



Progress and challenge of microRNA research in immunity

Hyang-Mi Lee¹, Duc T. Nguyen¹ and Li-Fan Lu^{1,2} *

¹ Division of Biological Sciences, University of California, San Diego, La Jolla, CA, USA

² Moores Cancer Center, University of California, San Diego, La Jolla, CA, USA

Edited by:

Ryan Michael O'Connell, University of Utah, USA

Reviewed by:

Ram Savan Savan, University of Washington, USA

Silvia Monticelli, Institute for Research in Biomedicine, Switzerland

*Correspondence:

Li-Fan Lu, Division of Biological Sciences, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA
e-mail: lifanlu@ucsd.edu

MicroRNAs (miRNAs) are 19–24 nucleotide long non-coding RNA species that regulate the expression of multiple target genes at the post-transcriptional level. They are required for normal immune system development and function, and their expression is dynamically regulated in different immune cell subsets during lineage differentiation and immune response. Aberrant expression of miRNAs results in dysregulated innate and adaptive immunity. This in turn can lead to failure to fight against invading pathogens and the development of autoimmune diseases and hematopoietic malignancies. In this article, we review current progress in miRNA research in immunity in both physiological and pathological settings. We also discuss research limitations and challenges that researchers are just beginning to solve.

Keywords: microRNA (miRNA), post-transcriptional regulation, hematopoiesis, immune regulation, immune dysfunction

INTRODUCTION

Gene expression is post-transcriptionally regulated by different types of non-coding RNAs. Among them, microRNAs (miRNAs) inhibit translation or facilitate degradation of target messenger RNAs (mRNAs; Carthew and Sontheimer, 2009). Primary miRNA transcripts are produced by RNA polymerases II and III and processed in the nucleus by the RNase III enzyme Droscha into pre-miRNAs (Lee et al., 2002, 2003, 2004; Yi et al., 2003; Lund et al., 2004; Han et al., 2006). Once shuttled into the cytoplasm, pre-miRNAs are further processed by another RNase III enzyme, Dicer, to produce 19- to 24- base-pair long polynucleotides. These mature miRNAs are incorporated into the RNA-induced silencing complex (RISC), where they interact with the core component protein Argonaute (Ago; Grishok et al., 2001; Hutvagner et al., 2001; Ketting et al., 2001; Hutvagner and Zamore, 2002; Lee et al., 2002; Mourelatos et al., 2002; Lingel et al., 2003). RISC is the functional unit of miRNA-mediated regulation. It uses the “seed sequence” of the miRNA to recognize complementary regions mainly in the 3' UTRs of mRNAs being targeted for degradation or translational silencing (Hutvagner and Zamore, 2002; Lewis et al., 2005; Pillai et al., 2007). Recent studies have revealed the critical role of miRNAs in tuning immunity. Immune cells express unique miRNA profiles which contribute to their respective functions (Kuchen et al., 2010) and change their miRNA repertoires in response to varying stimuli such as T cell receptor (TCR) activation (Bron-evetsky et al., 2013). The past decade has seen many fascinating discoveries about the role of miRNAs in immunity. Unfortunately, the complex natures of the miRNA-mediated gene regulation as well as existing technical challenges have also slowed down research progress.

CURRENT PROGRESS IN miRNA RESEARCH IN IMMUNITY PROGRESS IN FUNCTIONAL ASSESSMENT OF miRNAs IN IMMUNE CELL DEVELOPMENT AND FUNCTION

MicroRNAs were initially discovered for their role in influencing cell fate and differentiation decisions during the development of

an organism (Bartel, 2004). In the past decade, mounting evidence has demonstrated that miRNAs are equally important in regulating the immune system. Efforts to discover the cellular and molecular mechanisms of miRNA-mediated immune regulation have relied on gain-of-function and loss-of-function approaches. The general importance of miRNAs in immune cells has been repeatedly confirmed by deletion of key components of the miRNA biogenesis pathway such as Ago, Dicer, and Droscha (Cobb et al., 2005, 2006; Muljo et al., 2005; O'Carroll et al., 2007; Koralov et al., 2008). These gross loss-of-function experiments revealed two important characteristics of miRNA-mediated regulation. First, miRNAs regulate the survival and proliferative function of precursor cells and influence the number and type of differentiated cells that are produced during hematopoiesis and immune responses. In some instances, deletion of all miRNAs greatly promoted one cell type while impairing another. Second, immune cells require miRNAs to carry out their normal functions. Indeed, deletion of Dicer or Droscha in regulatory T (Treg) cells compromised their suppressive capacity and resulted in autoimmune phenotypes (Chong et al., 2008; Liston et al., 2008; Zhou et al., 2008). Taken together, it was reasonable to conclude that miRNA-mediated gene regulation is involved in controlling all aspects of immunity and miRNA dysregulation results in immune-associated phenotypes such as chronic inflammation and autoimmunity by disrupting the normal development, homeostasis, and function of immune cells.

In the past several years, functional studies have further expanded the list of cell types and function regulated by individual miRNAs (Table 1). These studies began to discover mechanisms by which miRNAs regulate immune processes. A given miRNA can influence immune cell development by directly inhibiting transcription factors (TFs) and repressors that are crucial for determining cell-type specific differentiation and maintaining lineage identity (Fontana et al., 2007; Johnnidis et al., 2008; Du et al., 2009). miRNAs can also modulate immune responses through targeting key signaling molecules downstream of different immune

Table 1 | miRNAs involved in immune system.

	Function	miRNA
Innate immunity	Granulocyte development	miR-155, miR-223
	Monocyte development	miR-155, miR-17-92
	Neutrophil function	miR-223
	Macrophage activation	miR-155, miR-146a, miR-21
	Dendritic cell function	miR-155
Adaptive immunity	T cell development	miR-181
	B cell development	miR-150
	T cell proliferation	miR-182, miR-214
	Th1, 17 cell differentiation	miR-155, miR-210, miR-326
	Tfh cell differentiation	miR-10a, miR-17-92
	Treg cell function	miR-155, miR-146a
	CD8T cell function	miR-155
	B cell function	miR-155, miR-150
	Immunological diseases	Autoimmunity
<i>RA</i> miR-23b, miR-146a, miR-155, miR-223		
<i>MS</i> miR-155, miR-326, miR-23b, miR-124		
Infectious disease		miR-155
Immune cell malignancy	miR-15a, miR-16, miR-17-92, miR-155, miR-223, miR-29b	

cell-type specific receptors such as B and T cell receptors as well as innate pathogen recognition receptors (Li et al., 2007; Androulidaki et al., 2009; Hou et al., 2009; O'Connell et al., 2009; Belver et al., 2010; Sheedy et al., 2010). Through repressing the expression of their many targets, miRNAs exert varied, subtle, and often contrasting influence.

miRNA in adaptive immunity

Loss-of-function and gain-of-function studies of individual miRNAs have revealed that a given miRNA can impact different aspects of adaptive immune cell development and function. For example, miR-181 is a positive regulator of B cell differentiation and ectopic expression results in a substantial increase in B cells (Chen et al., 2004). Similarly, miR-17~92 has been shown to be critical in promoting early B cell development, as loss of miR-17~92 leads to increased Bim expression and apoptosis at the pro-B cell to pre-B cell transition (Ventura et al., 2008). In contrast, miR-150 limits early B cell differentiation, since forced expression of miR-150, which targets c-Myb, impaired transition from pro-B cells to pre-B cells (Xiao et al., 2007). In the periphery, several studies have found that miR-155 plays a key role in controlling B cell biology. Mice deficient of miR-155, which is induced during germinal center (GC) reaction *in vivo*, have defects in both antibody secretion and class switching (Thai et al., 2007; Vigorito et al., 2007). The phenotype seems to be a consequence of repressing a number of genes including PU.1 and AID, an enzyme critical for somatic hypermutation and antibody class switching (Vigorito et al., 2007; Teng et al., 2008). In contrast, there is increased follicular B cell activation with enhanced antibody secretion upon T cell-dependent

antigen immunization in mice deficient of miR-150 (Xiao et al., 2007).

In T cells, emerging data has suggested that miRNAs also regulate the development and function of different T cell subsets required for adaptive immune response. Loss of miR-155 enhanced Th2 but impaired Th1 and Th17 differentiation (Rodriguez et al., 2007; O'Connell et al., 2010). Th17 differentiation was shown to be regulated by miR-326, too (Du et al., 2009). Recently, attention has also turned to miRNA regulation in follicular T (Tfh) cells, the T cell subset that helps activate B cells during humoral response. Bcl-6, a critical TF for Tfh differentiation, has been shown to regulate expression of several miRNAs (Yu et al., 2009), and miR-10a was known to modulate plasticity of Tfh cells (Takahashi et al., 2012). The latest studies have demonstrated several mechanisms through which miR-17~92 regulates Tfh differentiation that involve targeting ROR α and phosphatase, PHLPP2 (Baumjohann et al., 2013; Kang et al., 2013). Similarly, insight into the cell-extrinsic role of miRNAs might be gained from research on Treg cells. It has been reported that miR-155 and miR-146a can influence Treg homeostasis and suppressor function through targeting SOCS1 and Stat1, respectively (Lu et al., 2009, 2010).

miRNA in innate immunity

The role of individual miRNAs in controlling the development and function of innate immune cells has also been well documented. For example, miR-17~92 has been shown to be important in monocyte differentiation. miR-17~92 targets

Runx1, which promotes monocytopoiesis, while Runx1 suppresses miR-17-92 by binding to its promoter region (Fontana et al., 2007). The range and complexity of miRNA involvement in innate immunity have been further demonstrated through studies of pattern recognition receptor pathways. Toll like receptor (TLR) signaling was discovered to induce expression of a variety of miRNAs including miR-155, miR-146a, and miR-21 (Taganov et al., 2006; O'Connell et al., 2007; Sheedy et al., 2010). In mouse macrophage, miR-155 induced by TLR ligands represses negative regulators of TLR signaling such as SHIP1 and SOCS1 (Androulidaki et al., 2009; O'Connell et al., 2009). In contrast, miR-146a acts as a negative regulator of NF- κ B through IRAK1 and TRAF6, and deficiency in miR-146a leads to autoimmunity and myeloid malignancy (Taganov et al., 2006; Boldin et al., 2011; Zhao et al., 2011). The function of miR-146a as a negative regulator of inflammation is also implicated in RIG-I-dependent type 1 interferon (IFN) production by macrophages upon viral infection, in which miR-146a targets IRAK2 (Hou et al., 2009). The discovery of these interactions evidence the dynamism of miRNA activity: inflammatory stimuli can influence miRNA expression, and in turn, individual miRNAs tightly regulate innate immunity by targeting specific mRNAs involved in the activation and resolution of immune responses.

PROGRESS IN FUNCTIONAL ASSESSMENT OF miRNAs IN IMMUNE DISEASES

Given that miRNAs tune immune cells to function properly, it was not surprising that abnormal miRNA expression leads to immunological disorders. To date, much progress has been made to correlate specific miRNAs with particular disease states, and a large number of miRNAs have been reported to be up- or down-regulated in certain autoimmunity, infectious diseases, and cancers. These aberrant miRNAs have been thought responsible for the inappropriate expression of target proteins associated with the respective pathologies.

miRNA in autoimmunity

Recent studies have identified abnormal miRNA expression in many autoimmune diseases including systemic lupus erythematosus (SLE), multiple sclerosis (MS) and rheumatoid arthritis (RA) and the functional relevance of specific miRNAs has been explored in the corresponding mouse models (Junker et al., 2010; Ceribelli et al., 2011; Amarilyo and La Cava, 2012). In human lupus patients, decreased expression of miR-146a leads to hyperactivation of type I IFN and decreased miR-125a to elevated inflammatory chemokine, RANTES (Tang et al., 2009; Zhao et al., 2010). Another set of miRNAs, miR-155 and miR-15a, was found to be increased in the mouse lupus model where Treg cell activity and autoantibody production were affected (Divekar et al., 2010; Yuan et al., 2012). Unlike in lupus, miR-146a is upregulated in RA synovial tissue, where it presumably suppresses proinflammatory cytokines such as TNF α (Nakasa et al., 2008). Similarly, miR-155 and miR-223 are highly expressed in synovial fibroblasts and T cells from RA patients, respectively (Stanczyk et al., 2008; Fulci et al., 2010). Mouse models of arthritis have demonstrated the involvement of miR-155 in regulating B cell and Th17 cell functions attributed to

disease development (Kurowska-Stolarska et al., 2011). Among the many miRNAs dysregulated in MS (Junker, 2011), miR-155 was found to modulate astrocyte function in MS and Th17 differentiation in the mouse experimental autoimmune encephalomyelitis (EAE) model (Junker et al., 2009; O'Connell et al., 2010). miR-124 is able to control neuroinflammation by keeping microglia quiescent in steady-state condition; its downregulation at the onset of EAE results in microglia activation and inflammation (Ponomarev et al., 2010). Other autoimmune inflammation including type I diabetes and inflammatory bowel disease (IBD) have been linked to many miRNAs, too (Hezova et al., 2010; Oertli et al., 2011). Nonetheless, the targets of these miRNAs and their mechanisms for regulating autoimmunity remain to be discovered.

miRNA in infectious diseases

Several functional studies thus far have demonstrated an important role of miR-155 in host defense against microbial infections. Lack of miR-155 resulted in impaired effector CD8+ T cell function during acute or chronic lymphocytic choriomeningitis virus (LCMV) infection, and defective memory cell differentiation upon infection with *Listeria monocytogenes* (Dudda et al., 2013; Gracias et al., 2013; Lind et al., 2013). Perhaps one of the more surprising discoveries was that miRNAs are directly involved in interactions between host immune responses and infecting pathogens. The fact that viruses themselves generate miRNAs regulating expression of both viral and host genes highlights an essential role of miRNAs in immune responses against infection (Sullivan and Ganem, 2005). Viral miRNA expressed late in SV40 infection down regulates the expression of viral T-antigens in order to avoid alerting cytotoxic T cells (Sullivan et al., 2005). On the other hand, the immune system exerts antiviral activity by regulating the expression of miRNAs in host cells (Pedersen et al., 2007). Some of these host miRNAs were predicted to directly target viral genes. As mediators of host-pathogen interaction, miRNAs influence the outcome of infectious diseases.

miRNA in cancer

Differential expression patterns of miRNA have also been found in various malignancies and correlated with clinical outcome (Mi et al., 2007; Marcucci et al., 2008). Studies on the functional relevance of individual miRNAs have revealed that miRNAs can directly modulate the expression levels of oncogenes and tumor suppressor genes, and influence epigenetic regulation, all of which contribute ultimately to tumor development. For example, miRNAs that target anti-apoptotic protein BCL-2 have been found to be deleted in chronic lymphocytic leukemia (CLL; Calin et al., 2002; Cimmino et al., 2005). In mouse lymphocytes, forced expression of miR-17-92 leads to a lymphoproliferative phenotype through targeting tumor suppressive proteins such as PTEN and BIM (Xiao et al., 2008). miR-155 was also found overexpressed in B cell lymphomas, and subsequently shown to target SHIP and C/EBP β involved in IL-6 signaling (Costinean et al., 2006, 2009). Oncogenic protein can silence the transcription of miR-223 by recruiting chromatin remodeling enzymes (Fazi et al., 2007), while miR-29b promotes expression of tumor suppressor genes by repressing DNA methyltransferases in acute

myeloid leukemia (AML; Garzon et al., 2009). Research on the role of miRNAs in immune cell malignancies complemented concurrent research on how miRNAs regulate proliferation and differentiation.

CURRENT CHALLENGES IN miRNA RESEARCH IN IMMUNITY

MicroRNAs control many important immunological processes, and much like TFs, they exhibit diverse effects through their action on multiple mRNA species. As such, miRNA regulatory networks are complex, and before designing any kind of treatment, the networks must be understood in all their complexities. Despite the great efforts that have been committed to discover the precise role of miRNAs in the immune system, many issues remain unsolved. Some of these are technical limitations of current approaches, such as the sensitivity of *in vivo* and *in vitro* assays, and the ability to isolate sufficient cells of certain immune cell subsets for miRNA profiling and functional analysis. At the same time, the biology of miRNA-mediated regulation also presents inherent difficulties, such as transient low level induction of miRNAs under certain circumstances and the presence of isomiRs (Morin et al., 2008). Here, we will discuss two major challenges that researchers are just beginning to solve.

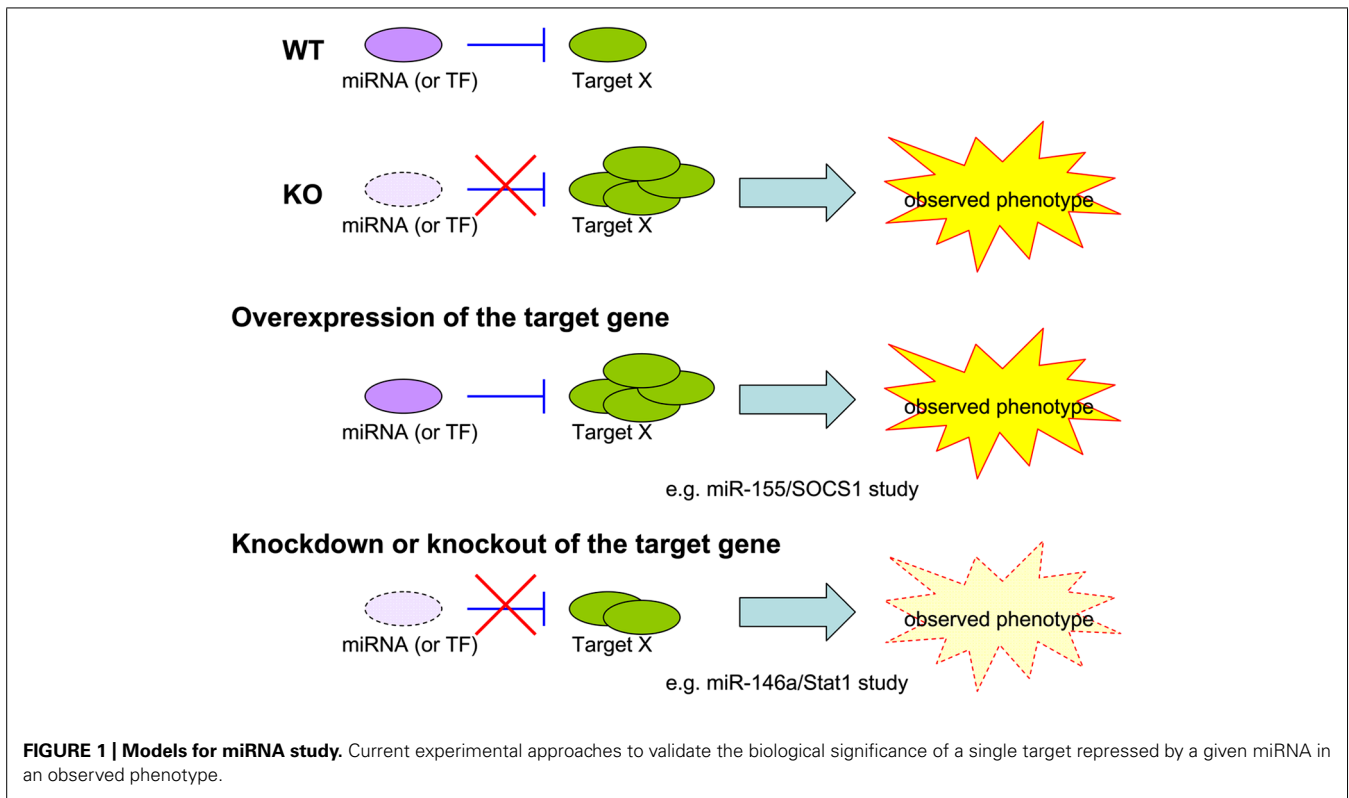
CHALLENGE OF miRNA TARGET IDENTIFICATION

In the past decade, many computational algorithms have been developed to identify potential miRNA target genes (Bartel, 2009). With time, performance and target prediction have improved significantly, and different prediction methods now share a high degree of overlap. Advances in computational prediction could be largely attributed to the recognition of the importance of seed pairing (Lewis et al., 2005). Unfortunately, many important functional miRNA targets could not be identified due to the inability of these tools to find miRNA binding sites with seed mismatches (Doran and Strauss, 2007). Moreover, most of the existing miRNA target predictions have been restricted to mRNA 3' UTRs. Genes that are regulated by miRNA through binding in the 5' untranslated, promoter or protein coding regions were likely missed (Lytle et al., 2007; Place et al., 2008; Tay et al., 2008). A few years ago, High-throughput sequencing of RNA isolated by crosslinking immunoprecipitation (HITS-CLIP) or photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation (PAR-CLIP) techniques were developed (Chi et al., 2009; Hafner et al., 2010; Zisoulis et al., 2010; Van Wynsberghe et al., 2011). These experimental approaches promised to provide direct biochemical evidence of specific miRNA-mRNA interactions without the false positives and negatives of bioinformatic prediction, but they had their own limitations. Because biochemical identification of Ago binding sites came from HITS analysis of pooled mRNA after Ago immunoprecipitation, there was no easy way to identify the corresponding miRNAs responsible for Ago binding. The difficulty increased when it was discovered that a substantial number of Ago binding sites identified in those studies did not contain clear seed matches. It was uncertain whether this apparently seedless targeting was caused by non-canonical miRNA-target interactions or miRNA-independent mechanisms (Leung et al., 2011). One strategy to overcome the uncertainty was to perform differential HITS-CLIP

(dCLIP) analysis and compare mRNA expression changes in T cells with or without a single miRNA; in this case, miR-155 was chosen (Loeb et al., 2012). Combined with luciferase reporter assay and site-directed mutagenesis studies, the authors demonstrated that miR-155 could target and repress genes through binding to sites without canonical seed matching. Finally, since many Ago-interacting proteins have been described in the past and it seems highly unlikely that all of them constitute a common complex (Nilsen, 2007), it is plausible that the cell type of interest or even the differentiation state of the cell could all impact miRNA-mediated gene regulation. Thus, it will be useful to conduct the aforementioned dCLIP analysis with a given miRNA in other immune cell types in a genetically controlled manner to gain clearer understanding of the role of miRNA in immune system.

CHALLENGE OF FUNCTIONAL VALIDATION OF miRNA TARGETS

As 100s of genes could be regulated by a single miRNA, its loss often leads to multiple and complicated biological consequences. Because many of the targets could also operate in a collaborative or competitive manner, it is almost impossible to attribute an observed miRNA-dependent phenotype to the regulation of a single target. To resolve this second challenge in miRNA research in immunity, studies heretofore have mostly relied on two genetic approaches: (1) an overexpression approach in which a chosen miRNA-dependent phenotype is recapitulated upon overexpression of a proposed miRNA target in a WT animal [i.e., our miR-155/SOCS1 study in Treg cells (Lu et al., 2009)]; (2) a knock-down/knockout approach in which a selected miRNA-dependent phenotype is rescued by knocking down the proposed miRNA target in the miRNA KO animal [i.e., our miR-146a/Stat1 study in Treg cells (Lu et al., 2010); **Figure 1**]. While both approaches are valid and provide strong correlative support for hypothesized models, neither could faithfully represent the dynamic miRNA-mediated regulation in a given cell type and in a given time *in vivo*, as both miRNAs and their targets are also subjected to regulation in response to different stimulation and environmental cues. The ideal method to address this challenge is to generate a mutant mouse line harboring mutations in the miRNA binding site of the target gene. The introduced mutations should only disrupt the interaction of the selected miRNA with the gene of interest. By comparing these mice to miRNA-deficient mice, one would be able to isolate the effects of a miRNA to one key immune regulator and the biological significance of single target repression in miRNA-mediated immune regulation could be determined. The method is theoretically sound and should provide the most direct experimental evidence of how a single target controlled by one miRNA controls immune responsiveness. To date, however, it has only been taken in two studies, both of which demonstrated a key role of miR-155-mediated regulation of AID in controlling B cell function (Dorsett et al., 2008; Teng et al., 2008). One could argue that the impact of those studies is somewhat limited due to the restricted expression of the target gene, AID, in the B cell lineage. Considering the time and financial commitment needed to generate a mouse model that could only answer such a narrow question, it is not too surprising why this approach has not been applied to more miRNA research. Nevertheless, as the gene



targeting techniques [e.g., CRISPR/Cas-mediated genome engineering (Yang et al., 2013)] have been improving rapidly in the last couple years, more miRNA studies using the aforementioned knock-in type of approach should become available in the near future.

CONCLUDING REMARKS

In the past decade, intensive investigation in miRNA-mediated gene regulation has demonstrated that miRNAs are key regulators of the development and function of the immune system. As such, miRNAs are differentially expressed in immune cell subsets and tightly regulated to ensure homeostasis and proper immune response. Studies in different disease conditions have further revealed their role in immune system dysregulation and pathogenesis. Despite the highly complex nature of miRNA regulatory networks and the existence of aforementioned technical limitations, recent advances have made miRNA biology a fascinating subject in immunological research. From a basic immunological point of view, the control of immune cell biology by miRNAs provides a powerful model to dissect the molecular orchestration of cellular differentiation, function, and homeostasis. On a practical level, manipulating miRNA pathways in immune cells promises to offer novel therapeutic approaches in the treatment of autoimmunity, infectious disease, and immune malignancies.

ACKNOWLEDGMENTS

This work was supported by grants from the NIH R00-AI089935, R21-AI103646, and R01-AI108651 (Li-Fan Lu). Li-Fan Lu is a Kimmel Scholar and a Hellman Fellow.

REFERENCES

- Amarilyo, G., and La Cava, A. (2012). miRNA in systemic lupus erythematosus. *Clin. Immunol.* 144, 26–31. doi: 10.1016/j.clim.2012.04.005
- Androulidaki, A., Iliopoulos, D., Arranz, A., Doxaki, C., Schworer, S., Zacharioudaki, V., et al. (2009). The kinase Akt1 controls macrophage response to lipopolysaccharide by regulating microRNAs. *Immunity* 31, 220–231. doi: 10.1016/j.immuni.2009.06.024
- Bartel, D. P. (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116, 281–297. doi: 10.1016/S0092-8674(04)00045-5
- Bartel, D. P. (2009). MicroRNAs: target recognition and regulatory functions. *Cell* 136, 215–233. doi: 10.1016/j.cell.2009.01.002
- Baumjohann, D., Kageyama, R., Clingan, J. M., Morar, M. M., Patel, S., de Kouchkovsky, D., et al. (2013). The microRNA cluster miR-17 approximately 92 promotes TFH cell differentiation and represses subset-inappropriate gene expression. *Nat. Immunol.* 14, 840–848. doi: 10.1038/ni.2642
- Belver, L., de Yébenes, V. G., and Ramiro, A. R. (2010). MicroRNAs prevent the generation of autoreactive antibodies. *Immunity* 33, 713–722. doi: 10.1016/j.immuni.2010.11.010
- Boldin, M. P., Taganov, K. D., Rao, D. S., Yang, L., Zhao, J. L., Kalwani, M., et al. (2011). miR-146a is a significant brake on autoimmunity, myeloproliferation, and cancer in mice. *J. Exp. Med.* 208, 1189–1201. doi: 10.1084/jem.20101823
- Bronevetsky, Y., Villarino, A. V., Easley, C. J., Barbeau, R., Barczak, A. J., Heinz, G. A., et al. (2013). T cell activation induces proteasomal degradation of Argonaute and rapid remodeling of the microRNA repertoire. *J. Exp. Med.* 210, 417–432. doi: 10.1084/jem.20111717
- Calin, G. A., Dumitru, C. D., Shimizu, M., Bichi, R., Zupo, S., Noch, E., et al. (2002). Frequent deletions and down-regulation of microRNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc. Natl. Acad. Sci. U.S.A.* 99, 15524–15529. doi: 10.1073/pnas.242606799
- Carthew, R. W., and Sontheimer, E. J. (2009). Origins and mechanisms of miRNAs and siRNAs. *Cell* 136, 642–655. doi: 10.1016/j.cell.2009.01.035
- Ceribelli, A., Yao, B., Dominguez-Gutierrez, P. R., and Chan, E. K. (2011). Lupus T cells switched on by DNA hypomethylation via microRNA? *Arthritis Rheum.* 63, 1177–1181. doi: 10.1002/art.30192

- Chen, C. Z., Li, L., Lodish, H. F., and Bartel, D. P. (2004). MicroRNAs modulate hematopoietic lineage differentiation. *Science* 303, 83–86. doi: 10.1126/science.1091903
- Chi, S. W., Zang, J. B., Mele, A., and Darnell, R. B. (2009). Argonaute HITS-CLIP decodes microRNA-mRNA interaction maps. *Nature* 460, 479–486. doi: 10.1038/nature08170
- Chong, M. M., Rasmussen, J. P., Rudensky, A. Y., and Littman, D. R. (2008). The RNaseIII enzyme Droscha is critical in T cells for preventing lethal inflammatory disease. *J. Exp. Med.* 205, 2005–2017. doi: 10.1084/jem.20081219
- Cimmino, A., Calin, G. A., Fabbri, M., Iorio, M. V., Ferracin, M., Shimizu, M., et al. (2005). miR-15 and miR-16 induce apoptosis by targeting BCL2. *Proc. Natl. Acad. Sci. U.S.A.* 102, 13944–13949. doi: 10.1073/pnas.0506654102
- Cobb, B. S., Hertweck, A., Smith, J., O'Connor, E., Graf, D., Cook, T., et al. (2006). A role for Dicer in immune regulation. *J. Exp. Med.* 203, 2519–2527. doi: 10.1084/jem.20061692
- Cobb, B. S., Nesterova, T. B., Thompson, E., Hertweck, A., O'Connor, E., Godwin, J., et al. (2005). T cell lineage choice and differentiation in the absence of the RNase III enzyme Dicer. *J. Exp. Med.* 201, 1367–1373. doi: 10.1084/jem.20050572
- Costinean, S., Sandhu, S. K., Pedersen, I. M., Tili, E., Trotta, R., Perrotti, D., et al. (2009). Src homology 2 domain-containing inositol-5-phosphatase and CCAAT enhancer-binding protein beta are targeted by miR-155 in B cells of Emicro-miR-155 transgenic mice. *Blood* 114, 1374–1382. doi: 10.1182/blood-2009-05-220814
- Costinean, S., Zanoni, N., Pekarsky, Y., Tili, E., Volinia, S., Heerema, N., et al. (2006). Pre-B cell proliferation and lymphoblastic leukemia/high-grade lymphoma in E(mu)-miR155 transgenic mice. *Proc. Natl. Acad. Sci. U.S.A.* 103, 7024–7029. doi: 10.1073/pnas.0602266103
- Divekar, A. A., Dubey, S., Gangalum, P. R., and Singh, R. R. (2010). Dicer insufficiency and microRNA-155 overexpression in lupus regulatory T cells: an apparent paradox in the setting of an inflammatory milieu. *J. Immunol.* 186, 924–930. doi: 10.4049/jimmunol.1002218
- Doran, J., and Strauss, W. M. (2007). Bio-informatic trends for the determination of miRNA-target interactions in mammals. *DNA Cell Biol.* 26, 353–360. doi: 10.1089/dna.2006.0546
- Dorsett, Y., McBride, K. M., Jankovic, M., Gazumyan, A., Thai, T. H., Robbiani, D. F., et al. (2008). MicroRNA-155 suppresses activation-induced cytidine deaminase-mediated Myc-Igh translocation. *Immunity* 28, 630–638. doi: 10.1016/j.immuni.2008.04.002
- Du, C., Liu, C., Kang, J., Zhao, G., Ye, Z., Huang, S., et al. (2009). MicroRNA miR-326 regulates TH-17 differentiation and is associated with the pathogenesis of multiple sclerosis. *Nat. Immunol.* 10, 1252–1259. doi: 10.1038/ni.1798
- Dudda, J. C., Salaun, B., Ji, Y., Palmer, D. C., Monnot, G. C., Merck, E., et al. (2013). MicroRNA-155 is required for effector CD8+ T cell responses to virus infection and cancer. *Immunity* 38, 742–753. doi: 10.1016/j.immuni.2012.12.006
- Fazi, F., Racanicchi, S., Zardo, G., Starnes, L. M., Mancini, M., Travaglini, L., et al. (2007). Epigenetic silencing of the myelopoiesis regulator microRNA-223 by the AML1/ETO oncoprotein. *Cancer Cell* 12, 457–466. doi: 10.1016/j.ccr.2007.09.020
- Fontana, L., Pelosi, E., Greco, P., Racanicchi, S., Testa, U., Liuzzi, F., et al. (2007). MicroRNAs 17-5p-20a-106a control monocytopoiesis through AML1 targeting and M-CSF receptor upregulation. *Nat. Cell Biol.* 9, 775–787. doi: 10.1038/ncb1613
- Fulci, V., Scappucci, G., Sebastiani, G. D., Giannitti, C., Franceschini, D., Meloni, F., et al. (2010). miR-223 is overexpressed in T-lymphocytes of patients affected by rheumatoid arthritis. *Hum. Immunol.* 71, 206–211. doi: 10.1016/j.humimm.2009.11.008
- Garzon, R., Heaphy, C. E., Havelange, V., Fabbri, M., Volinia, S., Tsao, T., et al. (2009). MicroRNA 29b functions in acute myeloid leukemia. *Blood* 114, 5331–5341. doi: 10.1182/blood-2009-03-211938
- Gracias, D. T., Stelekati, E., Hope, J. L., Boesteanu, A. C., Doering, T. A., Norton, J., et al. (2013). The microRNA miR-155 controls CD8(+). T cell responses by regulating interferon signaling. *Nat. Immunol.* 14, 593–602. doi: 10.1038/ni.2576
- Grishok, A., Pasquinelli, A. E., Conte, D., Li, N., Parrish, S., Ha, I., et al. (2001). Genes and mechanisms related to RNA interference regulate expression of the small temporal RNAs that control *C. elegans* developmental timing. *Cell* 106, 23–34. doi: 10.1016/S0092-8674(01)00431-7
- Hafner, M., Landthaler, M., Burger, L., Khorshid, M., Hausser, J., Berninger, P., et al. (2010). Transcriptome-wide identification of RNA-binding protein and microRNA target sites by PAR-CLIP. *Cell* 141, 129–141. doi: 10.1016/j.cell.2010.03.009
- Han, J., Lee, Y., Yeom, K. H., Nam, J. W., Heo, I., Rhee, J. K., et al. (2006). Molecular basis for the recognition of primary microRNAs by the Droscha-DGCR8 complex. *Cell* 125, 887–901. doi: 10.1016/j.cell.2006.03.043
- Hezova, R., Slaby, O., Faltejskova, P., Mikulkova, Z., Buresova, I., Raja, K. R., et al. (2010). microRNA-342, microRNA-191 and microRNA-510 are differentially expressed in T regulatory cells of type 1 diabetic patients. *Cell. Immunol.* 260, 70–74. doi: 10.1016/j.cellimm.2009.10.012
- Hou, J., Wang, P., Lin, L., Liu, X., Ma, F., An, H., et al. (2009). MicroRNA-146a feedback inhibits RIG-I-dependent Type I IFN production in macrophages by targeting TRAF6, IRAK1, and IRAK2. *J. Immunol.* 183, 2150–2158. doi: 10.4049/jimmunol.0900707
- Hutvagner, G., McLachlan, J., Pasquinelli, A. E., Bálint, E., Tuschl, T., and Zamore, P. D. (2001). A cellular function for the RNA-interference enzyme Dicer in the maturation of the let-7 small temporal RNA. *Science* 293, 834–838. doi: 10.1126/science.1062961
- Hutvagner, G., and Zamore, P. D. (2002). A microRNA in a multiple-turnover RNAi enzyme complex. *Science* 297, 2056–2060. doi: 10.1126/science.1073827
- Johnnidis, J. B., Harris, M. H., Wheeler, R. T., Stehling-Sun, S., Lam, M. H., Kirak, O., et al. (2008). Regulation of progenitor cell proliferation and granulocyte function by microRNA-223. *Nature* 451, 1125–1129. doi: 10.1038/nature06607
- Junker, A. (2011). Pathophysiology of translational regulation by microRNAs in multiple sclerosis. *FEBS Lett.* 585, 3738–3746. doi: 10.1016/j.febslet.2011.03.052
- Junker, A., Hohlfeld, R., and Meinel, E. (2010). The emerging role of microRNAs in multiple sclerosis. *Nat. Rev. Neurol.* 7, 56–59. doi: 10.1038/nrneuro.2010.179
- Junker, A., Krumbholz, M., Eisele, S., Mohan, H., Augstein, F., Bittner, R., et al. (2009). MicroRNA profiling of multiple sclerosis lesions identifies modulators of the regulatory protein CD47. *Brain* 132, 3342–3352. doi: 10.1093/brain/awp300
- Kang, S. G., Liu, W. H., Lu, P., Jin, H. Y., Lim, H. W., Shepherd, J., et al. (2013). MicroRNAs of the miR-17 approximately 92 family are critical regulators of T(FH) differentiation. *Nat. Immunol.* 14, 849–857. doi: 10.1038/ni.2648
- Ketting, R. E., Fischer, S. E., Bernstein, E., Sijen, T., Hannon, G. J., and Plasterk, R. H. (2001). Dicer functions in RNA interference and in synthesis of small RNA involved in developmental timing in *C. elegans*. *Genes Dev.* 15, 2654–2659. doi: 10.1101/gad.927801
- Koralov, S. B., Muljo, S. A., Galler, G. R., Krek, A., Chakraborty, T., Kanellopoulou, C., et al. (2008). Dicer ablation affects antibody diversity and cell survival in the B lymphocyte lineage. *Cell* 132, 860–874. doi: 10.1016/j.cell.2008.02.020
- Kuchen, S., Resch, W., Yamane, A., Kuo, N., Li, Z., Chakraborty, T., et al. (2010). Regulation of microRNA expression and abundance during lymphopoiesis. *Immunity* 32, 828–839. doi: 10.1016/j.immuni.2010.05.009
- Kurowska-Stolarska, M., Alivernini, S., Ballantine, L. E., Asquith, D. L., Millar, N. L., Gilchrist, D. S., et al. (2011). MicroRNA-155 as a proinflammatory regulator in clinical and experimental arthritis. *Proc. Natl. Acad. Sci. U.S.A.* 108, 11193–11198. doi: 10.1073/pnas.1019536108
- Lee, Y., Ahn, C., Han, J., Choi, H., Kim, J., Yim, J., et al. (2003). The nuclear RNase III Drosha initiates microRNA processing. *Nature* 425, 415–419. doi: 10.1038/nature01957
- Lee, Y., Jeon, K., Lee, J. T., Kim, S., and Kim, V. N. (2002). MicroRNA maturation: stepwise processing and subcellular localization. *EMBO J.* 21, 4663–4670. doi: 10.1093/emboj/cdf476
- Lee, Y., Kim, M., Han, J., Yeom, K. H., Lee, S., Baek, S. H., et al. (2004). MicroRNA genes are transcribed by RNA polymerase II. *EMBO J.* 23, 4051–4060. doi: 10.1038/sj.emboj.7600385
- Leung, A. K., Young, A. G., Bhutkar, A., Zheng, G. X., Bosson, A. D., Nielsen, C. B., et al. (2011). Genome-wide identification of Ago2 binding sites from mouse embryonic stem cells with and without mature microRNAs. *Nat. Struct. Mol. Biol.* 18, 237–244. doi: 10.1038/nsmb.1991
- Lewis, B. P., Burge, C. B., and Bartel, D. P. (2005). Conserved seed pairing, often flanked by adenosines, indicates that thousands of human genes are microRNA targets. *Cell* 120, 15–20. doi: 10.1016/j.cell.2004.12.035
- Li, Q. J., Chau, J., Ebert, P. J., Sylvester, G., Min, H., Liu, G., et al. (2007). miR-181a is an intrinsic modulator of T cell sensitivity and selection. *Cell* 129, 147–161. doi: 10.1016/j.cell.2007.03.008

- Lind, E. F., Elford, A. R., and Ohashi, P. S. (2013). Micro-RNA 155 is required for optimal CD8+ T cell responses to acute viral and intracellular bacterial challenges. *J. Immunol.* 190, 1210–1216. doi: 10.4049/jimmunol.1202700
- Lingel, A., Simon, B., Izaurralde, E., and Sattler, M. (2003). Structure and nucleic-acid binding of the *Drosophila* Argonaute 2 PAZ domain. *Nature* 426, 465–469. doi:10.1038/nature02123
- Liston, A., Lu, L. F., O'Carroll, D., Tarakhovskiy, A., and Rudensky, A. Y. (2008). Dicer-dependent microRNA pathway safeguards regulatory T cell function. *J. Exp. Med.* 205, 1993–2004. doi: 10.1084/jem.20081062
- Loeb, G. B., Khan, A. A., Canner, D., Hiatt, J. B., Shendure, J., Darnell, R. B., et al. (2012). Transcriptome-wide miR-155 binding map reveals widespread noncanonical microRNA targeting. *Mol. Cell* 48, 760–770. doi: 10.1016/j.molcel.2012.10.002
- Lu, L. F., Boldin, M. P., Chaudhry, A., Lin, L. L., Taganov, K. D., Hanada, T., et al. (2010). Function of miR-146a in controlling Treg cell-mediated regulation of Th1 responses. *Cell* 142, 914–929. doi: 10.1016/j.cell.2010.08.012
- Lu, L. F., Thai, T. H., Calado, D. P., Chaudhry, A., Kubo, M., Tanaka, K., et al. (2009). Foxp3-dependent microRNA155 confers competitive fitness to regulatory T cells by targeting SOCS1 protein. *Immunity* 30, 80–91. doi: 10.1016/j.immuni.2008.11.010
- Lund, E., Guttinger, S., Calado, A., Dahlberg, J. E., and Kutay, U. (2004). Nuclear export of microRNA precursors. *Science* 303, 95–98. doi: 10.1126/science.1090599
- Lytle, J. R., Yario, T. A., and Steitz, J. A. (2007). Target mRNAs are repressed as efficiently by microRNA-binding sites in the 5' UTR as in the 3' UTR. *Proc. Natl. Acad. Sci. U.S.A.* 104, 9667–9672. doi: 10.1073/pnas.0703820104
- Marcucci, G., Radmacher, M. D., Maharry, K., Mrózek, K., Ruppert, A. S., Paschka, P., et al. (2008). MicroRNA expression in cytogenetically normal acute myeloid leukemia. *N. Engl. J. Med.* 358, 1919–1928. doi: 10.1056/NEJMoa074256
- Mi, S., Lu, J., Sun, M., Li, Z., Zhang, H., Neilly, M. B., et al. (2007). MicroRNA expression signatures accurately discriminate acute lymphoblastic leukemia from acute myeloid leukemia. *Proc. Natl. Acad. Sci. U.S.A.* 104, 19971–19976. doi: 10.1073/pnas.0709313104
- Morin, R. D., O'Connor, M. D., Griffith, M., Kuchenbauer, F., Delaney, A., Prabhu, A. L., et al. (2008). Application of massively parallel sequencing to microRNA profiling and discovery in human embryonic stem cells. *Genome Res.* 18, 610–621. doi: 10.1101/gr.7179508
- Mourelatos, Z., Dostie, J., Paushkin, S., Sharma, A., Charroux, B., Abel, L., et al. (2002). miRNPs: a novel class of ribonucleoproteins containing numerous microRNAs. *Genes Dev.* 16, 720–728. doi: 10.1101/gad.974702
- Muljo, S. A., Ansel, K. M., Kanelloupolou, C., Livingston, D. M., Rao, A., and Rajewsky, K. (2005). Aberrant T cell differentiation in the absence of Dicer. *J. Exp. Med.* 202, 261–269. doi: 10.1084/jem.20050678
- Nakasa, T., Miyaki, S., Okubo, A., Hashimoto, M., Nishida, K., Ochi, M., et al. (2008). Expression of microRNA-146 in rheumatoid arthritis synovial tissue. *Arthritis Rheum.* 58, 1284–1292. doi: 10.1002/art.23429
- Nilsen, T. W. (2007). Mechanisms of microRNA-mediated gene regulation in animal cells. *Trends Genet.* 23, 243–249. doi: 10.1016/j.tig.2007.02.011
- O'Carroll, D., Mecklenbrauker, I., Das, P. P., Santana, A., Koenig, U., Enright, A. J., et al. (2007). A Slicer-independent role for Argonaute 2 in hematopoiesis and the microRNA pathway. *Genes Dev.* 21, 1999–2004. doi: 10.1101/gad.1565607
- O'Connell, R. M., Chaudhuri, A. A., Rao, D. S., and Baltimore, D. (2009). Inositol phosphatase SHIP1 is a primary target of miR-155. *Proc. Natl. Acad. Sci. U.S.A.* 106, 7113–7118. doi: 10.1073/pnas.0902636106
- O'Connell, R. M., Kahn, D., Gibson, W. S., Round, J. L., Scholz, R. L., Chaudhuri, A. A., et al. (2010). MicroRNA-155 promotes autoimmune inflammation by enhancing inflammatory T cell development. *Immunity* 33, 607–619. doi: 10.1016/j.immuni.2010.09.009
- O'Connell, R. M., Taganov, K. D., Boldin, M. P., Cheng, G., and Baltimore, D. (2007). MicroRNA-155 is induced during the macrophage inflammatory response. *Proc. Natl. Acad. Sci. U.S.A.* 104, 1604–1609. doi: 10.1073/pnas.0610731104
- Oertli, M., Engler, D. B., Kohler, E., Koch, M., Meyer, T. F., and Müller, A. (2011). MicroRNA-155 is essential for the T cell-mediated control of *Helicobacter pylori* infection and for the induction of chronic Gastritis and Colitis. *J. Immunol.* 187, 3578–3586. doi: 10.4049/jimmunol.1101772
- Pedersen, I. M., Cheng, G., Wieland, S., Volinia, S., Croce, C. M., Chisari, F. V., et al. (2007). Interferon modulation of cellular microRNAs as an antiviral mechanism. *Nature* 449, 919–922. doi: 10.1038/nature06205
- Pillai, R. S., Bhattacharyya, S. N., and Filipowicz, W. (2007). Repression of protein synthesis by miRNAs: how many mechanisms? *Trends Cell Biol.* 17, 118–126. doi: 10.1016/j.tcb.2006.12.007
- Place, R. F., Li, L. C., Pookot, D., Noonan, E. J., and Dahiya, R. (2008). MicroRNA-373 induces expression of genes with complementary promoter sequences. *Proc. Natl. Acad. Sci. U.S.A.* 105, 1608–1613. doi: 10.1073/pnas.0707594105
- Ponomarev, E. D., Veremeyko, T., Barteneva, N., Krichevsky, A. M., and Weiner, H. L. (2010). MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP- α -PU.1 pathway. *Nat. Med.* 17, 64–70. doi: 10.1038/nm.2266
- Rodriguez, A., Vigorito, E., Clare, S., Warren, M. V., Couttet, P., Soond, D. R., et al. (2007). Requirement of bic/microRNA-155 for normal immune function. *Science* 316, 608–611. doi: 10.1126/science.1139253
- Sheedy, F. J., Palsson-McDermott, E., Hennessy, E. J., Martin, C., O'Leary, J. J., Ruan, Q., et al. (2010). Negative regulation of TLR4 via targeting of the proinflammatory tumor suppressor PDCD4 by the microRNA miR-21. *Nat. Immunol.* 11, 141–147. doi: 10.1038/ni.1828
- Stanczyk, J., Pedrioli, D. M., Brentano, F., Sanchez-Pernaute, O., Kolling, C., Gay, R. E., et al. (2008). Altered expression of MicroRNA in synovial fibroblasts and synovial tissue in rheumatoid arthritis. *Arthritis Rheum.* 58, 1001–1009. doi: 10.1002/art.23386
- Sullivan, C. S., and Ganem, D. (2005). MicroRNAs and viral infection. *Mol. Cell* 20, 3–7. doi: 10.1016/j.molcel.2005.09.012
- Sullivan, C. S., Grundhoff, A. T., Tevethia, S., Pipas, J. M., and Ganem, D. (2005). SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells. *Nature* 435, 682–686. doi: 10.1038/nature03576
- Taganov, K. D., Boldin, M. P., Chang, K. J., and Baltimore, D. (2006). NF- κ B-dependent induction of microRNA miR-146, an inhibitor targeted to signaling proteins of innate immune responses. *Proc. Natl. Acad. Sci. U.S.A.* 103, 12481–12486. doi: 10.1073/pnas.0605298103
- Takahashi, H., Kanno, T., Nakayama, S., Hirahara, K., Sciumè, G., Muljo, S. A., et al. (2012). TGF- β and retinoic acid induce the microRNA miR-10a, which targets Bcl-6 and constrains the plasticity of helper T cells. *Nat. Immunol.* 13, 587–595. doi: 10.1038/ni.2286
- Tang, Y., Luo, X., Cui, H., Ni, X., Yuan, M., Guo, Y., et al. (2009). MicroRNA-146A contributes to abnormal activation of the type I interferon pathway in human lupus by targeting the key signaling proteins. *Arthritis Rheum.* 60, 1065–1075. doi: 10.1002/art.24436
- Tay, Y., Zhang, J., Thomson, A. M., Lim, B., and Rigoutsos, I. (2008). MicroRNAs to Nanog, Oct4 and Sox2 coding regions modulate embryonic stem cell differentiation. *Nature* 455, 1124–1128. doi: 10.1038/nature07299
- Teng, G., Hakimpour, P., Landgraf, P., Rice, A., Tuschl, T., Casellas, R., et al. (2008). MicroRNA-155 is a negative regulator of activation-induced cytidine deaminase. *Immunity* 28, 621–629. doi: 10.1016/j.immuni.2008.03.015
- Thai, T. H., Calado, D. P., Casola, S., Ansel, K. M., Xiao, C., Xue, Y., et al. (2007). Regulation of the germinal center response by microRNA-155. *Science* 316, 604–608. doi: 10.1126/science.1141229
- Van Wynsberghe, P. M., Chan, S. P., Slack, F. J., and Pasquinelli, A. E. (2011). Analysis of microRNA expression and function. *Methods Cell Biol.* 106, 219–252. doi: 10.1016/B978-0-12-544172-8.00008-6
- Ventura, A., Young, A. G., Winslow, M. M., Lintault, L., Meissner, A., Erkeland, S. J., et al. (2008). Targeted deletion reveals essential and overlapping functions of the miR-17 through 92 family of miRNA clusters. *Cell* 132, 875–886. doi: 10.1016/j.cell.2008.02.019
- Vigorito, E., Perks, K. L., Abreu-Goodger, C., Bunting, S., Xiang, Z., Kohlhaas, S., et al. (2007). microRNA-155 regulates the generation of immunoglobulin class-switched plasma cells. *Immunity* 27, 847–859. doi: 10.1016/j.immuni.2007.10.009
- Xiao, C., Calado, D. P., Galler, G., Thai, T. H., Patterson, H. C., Wang, J., et al. (2007). MiR-150 controls B cell differentiation by targeting the transcription factor c-Myb. *Cell* 131, 146–159. doi: 10.1016/j.cell.2007.07.021
- Xiao, C., Srinivasan, L., Calado, D. P., Patterson, H. C., Zhang, B., Wang, J., et al. (2008). Lymphoproliferative disease and autoimmunity in mice with increased miR-17-92 expression in lymphocytes. *Nat. Immunol.* 9, 405–414. doi: 10.1038/ni1575
- Yang, H., Wang, H., Shivalila, C. S., Cheng, A. W., Shi, L., and Jaenisch, R. (2013). One-step generation of mice carrying reporter and conditional alleles by CRISPR/Cas-mediated genome engineering. *Cell* 154, 1370–1379. doi: 10.1016/j.cell.2013.08.022

- Yi, R., Qin, Y., Macara, I. G., and Cullen, B. R. (2003). Exportin-5 mediates the nuclear export of pre-microRNAs and short hairpin RNAs. *Genes Dev.* 17, 3011–3016. doi: 10.1101/gad.1158803
- Yuan, Y., Kasar, S., Underbayev, C., Vollenweider, D., Salerno, E., Kotenko, S. V., et al. (2012). Role of microRNA-15a in autoantibody production in interferon-augmented murine model of lupus. *Mol. Immunol.* 52, 61–70. doi: 10.1016/j.molimm.2012.04.007
- Yu, D., Rao, S., Tsai, L. M., Lee, S. K., He, Y., Sutcliffe, E. L., et al. (2009). The transcriptional repressor Bcl-6 directs T follicular helper cell lineage commitment. *Immunity* 31, 457–468. doi: 10.1016/j.immuni.2009.07.002
- Zhao, J. L., Rao, D. S., Boldin, M. P., Taganov, K. D., O'Connell, R. M., and Baltimore, D. (2011). NF-kappaB dysregulation in microRNA-146a-deficient mice drives the development of myeloid malignancies. *Proc. Natl. Acad. Sci. U.S.A.* 108, 9184–9189. doi: 10.1073/pnas.1105398108
- Zhao, X., Tang, Y., Qu, B., Cui, H., Wang, S., Wang, L., et al. (2010). MicroRNA-125a contributes to elevated inflammatory chemokine RANTES levels via targeting KLF13 in systemic lupus erythematosus. *Arthritis Rheum.* 62, 3425–3435. doi: 10.1002/art.27632
- Zhou, X., Jeker, L. T., Fife, B. T., Zhu, S., Anderson, M. S., McManus, M. T., et al. (2008). Selective miRNA disruption in T reg cells leads to uncontrolled autoimmunity. *J. Exp. Med.* 205, 1983–1991. doi: 10.1084/jem.20080707
- Zisoulis, D. G., Lovci, M. T., Wilbert, M. L., Hutt, K. R., Liang, T. Y., Pasquinelli, A. E., et al. (2010). Comprehensive discovery of endogenous Argonaute binding sites in *Caenorhabditis elegans*. *Nat. Struct. Mol. Biol.* 17, 173–179. doi: 10.1038/nsmb.1745

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 March 2014; accepted: 26 May 2014; published online: 12 June 2014.

Citation: Lee H-M, Nguyen DT and Lu L-F (2014) Progress and challenge of microRNA research in immunity. *Front. Genet.* 5:178. doi: 10.3389/fgene.2014.00178

This article was submitted to Non-Coding RNA, a section of the journal *Frontiers in Genetics*.

Copyright © 2014 Lee, Nguyen and Lu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.