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REVIEW ARTICLE

MicroRNAs in Human Diseases: From Autoimmune Diseases to Skin, Psychiatric and Neurodegenerative Diseases

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MicroRNAs (miRNAs) are small noncoding RNA molecules that negatively regulate gene expression via degradation or translational repression of their target messenger RNAs (mRNAs). Recent studies have clearly demonstrated that miRNAs play critical roles in several biologic processes, including cell cycle, differentiation, cell development, cell growth, and apoptosis and that miRNAs are highly expressed in regulatory T (Treg) cells and a wide range of miRNAs are involved in the regulation of immunity and in the prevention of autoimmunity. It has been increasingly reported that miRNAs are associated with various human diseases like autoimmune disease, skin disease, neurological disease and psychiatric disease. Recently, the identification of miRNAs in skin has added a new dimension in the regulatory network and attracted significant interest in this novel layer of gene regulation. Although miRNA research in the field of dermatology is still relatively new, miRNAs have been the subject of much dermatological interest in skin morphogenesis and in regulating angiogenesis. In addition, miRNAs are moving rapidly center stage as key regulators of neuronal development and function in addition to important contributions to neurodegenerative disorder. Moreover, there is now compelling evidence that dysregulation of miRNA networks is implicated in the development and onset of human neruodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette's syndrome, Down syndrome, depression and schizophrenia. In this review, I briefly summarize the current studies about the roles of miRNAs in various autoimmune diseases, skin diseases, psychoneurological disorders and mental stress.

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INTRODUCTION

The great discovery of microRNAs (miRNAs) has revolutionized current cell biology and medical science (1,2). miRNAs represent a large family of endogenous noncoding RNAs that comprise a fundamental layer of post-transcriptional regulation of gene expression (3,4). miRNAs are found in almost all species: virus, plants, nematodes, fly, fish, mouse, human, and are implicated in a wide array of cellular and developmental process (5). It has recently been shown that the main function of miRNAs in mammalian system is to decrease target messenger RNA (mRNA) levels (6). Recent evidence also suggests that the number of unique miRNA genes in human exceed 1,000, and may be as high as 20,000 and it is estimated that 20～30% of all human mRNA are miRNA targets (7). More recently, miRNA are also proving to be an important link between the innate and adaptive immune systems, and their dysregulation might have a role in the pathogenesis of various diseases (3,8,9).

miRNAs constitute a class of small endogenous noncoding RNAs of 19～23 nucleotides that negatively regulate gene expression (4,10). They are an abundant class of gene regulatory molecules in multicellular organisms and modulate the expression of many protein-coding genes (4,11,12). They are transcribed as a huge double-stranded primary transcript (pri-miR) by RNA polymerase II. Subsequently, nuclear enzyme Drosha (also known as ribonuclease III) and Pasha convert this precursor into a double-stranded miRNA precursor of

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~70 nulcleotide (pre-miR), which is next transported into the cytoplasm by a mechanisms involving the protein Exportin 5 (3,4,9,13). Finally, Dicer enzyme processes this precursor into the 22-nucleotide double-stranded miRNA. This duplex is then unwinded, and the leading strand ("guide strand"), one of the two strands, is incorporated into the RNA-induced silencing complex (RISC), which is comprise Agonaute and other proteins (3,13,14). miRNAs incorporated in the RISC are able to bind to the 3' untranslated region (UTR) of target mRNAs causing a block of translation or mRNA degradation depending on the level of complementarity (4,11). The other strand so-called "passenger strand" is degraded (3,4,15). Recent studies have clearly demonstrated that miRNAs play critical roles in several biologic processes, including cell differentiation, cell development, cell growth, and apoptosis by regulating gene expression through either the inhibition of mRNA translation or the induction of its degradation (9,16,17). The analysis of human neoplasias of different tissue origins has shown deregulated miRNA expression (18-20). miRNA expression can be induced or expressed by a variety of stimuli and mechanisms. These stimuli include direct transcriptional activation or repression from transcriptional enhancers, epigenetic modifications of the genome, genomic amplification or deletion, cellular stress and inflammatory stimuli (6,8,16,20). The effect of inducing or repressing miRNA expression can influence most biological processes, such as apoptosis, cell fate specification, cell proliferation, DNA repair, cell cycle, and DNA methylation (17,20,21).

As mentioned above, miRNAs also have an essential role in both the innate and adaptive immune system. Proper miRNA expression is required for correct differentiation of immune cells (22). Immune responses are symphonies of molecular and cellular interactions, with each player doing its part to produce the composite behavior we see as effective host defense, or when discoordinated, as immunopatholgy or immunodeficiency (23).

Lu et al. performed a comprehensive analysis to the human miRNA disease association data, which is manually collected from publication (24). Furthermore, importantly, it has been increasingly reported that miRNAs are associated with various human diseases like autoimmune diseases (25-30), skin diseases (15,31-33), neurological diseases (34,35), psychiatric diseases (36-38), cancer (3,17,39-43), cardiovascular diseases (44-47), asthma (48-50) and microbial infection (8,51-55).

Recent studies have revealed links between miRNA function and autoimmunity and have also showed the importance of miRNA regulation in safeguarding Treg cell function in the prevention of autoimmunity (9,56-60). Cobb et al. reported that regulatory T (Treg) cells have a miRNA expression profile distinct from conventional $CD4^+$ T cells (58). Moreover, Zhou et al. developed mice with conditional Dicer knockout within the Treg cells lineage and used these mice to monitor Treg cell development and function in the absence of functional miRNA (57). They reported that although thymic Treg cells developed normally in these miRNA-deficient mice, the cells exhibited altered differentiation and dysregulaltion in the periphery (57). Specifically, the Dicer-deficient Treg cells failed to remain stable and altered expression of multiple genes and proteins, including neuropilin 1, glucocorticoid-induced tumor necrosis factor receptor, and cytotoxic T lymphocytes antigen 4 (CTLA-4) associated with the Treg cells fingerprint, including Foxp3 (9,56-58). In addition to their instability, Dicer-deficient Treg cells lost suppressor activity *in vivo*, and the mice rapidly developed fatal systemic autoimmune disease resembling the Foxp3 KO phenotype (57). Interestingly, Liston et al. reported that in disease-free $Foxp3^{Cre/wt}Dicer^{fl/fl}$ mice, Dicer-deficient Treg cells retained some suppressive activity, albeit reduced compared to wild- type mice (56). However, in diseased $Foxp^{Cre}Dicer^{fl/fl}$ mice exhibiting inflammatory conditions, Dicer-deficient Treg cells were completely devoid of any suppressor activity (56). Depletion of miRNA within Treg cell lineage resulted in fatal autoimmune syndrome indistinguishable from that observed in Foxp3 mutant mice devoid of Treg cells (56). These data suggest that miRNAs preserve stable Treg cell function under inflammatory conditions and that Treg cells are indispensable for preventing autoimmunity. Moreover, recently, numerous studies provide evidence that Treg cells play important roles in human autoimmune diseases (9,31,59,61). It is becoming increasingly clear from cell culture and animal studies that proper miRNA regulation is critical for the prevention of autoimmunity and normal immune function. However, it is not yet well understood whether miRNA dysregulation could play a role in autoimmune disease pathogenesis in human patients. Several recent studies have uncovered possible roles for miRNAs regulation in autoimmune disease, specifically rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), asthma, inflammatory bowel disease (IBD) including Crohn's disease (CD) and ulcerative colitis (UC), autoimmune diabetes and psoriasis (9,21,60,61).

Recently, the identification of miRNAs in skin has added a new dimension in the regulatory network and attracted sig-

nificant interest in this novel layer of gene regulation (32,62,63). Although miRNA research in the field of dermatology is still relatively new, miRNAs have been the subject of much dermatological interest. miRNAs play a key role in skin morphogenesis and in regulating angiogenesis (62).

Aging-related neurodegenerative diseases are the culmination of many different genetic and environmental influences. Recent evidence suggests that miRNAs may be contributing factor in neurodegeneration (64). Although discovered in the framework of worm development, miRNA are now appreciated to play a dynamic role in many mammalian brain-related biochemical pathway, including neuroplasticity and stress responses (64). Research about miRNA in the context of neurodegeneration is accumulating rapidly (36,37,65-70). Psychiatric illnesses are disabling disorders with poorly understood underlying pathophysiologies (66). Interestingly, there is now compelling evidence that dysregulation of miRNA networks is implicated in the development and onset of human neruodegenerative diseases, such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), Tourette's syndrome, Down syndrome (DS), depression and schizophrenia (36,38,67-74). In this review, I briefly summarize the current knowledge of roles of miRNAs in autoimmune diseases, skin disease, and psychiatric and neurological disorders.

miRNAs IN RHEUMATOID ARTHRITIS (RA)

RA is a common chronic inflammatory disease characterized by raidographic joint destruction with severe functional deterioration and high mortality (9,75). A hallmark pathological feature of RA is the infiltration and accumulation of T cells in the synovium of joint (9,75). As discussed, dysregulation of miRNAs has been shown to be a hallmark of cancer and now investigators are examining their role in the pathogenesis of inflammatory diseases. Abnormal expression of miRNAs has also been found in patients with RA (26). Interestingly, miR-146 and miR-155 have been a particular focus for investigators, and these two miRNAs have been shown to be induced by proinflammatory stimuli such as Toll-like receptors (TLRs), IL-1 and, TNF-α (76-79). They have also been detected in synovial fibroblasts and rheumatoid synovial tissue (76). Both have multiple targets, with miR-146 inhibiting TLR signalling and miR-155 regulating Th1 cells and also, interestingly, positively regulating mRNA for TNF-α (76).

Stanczyk et al. provided the first description of increased expression of miR-146 and miR-155 in RA synovial fibroblasts compared with osteoarthritis synovial fibroblasts (79). Furthermore, compared with monocytes from RA peripheral blood, RA synovial fluid monocytes displayed higher levels of miR-155 (79). Additionally, transfection of miR-155 in RA synovial fibroblasts revealed matrix metalloproteinase 3 as a potential target of miR-155, suggesting that miR-155 might modulate downstream tissue damage (79). Recently, Nakasa et al. showed that miR-146 was highly expressed in RA synovial tissue compared with osteoarthritis and normal synovial tissue (78). *In situ* hybridization studies revealed that miR-146 expression could be detected in RA synovial tissue primarily in $CD68^+$ macrophages, but also in some $CD3^+$ T cell subsets and $CD79a^+$ B cells (78). Pauley et al. demonstrated differential expression of miRNA in peripheral blood mononuclear cells (PBMCs) of RA, with between 1.8-fold and 2.6-fold increase in miR-16, miR-132, miR-146 and miR-155 expression, whereas miRNA let-7a expression was not significantly different, as compared with healthy control individuals (77). Interestingly, increased miR-16 and miR-146 expression correlated with active disease in RA patients. However, there was no correlation between the observed increase in miRNA expression and the patients' age, race, or medications (77). In addition, two targets of miR-146a, namely TNF receptor- associated factor 6 (TRAF6) and IL-1 receptor-associated kinase 1 (IRAK-1), were similarly expressed between RA patients and control individuals, despite increased expression of miR-146a in patients with RA (77). *In vitro* studies revealed that repression of TRAF6 and/or IRAK1 in THP-1 human monocytes resulted in up to an 86% reduction in TNF-α production, implicating that normal miR-146a function could be critical for the regulation of TNF-α production (77). Given that prolonged TNF-α production is known to play a role in RA pathogenesis, these data suggest a possible mechanisms contributing to RA pathogenesis, where miR-146 is up-regulated but unable to properly regulate TRAF-6/IRAK 1, leading to prolonged TNF-α production in RA patients (77).

Recently, Luo et al. reported that miRNAs are key players in rheumatic diseases by regulating major pathogenic molecules, such as TNF, central signal pathways, such as type 1 IFN pathway and critical immunuoregulatory cells, such as Treg cells (80). They also reported that in animals, blockade of miRNA maturation by the deletion of Dicer or Drosha, interference with miRNA function by the mutation of Roquin and the altered expression of individual miRNA (miR-146a) or miRNA cluster (miR-17-92) all lead to the development of

autoimmune disease (80). Growing evidence also reveals the differential expression of certain immunity-regulating miRNA in rheumatoid patients (26,80). However, RA is an autoimmune pathology the etiology of which is still obscure. Although a multifactorial pathogenesis has been hypothesized, the precise mechanisms leading to the disease are still poorly understood at the molecular level (26). Recently, miRNA expression profile analysis highlighted that miR-223 is the only miRNA that is strikingly deregulated in peripheral T cells from RA patients compared with healthy donors (30). Further analysis by quantitative reverse transcription-polymerase chain analysis confirmed that miR-223 is over-expressed in T cells from RA patients compared with healthy donors (30). Moreover, purification of different T cell population from RA patients highlights that miR-223 is expressed at higher levels in naive $CD4^+$ cells, whereas its expression is barely detectable in Th-17 cells (30). A deeper analysis of the biologic functions and effects of the expression of miR-223 in T cells is needed to clarify the exact link between these findings and the disease. More recently, Li et al. investigated the expression pattern and function of miRNA in $CD4^+$ T cells from patients with RA (75). miRNA expression profile analysis revealed that miR-146a expression was significantly up-regulated while miR-363 and miR-498 were down-regulated in $CD4^+$ T cells of RA patients (75). Interestingly, the level of miR-146a expression was positively correlated with level of TNF-α, and *in vitro* studies showed TNF-α up-regulated miR-146a expression in T cells (75). Moreover, miR-146a over-expression was found to be suppress Jurkat T cell apoptosis. Additionally, transcriptome analysis of miR-146a over-expression in T cells identified Fas associated factor 1 (FAF1) as miR-146a-regulated gene, which was critically involved in modulating T cell apoptosis (75). These findings that miR-146a over-expression suppresses T cell apoptosis indicate a role of miR-146a in RA pathogenesis and provide potential novel therapeutic targets.

miRNAs IN SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

SLE is a systemic inflammatory autoimmune disease characterized by the presence of autoantibodies against numerous self-antigens including chromatin, ribonucleoproteins, and phospholipids (59,81). Clinical manifestations of SLE are diverse and include malar rash, photosensitivity, arthritis, glomerulonephritis, and neurological disorders (59,81,82). SLE is also characterized by loss of tolerance to self-antigens and activation of autoreactive T cells and Treg cells play a critical role in controlling the activation of autoreactive T cells (9,59,83). Several studies have found numerical and/or functional insufficiency of Treg cells in humans and mice with SLE (59,83). Dai et al. reported the findings of their microarray expression analysis of miRNA in PBMCs from 23 SLE patients and 10 healthy controls (82). In these SLE patients, 7 miRNAs (miR-196a, miR-17-5p, miR-409-3p, miR-141, miR-383, miR-112, and miR-184) were down-regulated and 9 miRNAs (miR-189, miR-61, miR-78, miR-21, miR-142-3p, miR-342, miR-299-3p, miR-198, and miR-298) were up-regulated as compared with healthy controls (82). These data suggest a possible role for miRNA as diagnostic markers and as factors involved in the pathogenesis of SLE. Currently, Divekar et al. investigated mechanisms of potential Treg cells defects in SLE using lupus-prone MRL-$Fas^{lpr/lpr}$ (MRL/lpr) and congenic Fas-intact MRL-$Fas^{+/+}$ mice and in non-autoimmune C3H/HeOuj mice (83). Surprisingly, they found a significant increase in $CD4^+CD25^+Foxp3^+$ Treg cells in speen, lymph nodes, and thymus of lupus-prone mice, albeit with an altered phenotype ($CD62L^-CD69^+$) and with a reduced suppressive capacity, in the lymphoid organs of MRL strains compared wtih non-autoimmune C3H/HeOuj mice (83). In addition, the authors found a profund reduction in Dicer expression and an altered miRNA profile in MRL/lpr Treg cells. They also found that the reduced functional capacity of MRL Treg cells was associated with a charactieristic phenotype, i.e., increased CD69 and reduced CD62L expression (83). Unexpectedly, despite having a reduced level of Dicer, MRL/lpr Treg cells exhibited a significant overexpression of several miRNAs, including let-7a, let-7f, miR-16, miR-23, miR-23b, miR-27b, miR 27a and miR-155 (83). Moreover, simultaneous appearance of Dicer infsufficiency and miR-155 overexpression in diseased mice suggests a Dicer-independent alternative mechanisms of miRNA regulation under inflammatory conditions (83). Using computational and experimental approaches, they further identified miR-155 to regulate altered phenotype of Treg cells in SLE. Importantly, they reported that the progression to autoimmune disease is associated with increased miR-155 expression despite a marked reduction in Dicer expression in Treg cells from MRL/lpr mice (83). These data suggest a role of Dicer and miR-155 in conferring Treg cell defect in SLE. Currently, Mellor and Munn also reported that despite critical role of Treg cells in maintaining periperal toleracne, when Treg cells are isolated from

noninflammed lymphoid tissues or blood of helathy individuals they are functionally quiescent (resting), and must be activated to manifest functional suppressive activity (84). Conversely, under cetain inflammatory conditions, surpriingly, Treg cells may undergo rapid reprogramming to acquire helper/effector functions (84). Moreover, Treg cells and Foxp3 are heterogenous and Treg cells may promote pathology in autoimmune syndromes by undergoing reprogramming or manifesting less potent suppression (84). Taking together, identifying mechanisms underlying Treg c ell impairment in autoimmune diseases will open new avenues of modulating immune tolerance and suppressingdisease (83).

miRNAs IN DIABETES

Diabetes is the deadly global health problem. The discovery of miRNA and subsequent reports illustrating their roles in regulating glucose and lipid metabolism have opened up a novel mode of fine-tuning genes that control diverse facets of metabolic regulation (29). Maintenance of appropriate levels of circulatory glucose levels results from a balance between normal insulin secretion and action. Dysregulation at any step of this fine tuning is responsible for the initiation of type 1 diabetes and insulin resistance that culminates in type 2 diabetes (28,29). Apart from the various mechanistic regulators of insulin secretion and action, miRNAs have also emerged as novel regulator of these phenomena and hence appropriately referred to as "ribo-regulator of glucose homeostasis" (85). Along these lines, a major player that emerged as a significant mediator of insulin release and thereby of glucose homeostasis is the pancreatic islet specific miR-375 (29). It is one of the earliest miRNAs to be identified as possessing a validated functional role in the pancreas where it negatively regulates glucose-stimulated insulin release in a calcium independent manner (29). The authors found that over-expression of miR-375 led to significant reduced levels of Vtila protein (t-SNAREs yeast homologue 1A that is critical in insulin vesicle biogenesis and recycling) and the myotrophin (29). Quite interestingly, miR-375 was identified as the most abundant intra-islet miRNA (29). miR-375 appears to be the most well studied as far as the regulation of insulin release and glucose homeostasis is concerned. Very recent studies found 61 glucose regulated miRNAs from a total of 108 miRNAs in the mouse insulinoma cell line, MIN6 (29). Of these, most of the miRNAs up-regulated and only few that included miR-296, miR-184 and miR-160 were down-regulated

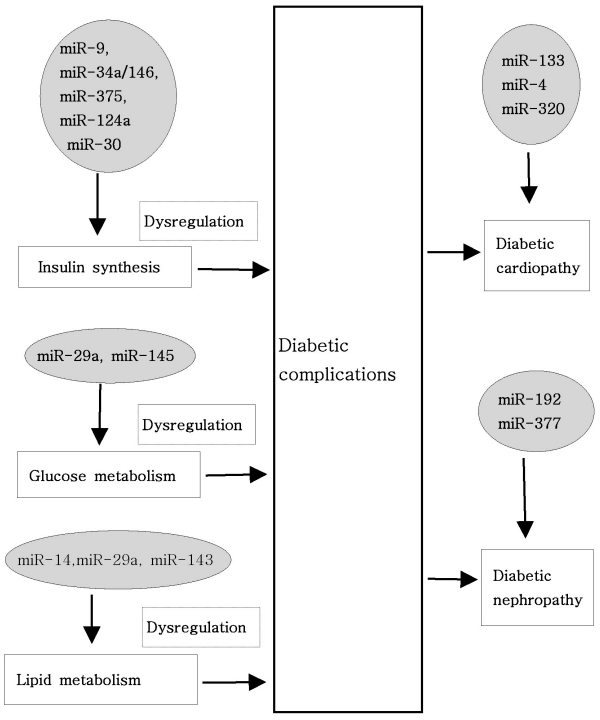

Figure 1. Various miRNAs are involved in diverse metabolic processes, diabetes and diabetic complications. A variety of miRNAs are involved in insulin synthesis, glucose metabolism and lipid metabolism. Dysregulations of diverse metabolic processes lead to diabetic complications, such as diabetic cardiopathy and diabetic nephropathy (See Text for details).

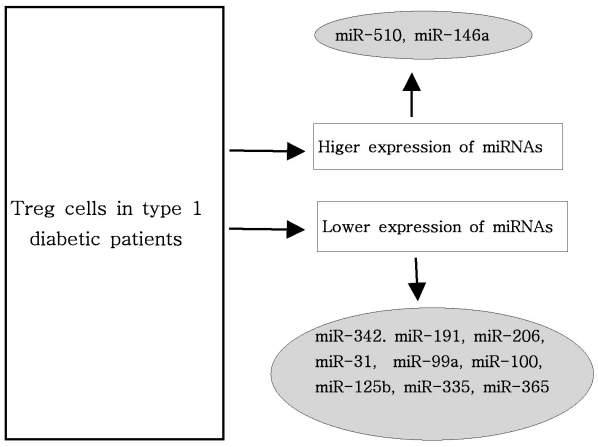

Figure 2. Changes of miRNA signatures of regulatory T (Treg) cells separated from peripheral blood of type 1 diabetic patients (See Text for details).

(29). Pandey et al. summarized features of the known roles of miRNAs in cellular functions (29). As shown in Fig. 1, the authors reported that various miRNAs have been identified to be critical in diverse metabolic process, dysregulation of which lead to diabetes and its complications (29): miRNAs involved in insulin synthesis are miR-9, miR-34a/146, miR-375, miR-124a, and miR-30d. miRNAs involved in glucose metabolism are miR-29a and miR-145. miRNAs involved in lipid metabolism are miR-14, mir-122, miR-143, miR-103/1l07 and miR-278 (29). As for diabetic complications, miRNAs involved in diabetic cardiomyopathy are miR-133, miR-1 and miR-320, and miRNAs involved in diabetic nephropathy are miR-192 and miR-377 (29).

As aformentioned, Treg cells are critical regulators of autoimmune diseases, including type 1 DM (9,31,59). It is hypothesized that Treg cell function can be influenced by changes in the expression of specific miRNAs. Recently, Hezova et al. performed miRNA profiling in a population of Treg cells separated from peripheral blood of five type 1 diabetic patients and six healthy donors (86). In Treg cells of diabetic patients they found significantly increase expression of miR-510 and decreased expression of both miR-342 and miR-191, as shown in Fig. 2 (86). When comparing Treg cells and conventional T cells, they revealed that Treg cells had significant higher expression of miR-146a and lower expression of eight specific miRNAs (miR-20b, miR-31, miR-99a, miR-100, miR-125b, miR-151, miR-335, and miR-365). This may be the first study demonstrating changes in miRNA expression profiles occurring in Treg cells of type 1 DM patients and a miRNAs signature of adult Treg cells (86).

DM impairs endothelial cell (EC) function and postischemic reparative neovascularization by molecular mechanisms that are not fully understood. A recent study showed that miR-503 expression in ECs is up-regulated in culture conditions mimicking DM (high D-glucose) and ischemia-associated starvation (low growth factors) and that miR-503 expression is increased in ischemic limb muscles of streptozotocin-diabetic mice and in ECs enriched from these muscles (25). The authors also investigated miR-503 and target gene expression in muscular specimens from the amputated ischemic legs of diabetic patients. In addition, they found that in diabetic muscles, miR-503 expression was remarkably higher and it inversely correlated with cdc25 protein expression, and that plasma miR-503 levels were also elevated in the diabetic individuals (25). These data suggest miR-503 as a possible therapeutic target in diabetic patients with critical limb ischemia.

miRNAs IN MULTIPLE SCLEROSIS (MS)

As a prototype of organ-specific autoimmune disease, MS is manifested by chronic inflammatory demyelination of the central nervous system (CNS) and is one of the foremost cause of nontraumatic neurological disability in young adults (87). The disease is clinically heterogenous, with abut 80% of patients developing the relapsing-remitting multiple sclerosis (RRMS) subtype (21,87,88). Because of limited understanding of the pathogenesis of MS and a lack of sensitive biomarkers, according to the present criteria, the diagnosis of MS still depends on repeated occurrence of the disease (87). In addition, the signs and symptoms of MS usually share considerable similarity with those of other CNS inflammatory diseases, such as neuromyelitis optica and this leads to considerable therapeutic and diagnostic difficulties (88). However, $CD4^+$ T cell-mediated autoimmunity has long been accepted as one of the most important aspects of MS pathogenesis, especially for the early initiation disease (87). Importantly, Keller et al. investigated the expression profiles of 866 human miRNAs (87). In detail, they analyzed the miRNA expression in blood cells of 20 patients with RRMS and 19 healthy controls using human miRNA microarray and the Geniom Real Time Analyzer platform. They identified 165 miRNAs that were significantly up- or down-regulated in patients with RRMS as compared to healthy controls (87). They also found that the best single miRNA marker, hsa-miR-145, allowed discriminating MS from controls with a specificity of 89.5%, a sensitivity of 90.0%, and an accuracy of 89.7%. Additionally, they found that a set of 48 miRNAs that was evaluated by radial basis function kernel support vector machines and 10-fold cross validation yielded a specificity of 95%, sensitivity of 97.6%, and an accuracy of 96.3%. While 43 of the 165 miRNAs deregulated in patients with MS have previously been related to other human disease, the remaining 122 miRNAs are exclusively associated with MS (87). These data suggest that miRNA expression signature may represent a potentially useful biomarker for the diagnosis for MS and that dysregulation of miRNA expression could play a role in the complex pathogenesis of MS.

As mentioned, defects in Treg-cell functions have been described in MS and a major goal of MS immunotherapy is to induce Treg cells in a physiological fashion (21). Clinical studies in MS patients showed that Treg cell dysfunction occurred in the initial stage of the disease (21). The immunosuppressive drugs including glatiramer acetate (GA) now

approved for the clinical treatment of MS work mainly by increasing the frequency of Treg cells or by changing the Th1-Th2 bias (88,89). GA is a mixture of synthetic polypeptides composed of four amino acids resembling myelin basic protein (89). Interestingly, miR-155 deficiency in Treg cells results in increased suppressor of cytokine signaling 1 (SOCS1) expression accompanied by impaired activation of signal transducer and activator of transcription 5 (STAT5) transcription factor in response to limiting amount of IL-2 (90). Foxp3 dependent regulation of miR-155 maintains competitive fitness of Treg cell subsets by targeting SOCS 1 (90). A recent study by Du et al. (88) identified Th-17 cell-associated miR-326, whose expression was highly correlated with disease severity in patients with MS and mice with experimental autoimmune encephalitis (EAE). *In vivo* silencing of miR-326 resulted in fewer Th-17 cells and mild EAE, and its overexpression led to more Th-17 cells and severe EAE (88). They also found that miR-326 promoted Th-17 differentiation by targeting Ets-1, a negative regulator of Th-17 differentiation. These results suggest a critical role for miR-326 in the regulation of Th-17 differentiation and the pathogenesis of MS. More recently, De Santis et al. performed a genome-wide expression analysis of human miRNAs in $CD4^{+}CD25^{high}$ *bona fide* Treg cells obtained from peripheral blood of MS patients and healthy donors (27). They found 23 human miRNAs differentially expressed between $CD4^{+}CD25^{high}$ *bona fide* Treg cells from MS patients vs. healthy donors, but, conversely, among the deregulated miRNAs, members of the miR-106b-25 were found downregulated in MS patients when compared to healthy donors in $CD4^{+}CD25^{high}$ $CD127^{dim/-}$ Treg cells (27). Interestingly, the ratio between Treg/Teff showed an enrichment of these miRNA in Treg cells derived from patients if compared to healthy controls (27). This is the first study that investigates miRNA expression profile in $CD4^{+}$ $CD25^{high}$ Treg cells isolated from peripheral blood of MS patients. These data suggest that the deregulation of this miRNA cluster may alter Treg cell activity in course of MS, by altering TGF-β biological functions and that the abnormal expression of miRNAs in Treg cells might play a role in the pathogenesis of MS (27). Emerging evidence suggest that miRNA dysregulation may contribute to the pathogenesis of MS. In the near future, further understanding of the role of miRNAs in intracellular signaling, the expression of proteins involved in immune response, modulation of cytokines and chemokines, adhesion and costimulatory molecules and the interplay between the immune system and CNS should help to define the role of miRNAs in autoimmunity, and provide an exciting framework for developing new biomarkers and new therapeutic interventions in MS (21).

miRNAs IN ASTHMA

Asthma is a chronic inflammatory disease of the airway, tissue remodeling, and a decline in respiratory function. The clinical condition is characterized by episodic breathlessness and wheezing, together with enhanced airway hyperresponsiveness (49). The traditional view that interindividual risk for asthma, like other complex disease, is determined solely by interactions between genetic polymorphisms and environmental exposures needs to be reconcile with new findings of a large body research, suggesting that epigenetic mechanisms also may contribute (49). These mechanisms include genomic imprinting, histone modification, altered DNA methylation of regulatory sequences in Th and other genes, and regulation by miRNA, which may change asthma risk after conception via environmentally mediated epigenetic disruption of gene expression (48,91). As discussed, aberrant expression of miRNA has been shown to contribute to the pathogenesis of many human diseases and may serve as valuable diagnostic or prognostic disease markers (27,60). However, studies relevant to asthma or asthma risk are still lacking, except for a recent report demonstrating that + 3142C/G allele in the HLG mRNA influences miRNA targeting of HLA-G and is associated with risk asthma (49). As mentioned, Tan et al. identified HLA-G that is a nonclassic, class 1 HLA molecule possessing important immunomodulatory properties, as an asthma-susceptibility gene and discovered the risk of asthma in a child was determined by both the child's HLA-G genotype and the mother's affection status (48). They also reported a single nucleotide polymorphisms (SNP) in the 3'UTR of HLA-G that influence the targeting of three miRNAs to this gene, suggesting that allele-specific targeting of these miRNAs accounts, at least in part, for their earlier observations on HLA-G and the risk of asthma (48). These findings suggest that despite many limitations, there is a great promise that the study of environmental epigenetics will help us understand a theoretically preventable disease.

Lu et al. identified a miRNA signature in allergic airway inflammation, which includes miR-21 that modulated IL-12 (92). In details, they identified 21 miRNAs with differential expression between doxycycline-induced lung-specific IL-13

transgenic mice (with allergic airway inflammation) and control mice. In particular, they observed over-expression of miR-21 and under-expression of miR-1 in the induced IL-13 transgenic mice compared with control mice (92). Although IL-13-induced miR-21 expression was IL-13Rα1 dependent, allergen-induced miR-21 expression was mediated mainly independent of IL-13Rα1 and STAT6 (92). Notably, predictive algorithms identified potential direct miR-21 targets among IL-13-regulated lung transcripts, such as IL-12p35 mRNA, which was decreased in IL-13 transgenic mice (92). Mutating miR-21 binding sites in IL-12p35 3'UTR abrogated miR-21-mediated repression (92). Together, they have identified a miRNA signature in allergic airway inflammation, which includes miR-21 that modulates IL-12, a molecule germane to Th cell polarization (92).

As discussed, allergic asthma is an inflammatory disease of the lung characterized by abnormal Th-2 lymphocyte response to inhaled antigens (92). The molecular mechanisms leading to the generation of Th-2 response remain unclear. Recently, Mattes et al. showed that *in vivo* activation of TLR4 by house dust mite antigens leads to the induction of allergic disease, a process that is associated with expression of a unique subset of miRNAs (49). They also reported that selective blockade of miR-126 suppressed the asthmatic phenotype, resulting in diminished Th-2 responses, inflammation, airways hyperresponsiveness, eosinophil recruitment, and mucus hypersecretion (49). In addition, they observed that miR-126 blockade resulted in augmented expression of POU domain class 2 associating factor 1, which activated the transcription factor (TF) PU.1 that alters Th-2 cell function via negative regulation of GATA3 expression (49). These findings suggest that targeting miRNA in the airways may lead to anti-inflammatory treatment of allergic asthma.

Evidence increasingly assigns an immunosuppressive role for miRNA in immunity, but relatively few miRNAs have been studies, and an overall understanding of the importance of these regulatory transcripts in complex *in vivo* systems is lacking. Recently, Polikepahad et al. performed the global analysis of miRNA expression and function in allergic lung disease, an experimental model of asthma, employing multiple technologies (50). Deep sequencing and microarray analyses of the mouse lung short RNAome revealed numerous extant and novel miRNA and other transcript classes (50). Interestingly, similar to mRNAs, lung miRNA expression changed dynamically during the transition from the naive to the allergic state, suggesting numerous functional relationships (50). A possible role for miRNA editing in altering the lung mRNA target repertoire was also identified. Multiple members of the highly conserved let-7 miRNA family were the most abundant lung miRNAs, and they confirmed *in vitro* that IL-13, a cytokine essential for expression for allergic lung disease, is regulated by mmu-let-7a (50). These findings revealed unexpected complexity in miRNAome underlying allergic lung disease and demonstrated that a proinflammatory role of let-7 miRNAs (50).

miRNAs IN PSORIASIS

Psoriasis is a skin disorder that is characterized by erythematous scaling plaques, which are the result of inflammatory infiltrates. Psoriasis is thought to be a T cell-mediated disease of autoimmune origin, based on histological findings, mouse models, and the therapeutic efficacy of TNF-targeted therapies (31). Psoriasis is the most prevalent chronic inflammatory skin disease in adults, with a substantial negative impact on the patient's quality of life. Interestingly, Sonkoly et al. showed that psoriasis-affected skin has a specific miRNA expression profile when compared with healthy human skin or with another chronic inflammatory skin disease, atopic eczema (93). Among the psoriasis specific miRNAs, the authors identified leukocyte-derived miRNAs and one keratinocyte-derived miRNA, miR-203 (93). In a panel of 21 different human organs and tissues, miR-203 showed a highly skin-specific expression profile (93). Among the cellular constituents of the skin, it was exclusively expressed by keratinocytes. The up-regulation of miR-203 in psoriatic plaques was concurrent with the down-regulation of an evolutionary conserved target of miR-203, SOCS-3, which is involved in inflammatory responses and keratinocyte functions (93). These results suggest that miRNA deregulation is involved in the pathogenesis of psoriasis and contributes to the dysfunction of the cross talk between resident and infiltrating cells. As mentioned, miRNAs were implicated in the pathogenesis of psoriasis and atopic eczema, the two most common chronic inflammatory disorders in skin (94). In particular, miR-203, the first skin-specific miiRNA, showing an intriguing expression profile being confined to skin epithelium, is specifically over-expressed in psoriasis (94). Interestingly, the authors found that miR-146a, another miRNA showing specific up-regulation in psoriasis, is involved in the regulation of innate immune responses and the TNF-pathway and that miR-125b, another miRNA involved in TNF-pathway, is also

deregulated in psoriasis and atopic eczema (94). As skin inflammation may serve as a model for chronic inflammatory disorders, it is likely that miRNAs involved in skin inflammation will eventually emerge in other inflammatory or autoimmune disorders, and some of these may become disease markers and therapeutic targets (94).

A recent study explored the association of miR-146a variant rs2910164 and of two IRAK1 (target of miR146a) polymorphisms rs3027898 and rs1059703 with psoriasic arthritis (83). Additionally, they observed strong statistical significant difference in IRAK1 rs3027898 polymorphism distribution between patients with psoriasic arthritis and controls (33). Marginally significant difference was observed in distribution of IRAK1 rs1059703 genotypes between patients with psoriasic arthritis and controls, but no difference was observed in miR-146a rs2920164 distribution (33). They noted that this is the first study that addresses IRAK1 rs3027898 polymorphisms association with susceptibility of psoriasic arthritis, but further studies could help to understand the extent of the proposed association.

miRNAs IN INFLAMMATORY BOWEL DISEASE (IBD)

CD and UC are the 2 predominant types of idiopathic IBD that are distinguished by their underlying pathology (31,95). Despite pathological differences, both disease are thought to be T cell-driven disease and to result from a loss of immune tolerance in the gut (31). Treg cells have a central role in the maintenance of tolerance in the gut which is exemplified by the wasting disease and gastritis that develop in mice lacking Treg cell (31). In a study conducted by Dalal and Kwon (61), sigmoid colon biopsy miRNA microarray profiles for healthy control subjects and patients with active UC, inactive UC, chronic active CD, irritable bowel syndrome, and microscopic colitis were compared. This comparison revealed that 3 miRNAs (miR-192, miR-375, and miR-422b) were significantly decreased in the UC tissues, while 8 miRNAs (miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f) were significantly increased in active UC tissues (61). And, miR-192 and miR-21 were the most highly expressed of the active UC-associated miRNAs in human colonic tissues (61).

Wu et al. examined whether miRNAs are differentially expressed in UC tissues and are associated with expression of genes that regulate inflammation (96). They found that active UC was associated with the differential expression of 11 miRNAS; 3 were significantly decreased and 8 were significantly increased in UC tissues. *In situ* hybridization analysis indicated that miR-192, an miRNA with decreased expression in active UC, was predominantly localized to colonic epithelial cells (96). They also found that macrophage inflammatory peptide (MIP)-2 α, a chemokine expressed by epithelial cells, was identified as a target of miR-192 (96). Moreover, they reported that in colon epithelial cells, induction of MIP-2α expression by TNF-α was accompanied by a concomitant reduction in miR-192 expression and miR-192 was observed to regulate the expression of MIP-2α (96). These findings expand the known roles of miRNAs, indicating that tissues from patients with UC, and possibly other chronic inflammatory diseases, have altered miRNA expression patterns. These finding also demonstrate that miRNAs regulate colonic epithelial cell-derived chemokine expression (96). Recently, Wu et al. investigated miRNA expression in CD patients (97). They performed miRNA microarray analysis followed by RT-PCR confirmation on sigmoid colon pinch biopsies from 5 patients with chronically active CD and 13 control individuals. This comparison revealed that expression of miR-23b, miR-106, and miR-191 was increased in tissues from patients with active CD, while miR-19b and miR-629 were decreased in CD patients as compared to normal, healthy controls (97). A study currently reported that 5 miRNAs were significantly increased and 2 miRNAs (149* and miRplus-F1065) were significantly decreased in the blood of active CD patients as compared to healthy controls (95). The authors also found that 12 miRNAs were significantly increased and miRNA-505* was significantly decreased in the blood of active UC patients as compared to healthy controls and that 10 miRNAs were significantly increased and one miRNA was significantly decreased in the blood of active UC patients as compared to active CD patients (95). They concluded that peripheral blood miRNAs can be used to distinguish active CD and UC from healthy controls (95). These data support the evidence that CD and UC are associated with different circulating immune cell types and that the differential expression of peripheral blood miRNAs may form the basis of future diagnostic tests for IBD (95). Another recent study demonstrated that in UC patients, 9 miRNAs (miR- 28-5p, miR-151-5p, miR-199a-5p, miR-340, miRplus-E1271, miR-3180-3p, miRplus-E1035, miRplus-E1153, and miRplus-F1159) were increased in the peripheral blood of patients with active UC, but not those with inactive UC (61). Among the 14 patients in the active CD group, miRNA expression did not differ sig-

nificantly between the Crohn's ileitis and Crohn's colitis subgroup (61). While UC and CD represent distinct disease with some overlap, identification of distinct miRNA expression profiles may provide an early method to determine a patients's disease course (61). After the functional consequences of alterations in miRNA expression are established, miRNA may also become the target of future treatment.

miRNAs IN SKIN DISEASES

Skin is the biggest organ in mammals and protect the body from environmental hazard and prevents dehydration. Embryonic skin morphogenesis and homeostasis of adult skin require an accurately controlled gene expression in spatiotemporally specific manner (32). The vascular endothelial growth factor signaling path seem to be under repressor control by miRNAs (98). It is critically important to recognize that the understanding of cutaneous wound healing is incomplete without appreciating the functional significance of wound-induced miRNA (98). A study observed that the cutaneous wound healing process involved changes in the expression of specific miRNA at specific phases of wound healing (98). miRNAs that regulate angiogenesis include miRNA-17-5p, cluster 17-92, miR-27a, miR-27b, miR-126, miR-130z, miR-210, miR-221, miR-222, miR-378, and the let7 family (99). Skin represents the largest organ in the human body, and its morphogenesis has been shown to require highly coordinated and undisrupted miRNA metabolism (99). Recent studies reported that miRNAs are involved in skin morphogenesis, hair follicle morphogenesis, cutaneous wound healing, skin carcinogenesis and autoimmune and chronic inflammatory diseases affecting skin such as SLE, and psoriasis (62,63,100).

Owing to its highly spatiotemporally specific expression pattern, miR-203 was the first miRNA investigated in the skin (32). As aforementioned, Sonkoly et al. examined miRNA expression profile in the skin from patients with psoriasis, a common chronic inflammatory skin disease (93). The authors reported that miR-203 was significantly up-regulated in skin from patients with psoriasis and that miR-203 has 10 nucleotides with complementarity to the 3'UTR of SOCS-3 mRNA (93). Decreased SOCS-3 protein expression, but not SOCS-3 mRNA, was also found in psoriasis skin compared with healthy skin, suggesting posttranscriptional repression of SOCS-3 (93,100). Further supporting a role for miR-203 in SOCS-3 regulation, a mutually exclusive expression pattern of miR-203 and SOCS-3 was observed in the skin from healthy subjects and patients with psoriasis (100). SOCS-3 was strongly expressed by the basal layer of keratinocytes in healthy skin, while it was suppressed in epidermis of psoriasis lesions (93). These data suggest that down-regulation of miR-203 may induce relief of posttranscriptional suppression of SOCS-3 expression in keratinocytes in patients with psoriasis. Since SOCS-3 is a negative regulator of IL-6 and IFN-γ-induced signaling, up-regulation of SOCS-3 could result in constitutive activation of STAT3, a downstream effector of the IL-6 and IFN-γ receptor signaling pathways (100). This impaired negative feedback regulation in keratinocytes may consequently contributed to prolonged skin inflammation (15,93). These data suggest that since miRNAS are master switches that ultimately affect complex cellular processes, and functions through the regulation of several proteins, miRNA- based therapies may be more effective than drugs targeting single proteins and that the disease-specific miRNAs identified in this study can be used for potential therapeutic target in the treatment of chronic skin inflammation (15,93).

Clues for the functions of other skin-expressed miRNAs have also come from studies of their function in human disease. miR-200 and miR-205 are both highly expressed in normal skin, and have been shown to specifically target the mRNA of the transcriptional repressor of E-Cadherin, ZEB1 and ZEB2 (32). The study have also shown that high expression of several miRNAs in the epidermis and hair follicle is necessary for normal skin development (32). Using a mouse model of embryonic skin, progenitor cells were targeted for Dicer knockout (63). The skin epithelium in Dicer knockout mice failed to produce mature miRNAs, and embryonic hair germs were found to evaginate into the epidermis rather than invaginate normally toward the dermis (63). Their further investigation also revealed a disturbance in the architecture of other epithelial tissues including the filiform papillae of the tongue epithelium and rudimentary sweat glands of the plantar footpad epithelium (63). These results indicate that miRNA are also necessary for the morphogenesis of other stratified epithelia (32). Interestingly, a more recent study showed that miR-155 is one of the highest-ranked up-regulated miRNAs in patients with atopic dermatitis and in the skin miR-155 was predominantly expressed in infiltrating immune cells (101). This study also showed that miR-155 was up-regulated during T-cell differentiation/activation and was markedly induced by T-cell activators in PBMCs *in vitro* and by superantigen and allergens in the skin *in vivo*. Moreover, in this study, CTLA-4, an important negative regulator of

T-cell activation, was identified as a direct target of miR-155 (101). Over-expression of miR-155 in Th cells resulted in decreased CTLA-4 levels accompanied by an increased proliferative response (101). These data strongly suggest that miR-155 may contribute to chronic skin inflammation by increasing the proliferative response of Th cells through the down-regulation of CTLA-4 (101). With the initial characterization of miRNA functions in mammalian skin, now we start to appreciate the significance of an accurately regulated protein output not only in normal skin development, but also in human skin diseases (32,63,101).

Now, the stage is set to understand individual miRNA function and how critical biological events are controlled by this class of small RNA molecules. miRNAs are involved in regulating epithelial anti-microbial defenses by targeting by epithelial effector molecules and/or influencing intracellular signaling pathway (100). Moreover, aberrant miRNA expression has been implicated in the pathogenesis of various disease at the skin and mucosa (32,63,101). Increasing understanding of the role of miRNA in epithelial immunoregulation and identification of miRNAs of pathogenetic significance will enhance our understanding of epithelial immunobiology and immunopathology (100).

miRNAs IN PSYCHIATRIC AND NERUOLOGICAL DISORDERS AND MENTAL STRESS

Psychiatric illness are disabling disorders with poorly understood underlying pathophysiologies. However, it is becoming increasingly evident that these illness results from disruption across whole cellular networks rather than any particular monoamine system (66). Recent evidence continues to support the hypothesis that these illness such as schizophrenia, bipolar disorders, PD and major depressive disorders arise from impairments in cellular plasticity cascades, which lead to aberrant information processing in the circuits that regulate mood, cognition, and neurovegetative functions, such as sleep, appetite, and energy (66). Psychiatric disorders are associated with a higher degree of comorbidity with other diseases, such as cardiovascular disease, obesity, thyroid problems, and diabetes (66).

The effects of miRNA-mediated modulation of gene expression during multiple steps of neuronal development, from early neurogenesis to synaptogenesis, have been well documented across the animal kingdom (65). As regards human miRNAs, it was estimated, based on high-throughput sequencing data, the number of miRNAs expressed in the human brain may well exceed one-thousand (65,102). Interestingly, many miRNAs expressed in the human brain are not conserved beyond primates (34,65,102). Although functions have been assigned to only very few brain-specific miRNAs, increasing evidence suggests key roles in normal development, differentiation events, and homeostasis, as well as in related pathological conditions (34,65,102). A variety of miRNAs have been found in the CNS, and are believed to play major physiological roles in neuronal development (34,35,103). Neurodegenerative diseases results from dysfunction, progressive deterioration, and extensive loss of neurons in the CNS and/or peripheral nervous systems (65,102). Interestingly, miRNAs are altered by stress, glucocorticoides, mood stabilizer in a particular psychiatric disorder and schizophrenia (66). Now, miRNAs are moving rapidly center stage as key regulators of neuronal development and function in addition to important contributions to neurodegenerative disorder (34,35,104).

Amyotrophic lateral sclerosis (Lou Gehrig's disease) is a neurodegenerative disease that specifically affects upper and lower motor neurons (MNs), leading to progressive paralysis and death (35). Similarly, juvenile forms of motor neuron diseases (MND) are related to posttranscriptional regulators of gene expression (35). This emerging appreciation of RNA regulatory function in neurons suggests that miRNA is involved in the pathogenesis of MNDs. It has been shown that miRNA dysfunction causes spinal muscular atrophy (SMA) and that the heavy neurofilament subunit is a target of miR-9, a miRNA that is specifically down-regulated in a genetic model of SMA (35). These data provide evidence for miRNA function in spinal motor neuron disease and emphasize the potential role of miR-9-based regulatory mechanisms in adult neurons and neurodegenerative states (35).

A number of reports have emerged showing neurological disease-related perturbation of miRNAs (38,67,68). These alteration in miRNA expression may be a direct consequence of disease or may occur as a result of the loss of a specific cell population (38,67). Altered expression of miRNAs prior to the onset of or during the course of disease pathology raises the possibility that expressing or inhibiting specific miRNAs might ameliorate the disease process and provide an effective treatment (70,104,105).

Importantly, altered expression of miRNA has been observed in PD (67,68), AD (36,38,102,106), HD (68), Tourette's syndrome (71), DS (70,72), DiGeorge syndrome (70),

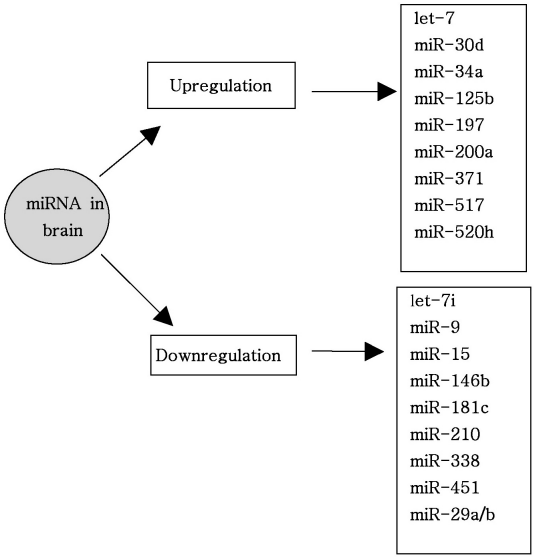

Figure 3. Altered patterns of miRNA expression in brain parenchyma and cerebrospinal fluid of patients with Alzheimer's disease.

prion disease (105) and Rett syndrome (70,71). Additionally, psychiatric and neurological disorders, including schizophrenia, depression and mental health disorders also appear to involve changes in miRNA expression (34,37,66,73,74,104).

As regards AD, increasing evidence suggests role for miRNAs in the pathology of AD, particularly with respect to the regulation of β-amyloid precursor protein-converting enzyme 1 (BACE1). Among the AD-related miRNA expression changes, miR-107 was exceptional because miR-107 levels decreased significantly even in patients with the earliest stage of pathology (38). Interestingly, particular cerebral cortical laminas involved by AD pathology exhibit diminished neuronal miR-107 expression (38). Computational analysis predicted that the 3'UTR of BACE1 mRNA is targeted multiply by miR-107 (38). Together, the study indicated that miR-107 may be involved in accelerated disease progression through regulating BACE1 (38). Interestingly, mutations in the APP and PSEN genes cause Aβ accumulation and familial AD (106,107). Recently, Hébert et al. investigated changes in miRNA expression profiles of sporadic AD patients and found that several miRNAs potentially involved in the regulation of APP and BACE1 expression appeared to be decreased in diseased brain (106). They also showed that miR-29a, miR-29b-1 and miR-9 can regulate BACE1 expression *in vitro* and that the miR-29a/b-1 cluster was significantly decreased in AD patients displaying abnormally high BACE1 protein (106). Additionally, they provided evidence for a potential causal relationship between miR-29a/b-1 expression and Aβ generation in a cell culture model. They also proposed that loss of specific miRNAs can contribute to increased BACE1 and Aβ levels in AD (106). These findings suggest a loss-of-function mechanisms contributing to sporadic AD and also provide an interesting molecular link between sporadic AD and the amyloid cascade. In different studies on miRNA expression profiling of AD-affected brain, the up-regulation of miR-125b and down-regulation of miR-9 and miR-210 have been consistently reported (36). The up-regulation of miR-197 and down-regulation of miR-15, miR-146b, miR-181c and miR-338 are commonly altered in AD brain parenchyma and cerebrospinal fluid, as shown in Fig. 3 (36). A recent study (67) investigated the role of miRNAs in the terminal differentiation, function, and survival of mammalian dopaminergic neurons (DNs). The authors identified miR-133b, that is specifically expressed in midbrain DNs and deficient in PD midbrain tissue that has lost midbrain DNs (67). Moreover, they also reported that miR-133b regulates the maturation and function of midbrain DNs within a negative feedback circuit that includes the paired-like homeodomain transcription factor Pitx3 (102).

HD is an autosomal dominant neurodegenerative disease caused by CAG trinucleotide repeat expansion in huntingtin, which encodes Huntingtin (Htt). Although Htt is ubiquitously expressed, patients with HD show predominantly CNS manifestations (68). Patients with HD experience abnormal motor movements, cognitive decline and psychiatric disturbances that frequently result in premature death (68). One of the molecular phenotype in HD patients is transcriptional misregulation in striatum and distinct cortical regions (68). One putative mechanisms underlying the transcriptional changes is aberrant cellular distribution of the transcriptional repressor RE1-silencing TF (REST, also known as neuron restrictive silencer factor, NRSF) (68). The transcription factor REST silences neuronal gene expression in non-neuronal cells (68). In neurons, the protein is sequestered in the cytoplasm in part through binding to Htt and polyglutamine expansions in Htt which caused HD, abrogates REST-Htt binding (68). Packer et al. reported that levels of several miRNAs with upstream RE1 sites are decreased in HD patient cortices relative to healthy controls (68). Interestingly, one of these, the bifunctional brain enriched miR-9/miR-9*, targets two components of the REST complex: miR-9 targets REST and miR-9* targets CoREST (68). These data provided evidence for a dou-

ble negative feedback loop between the REST silencing complex and the miRNAs it regulates (68).

DS or Trisomy 21, is the most common genetic cause of cognitive impairment and congenital heart defects in the human population (72). Bioinformative analysis demonstrated that human chromosome 21 (Hsa21) harbors 5 miRNA genes; miR-99a, let-7c, miR-125b-2, miR-155, and miR-802 (72). Importantly, miRNA expressing profiling, miRNA RT-PCR, and miRNA *in situ* hybridization experiments showed that these miRNAs are over-expressed in fetal brain and heart specimens from individuals with DS when compared with age- and sex-matched controls (72). The authors hypothesized that trisomic 21 gene dosage over-expression of Hsa21-derived miRNAs results in the decreased expression of specific target proteins and contribute, in part, to features of the neuronal and cardiac DS phenotype (72). They also noted that Hsa21-derived miRNAs may provide novel therapeutic targets in the treatment of individuals with DS. Moreover, improved computational and experimental methods continue to reveal the location of new miRNAs, suggesting that there remain unidentified miRNAs residing on chromosome 21, and in a DS critical region (DSCR), which could make excellent candidates to study the molecular pathogenesis of DS further (70).

Schizophrenia is a severely debilitating psychiatric disorder characterized by a diverse range of symptoms. While extensive research has not determined the definitive cause(s), it is generally accepted that a number of influences including genetic, epigenetic, environmental and developmental factors are involved (32). Accumulating evidence showed numerous miRNAs associated with psychiatric disease (34,37,66,73,74). Perkins et al. hypothesized that schizophrenia might be associated with altered miRNA profiles (73). To investigate this possibility, they compared the expression of 264 human miRNAs from postmortem prefrontal cortex (Brodmann's area 9) tissue of individuals with schizophrenia or schizoaffective patients to tissue of 21 psychiatrically unaffected individuals (73). Importantly, they identified 16 differentially regulated miRNAs, 15 of which were down-regulated in schizophrenia. Of these, miR-26b, miR-30b, miR-29b, and miR-106b showed the greatest fold change, although all fold changes were less than 2-fold. Interestingly, for several of the differentially-expressed miRNAs, the ratio of mature miRNA to pri-miRNA was lower in schizophrenia, suggesting a disruption in miRNA biogenesis in schizophrenia (73). Burmistrova et al. reported that genetic association analysis of 300 schizophrenia and 316 normal control individuals revealed no statistically significant association of any of the miR-130b allelic variants with schizophrenia (108). Recently, however, Beveridge et al. observed miRNA dysregulaton and altered miRNA biogenesis in schizophrenia brain tissue (37). Protein encoding genes have long been the major targets for research in schizophrenia genetics. However, with the identification of regulatory miRNAs as important in brain development and function, miRNA genes have emerged as candidates for schizophrenia-associated genetic factors (109). Hansen et al. found nominal association between brain-expressed miRNAs and schizophrenia for two SNPs in miRNAs rs17578796 and rs1700 located in has-miR-206 and hsa-miR-198 respectively (109). More recently, Guo et al. have suggested that changes in gene expression may play an important role in etiology of schizophrenia, and that miRNAs and TFs are primary regulators of this gene expression (110). This study found that a TF regulates transcription of its target gene by specifically binding to the TF binding site (TFBS) in the gene's promotor region (110). Since expression of miRNA may be regulated by TF, TF and miRNA reciprocally regulate one another to form feedback loops, or alternatively, both TF and miRNA may regulate their target genes and form feedforward loops (FFLs) (110).

Additionally, Guo et al. identified 32 FFLs among compiled schizophrenia-related miRNAs, TFs and schizophrenia candidate genes (SZGenes) and reported that these observed FFLs were significantly enriched in SZGenes (110). With these findings, they also constructed a novel miRNA-TF regulatory network for schizophrenia (Fig. 4). Importantly, Beveridge et al. reported that striking deviation in global miRNA expression was observed in postmortem tissue from both the superior temporal gyrus (STG) and the dorsolateral prefrontal cortex (DLPFC) and seemed to involve an increase in miRNA biogenesis (74). The authors also observed schizophrenia-associated up-regulation of a very large number of miRNAs (74): 21% of expressed miRNAs in the STG and 9.5% of expressed miRNAs in the DLPFC. Additionally, they found that up-regulated miRNAs were miR-181b, miR-219, and members of the miR-15 family. Surprisingly, of the 81 dysregulated miRNAs, only 4 were up-regulated in both the STG and DLPFC (miR-128a, miR-16, miR-20a, and miR-338) (74). Together, their data suggest that schizophrenia is associated with a global increase in miRNA biogenesis and expression in the cerebral cortex. This could have profound neurodevelopmental and broader neurological implications in the cortext of schizophrenia by influencing genes involved in cortical structure and neural plasticity (74). A more complete picture of the

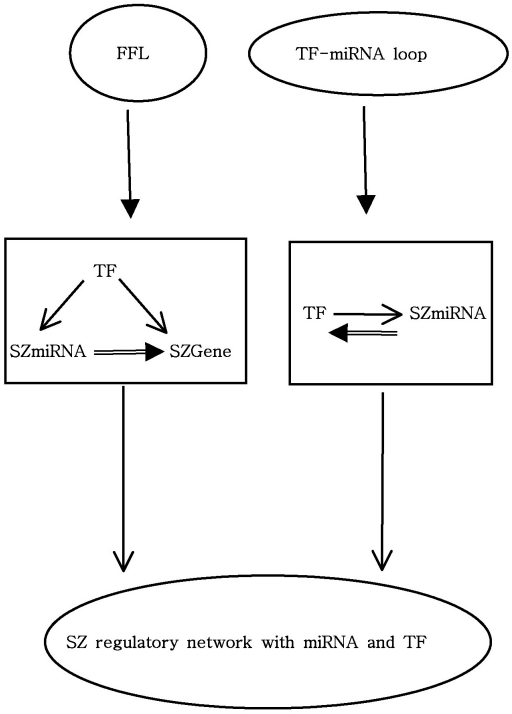

Figure 4. A overview of microRNA (miRNA)-transcription (TF) regulatory networks in schiziophrenia. A TF regulates transcription of its target gene by specifically binding to the transcription factor binding site in gene's promotor region. TFs activate schizophrenia-related miRNAs (SZmiRNAs) and schizophrenia candidate genes (SZGenes). However, SZmiRNAs inhibit SZGenes and TFs. Both TF and miRNA regulate their target genes and form feedforward loops (FFLs). It was found that FFLS were significantly enriched in schizophrenia. → Activation; ⇒ Inhibition. (See Text for details).

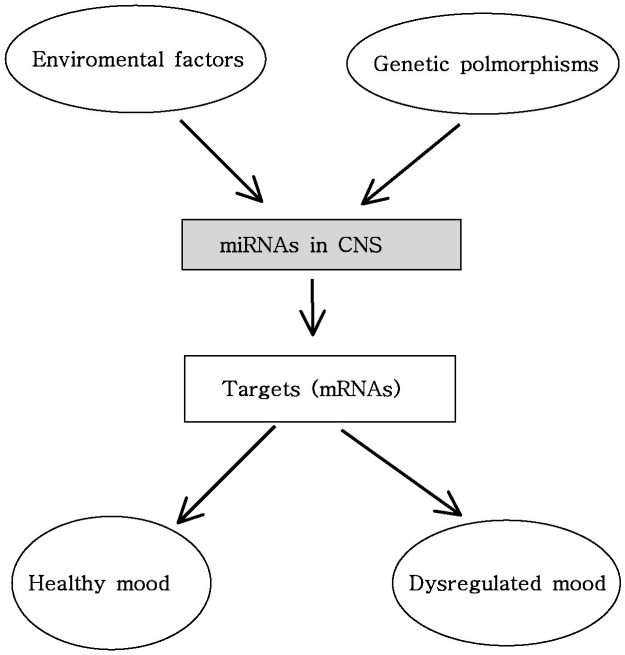

Figure 5. miRNAs influence the pathophysiology of psychiatric disorders. A variety of miRNAs are found in the central nervous system (CNS), and are believed to play critical roles in brain development and structural plasticity. Modifiable changes in epigenetic or miRNA expression along with genetic polymorphisms activate or inhibit miRNA in CNS and lead to either healthy or dysregulated mood. As regards therapeutic potential of miRNA in psychiatric diseases, targetting miRNAs may provide insight into the common and unique pathway. Elucidating more miRNAs and predicted targets may reveal novel therapies that modified plasticity cascades to restore synaptic function, neuronal circuity, and mood regulation.

miRNAs that are dysregulated in psychiatric illness may improve our understanding of the molecular mechanisms underlying neuropsychiatric phenotypes, and due to their tuning effect on large numbers of protein, miRNAs may ultimately represent a new therapeutic target for psychiatric disease (Fig. 5).

Mammalian psychological stress is known to induce prominent changes in neuronal activity and gene regulation across multiple brain region (111). Mental stress modifies both cholinergic neurotransmission and alternative splicing in the brain (111). Recently, Meerson et al. reported that stress changes brain miRNA expression and that some of these stress-regulated miRNAs regulate alternative splicing (111). Interestingly, they also reported that acute and chronic immobilization stress differentially altered the expression of numerous miRNAs in two stress-responsive regions of the rat brain, the hippocampal CA1 region and the central nucleus of the amygdala and that miR-134 and miR-183 levels both increased in the amygdala following acute stress, compared to unstressed controls (111). Interestingly, moreover, the authors showed that chronic stress decreased miR-134 levels, whereas miR-183 remained unchanged in both the amygdala and CA1 (111). They also found that miR-134 and miR-183 share a common predicted mRNA target, encoding the splicing factor SC35 (111). Importantly, chronic psychosocial stress is known to have adverse physiological effects that contribute to cardiovascular disease, impaired immune function, inflammatory diseases, and impaired neuronal function and behavior (66). Glucocorticoids are one of the prominent mediators of cellular stress effect on neuronal function and behavior, and are known to structurally alter brain cytoarchitecture in regions that contribute to cognition, memory, and emotion (66). During the cellular stress response, miRNA have the capacity to change from translation suppressor to activators by forming

new interaction between miRNA/Argonaute complexes and RNA-binding protein that alter their subcellular localization (66). As described, accumulating evidence demonstrated that miRNAs are altered by stress, glucocorticoid, mood stabilizer (lithium and valproate) and in a particular psychic disorder, schizophrenia (37,73,74). Interestingly, brief exercise alters miRNA profile in circulating neutrophils in humans (112).

CONCLUSION

MicroRNAs (miRNAs) are small noncoding RNA molecules that negatively regulate gene expression via degradation or translational repression of their target messenger RNAs (mRNAs). Recent studies have clearly demonstrated that miRNAs are highly expressed in regulatory T (Treg) cells and a range of miRNAs are involved in the regulation of immunity and in the prevention of autoimmunity. It has been increasingly reported that miRNAs are associated with various human diseases like autoimmune disease, skin disease, neurological disease and psychiatric disease. Recent studies have revealed that importance of miRNA regulation in safeguarding Treg cell function in the prevention of autoimmunity and autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, psoriasis, asthma, inflammatory bowel disease including Crohn's disease, ulcerative colitis, and autoimmune diabetes. Although miRNA research in the field of dermatology is still relatively new, miRNAs have been the subject of much dermatological interest in skin morphogenesis and in regulating angiogenesis. Moreover, there is now compelling evidence that dysregulation of miRNA networks is implicated in the development and onset of human neruodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, Huntington's disease, Tourette's syndrome, Down syndrome, depression and schizophrenia. In this review, I briefly summarized the current studies about the roles of miRNAs in various autoimmune diseases, skin diseases, psychoneurological disorders and mental stress. This review also explored the potential roles miRNAs can play in a variety of diseases, and suggested some possible therapeutic application for restoring or inhibiting miRNA function. The next few years should see many studies that further unravel the role of miRNAs and the molecular basis for their action in pathogenesis of diseases and immunity in addition to new efforts to harness this molecule for therapy.

CONFLICTS OF INTEREST

The author have no financial conflict of interest.

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