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BRIEF REPORT

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T-cell prolymphocytic leukemia is associated with deregulation of oncogenic microRNAs on transcriptional and epigenetic level

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Abstract

Deregulation of micro(mi)-RNAs is a common mechanism in tumorigenesis. We investigated the expression of 2083 miRNAs in T-cell prolymphocytic leukemia (T-PLL). Compared to physiologic CD4+ and CD8+ T-cell subsets, 111 miRNAs were differentially expressed in T-PLL. Of these, 33 belonged to miRNA gene clusters linked to cancer. Genomic variants affecting miRNAs were infrequent with the notable exception of copy number aberrations. Remarkably, we found strong upregulation of the miR-200c/-141 cluster in T-PLL to be associated with DNA hypomethylation and

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active promoter marks. Our findings suggest that copy number aberrations and epigenetic changes could contribute to miRNA deregulation in T-PLL.

KEYWORDS
epigenetic, genomic, micro-RNAs, T-cell prolymphocytic leukemia, T-cells

1 | INTRODUCTION

T-cell prolymphocytic leukemia (T-PLL) is an adulthood rare aggressive leukemia. Though the tumor cells exhibit a mature post-thymic immunophenotype[1]; recent genomic analyses suggested the initiating genetic event to occur in a thymic differentiation stage.[2] Activation of the oncogenes *TCL1A* or *MTCP1* by inv(14)(q11q32)/t(14;14)(q11;q32) or t(X;14)(q28;q11), respectively, are the genetic hallmarks of T-PLL.[3–6] Additional aberrations include deletions at 11q22.3 targeting *ATM*[7,8] and mutations in the genes in JAK–STAT pathway.[9–12] Transcriptomic studies indicated deregulations of the *JAK–STAT* pathway[13] and of the T-cell receptor signaling to be central to pathogenesis of T-PLL.[14]

MicroRNA (miRNA) deregulation is a recurrent event in cancer, including lymphatic neoplasms, as exemplified by the miR-34b/c and miR-15b/16-2 clusters in chronic lymphocytic leukemia (CLL).[15] Nevertheless, data on the miRNAs in T-PLL are limited. Two recent studies using small RNA sequencing reported 34 and 35 miRNAs to be deregulated in T-PLL as compared to normal CD3+ and effector CD4+ T-cells, respectively.[16,17] Another recent array-based miRNA expression profiling study described 17 differentially expressed miRNAs in T-PLL compared to the healthy CD3+ T-cells.[18] Here, we employed an orthogonal technique, that is, ribonuclease protection-based assay, to investigate the expression of 2083 miRNAs in T-PLL samples and normal T-cell populations. Moreover, to explore the reasons for miRNA deregulation in T-PLL; we integrated genomic data as well as epigenomic profiles of T-PLL.

2 | MATERIALS AND METHODS

2.1 | T-PLL samples and cell lines

T-PLL cells of seven patients were previously analyzed using whole-genome sequencing (WGS)[2]; non-malignant CD4+ and CD8+ T-cells from three healthy donors and the cell lines SUP-T11 and JURKAT were investigated for miRNA expression (Table S1 and Supplementary methods). To detect copy number aberrations (CNAs) at miRNA genes, we used an independent data set of 25 T-PLL cases and SUP-T11 (Table S1). The study was performed in agreement with the guidelines of Institutional Review Boards of the involved centers. Moreover, published or publicly available data from WGS, mRNA sequencing (RNA-seq), whole-genome bisulfite sequencing (WGBS) and chromatin immunoprecipitation sequencing (ChIP-seq) of T-PLL cases, and non-malignant T-cell populations were mined (Supplementary data, Tables S1 and S2).

2.2 | HTG miRNA whole-transcriptome assay and quality control

We applied the HTG EdgeSeq Whole-transcriptome Assay (HTG Molecular, Tucson, AZ) covering 2083 miRNAs using the manufacturer's instructions. Subsequent sequencing was performed with Illumina NextSeq (San Diego, CA) generating raw counts for the 2083 miRNAs per sample. The HTG miRNA whole-transcriptome assay was developed based on the mature human miRNA sequences in the database miRbase v20 (2013), which consisted of 2083 miRNAs. The current miRbase v22 (2018) http://www.mirbase.org/ (accessed on December 23, 2021) consists of 2884 miRNAs. MiRbase v20 covers 71.5% of the miRNAs from v22 version. Quality control was performed using HTG REVEAL 3.0 (Supplementary methods).

2.3 | Data analysis

Differential miRNA expression between T-PLL and non-malignant T-cells was assessed using the R package "DEseq2."[19] To detect miRNA clusters with maximal, inter miRNA distance of 10,000 bp, we used the miRBase (v22.1; http://www.mirbase.org/, accessed on February 12, 2021). Principal component analyses (PCA) and heatmaps were done using OMICS Explorer 3.2 (Qlucore, Lund, Sweden) (Supplementary methods).

2.4 | Copy number arrays

Eighteen of the 25 T-PLL cases and SUP-T11 were analyzed using the Genome-Wide Human SNP 6.0 microarray (Affymetrix, Santa Clara, CA) and in one case, the Genome-Wide Human OncoScan FFPE Assay (Affymetrix, Santa Clara, CA) was employed. Nexus 6.0 (Biodiscovery, El segundo, CA) was used for global analyses and visualization. Seven of the 25 samples were previously analyzed.[7] GISTIC 2.0 (v7) (Broad Institute, MA)[20] was used to determine the minimal regions of genomic alterations.

3 | RESULTS

3.1 | Differential expression of miRNAs in T-PLL

We measured the expression of 2083 miRNAs in 7 T-PLL samples and 3 samples each of CD4+ and CD8+ T-cell populations from healthy donors and the cell lines SUP-T11 and JURKAT. We explored previously published WGS data of these seven T-PLL cases,[2] which harbored a *TCRAD::TCL1A* ($n = 6$) or *TCRAD::MTCP1* ($n = 1$) juxtaposition, and of SUP-T11 with *TCRAD::TCL1A* fusion (total $n = 8$) for single nucleotide variants (SNVs), indels, and structural variants (SVs) for genes frequently altered in T-PLL (*ATM*, *JAK3*, *STAT5B*, *KMT2C*, *KMT2D*, *ILK*, *CDC27*, *CXCR4*, *and TP53*).[14] Thereby, we found SNVs to recurrently affect *ATM* (3/8 cases), *STAT5B* (3/8 cases), and *KMT2D* (2/8 cases) and SVs affecting *ATM* (3/8 cases) and *TP53* (2/8 cases).

Next, we performed unsupervised clustering and PCA on these 2083 miRNAs in T-PLL and non-malignant T-cells ($\sigma/\sigma_{max} = 6.2e\text{-}4$), which revealed 621 top-most variable miRNAs. Both PCA and hierarchical clustering heatmap indicated differences in the miRNA profiles between T-PLL samples and healthy controls (Figure S1). In a supervised analysis, we found 111 of the 2083 miRNAs to be differentially expressed between T-PLLs ($n = 7$) and non-malignant T-cell subsets (CD4+ and CD8+ combined ($n = 6$), adjusted p (adj$p$) <0.0001; Figure 1, Table S3). From those 111 miRNAs, 27 miRNAs were downregulated (log2 fold change ([log2fc] < −1) and 84 upregulated (log2fc >1) in T-PLL compared to healthy controls. The top upregulated miRNAs were miR-200c-3p, miR-141-3p, miR-141-5p, and miR-363-3p; the top downregulated miRNAs were miR-1324, miR-6773-3p, miR-6774-5p, and miR-618 (Figure S2). Displaying the 111 miRNAs in the T-cell leukemia cell lines SUP-T11 and JURKAT (Figures S3 and S4), we noted both overlap and differences with the primary T-PLL samples.

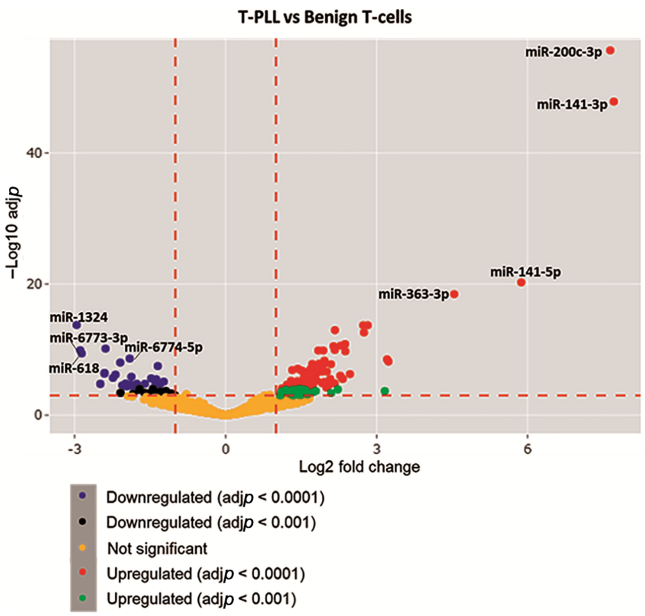

FIGURE 1 Differentially expressed miRNAs in T-cell prolymphocytic leukemia (T-PLL) as compared to non-malignant T-cell populations. Volcano plot showing the log2 of the fold change in miRNA expression (T-PLL/T-cells) on the *X*-axis and the corresponding-log10 adjusted *p* value (adj*p*) on the *Y*-axis for all identified miRNAs ($n = 2083$). The miRNAs significantly downregulated in T-PLL as compared to the healthy controls are shown in blue (adj$p$ < 0.0001) or black (adj$p$ < 0.001), respectively, while significantly upregulated miRNAs appear in red (adj$p$ < 0.0001) or green (adj$p$ < 0.001), respectively. The miRNAs, which are not significantly differentially expressed are depicted in orange

3.2 | Differentially expressed miRNA clusters in T-PLL

We observed that 33 of the 111 differentially expressed miRNAs belonged to 13 miRNA clusters. Out of these 13 clusters, in 4 clusters all the miRNAs within the cluster were differentially expressed, whereas the remaining 9 clusters consisted of 50%–90% of differentially expressed miRNAs per cluster (Table S4). Overall, we detected a significant enrichment of deregulated miRNAs within clusters when compared to the deregulated miRNAs, which are not in clusters in T-PLL (Chi-square test, $p < 0.05$).

3.3 | Genomic variants at deregulated miRNA loci

To investigate CNAs at miRNA genes, we used SNP-array data of 26 independent T-PLL cases (including SUP-T11). We discovered that 11 of the 111 deregulated miRNAs in T-PLL mapped to commonly altered genomic regions in T-PLL. Minimal regions of loss were identified in 6q23.3 comprising miR-4639-3p, miR-6780b-3p, miR-7161-3p, in 16q24.3 comprising miR-6773-3p, miR-6774-5p, and in 21q21.1 comprising miR-6814, respectively. These miRNAs were all downregulated in T-PLL. We detected gains in 22q13.31 containing the miR-378i, which was upregulated in T-PLL (Table S5). In addition, we observed upregulation of the miRNA clusters miR-30b/d and miR-301b/130b mapping to frequently gained regions in 8q and 22q in T-PLL[7] (Figure S5). Next, we mined WGS data of 17 previously published T-PLL cases[2] from which 7 cases were included in present miRNA analysis. We detected no SVs, SNVs, or indels targeting differentially expressed miRNA genes. Thus, on the genomic level CNAs rather than the SVs, SNVs, or indels seem to contribute to the differential expression of miRNA genes in T-PLL.

3.4 | Differentially methylated regions at the deregulated miRNAs

Finally, we investigated the DNA methylome of 3 T-PLL cases (case 124 was included in miRNA analysis) and non-malignant T-cell subsets (Wiehle et al., unpublished data) at the 111 differentially expressed miRNA genes. We analyzed the WGBS data for differentially methylated regions (DMRs) in T-PLL compared to normal T-cells, focusing on the proximity (+/− 1500 bps) of differentially expressed miRNA

genes. Thereby we detected a DMR upstream (−5′end) of the miR-324 locus and two DMRs at the miR-200c/-141 cluster, which were significantly hypomethylated in T-PLL ($q < 0.05$) (Table S6, Figures S6 and S7). In contrast, a DMR upstream of miR-618 was significantly hypermethylated in T-PLL ($q < 0.05$) (Figure S8). We analyzed the ChIP-seq data at these miRNAs gene loci and detected promoter-specific histone marks at the miR-200c/141 in T-PLL, but not in normal T-cells (Figure S6). Finally, using RNA-seq data, we evaluated mRNA expression of host genes (*ACADVL* and *LIN7A*) of the miRNAs miR-324 and miR-618, respectively, and at the genes (*PTPN6* and *PHB2*) in proximity of the miR-200c/-141 cluster. However, we could not detect significant mRNA expression differences in the host and neighboring genes between T-PLL and normal T-cell subsets. (Figures S6–S8). These findings suggest that epigenetic reprogramming could be associated with deregulated miRNA expression in T-PLL.

4 | DISCUSSION

Here we report 111/2083 miRNAs to be differentially expressed in T-PLL. The miRNAs identified herein are significantly enriched for miRNAs reported by RNA-seq (hypergeometric distribution, $p \leq 0.05$).[16–18] Remarkably, we observed a better overlap of differentially expressed miRNAs with miRNA-sequencing studies than with the array-based studies (Fischer's exact test, $p < 0.05$). We found overlap and differences between the T-PLL samples and the T-cell leukemia cell lines, SUP-T11 and JURKAT. We take these patterns as an indication that it is at least arguable if all 111 differentially expressed miRNAs are indeed T-PLL "specific" though cell lines are known to acquire unspecific deregulations due to the artificial culture conditions.

The top upregulated cluster miR-200c/-141 that we found here has been described as significantly upregulated in T-PLL by small RNA-sequencing[16,17] and upregulation of clusters miR-106a/-363 and miR-106b-25/miR-17-92 are in line with studies in T-cell leukemias.[21,22] We also observed downregulation of miR-618, which was previously reported in acute myeloid leukemia.[23] With regard to clinical significance of our findings, it is noteworthy that Erkeland et al.,[17] showed overexpression of miR-181a/b to be associated with an enhanced NOTCH and TCR signaling in T-PLL, and aberrant expression of miR-200c/141 to pose an effect on TGF-β-controlled mechanisms. In addition, overexpression of these clusters has been linked with increased white blood cell counts and more unfavorable outcome in T-PLL.[17]

Recurring genomic imbalances in 8q, 9p, 11q, 17p, and 22q are known to affect specific genes in T-PLL.[7,14] Likewise, our study shows upregulation of the miRNA clusters miR-30b/d, miR-301b/130b, and miR-378i mapping to frequently gained regions in 8q and 22q in T-PLL.[7] Whereas, on a global level, we observed no significant enrichment of deregulated miRNAs in CNAs in T-PLL, our data might suggest distinct CNA to target a few miRNAs (ie, 11/111) for deregulation in T-PLL. Thus, we observed that a few CNAs, but no SVs, SNVs, or indels, were associated with deregulated miRNA gene expression.

Deletion and deregulation of miR-34b/c being part of the TP53-suppressor network has been reported in T-PLL.[14] Here, we did not find differences in miRNA expression of T-PLL with and without *TP53* pathogenic variants exceeding the expected number of falsepositives (*t*-test, $q = 0.05$), though the power for this analysis was limited due to sample size. In line with this, we could not detect deregulation of miRNA 34b/c previously linked to TP53 function in the T-PLL samples analyzed herein. Corroborating previous reports, we detected somatic alterations of the genes *ATM* and *STAT5B* in several of the T-PLL cases studied.[14] In this context, it is remarkable that previous studies have shown that upregulation of miR-18a suppresses ATM[24] and that the miR-17/92 cluster is under control of STAT5.[25] Here, we show upregulation of miR-18a and of the miR-17/92 in T-PLL. It is intriguing to speculate that the upregulation of the former might contribute to the dysregulation of (the non-mutated allele of) ATM, and that the upregulation of the latter is consequence of the JAK–STAT pathway activation in T-PLL. Thus, our findings might suggest an interplay of somatic mutations and miRNA deregulation.

Studies have shown that epigenetic mechanisms like DNA methylation and histone modifications significantly affect miRNA expression leading to oncogenic transformation.[26] The epigenetic landscape of miRNAs in T-PLL has not yet been studied. Therefore, as potential alternative mechanisms of miRNA deregulation, we detected DNA hypomethylation at the top differentially expressed miR-200c/141 cluster, which also showed gain of active promoter histone marks in T-PLL. In contrast, in breast cancer, the miR-200c/-141 cluster has been reported to be repressed by DNA methylation of the promoter region.[27] We also report hypomethylated DMRs in association with the upregulation of miR-324, which has been also reported to be upregulated in chronic myeloid leukemia.[28] Moreover, we found hypermethylated DMRs at miR-618, which is downregulated in T-PLL. These findings suggest an intricate interaction between miRNA expression and other epigenetic mechanisms like DNA methylation and chromatin modifications in T-PLL. In conclusion, using a miRNome-wide approach orthogonal to RNA-seq our study provides a set of significantly deregulated miRNAs in T-PLL. Moreover, our study highlights epigenetic modifications, besides CNAs, as possible underlying mechanisms of miRNA deregulation in T-PLL.

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CONFLICT OF INTEREST

Reiner Siebert: Our laboratory received reagents for reduced prices from HTG for testing the technology. We have grant support from the German Research Foundation (DFG). All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study will be available on request from the authors and some data are derived from public domain resources.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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