MicroRNAs in Cutaneous T-Cell Lymphoma: The Future of Therapy

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MicroRNAs (miRs) are small, noncoding RNAs with numerous cellular functions. With advancing knowledge of the many functions of miRs in cancer pathogenesis, there is emerging interest in miRs as therapeutic targets in cancers. One disease that poses an intriguing model for miR therapy is cutaneous T-cell lymphoma, a rare disease featuring malignant $CD4^+$ T cells that proliferate in the skin. The hallmark of cutaneous T-cell lymphoma progression is epigenetic dysregulation, with aberrant miR levels being a common feature. This review aims to summarize the rapidly emerging advances in the development of miR-based therapies in cancers, with a special emphasis on CTCL.

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INTRODUCTION

MicroRNAs (miRs) are small (18–22-nucleotide), single-stranded RNA molecules with diverse cellular and extracellular activities. A single miR can interact with and regulate numerous targets (>100 on average), and most transcripts of protein-coding genes can be regulated by multiple mature miRs (Di Leva et al., 2014; Friedman and Jones, 2009). Because of the complex and critical function of miRs, their expression and activity are tightly regulated in the cell.

Profiling of miR expression, which will be discussed in the context of cancer, has shown expansive changes in miR expression in disease states, including cancers. These changes in expression are accomplished via transcriptional regulation and posttranscriptional changes, as well as in response to cellular signaling pathways such as cytokine binding (Obernosterer et al., 2006; Yang and Wang, 2011). Transcriptional regulation of miR expression can be accomplished through altered epigenetic modifications such as methylation or histone acetylation at the promoter of the host gene (Deneberg et al., 2014; Gulyaeva and Kushlinskiy, 2016). Notably, miRs themselves can regulate the expression of these epigenetic modifiers and therefore affect the expression of other miRs in the cell (Garzon et al., 2009; Varambally et al., 2008).

Many miRs map to genomic regions frequently altered in cancer, such as loss of heterozygosity regions, amplified regions, breakpoint regions, and fragile sites. These fragile sites are common sites for chromosomal breaks, translocations, and rearrangements, as well as deletion or viral integration (Calin et al., 2004; Laganà et al., 2010). Incredibly, losses or gains in single miRs can have dramatic effects on cellular function, such as deletion of miR-15a/16-1 in lymphomagenesis (Calin et al., 2002; Raveche et al., 2007). This observation highlights the importance of miR dysregulation in the initiation and progression of cancers, and thus forms the basis of their potential use as cancer therapies.

miR THERAPY IN CANCER

Targeted therapy is emerging as the most promising therapeutic approach in cancer treatment. Nonspecific cytotoxic therapies have given way to small molecules, biologics, and immunotherapies. In addition to having more specific cellular targets, these approaches have improved safety profiles and improved efficacy for many patients. However, therapeutic resistance has been limiting to the overall success of many targeted therapies. miRs represent intriguing targets for cancer therapy for multiple reasons. A single miR likely has numerous cellular targets and, therefore, wide-ranging effects on cellular function. Additionally, miRs have significant context specificity, meaning that their expression and activity differ in different tissues. Thus, using miRs as targets for therapy represents an opportunity for patient/tumor specificity and cell-type specificity while affecting multiple cellular targets that may cooperate to result in impaired malignant cell proliferation and survival. Because of this hope of therapeutic success, there are currently several early-phase clinical trials for miR-based therapies and miR-targeting therapies for cancer and other diseases.

Depending on the tissue type or cell type, a particular miR may have tumor-suppressive, oncogenic, or mixed functions. The complex biology of miRs necessitates extensive mechanistic study and preclinical assessment to support early development of miR-based therapies. Based on the disease miR expression profile, it may be advantageous to either rescue or inhibit the expression of a single miR.

Tumor-suppressive miRs are those that maintain basal cellular function through regulation of genes involved in the cell cycle, proliferation, and apoptosis. In many tumors, the expression of these protective miRs may be lost through multiple mechanisms, including genomic losses or deletion, transcriptional repression, or loss or dysfunction of miR biogenesis proteins (Williams et al., 2016).

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Abbreviations: CTCL, cutaneous T-cell lymphoma; MF, mycosis fungoides; miR, microRNA; SS, Sézary syndrome

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Table 1. MicroRNA Profiling in CTCL

Application	Methodology	Up-regulated miRs	Down-regulated miRs	Reference
Diagnosis of CTCL vs. BID	Microarray followed by PCR	326 663b 711 155	203 205	Ralfkiaer et al. (2011)
Diagnosis of CTCL vs. BID	Microarray	155 21 142 146 181a/b	141/200c	Sandoval et al. (2015)
Diagnosis of SS	Microarray	21 214 486		Narducci et al. (2011)
Diagnosis of C-ALCL vs. BID	Microarray followed by PCR	155 27b 30c 29b		Benner et al. (2012a)
Diagnosis of aggressive CTCL variants	PCR	181a 93 34a		Marosvári et al. (2015)

Abbreviations: BID, benign inflammatory dermatoses; C-ALCL: cutaneous anaplastic large cell lymphoma; CTCL, cutaneous T-cell lymphoma; miR, microRNA; SS, Sézary syndrome.

It has been established in a laboratory setting and in preclinical models that restoring miR levels can inhibit tumor growth (Ji et al., 2008; Ofek et al., 2016). The significant challenge for miR mimic therapy has been inefficient cellular delivery. Several ongoing preclinical studies of miR mimics in lung cancer use delivery strategies such as EDV nanocells (EnGeneIC Dream Vector; EnGeneIC Ltd, New South Wales, Australia), viral vectors, and liposomes (MacDiarmid et al., 2007; Reid et al., 2016). EDV nanocells feature nonviable minicells coated with bispecific antibody to target cancer cells. This technology has been used in the preclinical setting for delivery of miR mimics to tumors in vivo for mesothelioma (Reid et al., 2013; Williams et al., 2015) and adrenal cortical carcinoma (Glover et al., 2015). EDV nanocells have already been used safely in first-in-human studies for delivery of chemotherapeutics (Whittle et al., 2015).

Two recently initiated phase I trials include a miR-34 mimic with an indication for several types of cancer and a miR-16 mimic for non-small cell lung cancer. The former uses a liposomal delivery system but has been halted because of immune-related adverse events (Bouchie, 2013; Chakraborty et al., 2017). The latter uses a delivery system termed a *targomiR*, in which the double-stranded synthetic mimic RNA is coupled with a nanoparticle and a targeting moiety—in this case, directing the minicell to EGFR-expressing cells (Reid et al., 2016).

Several oncogenic miRs have been identified in different cancer cell types that target tumor suppressors for degradation. These miRs are up-regulated and overexpressed through several mechanisms, including chromosomal or gene duplication, amplification, and transcriptional up-regulation (Jansson and Lund, 2012; Zhang et al., 2007).

AntagomiRs are single-stranded antisense oligonucleotides that are complementary to the endogenous miR (Czech, 2006). AntagomiRs block binding of the specific miR to endogenous mRNA targets. These have a strong affinity for their target and are resistant to nucleases, and they have been used successfully in animal models (Elmén et al., 2008a, 2008b).

More recently developed strategies include the use of miR sponge and miR masking. Specific sponges selectively sequester the endogenous miR, thus allowing expression of the target mRNAs (Ebert et al., 2007; Li et al., 2015). miR masking involves the use of a chemically modified antisense oligonucleotide complementary to the mRNA target of an endogenous miR. Thus, the mask de-represses the target gene and does not interact with the target miR (Wang, 2011).

miRs IN CUTANEOUS T-CELL LYMPHOMA

The largest category of primary cutaneous lymphomas (~70%) derives from mature skin-resident or skin-homing T cells, referred to as *cutaneous T-cell lymphoma* (CTCL). Mycosis fungoides (MF), the most common subtype of CTCL, may progress slowly through skin-limited stages, but in a portion of patients the disease will advance and may spread to involve lymph nodes, viscera, and blood, known as *Sézary syndrome* (SS). SS may arise de novo in some patients, the disease course is often very rapid, and it is uniformly fatal (Benner et al., 2012b; Kohnken et al., 2016).

Patients with early-stage disease can benefit from skin-directed therapies; however, for most patients the disease will progress despite these treatments. At the time of tumor stage or visceral spread, systemic therapies are initiated. These include immune-modulatory therapies and, recently, histone deacetylase inhibitors. These systemic therapies have variable responses, around 30% for most (Olsen et al., 2007; Virmani et al., 2017), but with high rates of relapse and development of clinical resistance. These challenges highlight the need for better understanding of disease pathogenesis, early diagnosis, and identification of innovative therapeutic targets.

The new age of personalized medicine has yielded side-by-side advancement in diagnosis and treatment of individual

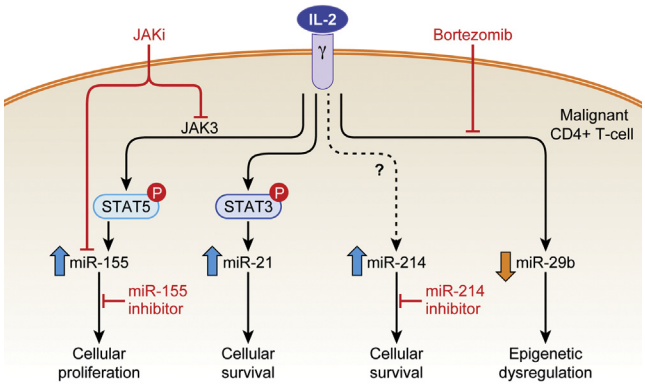

Figure 1. MicroRNAs in CTCL. IL-2 family cytokines signal through the common γ receptor with downstream signaling mediated by JAK/STAT proteins. JAK3 activates STAT5 by inducing its phosphorylation. STAT5 induces increased expression of miR-155, which then has numerous effects on cellular proliferation. JAK inhibitors have been shown to reduce miR-155 level. MRG-106 (miR-155 inhibitor) is in clinical trials for the treatment of CTCL. STAT3 is constitutively activated in many CTCL patients, but it may also be activated by IL-2 signaling. STAT3 induces miR-21 expression, which then supports cellular survival. There is currently no known regulation of miR-214 level by IL-2. Elevated miR-214 in CTCL contributes to cellular survival, and miR-214 inhibition has been investigated as a therapy for CTCL. IL-2 family signaling induces transcriptional repression of miR-29b, a mechanism that can be inhibited by bortezomib. miR-29b has many epigenetic modifiers as downstream targets. Rescue of miR-29b level is proposed as a potential therapeutic strategy for CTCL. CTCL, cutaneous T-cell lymphoma; miR, microRNA, P, phosphorylation.

tumors. miR profiling, the investigation of differential miR expression in CTCL patients, has emerged as a useful tool to study the biology of tumor cells and tissues and to aid in diagnosis of disease (Ralfkiaer et al., 2011, 2014). Furthermore, miR profiling has also been suggested for use in prognostication and monitoring of therapeutic response in CTCL (Lindahl et al., 2018; Shen et al., 2018).

Several studies have been done in recent years to explore the miRnome of CTCL patients. Epigenetic dysregulation in general is a hallmark feature of CTCL progression, and many miRs have been shown to be altered in this disease (de Silva et al., 2014; Ralfkiaer et al., 2011) (Table 1).

Because of the diverse targets of miRs and their critical role in cellular function, restoration of basal miR expression poses an intriguing therapeutic strategy. miR-based therapies may represent favorable adjunct treatment options to enhance sensitivity to chemotherapy or other targeted drugs.

As examples, miRs known to play a role in the clinical response to chemotherapy in different cancer types include miR-203 for tyrosine kinase inhibitors in lung cancer based on its targeting of Src kinase (Garofalo et al., 2011), miR-155 for doxorubicin and others based on its targeting of FOXO3A (Kong et al., 2010), miR-214 for cisplatin in ovarian cancer based on its targeting of PTEN (Yang et al., 2008), miR-181a/b for nucleoside analogs in leukemia based on their targeting of anti-apoptotic proteins such as Bcl-2 (Zhu et al., 2012), and miR-29b for gemcitabine in cholangiocarcinoma based on its targeting of promigratory proteinase MMP2 (Okamoto et al., 2013). miR/mRNA network analyses on resistant and sensitive cells may assist in the identification of more of these potentially targetable pathways (Hiddingh et al., 2014).

miR TARGETS IN CTCL

CTCL provides a unique and desirable disease setting for testing innovative miR-based therapies (Figure 1 and Table 2). First, it is a severe and uniformly fatal disease with few effective therapeutic options, and therefore there is abundant potential for improved therapies to make a significant clinical impact. Second, the tumor is in the skin, making it easily visible and accessible for therapeutic delivery. Finally, therapeutic improvement can be readily monitored clinically and by relatively noninvasive means such as skin biopsy. Indeed, several miR-based therapies in development rely on intradermal or subcutaneous injection of their lead compounds, largely addressing bioavailability challenges for MF patients.

Cytokine signaling and tumor microenvironment are thought to contribute to miR dysregulation in multiple disease states, including multiple sclerosis (de Faria et al., 2012) and colorectal cancer (Pucci and Mazzarelli, 2011). In CTCL, almost all members of the IL-2Rγ cytokine family have been implicated in the disease pathogenesis and progression, and downstream signaling of these cytokines may influence the tumor microenvironment (Krejsgaard et al., 2017). One such γ-chain cytokine, IL-15, is a chronic inflammatory cytokine that is known to play a critical role in oncogenesis of cancers including CTCL (Mishra et al., 2014, 2016; Waldmann, 2013). IL-15 is up-regulated in CTCL patients in a stage-dependent manner and results in a host of downstream effects that contribute to CTCL pathogenesis. It has been shown that some of the effects of IL-15 signaling are epigenetic (Kohnken et al., 2018; Mishra et al., 2012). In the following sections, we discuss four miRs that have well-described roles in CTCL pathogenesis and thus serve as potential therapeutic targets. The expression of three of these miRs is known to be affected by IL-15 signaling, providing a disease setting that allows further study of this mechanistic interaction between microenvironment and miR expression in cancer.

miR-21

miR-21 is considered oncogenic in several tumor types, including SS. Indeed, miR-21 is aberrantly expressed in malignant skin lymphocytes of CTCL patients (Lindahl et al., 2016). The overexpression of miR-21 imparts tumorigenic effects such as enhanced proliferation, invasion, and migration in solid tumors such as breast, cervical, and colorectal cancer, in part through its targeted degradation of tumor suppressor PTEN (Li et al., 2016; Xu et al., 2015; Yan et al., 2011). Furthermore, overexpression of miR-21 is associated with acquired resistance to tyrosine kinase inhibitors in lung cancer, also related to its effect on PTEN expression (Shen et al., 2014).

It has been shown in several recent genomic studies that signaling molecule STAT3, which is downstream of cytokine signaling, such as with IL-2 family members, is constitutively activated in CTCL neoplastic cells (Nielsen et al., 1997; Sommer et al., 2004; Zhang et al., 1996). miR-21 was shown to be a direct target of STAT3 in SS, such that signaling through the common γ chain results in activation of STAT3 and up-regulation of miR-21 (van der Fits et al., 2011).

Table 2. MicroRNA Targets in CTCL

Characteristics	miR-21	miR-155	miR-214	miR-29b
Type	Oncogenic	Oncogenic	Oncogenic	Tumor suppressive
Profile in CTCL patients	Up-regulated	Up-regulated, stage-dependent	Up-regulated	Down-regulated
Specificity	Poor	High	—	—
Association with outcome	N/A	N/A	Yes	N/A
Important targets	PTEN	FOXO3A	PTEN LHX6 Bcl2 KLF12	MMP-2 DNMT3 SP-1 BRD4
Cellular effects	Proliferation, invasion, migration		Survival, response to therapy	Epigenetic dysregulation
Role in resistance	High expression imparts resistance to TKIs	High expression imparts resistance to doxorubicin	Knockdown resensitizes to TKIs, high expression imparts resistance to cisplatin	High expression imparts resistance to gemcitabine
Results of preclinical targeting	Silencing in SS cells results in apoptosis	Inhibition decreases malignant cell proliferation	Inhibition is efficacious in CTCL mice	Rescue by bortezomib reduces cellular survival and proliferation

Abbreviations: CTCL, cutaneous T-cell lymphoma; miR, microRNA; N/A, not applicable; SS, Sézary syndrome; TKI, tyrosine kinase inhibitor.

STAT5, also downstream of IL-2 cytokines including IL-15, was also shown to induce miR-21 expression by binding to its promoter region (Lindahl et al., 2016). Silencing of miR-21 in primary SS cells, as well as the use of antagomir to miR-21, resulted in apoptosis (Narducci et al., 2011; Ralfkiaer et al., 2011; van der Fits et al., 2011).

miR-21 overexpression was also described in other inflammatory conditions and is thus not useful in CTCL diagnosis. Important to the consideration of miR-21 as a potential therapeutic target in CTCL are the data showing aberrant overexpression of miR-21 in skin stroma (Lindahl et al., 2016) of CTCL patients. Thus, its dysregulation is not specific to the neoplastic population. This may limit any therapeutic inhibition of miR-21 that does not specifically target the neoplastic population via some modification of the drug compound.

miR-155

miR-155 is constitutively overexpressed in malignant cells from CTCL patients, which has been associated with specific action of STAT5. Indeed, supplementation of primary cells with IL-15 induces miR-155 expression, whereas use of a JAK inhibitor decreases it (Kopp et al., 2013a). Inhibition of miR-155 inhibits proliferation of malignant T cells (Kopp et al., 2013a).

Disease progression is of particular research and clinical interest in CTCL, because stage of disease significantly affects prognosis (Kohnken et al., 2016; Virmani et al., 2017). Two studies have noted higher miR-155 levels in advanced-stage MF patients (Fava et al., 2017; Moyal et al., 2013) and suggest that miR-155 may be involved in the progression of CTCL. STAT5 was shown to decrease expression of putative tumor suppressor SATB1 via induction of miR-155 in a disease stage-dependent manner (Fredholm et al., 2018). Furthermore, it was shown using in situ hybridization that miR-155 was more highly expressed in malignant cells than in non-neoplastic infiltrating lymphocytes (Kopp et al., 2013b).

One of the few current clinical trials involving the targeting of miR in cancer is a miR-155 inhibitor, currently being investigated for the indication of CTCL (Querfeld et al., 2017). An oligonucleotide developed by miRagen Therapeutics (Boulder, CO) is currently being evaluated in a first-in-human study in MF patients. Administration of this drug is intratumoral or subcutaneous, highlighting the benefits of MF as an indication for this type of therapy, because the neoplasm is readily accessible for practical and efficient delivery of the compound. Thus far, the drug has been well tolerated. Furthermore, early data suggest efficacy with increased tumor cell death (Querfeld et al., 2017). This ongoing clinical trial provides a prime example of the use of preclinical data to support the development of a miR-based therapy and further highlights the benefits of a cutaneous neoplasm as an early potential indication for these types of therapies.

miR-214

miR-214 expression is often significantly correlated with overall survival in various cancer types (Feng et al., 2017). As mentioned, miR-214 has extensive implications for diagnosis and prognostication of CTCL. In fact, miR-214 represents one of the four most differentially expressed miRs in SS patients (Qin et al., 2012).

Through its targeting of anti-apoptotic Bcl-2 (Wang et al., 2013) and tumor-suppressor PTEN (Wang et al., 2012), miR-214 has effects on cellular survival and response to chemotherapy. Because of the multitude of critical cellular targets of miR-214, it has been characterized as a master miRNA with regard to essential drug resistance pathways (An et al., 2017). Thus, targeting miR-214 may improve sensitivity of cancer cells to numerous types of anticancer drugs. For example, a recent study in non-small cell lung cancer showed reversal of resistance to erlotinib through down-regulation of miR-214 (Liao et al., 2017).

Because of increased expression of miR-214 and its proposed oncogenic role in CTCL, we sought to explore the potential efficacy of inhibiting its expression. We used a miR-

214 inhibitor in vivo in a mouse model of CTCL that is highly translatable to the human disease (Mishra et al., 2016). Administered by subcutaneous injection, a specific inhibitor to miR-214 resulted in clinical improvement of gross disease in CTCL mice compared with scrambled control (Kohnken et al., 2017). On examination of the lesions histologically, miR-214 inhibitor–treated mice were significantly improved compared with control animals. This preclinical efficacy study supports the future investigation of inhibiting miR-214 as a therapeutic strategy in CTCL.

miR-29b

A recent characterization of miRs as epi-miRs is an apt description for miR-29b. *Epi-miRs* are those that have extensive effects on epigenetic regulators, thus influencing the overall epigenetic landscape of the cell. miR-29b is known to target and down-regulate histone deacetylase HDAC4 in multiple myeloma (Amodio et al., 2012, 2016) and DNA methyltransferase DNMT3 in acute myeloid leukemia (Cui et al., 2015). Additionally, miR-29b targets pro-survival genes such as SP-1 (Eiring et al., 2010). Associated with these many functions, miR-29b is often considered to act as a tumor suppressor, and its expression is down-regulated in many cancer types (Yan et al., 2015).

Epigenetic dysregulation is an important hallmark of CTCL disease progression. We recently described decreased miR-29b expression in CTCL patients compared with normal donors (Kohnken et al., 2018). We have shown the role of IL-15 signaling in driving the decrease in expression of miR-29b in large granular lymphocytic leukemia and CTCL, both neoplasms driven by IL-15 (Mishra et al., 2012). IL-15 and miR-29b seem to cooperate to contribute to widespread epigenetic dysregulation in these neoplasms. Adding to the known targets of miR-29b that affect the epigenetic landscape of neoplastic cells, we describe BRD4, which has been shown to be a survival factor in several types of tumors (Delmore et al., 2011; Herrmann et al., 2012). Indeed, pharmacologic rescue of miR-29b by bortezomib or direct transfection of neoplastic cells with a miR-29b mimic results in reduced cellular survival and proliferation with decreased protein expression of BRD4 (Kohnken et al., 2018).

CONCLUSION

Mechanisms of regulation of miRs and emerging mechanisms of miR function are being discovered at a rapid pace. This review seeks to provide a comprehensive yet approachable summary of the emerging world of miR therapeutics. miR-based therapy represents the latest example of the capacity for improving the lives of people through the benefit of basic science. The success of these programs, which seek to integrate the complexities of RNA biology with the necessity of a cure, will rely on the successful cooperation of researchers, clinicians, and pharmacologists in advancing of the future of therapy.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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