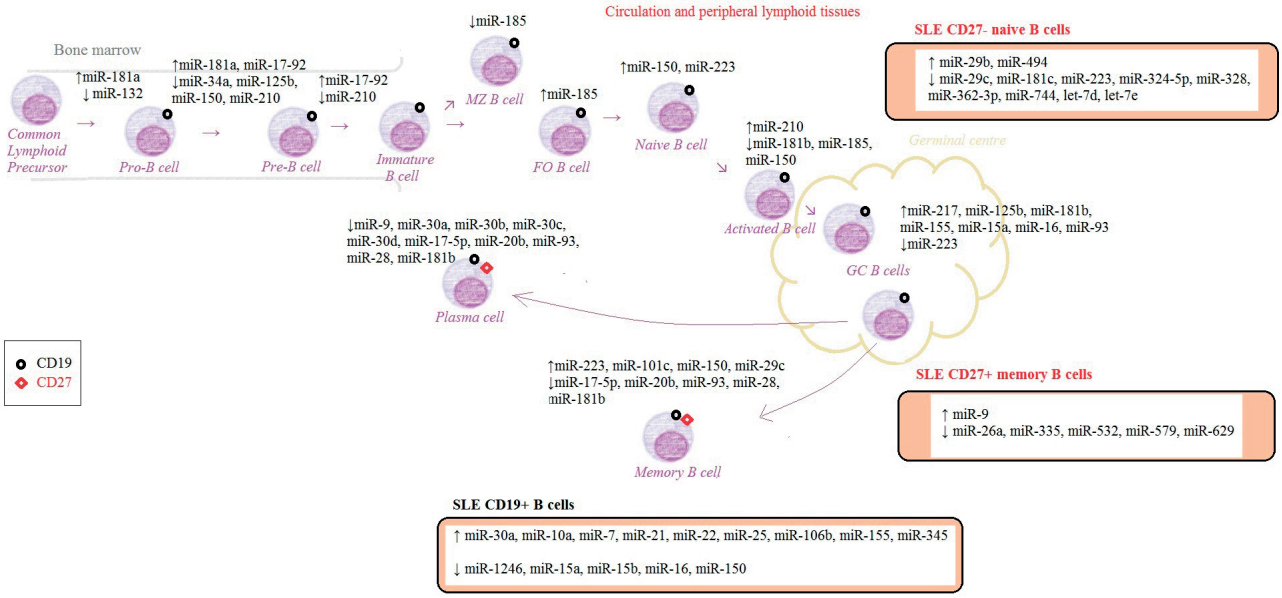

Fig. 3. MiRs involvement in B cell differentiation and variations of miRs expression in B cells obtained from patients with SLE. In SLE CD19+ B cells obtained from circulation are differentially expressed several miRs (ref.[27,103,142-144]). In right side of the figure are boxes with differentially expressed miRs in naive CD27– and memory CD27+ SLE B cells[145].
Abbreviations: MZ- marginal zone B cells, FO- follicular B cells, CSR - class switch recombination, SHM -somatic hypermutation, GC - germinal centre, SLE – systemic lupus erythematosus, (↓) underexpression, (↑) overexpression.

and the peripheral compartment is supported by tight regulation of function of B cells receptor (BCR) and antibodies synthesis. The survival and function of B cells is determined by several crucial points either of immunoglobulin gene rearrangement by VDJ recombination during pro-B to pre-B cells transition in bone marrow or differentiation of immature B cells into marginal zone (MZ) or follicular (FO) B cells, or even somatic hypermutation (SHM) and class switch recombination (CSR) during activation in the periphery. The mechanisms of central and peripheral tolerance guarantee that only functional BCR B cells undergo the next step of development. Each step of B cells maturation, however, may tip over and produce autoreactive B cells.

Different patterns of miRs are expressed in each stage of B cell development, particularly in bone marrow and peripheral lymphoid tissue or the circulatory system, and can critically regulate the maturation process in a positive or negative manner, see Fig. 3. Experimentally, *in vitro* or *in vivo* ablation of Dicer leads to disruption of miRs synthesis and causes the blocking of the development process in the early stages[124] as well as maturation of B cells into MZ or follicular FO B cells[83] or terminal maturation of B cells into memory and plasma cells during T cell-dependent immune response[125]. During the early development of B cells in bone marrow is highly expressed miR-181a (ref.[126]), but alleviated levels of miR-132 are required for early transition of pro-B cells[127]. Similarly, the over-expressed miR-17-92 cluster is essential for survival of B cell precursors, differentiation from pro-B to pre-B cells and latter into immature B cells[128,129], however, there are variations between adult and paediatric age[129]. On contrary, studies based on over-expressed experiments established important role of miR-34a, miR-150, miR-125 and miR-210 for correct transition of pro-B to pre-B cells[130,131]. The first two miRs target transcription factor Foxp1 and c-myb, respectively, and regulate apoptosis and survival pro-B or pre-B cells.

In periphery, immature B cells progress into mature MZ or FO B cells. Interestingly, *Cd19*-Cre$^{ki/+}$Dicer$^{fl/fl}$ mice develop reduced total numbers of mature B cells, but MZ B cells are favouring over FO B cells[83]. MZ B cells mostly reside in the spleen and can be generated from B cells with autoreactive BCR signalling rather than FO B cells that circulate, form B cells follicles and undergo further maturation in a T-dependent manner in germinal centres (GC). The miR-185 is responsible for MZ or FO B cells differentiation, while targeting bruton tyrosine kinase (Btk), the downstream of BCR (ref.[83]), see Fig.3.

In GC, miR-181b, miR-155 miR-93 are involved in the setting up of antibodies isotype and BCR affinity maturation, see Fig.3. All in stimulated B cells directly regulate activation-induced cytidine deaminase (AID), enzyme critical for CSR (ref.[132-134]). The miR-155, moreover, directly suppress PU.1 transcription factor, playing a role in the CSR and during initiation of plasma cell differentiation[135]. The miR-217 positively regulates in GC CSR and SHM as well as differentiation of plasma and memory B cells[131]. The other GC miR-125b and miR-223, target transcriptional factors IRF-4 or blimp-1 and LMO2 (ref.[134,136]), respectively. The first two factors are essential for plasma cells differentiation. Moreover, blimp-1 is directly targeted by two others miRNAs involved in the GC B cells to plasma cells transition, miR-9 and miR-30 family[134]. The regulation of apoptosis during GC B cells maturation is tightly regulated, the anti-apoptotic bcl-2 protein is down-regulated in GC B cells and both GC elevated miR-15a and miR-16 directly inhibit it[136]. Mature

B cells express miR-150 and miR-185, but expression of both is after activation reduced[131,137]. The miR-185 indirectly supports B cell activation such as production of IgG and TNF-α cytokine while negatively regulate the EphB2 expression[137]. On contrary, miR-210 is induced after B cell activation[130]. The two members of cluster miR-17-92 (miR-17-5p, miR-20b), miR-28 and miR-181b are involved in transition GC B cells to memory B cells[134]. Tree miRs – miR-101c, miR-150 and miR-29c are highly expressed in memory B cell compared to GC centroblast[136].

In the MRL/lpr mouse model of SLE, it has been demonstrated that deficiency of AID ameliorates disease course, especially autoantibody production and kidney involvement[138]. Moreover, AID overexpression has been found to be regulated by miR-155, miR-17 and miR-181b in SLE patients with high disease activity[94]. The importance of MiRs in AID activity and subsequently B cells functions has been elucidated in mouse models. *Dicer1*$^{fl/fl}$*AicdaCre*$^{/+}$ mice that have ablated Dicer in activated B cells exhibit defective GC formation and absence of memory and plasma cells[125]. Moreover, Dicer deficiency in antigen-activated B cells reduces the generation of high-affinity class-switched antibodies[125]. On the other hand, in the absence of Dicer in *Cd19*-Creki/+Dicer$^{fl/fl}$ mice, B cells with skewed BCR formation occur, and female mice are prone to producing anti-dsDNA and anti-cardiolipin autoantibodies during ageing[83]. Similarly, the other miR-210 knockdown mouse model spontaneously develops autoantibodies such as ANA or anti-dsDNA during ageing[130], and the ectopic over-expression of miR-210 *in vivo* leads to B-cell functional abnormalities such as impaired isotype switching to IgG1 (ref.[130]). On the other hand, in miR-146a transgenic mice during GC formation, miR-146a directly target Fas on 3′-UTR, and these mice develop increased levels of IgG autoantibodies, but anti-dsDNA or ANA were not detected[139]. Thus, miRs are critical for GC processing of B cells, and moreover, have a spatiotemporal dose-dependent effect on antibody production and GC function. Disharmony of the miRs orchestra within GC should prefer the autoreactive fate for B cells during their terminal differentiation.

In view on the fact that miRs can drive B cell functions towards autoimmunity, several studies focused on miRs analyses of B cells in SLE-prone mouse models and in particular on CD19+ B cells obtained from SLE patients.

Several miRs are differentially expressed in splenic B cells in mice models of SLE. Elevated levels of miR-21 and miR-146a in B6.Sle123 lupus mouse B cells correlate with disease severity, and treatment with anti-miR-21 ameliorates splenomegaly[113]. Two other mouse models of SLE, MRL/MpJ-Fas^{lpr}/J (MRL-lpr) and congenic lupus strain B6.MRL-Fas^{lpr}/J (B6-lpr) have exbihited dysregulation of miRs expression in splenocytes compared to controls. B cell splenocytes express elevated levels of miR-155 in both MRL-lpr and B6-lpr strains, but downregulation of miR-150 has been found in MRL-lpr (ref.[140]). On the other hand, the mouse model of SLE with deficiency in miR-155 (miRNA-155$^{-/-}$*Fas*$^{lpr/lpr}$) exhibit lower levels of IgG and IgM autoantibodies, but the proportions of spleen B cells (B220^{+}, B220^{+}IgM^{+}, B220^{+}IgD^{+}) did not differ in *Fas*$^{lpr/lpr}$ (ref.[88]). The autoimmune condition is more likely caused by abnormal communication between T_{FH} cells and B cells than by direct changes in B cell splenocytes in this model. Further insight into the spleen B cell subpopulation is provided by a study that used (NZB X NZW) F1 mice (B/W) treated with IFN-α, which develop anti-dsDNA antibodies and changes in the splenic miRs profile, mainly overexpression of miR-15a (ref.[97]). MiR-15a is directly involved in apoptotic processes by targeting bcl-2. In B/W mice, there is an imbalance between regulatory spleen B cells and hyperactive B-2 subsets. MiR-15a is overexpressed in B regulatory cells, and miR-15a-induced loss of these cells may lead to autoantibody production[97]. B-2 cells, moreover, exhibit elevated miR-155 in B6.Sle123 SLE models that correlate with disease severity[113]. The effect of miR-155 on autoantibody production has been elucidated in detail by a study done on miR-155$^{-/-}$-B6-*Fas*^{lpr} mice, which exhibit lower frequency of GC B cells, resulting in a reduction of isotype-switched IgG antibodies and lower levels of anti-dsDNA antibodies[141]. The diminished B cell proliferation in this model is caused mainly by enhanced activation of SH2 domain-containing inositol 5′-phosphatase 1 (SHIP-1) and subsequent ERK phosphorylation after BCR – FcγRIIB signalling. SHIP-1 is downregulated and ERK is enhanced in activated *Fas*^{lpr} B cells, but not in miR-155$^{-/-}$ B cells, and more importantly, miR-155 deficiency in *Fas*^{lpr} mice restores SHIP-1 expression, moderate ERK phosphorylation and IgG antibody production[141]. The other miR supposed to directly support B cell hyperactivity, miR-30a, has been found to be elevated in human SLE B cells. MiR-30a directly binds to the 3'UTR of Lyn mRNA and inhibits its expression in B cells. Subsequent *in vitro* studies demonstrate that miR-30a, via the Lyn pathway, caused B cells to overproduce IgG and enhanced their proliferation[142].

In human SLE, different patterns of miRs expression in B cells could serve as a marker of disease activity or clinical manifestations and might provide new insights into the pathogenesis of SLE. Fig. 3 illustrates differentially expressed miRs in CD19+ B cells in human SLE. Martinez-Ramos et al. performed a microRs assay including 377 miRs in CD19+ B cells obtained from 46 SLE inactive patients. Further validations have shown that only miR-10a and miR-345 are overexpressed in SLE compared to healthy controls, and have been identified by computational means as targets for IL-8 and IRF-8 (ref.[103]). These findings, in accordance with previous studies, demonstrate the positive correlation between serum levels of IL-8 with SLE disease activity, autoantibodies production and renal involvement. Recently, a high-throughput miR microarray measuring the activities of 371 miRs identified six differentially expressed miRs (3 up- and 3 downregulated), but only miR-1246 was found to be alleviated in CD19+ B cells of active SLE patients in contrast to inactive SLE or healthy controls. Further *in vitro* study confirmed no influence of treatment, most notably by prednisone, on this observation, and moreover, identified a pathogenetic mechanism of miR-1246 in B cells. MiR-1246 inhibits, by interacting with its 3′-UTR, early B cell factor 1 (EBF1), which is necessary for B

cell maturation (pro-B cells, MZ B cells and peripheral B cells) and signalling, including the expression of co-stimulatory molecules such as CD40, CD80 and CD86 (ref.[144]). In active SLE, B cells showed activation of the PI3K/AKT-p53 signalling pathway leading to alleviation of miR-1246 and enhanced EBF-1 expression[143]. The other miRs aberrantly expressed in CD19+ B cells in SLE patients compared to controls in the study by Stagakis et al., are, unfortunately, not related to disease activity. MiR-21, miR-25 and miR-106b, which are elevated in B cells, are upregulated in T cells as well, and the positive correlation with SLEDAI in total PBMCs should not be ascribed to B cells[27]. However, elevated miR-21 in B cells has been confirmed in further studies to be associated with disease severity[144] and lupus nephritis[145]. Recently, Wu et al. demonstrated elevated levels of miR-7, miR-21 and miR-22 in B cells of newly diagnosed treatment-*naïve* SLE patients[144]. All three miRs are upregulated by IL-21 and could downregulate phosphatase and the tensin homologue (PTEN), whose levels are alleviated in immature, *naïve* and plasma SLE B cells[144]. PTEN regulates BCR signalling and suppress the activity of the PI3K pathway. Furthermore, conditional deletion of PTEN leads to aberrant CSR and augmentation of autoreactive fate of B cells, in particular maturation of MZ B cells[146]. Additionally, an miR-7 antagomir is able, via IL-21-induced PTEN expression, to elicit a positive effect of IL-21 on plasma cells maturation[144]. Very recently, a study done on two ethnicities, Chilean and French, determined the miRs expression in B cell subsets of untreated active SLE patients[145]. Although the number of patients is limited, both ethnicities show the same dissimilarities in miRs expression in *naïve* CD27- and memory CD27+ B cells. Using microarray analyses comparing the expression levels of 782 miRs, out of which 11 (2 up- and 9 down-regulated) and 6 (1up- and 5 down-regulated) miRs differentially expressed in *naïve* CD27- and memory CD27+ B cells, respectively (Fig. 3). Moreover, in the lupus nephritis group compared to the SLE group, miR-145 was upregulated, yet levels of miR-18b, miR-21, miR-29c, miR-345 and miR-365 were alleviated[145].

Conclusion and future perspectives

Although the amount of available information about miRs in the pathogenesis of autoimmune diseases is growing exponentially, in this review we examine the participation of miRs in SLE development in light of recent findings. Although new therapies for SLE are coming[3], the treatment of SLE flares with regard to miscellaneous clinical features remains challenging[2-3]. It is necessary to discover new ways how to treat and monitor the disease and predict flares. MiRs are molecules with the potential to serve as markers of the disease as well as a future therapeutic option. SLE mouse models with knockdown miR-155 exhibit a milder disease with smaller amounts of IgG antibodies[88]. Whereas miR-155 is one of the fully occupied miRs in innate as well as adaptive immune responses, further studies to exclude infection, malignancies and other adverse effects following inhibition of miR-155 *in vivo* are intensively required. Interestingly, in mouse models of amyotrophic lateral sclerosis, treatment by anti-miR-155 prolonged survival[147], but the adverse effects are not known. In human medicine, anti-miR therapies, e.g. anti-miR-122 in the treatment of hepatitis C, anti-miR-208 in heart failure or anti-miR-33 in atherosclerosis represent potential future therapeutic options, which are being pursued in ongoing clinical trials[148]. In SLE, however, no clinical trials have so far focused on anti-miR treatment.

The clinical diversity is reflected in different patterns of miRs expression. Interestingly, in the serum or in PBMCs, miR-146a, miR-126, miR-451, miR-142 and miR-21 correlate with disease activity or clinical manifestations[22,23,30,94,98,106]. Further studies will show whether miRs could be used as markers for monitoring the disease, predicting flares or determining the best treatment.

ABBREVIATIONS

DNA, Deoxyribonucleic acid; CI, confidentality interval; DC, Dendritic cells; miR, (miRNA), Micro ribonucleic acid; OR, Odds ratio; PBMC, Peripheral mononuclear cells; RNA, Ribonucleic acid; SLE, Systemic lupus erythematosus; SNP, Single nucleotide polymorphism; UTR, Untranslated region.

Acknowledgement: The author would like to thank Marie Cerna for critical reading of the text and Alena Swientekova for her help with searching and organizing the literature.
This study was supported by grant IGA NT 13707 awarded by the Czech Ministry of Health (MHCR) and by the project MHCR for conceptual development of research organization 023728 (Institute of Rheumatology).
Conflict of interest statement: The author states that there are no conflicts of interest regarding the publication of this article.

REFERENCES

1. Rahman A, Isemberg DA. Mechanisms of disease Systemic lupus erythematosus. N Engl J Med 2008;358(9):929-39.
2. Wilhelmus S, Bajema IM, Bertsias GK, Boumpas DT, Gordon C, Lightstone L, Tesar V, Jayne DR. Lupus nephritis management guidelines compared. Nephrol Dial Transplant 2015 Apr 28. pii: gfv102. [Epub ahead of print]
3. Fireti M, Heuser W, Bliss J. Efficacy of novel monoclonal antibody belimumab in the treatment of lupus nephritis. J Pharmacol Pharmacother 2015;6(2):71-6.
4. McMurray RW, May W. Sex hormones and systemic lupus erythematosus: review and meta-analysis. Arthritis Rheum 2003;48(8):2100-10.
5. Pons-Estel GJ, Alarcón GS, Scofield L, Reinlib L, Cooper GS.Understanding the epidemiology and progression of systemic lupus erythematosus. Semin Arthritis Rheum 2010;39(4):257-68.
6. Korbet SM, Schwartz MM, Evans J, Lewis EJ, Collaboratice Study Group. Severe lupus nephritis: racial differences in presentation and outcome. J Am Soc Nephrol 2007;18(1):244-54.
7. Gualtierotti R, Biggioggero M, Penatti AE, Meroni PL. Updating on the pathogenesis of systemic lupus erythematosus. Autoimmun Rev 2010;(1):3-7.
8. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993;75(5):843-54.

9. Griffiths-Jones S, Grocock RJ, van Dongen S, Bateman A, Enright AJ. miRBase: microRNA sequences, targets and gene nomenclature. Nucleis Acids Res 2006;34(Database isme):D140-4.
10. Kozomara A, Griffiths-Jones S. miRBase: annotating high confidence microRNAs using deep sequencing data. Nucleic Acids Res 2014;42(Database isme):D68-73.
11. Griffiths-Jones S. The microRNA Registry. Nucleic Acids Res 2004 Jan 1;32(Database issue):D109-11.
12. Herranz H, Cohen SM. MicroRNAs and gene regulatory networks: managing the impact of noise in biological systems. Genes Dev 2010;24(13):1339-44.
13. Bertoli G, Cava C, Castiglioni I. MicroRNAs: New Biomarkers for Diagnosis, Prognosis, Therapy Prediction and Therapeutic Tools for Breast Cancer. Theranostics 2015;5(10):1122-43. doi:10.7150/thno.11543
14. Peng Y, Yu S, Li H, Xiang H, Peng J, Jiang S. MicroRNAs: emerging roles in adipogenesis and obesity. Cell Signal 2014;26(9):1888-96.
15. Churov AV, Oleinik EK, Knip M. MicroRNAs in rheumatoid arthritis: Altered expression and diagnostic potential. Autoimmun Rev 2015;11:1029-37. doi: 10.1016/j.autrev.2015.07.005
16. Chen CZ, Schaffert S, Fragoso R, Loh C. Regulation of immune responses and tolerance: the microRNA perspective. Immunol Rev 2013;253(1):112-28.
17. Weber JA, Baxter DH, Zhang S, Huang DY, Huang KH, Lee MJ, Galas DJ, Wang K. The microRNA spectrum in 12 body fluids.Clin Chem 2010;56(11):1733-41.
18. Steen SO, Iversen LV, Carlsen AL, Burton M, Nielsen CT, Jacobsen S, Heegaard NH. The circulating cell-free microRNA profile in systemic sclerosis is distinct from both healthy controls and systemic lupus erythematosus. J Rheumatol 2015;42(2):214-21.
19. Carlsen AL, Schetter AJ, Nielsen CT, Lood C, Knudsen S, Voss A, Harris CC, Hellmark T, Segelmark M, Jacobsen S, Bengtsson AA, Heegaard NH. Circulating microRNA expression profiles associated with systemic lupus erythematosus. Arthritis Rheum 2013;65(5):1324-34.
20. Tang ZM, Fang M, Wang JP, Cai PC, Wang P, Hu LH. Clinical relevance of plasma miR-21 in new-onset systemic lupus erythematosus patients. J Clin Lab Anal 2014;28(6):446-51.
21. Wang H, Peng W, Ouyang X, Li W, Dai Y. Circulating microRNAs as candidate biomarkers in patients with systemic lupus erythematosus. Trans Res 2012;160(3):198-206.
22. Wang G, Tam LS, Li EK, Kwan BC, Chow KM, Luk CC, Li PK, Szeto CC. Serum and urinary free microRNA level in patients with systemic lupus erythematosus. Lupus 2011;20(5):493-500.
23. Wang G, Tam LS, Li EK, Kwan BC, Chow KM, Luk CC, Li PK, Szeto CC. Serum and urinary cell-free MiR-146a and MiR-155 in patients with systemic lupus erythematosus. J Rheumatol 2010;37(12):2516-22.
24. Dai Y, Huang YS, Tang M, Lv TY, Hu CX, Tan YH, Xu ZM, Yin YB. Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. Lupus 2007;16(12):939-46.
25. Liu D, Zhao H, Zhao S, Wang X. MicroRNA expression profiles of peripheral blood mononuclear cells in patients with systemic lupus erythematosus. Acta Histochem 2014;116(5):891-7.
26. Tang Y, Luo X, Cui H, Ni X, Yuan M, Guo Y, Huang X, Zhou H, de Vries N, Tak PP, Chen S, Shen N. MicroRNA-146a contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. Arthritis Rheum 2009;60(4):1065-75.
27. Stagakis E, Bertsias G, Verginis P, Nakou M, Hatziapostolou M, Kritikos H, Iliopoulos D, Boumpas DT. Identification of novel microRNA signatures linked to human lupus disease activity and pathogenesis: miR-21 regulates aberrant T cell responses through regulation of PDCD4 expression. Ann Rheum Dis 2011;70(8):1496-506.
28. Chen W, Tan K, Huang J, Yu X, Peng W, Chen Y, Lin X, Chen D, Dai Y. Analysis of microRNAs in patients with systemic lupus erythematosus, using Solexa deep sequencing. Connect Tissue Res 2014;55(3):187-96.
29. Zhu J, Huang X, Su G, Wang L, Wu F, Zhang T, Song G. High expression levels of micrRNA-629, microRNA-525-5p and micrRNA-516-35 in paediatric systemic lupus erythematosus. Clin Rheumatol 2014;33(6):807-15.
30. Pan W, Zhu S, Yuan M, Cui H, Wang L, Luo X, Li J, Zhou H, Tang Y, Shen N. Micro-RNA 21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+ T cells by directly or indirectly targeting DNA methyltransferase 1. J Immunol 2010;184:6773-81.
31. Libri V, Miesen P, van Rij RP, Buck AH. Regulation of microRNA biogenesis and turnover by animals and their viruses. Cell Mol Life Sci 2013;70(19):3525-44.
32. Londin E, Loher P, Telonis AG, Quann K, Clark P, Jing Y, Hatzimichael E, Kirino Y, Honda S, Lally M, Ramratnam B, Comstock CE, Knudsen KE, Gomella L, Spaeth GL, Hark L, Katz LJ, Witkiewicz A, Rostami A, Jimenez SA, Hollingsworth MA, Yeh JJ, Shaw CA, McKenzie SE, Bray P, Nelson PT, Zupo S, Van Roosbroeck K, Keating MJ, Calin GA, Yeo C, Jimbo M, Cozzitorto J, Brody JR, Delgrosso K, Mattick JS, Fortina P, Rigoutsos I. Analysis of 13 cell types revers evidence for the expression of numerus novel primate- and tissue-specific microRNAs. Proc Natl Acad Sci U S A 2015;112(10):E1106-15.
33. Saini HK, Griffiths-Jones S, Enright AL. Genomic analysis of human microRNA transcripts. Proc Natl Acad Sci U S A 2007;104(45):17719-24.
34. Abdelfattah AM, Park C, Choi MY. Update on non-canonical microRNAs. Biomol Concepts 2014;5(4):275-87.
35. Lee Y, Kim M, Han J, Yeom KH, Lee S, Baek SH, Kim VN. MicroRNA genes are transcribed by RNA polymerase II. EMBO J 2004;23(20):4051-60.
36. Borchert GM, Lanier W, Davidson BL. RNA polymerase III transcribes human microRNAs. Nat Struct Mol Biol 2006;13(12):1097-101.
37. Lee Y, Ahn C, Han J, Choi H, Kim J, Yim J, Lee J, Provost P, Rådmark O, Kim S, Kim VN. The nuclear RNase III Drosha initiates microRNA processing. Nature 2003;425(6956):415-9.
38. Okada C, Yamashita E, Lee SJ, Shibata S, Katahira J, Nakagawa A, Yoneda Y, Tsukihara T. A high-resolution structure of the pre-microRNA nuclear export machinery. Science 2009;326(5957):1275-9.
39. Bernstein E, Caudy AA, Hammond SM, Hannon GJ. Role for a bidentate ribonuclease in the initiation step of RNA interference. Nature 2001;409(6818):363-6.
40. Gregory RI, Chendrimada TP, Cooch N, Shiekhattar R. Human RISC couples microRNA biogenesis and posttranscriptional gene silencing. Cell 2005;123(4):631-40.
41. Fabian MR, Sonenberg N. The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC. Nat Struct Mol Biol 2012;19(6):586-93.
42. Zhou H, Rigoutsos I. MiR-103a-3p targets the 5' UTR of GPRC5A in pancreatic cells. RNA. 2014;20(9):1431-9.
43. Cesana M, Cacchiarelli D, Legnini I, Santini T, Sthandier O, Chinappi M, Tramontano A, Bozzoni, I. A long noncoding RNA controls muscle differentiation by functioning as a competing endogenous RNA. Cell 2011;147(2):358-69.
44. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. Nature 2013;495(7441):384-8.
45. Bartel DP MicroRNAs: target recognition and regulatory functions. Cell 2009;136(2):215-33.
46. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res 2009;19(1):92-105.
47. Luo X, Yang W, Ye DQ, Cui H, Zhang Y, Hirankarn N, Qian X, Tang Y, Lau YL, de Vries N, Tak PP, Tsao BP, Shen N. A Functional Variant in MicroRNA-146a Promoter Modulates Its Expression and Confers Disease Risk for Systemic Lupus Erythematosus. PLoS Genet 2011;(6):e1002128.
48. Tang Q, Yang Y, Zhao M, Liang G, Wu H, Liu Q, Xie Y, Li D, Dai Y, Yung S, Chan TM, Lu Q Mycophenolic acid upregulates miR-142-3P/5P and miR-146a in lupus CD4+ cells. Lupus 2015;24(9):935-42.
49. Li X, Tian X, Zhang B, Zhang Y, Chen J. Variation in dicer gene is associated with increased survival in T-cell lymphoma. PLoS One 2012;7(12):e51640.
50. Nothnick WB, Healy C, Hing X. Steroidal regulation of uterine miRNAs is associated with modulation of the miRNA biogenesis components Exportin-5 and Dicer1. Endocrine 2010;37(2):265-73.
51. Jakymiw A, Ikeda K, Fritzler MJ, Reeves WH, Satoh M, Chan EK. Autoimmune targeting of key components of RNA interference. Arthritis Res Ther 2006;8(4):R87.
52. Peterson SM, Thompson JA, Ufkin ML, Sathyanarayana P, Liaw L, Congdon CB Common features of microRNA target prediction tools. Front Genet 2014;5:23. doi: 10.3389/fgene.2014.00023. eCollection 2014
53. Hogg DR, Harries LW. Human genetic variation and its effect on miRNA biogenesis, activity and function. Biochem Soc Trans 2014;42(4):1184-9.

54. Nigita G, Veneziano D, Feroo A. A-to-I RNA Editing: Current knowledges sources and computational approaches with speccial emphasis on non-coding NA molecules. Front Bioeng Biotechnol 2015;25(3):37. doi: 10.3389/fbioe.2015.00037. eCollection 2015
55. Katakowski M, Buller B, Wang X, Rogers T, Chopp M. Functional microRNA is transferred between glioma cells. Cancer Res 2010;70(21):8259-63.
56. Hunter MP, Ismail N, Zhang X, Aguda BD, Lee EJ, Yu L, Xiao T, Schafer J, Lee ML, Schmittgen TD, Nana-Sinkam SP, Jarjoura D, Marsh CB. Detection of microRNA expression in human peripheral blood microvesicles. PLoS One 2008;3(11):e3694.
57. Mittelbrunn M, Gutiérrez-Vázquez C, Villarroya-Beltri C, González S, Sánchez-Cabo F, González MÁ, Bernad A, Sánchez-Madrid F.Unidirectional transfer of microRNA-loaded exosomes from T cells to antigen-presenting cells. Nat Commun 2011;2:282.
58. Vickers KC, Palmisano BT, Shoucri BM, Shamburek RD, Remaley AT. MicroRNAs are transported in plasma and delivered to recipient cells by high-density lipoproteins. Nat Cell Biol 2011;13(4):423-33.
59. Arroyo JD, Chevillet JR, Kroh EM, Ruf IK, Pritchard CC, Gibson DF, Mitchell PS, Bennett CF, Pogosova-Agadjanyan EL, Stirewalt DL, Tait JF, Tewari M. Argonaute2 complexes carry a population of circulating microRNAs independent of vesicles in human plasma. Proc Natl Acad Sci USA 2011;108(12):5003-8.
60. Wang K, Zhang S, Weber J, Baxter D, Galas DJ. Export of microRNAs and microRNA-protective protein by mammalian cells. Nucleic Acids Res 2010;38(20):7248-59.
61. Chevillet JR, Kang Q, Ruf IK, Briggs HA, Vojtech LN, Hughes SM, Cheng HH, Arroyo JD, Meredith EK, Gallichotte EN, Pogosova-Agadjanyan EL, Morrissey C, Stirewalt DL, Hladik F, Yu EY, Higano CS, Tewari M. Quantitative and stoichiometric analysis of the microRNA content of exosomes. Proc Natl Acad Sci USA 2014;111(41):14888-93.
62. Perez-Hernandez J, Forner MJ, Pinto C, Chaves FJ, Cortes R, Redon J. Increased Urinary Exosomal MicroRNAs in Patients with Systemic Lupus Erythematosus. PloS One 2015;10(9):e0138618.
63. Ichii O, Otsuka-Kanazawa S, Horino T, Kimura J, Nakamura T, Matsumoto M, Toi M, Kon Y. Decreased miR-26a expression correlates with the progression of podocyte injury in autoimmune glomerulonefritis. PLoS One 2014;9(10):e110383.
64. Guerra SG, Vyse TJ, Cunninghame Graham DS. The genetics of lupus: a functional perspective. Arthritis Res Ther 2012;14(3):211.
65. Leng RX, Wang W, cen H, Zhou M, Feng CC, Zhu Y, Yang XK, Yang M, Zhai Y, Wang XS, Li R, Chen GM, Chen H, Pan HF, Ye DQ. Gene-gene and gene-sex epistatic interactions of MiR146a, IRF5, IKZF1, ETS1 and IL21 in systemic lupus erythematosus. PloS One 2012;7(12):e51090.
66. Fu L, Jin L, Yan L, Shi J, Wang H, Zhou B, Wu X. Comprehensive review of genetic association studies and meta-analysis on miRNA polymorphisms and rheumatoid arthritis and systemic lupus erythematosus susceptibility. Human Immunol 2014;Sep 11 [Epub ahead of print] doi: 10.1016/j.humimm.2014.09.002
67. Zhang J, Yang B, Ying B, Li D, Shi Y, Song X, Cai B, Huang Z, Wu Y, Wang L.Association of pre-microRNAs genetic variants with susceptibility in systemic lupus erythematosus. Mol Biol Rep 2011;38(3):1463-8.
68. International Consortium for Systemic Lupus Erythematosus Genetics (SLEGEN), Harley JB, Alarcón-Riquelme ME, Criswell LA, Jacob CO, Kimberly RP, Moser KL, Tsao BP, Vyse TJ, Langefeld CD, Nath SK, Guthridge JM, Cobb BL, Mirel DB, Marion MC, Williams AH, Divers J, Wang W, Frank SG, Namjou B, Gabriel SB, Lee AT, Gregersen PK, Behrens TW, Taylor KE, Fernando M, Zidovetzki R, Gaffney PM, Edberg JC, Rioux JD, Ojwang JO, James JA, Merrill JT, Gilkeson GS, Seldin MF, Yin H, Baechler EC, Li QZ, Wakeland EK, Bruner GR, Kaufman KM, Kelly JA. Genome-wide association scan in women with systemic lupus erythematosus identifies susceptibility variants in ITGAM, PXK, KIAA1542 and other loci. Nat Genet 2008;40(2):204-10.
69. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, Ortmann W, Kosoy R, Ferreira RC, Nordmark G, Gunnarsson I, Svenungsson E, Padyukov L, Sturfelt G, Jönsen A, Bengtsson AA, Rantapää-Dahlqvist S, Baechler EC, Brown EE, Alarcón GS, Edberg JC, Ramsey-Goldman R, McGwin G Jr, Reveille JD, Vilá LM, Kimberly RP, Manzi S, Petri MA, Lee A, Gregersen PK, Seldin MF, Rönnblom L, Criswell LA, Syvänen AC, Behrens TW, Graham RR. A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet 2009;41(11):1228-33.
70. Yang W, Shen N, Ye DQ, Liu Q, Zhang Y, Qian XX, Hirankarn N, Ying D, Pan HF, Mok CC, Chan TM, Wong RW, Lee KW, Mok MY, Wong SN, Leung AM, Li XP, Avihingsanon Y, Wong CM, Lee TL, Ho MH, Lee PP, Chang YK, Li PH, Li RJ, Zhang L, Wong WH, Ng IO, Lau CS, Sham PC, Lau YL, Asian Lupus Genetics Consortium. Genome-wide association study in Asian populations identifies variants in ETS1 and WDFY4 associated with systemic lupus erythematosus. PLoS Genet 2010;6(2):e1000841.
71. Löfgren SE, Frostegård J, Truedsson L, Pons-Estel BA, D'Alfonso S, Witte T, Lauwerys BR, Endreffy E, Kovács L, Vasconcelos C, Martins da Silva B, Kozyrev SV, Alarcón-Riquelme ME..Genetic association of miRNA-146a with systemic lupus erythematosus in Europeans through decreased expression of the gene. Genes Immun 2012;13(3):268-74.
72. Zhong H, Li XL, Li M, Hao LX, Chen RW, Xiang K, Qi XB, Ma RZ, Su B. Replicated associations of TNFAIP3, TNIP1 and ETS1 with systemic lupus erythematosus in a southwestern Chinese population. Arthritis Res Ther 2011;13(6):R186.
73. Tang ZM, Wang P, Chang PP, Hasahya T, Xing H, Wang JP Hu LH. Association between rs2431697 T allele on 5q33.3 and systemic lupus erythematosus: case-control study and meta-analysis. Clin Rheumatol 2015;24(11)1893-902.
74. Jazdzewski K, Murray EL, Franssila K, Jarzab B, Schoenberg DR, de la Chapelle A. Common SNP in pre-miR-146a decreases mature miR expression and predisposes to papillary thyroid carcinoma. Proc Natl Acad Sci USA 2008;105(20):7269-74.
75. Li C, Fu W, Zhang Y, Zhou L, Mao Z, Lv W,, Li J, Zhou Y. Meta-Analysis of MicroRNA-146a rs2910164 G>C Polymorphism Association with Autoimmune Diseases Susceptibility, an Update Based on 24 Studies. Plos One 2015;10(4):e0121918.
76. Ji JD, Cha ES, Lee WJ. Association of miR-146a polymorphisms with systemic lupus erythematosus: a meta-analysis. Lupus 2014;23(10):1023-30.
77. Jiménez-Morales S, Gamboa-Becerra R, Baca V, Del Río-Navarro BE, López-Ley DY, Velázquez-Cruz R, Saldaña-Alvarez Y, Salas-Martínez G, Orozco L. MiR-146a polymorphism is associated with asthma but not with systemic lupus erythematosus and juvenile rheumatoid arthritis in Mexican patients. Tissue Antigens 2012;80(4):317-21.
78. Hughes GC, Choubey D. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. Nat Rev Rheumatol 2014;10(12):740-51.
79. Smith-Bouvier DL, Divekar AA, Sasidhar M, Du S, Tiwari-Woodruff SK, King JK, Arnold AP, Singh RR, Voskuhl RR A role for sex chromosome complement in the female bias in autoimmune disease. J Exp Med 2008;205(5):1099-108.
80. Dong G, Fan H, Yang Y, Zhao G, You M, Wang T, Hou Y. 17β-Estradiol enhances the activation of IFN-α signalling in B cells by down-regulating the expression of let-7e-5p, miR-98-5p and miR-145a-5p that target IKKε. Biochim Biophs Acta 2015;1852 (8):1585-98.
81. Dai R, Phillips RA, Zhang Y, Khan D, Crasta O, Ansar Ahmed S. Suppression of LPS-induced interferon-gamma and nitric oxide in splenic lymphocytes by select estrogen-regulated microRNAs: a novel mechanism of immune modulation. Blood 2008;112(12):4591-7.
82. Wang C, Ahlford A, Laxman N, Nordmark G, Eloranta ML, Gunnarsson I, Svenungsson E, Padyukov L, Sturfelt G, Jönsen A, Bengtsson AA, Truedsson L, Rantapää-Dahlqvist S, Sjöwall C, Sandling JK, Rönnblom L, Syvänen AC. Contribution of IKBKE and IFIH1 gene variants to SLE susceptibility. Genes Immun 2013;14(4):217-22.
83. Belver L, de Yebenes VG, Ramiro AR. MicroRNA prevent the generation of autoreactive antibodies. Immunity 2010;33(5):713-22.
84. Dai R, McReynolds S, Leroith T, Heid B, Liang Z, Ahmed SA. Sex differences in the expression of lupus-associated miRNAs in splenocytes from lupus-prone NZB/WF1 mice. Biol Sex Differ 2013;4(1):19.
85. Khan D, Dai R, Ansar Ahmed S. Sex differences and estrogen regulation of miRNAs in lupus, a prototypical autoimmune disease. Cell Immunol 2015;294(2):70-9.
86. Cooney CM, Bruner GR, Aberle T, Namjou-Khales B, Myers LK, Feo L, Li S, D'Souza A, Ramirez A, Harley JB, Scofield RH. 46,X,del(X)(q13) Turner's syndrome women with systemic lupus erythematosus in a pedigree multiplex for SLE. Genes Immun 2009;10(5):478-81.
87. Boldin MP, Taganov KD, Rao DS, Yang L, Zhao JL, Kalwani M, Garcia-Flores Y, Luong M, Devrekanli A, Xu J, Sun G, Tay J, Linsley PS, Baltimore D.miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. J Exp Med 2011;208(6):1189-201.

88. Xin Q, Li J, Dang J, Bian X, Shan S, Yuan J, Qian Y, Liu Z, Liu G, Yuan Q, Liu N, Ma X, Gao F, Gong Y, Liu Q miR-155 deficiency ameliorates autoimmune inflammation of systemic lupus erythemasus by targeting S1pr1 in Faslpr/lpr Mice. J Immunol 2015;194(11):5437-45.
89. Jego G, Palucka AK, Blanck JP, Chalouni C, Pascual V, Banchereau J. Plasmacytoid dendritic cells induce plasma cell differentiation through type I interferon and interleukin 6. Immunity. 2003;19(2):225-34.
90. Li H, Fu YX, Wu Q, Zhou Y, Crossman DK, Yang P, Li J, Luo B, Morel LM, Kabarowski JH, Yagita H, Ware CF, Hsu HC, Mountz JD. Interferon-induced mechanosensing defects impede apoptotic cell clearance in lupus. J Clin Invest 2015;125(7):2877-90.
91. Karrich JJ, Jachimowsky LC, Libouban M, Iyer A, Branwijk K, Taanman-Kueter EW, Nagasawa M, deJong EC, Uitenbogaart CH, Blom B. MicroRNA-146a regulates survival and maturation of human plasmocytoid dendritic cells. Blood 2013;122(17):3001-9.
92. Charrier E, Cordeiro P, Cordeau M, Dardari R, Michaud A, Harnois M, Merindol N, Herblot S, Duval M. Post-transcriptional down-regulation of Toll-like receptor signaling pathway in umbilical cord blood plasmacytoid dendritic cells. Cell Immunol 2012;276(1-2):114-21.
93. Zhou H, Huang X, Cui H, Luo X, Tang Y, Chen S, Wu L, Shen N. miR-155 and its star-form partner miR-155* cooperatively regulate type I interferon production by human plasmacytoid dendritic cells. Blood 2010;116(26):5885-94.
94. Kaga H, Komatsuda A, Omokawa A, Ito M, Teshima K, Tagawa H, Sawada K, Wakui H. Downregulated expression of miR-155, miR-17, and miR-181b, and upregulated expression of activation-induced cytidine deaminase and interferon-α in PBMCs from patients with SLE. Mod Rheumatol 2015;25(6):865-70. doi:10.3109/14397595.2015.1030102
95. Taganov KD, Boldin MP, Chang KJ, Baltimore D. NF-kappaB-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. Proc Natl Acad Sci USA 2006;103(33):12481-6.
96. Li Y, Fan X, He X, Sun H, Zou Z, Yuan H, Xu H, Wang C, Shi X. MicroRNA-466l inhibits antiviral innate immune response by targeting interferon-alpha. Cell Mol Immunol 2012;9(6):497-502.
97. Yuan Y, Kasar S, Underbayev C, Vollenweider D, Salerno E, Kotenko SV, Raveche E Role of microRNA-15a in autoantibody production in interferon-augmented murine model of lupus. Mol Immunol 2012;52(2):61-70.
98. Hashad DI, Abdelmagid MH, Elsherif SH. MicroRNA 146a expression in lupus patients with and without renal complications. J Clin Lab Anal 2012;26(1):35-40.
99. Schiffer L, Bethunaickan R, Ramanujam M, Huang W, Schiffer M, Tao H, Madaio MM, Bottinger EP, Davidson A. Activated renal macrophages are markers of disease onset and disease remission in lupus nephritis. J Immunol 2008;180(3):1938-47.
100. Zhang W, Xu W, Xiong S. Blockage of Notch1 signaling aleviates murine lupus via blunting macrophage activation and M2b polarization. J Immunol 2010;184(11):6465-78.
101. Xiao P, Dong C, Yue Y, Xiong S. Dynamic expression of microRNAs in M2b polarized macrophages associated with lupus erythematosus. Gene 2014;547(2):300-9.
102. Konya C, Paz Z, Tsokos GC. The role of T cells in systemic lupus erythematosis: an update. Curr Opin Rheumatol 2014;26(5):493-501.
103. Martinez-Ramos R, Garcia-Iozano JR, Lucena JM, Castillo-Palma MJ, Garcia-Hernandez F, Rodriguez MC, Nunez-Roldan A, Gonzalez-Escribano MF. Differential expression pattern of microRNAs in CD4+ and CD19+ cells from asymptomatic patients with systemic lupus erythematosus. Lupus 2014;23(4):353-9.
104. Zhao S, Wang Y, Liang Y, Zhao M, Long H, Ding S, Yin H, Lu Q. MicroRNA-126 regulates DNA methylation in CD4+ T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1. Arthritis Rheum 2011;63(5):1376-86.
105. Qin H, Zhu X, Liang J, Wu J, Yang Y, Wang S, Shi W, Xu J. MicroRNA-29b contributes to DNA hypomethylation of CD4+ T cells in systemic lupus erythematosus by indirectly targeting DNA methyltransferase 1. J Dermatol Sci 2013;69(1):61-7.
106. Zhao M, Liu S, Luo S, Wu H, Tang M, Cheng W, Zhang Q, Zhang P, Yu X, Xia Y, Yi N, Gao F, Wang L, Yung S, Chan TM, Sawalha AH, Richardson B, Gershwin ME, Li N, Lu Q. DNA methylation and mRNA and microRNA expression of SLE CD4+ T cells correlate with disease phenotype. J Autoimm 2014;54(SI):127-36.
107. Ding S, Liang Y, Zhao M, Liang G, Long H, Zhao S, Wang Y, Yin H, Zhang P, Zhang Q, Lu Q. Decreased micro-RNA-142-3p/5p expression causes CD4+ T cell activation and B cell hyperstimulation in systemic lupus erythematosus. Arthritis Rheum 2012;64(9):2953-63.
108. Yang L, Boldin MP, Yu Y, Liu CS, Ea CK, Ramakrishnan P, Taganov KD, Zhao JL, Baltimore D. MiR-146a controls the resolution of T cell responses in mice. J Exp Med 2012;209(9):1655-70.
109. Saki N, Abroun S, Soleimani M, Hajizamani S, Shahjahani M, Kast RE, Mortazavi Y. Involvement of MicroRNA in T-Cell Differentiation and Malignancy. Int J Hematol Oncol Stem Cell Res 2015;9(1):33-49.
110. Hagiwara E, Gourley MF, Lee S, Klinman DK. Disease severity in patients with systemic lupus erythematosus correlates with an increased ratio of interleukin 10: interferon-gamma-secreting cells in peripheral blood. Arthritis Rheum 1996;39(3):379-85.
111. Fan W, Liang D, Tang Y, Qu B, Cui H, Luo X, Huang X, Chen S, Higgs BW, Jallal B, Yao Y, Harley JB, Shen N. Identification of microRNA-31 as a novel regulator contributing to impaired interleukin-2 production in T cells from patients with systemic lupus erythematosus. Arthritis Rheum 2012;64(11):3715-25.
112. Lu LF, Thai TH, Calado DP, Chaudhry A, Kubo M, Tanaka K, Loeb GB, Lee H, Yoshimura A, Rajewsky K, Rudensky AY. Foxp3-dependent microRNA155 confers competitive fitness to regulatory T ells by targeting SOCS1 protein. Immunity 2009;30(1):80-91.
113. Garchow BG, Bartulos Encinas O, Leung YT, Tsao PY, Eisenberg RA, Caricchio R, Obad S, Petri A, Kauppinen S, Kiriakidou M.Silencing of microRNA-21 in vivo ameliorates autoimmune splenomegaly in lupus mice. EMBO Mol Med 2011;3(10):605-15.
114. Lu MC, Yu CL, Chen HC, Yu HC, Huang HB, Lai NS. Aberrant T cell expression of Ca2+ influx-regulated miRNAs in patients with systemic lupus erythematosus promotes lupus pathogenesis. Rheumatology 2015;54(2):343-8.
115. Lu MC, Lai NS, Chen HC, Yu HC, Huang KY, Tung CH, Huang HB, Yu CL. Decreased microRNA(miR)-145 and increased miR-224 expression in T cells from patients with systemic lupus erythematosus involved in lupus immunopathogenesis. Clin Exp Immunol 2013;171(1):91-9.
116. Qin A, Wen Z, Zhou Y, Li Y, Li Y, Luo J, Ren T, Xu L. MicroRNA-126 regulates the induction and function of $CD4^+$ $Foxp3^+$ regulatory T cells through PI3K/AKT pathway. J Cell Mol Med 2013;17(2):252-64.
117. Rouas R, Fayyad-Kazan H, El Zein N, Lewalle P, Rothé F, Simion A, Akl H, Mourtada M, El Rifai M, Burny A, Romero P, Martiat P, Badran B. Human natural Treg microRNA signature: role of microRNA-31 and microRNA-21 in FOXP3 expression. Eur J Immunol 2009;39(6):1608-18.
118. Luo X, Zhang L, Li M, Zhang W, Leng W, Zhang F, Zhao Y, Zeng X. The role of miR-125b in T lymphocytes in the pathogenesis of systemic lupus erythematosus. Clin Exp Rheumatol 2013;31(2):263-71.
119. Zhao X, Tang Y, Qu B, Cui H, Wang S, Wang L, Luo X, Huang X, Li J, Chen S, Shen N MicroRNA-125a contributes to elevated inflammatory chemokine RANTES levels via targeting KLF13 in systemic lupus erythematosus. Arthritis Rheum 2010;62(11):3425-35.
120. Kang SG, Liu WH, Lu P, Jin HY, Lim HW, Shepherd J, Fremgen D, Verdin E, Oldstone MB, Qi H, Teijaro JR, Xiao C. MicroRNAs of the miR-17 approximately 92 family are critical regulators of T(FH) differentiation. Nat Immunol 2013;14(8):849-57.
121. Takahashi H, Kanno T, Nakayamada S, Hirahara K, Sciumè G, Muljo SA, Kuchen S, Casellas R, Wei L, Kanno Y, O'Shea JJ. TGF-beta and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. Nat Immunol 2012;13(6):587-95.
122. Chauhan SK, Singh VV, Rai R, Rai M, Rai G. Differential microRNA profile and post-transcriptional regulation exist in systemic lupus erythematosus patients with distinct autoantibody species. J Clin Immunol 2014;34(4):491-503.
123. Pratama A, Srivastava M, Williams NJ, Papa I, Lee SK, Dinh XT, Hutloff A, Jordan MA, Zhao JL, Casellas R, Athanasopoulos V, Vinuesa CG. MicroRNA-146a regulates ICOS-ICOSL signalling to limit accumulation of T follicular helper cells and germinal centres. Nat Commun 2015;6:6436.
124. Koralov SB, Muljo SA, Galler GR, Krek A, Chakraborty T, Kanellopoulou C, Jensen K, Cobb BS, Merkenschlager M, Rajewsky N, Rajewsky K. Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. Cell 2008;132(5):860-74.
125. Xu S, Guo K, Zeng Q, Huo J, Lam KP. The RNase III enzyme Dicer is es-

sential for germinal center B-cell formation. Blood 2012;119(3):767-76.
126. Georgantas RW 3rd, Hildreth R, Morisot S, Alder J, Liu CG, Heimfeld S, Calin GA, Croce CM, Civin CI. CD34+ hematopoietic stem-progenitor cell microRNA expression and function: a circuit diagram of differentiation control. Proc Natl Acad Sci 2007;104(8):2750-5.
127. Mehta A, Mann M, Zhao JL, Marinov GK, Majumdar D, Garcia-Flores Y, Du X, Erikci E, Chowdhury K, Baltimore D. The microRNA-212/132 cluster regulates B cell development by targeting Sox4. J Exp Med 2015;212(10):1679-92.
128. Ventura A, Young AG, Winslow MM, Lintault L, Meissner A, Erkeland SJ, Newman J, Bronson RT, Crowley D, Stone JR, Jaenisch R, Sharp PA, Jacks T. Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. Cell 2008;132(5):875-86.
129. Jensen K, Brusletto BS, Aass HC, Olstad OK, Kierulf P, Gautvik KM. Transcriptional profiling of mRNAs and microRNAs in human bone marrow precursor B cells identifies subset- and age-specific variations. PLoS One 2013;8(7):e70721.
130. Mok Y, Schwierzeck V, Thomas DC, Vigorito E, Rayner TF, Jarvis LB, Prosser HM, Bradley A, Withers DR, Mårtensson IL, Corcoran LM, Blenkiron C, Miska EA, Lyons PA, Smith KG MiR-210 is induced by Oct-2, regulates B cells, and inhibits autoantibody production. J Immunol 2013;191(6):3037-48.
131. Fernando TR, Rodriquez-Malave NI, Rao DS. MicroRNA in B cell development and malignancy. J Hematol Oncol 2012;5(1):7.
132. Teng G, Hakimpour P, Landgraf P, Rice A, Tuschl T, Casellas R, Papavasiliou FN. MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. Immunity 2008;28(5):621-9.
133. de Yébenes VG, Belver L, Pisano DG, González S, Villasante A, Croce C, He L, Ramiro AR miR-181b negatively regulates activation-induced cytidine deaminase in B cells. J Exp Med 2008;205(10):2199-206.
134. Zhang J, Jima DD, Jacobs C, Fischer R, Gottwein E, Huang G, Lugar PL, Lagoo AS, Rizzieri DA, Friedman DR, Weinberg JB, Lipsky PE, Dave SS. Patterns of microRNA expression characterize stages of human B-cell differentiation. Blood 2009;113(19):4586-94.
135. Lu D, Nakagawa R, Lazzaro S, Staudacher P, Abreu-Goodger C, Henely T, Boiani S, Leyland R, Galloway A, Andrews S, Butche G, Nutt SL, Turner M, Vigorito E. The miR-155-PU.1 axis acts on Pax5 to enable efficient terminal B cell differentiation. J Exp Med 2014;211(11):2183-98.
136. Malumbres R, Sarosiek KA, Cubedo E, Ruiz JW, Jiang X, Gascoyne RD, Tibshirani R, Lossos IS. Differentiation stage-specific expression of microRNAs in B lymphocytes and diffuse large B-cell lymphomas. Blood 2009;113(16):3754-64.
137. Yu M, Liang W, Wen S, Zhao T, Zhu MX, Li HH, Long Q, Wang M, Cheng X, Liao YH, Yuan J. EphB2 contributes to human naive B-cell activation and is regulated by miR-185. FASEB J 2014;28(8):3609-17.
138. Diaz M. The role of activation-induced deaminase in lupus nephritis. Autoimmunity 2013;46(2):115-20.
139. Guo Q, Zhang J, Li J, Zou L, Zhang J, Xie Z, Fu X, Jiang S, Chen G, Jia Q, Li F, Wan Y, Wu Y. Forced miR-146a expression causes autoimmune lymphoproliferative syndrome in mice via downregulation of Fas in germinal center B cells. Blood 2013;121(24):4875-83.
140. Dai R, Zhang Y, Khan D, Heid B, Caudell D, Crasta O, Ahmed SA. Identification of a common lupus disease-associated microRNA expression pattern in three different murine models of lupus. PLoS One 2010;5(12):e14302.
141. Thai TH, Patterson HC, Pham DH, Kis-Toth K, Kaminski DA, Tsokos GC. Deletion of microRNA-155 reduces autoantibody responses and alleviates lupus-like disease in the Fas(lpr) mouse. Proc Natl Acad Sci USA 2013;110(50):20194-9.
142. Liu Y, Dong J, Mu R, Gao Y, Tan X, Li Y, Li Z, Yang G. MicroRNA-30a promotes B cell hyperactivity in patients with systemic lupus erythematosus by direct interaction with Lyn. Arthritis Rheum 2013;65(6):1603-11.
143. Luo S, Lieu Y, Liang G, Zhao M, Wu H, Lianf Y, Qiu X, Tan Y, Dai Y, Zung S, C TM, Lu Q. The role of microRNA-1246 in the regulation of B cell activation and the pathogenesis of systemic lupus erythematosus. Clin Epigenetics 2015;7(1):24.
144. Wu XN, Ye YX, Niu JW, Li Y, Li X, You X, Chen H, Zhao LD, Zeng XF, Zhang FC, Tang FL, He W, Cao XT, Zhang X, Lipsky PE. Defective PTEN regulation contributes to B cell hyperresponsiveness in systemic lupus erythematosus. Sci Transl Med 2014;6(246):246ra99.
145. Duroux-Richard I, Cuenca J, Ponsolles C, Piñeiro AB, Gonzalez F, Roubert C, Areny R, Chea R, Pefaur J, Pers YM, Figueroa FE, Jorgensen C, Khoury M, Apparailly F · MicroRNA Profiling of B Cell Subsets from Systemic Lupus Erythematosus Patients Reveals Promising Novel Biomarkers. Int J Mol Sci 2015;16(8):16953-65.
146. Anzelon AN, Wu H, Rickert RC. Pten inactivation alters peripheral B lymphocyte fate and reconstitutes CD19 functions. Nat Immunol 2003;4(3):287-94.
147. Koval ED, Shaner C, Zhang P, du Maine X, Fischer K, Tay J, Chau BN, Wu GF, Miller TM. Method for widespread microRNA-155 inhibition prolongs survival in ALS-model mice. Hum Mol genet 2013;22(20):4127-35.
148. van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med 2014;6(7):851-64.