High Expression of TET1 Predicts Poor Survival in Cytogenetically Normal Acute Myeloid Leukemia From Two Cohorts

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1. Introduction

Acute myeloid leukemia (AML) is a group of molecular and clinical heterogeneity of hematological malignancies with adverse clinical outcome. The poor outcome may partly be explained by the lack of molecular markers to risk stratification for personalized therapy. Although chromosomal abnormalities have been validated as an effective tool for the risk stratification, chromosomal lesions are identified in approximately 50% of all AML patients. In contrast, about 50% of all AML cases are cytogenetically normal (CN) (Rowe, 2016). In order to refine classification for CN-AML patients, molecular diagnosis such as NPM1, FLT3-ITD, and CEBPA mutational analysis is crucial (Becker et al., 2010). Additionally, abnormal expression of some oncogenes like MLL, ERG, EVI1, the brain and acute leukemia cytoplasmic and isocitrate dehydrogenase 1 have been described previously in studies from other and our groups as prognostic biomarkers (Damiani et al., 2013; Ma et al., 2015; Haferlach et al., 2012).

Recently, with the extensive research of leukemogenesis and the development of new techniques, more and more novel biomarkers relevant to epigenetic alterations have emerged as candidates for disease detection, diagnosis and prognosis. For example, 5-hydroxymethylcytosine (5hmC), also called the “sixth DNA base”, is catalyzed by the Ten-Eleven-Translocation (TET) family proteins, which are involved in the DNA demethylation process. Several studies demonstrated the expression of the TET1 protein and 5hmC is markedly reduced in a wide range of solid tumors like colon cancer (Neri et al., 2015) and gastric cancer (Frycz et al., 2014), suggesting that TET1 functions as a tumor suppressor in these types of cancers. With respect to hematologic disease like leukemia, studies demonstrated an up-regulation of TET1 was observed in MLL-rearranged leukemia and plays an indispensable oncogenic role in the development of MLL-rearranged leukemia in vitro and in vivo (Huang et al., 2016; Ittel et al., 2013; Huang et al., 2013a). Further studies revealed that several essential downstream direct target genes of MLL fusions, such as HOXA9, MEIS1, and PBX3 have been shown to be critical for the development, maintenance and leukemia stem cells (LSCs) self-renewal of MLL-rearranged leukemia are also direct target genes of TET1 (Huang et al., 2016; Wong et al., 2007; Zhu et al., 2016). Taken together, these results highlight TET1 functions as a potent oncogenic role in MLL-rearranged leukemia. However, it is not yet known about the clinical relevance and the upstream regulation mechanism of TET1 expression in non-MLL-rearranged leukemia, especially CN-AML. In this study, we found

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high TET1 expression is associated with poor survival in the two independent cohort of AML patients, and provide the putative miRNA and mRNA regulation mechanism to decipher the biologic insights in high TET1 expressers with CN-AML.

2. Methods

2.1. Patients

AML patients with age >14 at diagnosis were included in this study. We collected the clinical data of 360 AML patients from medical records between January 2010 and July 2016. WHO classification, conventional cytogenetic banding assay, and molecular analyses were performed centrally in Zhejiang Institute of Hematology (ZIH), China as previously described in AML diagnosis (Wang et al., 2013). Patients were treated with intensive induction chemotherapy as previous reported (Jin et al., 2013). After the complete remission induction, younger patients were treated with a high-dose of cytarabine-based chemotherapy, whereas older patients were treated in an individualized manner decided by the physicians, as described previously (Wang et al., 2013). In the consolidation therapy, twenty-nine patients in this cohort received allogeneic transplantation. In addition, the published TCGA data was used as an external validation (https://tcga-data.nci.nih.gov/tcga/)(Cancer Genome Atlas Research N et al., 2013). All of the patients provided written informed consent to participate in the study. This study was approved by the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University.

2.2. Cyogenetic and Gene Mutation Analysis

Chromosomal abnormalities and gene mutations of NPM1, FLT3-ITD, CEBPA, DNMT3A, IDH1 and IDH2 were analyzed by as previously described (Chen et al., 2014). The researchers conducted the above cyogenetics analyses blinded to both the levels of TET1 expression and clinical outcome.

2.3. Quantitative Reverse Transcriptase-PCR

The researchers conducted PCR experiments without the knowledge of clinical outcome. The methods for RNA extraction, complementary DNA synthesis and quantitative PCR were reported previously (Yu et al., 2017). The commonly used housekeeping (HK) genes like β-actin, α-tubulin, GUS and GAPDH were measured. In order to select the suitable HK genes in our cohort, we performed GeNorm analysis using R package “NormqPCR” (Perkins et al., 2012). As a result, the M values of β-actin, α-tubulin, GUS and GAPDH were 0.11, 0.08, 0.08 and 0.07, respectively. Thus, GAPDH was selected as the most stable HK gene owing to the lowest M-value. PCR reactions were performed in a total volume of 25 μl containing 1 μl of 100 ng/μl sample cDNA, 12.5 μl of 2 × PCR Mix, 1 μl of 0.5 μM of each primer, and 10.5 μl of ddH2O. mRNA levels were normalized to GAPDH housekeeping gene. The following primers were used for quantitative PCR:

**TET1** 5'-TTCGGACTGACAACTTAG-3' (sense) and 5'-ATGCCACCCCTTTCGTTGGTGT-3' (antisense); **TET2** 5'- CCCTCTGGGATTGTGCTG-3' (sense) and 5'-GGGGATGCTGCTGCTG-3' (antisense); **TET3** 5'- AAGAACACCTCGAAGGTCC-3' (sense) and 5'-GGTGTCACCTGTGTTCGAAG-3' (antisense); **GAPDH** (control), 5'- ATGGGGAAGGTAAGAGTGTC-3' (sense) and 5'-GGTCATTGAGGACACAATATC-3' (antisense).

2.4. MicroRNA Experiments

For the miRNA measurement, total RNA was obtained using a mirNeasy Mini Kit (Cat # 217004,QIAGEN, GmbH, Germany) following the manufacturer’s instructions and subsequently checked for a RNA integrity number (RIN) to inspect RNA integrity by an Agilent Bioanalyzer 2100 (Agilent technologies, Santa Clara, CA, US). The detailed methods for the miRNA experiments were described previously (Yu et al., 2017). We deposited the raw and processed data at the National Center for Biotechnology Information Gene Expression Omnibus (reporitory number GSE103431).

2.5. Gene Expression Arrays

Affymetrix Human Genome U133 Plus 2.0 Array GeneChip microarrays were used to assess the total RNA samples. The clinical annotation and microarray data of 12 and 10 samples were published previously (Shen et al., 2011; Wang et al., 2013b). GSE27187 raw data were downloaded from the GEO database (www.ncbi.nlm.nih.gov/geo). The raw data of 22 samples were pre-processed using functional normalization in the affy R package (Gautier et al., 2004). The Cancer Genome Atlas (TCGA) mRNA gene expression profiling data were generated by Affymetrix Human Genome U133Plus2.0 GeneChips. Gene expression of TCGA data was used for extended analyses. The relative expression of TET1 in the TCGA cohort was calculated by the ratio of TET1 to GAPDH transcript levels.

2.6. Definition of Clinical End Points and Statistical Analysis

Descriptive statistics including frequency counts, median and range were used to describe patient characteristics. The main objective of this study was to explore the prognostic value of TET1 expression in AML patients. Overall survival (OS) was defined as time from date of diagnosis until death due to any cause or the last follow-up, and event-free survival (EFS) was defined as time from date of diagnosis until removal from study due to non-complete remission, relapse, or death. The adjusted variables like age, WBC, ELN favorable genotype, genes of DNMT3A, IDH1 and IDH2 mutations, BMT and treatment protocols are regarded as the well-established predictors for AML patients. Based on the rule of sample size calculation: 10 events per variable (Collins et al., 2015), we should enroll 300 patients with 90 deaths (the 3-year survival rate of Chinese patients is 30% (Wang et al., 2013)) to assess 9 variables in the Cox regression model. Because EFS estimated multiple clinical events including death, disease relapse, and treatment response, EFS was selected to estimate the cutoff value of TET1 expression. To explore the patients with the best EFS, we subdivided the development cohort into four quartiles (Q1: <25%, Q2: 25%–50%, Q3: 50%–75%, Q4: 75%) according to the expression value of TET1 (Fig. S1). The survival curves between Q1 and Q2 were comparable, while those in Q3 and Q4 had similarly poor EFS compared with those in Q1. Thus, we dichotomized these patients into high and low TET1 groups based on the median value (Fig. 1). Comparison of survival curves were based on the Gehan-Wilcoxon and log-rank test. The proportional-hazards assumption was checked for each variable before fitting Cox models. A limma package (Ritchie et al., 2015) in R software was used to test for the difference of microRNA and mRNA signatures between high and low TET1 expressers. Hierarchical clustering based on expression levels of these mRNAs was performed and visualized by heatmap. Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were created with ClueGO v2.3.4 (Bindea et al., 2013) and visualizing by Cytoscape software (Shannon et al., 2003). The topgene analysis was done on the platform (https://topgene.cchmc.org/prioritization.jsp). Interaction of miRNA and mRNA integrative analyses in silico were using the mirtar platform (http://mirtar.mbc.nctu.edu.tw/human/index.php). All statistical analyses were conducted with R statistical packages, version 3.4.1 (www.r-project.org). The two-sided level of significance was set at p-value < 0.05.

3. Results

3.1. Characteristics of CN-AML Patients with High TET1 Expression

TET1 expressions were measured in BM samples from 360 CN-AML patients at diagnosis. The median value of TET1 transcript level was
0.73 expression value of TET1/GAPDH with the interquartile range from 0.39 to 1.37. We classified patients into high and low expression based on the median value. The median and interquartile range of TET1 expression were 1.38 (0.97, 2.21) and 0.39 (0.26; 0.53) for high and low expressers, respectively. Clinical characteristics of patients with high TET1 expression are summarized in Table 1. High expressers were more frequent in AML FAB subtype M0 (15.6% vs. 6.1%) and M1 (12.2% vs. 6.1%) morphology than low expressers. TET1 expressions were positively correlated to TET2 and TET3 expressions. However, there was no statistically significant correlation between TET1 expression and other variables including age, sex, white blood cell counts (WBC), hemoglobin levels, platelet counts, percentage of bone marrow blasts, genes of FLT3-ITD, NPM1, IDH1, and IDH2 mutations, and treatment protocols (Table 1).

3.2. Overexpression of TET1 Associated with Poor Clinical Outcome in CN-AML Patients

In our patients, three years overall survival (OS) rate and event free survival (EFS) rate were 34% and 31%, respectively. High TET1 expressers (n = 180) had more adverse OS, EFS, and complete remission rate compared to low expressers (n = 180) (Table S1, Fig. 1A–B). However, there was no significant difference between high and low TET2 or TET3 expressers for OS and EFS (Figs. S2–S3). Moreover, in the subgroup analyses we found TET1 expressions can further stratify CN-AML patients with favorable ELN genotype into different subgroups with respect to OS and EFS (Fig. S4). In order to exclude the potential confounders factors, we conducted multivariate analyses. As shown in Table 2, TET1 expression was still an independent prognostic factor after adjusting for age, WBC, ELN risk groups, and genes of NPM1, IDH1 and IDH2 mutations regardless of CR [OR (95%CI), 0.354 (0.204, 0.602); P < 0.001], OS [HR (95%CI), 1.614 (1.154, 2.256); P = 0.005] and EFS [HR (95%CI), 1.607 (1.169, 2.21); P = 0.004]. Moreover, we also conducted landmark analysis by including patients whose survival was >30 days in order to ignore the cause of induction death by intensive chemotherapy. As a result, high expression of TET1 was still an independent prognostic factor for OS [HR (95%CI), 1.607 (1.169, 2.21); P = 0.002] and EFS [HR (95%CI), 1.607 (1.169, 2.21); P = 0.004].

Fig. 1. Survival curves of CN-AML patients. Kaplan-Meier estimates of EFS (A) and OS (B) by high and low TET1 expression for our patients, and EFS (C) and OS (D) for patients from the TCGA cohort, respectively.

Table 1
Characteristics of CN-AML patients by high and low TET1 expression.

| Variables | Low expression | High expression | P value |
|-----------|----------------|----------------|--------|
| Number(%) | 180 (50%)      | 180 (50%)      |        |
| Male, n(%) | 107 (59.4)     | 103 (57.2)     | 0.748  |
| Age, median[IQR], years | 53.00 (42.00, 65.00) | 55.00 (39.00, 63.00) | 0.812 |
| WBC, median[IQR], ×10^9/L | 12.10 (2.75, 49.12) | 11.64 (2.40, 63.97) | 0.825 |
| HB, median[IQR], g/L | 87.00 (69.75, 103.12) | 84.00 (65.05, 103.00) | 0.292 |
| FLT3-ITD, median[IQR], ×10^9/L | 120.00 (24.75, 92.50) | 66.00 (26.00, 88.25) | 0.886 |
| BM blast, median[IQR], % | 64.50 (39.12, 78.00) | 67.50 (41.88, 83.12) | 0.211 |
| Treatment, n(%) | 11 (6.1) | 22 (12.2) | 0.533 |
| NPM1 | 61 (33.9) | 117 (65.0) | 0.005 |
| IDH1 | 16 (8.9) | 17 (9.4) | 1.000 |
| IDH2 | 22 (12.2) | 26 (14.4) | 0.330 |
| ELN favorable group, n(%) | 55 (30.0) | 45 (24.5) | 0.600 |
| Treatment, n(%) | 49 (26.7) | 42 (23.3) | 0.060 |

Abbreviations: WBC, white blood cell; HB, hemoglobin; IDH, IDH1, IDH2, platelet counts; BM, bone marrow; FAB, French-American–British classification systems; DM: Double-allele. The protocols used for induction therapy in different groups including HAA, homoharringtonine-based treatment (homoharringtonine 2 mg/m2/day for 3 days, cytarabine 75 mg/m2 twice daily for 7 days, aclarubicin 12 mg/m2 daily for 7 days) regimen; DA, daunorubicin 45 mg/m2 daily for 3 days and cytarabine 100 mg/m2 daily for 7 days; IA, idarubicin 6–8 mg/m2 daily for 7 days and aclarubicin 20 mg/m2 daily for 5 days. IQR, interquartile. BMT, bone marrow transplantation. ELN (European leukemia Net) favorable genotype represents NPM1 mutation and FLT3-ITD negative or double allele CEBPA mutations.
Fig. S8). Notably, we found several upregulated hub genes involving apoptosis, MAPK signaling pathway, proteoglycans in cancer and tuberculosis.

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Table 2 Multivariable analyses of clinical outcome for patients with CN-AML

| Variables | Complete remission | Overall survival | Event free survival |
|-----------|--------------------|-----------------|--------------------|
|           | P value OR (95%CI) | P value HR (95%CI) | P value HR (95%CI) |
| TET1 expression (High vs. Low) | <0.001 0.354(0.204, 0.602) | 0.005 1.614(1.154, 2.256) | 0.004 1.607(1.169, 2.210) |
| Age       | 0.023 0.519(0.294, 0.912) | <0.001 2.132(1.506, 3.016) | <0.001 1.996(1.436, 2.776) |
| WBC       | 0.062 0.600(0.349, 1.020) | <0.001 1.876(1.401, 2.787) | 0.001 1.724(1.242, 2.394) |
| ENL favorable group | 0.009 2.300(1.249, 4.355) | <0.001 0.401(0.260, 0.620) | <0.001 0.466(0.311, 0.696) |
| DNMT3A     | 0.267 0.660(0.313, 1.372) | 0.001 2.087(1.362, 3.198) | <0.001 1.941(1.297, 2.904) |
| IDH1       | 0.035 0.460(0.221, 0.943) | 0.042 1.596(1.016, 2.506) | 0.019 1.667(1.088, 2.354) |
| IDH2       | 0.173 0.611(0.295, 1.239) | 0.658 0.901(0.569, 1.428) | 0.881 1.034(0.669, 1.599) |
| Treatment protocols |                      |                 |                    |
| HAA vs. DA | 0.024 2.731(1.154, 6.643) | 0.06 0.601(0.354, 1.022) | 0.084 0.645(0.392, 1.060) |
| IA vs. DA  | 0.001 3.098(1.532, 5.929) | 0.001 0.522(0.354, 0.766) | <0.001 0.565(0.389, 0.820) |
| BMT       | 0.251 1.909(0.666, 6.349) | 0.014 0.368(0.106, 0.817) | 0.097 0.566(0.283, 1.08) |

Abbreviations: WBC, white blood cell; The treatment protocols used for induction therapy in different groups including HAA, homoharringtonine-based treatment (homoharringtonine 2 mg/m²/day for 3 days, cytarabine 75 mg/m² twice daily for 7 days, aclarubicin 12 mg/m² daily for 7 days) regiment; DA, daunorubicin 45 mg/m² daily for 3 days and cytarabine 100 mg/m² daily for 7 days; IA, idarubicin 6–8 mg/m² daily for 7 days and aclarubicin 20 mg/m² daily for 5 days. BMT, bone marrow transplantation. ELN (European leukemia Net) favorable genotype represents NPM1 mutant and FLT3-ITD negative or double allele CEBPA mutations.

In this study, we firstly selected 91 CN-AML patients with normal karyotype based on cytogenetic classification from the TCGA cohort to validate our results. We defined the cutoff value using the same method based on the median value of TET1 expression in the TCGA cohort. Consequently, poor survivals were still observed in patients with high TET1 expressers (Fig. 1C–D). However, no significant differences of OS and EFS were observed in the TCGA cohort with respect to TET2 or TET3 expressions (Fig. S5). Secondly, in the 197 total AML patients, TET1 expressers (continuous variable, log2 transformation) were associated with poor OS [HR(95%CI): 1.13(0.99,1.28), P = 0.075] and EFS[HR(95%CI): 1.15[1.02,1.29], P = 0.024], respectively. Thus, the expression of TET1 was indeed a poor predictor in different populations.

In order to further understand the regulated mechanism, we conducted the integrative analysis of mRNA and miRNA interaction between high and low TET1 expressers. Thirty-five genes were upregulated in high TET1 expressers were predicted to be targeted by miR-616 and miR-21 and miR-16 were seen significant changes in high TET1 expressers from an independent cohort of TCGA patients with CN-AML (Fig. 2B–E).

In order to further understand the regulated mechanism, we conducted the integrative analysis of mRNA and miRNA interaction between high and low TET1 expressers. Thirty-five genes were upregulated in high TET1 expressers were predicted to be targeted by miR-616 and miR-21. By contrast, we found 42 downregulated in high TET1 expressers were predicted to be targeted by high expression of miR-127-5p and miR-494, respectively.

After combining the differentially expressed miRNAs and pathways together, we found miR-494 and miR-127-5p were upregulated in high TET1 expressers (Table S5 and Fig. S8), and genes of RAB11FIP5, RAB11FIP1 in the endocytosis pathway and ITGAX in the tuberculosis pathway were downregulated (Table S3). In silico analysis, miR-127-5p can regulate genes of RAB11FIP1 in the endocytosis pathway and ITGAX in the tuberculosis pathway, and miR-494 can regulate RAB11FIP5 in endocytosis pathway (Fig. S8), implicating some novel mRNA-miRNA regulated pathways occurring in high TET1 expressers.

In order to further understand the regulated mechanism, we conducted the integrative analysis of mRNA and miRNA interaction between high and low TET1 expressers. Thirty-five genes were upregulated in high TET1 expressers were predicted to be targeted by miR-616 and miR-21 (Fig. 3). By contrast, we found 22 genes downregulated in high TET1 expressers were predicted to be targeted by high expression of miR-127-5p and miR-494, respectively. Additionally, 230 TET1 co-expressed genes in the TCGA cohort (Jamalpour et al., 2017) can be found as part of differently expressed genes in high TET1 expressers (Table S3). Moreover, these differently expressed genes were enriched in 16 molecular functions: RNA and DNA binding, methyltransferase activity, DNA binding transcription factor activity, lipopolysaccharide receptor activity, etc. (Table S4).

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unknown. In this study, we found CN-AML patients with high TET1 expression obtained higher frequency of NPM1 mutations and FAB M0/1 morphology. These results supported the hypothesis that increasing TET1 expression might block hematopoietic stem cell differentiation. Taken together, the clinical characteristics of high TET1 expressers implied TET1 expression level might be associated with a poor outcome. As expected, we found that high TET1 expressers harbored poor overall survival in the two independent cohorts of CN-AML patients. This result is also supported by the study that TET1 acts as an oncogene in leukemia development (Huang et al., 2013a).

In order to further understand the underlying biological insights in high TET1 CN-AML, we analyzed genes expression profiles in two independent cohorts of CN-AML patients. First, we found 1127 significantly expressed genes in high TET1 expressers. These interesting genes were involved in 10 pathways together with several hub genes, which can be used as potential drug targets in the future. Specifically, in high TET1 expressers the downregulated hub gene like RAB11FIP1 has been described as tumor suppressors, and the downregulated pathways involving in innate immune reaction like endocytosis, tuberculosis, influenza A and MAPK signaling pathways might lead to leukemia development (Boulay et al., 2016). At the same time, high TET1 expressers exhibit high activity of DNA and protein turnover, presenting with upregulation of purine and pyrimidine metabolism, RNA transport and ribosome biogenesis. These results might help us to explain the poor survival of the high TET1 expression in CN-AML.

In order to further understand the biological links, we analyzed miRNAs profiles relevant to TET1 expression. As a result, we found four miRNAs, miR-127-5p, miR-494, miR-616 and miR-21, with robust changes in high TET1 expressers from the different cohorts of patients. The function of miR-494 and miR-127 is reported as an oncogene in the different context of tissues. For example, several authors have described them as oncomiRs in lung cancer (Shi et al., 2017), colorectal cancers (Sun et al., 2014), lymphoma and leukemia (Shi et al., 2017; Diakos et al., 2010). Here, we found miR-127-5p and miR-494 were positively correlated with the high TET1 expression, supporting their function as oncogenes in CN-AML. Moreover, their oncogenic function can be deciphered by their putative targeting genes, which have been described as tumor suppressors like ITGAX (Ma et al., 2015) and SLC46A2 (Kim et al., 2015). Notably, we also found downregulated SGSH expression was predicted to be targeted by miR-127 and miR-494 in high TET1 expressers (Fig. 3). SGSH is one of enzymes in the lysosomal degradation, which often correlates with poor prognosis and increased recurrence in many cancers (Piao and Amaravadi, 2016). Recently, targeting lysosomes is reported as a novel therapeutic strategy to eradicate imatinib-resistant chronic myelogenous leukemia cells (Piao and Amaravadi, 2016; Puissant et al., 2010). These results implied miR-127 and miR-494 might subvert lysosomal proteases via downregulated expression of SGSH leading to leukemia development. Thus, the poor prognosis of high TET1 expressers maybe explained by the aberrant expressions of miR-127 and miR-494 and their targeting genes.

Fig. 2. Heatmap plot illustrating the microRNAs expression between high and low TET1 expression(A). Validation of microRNAs expression (B-E) in patients with low vs high TET1 expression in TCGA cohort.
With respect to the function of miR-21, it has been reported miR-21 is required for maintaining the imatinib-resistant phenotype of CML stem cells (Wang et al., 2015), and upregulation of miR-21 is a poor prognostic marker in acute lymphoblastic leukemia (ALL) (Labib et al., 2017). These reports supported miR-21 as an oncogene in ALL and CML leukemia. However, downregulated expression of miR-21 in AML was also reported (Diaz-Beya et al., 2013) and seemed to act as a tumor suppressor. Here, we found miR-21 was significantly downregulated in high TET1 expressers, supporting the function as a tumor suppressor. The exact function of miR-616 is not known in hematological disease, but it is thought to play a tumor suppressor role in CN-AML. In the current study, we found miR-616 was downregulated in high TET1 expressers and negatively correlated to the expression of several targeting genes which have been demonstrated as a tumor promoter like CHD6V (Douet-Guilbert et al., 2015), TCF4 (Ishiguro et al., 2016), VANGL1 (Cetin et al., 2015), or associated with poor clinical outcome such as WARS2 (Huang et al., 2013b) and NOP16 (Zhang et al., 2014).

In conclusion, we uncovered high TET1 expression could predict unfavorable survival in CN-AML patients. It is worthy to note that the prognostic value of the biomarker is dependent on the different treatment protocols. For example, the poor predictor of prognostic value of the biomarker is dependent on the different treatment protocols. For example, the poor predictor of miR-494 and miR-127-5p was respectively involved in downregulation of the tuberculosis and endocytosis pathway by targeting genes of RAB11FIP5, ITGAX and RAB11FIP1 in high TET1 expressers (Fig. S8). Thus, targeting miR-494 expression and miR-127-5p may be a novel treatment strategy in CN-AML with high TET1 expressers. These results also require more experimental clarification.

Conflict of interest disclosures

The authors declare that they have no competing interests.

Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebiom.2018.01.031.

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