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# Roles of MicroRNA in T-Cell Leukemia

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## 1. Introduction

Previously, cancer researchers have been focused on the genes that code proteins. They have considered those effects on tumorigenesis. However, discoveries of microRNAs (miRNAs) have shed a light on the role of non-protein-coding RNAs in tumorigenesis. The first small non-coding RNA, named *lin-4* in *Caenorhabditis elegans* (*C. elegans*) was described by Lee et al in 1993 (Lee et al., 1993). *Lin-4* codes miRNA that regulates the timing of *C. elegans* larval development by translational repression (Ambros, 2000). Since then, many miRNAs in different organisms such as plants, *C. elegans*, Drosophila, and mammals including humans have been discovered substantially. Up to now, the human genome is predicted to encode as many as 1,000 miRNAs.

miRNAs belong to a class of regulatory genes that are single-stranded 19-25 nucleotides non-cording RNAs and are generated from endogenous hairpin-shaped transcripts (Kim, 2005). miRNA genes are located either within the introns or exons of protein-coding genes (70%) or in intergenic regions (30%). More than 50% of mammalian miRNAs are located within the intronic regions of protein-coding genes. Most of the intronic or exonic miRNAs are transcribed in parallel with their host genes, indicating that these miRNAs use their host genes transcriptional machinalies. On the other hand, miRNAs produced from intergenic regions are transcribed separately from internal promoters (Rodriguez et al., 2004).

The first step of miRNA synthesis is the transcription of primary miRNA (pri-miRNA) from *miRNA* genes (Fig.1). pri-miRNAs are transcribed in a RNA polymerase II (Pol II) - dependent manner as several hundreds or thousands of nucleotides long polyadenylated RNAs. In the nucleus, the pri-miRNA is processed to a precursor miRNA (pre-miRNA) of 60-100 nucleotides in length with a stem-loop structure by the nuclear protein Drosha that belongs to class II RNase III. Drosha interacts with its cofactor DGCR8 (the DiGeorge syndrome critical region gene 8 protein). Then, the pre-miRNA is exported from the nucleus to the cytoplasm by the Exportin 5/Ran-GTP complex. In the cytoplasm, the pre-miRNA is cleaved by class III RNase III, Dicer, which is a 200-kDa protein and miRNA is produced. Primary function of miRNAs in the cytoplasm is the negative regulation of gene expression by binding to complementary target sequences in the 3' untranslated region (UTR) of mRNA. Binding of a miRNA to the target mRNA typically leads to translational repression or degradation of mRNA, which means that miRNAs repress the expression of the target genes. In mammals, miRNAs guide the RNA induced silencing complex (RISC) to

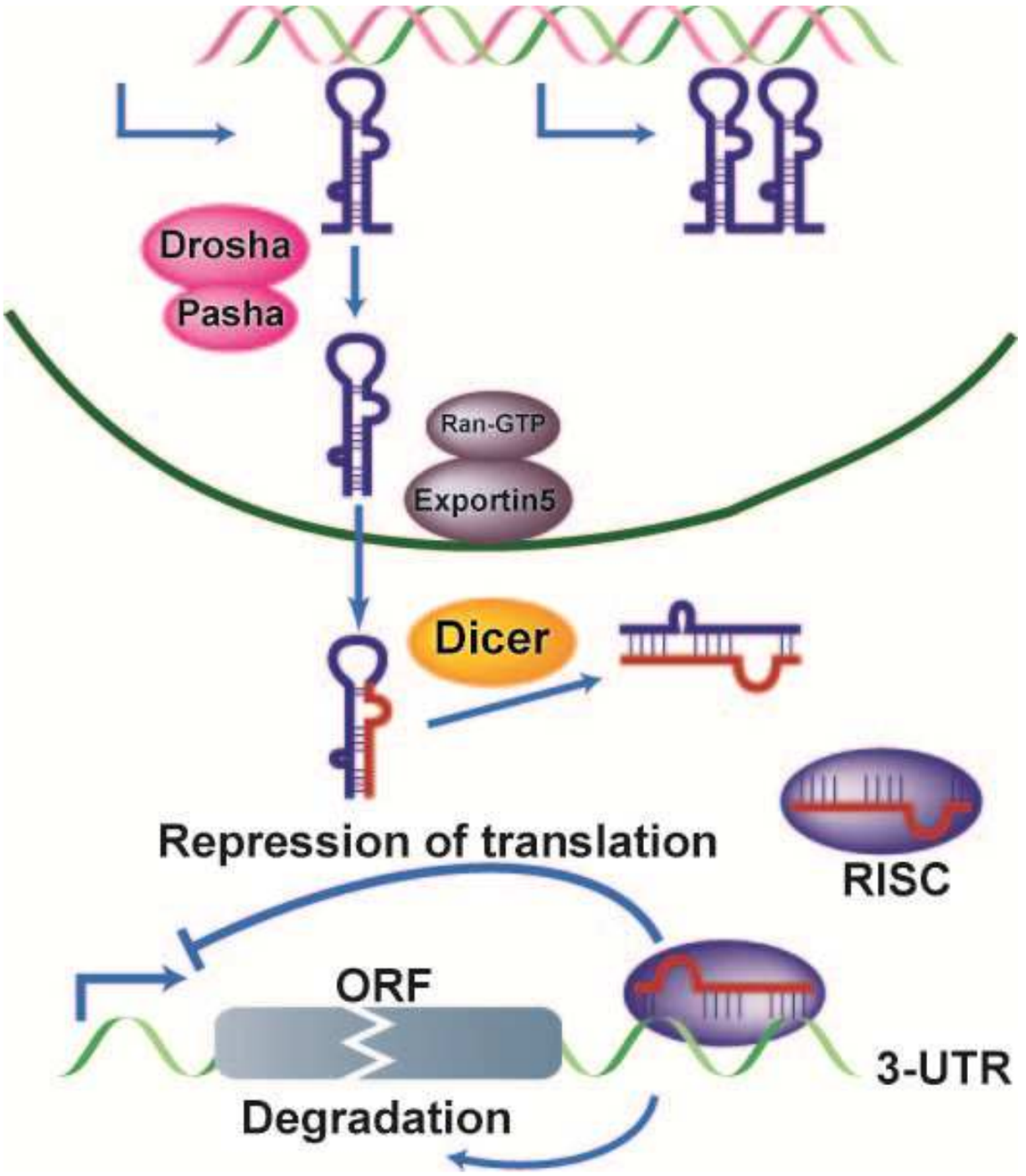


Fig. 1. miRNA biogenesis

complementary target sites of their specific target mRNAs, where endonucleolytically active Ago protein cleaves the mRNAs (Martinez et al., 2002). In contrast, other miRNAs predominantly bind to partially complementary target sites. Such imperfect binding between miRNAs and target mRNAs leads to repression of translation and/or deadenylation, followed by destabilization of the target mRNAs (Pillai et al., 2007). miRNAs are estimated to regulate more than 30% of mRNAs. Therefore, miRNAs have many roles in biological processes, such as development, differentiation, cell proliferation, apoptosis, and

stress responses (Bartel, 2004). Moreover, one target gene usually contains binding sites for multiple miRNAs, allowing miRNAs to form more complex regulatory networks of gene expression (Lewis et al., 2003).

## 2. microRNA in cancer

Over the recent years, many miRNAs have been implicated in many human cancers. The first evidence for the importance of miRNAs in human cancer was the discovery of the loss of miR-15a/miR-16-1 cluster in chronic lymphocytic leukemia (CLL) (Calin et al., 2002). Since then, aberrant numerous miRNAs expression has been shown to be involved in the development of human cancers.

Many miRNAs have been shown to function as oncogenes in human cancers. Among them, miR-155, which is encoded by nucleotides 241 – 262 of B-cell integration cluster (*BIC),* is the first miRNAs linked with cancer (Metzler et al., 2004). After the discovery, many research groups have shown that *miR-155* is highly expressed in various human cancers, including childrend's Burkitt's lymphoma (Metzler et al., 2004), Hodgkin's lymphoma, CLL (Kluiver et al., 2005), primary mediastinal non-Hodgkin's lymphoma (Calin et al., 2005), acute myelogenous leukemia (Garzon et al., 2008), lung cancer, breast cancer (Volinia et al., 2006), and pancreatic cancer (Greither et al., 2010). *miR-155* transgenic mice develop acute lymphoblastic leukemia (ALL) and high-grade lymphoma (Costinean et al., 2009). These results support the idea that miR-155 plays a role as oncogene *in vivo*.

On the other hand, many miRNA encoding genes have been shown as tumor suppressor genes. As mentioned above, miR-15a/miR-16-1 cluster was the first to establish the link between miRNAs and cancer. This study showed loss of miR-15a/miR-16-1 cluster, which are located at chromosome 13q14, a region deleted in more than 65% of B cell CLL (Calin et al., 2002). These miRNAs induce apoptosis through the negative regulation of the anti-apoptotic gene *Bcl2* (Cimmino et al., 2005). Indeed, down-regulation of miR-15a/miR-16-1 has been associated with the pathogenesis of CLL (Calin et al., 2008). These data support the idea that miR-15a/miR-16-1 plays a role as tumor-suppressor genes.

In this review, we introduce the accumulating evidences for the central roles that miRNAs play in hematological malignancy, in particular focusing on their role in T-cell leukemia and lymphoma.

## 3. microRNA in T-cell leukemia and lymphoma

### 3.1 Acute lymphoblastic T-cell leukemia/lymphoma (T-ALL)

Acute lymphoblastic leukemia (ALL) is the most common neoplasm in children, while it is relatively rare in adults. Although ALL originates from either B or T-cell progenitors, most cases are of B-cell ALL (B-ALL) (Pui & Evans, 2006). The less common type, T-cell ALL (T-ALL) is induced by the transformation of T-cell progenitors, and is diagnosed in 10-15% of children and 25% of adults with ALL (Copelan & McGuire, 1995). Molecular mechanisms of leukemogenesis of T-ALL have been investigated intensively. Recent studies revealed that 50-70% of T-ALLs have gain-of-function mutations in *Notch1*, a gene that is essential for T-cell development (Ferrando, 2009). miRNAs expression profiles in T- and B-ALL are highly associated with the lineage from which the leukemia derived (Lu et al., 2005). Some miRNAs can be discriminative of T-ALL versus B-ALL (Fulci et al., 2009). Although

miRNAs that associated with leukemogenesis of B-ALL have been well documented (Lawrie, 2008), a few studies have been demonstrated association between particular miRNA and pathogenesis of T-ALL.

Recently, Mavrakis et al. have revealed association between miR-19 and leukemogenesis in T-ALL (Mavrakis et al., 2010). miR-19 was identified within the miR-17-92 cluster. The cluster is located at human chromosome 13q31 in a genomic region that is often amplified in many human cancers (Lu et al., 2005; Nagel et al., 2009). This cluster is also implicated in human hematopoietic malignancies (He et al., 2005; Mendell, 2008; Xiao et al., 2008). Xiao et al. have shown that miR-17-92 cluster is highly expressed in hematopoietic tumors and promotes lymphomagenesis *in vivo* (Xiao et al., 2008). Indeed, retroviral expression of miR-17-92 cluster genes accelerates c-Myc-induced B-cell lymphoma (Mu et al., 2009). The miR-17-92 cluster encodes 15 miRNAs including miR-19 with overlapping functions in development (Ventura et al., 2008). More recently, Mavrakis et al. demonstrated that miR-19 expresses at levels seen in other human tumors, enhances lymphocyte survival and is sufficient to cooperate with Notch1 in T-ALL *in vivo*. They found a 5-17 fold increase in miR-19 expression in T-ALL, and less for other miRNAs in the miR-17-92 cluster. miR-19 has a distinct ability to enhance lymphocyte survival *in vitro*. miR-19 target genes were identified by a large-scale short hairpin RNA screening, including multiple negative regulators in PI3K pathway such as PTEN, Bim, AMP-activated kinase (Prkaa1), and PP2A (Mavrakis & Wendel, 2010). The expression of these genes is regulated by miR-19 in lymphocytes, indicating that miR-19 produces a coordinate clampdown on multiple negative regulators of PI3K-related survival signals (Mavrakis et al., 2010).

Bhatia et al. recently reported downregulation of the expression of miR-196b in the human T-cell leukemia cell line, and T-ALL patients samples (Bhatia et al., 2011). Same group has shown that miR-196b has the capacity to downregulation the overamplified *c-myc* gene, recognized as a common pathogenomic feature leading to many cancers including B-ALL (Bhatia et al., 2010). In addition, they have demonstrated that miR-196b downregulation several *c-myc* effector genes like human telomerase reverse transcriptase (hTERT), the catalytic component of telomerase enzyme responsible for unlimited proliferative potential of cancerous cells, Bcl-2, the anti-apoptotic protein involved in inhibition of cellular apoptosis, and apoptosis antagonizing transcription factor (AATF). Indeed, restoration of miR-196b in EB-3 cells derived from a Burkitt lymphoma leads to significant downregulation of *c-myc* and its effector genes and qualifies for tumor suppressor function in B-ALL (Bhatia et al., 2010). On the contrary, miR-196b loses its ability to down regulate *c-myc* gene in T-ALL as a consequence of mutations in its target binding region in 3'UTR of *c-myc* gene (Bhatia et al., 2011). Although miR-196b is implicated to have different functions in T-ALL from in B-ALL, the role of miR-196b on leukemogenesis of T-ALL is still unclear. Another group's recent study has shown that miR-196a and miR-196b as regulators of the oncogenic ETS transcription factor *ERG* (Coskun et al., 2011). *ERG* has been known as playing important physiological and oncogenic roles in hematopoiesis (Baldus et al., 2006). It is also a prognostic factor in a subset of adult patients with T-ALL (Baldus et al., 2006; Loughran et al., 2008). They found that miR-196a and miR-196b expression was associated with an immature immunophenotype (CD34 positive) in T-ALL patients (Coskun et al., 2011). These findings indicate miR-196a and miR-196b as *ERG* regulators and implicate a potential role for these miRNAs in T-ALL.

### 3.2 Adult T-cell leukemia/lymphoma (ATLL)

ATLL is an aggressive lymphoproliferative disorder that occurs in individuals infected with human T-cell leukemia virus type 1 (HTLV-1) (Matsuoka & Jeang, 2007). HTLV-1 causes ATLL in 3-5% of infected individuals after a long latent period of 40-60 years (Tajima, 1990). More than 20 million people are infected with HTLV-1 worldwide. ATLL occurs mainly in regions where HTLV-1 is endemic, mainly southern Japan, West Africa, and the Caribbean basin. ATLL is classified into four clinical subtypes termed acute, lymphoma, smoldering, and chronic. The prognosis of ATLL patients remains poor with a median survival time of 13 months in aggressive cases (Yamada et al., 2001). HTLV-1 encodes a protein Tax in its genome. The malignant growth and survival of HTLV-1-infected T-cells can be attributed to Tax, that is a modulator of many transcription factors and associations with molecules of signal transduction pathways that alter expression of host-cell genes involved in proliferation, apoptosis, and genetic stability (Marriott & Semmes, 2005; Boxus et al., 2008). Recent studies have shown the interactions between HTLV-1 and the miRNA regulatory network.

miRNA expression profiling studies in HTLV-1-infected T-cell lines and ATLL patients samples have been performed by some groups (Pichler et al., 2008; Yeung et al., 2008; Bellon et al., 2009). Pichler et al. demonstrated that 4 miRNAs (miR-21, miR-24, miR-146a, and miR-155) are upregulated and miR-223 is downregulated in HTLV-1-transfected cells by real-time RT-PCR to analyze selected sets of miRNAs that already been implicated in oncogenic transformation (Pichler et al., 2008). Bellon et al. idenentified aberrant expression of hematopoietic-specific miRNAs included miR-150, miR-155, miR-223, miR-142-3p, and miR142-5p (upregulated) and miR-181a, miR-132, miR-125a, and miR-146b (downregulated) in ATLL cells versus control peripheral blood mononuclear cells (PBMC) and CD4+ T-cells, and HTLV-1-infected cells lines *in vitro* and uncultured *ex vivo* ATLL cells (Bellon et al., 2009). These results were confirmed by real-time RT-PCR in additional ATLL cases and infected cell lines. They also demonstrated that treatment of HTLV-1-infected cell lines with an NF-κB inhibitor (pathenolide) or JNK inhibitor (JNK II) resulted in reduced levels of the miR-155 precursor (Bellon et al., 2009).

Moreover, Yeung et al. demonstrated that 6 miRNAs (miR-9, miR-17-3p, miR-20b, miR-93, miR-130b, and miR-18a) are upregulated and 9 mi-RNAs (miR-1, miR-144, miR-126, miR-130a, miR-199a*, miR-338, miR-432, miR-335, and miR-337) are downregulated both in HTLV-1-transformed cell lines and primary ATLL cells (Yeung et al., 2008). To distinguish miRNAs that are responding to proliferative stimuli, they also examined PBMC exposed to phorbol-12-myristate 13-acetate (PMA) compared to untreated PBMC. By these comparisons, they identified 3 miRNAs (miR-93, miR-130b, and miR-18a) that were upregulated in ATLL cells, HTLV-1-infected cell lines and PMA-treated cells, an additional miRNA, miR-335, was downregulated in all three cell types. Then they focused on miR-93 and miR-130b, those were confirmed increased expression in the ATLL samples by real-time RT-PCR. These miRNAs served to regulate tumor protein 53-induced nuclear protein 1 (TP53INP1), that is a cellular tumor suppressor protein whose activity governs cellular survival and proliferation (Yeung et al., 2008). Pichler et al. have shown that TP53INP1 is a potential mRNA target of miR-21, miR-24, miR-146a, and miR-155 (Pichler et al., 2008) .TP53INP1 is induced by the p53 response triggered by various stress treatments such as gamma irradiation, UV irradiation, and oxidative stress. Accumulation of TP53INP1 results in a block in the cell cycle at $G_1$ (Tomasini et al., 2003) and triggers apoptosis through increased phosphorylation of p53 on Ser46 (Okamura et al., 2001) and upregulation of

selected p53-responsive genes such as p53AIP1 (Okamura et al., 2001), p21 and Bax (Tomasini et al., 2001). These results suggest that miRNAs enhance cell growth and suppress apoptosis through targeting TP53INP1.

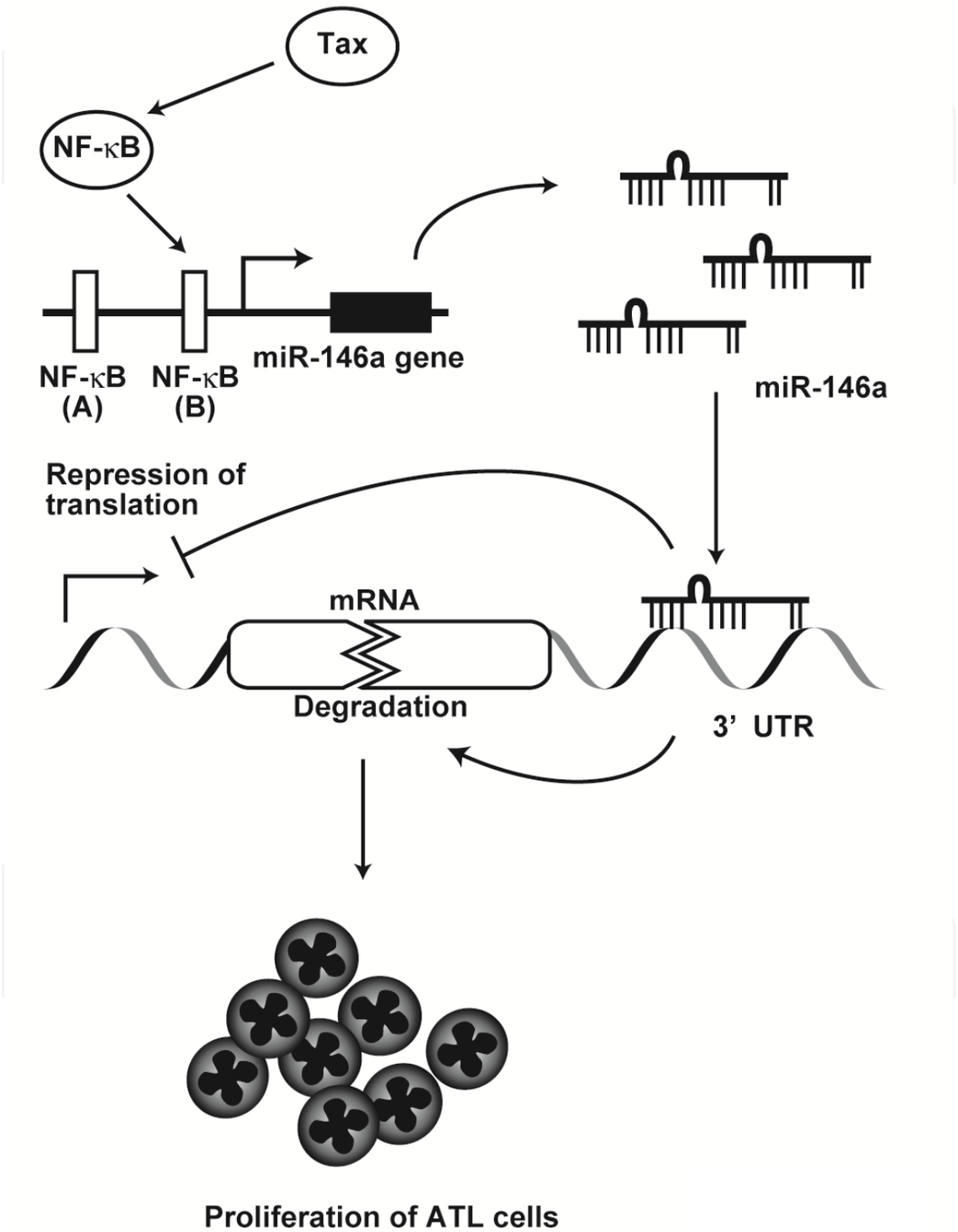


Fig. 2. Schematic representation of the effects of Tax on miR-146a expression (Tomita et al., 2011)

Although several miRNA profiling experiments accumulate miRNA subsets up or downregulated in HTLV-1-infected T-cell lines and ATLL patient's samples, data of miRNA expression profiles are not consistent in these reports. This inconsistency could be due to methodological differences in the techniques employed to prepare RNA from the cells and/or to hybridize probes to microarray.

Among the miRNA expression profilings, miR-146a was found to be activated by Tax in an NF-κB-dependent manner (Pichler et al., 2008). Two potential NF-κB binding sites were identified in the miR-146a promoter. They found that the proximal NF-κB binding site on the *miR-146a* gene is responsible for transcriptional activation by Tax (Pichler et al., 2008). Recently, our group demonstrated that *miR-146a* gene expression is activated by Tax in NF-κB-dependent manner (Tomita et al., 2011). We found that the miR-146a promoter was highly bound by NF-κB complexes in HTLV-1-infected cells, while treatment with the NF-κB inhibitor Bay11-7082 reduced binding and interfered with expression of the miR-146a (Tomita et al., 2011). In contrast to Picheler's results, we observed binding between NF-κB protein and distal NF-κB binding site, not proximal one (Fig. 2). Moreover, we observed that miR-146a plays an important role in the growth of HTLV-1-infected T-cells (Tomita et al., 2011). Treatment of HTLV-1-infected cell lines with an anti-miR-146a inhibitor interfered with their growth and increased the expression levels of TRAF6, a predicted target for miR-146a. On the other hand, a growth-enhancing effect was observed in HTLV-1-infected cell line forced to overexpress miR-146a. These results suggest that miR-146a might be a good therapeutic target in ATLL.

Recently, Sasaki et al. demonstrated that ATLL cells showed a decreased level of miR-101 and miR-128a expression compared with the cells from HTLV-1 carriers (Sasaki et al., 2011). Moreover, there was a clear inverse correlation between *Enhancer of zeste homolog 2* (EZH2) expression and miR-101 expression or *EZH2* expression and miR-128a expression, suggesting that increased EZH2 is caused by the decrease in these miRNAs expression (Sasaki et al., 2011). EZH2 is a critical component of polycomb repressive complex 2 (PRC2), which mediates epigenetic gene silencing through trimethylation of H3K27 (Cao et al., 2002; Czermin et al., 2002). ATLL patients with high *EZH2* expression showed shorter survival than patients with low *EZH2* expression (Sasaki et al., 2011), indicating that increased EZH2 plays a role in the process of ATLL progression.

### 3.3 Sézary syndrome and mycosis fungoides

Sézary syndrome is a rare aggressive form of primary cutaneous T-cell lymphoma characterized by erythroderma, generalized lymphadenopathy, and the presence of neoplastic cerebriform nucleated $CD4^+$ T-cells (Sézary cells) in peripheral blood. Patients with Sézary syndrome have a high leukemic burden and a poor prognostic outcome, with an estimated 5-year survival of only 24% (Willemze et al., 2005). Mycosis fungoides, the most common cutaneous T-cell lymphoma, is a malignancy of mature, skin-homing T-cells. Sézary syndrome is often considered to represent a leukemic phase of mycosis fungoides. Recently, Ballabio et al. performed miRNA profile of $CD4^+$ T-cells from Sézary syndrome patients. They identified 114 miRNAs specifically expressed in Sézary syndrome (Ballabio et al., 2010). They demonstrated that levels of 4 microRNAs (miR-150, miR-191, miR-15a, and miR-16) correctly predicted diagnosis of Sézary syndrome with 100% accuracy, whereas miR-223 and miR-17-5p were 96% accurate. Further analysis revealed that levels of miR-223 distinguished Sézary syndrome samples from healthy controls and patients with mycosis

fungoides in more than 90% of samples (Ballabio et al., 2010). miR-342 expression in Sézary syndrome was negatively regulated by miR-199a* expression. Transfection with either miR-342 or miR-199a* inhibitor resulted in a significant increase in levels of apoptosis of SeAx cells, suggesting that downregulation of miR-342 plays an important role in the pathogenesis of Sézary syndrome by inhibiting apoptosis (Ballabio et al., 2010). These data indicate that miRNAs are important in the pathogenesis of Sézary syndrome and provide possibilities for the diagnosis and treatment of this disease.

### 3.4 Anaplastic large-cell lymphoma

Anaplastic large cell lymphoma (ALCL) with anaplastic lymphoma kinase (ALK)-positive is a T-cell lymphoma consisting of lymphoid cells that are usually large with abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, with *ALK* gene rearrangements. It tends to occur in children or young adults. The most commonly involved extranodal sites are skin, bone, soft tissues, lung and liver. The 5-year survival of ALCL with ALK-positive patients is about 70%, in contrast to ALCL with ALK-negative, which shows poor prognosis (Swerdlow et al., 2008). Recently, Merkel et al. demonstrated that five members of the miR-17–92 cluster were expressed more highly in ALCL with ALK-positive, whereas miR-155 was expressed more than 10-fold higher in ALCL with ALK-negative. Moreover, miR-101 was downregulated in all ALCL model systems, but forced expression of miR-101 attenuated cell proliferation only in ALK-positive and not in ALK-negative cell lines, suggesting different modes of ALK-dependent regulation of its target proteins (Merkel et al., 2010). For future therapeutical and diagnostic application, it will be interesting to study the physiological implications and prognostic value of the identified miRNA profiles.

## 4. Conclusion

Molecular targeting therapy based on miRNAs hold great promise for the development of more effective and less toxic personalized treatment strategies against cancer. Approach of targeting therapy needs deeper knowledge of the molecular changes that associate with development and progression of the diseases. The research on miRNAs is rapidly progressing from *in vitro* to *in vivo* and this becomes a powerful tool for molecular targeting therapy for human cancers. Although there is emerging evidence that miRNAs are involved in the pathogenesis of many cancers, including B-cell lymphomas, there are very little published data on the involvement of miRNAs in human T-cell leukemias/lymphomas that were discussed in this review. It is necessary to accumulate more molecular data that indicate association between miRNAs and T-cell leukemia/lymphoma.

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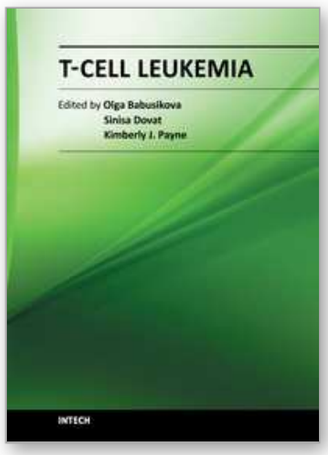


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The purpose of this book is to provide a comprehensive review of the scientific advances in T-cell malignancies and to highlight the most relevant findings that will help the reader understand both basic mechanisms of the disease and future directions that are likely to lead to novel therapies. In order to assure a thorough approach to these problems, contributors include basic scientists, translational researchers and clinicians who are experts in this field. Thus, the target audience for this book includes both basic scientists who will use this book as a review of the advances in our fundamental knowledge of the molecular mechanisms of T-cell malignancies, as well as clinicians who will use this book as a tool to understand rationales for the development of novel treatments for these diseases.



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