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REVIEW ARTICLE

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The MicroRNA-326: Autoimmune diseases, diagnostic biomarker, and therapeutic target

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MicroRNAs (miRNAs) are uniquely regulated in healthy, inflamed, activated, cancerous, or other cells and tissues of a pathological state. Many studies confirm that immune dysregulation and autoimmune diseases with inflammation are correlated with various miRNA expression changes in targeted tissues and cells in innate or adaptive immunity. In this review, we will explain the history and classification of epigenetic changes. Next, we will describe the role of miRNAs changes, especially mir-326 in autoimmunity, autoinflammatory, and other pathological conditions. A systematic search of MEDLINE, Embase, and Cochrane Library was presented for all related studies from 1899 to 2017 with restrictions in the English language. In recent years, researchers have concentrated on mostly those roles of miRNA that are correlated with the inflammatory and anti-inflammatory process. Latest studies have proposed a fundamental pathogenic role in cancers and autoinflammatory diseases. Studies have described the role of microRNAs in autoimmunity and autoinflammatory diseases, cancers, and so on. The miRNA-326 expression plays a significant role in autoimmune and other types of diseases.

KEYWORDS
autoimmune diseases (AD), diagnostic biomarker, epigenetic, microRNAs (miRNAs), mir-326, therapeutic target

1 | INTRODUCTION

Autoimmunity is present in everybody to some extent. However, autoimmunity can be the origin of a wide range of identified human diseases. Autoimmune diseases (AD) happen when mild autoimmunity starts making progression toward pathogenic autoimmunity. Up to 10% of the world's population suffers from AD and 80% of them are women. In recent years, our knowledge about etiology of AD has increased significantly (Lohi et al., 2007). Genetic factors, sex, environmental factors, and epigenetic markers play the most significant role in the pathogenesis of AD (Bach, 2002).

MiRNA is one of the epigenetic factors. miRNAs affect the immune response by involving in development, maturation, and functions of immune cells (Tufekci, Oner, Genc, & Genc, 2010). Besides, miRNAs play a key role in the posttranscriptional regulation of most gene regulatory pathways and adjust both the innate and adaptive immune responses. Many studies emphasize that miRNAs play an important role in the pathogenesis of cancer, autoimmune, and autoinflammatory diseases by modifying the immune response (Iborra, Bernuzzi, Invernizzi, & Danese, 2012). Most recently, miR-326 has been explored widely and it has emerged as a key regulator of different biological processes such as metabolism of glucose and lipids (Lee & Kemper, 2010; Y. Li et al., 2016); immune cell lineage obligation; maturation, differentiation, and maintenance of immune homeostasis; normal function (Bartel, 2004; Lagos-Quintana, Rauhut, Lendeckel, & Tuschl, 2001), TH17 differentiation (C. Du et al., 2009), dendritic cell function (Mycko et al., 2012), acute rejection after heart transplantation (I. S. Dewi, Torngren, Gidlöf, Kornhall, & Öhman, 2013); as well as cellular growth and proliferation. miR-326 may also be used as potential biomarkers and therapy targets in many kinds of cancers (S. Zhou et al., 2014). Many studies have shown

the involvement of miR-326 in cell apoptosis, invasion, metabolism, tumor growth (Karsy, Arslan, & Moy, 2012; Kefas et al., 2009; Kefas et al., 2010), embryonic development (S. Wang, Wan, & Ruan, 2016), chemotherapy resistance (D. Y. Liang, Hou, Luo, & Ao, 2016; Z. Liang et al., 2010), immune response (I. Dewi, Gidlöf, Ivars, & Öhman, 2014), inflammation, oncogenesis (Feng et al., 2014; L. Cheng et al., 2014; N. Wu, Zhang, Bai, Han, & Li, 2014; Rostas et al., 2014), and autophagy (F. Du, Feng, Fang, & Yang, 2015). The expression of rno-miR-326 was involved in the adipogenic differentiation process (Tang et al., 2009).

The aim of the present study is to review the effects of miRNAs, particularly miR-326, on immune cells and the development of AD. We will discuss the potential of miR-326 as a new diagnostic biomarker and therapeutic target for many diseases, including AD.

2 | EFFECTIVE FACTORS IN AUTOIMMUNITY

2.1 | Genetic factors

Genetic factors, including T-cell receptors and major histocompatibility complexes (MHC) genes like the human leukocyte antigen (HLA) B27, HLA DR2, and HLA DR3 play a major role in the pathogenesis of many immune disorders (Klein & Sato, 2000). Another kind of protein gene called tyrosine phosphatase non-receptor Type 22 (PTPN22), has been associated with multiple AD, such as rheumatoid arthritis (RA), Graves' disease, systemic lupus erythematosus (SLE), psoriatic arthritis, Addison's disease, myasthenia gravis, vitiligo, Type 1 diabetes (T1D), systemic sclerosis, juvenile idiopathic arthritis, and Hashimoto's thyroiditis (Gregersen & Olsson, 2009). Mutations in the transcription factor Foxp3 which has a critical role in the development of Treg cells cause susceptibility to some AD, like Behcet's disease (BD) (Hosseini et al., 2015). Polymorphisms of cytokines genes have an important role in the pathogenesis of AD (Bonyadi et al., 2009; Dehghanzadeh et al., 2016). Mutations in the gene responsible for familial Mediterranean fever disease may act as a susceptibility genetic factor for AD (Esmaeili et al., 2011; Table 1).

2.2 | Sex

While most AD occur more predominantly in women, some are more frequent in males—for example, ankylosing spondylitis (AS), T1D, granulomatosis with polyangiitis, Crohn's disease, primary sclerosing cholangitis, and psoriasis (Hayter & Cook, 2012; McCoy, 2009). Despite the high incidence of AD in women, the severity of most of these diseases, such as Hashimoto's thyroiditis, Graves' disease, multiple sclerosis (MS), myasthenia gravis, SLE, RA, and primary sclerosing cholangitis, is seen more in men (McCoy, 2009; Table 1).

2.3 | Environmental factors

Infectious diseases are one of the environmental factors that have an inverse relationship with AD (Wållberg & Harris, 2005). For example, Coxsackievirus B and Klebsiella pneumonia are strongly correlated with T1D and AS, respectively (Rashid & Ebringer, 2007; Vreugdenhil et al., 1998). Chemical agents and medications can also be correlated with the stimulation and development of AD (Pretel, Marquès, & España, 2014). Smoking is now confirmed as a significant risk factor for the incidence and severity of RA (Anderson, Meyer, Ally, & Tikly, 2016). Vitamin D, in addition to having a key role in the metabolism of calcium and phosphorus, and bone formation, plays a critical role in the maintaining of immune system homeostasis. The role of vitamin D deficiency in the pathogenesis of AD such as MS, RA, BD and oral aphthous ulceration has been reported (Khabbazi et al., 2014; Kolahi et al., 2015; Szodoray et al., 2008).

TABLE 1 HLA serotype associated with autoimmunity diseases susceptibility (Janeway, Travers, Walport & Shlomchik, 2001)

Disease	HLA allele	Relative risk	Sex ratio (F/M)
Ankylosing spondylitis	B27	87.4	0.3
Acute anterior uveitis	B27	10	<0.5
Goodpasture's syndrome	DR2	15.9	~1
Multiple sclerosis	DR2	4.8	10
Graves' Disease	DR3	37	4–5
Myasthenia gravis	DR3	2.5	~1
Systemic lupus erythematous	DR3	5.8	10–20
Type 1 insulin-dependent diabetes mellitus	DR3/DR4 heterozygote	~25	~1
Rheumatoid arthritis	DR4	4.2	3
Pemphigus vulgaris	DR4	14.4	~1
Hashimoto's thyroiditis	DR5	3.2	4–5

Note. HLA: human leukocyte antigen.

2.4 | Epigenetic markers

DNA methylation, histone posttranslational modifications, and microRNAs are epigenetic markers involved in genetic programs regulating immune responses (Alipour et al., 2018). Gene expression is influenced by epigenetic modifications; it also modifies B cell functions, such as somatic hypermutation (SHM), class switch DNA recombination, SHM, and differentiation of plasma cells, thereby informing the antibody responses (Zan, Tat, & Casali, 2014).

3 | MicroRNAs

MiRNAs are short non-coding ribonucleic acids about 19–23 nucleotides in length. They can serve as posttranscriptional negative regulators of gene expression via the junction to messenger RNAs (mRNAs) in various groups of animals, plants, and viruses. This

mechanism regulates more than two-thirds of functional proteins coding genes (X. Zhang, Dong, & Tian, 2015).

Moreover, miRNAs act by binding to the 3′- the untranslated reign (3′-UTR) of target mRNAs and repressing protein production by destabilizing mRNA and translational silencing. Nonetheless, some investigations state that miRNAs may also interact with sequences, even in the 5′-UTR, promoter, or coding regions of their target genes. The miRNAs expression level disorders have been associated with the susceptibility to AD. Therefore, they are introduced as potential diagnostic or prognostic biomarkers; they are also considered as a target for treatment of diseases (Chatzikyriakidou, Voulgari, Georgiou, & Drosos, 2012). It is estimated that miRNA genes consist 1%–5% of the human genome, and mammalian miRNAs are identified as having the control for about 30% of all coding genes. Various miRNAs can target an mRNA, and there is no linear correlation between miRNA and mRNA expression (Rani, 2017). The majority of miRNA genes (about 80%) have been identified in the intron region of either protein or non-protein coding transcripts. Only a few miRNA genes (20%) are in the exon region of noncoding RNAs (Rodriguez, Griffiths-Jones, Ashurst, & Bradley, 2004; V. N. Kim & Nam, 2006). miRNAs serve as controls of processes, such as early development, developmental timing, proliferation, immune response, hematopoiesis, apoptosis (X. Zhang et al., 2015), differentiation (Y. Wang, Keys, Au-Young, & Chen, 2009), cell fate determination, signal transduction, organ development (Alvarez-Garcia & Miska, 2005; L. He & Hannon, 2004; Miska, 2005), embryonic development, inflammation, and oncogenesis, as well as cellular growth (S. Wang et al., 2016; X. Zhang et al., 2015). They are also linked to various cellular activities such as immune response, insulin secretion, neurotransmitter synthesis, circadian rhythm, and viral replication (X. Zhang et al., 2015). miRNA expression alteration plays an important role in various human disorders such as cancer (Alvarez-Garcia & Miska, 2005), developmental abnormalities (Kloosterman, Lagendijk, Ketting, Moulton, & Plasterk, 2007), cardiovascular disorders (Y. Cheng et al., 2007), schizophrenia (Hansen et al., 2007), neurodegenerative diseases, diabetes, kidney diseases, liver diseases (Alizadeh et al., 2015), and altered immune system function (X. Zhang et al., 2015). The dysregulation of miRNAs could be the result of multiple environmental factors such as sex hormones and viral or bacterial infections (Alipour et al., 2017; G. Liu & Abraham, 2013).

In the last decade, an unexpected discovery established that miRNAs exist in human plasma. It was not expected that miRNAs could survive in this environment because of the presence of RNase enzymes in the plasma. It is now recognized that miRNAs are bound to protein and high-density lipoprotein (HDL); they are encapsulated in lipid exosomes that protect them against degradation. Furthermore, miRNAs have been extracted from other extracellular fluids—for example, urine, stool, and saliva. Many studies have been conducted on the profile of miRNAs in all fluids as well as in individuals with and without diseases (Hammond, 2015).

3.1 | Role of miRNAs in immune responses

Some studies have shown that miRNAs perform a vital function in the control of different aspects of innate immunity—for example, the control of microbial killing, the creation of cytokines, and antigen delivered by MHC molecules. Moreover, miRNAs' other function was recognized in the categorization of T cells into different type effector T helper cell subsets—for example, T helper (Th) 1, Th2, Th17, Th9, follicular T helper, and regulatory T cells (Treg). MiRNAs perform a vital role in the expansion of Th17 cells. The induction and repression of the miRNA expression in response to inflammation can influence various biological functions and induce pro-inflammatory or anti-inflammatory effects. Therefore, they are the central regulators of inflammation. Some studies show that a critical miRNA-mediated regulatory pathway prevents lymphocyte accumulation and autoimmunity, thereby revealing the vital role of miRNA regulation in Treg function (Tufekci et al., 2010).

Moreover, miRNAs affect the development of $CD8^+$T cells (miR-150, miR-21, and miR-155), Th2 (miR-150 or miR-146a), Th1 (miR-147 or miR-155), and Th17 (miR-326; Husakova, 2016). The in vivo functions of most miRNAs are unknown to a great extent. Generally, the study of the role of miRNAs in autoimmunity not only helps to understand the pathogenesis of these diseases but also contributes to emerging methods for the prevention and treatment of these serious diseases.

3.2 | Effect of miRNAs in Th17 cell differentiation

Th17 cells, a new subset of T-helper cells that is capable of producing interleukin-17 (IL-17), play an essential role in the formation of various autoimmune-mediated inflammatory diseases. Th17 cells are involved in the pathogenesis of chronic AD, and Th17 differentiation regulators are considered to have the important potential for clinical applications in the diagnosis or treatment of these immune disorders (Miossec, Korn, & Kuchroo, 2009; Tesmer, Lundy, Sarkar, & Fox, 2008). Previous studies have shown that miR-21, miR-155, miR-301a, miR-326, the miR-17–92 cluster, and the miR-132/212 cluster act as upregulators of Th17 differentiation. For example, miR-155 enhances the development of inflammatory T cells (Th1 and Th17 cells) and facilitates Th17 cell formation through cytokines produced by DCs. Also, miR-10a, miR-20b, and miR-210 act as negative regulators of Th17 differentiation. The decrease in miR-210 increases the Th17 differentiation under hypoxic conditions (X.-M. Xu & Zhang, 2016).

3.3 | MicroRNAs and AD

Failure of miRNAs control in the development of immune cells may cause autoimmune disorders such as SLE, RA, idiopathic thrombocytopenic purpura (ITP), ulcerative colitis, psoriasis, primary biliary cirrhosis, primary Sjogren's syndrome, and MS. Many autoimmune susceptibility genes are affected with various miRNAs, but specific mechanisms that miRNAs use to increase or inhibit autoimmunity are not known yet. In many cases, the functions of specific miRNAs in AD have been confirmed in vitro and their causal capacity in vivo is still unclear (Tufekci et al., 2010; Table 2). The over-expression of miR-326 is correlated with experimental autoimmune encephalomyelitis (EAE) in mice and disease severity in MS (C. Du et al., 2009). In addition,

TABLE 2 MiRNAs associated with autoimmune diseases

Disease	miRNA involved	Ref
Multiple sclerosis	miR-19a, miR-19b, miR-15b, miR-17, miR-17-5p, miR-17–92, miR-18b,miR-20, miR-20b, miR-23a, miR-34a, miR-96, miR-106b, miR-132, miR-142-3p, miR-145, miR-148a, miR-155, miR-184, miR-186, miR-193, miR-199a-3p miR-223, miR-326, miR-422a, miR-491-5p miR-493, miR-584, miR-599, miR-664, miR-1275	(Fenoglio et al., 2016; Guerau-de-Arellano, Alder, Ozer, Lovett-Racke, & Racke, 2012; Lewis, Burge, & Bartel, 2005; Tufekci et al., 2010)
Diabetes mellitus, Type 1	miR-21, miR-22, miR-25, miR-34a, miR-93, miR-125a-5p, miR-146a, miR-150, miR-155, miR-191, miR-326, miR-342, miR-424, miR-510, miR-541	(Assmann et al., 2017; Estrella, Garcia-Diaz, Codner, Camacho-Guillen, & Perez-Bravo, 2016; Han, Shi, Peng, & Gao, 2012; Hezova et al., 2010; Nielsen et al., 2012; Salas-Perez et al., 2013; Sebastiani et al., 2011; Sebastiani et al., 2017; G. Wang, Gu, Xu, Zhang, & Yang, 2017; Q. J. Zhang, Li, & Zhang, 2017)
Diabetes mellitus, Type 2	miR-1, miR-7, miR-9, miR-15a/b, miR-16, miR-21, miR-27b miR-29, miR-33a/b, miR-34a, miR-96, miR-103, miR-107, miR-124a, miR-126, miR-128a, miR-133a/b, miR-143, miR-144, miR-145, miR-146, miR-146a, miR-150, miR-181b, miR-182, miR-186, miR-195, miR-223, miR-320, miR-375miR-376, miR-383, miR-384-5p, let-7a, let-7f, let-7g	(Chakraborty, Doss, Bandyopadhyay, & Agoramoorthy, 2014; Löfgren et al., 2012)
Rheumatoid arthritis	miR-15a, miR-16, miR-19, miR-27a, miR-124a, miR-126, miR-129-3p, miR-132, miR-138, miR-146, miR-146a, miR-155, miR-203, miR-210, miR-223, miR-338-5p, miR-346, miR-363, miR-451, miR-498, miR-518a-5p, miR-573, miR-650	(Abdul-Maksoud et al., 2017; Chatzikyriakidou et al., 2012; C. Y. Chen, Fuh et al., 2017; C. Y. Chen, Su et al., 2017; Furer, Greenberg, Attur, Abramson, & Pillinger, 2010; Z. Li, Cai, & Cao, 2016; F. Pan et al., 2017; Tsai et al., 2017; L. Wang et al., 2016; Z. C. Wang et al., 2015; X. Xu et al., 2017; Y. Yang et al., 2017; Ye, Gao, & Yang, 2017; H. J. Zhang et al., 2017)
Systemic lupus erythematosus	miR-17-5p, miR-21, miR-61, miR-78, miR-112, miR-125a, miR-126, miR-141, miR-142-3, miR-146a, miR-148a, miR-155و miR-181a, miR-184, miR-189, miR-196a, miR-198, miR-298, miR-299-3p, miR-326, miR-342, miR-371-5P, miR-383, miR-409-3p, miR-423-5P, miR-516-5p, miR-637, miR-1224-3P,	(Dai et al., 2009; Furer et al., 2010; Lashine, Salah, Aboelenein, & Abdelaziz, 2015; Lashine, Seoudi, Salah, & Abdelaziz, 2010; W. Pan et al., 2010; Sun et al., 2016; Te et al., 2010; S. Zhao et al., 2011; X. Zhao et al., 2010)
Sjogren's syndrome	miR-17–92, miR-181a	(Alevizos, Bajracharya, Alexander, Turner, & Illei, 2009; Peng et al., 2014)
Psoriasis	mir17–92, miR-19a, miR-21, MiR-99a, miR125b, miR-146a, miR-150, miR-155, miR-217, miR-369 miR-492, miR-1266	(Guo et al., 2013; Hirao et al., 2013; Ichihara et al., 2012; Y. Li, Su, Li, Chen, & Zhang, 2017; Sonkoly et al., 2007; D. Wu et al., 2017; L. S. Wu et al., 2011; L. Xu et al., 2017; Z. Yang et al., 2016; H. Zhu, Hou, Liu, & Li, 2016)
Familial Mediterranean fever	MiR-4520a	(Latsoudis et al., 2017)
Primary biliary cirrhosis	miR-26a, miR-92a, miR-122a, miR-197-3p, miR-299-5p, miR-328, miR-505-3p, miR-506, miR-let-7b	(Castro & Rodrigues, 2012; D. Y. Liang et al., 2016; Ninomiya et al., 2013; Padgett et al., 2009; Qian et al., 2013)
Inflammatory bowel diseases	miR-10a, miR-21, miR-31, miR-34c, miR-122, miR-126, mir146a, miR-155, miR-192, miR-223, miR-301a, miR-320, miR-375, miR-595, miR-655, miR-1246	(Beres et al., 2016; T. Chen, Xue, Lin, & Huang, 2017; C. He et al., 2016; Iborra et al., 2012; G. W. Krissansen et al., 2015; M. Li et al., 2017; Pierdomenico et al., 2016; Thorlacius-Ussing, Schnack Nielsen, Andersen, Holmstrom, & Pedersen, 2017; H. Wang et al., 2016; W. Wu et al., 2015; C. Zhang et al., 2014)
Idiopathic thrombocytopenicpurpura	miR-17-5p, miR-21, miR-61, miR-78, miR-112, miR-141, miR-142-3p, miR-146a, miR-155, miR-181a, miR-189, miR-196a, miR-206,	(Dai et al., 2007; L. Liu et al., 2016)

(Continues)

TABLE 2 (Continued)

Disease	miRNA involved	Ref
	miR-207, miR-214, miR- 296, miR-298, miR-299-3p, miR-326, miR-342, miR-379, miR-383, miR-409-3p, miR-513	
Ulcerative colitis	miR-29b-3p, miR-122-5p, miR-140-5p, miR-140-3p, miR-146a-3p,miR-148a-3p, miR-150-5p, miR-152-3p, miR-192-5p, miR-194-5p, miR-195a-5p, miR-199a-3p, miR-335-5p, miR-375-3p	(Viennois et al., 2017)

miR-155 increases in the central nervous system (CNS) of patients with MS (O'Connell, Kahn et al., 2010). Recently, it has been illustrated that miRNAs are necessary for normal immune T-cell functions; some specific miRNAs have been observed to change in several autoimmune pathologies and are directly or indirectly correlated with the functions or development of T-cell (O'Connell, Rao, Chaudhuri, & Baltimore, 2010). This fact supports interferon gamma (IFN-γ) and IL-17A production in T cells, which are responsible for Th1 and Th17 development, affect the programmed cell death protein 4 (PDCD4) and repress apoptosis (Ma et al., 2014). The involvement of some cytokines, such as IFN-γ and IL-17, has been demonstrated in some diseases, but it has not yet been proved in case of some other diseases (Maghsood, Jadideslam, Fallah, & Bazmani, 2014).

3.4 | MicroRNAs in diagnosis

Extensive changes in the expression of miRNAs have the potential for clinical diagnosis based on miRNA signatures in various diseases. Investigators have recently focused on developing miRNAs signature for disease diagnosis, identifying cancers of unknown primary origin, and prediction of response to therapy and drug resistance. The level of miRNAs in the body fluids is pretty low (Tufekci et al., 2010). Moreover, miRNAs are more stable than mRNA and can be recovered from several sources with a low overall RNA quality—even from formalin fixed paraffin sections; they are excellent candidates for being used as disease biomarkers. As of now, no in vitro diagnostic-utilizing miRNA signature has obtained FDA approval. However, some of the companies are providing laboratory developed tests that apply miRNA signature for cancer diagnosis (Hammond, 2015). While many studies have described extracellular miRNA signatures for diseases, it is still not clear whether these signatures have acceptable accuracy and sensitivity for clinical diagnosis.

3.5 | MicroRNA in therapy

MiRNAs could also be a potential target for novel therapies in the treatment/prevention of autoimmunity. The expression of miRNAs has changed in various illnesses. A group of miRNAs is under-expressed, while some are over-expressed in a particular disease. MiRNAs have a unique feature that is very attractive in terms of medication development (Hammond, 2015). They are small molecules, with well-known sequences and are often conserved among species (Hammond, 2015). Two main strategies to manipulate miRNAs are inhibition of specific miRNA to increase the expression of target genes by antisense oligonucleotide and miRNA replacement for downregulating the target genes (Christopher et al., 2016). An antisense oligonucleotide includes a family of RNAs that presents high affinity for binding to complementary RNA molecules and high sustainability in blood and tissues. Depending on the miRNA and underlying disease, miRNA antisense inhibitors or mimickers can be used for treatment. Regulus drug (RG-101) that is an antisense inhibitor of miR-122 was developed for treatment of Hepatitis C virus infection and is currently in Phase II trial (Hammond, 2015; van der Ree et al., 2017).

4 | MiR-326

MiR-326 has 20 nucleotides that are coded by intron 1 of chromosome 11; it was originally identified as a neural-specific miRNA in neurons. These miRNAs play critical roles in the regulation of the host genome expression at the post-transcriptional level (Ferretti et al., 2008). It is possible that miR-326 expression is positively associated with the beta gene expression of the beta-arrestin gene. MiRNAs expression, especially miR-326, miR-330, and miR-3099, increase during brain development and neural stem cell differentiation (Choi, Woo, Jou, & Joe, 2016). Over-expression of miR-326 is associated with the pathogenesis of AD as either direct or indirect processes (C. Du et al., 2009).

4.1 | The importance of miR-326 in T-cell differentiation

Tregs are subsets of Th17 cells and are regulated by miR-326 that binds to the target v-ets avian erythroblastosis virus E26 oncogene homolog 1 (Ets-1) gene; they increase the differentiation of these cells and production of interleukin 17 (IL17; Rouas et al., 2009). Deficiency of regulatory T cells activity is one of the mechanisms that enable autoimmune cells to attack tissues.

C. Du et al. (2009) showed that alterations in miR-326 expression in Th17 cells contribute to the pathogenesis of MS. In their study on 42 patients with MS and 43 mice with EAE, miR-326 expression was increased and it was highly correlated with disease severity. They found that miR-326 promotes the differentiation of the Th17 by targeting the ETS-1, the negative regulator of the Th17 differentiation (C. Du et al., 2009).

4.2 | The Regulation of miR-326

Only Kefas et al. (2010) and Kefas et al. (2009) have investigated miR-326 expression and functions so far. They observed that by targeting Notch1/2 and Pyruvate kinase M2 (PKM2), miR-326 was able to reduce proliferation and invasiveness in a subset of various cell lines. They suggested that miR-326 and Notch1 regulate each other in a negative feedback manner (Møller et al., 2013). miR-326 regulates Notch-1 expression directly and is itself regulated by a feedback loop. This indicates that it could regulate the expression of PKM2, the knockdown of which might alter the GBM cell line (glioblastoma) and CSC growth, invasion, and metabolic activity (Kefas et al., 2009). miR-326 targets PKM2 with a resulting reduction in ATP levels which is correlated with a less mechanistic target of rapamycin signaling and less invasion (Møller et al., 2013).

CD_{47} is a transmembrane protein that plays the main role in the control of migration and macrophage phagocytosis. It is a direct target of miR-326. This interaction during autoimmune disease promotes the differentiation of Th17 cells (Alvarez-Arellano, de León-Guerrero, Meza-Sosa, Jiménez-Ferrer, & Pérez-Martínez, 2013; Junker et al., 2009; Figure 1).

4.3 | Targets of miR-326 related to AD

A number of miR-326 targets are ABCC1, ADAM17, CD47, ETS-1, GLI1, IL10, IL17A, IL17D, PKM2, PTEN, SMO, vitamin D3 receptor (VDR; Koutova et al., 2015; Sebastiani et al., 2011), and so on. MiR-326 binds to the 3′ noncoding regions of mRNA complementarily. Bioinformatic target genes analysis indicated that VDR and ETS-1 are the targets for miR-326. Both VDR and ETS-1 are involved in regulating the homeostasis of immune cells and perhaps any change in any one of them triggers AD. The increase in miR-326 may be due to the changes in the host gene expression in T1D patients. Probably, one of the target genes for miR-326 is VDR gene and the overexpression of miR-326 gene inhibits the VDR expression in immune cells (Sebastiani et al., 2011). The introducing of VDR as the target of miR-326 may be the key to the emergence of new therapeutic strategies for autoimmune diabetes (Dotta et al., 2011).

The ETS-1 gene encoding is a transcription factor that directly regulates the cytokine and chemokine genes expression. It is present in the regulation of the differentiation and proliferation of lymphoid cells. Ets1, a reverse regulator of Th17 differentiation, was known as a functional target of miR-326 by showing that a "miR-326-resistant" Ets1 variant exhibited normal differentiation of Th17 (Kroesen et al., 2015). Recent studies have shown that miR-326 could regulate Th17 differentiation by targeting Ets-1, which is associated with the pathogenesis of some disorders such as MS (C. Du et al., 2009). In this regard, Ets-1 deficient T helper cells create a differentiation between Th17 cells and upregulated IL22 and IL23 receptor expression (Moisan, Grenningloh, Bettelli, Oukka, & Ho, 2007). Moreover, the targeting of Ets-1 by miR-326 promotes Th17 differentiation (C. Du et al., 2009).

5 | MiR-326 IN VARIOUS AD

5.1 | Multiple sclerosis

Many studies show that miR-326 has been overexpressed in brain white matter lesions of the mouse models of MS and peripheral blood mononuclear cells (PBMCs), and brain white matter lesions of patients with MS. miRNA expression profiling demonstrated that miR-326 levels

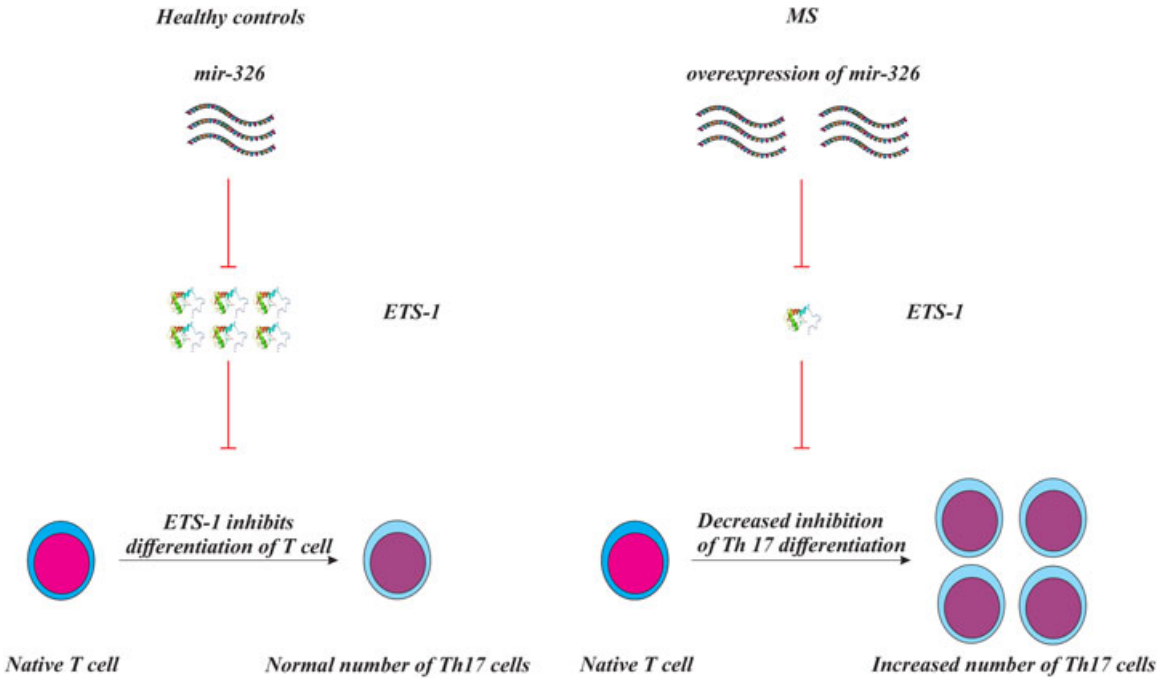

FIGURE 1 The association of miR-326 with Th17 developing [Color figure can be viewed at wileyonlinelibrary.com]

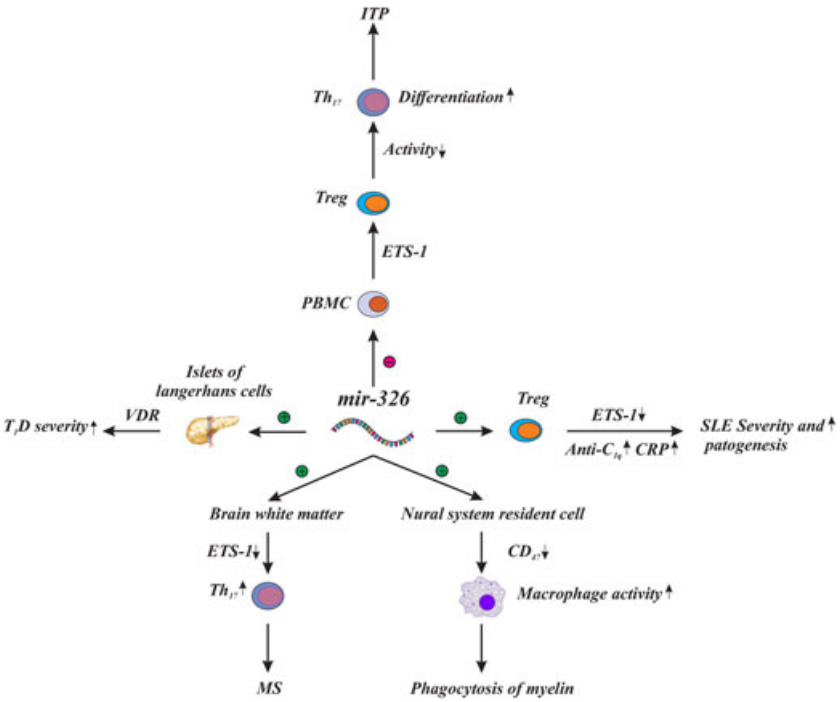

FIGURE 2 The association of miR-326 with autoimmune diseases [Color figure can be viewed at wileyonlinelibrary.com]

may change in the PBMCs (Fenoglio et al., 2011; Otaegui et al., 2009), whole blood (Cox et al., 2010; Keller et al., 2009), and serum (J. Zhang et al., 2014) in patients with MS. Cox et al. (2010) studied 27 miRNA expressions in peripheral blood samples of 59 treatment native patients with MS and 37 controls. However, they could not show a significant difference in the miR-326 expression in MS cases and controls (Cox et al., 2010). C. Du et al. (2009), in their study on patients with MS and mice with EAE, found that miR-326 increases Th17 differentiation and has a vital role in the pathogenesis of MS. They showed that the in vivo silencing of miR-326 reduces the Th17 cells and lead to a milder EAE (C. Du et al., 2009). The over-expression of miR-326 led to more Th17 cells and severe EAE (C. Du et al., 2009). miR-326 was significantly increased in peripheral blood leukocytes and $CD4^+$ T cells from EAE mice, especially in C-C chemokine receptor type 6 (CCR6) expressing Th17 cells. Moreover, its over-expression by targeting Ets-1, a negative regulator of Th17 differentiation, is closely correlated with Th17 differentiation and induction of EAE attacks. Junker et al. (2009) have studied the tissue blocks of 20 MS patients and none healthy control subjects. They have shown that miR-326 is attached to 3′-UTR of CD47 in brain resident cells releasing macrophages from the inhibitory regulator, thereby increasing myelin phagocytosis and downregulating CD47 in cell culture (Junker et al., 2009).

In a study by Waschbisch et al. (2011), which involved 74 patients with relapsing remitting multiple sclerosis (RRMS) and 32 healthy controls, it has been shown that miR-326, miR-155, miR-146a, and miR-142-3p were highly expressed in PBMCs from patients with RRMS compared with controls. Honardoost and his colleagues have studied 20 patients with MS in the relapsing phase, 20 patients with MS in the remitting phase, and 20 healthy controls (Honardoost, Kiani-Esfahani, Ghaedi, Etemadifar, & Salehi, 2014). They suggested that miR-326 is a diagnostic biomarker for distinguishing between the relapsing and remitting phases of MS and plays a major role in the pathogenesis differentiation of pathogenic Th17 cells during the pathogenesis of MS by having an influence on the major elements of the TGF-β signaling pathway (Honardoost et al., 2014). Moreover, Niwald, Migdalska-Sęk, Brzeziańska-Lasota, and Miller (2017) have studied 36 patients with MS: 23 were in the remission phase (stable), 13 in the early phase of remission and 10 healthy volunteers. They have shown that the miRNA profile is different in the remission phase (stable) and the early phase of remission (post-acute) stages in MS (Niwald et al., 2017). This may suggest that the increase of miRNAs may be used as a marker for MS and plays critical roles in MS pathogenesis (C. Du et al., 2009; Junker et al., 2009; Ma et al., 2014) (Figure 2).

5.2 | Diabetes type 1

T1D is a multi-genic autoimmune disorder and develops by immune destruction of insulin-producing beta cells of the pancreas, which leads to insulin deficiency. Sebastiani et al. (2011) in a study on 19 T1D patients have distinguished that an over-expression of miR-326 could drive the downregulation of VDR in immune cells. VDR is produced by a large number of immune cells, such as activated T cells, and plays a significant role in immune signaling pathways. Altered VDR function due to VDR polymorphism has been introduced in the pathogenesis of some AD (Khodadadi et al., 2013; Sebastiani et al., 2011).

5.3 | Immune thrombocytopenia

ITP is an autoimmune disease characterized by peripheral destruction of platelets. MiR-326 is also involved in regulating the

anti-apoptotic Bcl-xL gene expression and apoptosis in platelets. miR-326 expression increases by storing apheresis platelets in vitro (Yu et al., 2015) and decreases in ITP (L. Liu et al., 2016). Liu et al. have studied miR-155, miR-146a, miR-326, miR-142-3p, miR-17-5p, miR-21, and miR-181a in Th cells' subsets of 46 ITP patients and 39 healthy controls. They showed that the expression of miR-146a, miR-326, or miR-142-3p in ITP patients decreased. They have concluded that abnormal Tregs differentiation and function in patients with ITP is due to the abnormal expression profile of immune-related miRNAs (L. Liu et al., 2016).

5.4 | Systemic lupus erythematosus

SLE is a typical autoimmune disease that tolerance failure plays an important role in its pathogenesis. J.-Q. Chen et al. (2017) in a study on eight SLE patients showed that miR-148a-3p, miR-152, miR-155, miR-223, miR-224, miR-326, and miR-342 increased. Moreover, Sun et al. (2016) in a study on 53 patients with SLE described the over-expression of miR-326 and decreased the level of Ets-1 mRNA. In addition, a recent study by Xia et al. showed the role of mir-326 in regulating B cell differentiation into plasmablast, autoantibody-secreting cells in SLE (Xia et al., 2018).

5.5 | MiR-326 in other diseases

Most recently, much evidence have been found about the involvement of miR-326 downregulation in the development and progression of different malignancies like colorectal cancer (G. Chen et al., 2016), non-small cell lung cancer (NSCLC; R. Wang, Chen, & Shu, 2015), lung cancer (Cai et al., 2015), glioma and brain cancer (Khan, Ullah, Hussein, & Saini, 2017), breast cancer (D. Y. Liang et al., 2016; Z. Liang et al., 2010), prostate cancer (H. Kristensen et al., 2016), esophageal cancer (Hong et al., 2014), cutaneous T-cell lymphoma (CTCL; Ralfkiaer et al., 2011), gastric cancer (Y. Li, Gao, Xu, Ma, & Yang, 2015), pancreatic ductal adenocarcinoma (Z. L. Zhang et al., 2015), hepatocellular carcinoma (HCC; Hu, Ran, Chen, Zhang, & Xu, 2017), medulloblastoma (Ferretti et al., 2008), acute myelogenous leukemia (Koutova et al., 2015), and chronic myelogenous leukemia (CML; Babashah et al., 2013). miR-326 is also involved in the pathogenesis of idiopathic pulmonary fibrosis (Das et al., 2014), and HIV infection (Houzet et al., 2012).

6 | MiR-326 AS A DIAGNOSTIC BIOMARKER

MiR-326 may be accepted as the diagnostic marker for MS (Huang et al., 2016; Kucukali, Kurtuncu, Coban, Cebi, & Tuzun, 2015; Ma et al., 2014) and discriminates between relapsing and remitting phases of the disease (Honardoost et al., 2014). Plasma miR-326 may be used as minimally invasive independent molecular biomarkers to predict resistance to chemotherapy in patients with advanced lung adenocarcinoma (LAC; J. Zhu et al., 2016) and prognostic value in prostate cancer (H. Kristensen et al., 2016) and glioma (Khan et al., 2017). The miR-326/FSCN1 pathway may be a novel diagnostic marker in gastric cancer (Ji, Zhang, Kong, Ma, & Hua, 2017; Y. Li et al., 2015). Moreover, miR-326 along with some other miRNAs can be used with an accuracy of about 90% in differentiating between CTCL and benign skin lesions (Ralfkiaer et al., 2011).

7 | miR-326 AS A THERAPEUTIC TARGET FOR TREATMENT

7.1 | Autoimmune diseases

MiR-326 acts as an up-regulator of Th17 differentiation. Th-17 has an important role in the pathogenesis of AD like RA, seronegative spondyloarthropathies, MS, and BD. The role of vitamin D deficiency in the pathogenesis of RA, SLE, D1M, and BD is well known. Over-expression of miR-326 gene inhibits the VDR expression. Increasing the expression of miR-326 by increasing the Th17 differentiation and inhibiting the expression of VDR promote autoimmunity and it is now logical to consider the possibility of using miR-326 as a therapeutic target.

Du et al. showed that the in vivo silencing of miR-326 reduces the TH-17 cells and leads to milder EAE. Ingwersen et al. (2015) reported that miR-326 downregulated after treatment with natalizumab in patients with MS. Natalizumab is a monoclonal antibody which binds to integrins and suppresses their interaction with vascular cell-adhesion molecules-1 (Wu & Chen, 2016). This impairs leukocyte adhesion and transmigrates across blood–brain barrier (BBB) into the CNS (T. Wu & Chen, 2016). Ets-1 is a target of miR-326 which plays an important role in regulating Th17 immune responses and BBB breakdown (Wu & Chen, 2016).

7.2 | Malignancies

In contrast to AD, miR-326 is under-expressed in malignancies. miR-326 is negatively correlated with multidrug resistance-associated protein (MRP-1) expression in breast cancer and can be a useful factor for preventing and reversing multidrug resistance in tumor cells (D. Y. Liang et al., 2016; Z. Liang et al., 2010). It down-regulates MRP-1 expression and sensitizes cancer cells to VP-16 and doxorubicin; thus, it can be used in anti-cancer therapy (An, Sarmiento, Tan, & Zhu, 2016; Z. Liang et al., 2010). Histone deacetylase-3 (HDAC3) creates a negative feedback loop with miR-326 and controls the responses to cancer drugs. MiR-326 and HDAC3 present strategies for the improvement of anti-cancer therapeutics. MiR-326 decreases the programmed cell death effect of anticancer drugs, and the miR-326 inhibitor enhances the apoptotic effect of anticancer drugs. HDAC3 and miR-326 act upstream of the cancer-associated gene, and it is shown that the miR-326- HDAC3 feedback loop can be used as a target for the development of anti-cancer therapeutics (Y. Kim et al., 2014).

The miR-326/SMO axis can be a potential alternative therapeutic pathway for gliomas in future (W. Du et al., 2015). miR-326, through HOTAIR, has tumor-suppressive effects, and the HOTAIR-miR-326-fibroblast growth factor 1 (FGF1) axis might represent a promising

therapeutic strategy for the therapy of glioma patients (Ke et al., 2015). Although inhibition of the miR-326 expression may have a therapeutic effect, chronic inhibition of that may exert an oncogenic role in glioma patient. It has been shown that Notch and miR-326 inhibit each other and create an axis called Notch/miR-326 axis. This axis can be used as a therapeutic potential for treating glioblastoma (Kefas et al., 2010) and brain cancer (Kefas et al., 2009).

MiR-326/nucleosome-binding protein 1 (miR-326/NSBP1) is a promising candidate target for generating new anticancer therapeutics for NSCLC (D. Li, Du, Liu, & Li, 2016). MiR-326 is a potential tumor suppressor and may be used in the treatment of cervical cancer (P. Zhang et al., 2017), pancreatic ductal adenocarcinoma (Z. L. Zhang et al., 2015), HCC (J. Zhang, Chong, Chen, & Lai, 2015), osteosarcoma (Cao, Wang, & Wang, 2016), and CML (Babashah et al., 2013).

In future, a better understanding of the function of miRNAs in intracellular signaling, the expression of proteins associated with immune responses, the modulation of cytokines and chemokines, and the adhesion and costimulatory molecules, should improve defining the functions of miRNAs in autoimmunity and present an interesting framework for developing new biomarkers and new therapeutic trials in AD. Further research is required to completely understand the role of miRNAs in the pathology and physiology of inflammation and immune system. An investigation has been proposed into diagnostic biomarkers and possible therapeutic targets in AD and cancers, but their clinical application is less well known in immune disorders. We have summarized the available knowledge about miRNAs and miR-326; however, more studies are required in this area.

8 | CONCLUSION

Efficient management of autoimmune and malignant diseases depends on early diagnosis and treatment. MiRNAs have high sensitivity and specificity due to their specific characteristics. MiRNAs are highly stable in the body fluids. Therefore, they can serve as a useful biomarker for diagnostic and prediction of prognostic.

MiR-326 is a key miRNA with functional relevance in the lymphocytes biology, tumors, and AD, including MS, T1D, SLE, and ITP. It also can be used as a diagnostic biomarker in MS, pancreatic ductal adenocarcinoma, hepatocellular carcinoma, osteosarcoma, CML, LAC, prostate cancer, glioma, and gastric cancer. MiR-326 may be a therapeutic target for MS, SLE, glioma, NSCLC, and cervical cancer.

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REFERENCES

Abdul-Maksoud, R. S., Sediq, A. M., Kattaia, A., Elsayed, W., Ezzeldin, N., Abdel Galil, S. M., & Ibrahem, R. A. (2017). Serum miR-210 and miR-155 expression levels as novel biomarkers for rheumatoid arthritis diagnosis. *British Journal of Biomedical Science*, 1–5.

Alevizos, I., Bajracharya, S., Alexander, S., Turner, R., & Illei, G. (2009). MicroRNA profiling of minor salivary glands identifies disease and inflammation biomarkers in Sjogren's syndrome patients. *Arthritis & Rheumatism*, *60*(10), S733.

Alipour, S., Nouri, M., Khbbazi, A., Samadi, N., Babaloo, Z., Abolhasani, S., … Sakhimia, E. (2018). Hypermethylation of IL-10 gene is responsible for its low mRNA expression in Behcet's disease. *Journal of Cellular Biochemistry*, *119*(8), 6614–6622.

Alipour, S., Nouri, M., Sakhinia, E., Samadi, N., Roshanravan, N., Ghavami, A., & Khabbazi, A. (2017). Epigenetic alterations in chronic disease focusing on Behcet's disease. *Biomedicine & Pharmacotherapy*, *91*, 526–533.

Alizadeh, E., Akbarzadeh, A., Eslaminejad, M. B., Barzegar, A., Hashemzadeh, S., Nejati-Koshki, K., & Zarghami, N. (2015). Up regulation of liver-enriched transcription factors HNF4a and HNF6 and liver-specific microRNA (miR-122) by inhibition of Let-7b in mesenchymal stem cells. *Chemical Biology & Drug Design*, *85*(3), 268–279.

Alvarez-Arellano, L., de León-Guerrero, S. D., Meza-Sosa, K. F., Jiménez-Ferrer, I., & Pérez-Martínez, L. (2013). Neurodegenerative disorders and inflammation. *Molecular Aspects of Inflammation Kerala, Research Signpost*, 173–207.

Alvarez-Garcia, I., & Miska, E. A. (2005). MicroRNA functions in animal development and human disease. *Development*, *132*(21), 4653–4662.

An, X., Sarmiento, C., Tan, T., & Zhu, H. (2016). Regulation of multidrug resistance by microRNAs in anti-cancer therapy. *Acta Pharmaceutica Sinica B*.

Anderson, R., Meyer, P. W., Ally, M. M., & Tikly, M. (2016). Smoking and air pollution as pro-inflammatory triggers for the development of rheumatoid arthritis. *Nicotine & Tobacco Research*, *18*(7), 1556–1565.

Assmann, T. S., Duarte, G. C., Brondani, L. A., de Freitas, P. H., Martins, E. M., Canani, L. H., & Crispim, D. (2017). Polymorphisms in genes encoding miR-155 and miR-146a are associated with protection to type 1 diabetes mellitus. *Acta Diabetologica*, *54*(5), 433–441.

Babashah, S., Sadeghizadeh, M., Hajifathali, A., Tavirani, M. R., Zomorod, M. S., Ghadiani, M., & Soleimani, M. (2013). Targeting of the signal transducer Smo links microRNA-326 to the oncogenic Hedgehog pathway in CD34+CML stem/progenitor cells. *International Journal of Cancer*, *133*(3), 579–589.

Bach, J.-F. (2002). The effect of infections on susceptibility to autoimmune and allergic diseases. *New England Journal of Medicine*, *347*(12), 911–920.

Bartel, D. P. (2004). MicroRNAs: Genomics, biogenesis, mechanism, and function. *Cell*, *116*(2), 281–297.

Beres, N. J., Szabo, D., Kocsis, D., Szucs, D., Kiss, Z., Muller, K. E., … Veres, G. (2016). Role of altered expression of miR-146a, miR-155, and miR-122 in pediatric patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *22*(2), 327–335.

Bonyadi, M., Jahanafrooz, Z., Esmaeili, M., Kolahi, S., Khabazi, A., Ebrahimi, A. A., … Dastgiri, S. (2009). TNF-alpha gene polymorphisms in Iranian Azeri Turkish patients with Behcet's Disease. *Rheumatology International*, *30*(2), 285–289.

Cai, M., Wang, Z., Zhang, J., Zhou, H., Jin, L., Bai, R., & Weng, Y. (2015). Adam17, a target of Mir-326, promotes Emt-induced cells invasion in lung adenocarcinoma. *Cellular Physiology and Biochemistry: International Journal of Experimental Cellular Physiology, Biochemistry, and Pharmacology*, *36*(3), 1175–1185.

Cao, L., Wang, J., & Wang, P. Q. (2016). MiR-326 is a diagnostic biomarker and regulates cell survival and apoptosis by targeting Bcl-2 in osteosarcoma. *Biomedicine & Pharmacotherapy*, *84*, 828–835.

Castro, R. E., & Rodrigues, C. M. (2012). Targeting miR-506 in primary biliary cirrhosis to support the HCO3- umbrella. *Clinics and Research in Hepatology and Gastroenterology*, *36*(5), 402–404.

Chakraborty, C., Doss, C. G., Bandyopadhyay, S., & Agoramoorthy, G. (2014). Influence of miRNA in insulin signaling pathway and insulin

resistance: Micro-molecules with a major role in type-2 diabetes. *Wiley Interdisciplinary Reviews: RNA*, *5*(5), 697–712.

Chatzikyriakidou, A., Voulgari, P. V., Georgiou, I., & Drosos, A. A. (2012). miRNAs and related polymorphisms in rheumatoid arthritis susceptibility. *Autoimmunity Reviews*, *11*(9), 636–641.

Chen, C. Y., Fuh, L. J., Huang, C. C., Hsu, C. J., Su, C. M., Liu, S. C., … Tang, C. H. (2017). Enhancement of CCL2 expression and monocyte migration by CCN1 in osteoblasts through inhibiting miR-518a-5p: Implication of rheumatoid arthritis therapy. *Scientific Reports*, *7*(1), 421.

Chen, C. Y., Su, C. M., Hsu, C. J., Huang, C. C., Wang, S. W., Liu, S. C., … Tang, C. H. (2017). CCN1 promotes VEGF production in osteoblasts and induces endothelial progenitor cell angiogenesis by inhibiting miR-126 expression in rheumatoid arthritis. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*, *32*(1), 34–45.

Chen, G., Han, N., Li, G., Li, X., Li, G., Li, Z., & Li, Q. (2016). Time course analysis based on gene expression profile and identification of target molecules for colorectal cancer. *Cancer Cell International*, *16*(1), 22.

Chen, J.-Q., Papp, G., Póliska, S., Szabó, K., Tarr, T., Bálint, B. L., … Zeher, M. (2017). MicroRNA expression profiles identify disease-specific alterations in systemic lupus erythematosus and primary Sjögren's syndrome. *PLoS One*, *12*(3), e0174585.

Chen, T., Xue, H., Lin, R., & Huang, Z. (2017). MiR-34c and PlncRNA1 mediated the function of intestinal epithelial barrier by regulating tight junction proteins in inflammatory bowel disease. *Biochemical and Biophysical Research Communications*, *486*(1), 6–13.

Cheng, L., Yang, T., Kuang, Y., Kong, B., Yu, S., Shu, H., … Gu, J. (2014). MicroRNA-23a promotes neuroblastoma cell metastasis by targeting CDH1. *Oncology Letters*, *7*(3), 839–845.

Cheng, Y., Ji, R., Yue, J., Yang, J., Liu, X., Chen, H., … Zhang, C. (2007). MicroRNAs are aberrantly expressed in hypertrophic heart: Do they play a role in cardiac hypertrophy?. *The American Journal of Pathology*, *170*(6), 1831–1840.

Choi, I., Woo, J. H., Jou, I., & Joe, E. H. (2016). PINK1 deficiency decreases expression levels of mir-326, mir-330, and mir-3099 during brain development and neural stem cell differentiation. *Experimental Neurobiology*, *25*(1), 14–23.

Christopher, A. F., Kaur, R. P., Kaur, G., Kaur, A., Gupta, V., & Bansal, P. (2016). MicroRNA therapeutics: Discovering novel targets and developing specific therapy. *Perspectives in Clinical Research*, *7*(2), 68.

Cox, M. B., Cairns, M. J., Gandhi, K. S., Carroll, A. P., Moscovis, S., Stewart, G. J., … Lechner-Scott, J. (2010). MicroRNAs miR-17 and miR-20a inhibit T cell activation genes and are under-expressed in MS whole blood. *PLoS One*, *5*(8), e12132.

Dai, Y., Huang, Y.-S., Tang, M., Lv, T.-Y., Hu, C.-X., Tan, Y.-H., … Yin, Y.-B. (2007). Microarray analysis of microRNA expression in peripheral blood cells of systemic lupus erythematosus patients. *Lupus*, *16*(12), 939–946.

Dai, Y., Sui, W., Lan, H., Yan, Q., Huang, H., & Huang, Y. (2009). Comprehensive analysis of microRNA expression patterns in renal biopsies of lupus nephritis patients. *Rheumatology International*, *29*(7), 749–754.

Das, S., Kumar, M., Negi, V., Pattnaik, B., Prakash, Y., Agrawal, A., & Ghosh, B. (2014). MicroRNA-326 regulates profibrotic functions of transforming growth factor-β in pulmonary fibrosis. *American Journal of Respiratory Cell and Molecular Biology*, *50*(5), 882–892.

Dehghanzadeh, R., Babaloo, Z., Sakhinia, E., Khabazi, A., Shanehbandi, D., Sadigh-Eteghad, S., & Gharibi, T. (2016). IL-27 gene polymorphisms in Iranian patients with Behcet's disease. *Clinical Laboratory*, *62*(5), 855–861.

Dewi, I., Gidlöf, O., Ivars, F., & Öhman, J. (2014). The alteration of MiR-326 and MiR-142-3p expressions during immune activation is positively correlated with graft-protective cytokine TGF-beta. *The Journal of Heart and Lung Transplantation*, *33*(4), S253–S254.

Dewi, I. S., Torngren, K., Gidlöf, O., Kornhall, B., & Öhman, J. (2013). Altered serum miRNA profiles during acute rejection after heart transplantation: Potential for non-invasive allograft surveillance. *The Journal of Heart and Lung Transplantation*, *32*(4), 463–466.

Dotta, F., Sebastiani, G., Grieco, F. A., Spagnuolo, I., Galleri, L., & Cataldo. D. (2011). Increased expression of microRNA miR-326 in type 1 diabetic patients with ongoing islet autoimmunity. *Diabetes/Metabolism Research and Reviews*, *27*(8), 862–866.

Du, C., Liu, C., Kang, J., Zhao, G., Ye, Z., Huang, S., … Pei, G. (2009). MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis. *Nature Immunology*, *10*(12), 1252–1259.

Du, F., Feng, Y., Fang, J., & Yang, M. (2015). MicroRNA-143 enhances chemosensitivity of Quercetin through autophagy inhibition via target GABARAPL1 in gastric cancer cells. *Biomedicine & Pharmacotherapy*, *74*, 169–177.

Du, W., Liu, X., Chen, L., Dou, Z., Lei, X., Chang, L., … Sun, Y. (2015). Targeting the SMO oncogene by miR-326 inhibits glioma biological behaviors and stemness. *Neuro-Oncology*, *17*(2), 243–253.

Esmaeili, M., Bonyadi, M., Khabbazi, A., Ebrahimi, A. A., Sharif, S. K., Hajialilo, M., … Dastgiri, S. (2011). Common MEFV mutations in Iranian Azeri Turkish patients with Behcet's disease. *Scandinavian Jouranl of Rheumatology*, *40*(5), 383–386.

Estrella, S., Garcia-Diaz, D. F., Codner, E., Camacho-Guillen, P., & Perez-Bravo, F. (2016). Expression of miR-22 and miR-150 in type 1 diabetes mellitus: Possible relationship with autoimmunity and clinical characteristics. *Medicina Clinica*, *147*(6), 245–247.

Feng, X., Wang, Y., Ma, Z., Yang, R., Liang, S., Zhang, M., … Fan, D. (2014). MicroRNA-645, up-regulated in human adencarcinoma of gastric esophageal junction, inhibits apoptosis by targeting tumor suppressor IFIT2. *BMC Cancer*, *14*(1), 1.

Fenoglio, C., Cantoni, C., de Riz, M., Ridolfi, E., Cortini, F., Serpente, M., … Scarpini, E. (2011). Expression and genetic analysis of miRNAs involved in CD4+cell activation in patients with multiple sclerosis. *Neuroscience Letters*, *504*(1), 9–12.

Fenoglio, C., de Riz, M., Pietroboni, A. M., Calvi, A., Serpente, M., Cioffi, S. M., … Galimberti, D. (2016). Effect of fingolimod treatment on circulating miR-15b, miR23a and miR-223 levels in patients with multiple sclerosis. *Journal of Neuroimmunology*, *299*, 81–83.

Ferretti, E., de Smaele, E., Miele, E., Laneve, P., Po, A., Pelloni, M., … Screpanti, I. (2008). Concerted microRNA control of Hedgehog signalling in cerebellar neuronal progenitor and tumour cells. *The EMBO Journal*, *27*(19), 2616–2627.

Furer, V., Greenberg, J. D., Attur, M., Abramson, S. B., & Pillinger, M. H. (2010). The role of microRNA in rheumatoid arthritis and other autoimmune diseases. *Clinical Immunology*, *136*(1), 1–15.

Gregersen, P. K., & Olsson, L. M. (2009). Recent advances in the genetics of autoimmune disease. *Annual Review of Immunology*, *27*, 363–391.

Guerau-de-Arellano, M., Alder, H., Ozer, H. G., Lovett-Racke, A., & Racke, M. K. (2012). miRNA profiling for biomarker discovery in multiple sclerosis: From microarray to deep sequencing. *Journal of Neuroimmunology*, *248*(1-2), 32–39.

Guo, S., Zhang, W., Wei, C., Wang, L., Zhu, G., Shi, Q., … Li, C. (2013). Serum and skin levels of miR-369-3p in patients with psoriasis and their correlation with disease severity. *European Journal of Dermatology: EJD*, *23*(5), 608–613.

Hammond, S. M. (2015). An overview of microRNAs. *Advanced Drug Delivery Reviews*, *87*, 3–14.

Han, B., Shi, X., Peng, Q., & Gao, W. (2012). Study on genetic variance of miR-541 in Type 1 diabetes. *ISRN Endocrinology*, *2012*, 630861.

Hansen, T., Olsen, L., Lindow, M., Jakobsen, K. D., Ullum, H., Jonsson, E., … Agartz, I. (2007). Brain expressed microRNAs implicated in schizophrenia etiology. *PLoS One*, *2*(9), e873.

Hayter, S. M., & Cook, M. C. (2012). Updated assessment of the prevalence, spectrum and case definition of autoimmune disease. *Autoimmunity Reviews*, *11*(10), 754–765.

He, C., Shi, Y., Wu, R., Sun, M., Fang, L., Wu, W., … Liu, Z. (2016). miR-301a promotes intestinal mucosal inflammation through induction of IL-17A and TNF-alpha in IBD. *Gut*, *65*(12), 1938–1950.

He, L., & Hannon, G. J. (2004). MicroRNAs: Small RNAs with a big role in gene regulation. *Nature Reviews Genetics*, *5*(7), 522–531.

Hezova, R., Slaby, O., Faltejskova, P., Mikulkova, Z., Buresova, I., Raja, K. R. M., … Michalek, J. (2010). microRNA-342, microRNA-191 and microRNA-510 are differentially expressed in T regulatory cells of type 1 diabetic patients. *Cellular Immunology*, *260*(2), 70–74.

Hirao, H., Jinnin, M., Ichihara, A., Fujisawa, A., Makino, K., Kajihara, I., … Ihn, H. (2013). Detection of hair root miR-19a as a novel diagnostic marker for psoriasis. *European Journal of Dermatology: EJD*, *23*(6), 807–811.

Honardoost, M. A., Kiani-Esfahani, A., Ghaedi, K., Etemadifar, M., & Salehi, M. (2014). miR-326 and miR-26a, two potential markers for diagnosis of relapse and remission phases in patient with relapsing-remitting multiple sclerosis. *Gene*, *544*(2), 128–133.

Hong, C.-C., Chen, P.-S., Chiou, J., Chiu, C.-F., Yang, C.-Y., Hsiao, M., … Hsu, N.-W. (2014). miR326 maturation is crucial for VEGF-C–driven cortactin expression and esophageal cancer progression. *Cancer Research*, *74*(21), 6280–6290.

Hosseini, A., Shanehbandi, D., Estiar, M. A., Gholizadeh, S., Khabbazi, A., Khodadadi, H., … Babaloo, Z. (2015). A single nucleotide polymorphism in the FOXP3 gene associated with Behcet's disease in an Iranian population. *Clinical Laboratory*, *61*(12), 1897–1903.

Houzet, L., Klase, Z., Yeung, M. L., Wu, A., Le, S. Y., Quinones, M., & Jeang, K. T. (2012). The extent of sequence complementarity correlates with the potency of cellular miRNA-mediated restriction of HIV-1. *Nucleic Acids Research*, *40*(22), 11684–11696.

Hu, S., Ran, Y., Chen, W., Zhang, Y., & Xu, Y. (2017). MicroRNA-326 inhibits cell proliferation and invasion, activating apoptosis in hepatocellular carcinoma by directly targeting LIM and SH3 protein 1. *Oncology Reports*, *38*(3), 1569–1578.

Huang, Q., Xiao, B., Ma, X., Qu, M., Li, Y., Nagarkatti, P., … Zhou, J. (2016). MicroRNAs associated with the pathogenesis of multiple sclerosis. *Journal of Neuroimmunology*, *295*, 148–161.

Husakova, M. (2016). MicroRNAs in the key events of systemic lupus erythematosus pathogenesis. *Biomedical Papers*, *160*(3), 327–342.

Iborra, M., Bernuzzi, F., Invernizzi, P., & Danese, S. (2012). MicroRNAs in autoimmunity and inflammatory bowel disease: Crucial regulators in immune response. *Autoimmunity Reviews*, *11*(5), 305–314.

Ichihara, A., Jinnin, M., Oyama, R., Yamane, K., Fujisawa, A., Sakai, K., … Ihn, H. (2012). Increased serum levels of miR-1266 in patients with psoriasis vulgaris. *European Journal of Dermatology: EJD*, *22*(1), 68–71.

Ingwersen, J., Menge, T., Wingerath, B., Kaya, D., Graf, J., Prozorovski, T., … Scheffler, M. (2015). Natalizumab restores aberrant miRNA expression profile in multiple sclerosis and reveals a critical role for miR-20b. *Annals of Clinical and Translational Neurology*, *2*(1), 43–55.

Janeway, C. A. Jr., Travers, P., Walport, M., & Shlomchik, M. J. (2001). Autoimmune responses are directed against self antigens. In *Immunobiology: The immune system in health and disease* (5th edition). New York: Garland Science.

Ji, S., Zhang, B., Kong, Y., Ma, F., & Hua, Y. (2017). MiR-326 inhibits gastric cancer cell growth through downregulating NOB1. *Oncology Research Featuring Preclinical and Clinical Cancer Therapeutics*, *25*(6), 853–861.

Junker, A., Krumbholz, M., Eisele, S., Mohan, H., Augstein, F., Bittner, R., … Meinl, E. (2009). MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47. *Brain: A Journal of Neurology*, *132*(Pt 12), 3342–3352.

Karsy, M., Arslan, E., & Moy, F. (2012). Current progress on understanding microRNAs in glioblastoma multiforme. *Genes & Cancer*, *3*(1), 3–15.

Ke, J., Yao Y-l, Zheng, J., Wang, P., Liu, Y.-h, Ma, J., … Wang, Z.-h (2015). Knockdown of long non-coding RNA HOTAIR inhibits malignant biological behaviors of human glioma cells via modulation of miR-326. *Oncotarget*, *6*(26), 21934.

Kefas, B., Comeau, L., Erdle, N., Montgomery, E., Amos, S., & Purow, B. (2010). Pyruvate kinase M2 is a target of the tumor-suppressive microRNA-326 and regulates the survival of glioma cells. *Neuro-Oncology*, *12*(11), 1102–1112.

Kefas, B., Comeau, L., Floyd, D. H., Seleverstov, O., Godlewski, J., Schmittgen, T., … Lee, J. (2009). The neuronal microRNA miR-326 acts in a feedback loop with notch and has therapeutic potential against brain tumors. *Journal of Neuroscience*, *29*(48), 15161–15168.

Keller, A., Leidinger, P., Lange, J., Borries, A., Schroers, H., Scheffler, M., … Meese, E. (2009). Multiple sclerosis: MicroRNA expression profiles accurately differentiate patients with relapsing-remitting disease from healthy controls. *PLoS One*, *4*(10), e7440.

Khabbazi, A., Rashtchizadeh, N., Ghorbanihaghjo, A., Hajialiloo, M., Ghojazadeh, M., Taei, R., & Kolahi, S. (2014). The status of serum vitamin D in patients with active Behcet's disease compared with controls. *International Journal of Rheumatic Diseases*, *17*(4), 430–434.

Khan, I. N., Ullah, N., Hussein, D., & Saini, K. S. (2017). Current and emerging biomarkers in tumors of the central nervous system: Possible diagnostic, prognostic and therapeutic applications. *Seminars in Cancer Biology*, [Epub ahead of print]. https://doi.org/10.1016/j.semcancer.2017.07.004

Khodadadi, H., Khabazi, A., Ghaderian, S. M. H., Akhavan-Niaki, H., Emrahi, L., Estiar, M. A., … Kolahi, S. (2013). Molecular analysis of vitamin D receptor gene polymorphisms rs2228570 (*Fok*I) and rs1544410 (*Bsm*I) in patients with Behcet's disease. *Life Science Journal*, *10*(4).

Kim, V. N., & Nam, J.-W. (2006). Genomics of microRNA. *Trends in Genetics*, *22*(3), 165–173.

Kim, Y., Kim, H., Park, H., Park, D., Lee, H., Lee, Y. S., … Jeoung, D. (2014). miR-326-histone deacetylase-3 feedback loop regulates the invasion and tumorigenic and angiogenic response to anti-cancer drugs. *The Journal of Biological Chemistry*, *289*(40), 28019–28039.

Klein, J., & Sato, A. (2000). The HLA system. *New England Journal of Medicine*, *343*(10), 702–709.

Kloosterman, W. P., Lagendijk, A. K., Ketting, R. F., Moulton, J. D., & Plasterk, R. H. (2007). Targeted inhibition of miRNA maturation with morpholinos reveals a role for miR-375 in pancreatic islet development. *PLoS Biology*, *5*(8), e203.

Kolahi, S., Khabbazi, A., Khodadadi, H., Estiar, M., Hajialiloo, M., Emrahi, L., & Sakhinia, E. (2015). Vitamin D receptor gene polymorphisms in Iranian Azary patients with Behçet's disease. *Scandinavian Journal of Rheumatology*, *44*(2), 163–167.

Koutova, L., Sterbova, M., Pazourkova, E., Pospisilova, S., Svobodova, I., Horinek, A., … Korabecna, M. (2015). The impact of standard chemotherapy on miRNA signature in plasma in AML patients. *Leukemia Research*, *39*(12), 1389–1395.

Krissansen, G. W., Yang, Y., McQueen, F. M., Leung, E., Peek, D., Chan, Y. C., … Fraser, A. G. (2015). Overexpression of miR-595 and miR-1246 in the sera of patients with active forms of inflammatory bowel disease. *Inflammatory Bowel Diseases*, *21*(3), 520–530.

Kristensen, H., Thomsen, A. R., Haldrup, C., Dyrskjøt, L., Høyer, S., Borre, M., … Sørensen, K. D. (2016). Novel diagnostic and prognostic classifiers for prostate cancer identified by genome-wide microRNA profiling. *Oncotarget*, *7*(21), 30760.

Kroesen, B. J., Teteloshvili, N., Smigielska-Czepiel, K., Brouwer, E., Boots, A. M., van den Berg, A., & Kluiver, J. (2015). Immuno-miRs: Critical regulators of T-cell development, function and ageing. *Immunology*, *144*(1), 1–10.

Kucukali, C. I., Kurtuncu, M., Coban, A., Cebi, M., & Tuzun, E. (2015). Epigenetics of multiple sclerosis: An updated review. *NeuroMolecular Medicine*, *17*(2), 83–96.

Lagos-Quintana, M., Rauhut, R., Lendeckel, W., & Tuschl, T. (2001). Identification of novel genes coding for small expressed RNAs. *Science*, *294*(5543), 853–858.

Lashine, Y., Salah, S., Aboelenein, H., & Abdelaziz, A. (2015). Correcting the expression of miRNA-155 represses PP2Ac and enhances the release of IL-2 in PBMCs of juvenile SLE patients. *Lupus*, *24*(3), 240–247.

Lashine, Y., Seoudi, A., Salah, S., & Abdelaziz, A. (2010). Expression signature of microRNA-181-a reveals its crucial role in the pathogenesis of paediatric systemic lupus erythematosus. *Clinical and Experimental Rheumatology*, *29*(2), 351–357.

Latsoudis, H., Mashreghi, M. F., Grün, J. R., Chang, H. D., Stuhlmüller, B., Repa, A., … Häupl, T. (2017). Differential expression of miR-4520a associated with pyrin mutations in familial mediterranean fever (FMF). *Journal of Cellular Physiology*, *232*(6), 1326–1336.

Lee, J., & Kemper, J. K. (2010). Controlling SIRT1 expression by microRNAs in health and metabolic disease. *Aging*, *2*(8), 527–534.

Lewis, B. P., Burge, C. B., & Bartel, D. P. (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell*, *120*(1), 15–20.

Li, D., Du, X., Liu, A., & Li, P. (2016). Suppression of nucleosome-binding protein 1 by miR-326 impedes cell proliferation and invasion in non-small cell lung cancer cells. *Oncology Reports*, *35*(2), 1117–1124.

Li, M., Zhang, S., Qiu, Y., He, Y., Chen, B., Mao, R., … Chen, M. (2017). Upregulation of miR-665 promotes apoptosis and colitis in inflammatory bowel disease by repressing the endoplasmic reticulum stress components XBP1 and ORMDL3. *Cell Death & Disease*, *8*(3), e2699.

Li, Y., Gao, Y., Xu, Y., Ma, H., & Yang, M. (2015). Down-regulation of miR-326 is associated with poor prognosis and promotes growth and metastasis by targeting FSCN1 in gastric cancer. *Growth Factors*, *33*(4), 267–274.

Li, Y., Li, X., Sun W-k, Cheng, C., Chen Y-h, Zeng, K., … Liu, R. (2016). Comparison of liver microRNA transcriptomes of tibetan and yorkshire pigs by deep sequencing. *Gene*, *577*(2), 244–250.

Li, Y., Su, J., Li, F., Chen, X., & Zhang, G. (2017). MiR-150 regulates human keratinocyte proliferation in hypoxic conditions through targeting HIF-1alpha and VEGFA: Implications for psoriasis treatment. *PLoS One*, *12*(4), e0175459.

Li, Z., Cai, J., & Cao, X. (2016). MiR-19 suppresses fibroblast-like synoviocytes cytokine release by targeting toll like receptor 2 in rheumatoid arthritis. *American Journal of Translational Research*, *8*(12), 5512–5518.

Liang, D. Y., Hou, Y. Q., Luo, L. J., & Ao, L. (2016). Altered expression of miR-92a correlates with Th17 cell frequency in patients with primary biliary cirrhosis. *International Journal of Molecular Medicine*, *38*(1), 131–138.

Liang, Z., Wu, H., Xia, J., Li, Y., Zhang, Y., Huang, K., … Scala, S. (2010). Involvement of miR-326 in chemotherapy resistance of breast cancer through modulating expression of multidrug resistance-associated protein 1. *Biochemical Pharmacology*, *79*(6), 817–824.

Liu, G., & Abraham, E. (2013). MicroRNAs in immune response and macrophage polarization. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *33*(2), 170–177.

Liu, L., Hua, M., Liu, C., He, N., Li, Z., & Ma, D. (2016). The aberrant expression of microRNAs and correlations with T cell subsets in patients with immune thrombocytopenia. *Oncotarget*, *7*(47), 76453.

Lohi, S., Mustalahti, K., Kaukinen, K., Laurila, K., Collin, P., Rissanen, H., … Reunanen, A. (2007). Increasing prevalence of coeliac disease over time. *Alimentary Pharmacology & Therapeutics*, *26*(9), 1217–1225.

Löfgren, S. E., Frostegård, J., Truedsson, L., Pons-Estel, B. A., D'Alfonso, S., Witte, T., … Vasconcelos, C. (2012). Genetic association of miRNA-146a with systemic lupus erythematosus in Europeans through decreased expression of the gene. *Genes and Immunity*, *13*(3), 268–274.

Ma, X., Zhou, J., Zhong, Y., Jiang, L., Mu, P., Li, Y., … Nagarkatti, P. (2014). Expression, regulation and function of microRNAs in multiple sclerosis. *International Journal of Medical Sciences*, *11*(8), 810–818.

Maghsood, A. H., Jadideslam, G., Fallah, M., & Bazmani, A. (2014). Evaluation of IFN-γ polymorphism in visceral leishmaniasis. *Journal of Research in Health Sciences*, *14*(2), 136–139.

McCoy, K. (2009). Women and autoimmune disorders. Everydayhealth.com, December 2.

Miossec, P., Korn, T., & Kuchroo, V. K. (2009). Interleukin-17 and type 17 helper T cells. *New England Journal of Medicine*, *361*(9), 888–898.

Miska, E. A. (2005). How microRNAs control cell division, differentiation and death. *Current Opinion in Genetics & Development*, *15*(5), 563–568.

Moisan, J., Grenningloh, R., Bettelli, E., Oukka, M., & Ho, I.-C. (2007). Ets-1 is a negative regulator of Th17 differentiation. *Journal of Experimental Medicine*, *204*(12), 2825–2835.

Mycko, M. P., Cichalewska, M., Machlanska, A., Cwiklinska, H., Mariasiewicz, M., & Selmaj, K. W. (2012). MicroRNA-301a regulation of a T-helper 17 immune response controls autoimmune demyelination. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(20), E1248–E1257.

Møller, H. G., Rasmussen, A. P., Andersen, H. H., Johnsen, K. B., Henriksen, M., & Duroux, M. (2013). A systematic review of microRNA in glioblastoma multiforme: Micro-modulators in the mesenchymal mode of migration and invasion. *Molecular Neurobiology*, *47*(1), 131–144.

Nielsen, L. B., Wang, C., Sorensen, K., Bang-Berthelsen, C. H., Hansen, L., Andersen, M. L., … Mortensen, H. B. (2012). Circulating levels of microRNA from children with newly diagnosed type 1 diabetes and healthy controls: Evidence that miR-25 associates to residual beta-cell function and glycaemic control during disease progression. *Experimental Diabetes Research*, *2012*, 896362.

Ninomiya, M., Kondo, Y., Funayama, R., Nagashima, T., Kogure, T., Kakazu, E., … Shimosegawa, T. (2013). Distinct microRNAs expression profile in primary biliary cirrhosis and evaluation of miR 505-3p and miR197-3p as novel biomarkers. *PLoS One*, *8*(6), e66086.

Niwald, M., Migdalska-Sęk, M., Brzeziańska-Lasota, E., & Miller, E. (2017). Evaluation of selected microRNAs expression in remission phase of multiple sclerosis and their potential link to cognition, depression, and disability. *Journal of Molecular Neuroscience*, *63*(3–4), 275–282.

O'Connell, R. M., Kahn, D., Gibson, W. S., Round, J. L., Scholz, R. L., Chaudhuri, A. A., … Baltimore, D. (2010). MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity*, *33*(4), 607–619.

O'Connell, R. M., Rao, D. S., Chaudhuri, A. A., & Baltimore, D. (2010). Physiological and pathological roles for microRNAs in the immune system. *Nature Reviews Immunology*, *10*(2), 111–122.

Otaegui, D., Baranzini, S. E., Armañanzas, R., Calvo, B., Muñoz-Culla, M., Khankhanian, P., … Asensio, A. (2009). Differential micro RNA expression in PBMC from multiple sclerosis patients. *PLoS One*, *4*(7), e6309.

Padgett, K. A., Lan, R. Y., Leung, P. C., Lleo, A., Dawson, K., Pfeiff, J., … Gershwin, M. E. (2009). Primary biliary cirrhosis is associated with altered hepatic microRNA expression. *Journal of Autoimmunity*, *32*(3-4), 246–253.

Pan, F., Xiang, H., Yan, J., Hong, L., Zhang, L., Liu, Y., … Cai, C. (2017). Dendritic cells from rheumatoid arthritis patient peripheral blood induce Th17 cell differentiation via miR-363/Integrin alphav/TGF-beta Axis. *Scandinavian Journal of Immunology*, *85*(6), 441–449.

Pan, W., Zhu, S., Yuan, M., Cui, H., Wang, L., Luo, X., … Shen, N. (2010). MicroRNA-21 and microRNA-148a contribute to DNA hypomethylation in lupus CD4+T cells by directly and indirectly targeting DNA methyltransferase 1. *The Journal of Immunology*, *184*(12), 6773–6781.

Peng, L., Ma, W., Yi, F., Yang, Y. J., Lin, W., Chen, H., … Du, Q. (2014). MicroRNA profiling in Chinese patients with primary Sjogren syndrome reveals elevated miRNA-181a in peripheral blood mononuclear cells. *The Journal of Rheumatology*, *41*(11), 2208–2213.

Pierdomenico, M., Cesi, V., Cucchiara, S., Vitali, R., Prete, E., Costanzo, M., … Stronati, L. (2016). NOD2 is regulated by Mir-320 in physiological

conditions but this control is altered in inflamed tissues of patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *22*(2), 315–326.

Pretel, M., Marquès, L., & España, A. (2014). Drug-induced lupus erythematosus. *Actas Dermo-Sifiliográficas*, *105*(1), 18–30.

Qian, C., Chen, S. X., Ren, C. L., Zhong, R. Q., Deng, A. M., & Qin, Q. (2013). Abnormal expression of miR-let-7b in primary biliary cirrhosis and its clinical significance. *Zhonghua gan zang bing za zhi=Zhonghua ganzangbing zazhi=Chinese Journal of Hepatology*, *21*(7), 533–536.

Ralfkiaer, U., Hagedorn, P. H., Bangsgaard, N., Løvendorf, M. B., Ahler, C. B., Svensson, L., … Zibert, J. R. (2011). Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). *Blood*, *118*(22), 5891–5900.

Rani, S. (2017). MicroRNA profiling. Springer.

Rashid, T., & Ebringer, A. (2007). Ankylosing spondylitis is linked to Klebsiella—The evidence. *Clinical Rheumatology*, *26*(6), 858–864.

Rodriguez, A., Griffiths-Jones, S., Ashurst, J. L., & Bradley, A. (2004). Identification of mammalian microRNA host genes and transcription units. *Genome Research*, *14*(10a), 1902–1910.

Rostas, J. W., Pruitt, H. C., Metge, B. J., Mitra, A., Bailey, S. K., Bae, S., … Richards, W. O. (2014). microRNA-29 negatively regulates EMT regulator N-myc interactor in breast cancer. *Molecular Cancer*, *13*(1), 1.

Rouas, R., Fayyad-Kazan, H., El Zein, N., Lewalle, P., Rothé, F., Simion, A., … Burny, A. (2009). Human natural Treg microRNA signature: Role of microRNA-31 and microRNA-21 in FOXP3 expression. *European Journal of Immunology*, *39*(6), 1608–1618.

Salas-Perez, F., Codner, E., Valencia, E., Pizarro, C., Carrasco, E., & Perez-Bravo, F. (2013). MicroRNAs miR-21a and miR-93 are down regulated in peripheral blood mononuclear cells (PBMCs) from patients with type 1 diabetes. *Immunobiology*, *218*(5), 733–737.

Sebastiani, G., Grieco, F. A., Spagnuolo, I., Galleri, L., Cataldo, D., & Dotta, F. (2011). Increased expression of microRNA miR-326 in type 1 diabetic patients with ongoing islet autoimmunity. *Diabetes/Metabolism Research and Reviews*, *27*(8), 862–866.

Sebastiani, G., Ventriglia, G., Stabilini, A., Socci, C., Morsiani, C., Laurenzi, A., … Battaglia, M. (2017). Regulatory T-cells from pancreatic lymphnodes of patients with type-1 diabetes express increased levels of microRNA miR-125a-5p that limits CCR2 expression. *Scientific Reports*, *7*(1), 6897.

Sonkoly, E., Wei, T., Janson, P. C., Sääf, A., Lundeberg, L., Tengvall-Linder, M., … Scheynius, A. (2007). MicroRNAs: Novel regulators involved in the pathogenesis of psoriasis?. *PLoS One*, *2*(7), e610.

Sun, X. G., Tao, J. H., Xiang, N., Li, X. M., Wang, G. S., Fang, X., … Li, X. P. (2016). Negative correlation between miR-326 and Ets-1 in regulatory T cells from new-onset SLE patients. *Inflammation*, *39*(2), 822–829.

Szodoray, P., Nakken, B., Gaal, J., Jonsson, R., Szegedi, A., Zold, E., … Zeher, M. (2008). The complex role of vitamin D in autoimmune diseases. *Scandinavian Journal of Immunology*, *68*(3), 261–269.

Tang, Y.-F., Zhang, Y., Li, X.-Y., Li, C., Tian, W., & Liu, L. (2009). Expression of miR-31, miR-125b-5p, and miR-326 in the adipogenic differentiation process of adipose-derived stem cells. *OMICS: A Journal of Integrative Biology*, *13*(4), 331–336.

Te, J. L., Dozmorov, I. M., Guthridge, J. M., Nguyen, K. L., Cavett, J. W., Kelly, J. A., … Ojwang, J. O. (2010). Identification of unique microRNA signature associated with lupus nephritis. *PLoS One*, *5*(5), e10344.

Tesmer, L. A., Lundy, S. K., Sarkar, S., & Fox, D. A. (2008). Th17 cells in human disease. *Immunological Reviews*, *223*(1), 87–113.

Thorlacius-Ussing, G., Schnack Nielsen, B., Andersen, V., Holmstrom, K., & Pedersen, A. E. (2017). Expression and localization of miR-21 and miR-126 in mucosal tissue from patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, *23*(5), 739–752.

Tsai, C. H., Liu, S. C., Wang, Y. H., Su, C. M., Huang, C. C., Hsu, C. J., & Tang, C. H. (2017). Osteopontin inhibition of miR-129-3p enhances IL-17 expression and monocyte migration in rheumatoid arthritis. *Biochimica et Biophysica Acta*, *1861*(2), 15–22.

Tufekci, K. U., Oner, M. G., Genc, S., & Genc, K. (2010). MicroRNAs and multiple sclerosis. *Autoimmune Diseases*, *2011*, 807426.

van der Ree, M. H., de Vree, J. M., Stelma, F., Willemse, S., van der Valk, M., Rietdijk, S., … Beuers, U. (2017). Safety, tolerability, and antiviral effect of RG-101 in patients with chronic hepatitis C: A phase 1B, double-blind, randomised controlled trial. *The Lancet*, *389*(10070), 709–717.

Viennois, E., Zhao, Y., Han, M. K., Xiao, B., Zhang, M., Prasad, M., … Merlin, D. (2017). Serum miRNA signature diagnoses and discriminates murine colitis subtypes and predicts ulcerative colitis in humans. *Scientific Reports*, *7*(1), 2520.

Vreugdenhil, G., Geluk, A., Ottenhoff, T., Melchers, W., Roep, B., & Galama, J. (1998). Molecular mimicry in diabetes mellitus: The homologous domain in coxsackie B virus protein 2C and islet autoantigen GAD65 is highly conserved in the coxsackie B-like enteroviruses and binds to the diabetes associated HLA-DR3 molecule. *Diabetologia*, *41*(1), 40–46.

Wang, G., Gu, Y., Xu, N., Zhang, M., & Yang, T. (2017). Decreased expression of miR-150, miR146a and miR424 in type 1 diabetic patients: Association with ongoing islet autoimmunity. *Biochemical and Biophysical Research Communications*, *498*(3), 382–387.

Wang, H., Chao, K., Ng, S. C., Bai, A. H., Yu, Q., Yu, J., … Zhang, S. (2016). Pro-inflammatory miR-223 mediates the cross-talk between the IL23 pathway and the intestinal barrier in inflammatory bowel disease. *Genome Biology*, *17*, 58.

Wang, L., Song, G., Zheng, Y., Wang, D., Dong, H., Pan, J., & Chang, X. (2016). miR-573 is a negative regulator in the pathogenesis of rheumatoid arthritis. *Cellular & Molecular Immunology*, *13*(6), 839–849.

Wang, R., Chen, X.-F., & Shu, Y.-Q. (2015). Prediction of non-small cell lung cancer metastasis-associated microRNAs using bioinformatics. *American Journal of Cancer Research*, *5*(1), 32.

Wang, S., Wan, X., & Ruan, Q. (2016). The MicroRNA-21 in autoimmune diseases. *International Journal of Molecular Sciences*, *17*(6), 864.

Wang, Y., Keys, D. N., Au-Young, J. K., & Chen, C. (2009). MicroRNAs in embryonic stem cells. *Journal of Cellular Physiology*, *218*(2), 251–255.

Wang, Z. C., Lu, H., Zhou, Q., Yu, S. M., Mao, Y. L., Zhang, H. J., … Yan, W. J. (2015). MiR-451 inhibits synovial fibroblasts proliferation and inflammatory cytokines secretion in rheumatoid arthritis through mediating p38MAPK signaling pathway. *International Journal of Clinical and Experimental Pathology*, *8*(11), 14562–14567.

Waschbisch, A., Atiya, M., Linker, R. A., Potapov, S., Schwab, S., & Derfuss, T. (2011). Glatiramer acetate treatment normalizes deregulated microRNA expression in relapsing remitting multiple sclerosis. *PLoS One*, *6*(9), e24604.

Wu, D., Bi, X., Qu, L., Han, L., Yin, C., Deng, J., … Zhou, L. (2017). miRNA miR-17-92 cluster is differentially regulated in the imiqumod-treated skin but is not required for imiqumod-induced psoriasis-like dermatitis in mice. *Experimental Dermatology*, *26*(1), 82–84.

Wu, L. S., Li, F. F., Sun, L. D., Li, D., Su, J., Kuang, Y. H., … Chen, X. (2011). A miRNA-492 binding-site polymorphism in BSG (basigin) confers risk to psoriasis in central south Chinese population. *Human Genetics*, *130*(6), 749–757.

Wu, N., Zhang, C., Bai, C., Han, Y. P., & Li, Q. (2014). MiR-4782-3p inhibited non-small cell lung cancer growth via USP14. *Cellular Physiology and Biochemistry*, *33*(2), 457–467.

Wu, T., & Chen, G. (2016). miRNAs participate in MS pathological processes and its therapeutic response. *Mediators of Inflammation*, *2016*, 4578230.

Wu, W., He, C., Liu, C., Cao, A. T., Xue, X., Evans-Marin, H. L., … Cong, Y. (2015). miR-10a inhibits dendritic cell activation and Th1/Th17 cell immune responses in IBD. *Gut*, *64*(11), 1755–1764.

Wållberg, M., & Harris, R. A. (2005). Co-infection with Trypanosoma brucei brucei prevents experimental autoimmune encephalomyelitis in DBA/1 mice through induction of suppressor APCs. *International Immunology*, *17*(6), 721–728.

Xia, Y., Tao, J.-H., Fang, X., Xiang, N., Dai, X.-J., Jin, L., … Li, X.-P. (2018). MicroRNA-326 upregulates B cell activity and autoantibody production in lupus disease of MRL/lpr mice. *Molecular Therapy-Nucleic Acids*, *11*, 284–291.

Xu, L., Leng, H., Shi, X., Ji, J., Fu, J., & Leng, H. (2017). MiR-155 promotes cell proliferation and inhibits apoptosis by PTEN signaling pathway in the psoriasis. *Biomedicine and Pharmacotherapy*, *90*, 524–530.

Xu, X., Chen, H., Zhang, Q., Xu, J., Shi, Q., & Wang, M. (2017). MiR-650 inhibits proliferation, migration and invasion of rheumatoid arthritis synovial fibroblasts by targeting AKT2. *Biomedicine & Pharmacotherapy=Biomedecine & Pharmacotherapie*, *88*, 535–541.

Xu, X.-M., & Zhang, H.-J. (2016). miRNAs as new molecular insights into inflammatory bowel disease: Crucial regulators in autoimmunity and inflammation. *World Journal of Gastroenterology*, *22*(7), 2206.

Yang, Y., Wang, Y., Liang, Q., Yao, L., Gu, S., & Bai, X. (2017). MiR-338-5p promotes inflammatory response of fibroblast-like synoviocytes in rheumatoid arthritis via targeting SPRY1. *Journal of Cellular Biochemistry*, *118*(8), 2295–2301.

Yang, Z., Zeng, B., Tang, X., Wang, H., Wang, C., Yan, Z., … Xu, B. (2016). MicroRNA-146a and miR-99a are potential biomarkers for disease activity and clinical efficacy assessment in psoriasis patients treated with traditional Chinese medicine. *Journal of Ethnopharmacology*, *194*, 727–732.

Ye, Y., Gao, X., & Yang, N. (2017). LncRNA ZFAS1 promotes cell migration and invasion of fibroblast-like synoviocytes by suppression of miR-27a in rheumatoid arthritis. *Human Cell*, *31*(1), 14–21.

Yu, S., Huang, H., Deng, G., Xie, Z., Ye, Y., Guo, R., … Zhou, X. (2015). miR-326 targets antiapoptotic Bcl-xL and mediates apoptosis in human platelets. *PLoS One*, *10*(4), e0122784.

Zan, H., Tat, C., & Casali, P. (2014). MicroRNAs in lupus. *Autoimmunity*, *47*(4), 272–285.

Zhang, C., Zhao, Z., Osman, H., Watson, R., Nalbantoglu, I., & Lin, J. (2014). Differential expression of miR-31 between inflammatory bowel disease and microscopic colitis. *MicroRNA*, *3*(3), 155–159.

Zhang, H. J., Wei, Q. F., Wang, S. J., Zhang, H. J., Zhang, X. Y., Geng, Q., … Wang, X. H. (2017). LncRNA HOTAIR alleviates rheumatoid arthritis by targeting miR-138 and inactivating NF-kappaB pathway. *International Immunopharmacology*, *50*, 283–290.

Zhang, J., Cheng, Y., Cui, W., Li, M., Li, B., & Guo, L. (2014). MicroRNA-155 modulates Th1 and Th17 cell differentiation and is associated with multiple sclerosis and experimental autoimmune encephalomyelitis. *Journal of Neuroimmunology*, *266*(1), 56–63.

Zhang, J., Chong, C. C., Chen, G. G., & Lai, P. B. (2015). A seven-microRNA expression signature predicts survival in hepatocellular carcinoma. *PLoS One*, *10*(6), e0128628.

Zhang, P., Kong, F., Deng, X., Yu, Y., Hou, C., Liang, T., & Zhu, L. (2017). Micro RNA-326 suppresses the proliferation, migration and invasion of cervical cancer cells by targeting ELK1. *Oncology Letters*, *13*(5), 2949–2956.

Zhang, Q. J., Li, J., & Zhang, S. Y. (2017). Effects of TRPM7/miR-34a gene silencing on spatial cognitive function and hippocampal neurogenesis in mice with Type 1 diabetes mellitus. *Molecular Neurobiology*, *55*(2), 1568–1579.

Zhang, X., Dong, H., & Tian, Y. (2015). MicroRNA detection and pathological functions, Berlin Heidelberg: Springer.

Zhang, Z. L., Bai, Z. H., Wang, X. B., Bai, L., Miao, F., & Pei, H. H. (2015). miR-186 and 326 predict the prognosis of pancreatic ductal adenocarcinoma and affect the proliferation and migration of cancer cells. *PLoS One*, *10*(3), e0118814.

Zhao, S., Wang, Y., Liang, Y., Zhao, M., Long, H., Ding, S., … Lu, Q. (2011). MicroRNA-126 regulates DNA methylation in CD4+T cells and contributes to systemic lupus erythematosus by targeting DNA methyltransferase 1. *Arthritis & Rheumatism*, *63*(5), 1376–1386.

Zhao, X., Tang, Y., Qu, B., Cui, H., Wang, S., Wang, L., … Chen, S. (2010). MicroRNA-125a contributes to elevated inflammatory chemokine RANTES levels via targeting KLF13 in systemic lupus erythematosus. *Arthritis & Rheumatism*, *62*(11), 3425–3435.

Zhou, S., Yang, B., Zhao, Y., Xu, S., Zhang, H., & Li, Z. (2014). Prognostic value of microRNA-100 in esophageal squamous cell carcinoma. *Journal of Surgical Research*, *192*(2), 515–520.

Zhu, H., Hou, L., Liu, J., & Li, Z. (2016). MiR-217 is down-regulated in psoriasis and promotes keratinocyte differentiation via targeting GRHL2. *Biochemical and Biophysical Research Communications*, *471*(1), 169–176.

Zhu, J., Qi, Y., Wu, J., Shi, M., Feng, J., & Chen, L. (2016). Evaluation of plasma microRNA levels to predict insensitivity of patients with advanced lung adenocarcinomas to pemetrexed and platinum. *Oncology Letters*, *12*(6), 4829–4837.

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