Involvement of MicroRNA in T-Cell Differentiation and Malignancy

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ABSTRACT
MicroRNAs are 19-22 nucleotide RNAs involved in such important processes as development, proliferation, differentiation and apoptosis.Different miRNAs are uniquely expressed in lymphoid T cells, and play a role indevelopment and differentiation of various subtypes by targeting their target genes. Recent studies have shown that aberrant miRNA expression may be involved in T cell leukemogenesis and lymphogenesis, and may function as tumor suppressor (such as miR-451, miR-31, miR-150, and miR-29a) or oncogene (e.g. miR-222, miR-223, miR-17-92, miR-155). MiRNAs can be used as new biomarkers for prognosis and diagnosis or as an index of disease severity in T-cell leukemia and lymphoma. This article presents a review of studies in recent years on the role of miRNAs in T-cell development and their aberrant expression in pathogenesis of T-cell leukemia and lymphoma.Characterizing miRNAs can help recognize their role as new important molecules with prognostic and therapeutic applications.
KEYWORDS: MicroRNA, Leukemia, Lymphoma, Tumor Suppressor, Oncogene

INTRODUCTION

MicroRNAs(miRNA)are small 19-22 nucleotide non-coding, post- transcriptional regulatory RNA molecules involved in regulation of gene expression and a variety of biological processes like cell development, proliferation, differentiation, apoptosis and hematopoiesis [1,2].For miRNA biogenesis, Pri-miRNA with more than 1kb in length is first transcribed by RNA polymerase II, and is then converted to 70 nucleotide Pre-miRNA using a protein complex including nuclease Drosha and DiGeorge syndrome critical region gene 8 (DGCR8) [3]. Pre-miRNA is transported from nucleus to cytoplasm using exportin 5, and is converted to a double stranded 21-22 nucleotide miRNA by RNase III enzyme Dicer [4]. Only one strand of this mature miRNA is loaded on and incorporated with RNA-induced silencing complex (RISC). Single-strand mature miRNA ultimately drives RISC towards the 3'-UTR of the target mRNA to inhibit translation of mRNA or decrease stability [5,6].

T cells are differentiated in thymus, and can be categorized by expression of CD4 and CD8 phenotypes. Development of thymocytes begins from double negative [DN (CD4- CD8-)] stage, continues with double positive [DP (CD4+ CD8+)] stage and ends in single positive [SP (CD4+ or CD8+)] stage circulating in blood and peripheral lymph nodes[7]. When confronted with an infectious agent, naive CD4+ T-cell can be differentiated to at

least four effector lineages including T helper type 1 cells (Th1), Th2 cells, Th17 cells and regulatory T-cells (Treg cells), while naive CD8+ T-cell differentiates to cytotoxic effectors(8). Each of these populations has specific miRNA expression profiles, which participate in regulation of development from DN stage and in differentiation to different subtypes [9]. Dysregulated expression of miRNAs has been found to be involved in many cancers, including cancers of the immune cells [10]. In this paper, we first evaluate the role of different miRNAs in T-cell development and then altered expression of miRNAs in T-cell leukemia and lymphoma will be considered. Finally, prognostic and diagnostic importance and therapeutic use of miRNA will be discussed.

MicroRNAs and T-lymphocyte differentiation
Recent studies have shown that distinctive miRNAs are expressed in innate and acquired immune cells, and are involved in regulation of their development and function. Differentiation of various T-cell subgroups is regulated by targeting different proteins/molecules of signaling pathways by a variety of miRNAs, resulting in initiation or inhibition/termination of differentiation (Figure 1).

MiRNA-17-92
MiRNA-17-92 is highly expressed in T precursor cells, and is decreased after maturation. Bcl-2-interacting mediator of cell death (Bim) is the target gene of miR-17-92. MiR-17-92 also regulates the expression of phosphatase and tensin homolog (PTEN) tumor suppressor gene, which has been associated with lymphoproliferation in miR-17-92-transgenic models. All lymphocyte types in mice transfected with this miR-17-92 undergo expansion and show enhanced proliferation and survival, especially for CD4$^+$ T-cells [11, 12].
B-cell lymphoma 6 protein (Bcl-6)is involved in the development and function of T follicular helper cells (Tfh), inhibits the expression of miR-17-92 which silences CXCR5 and differentiation to Tfh results [13]. Increased expression of miR-17-92 at DN stage 1 results in autoimmunity, leading to increased

proliferation and survival of T-cells particularly effector CD4+ T-cells [14]. Expression of this miRNA is highly induced after T cell activation, decreased after clonal expansion and silenced during memory development [15]. Increased expression of miR-17-92 in effector CD8+ T cells enhances mTOR signaling. The results of Western Blot and FACS on miR-17-92-MIT-transduced P14 cells have confirmed decreased expression of negative regulators of PI3-Akt-mTOR signaling pathways such as phosphatase and tensin homolog (PTEN), programmed cell death 1 (PD1), B and T-lymphocyte associated (BTLA), resulting in increased mTOR signaling. This increased signaling directs differentiation towards short-lived terminal effector cells (Figure1) [15].Decreased expression of miR-17-92 has been observed during differentiation towards CD8+ T-cells(16), while its increased expression leads to increased expansion and proliferation of effector CD8+ T-cells(15), indicating its role in CD8 + T-cell effector activity in the face of virus.

MiRNA-125
MiRNA-125 regulates the genes encoding molecules involved in differentiation of naive CD4 + T-cells in humans but not in mice. These genes include IFN-γ, IL-2 receptor β, IL-10 receptor α and the transcriptional repressor Blimp-1 which undergo reduced expression by long-term expression of this miRNA. Transfecting naive CD4+ T-cells by synthetic miR-125 caused these cells to express lower levels of Th1 and Th2 memory surface molecules and show overexpression of naive CD45RA+, CD45RO-, indicating the role of mi-125 in maintenance of naive T-cell status. In fact, it prevents generation of the effector function in T- cells, which is indicated by reduced intracellular production of IFN-γ and IL-13. Reduced expression of miR-125 is associated with effector memory CD4+ T-cell phenotype [17]. MiR-125a is also involved in differentiation to Treg cells, and increased expression of it has been observed in Treg cells [18]. MiR-125 is highly expressed in hematopoietic stem cell (HSC), and is associated with increased self-renewal and
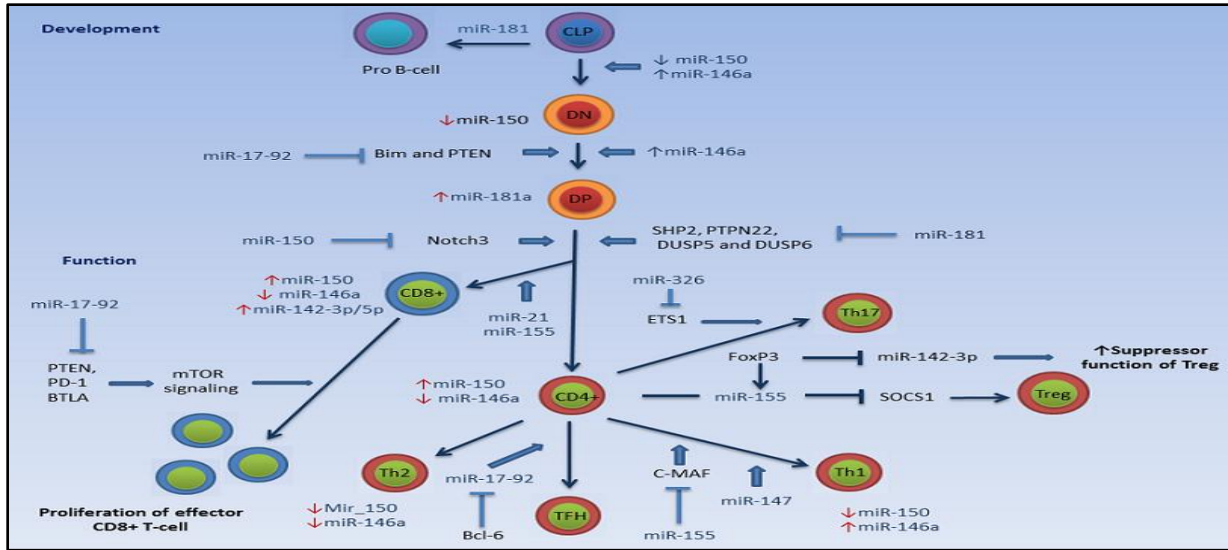
Figure1. Involvement of microRNAs in regulation of T-cell development and function

T-cell development in thymus is influenced by miR -17-92 and 181a. MiR-17-92 is involved in DN thymocyte to DP thymocyte transition by inhibiting the expression of PTEN and Bim, and miR-181 plays a role in transition of DP to SP thymocyte by inhibiting the expression of PTPN22, SHP2 and DUSP5/6. MiR-181a shows the highest expression in DP thymocyte stage. MiR-146a expression rises during the DN to DP transition, while its expression is decreased in SP stage. MiR-146a expression is increased and decreased in Th1 and Th2 cells by differentiation of naïve CD4+ T-cells, respectively. Expression of miR-150 is decreased during the evolution of T-cells, while it is increased in the final stage of development by formation of CD4+ and CD8 + T-cells. Expression of miR-150 is decreased after differentiation of naïve CD4+ T-cells to Th1 and Th2 subtypes. Bcl-6 plays a role in CD4+ T-cell differentiation to TFH by inhibiting expression of miR-17-92. MiR-155 inhibits SOCS1 and c-MAF, causing the differentiation of naïve CD4 + T-

cells to Treg and Th1, respectively. MiR-17-92 expression is increased upon contact with antigen by naïve CD8 + T-cells, leading to proliferation of effector CD8+ cells by inhibiting the expression of PTEN, PD-1 and BTLA.
Abbreviation: CLP: common lymphoid progenitor, **DN:** double negative, **DP**: double positive, **Bim:** Bcl-2-interacting mediator of cell death, **PTEN:** phosphatase and tensinhomologe, **SHP2:** SH2-domain-containing protein tyrosine phosphatase 2, **DUSP5/6**: dual-specificity protein phosphatase 5/6, **PTPN22**, protein tyrosine phosphatase, non-receptor type 22; **Notch 3:** Neurogenic locus notch homolog protein 3, **ETS1:** v-ets avian erythroblastosis virus E26 oncogene homolog 1, **PD-1,** programmed cell death, **BTLA,** B and T- lymphocyte associated, **mTOR:** signaling, mammalian target of rapamycin; **FoxP3:** forkhead box P3, **SOCS1:** Suppressor of cytokine signaling 1, **Bcl-6,** B-cell lymphoma 6 protein, **c-MAF,** macrophage-activating factor, **Th1:** T helper type 1 cells,**Th2:** T helper type 2 cells, **TH17:** T helper type 17 cells, **Treg:** regulatory T-cells, **TFH:** T follicular helper cell.

Survival [19]. Increased expression of miR-125 in HSC deviates differentiation toward the lymphoid lineage, which has a higher level of expression in common lymphoid progenitor (CLP) than common myeloid progenitor (CMP). Increased expression of miR-125b is related to lymphoproliferative disease associated with an increase in CD8+ expansion [20]. MiR-125b has an important role in T-ALL and B-ALL leukemogenesis, and facilitates leukemogenesis in lymphoma through down regulation in interferon regulatory factor-4(IRF4) expression, which plays a role in inhibiting proto-oncogene Bcl-6 [21].

MiRNA-146a
MiRNA-146a is an immune system regulator and is highly expressed in Treg and Th1 cells. The target genes of miR-146a include IL-1 receptor associated kinase 1 (IRAK1) and tumor necrosis factor

receptor-associated factor 6 (TRAF6), which are downregulated by this miRNA(11). It is expressed in immature megakaryocytes, primitive hematopoietic stem/progenitor cells (HSPC) and thymocytes, such that miRNA-146a has the highest expression in DP and DN thymocytes and the lowest expression level in SP thymocytes, and has also a low level of expression in myeloid and erythroid series [22]. Expression and phosphorylation of Signal transducer and activator 1 (STAT1) is increased in mice with miR-146a deficient Tregs, which functions as target gene for miR-146a. STAT1 is the essential transcription factor for Th1 differentiation. MiR-146a by decreasing the level of STAT1 enables Treg cells to suppress Th1 responses, i.e., it is involved in Treg cell-mediated Th1 regulation. Increased IFN-γ in Tregs is essential for controlling IFN-γ dependent Th1 immune responses at least by targeting STAT1,

which is the key molecule in IFN-γ signaling pathways [23]. The absence of miR-146a will disrupt the suppressor function of Treg cells and non-regulated IFN-γ responses by increasing the expression and activation of STAT1 [24]. MiR-146a functions as a negative regulator in toll-like receptor (TLR)/IL-1 signaling pathway by targeting TRAF6 and IRAK1 [23]. IL-1 stimulates the production of IL-17 in CD4+ T-cells including FoxP3 Treg [25]. IRAK1 causes Th17 differentiation in presence of TGF-β, and the absence of miR-146a could exacerbate Th17 responses and result in autoimmunity [26]. TRAF6 is essential in NF-κB activation and downstream of antigen receptor in T-cells(11). NF-κB (p50) is required for expression the induction of miR-146a during T-cell receptor (TCR) stimulation, and plays a role in memory T cell formation [27]. High expression of miR-146a downregulates IRAK1 expression with decreased NF-κB signaling [28].

Studying rheumatoid arthritis patients has indicated that miR-146a plays an important role in differentiation of IL-17 producing T-cells (Th17), and its high expression is directly associated with the expression of IL-17 in peripheral blood mononuclear cells (PBMC) and synovium in these patients [29]. MiR-146a has low and high expression in naive and memory T cells, respectively, such that by stimulation of primary T lymphocytes by phorbol myristate acetate (PMA) and ionomycin, the expression level of miR-146a is sharply increased after 8 days, which coincides with increased CD45R0 as a marker of memory cells [30]. In addition, the memory T cells producing miR-146a are involved in increased expansion by stimulation with anti-CD3 and anti-CD28 [27].Fas-associated death domain (FADD) is also a target for miR-146a, and increased level of this miRNA in T cells protects them against activation-induced cell death (AICD)(30). MiR-146a expression level remains high in Th1 following T naive activation, while it is decreased in Th2 [31]. Ectopic expression of miR-146a leads to significant up-regulation in the expression of transcription factors PU.1, C-fos, GATA3 and CCAAT/enhancer-binding protein alpha (C/EBPα), and slight up-regulation in expression of FoxP3 and Runx1, while leads to down-regulation in the expression of the transcription factors Notch-1, Lmo2, SOS1, Ikaros and STAT3. These results

suggest that ectopic overexpression of miR-146a does not induce differentiation of T-lymphoblasts, and only upregulates the molecules involved in T-cell activation [32]. In the study of Fallah P et al, increased expression of miR-146a in CD133+ cells, significant upregulation of Ikaros genes and specific T-cell markers CD2, CD4 and CD25 indicate the role of this miRNA in differentiation of CD133+ cells to T-lymphoid lineage [33].

MiRNA-150
This miRNA is required for differentiation of lymphocytes from their progenitors, and has a negative effect in proliferation and survival of T-cell acute lymphoblastic leukemia (T-ALL) cell line by targeting Notch3, the transcription factor involved in T cell differentiation and leukemogenesis [9]. Reduced level of mRNA and Notch3 protein and increased miR-150 expression has been observed during T cell maturation from DP to SP (CD4+, CD8+) phenotype [9]. Increased expression of this miRNA in both B and T lymphocytes and lack of its expression in monocytes has been observed [34]. High levels of this miRNA are expressed in mature T and B cells, and such that the miR-150 expression in thymic DN and SP cells is low and high respectively .Increased expression of miR-150 in hematopoietic stem and progenitor cells will cause no change in T cell development.

Expression of miR-150 is silenced in naive T-cells following TCR engagement and differentiation into Th1 and Th2 cells [11, 31]. CXCR4 is another target for miR-150. Expression of CXCR4 protein in mononuclear cells (MNCs) is increased following simultaneous knockdown of miR-150, and their migration is also enhanced, indicating the relationship between this miRNA and stem cell migration [36]. Increased expression of miR-150 in CD133+ cells upregulates the expression of Ikaros and CD4 marker genes, indicating its role in differentiation of CD4 T-lymphoblasts [33].

MiRNA-155
MiRNA-155 is involved in regulation of T cell lineage fate by targeting C-maf, and causes differentiation of T cells to Th1 [11]. Gene expression studies in miR-155 knockout mice indicate increased expression of Th2 cytokines such as IL-4, IL-5 and IL-10, the

transcription factor C-maf and Th2 differentiation [14, 37]. Expression of miR-155 is increased in response to inflammatory stimuli such as TRL-ligand and proinflammatory cytokines. It is important in hemostasis and overall survival in Treg by targeting suppressor of cytokine signaling (SOCS1) [38]. MiR-155 is constitutively expressed in a large number of Tregs in a FoxP3 dependent manner, so that there is an increased expression of miR-155 when Foxp3 is bound to promoter region of BIC gene which encodes miR-155, while the cells lacking FoxP3, B cells and myeloid cells temporarily display an increased expression of miRNA when activated [11, 23]. FoxP3 is involved in differentiation, homeostasis and function of Treg,and is essential in differentiation and proliferation but not immunosuppression of Treg cells by inducing the miR-155 expression. Expression of miR-155 causes increased proliferation through IL-2, STAT5 and IFN-γ signaling pathways by downregulation of SOCS1 expression [14, 23]. BIC/miR-155 plays a key role in homeostasis and function of the immune system, and its expression is increased in B and T lymphocytes and activated dendritic cells [39]. Studies in mice deficient in BIC-miR-155 have indicated that BIC-miR-155 is essential for regulating the development of Foxp3 + Tregs, and will not affect the Treg-suppressive activity [40]. In the study of Banerjee A et al, the use of miR-155 antagonism has increased the expression of IFN-γ receptor α chain in CD4 + T-cells, which has been introduced as the second target gene of miR-155. In fact, miR-155 causes differentiation towards Th1 by inhibiting IFN-γ signaling [41]. MiR-155 is also involved in differentiation and antiviral activity of CD8+ T-cells, so that increased expression of miR-155 has been observed in primary effector and effector memory CD8+ T-cells, and its decreased expression has been observed in naive and central memory cells [42]. In comparison to naive cells, expression of miR-155 along with miR-21 during differentiation of primary CD8+ T cells has been increased, indicating their role in CD8 + T-cell differentiation(16). Antiviral response of CD8+ T-cells is reduced in miR-155 deficient mice, while increased expression of miR-155 results in increase in such response in vivo [42]. The inhibition of miR-155 expression by IL-10 in response to LPS leads to increased expression of Src homology-2 domain-containing in-ositol 5-phosphatase 1(SHIP1) as a miR-155 target. SHIP1 coverts phosphatidylinositol triphosphate (PIP3) to phosphatidylinositol biphosphate (PIP2), reducing PIP3 levels and thus the pro-inflammatory response [43].Increased level of miR-155 has been observed in Hodgkin's and Burkitt's lymphoma [44].

MiRNA-181

MiRNA-181 is preferentially expressed in thymus, lungs and brain, and is expressed in detectable levels in the bone marrow and spleen [4]. High expression level of miR-181 in the spleen indicates its requirement and role in T-cell development [45]. MiR-181a and miR-181c have distinct functions in early T cell development. IL-2 plays a role in T-cell activation and proliferation, and has a binding site for miR-181c in its 3' UTR. Therefore, ectopic expression of this miRNA will negatively regulate CD4+ T-cell activation by inhibiting IL-2, whereas miRNA expression is reduced in effector state [46]. Mir-181a, which plays a role in differentiation and function of T-cells, is present during maturation of T-cell from DN stage1 to DN stage 3 before CD4+ and CD8+ stages, and is reduced in later development stages [47]. It reaches maximum expression in DP T-cell stage, resulting in DP thymocyte differentiation to SP thymocyte, but miR-181c does not play this role [48, 49]. MiR-181a functions as a regulator of TCR signaling after transcription, such that increased expression of miR-181a results in increased TCR signaling in T-cells and vice versa. This regulation is done by decreased expression of such tyrosine phosphatases as SH-2 domain containing protein tyrosine (SHP-2), non-receptor type 22 protein tyrosine phosphatase (PTPN22) and dual-specificity protein phosphatase 5 (DUSP5/6), leading to increased activity of lymphocyte cell specific protein (LCK) and extracellular signal-regulated kinase (ErK) as two TCR signaling molecules(38, 49). PTPN22 is a negative regulator of LCK in downstream TCR signaling. DUSP5 and DUSP6 inactivate ERK1/2 by dephosphorylating in different sites in nucleus and cytoplasm [50]. SHP-2 also mediates negative co-stimulatory signals elicited by CTLA-4 [51]. Activity of the mentioned phosphatases inhibits TCR signaling, and is involved in regulation of TCR sensitivity to

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antigen during positive selection [49]. DP cells have a high level of miR-181a. Expression of miR-181a is inversely related with the expression of Bcl-2, CD69 and TCRα as its targets, indicating its role in regulating positive selection in the thymus [12]. There is an increased expression of this miRNA in thymocytes, indicating its specific role in the early development of thymocytes in the thymus [52]. This miRNA directly drives HSC differentiation towards B cells [5]. Blocking miR-181a in DP cells inhibits both positive and negative selections [44].

MiRNA-182

Foxo family of transcription factors is important in homeostasis and immunological tolerance by controlling the development and function of B and T lymphocytes [53]. Studies have shown that FoxO1 factor is the target of miR-182 in activated T helper cells [54]. Induction of the cell cycle inhibitor p27 and Bim protein by FoxO1 inhibits lymphocyte proliferation and apoptosis. STAT5 is activated by TCR stimulation, IL-2 secretion and IL-2R signaling, and increases miR-182 expression by binding regulatory region of miR-182. In fact, miR-182 expression is directly dependent upon STAT5 activation. Continued expression of miR-182 in activated T helper cells inhibits higher levels of FoxO1 mRNA, resulting in increased clonal expansion of these cells [54, 55].

Other miRNAs

MiR-142 inhibits production of CD4+ and CD8+ T-cells, but has no effect upon B cells [45]. MiR-142-3p and 5p are among miRNAs with the highest expression in CD8+ T-cells [16]. Expression of miR-142-3p is inhibited by FoxP3, leading to increased production of cAMP and suppressor function of Treg cells [56]. MiR-142-3p targets the mRNA of glycoprotein A Repetitions Predominant (GARP), which is highly expressed when CD25 + CD4 T-cell activation occurs, thereby controlling this cell proliferation [57]. MiR-142-3p expression is reduced in effector T-cells but not in naive and memory T cells (58). MiR-147 is induced to differentiate naive CD4+ cells to Th1 cells [59]. Increased miR-106a expression in activated Jurkat T cells is responsible for downregulating the anti-inflammatory cytokine IL-10 [14]. The use of antagomirs for miR-126 reduces

Th2 cell responses [24]. MiR-21 and miR-31 affect FoxP3 expression in Treg cells, so that miR-31 binds the 3' UTR of FoxP3 gene, resulting in direct and negative regulation of its expression, while miR-21 indirectly causes increased expression of it [60]. MiR-21 expression plays an important role in antigen induced CD8 T-cell differentiation, such that its expression is higher in effector and memory CD8+ T-cells compared to naive T-cells [58]. MiR-326 promotes Th17 differentiation by targeting ETS-1 as a negative regulator of Th17, and its increased expression is strongly correlated with the severity of multiple sclerosis (MS) disease [61]. Finally, it can be concluded that the miRNAs 17-92,-125 and -181a are involved in T-cell development up to SP T-cell, and the miRNAs -150, -155,-146a, -182 and -326 play a role in function and differentiation of SP T-cells to various T-cell subtypes (Table 1).

MicroRNA and T-cell leukemia

T-ALL is a malignant disease of T-cell lymphoid progenitor cells, and is responsible for 15% of childhood ALL and 25% of adult ALL cases [63]. Juxtaposition of promoter and enhancer elements of TCR genes with transcription factor genes during VDJ recombination is among the cytogenetic changes causing T-ALL [64]. Cytogenetic changes play an important role in leukemogenesis in cancers of immune cells including T-ALL by altering the expression and function of miRNA, which can function as tumor suppressors or oncogenes (Table 2) [65]. For example, downregulation of miR-151-5p and miR-708 and upregulation of miR-196b in MLL-rearranged ALL and T-ALL subtype has been observed(66). In addition, t(8;14), t(5;10) and t(7;7) chromosomal translocations occurring in ALL affect different gene regions of various miRNAs including miR-196b (chr7p15), miR-148a (chr7p15) and miR-151 (chr8q24), leading to their upregulation or downregulation [63]. Comparison of miRNA expression in ALL subtypes has also indicated the effect of these chromosomal translocations. Each ALL subtype has its own specific miRNA expression profile. For example, reduced expression of miR-151 and increased expression of miR-424 and miR-148 is related to T-lineage ALL, while increased expression of miRNA-425-5p, -191, -128, -629,-146b and -126 is associated with B-lineage ALL [67]. Increased

expression of miR-196b is associated with increased activity of HOX gene family members in T-ALL patients with inversion in chromosome 7, and the relationship between this increased expression and leukemogenesis has not been elucidated and requires further studies [68]. T-cell acute lymphocytic leukemia protein 1(TAL1) complex is ectopically expressed after t(1;14) translocation in T-ALL [64]. This complex causes ectopic expression of miR-223 in transformed DP thymocytes by regulation of miR-223 expression as a direct transcriptional target in normal and malignant T cells. As a tumor suppressor, F-box/WD repeat-containing protein 7 (FBXW7) ubiquitin ligase is repressed through the mentioned pathway. Eventually, important oncoproteins such as c-MYC, MYB and Notch, which are involved in pathogenesis of T-ALL will be stabilized, and the malignant phenotype will appear in T-ALL [69]. Myeloid cell leukemia sequence1 (MCL1) is a target for FBXW7 E3 ligase, the level of which is increased in mouse leukemia expressing miR-223 [70]. MiR-223 is involved in myeloid differentiation, and is considered a myeloid miRNA. Overexpression of this miRNA is observed in T-ALL cases with similar gene profiles and phenotypic characteristics of acute myeloid leukemia (AML) with unfavorable outcomes [71]. Insulin-like growth factor 1 receptor (IGF1R) which plays a role in T-ALL cell growth and leukemia-initiating activity is miR-223 target in its 3'UTR, and its expression is inhibited by miR-223. On the other hand, Notch signaling negatively regulates the expression of mir-223. As a result, Notch signaling supports IGF1R expression directly during increased expression of IGF1R and indirectly through antagonizing miR-223 [72]. MiR-221 and miR-222 are involved in erythropoiesis and erythroid differentiation [73]. MiR-221 and miR-222 show the highest level of expression in early T-cell acute lymphoblastic leukemia (ETP-ALL), and miR-222 affects leukemogenesis by changing the expression of ETS1 proto-oncogene [74]. MiR-222 expression correlates with immature immunophenotype of T-ALL and ectopic expression of CD13 and CD33 myeloid markers, and association with these myeloid characters is due to decreased expression of ETS1 [74].cAMP/protein kinase A (PKA) causes deactivation of T cells and reduced cell proliferation through cyclin D3 downregulation and p27

upregulation [75]. MiR-142 has the highest level of expression in myeloid series but increased expression of it (miR-142-3p) increases leukemogenesis and proliferation by lowering cAMP levels and reducing PKA activity in T-leukemic cells [73, 76]. Hence, activating the cAMP/PkA pathway can be a therapeutic target. This same miRNA causes resistance of T-leukemic cells to glucocorticoid treatment by targeting glucocorticoid receptor (GRα) Mrna [76]. Glucocorticoids are among apoptosis inducing drugs in a wide variety of malignancies [77]. As a result, miR-142-3p plays an important role in T-ALL leukemogenesis, and may be a useful therapeutic target. Increased or decreased expression of miRNAs can be useful in determining prognosis and overall survival of leukemia. For example, increased expression of miR-221, miR-16 and miR-142-3p is related to shorter overall survival in T-ALL, and miR-221 has a poor prognosis [66, 76], [78]. In addition, increased expression of miR-33 in T-ALL causes unfavorable prognosis compared with normal thymocytes [79]. MiR-146a family has been recognized as immune system regulator [11]. In T-ALL, increased expression of miR-146a and miR-146b is associated with an immature immunophenotype and expression of CD34 and CD33. These two miRNAs play the role of ERG regulators in T-ALL and AML [80]. ETS transcription factor ERG plays an important role in hematopoiesis, and its increased expression is an adverse prognosis factor in T-ALL and AML(81). MiR-19 is highly expressed both in T-ALL patients and in cell lines. Its ectopic expression causes silencing of CYLD (Cylindromatosis (turban tumor syndrome) expression which is a negative regulator of NF-κB and JNK signaling, and thus NF-κB expression is induced [82].

Table 1. MicroRNAs relevant to T-lymphocyte differentiation, their target genes and functions

MicroRNAs	Expression	Target genes	Functions	References
miR-17-92	Highly expressed in T-cell precursor and decreased after maturation	Bim, PTEN PTEN, PD1, BTLA	Modulates DN to DP transition. Skews differentiation toward short-lived terminal effector cells by increasing mTOR signaling, promotes effector CD8+ T-cell expansion	(11, 12, 15)
miR-125	Highly expressed in Treg cells	IFN-γ, IL-2R β, IL-10Rα, Blimp1	Maintains the Naive state of T-cell. Involved in Treg differentiation	(17, 62)
miR-126	…..	….	Modulates Th2 responses	(24)
miR-142-3p	Highly expressed in CD8+ t-cells, downregulated in effector T-cells	…..	Repressed by FoxP3 leading to increased suppressor function of Treg cells, highly expressed in CD8+ T-cells	(16, 56, 58)
miR-146a	Highly expressed in DN, DP thymocytes, low expressed in SP thymocyte and Th2	IRAK1, TRAF6 STAT1	Highly expressed in Treg and Th1 cells. Plays a role in Treg cell-mediated Th1 responses	(11, 22) (23)
miR-147	……	…..	Modulates Th1 differentiation	(59)
miR-150	Low expression in DN but high expression in SP ,Silenced after differentiation	Notch3	Modulates maturation from DP to SP stage of thymocyte	(9, 11, 31, 35)
miR-155	…..	c-MAF, IFN-γRα SOCS1	Knockout mice have increased Th2 cell generation and reduced Th17 and Th1 cells. Regulates the development of Treg	(11, 41) (14)
miR-181a	Highly expressed in DP cells	SHP2, PTPN22, DUSP5, DUSP6 Bcl-2, CD69, TCR alpha	Increases TCR signaling in thymocytes and peripheral T-cells, Modulates T cell sensitivity in response to Antigens, Regulates T cell and B cell development Positive selection in thymocyte	(11, 38, 49) (12)
miR-181c	…..	IL-2	Negatively regulates CD4+ T-cell activation	(46)
miR-182	…..	FoxO1	Increases clonal expansion of activated T helper	(54)
miR-326	Increased expression is associated with severity of MS	Ets-1	Promotes Th17 differentiation	(61)

Bim: Bcl-2-interacting mediator of cell death, **PTEN**: phosphatase and tensinhomologe, **PD1**: programmed cell death 1, **BTLA**: B and T- lymphocyte associated, **DN**: double negative; **DP**, double positive, **SP**: single positive, **mTOR**: mammalian target of rapamycin; **Blimp1**, B lymphocyte-induced maturation protein-1, **FoxP3**: forkhead box P3, **IRAK1**: IL-1 receptor-associated kinase-1, **TRAF6**: tumor necrosis factor receptor-associated factor 6, **Notch3**: Neurogenic locus notch homolog protein 3; **c-MAF**, macrophage-activating factor, **SOCS1**, Suppressor of cytokine signaling 1, **SHP2**: SH2-domain-containing protein tyrosine phosphatase 2, **DUSP5**: dual-specificity protein phosphatase 5, **PTPN22**: protein tyrosine phosphatase, non-receptor type 22, **FoxO1**: Forkhead box protein O1, **MS**: multiple sclerosis: **Ets-1**: v-ets avian erythroblastosis virus E26 oncogene homolog 1.

NF-κB binds their upstream promoter regions and regulates their expression, and is one of the mechanisms regulating gene expression in T-ALL [82]. Expression of miR-451 as a tumor suppressor and direct inhibitor of MYC expression is inhibited in T-ALL, and is important in T-ALL oncogenesis by Notch [83]. T-ALL development by Notch oncogene is delayed through deletion in miR-181ab1, indicating the crucial role of miR-181ab in activating Notch oncogenic signals [52]. Lack of miR-181ab causes 32 % increase in median survival of T-ALL mice from 41 days to 54 days [52]. Activation of miR-17-92 by NK like homodomain proteins suppresses apoptosis in T-ALL by reducing the level of E2F1, and the cell survival is therefore increased [84]. Adult T-cell leukemia is a T-cell neoplasm in which the lymphocytes are transformed by type 1 Human T-cell leukemia virus (HTLV-1) with leukemia as the result [85]. Increased miR-155 in plasma and decreased miR-126 levels is correlated with poor prognosis in adult T-cell leukemia (ATL), and can be

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used as a new biomarker for assessing disease stage   and progression [86]. MiR-155 undergoes increased

Table 2. MicroRNAs relevant to T-cell malignancie, their targets and functions

Micro RNA	Aberrant Expression	Targets	T-cell malignancy relevance functions	Prognosis	Biological function	Ref.
miR-222	↑ in ETP-ALL	Ets-1	Associate with immature immunophenotype of T-ALL and aberrant expression of myeloid markers CD13 and CD33	NM	Oncogene	(74)
miR-223	↑ in T-ALL	FBXW7 ubiquitin ligase	Up-regulated by TAL1 complex and promotes the malignant phenotype.	poor	Oncogene	(69, 70)
miR-142-3p	↑ in T-ALL	cAMP/PKA GRα	Increases T-leukemic cell proliferation and leukemogenesis. leading to glucocorticoid resistance	Poor	Oncogene	(76)
miR-221	↑ in T-ALL	....	Associated with shorter OS	Poor	Oncogene	(78)
miR-19	↑ in T-ALL	CYLD	Induces NF-kB expression, promotes leukemogenesis	NM	Oncogene	(82)
miR-451	↓ in T-ALL	MYC	Its reppression is essential for Notch-induced T-ALL	NM	Tumor suppressor	(83)
miR-17-92	↑ in T-ALL	E2F1	Activated by NK like homodomain proteins, suppresses apoptosis and increases cell survival	NM	Oncogene	(84)
miR-146a	↑ in T-ALL		Associated with immature immunophenotypeabd expression of CD33 and CD34, acts as an ERG regulator in T-ALL	Increased ERG is related to adverse prognosis	Oncogene	(80)
	↑ in ATL		Induced by viral Tax protein through activation of NF-kB, Increases HTLV-1 positive T-cell growth	Increased NF-kB is related to prolonged survival	Oncogene	(88)
Plasma miR-155 + miR-126	↑ in ATL ↓ in ATL	.....	Novel biomarkers of progression and prognosis in ATL	Poor	Oncogene Tumor suppressor	(86)
miR-31	↓ in ATL	NIK	Suppresses ATL Cell Growth and Promotes Apoptosis by Inhibiting NF-kB	NM	Tumor suppressor	(90)
miR-155	↑ in ATL		Induced by viral Tax protein through activation of NF-kB and plays a role in biology and pathogenesis of ATL.	Increased NF-kB is related to prolonged survival	Oncogene	(87)
	↑ in CTCL and MF		STAT5/BIC/miR-155 pathway promotes the malignant T-cell proliferation in CTCL, most significant differentially expressed miRNA	NM	Oncogene	(99-101)
miR-122	↑ in CTCL	Akt (PKB)	Induces phosphorilation of Akt and maintains the CTCL cells from apopotosis induced by chemptherapy	Poor (in advanced stage of MF)	Oncogene	(94)
miR-21/miR-486/miR-214	↑ in SS	.....	Promote cell survival and apoptotic resistance of CTCL cell line, can be novel diagnostic/prognostic biomarkers	NM	Oncogenes	(98)
miR-155+miR-21	↑ in NK cell leukemia/lymphoma	PTEN, PDCD4, SHIP1	Play a NK-cell lymphomagenesis by downregulation target genes and upregulationpAkt	NM	Oncogene	(103)
miR-150	↓ in NKTL	DKC1, AKT2	Reduces levels of pAKT and increases tumor suppressors such as Bim and p53	NM	Tumor suppressor	(104)
miR-146a	↓ in NKTL	TRAF6	miR-146a downregulatesNFkB Activity via Targeting TRAF6, can be strong prognostic factor	Poor	Tumor suppressor	(108)
Plasma miR-221	↑ENKTCL	.....	Can be a prognostic factor for NK/Tcell lymphoma	Related to shorter OS after treatment	Oncogene	(105)
miR-29a	↓ in ENKTCL	MCL1	Participates in tumorigenesis and development of ENKTCL	NM	Tumor suppressor	(106)
miR-16	↑in T LBL/ALL	....	Can be a potential prognostic marker	Associated with longer OS	Oncogene	(109)
miR-193b	↓ in T-LBL	SMO	Activates the GLI/Hh pathway and promotes survival and cell proliferation	NM	Tumor suppressor	(110)

ETP/ALL: Early T-cell precursor acute lymphoblastic leukemia**, Ets-1:** v-ets avian erythroblastosis virus E26 oncogene homolog 1, **T-ALL:** T-cell acute lymphoblasti leukemia, **NM:** not mentioned, **FBXW7:** F-box/WD repeat-containing protein 7, **TAL1:** T-cell acute lymphocytic leukemia protein 1, **IGF1R:** insulin growth factor 1 receptor, **c-MYC:** v-myc avian myelocytomatosis viral oncogene homolog, **cAMP/PKA:** cyclic adenosin

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monophosphate/protein kinase A, **GRα:** glucocorticoid receptor-a, **OS:** overall survival, **CYLD:** Cylindromatosis (turban tumor syndrome); **NF-kB:** nuclear factor kappaB, **E2F1**: E2F transcription factor 1, **ERG**: v-etserythroblastosis virus E26 oncogene homologATL, Adult T-cell leukemia; **HTLV-1**; human T-cell leukemia virus type-I, **NIK**: NF-kB inducing kinase, **CTCL**, cutaneous T-cell lymphoma, **MF**, mycosis fungoides, **BIC:** B-cell integration cluster; STAT5, Signal Transducer and Activator of Transcription 5, Akt, also known as Protein Kinase B (PKB), **NK cell**: natural killer cell, **PTEN:** phosphatase and tensin homologue,

PDC4: programmed cell death 4, **SHIP1:** Src homology-2 domain-containing inositol 5-phosphatase 1, **SS:** Sezarysyndrom; **NKTL:** natural killer/T- cell lymphoma, **DKC1:** dyskeratosiscongenita 1; **Bim:** Bcl-2-interacting mediator of cell death, **p53:** protein 53 or tumor protein 53, TRAF6, tumor necrosis factor receptor-associated factor 6, **ENKTCL:** extranodal NK/T-cell lymphoma; **MCL1:** myeloid cell leukemia sequence 1 (BCL2-related), T LBL/ALL, T-lymphoblastic lymphoma/leukemia, **T-LBL:** T-cell lymphoblastic lymphoma, **SMO**: smoothened, frizzled family receptor, **Gli/Hh:** Gli/hed

expression in HTLV-1-positive T-cell line, and Tax protein is involved in this increased expression. Indeed, Tax leads to binding of NF-κB and activator protein-1 (AP-1) transcription factors to their respective sites in miR-155 gene promoter and transcription of miRNA gene, increasing growth of these cells, and is therefore involved in biology and pathogenesis of lymphoma type of ATL, adult T-cell leukemia/lymphoma (ATLL) [87]. Tax also induces the activity of miR-146a promoter via the NF-κB pathway, eventually enhancing the growth of HTLV-1 positive T-cells(88). Activation of NF-κB pathway is a hallmark of HTLV-1 infected cells and leukemic cells, and its abnormal activation is associated with prolonged survival, proliferation and invasiveness of ATL cells [89]. Tax is a 40-kDa transactivator protein and the main protein encoded by HTLV-1, stimulating and activating the expression of host cell genes through different signaling pathways such as NF-κB and AP-1, and is also involved in leukemogenesis [87, 88]. MiR-31 has been identified as a tumor suppressor because of inhibiting ATL cell growth and apoptosis through inhibition of NF-κB. NF-κB pathway is inhibited by inhibiting the expression of NF-κB inducing kinase (NIK) as target gene, and NIK and miR-31 expression is increased and decreased in ATL, respectively [90]. In the study of Bellon M et al, evaluation of miRNA expression levels in HTLV-1 infected cells (ATL) showed that the expression of -150, -155, -223, 142-3p,-142-5p miRNAs was increased, while the expression of -181a, -132,-125a and-146b miRNAs was decreased [18]. But ,contrary to previous reports, Yamagishi M and Watanabe T observed decreased expression of miR-223 in HTLV-1 infected cells [89].

MicroRNA and T-cell lymphoma
T-cell lymphomas form a heterogeneous group of T-cell derived lymphoid neoplasms comprising 10-

15% of non-Hodgkin's lymphomas. Natural killer cell lymphoma is also classified under T-cell category, and is known as T-cell and NK-cell lymphoma [91, 92]. By comparing miRNA expression in cutaneous T-cell lymphoma (CTCL) and benign skin Dx, increased expression of miR -326,-663b, -711 and decreased expression of miR - 203 and -205 can distinguish these two diseases with an accuracy of 90% [93]. Increased expression of miR-122 in CTCL induces AKT phosphorylation, and its activation regulates apoptosis by inhibiting PTEN, and the cell is thus protected against GSI-induced cytotoxicity. Increased expression of this miRNA in CTCL prevents from chemotherapy-induced apoptosis [94]. Therefore, targeting miR-122 may improve the outcome of chemotherapy [94]. AKT is an oncogene with a vital role in regulating the pathways involved in cell survival, proliferation and death [95]. Increased expression of miR-122 is associated with poor prognosis in an advanced stage of Mycosis Fungoides (MF) [94]. By evaluating the expression level of miR-223, Sézary syndrome (SzS) can be distinguished from MF with over 90% reliability. Downregulation of miR-342 and upregulation of miR-17-5p will decrease and increase cell apoptosis in SzS, respectively, which is involved in pathogenesis of the disease [96]. MiR-199a2 and -214 are inserted as a tandem in single transcript so-called-dynamin 3 opposite strand (DNM3oS). DNM3os is activated in SzS cells with increased expression of transcription factor TWIST, leading to increased expression of both miRNAs in SzS [97]. Upregulation of -21, -486, and -214 miRNA is involved in promoting cell survival in SzS, and contributes to resistance to apoptosis in CTCL cell lines, and even may be a new diagnostic/prognostic biomarker for this type of incurable CTCL [98]. Expression of miR-155 and its host gene BIC in malignant T-cells is increased in CTCL, and STAT5 plays an important role in regulation of increased

expression of (BIC/miR-155). STAT5/BIC/miR-155 pathway promotes the proliferation of malignant T cells [99]. By comparing miRNA expression in benign and malignant stages of MF, it has been found that miR-155 and miR-92a are the most significant differentially expressed miRNAs, while miR-93 is expressed 5.8 times higher in malignant stage [100]. MiR-155 is upregulated in MF [101]. There seems to be a relationship between MYC activation and increased target proteins of downregulated miRNAs such as MUM1, Blimp-1 and STMN1 involved in pathogenesis of natural killer T-cell lymphoma (NKTL). MiR-30b, -101,-26a/-b and -363 are among these miRNAs. PRDM1 (the gene encoding BLIMP1) and STMN1 are targets of the first two miRNA, respectively [102].

Expression level of miR-21 and miR-155 is specifically higher in NK-cell lymphoma line than normal NK cells. The transduction of these two miRNAs causes downregulation of PTEN, PDCD4 and SHIP1 and upregulationof phosphorylated AKT (pAKT), indicating their important role in NK-cell lymphoma genesis via activation of AKT signaling [103].Expression level of mir-150 in NKTL is much lower than that in normal NK cells. This miRNA directly downregulates the expression of dyskeratosis congenita 1(DKC1) and AKT2, decreases pAKT level and increases the level of BimandP53, which functions as a tumor suppressor as mentioned in NK/T-cell lymphoma [104]. Research by Guo HQ et al., has indicated the level of plasma miR-221 may have a diagnostic and prognostic significance in extranodal NK/T-cell lymphoma (ENKTCL). Indeed, there is an indirect relationship between plasma levels of miR-221 and overall survival after treatment in this lymphoma [105]. There is a negative correlation between the expression of miR-29a and MCL1, which is overexpressed in extranodal NK/T-cell lymphoma, indicating that MCL1 is the target gene for miR-29a. Therefore, they participate in tumorigenesis and development of ENKTCL [106].Expression of miR-223 and miR-886-3p is increased in nasal type NK/T-cell lymphoma, and miR-34c-5p expression is decreased in ENKTCL [107].Expression evaluation of miR-146a in NKTL tissue has indicated that patients with a low level of miR-146a expression are associated with chemo resistance and poor prognosis. This miRNA

functions as a tumor suppressor, so it can be used to determine prognosis in NKTL [108].Evaluation of the expression levels of miR-16 on paraffinized lymphnode samples of patients with T-lymphoblastic lymphoma/leukemia (T-LBL/ALL)has shown that patients with high levels of miR-16 have higher overall survival than patients with low levels of miR-16, and it can be used as a marker of prognosis in T LBL/ALL [108].Decreased expression ofmiR-193bin humans and miR-141and miR-30a in mouse increases smoothened (SMO)gene expression in T-cell lymphoblastic lymphoma, resulting inactivation of GLI/hedgehog (Hh) pathway and promoting cell proliferation and survival [109].A summary of the role of aberrant expression of miRNA in leukemogenesis and lymphogenesis has been presented in (Figure 2.)

DISCUSSION

According to presented contents, miRNAs are essential factors in regulation of normal lymphopoiesis; therefore, deregulation of their expression is associated with development of T-cell malignancies and pathogenesis of leukemia and lymphoma (Table 1, Table 2). Consequently, considering the studies, miRNAs can function as oncogenes or tumor suppressor genes in cancer cells [65]. The role of miRNAs in B-cell malignancies has also been reported, including miR-15a and miR-16-1, which induce apoptosis by inhibiting Bcl-2, and play the role of tumor suppressor. However, in chronic lymphocytic leukemia (CLL), reduced expression or deletion of these two miRNAs and increased Bcl-2 protein expression has been observed [110]. In addition, miR-29b and miR-181b play the role of tumor suppressor in CLL by targetingTCL1, playing the role of oncogene in CLL pathogenesis (95). Increased expression of miR-155 in diffuse large B-cell lymphomas and miR-181in AML, (M1 and M2) indicate their oncogenic role in leukemogenesis [111]. Dicer enzyme, which is involved in biogenesis of miRNA, is essential for T-cell biology as well as survival, proliferation and cytokine production during helper T-cell differentiation and its deletion can cause defects in T-cell development. As a result, disruption of miRNA biogenesis process could also be involved in development of T-cell malignancies [59,112]. For example, the role of Dicer in
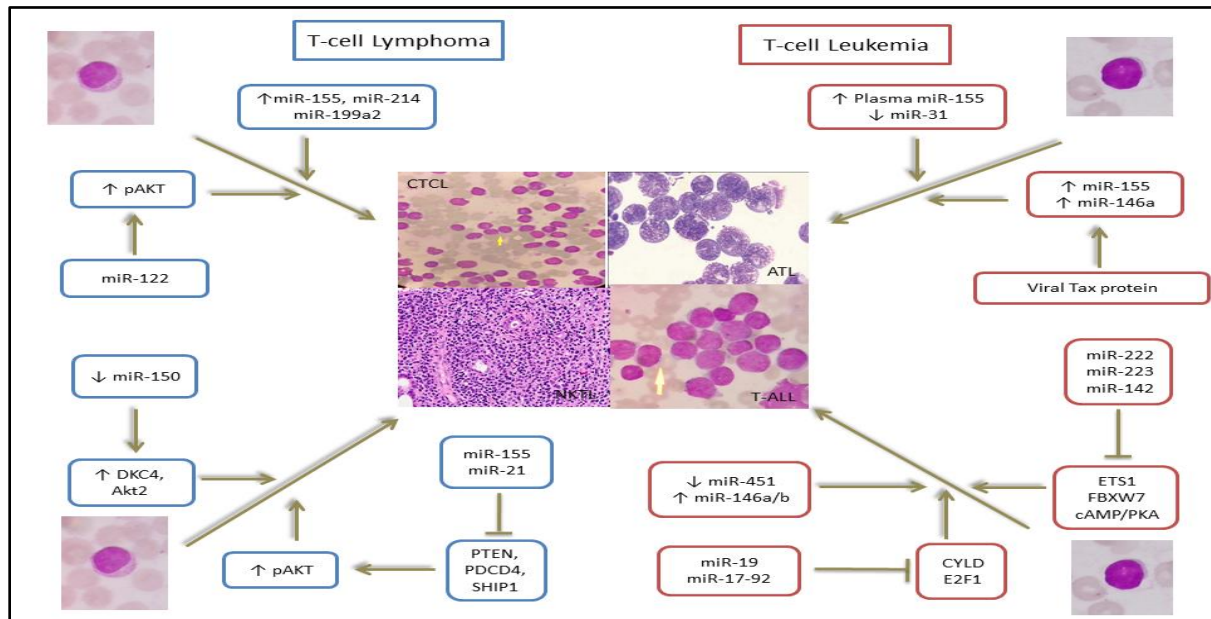
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Figure 2. Involvement of microRNAs in T-cell Leukemia and Lymphoma development

MicroRNAs known to be involved in pathogenesis of T-cell related leukemias and lymphomas through different mechanisms, including functioning as oncogenes or tumor suppressors. Increased expression of miR-155 and miR-146a plays an oncogene role by involvement of Tax protein and decreased expression of miR-31 as a tumor suppressor in ATL leukemogenesis. The expression of MiR -222, -223, -142, -19 and -17-92 as oncogenes is increased in T-ALL, leading to decreased expression of their target genes ETS1, FBXW7, cAMP/PKA, CYLD and E2F1, respectively. Decreased expression of miR-451 and increased expression of miR-141a/b are also involved in T-ALL leukemogenesis. Concurrent increase in the expression of miR-155 and miR-21, through reduced expression of PTEN, PDCD4 and SHIP1 along with eventual induction of Akt phosphorylation and decreased expression of miR-150 through increase in DKC4 and Akt2 have oncogene and tumor suppressor roles in NKTL, respectively, resulting in reduced apoptosis. Increased expression of micro-RNA -122, -155, -214, and-199a2 is also involved in CTCL lymphomagenesis.

ATL: adult T-cell leukemia, **T-ALL:** T-cell acute lymphoblastic leukemia, **CTCL:** cutaneous T-cell lymphoma, **NKTL:** natural killer/T-cell lymphoma, **pAkt:** phosphorylated Akt or protein kinase B, **PTEN:** phosphatase and tensin homologue, **PDC4:** programmed cell death 4, **SHIP1:** Src homology-2 domain-containing inositol 5-phosphatase 1, **DKC1:** dyskeratosiscongenita 1, **FBXW7**: F-box/WD repeat-containing protein 7,**cAMP/PKA:** cyclic adenosin monophosphate/protein kinase A, **CYLD:** Cylindromatosis (turban tumor syndrome), **E2F1:** E2F transcription factor 1.

promoting effector CD8+ T-cell responses to antigen has been determined in vivo, and it is also involved In activation and proliferation of CD8 + T-cells [113]. Dicer deletion in T-cell lineage causes reduction in the number of thymocytes and peripheral T-cells which is due to increased apoptosis [24]. Mice having Tregs deficient in Dicer are defective in differentiation towards functional Tregs, and have been eventually destroyed due to autoimmune disease within a few weeks [6]. Despite numerous studies on the expression level of miRNAs and their role in cell differentiation, identification of important miRNAs and the target genes involved in differentiation of T cell in leukemia and lymphoma requires further studies. These studies can be conducted to determine the relationship between miRNA with T-cell leukemia and lymphoma, cytogenetics, chromosomal translocations, CD marker expression and relationship with prognosis and treatment. As mentioned in this article, the use of miRNA can be helpful for therapeutic purposes, but few studies have been conducted in this regard.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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