Abstract. N^6^-methyladenosine (m^6A) is the most abundant eukaryote mRNA modification, modulated by regulators known as epigenetic writers, erasers and readers, which are known to serve crucial roles in mRNA metabolism. However, the role of m^6A during B-cell development and B-cell tumorigenesis remains poorly understood. By analyzing the gene expression profile of 123 mantle cell lymphoma cases from the Gene Expression Omnibus database, the present study demonstrated that one-half of the m^6A regulators were able to predict patient survival in mantle cell lymphoma, notably the m^6A.index. The expression levels of the m^6A regulators were regarded as good classifiers in mantle cell lymphoma. The m^6A.index-low mantle cell lymphoma type exhibited a poor patient survival and lower mRNA levels from the total transcriptome. The m^6A regulators may be associated with the cell division and the RNA metabolic pathways, which may result in poor survival of patients with mantle cell lymphoma.

Introduction

N^6^-methyladenosine (m^6A) is the most abundant eukaryote messenger RNA modification, modulated by regulators known as writers, erasers and readers (1). It is known to serve crucial roles in mRNA metabolism and is primarily involved in mRNA stability, mRNA splicing and protein translation (2-9). The proteins that are involved in m^6A modifications consist of ‘writers’, ‘erasers’ and ‘readers’. The m^6A writers are the m^6A methyltransferase enzymes, a 70-kDa complex consisting of 3 components: Methyltransferase like (METTL) 3, METTL14 and WT1 associated protein (WTAP), which methylate the adenosine motif (A) at the N6 position (10-12). The m^6A erasers comprise the m^6A demethyltransferase enzymes, including alpha-ketoglutarate-dependent dioxygenase FTO (FTO) and RNA demethylase ALKBH5 (ALKBH5), which are the first and second m^6A demethyltransferase enzymes (6,13-15). The m^6A readers consist of effectors (m^6A RNA binding protein) that decode the m^6A methylation code. The YTH domain family [YTH domain-containing family protein (YTHDF) 1, YTHDF2 and YTHDF3] and ELAV-like protein 1 (ELAVL1) are known as m^6A readers (2,3,16,17). The m^6A modification is associated with cancer progression. The m^6A demethylase ALKBH5 sustains forkhead box protein M1 expression and cell proliferation and maintains the tumorigenesis of glioblastoma stem-like cells (18). m^6A RNA methylation regulates the tumorigenesis of glioblastoma and the self-renewal of glioblastoma stem cells (19).

METTL3 is an m^6A writer associated with the formation of undifferentiated myeloid cells in acute myeloid leukemia (AML), as well as with chemo- and radio-resistance of pancreatic cancer cells (20,21). In addition, METTL3 serves an important role in the growth, survival and invasion of human lung cancer cells (22). Protein virilizer homolog (KIAA1429) was defined as a writer of m^6A in 2014 (23). KIAA1429 is a unique type of m^6A writer: i) Mammalian KIAA1429 (202 kDa) is the largest known component within the m^6A methyltransferase complex; ii) among all the components examined, the depletion of KIAA1429 resulted in the largest decrease in m^6A levels [KIAA1429 depletion led to a 60% decrease in m^6A levels, while METTL3, METTL14 and WTAP depletion resulted in 30, 40, and 50% decreases in m^6A levels, respectively (12); and iii) biochemical studies have indicated that KIAA1429 recruits METTL3/METTL14/WTAP, the catalytic core components (24-26). Therefore, KIAA1429 may serve as a scaffold molecule of the methyltransferase complex, and serve a unique role that is different from those of the catalytic core components METTL3, METTL14 and WTAP.

Dysregulation of N^6^-methyladenosine regulators predicts poor patient survival in mantle cell lymphoma

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FTO is a member of the m6A eraser family of proteins and has been demonstrated to promote AML and lung squamous cell carcinoma (LUSC) progression (27,28).

The expression levels of the m6A protein readers, including YTHDF1 and YTHDF2, were identified to be markedly associated with malignancy and poor prognosis of hepatocellular carcinoma (29,30). YTHDF2 and YTHDF3 were defined as readers of m6A in 2012 (16). YTHDF2 and YTHDF3 regulate messenger RNA stability (2,31). YTHDF1 was defined as a reader of m6A in 2014. YTHDF1 facilitates messenger RNA translation initiation, while ELAVL1 inhibits protein translation (3,32). It appears that YTHDF2 and YTHDF3 are more likely to regulate mRNA translation, while YTHDF1 and ELAVL1 are more likely to regulate mRNA translation.

Mantle cell lymphoma is a type of non-Hodgkin B cell lymphoma with a median age of diagnosis at 60 years (33,34). Mantle cell lymphoma has an aggressive phenotype and a rapid rate of progression, with a short median survival of 5-7 years (35). The investigation of the molecular mechanisms that contribute to the aggressive phenotype of mantle cell lymphoma may provide novel treatment strategies. Recently, previous studies demonstrated that m6A mRNA methylation regulators may be used for the prediction of poor survival in patients with mantle cell lymphoma.

Materials and methods

Data source. The Affymetrix Human Genome U133 Plus 2.0 array of 123 mantle cell lymphoma samples was retrieved from the NCBI Gene Expression Omnibus (GEO) database (GSE93291 dataset) (39,40). The detailed patient demographic data and disease characteristics for this dataset were published previously (39). The Affymetrix Human Genome U133 Plus 2.0 Array that contained 64 mantle cell lymphoma samples was retrieved from the NCBI GEO database (GSE21452) (41). GSE21452 was the first phase of the GSE93291 dataset.

Gene expression analysis. The probeset measures of all the arrays were calculated by robust multiaarray averaging. The relative RNA expression values were log-transformed (log2). The data were analyzed with an unpaired Student’s t-test and are presented as the mean ± SEM in scatter plots. P<0.05 was considered to indicate a statistically significant difference. Only genes with a fold change (log2) >1 or <-1 were defined as differentially expressed genes.

Definition of m6A.index for survival prediction. A comprehensive m6A.index was defined to predict the survival in patients with mantle cell lymphoma. The m6A.index was calculated using a previously described method (1), as follows:

\[ m6A.index_j = F_j / H_j, \]

where m6A.index represents the index of m6A of the jth sample for survival prediction. F_j represents the product of favorable gene expression of the jth sample. A total of 7 out of 10 m6A genes exhibited a hazard ratio <1 and were defined as ‘favorable genes’, which were favorable for the survival of mantle cell lymphoma. H_j represents the product of ‘harmful gene’ expression of the jth sample. A total of 3 out of 10 m6A genes (YTHDF1, KIAA1429 and ELAVL1) exhibited a hazard ratio >1 and were defined as ‘harmful genes’, which were harmful for the survival of mantle cell lymphoma.

The median of the m6A.index value from a cohort of mantle cell lymphoma, for example 123 patients with mantle cell lymphoma, was defined as the cut-off value for the m6A.index-low and m6A.index-high groups consisting of 62 and 61 samples, respectively. The correlation of the m6A.index with the gene expression levels of the marker (proliferation Ki-67 (Ki-67) was assessed using the Spearman’s correlation test and the pairwise colored scatter-plot was drawn based on a Kernel Density Estimation using the LSD package (version 4; cran.r-project.org/web/packages/LSD/index.html) in R.

Gene Ontology (GO) analysis. The Database for Annotation, Visualization and Integrated Discovery tool with default parameters was used for GO analysis (42). All enriched GO terms identified in the present study were manually prepared so that only selected, non-redundant GO terms in the ‘Biological Process’ category were identified.

Statistical analysis. The R software v3.1.3 (ggplot2 package) was used for the statistical analysis. Kaplan-Meier curves were used to plot survival curves of YTHDF3, METTL14, ALKBH5, ELAVL1 and KIAA1429 genes. For the YTHDF3, METTL14, ALKBH5 and ELAVL1 genes, the median of the gene expression value from a cohort of mantle cell lymphoma (123 patients with mantle cell lymphoma) was defined as the cut off value for the low and high expression groups. For KIAA1429 genes, the maximally selected rank statistics algorithm (survminer package) was used to define the low and high expression groups. Survival analysis of those genes was performed using the log-rank test. The heatmap depicted the cosine correlation similarity between 10 m6A regulators. Unpaired Student’s t-tests were used for the statistical analysis of quantitative variables. The data are expressed as the mean ± SEM in scatter plots. P<0.05 was considered to indicate a statistically significant difference.

Results

Specific m6A regulators predict patient survival in mantle cell lymphoma. To investigate the association between the m6A regulators [METTL3, METTL14, WTAP and KIAA1429 (writers); FTO and ALKBH5 (erasers); and YTHDF1, YTHDF3, YTHDF2 and ELAVL1 (readers)] and the survival of the patients with mantle cell lymphoma, the expression profiles of 123 mantle cell lymphoma samples from the GSE21452 dataset were analyzed. A total of 5 out of 10 m6A regulators revealed expression levels that were significantly associated with the survival of patients with mantle cell lymphoma (P<0.05, log-rank test). The 10 m6A regulators were classified according to the hazard ratio values. A total of 7 out of 10 m6A genes had a hazard ratio value <1 and were
Gene symbol
YTHDF3
METTL3
FTO
METTL14
ALKBH5
YTHDF2
WTAP
YTHDF1
KIAA1429
ELAVL1

Figure 1. Forest plots of 10 N6-methyladenosine regulators associated with survival. The black lines indicate lower and upper 95% confidence of the hazard ratios.

Figure 2. Kaplan-Meier curves measuring associations between overall survival and 4 N6-methyladenosine regulators in 123 patients with mantle cell lymphoma. YTHDF3 (P=0.0356), METTL14 (P=0.0435), ALKBH5 (P=0.0493) and ELAVL1 (P=0.003). The log-rank test was used to compare the Kaplan-Meier curves. YTHDF3, YTH domain-containing family protein 3; METTL14, methyltransferase like 14; ALKBH5, RNA demethylase ALKBH5; ELAVL1, ELAV-like protein 1.
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and ‘harmful’ genes were deemed significant predictors for mantle cell lymphoma patient survival.

Expression patterns of m6A regulators predict poor or favorable patient survival in patients with mantle cell lymphoma. An unsupervised clustering of the expression levels of the 10 m6A regulators was conducted in 123 patients with mantle cell lymphoma, and the cosine correlation similarity was presented as a heatmap (Fig. 3). Notably, it was identified that the 10 m6A regulators were classified into two groups; WTAP, ALKBH5 and METTL14 in one group, and the other 7 genes in a second group. ELAVL1 and KIAA1429, two of the most significantly ‘harmful’ genes, were clustered together in one group. The other 3 most significantly ‘favorable’ genes, YTHDF3, METTL3 and FTO, were also clustered together in one group. The clustering of ‘harmful’ and ‘favorable’ genes together in single groups suggests that the genes that are the most closely associated with survival cluster together. Furthermore, it was observed that the mantle cell lymphoma cancer type could be classified into two groups by fuzzy clustering (Fig. 4A). The ratio of the expression levels of ‘harmful genes’ to ‘favorable genes’ was estimated, which was termed as the m6A.index.

The m6A.index was highly associated with the survival of patients with mantle cell lymphoma (Fig. 4B; P<0.05). The hazard ratio of the m6A.index was 0.39 (95% CI, 0.24-0.65). The m6A.index reflected the imbalanced expression between ‘harmful genes’ and ‘favorable genes’ of the m6A regulators. The m6A.index-low group was associated with a poor patient survival in mantle cell lymphoma, while the m6A.index-high group was associated with a favorable patient survival in mantle cell lymphoma.

The correlation of the m6A.index with the gene expression levels of marker of proliferation Ki-67 (Ki-67) in 123 mantle cell lymphoma samples was analyzed (Fig. S2; Cor = -0.52; P=0.001; Spearman's correlation test). The m6A.index exhibited a negative correlation with Ki-67 and DNA polymerase genes (DNA polymerase alpha 1, catalytic subunit, DNA polymerase alpha 2, accessory subunit, DNA polymerase delta 1, catalytic subunit, DNA polymerase delta 2, accessory subunit and DNA polymerase theta). Although, the mutational status of tumor protein 53 (TP53), ATM serine/threonine kinase (ATM) and MYC proto-oncogene, BHLH transcription factor (MYC) could not be assessed using the data from the present study, the survival analysis of 123 patients with mantle cell lymphoma.
cell lymphoma was analyzed in association with Ki-67, ATM, MYC and TP53 gene expression (Fig. S2). Increased expression levels of MKI67 and MYC corresponded with poorer survival in patients with mantle cell lymphoma (Fig. S3; P=2.9x10^-11 and P=4.5x10^-4, respectively). The high expression levels of ATM and TP53 demonstrated the trend for predicting favorable survival in patients with mantle cell lymphoma (Fig. S3; P=7.5x10^-2 and P=1.1x10^-1, respectively). ATM and Ki -67 were differentially expressed between the m 6A. index-low and m6A.index-high groups (Fig. S3; P<0.05), while TP53 and MYC were not differentially expressed (P>0.05). Furthermore, the correlations between the m 6A.index with the expression of 17 proliferation-associated genes in 123 mantle cell lymphoma samples were calculated. A total of 16 of 17 proliferation-associated genes were highly correlated with the m6A.index (Fig. S4).

Figure 4. Groups of 10 m 6A regulators were used as a classifier in the 123 patients with mantle cell lymphoma. (A) The fuzzy clustering of 123 patients with mantle cell lymphoma as determined by the expression levels of the 10 m 6A regulators. PC1 and PC2 were the first and second components, respectively. Each point indicated a mantle cell lymphoma sample. Colors 1 (red) and 2 (green) denote two clusters. (B) Kaplan-Meier curves for assessment of the association between overall survival of 123 patients mantle cell lymphoma with m 6A.index (P<0.001). The log-rank test was used to compare the Kaplan-Meier curves. m 6A, N 6-methyladenosine.

Table I. Survival analysis of 10 m6A regulators.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Hazard ratio</th>
<th>95% confidence interval</th>
<th>P-value</th>
<th>m6A role</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELAVL1</td>
<td>2.46</td>
<td>1.35-4.48</td>
<td>0.0030</td>
<td>Reader</td>
</tr>
<tr>
<td>KIAA1429</td>
<td>2.09</td>
<td>1.21-3.62</td>
<td>0.0086</td>
<td>Writer</td>
</tr>
<tr>
<td>YTHDF3</td>
<td>0.51</td>
<td>0.27-0.96</td>
<td>0.0356</td>
<td>Reader</td>
</tr>
<tr>
<td>METTL14</td>
<td>0.68</td>
<td>0.47-0.99</td>
<td>0.0435</td>
<td>Writer</td>
</tr>
<tr>
<td>ALKBH5</td>
<td>0.70</td>
<td>0.49-1.00</td>
<td>0.0493</td>
<td>Reader</td>
</tr>
<tr>
<td>WTAP</td>
<td>0.81</td>
<td>0.65-1.02</td>
<td>0.0683</td>
<td>Reader</td>
</tr>
<tr>
<td>METTL3</td>
<td>0.59</td>
<td>0.32-1.07</td>
<td>0.0840</td>
<td>Reader</td>
</tr>
<tr>
<td>FTO</td>
<td>0.61</td>
<td>0.31-1.20</td>
<td>0.1519</td>
<td>Eraser</td>
</tr>
<tr>
<td>YTHDF2</td>
<td>0.77</td>
<td>0.51-1.16</td>
<td>0.2113</td>
<td>Reader</td>
</tr>
<tr>
<td>YTHDF1</td>
<td>1.29</td>
<td>0.51-3.30</td>
<td>0.5881</td>
<td>Reader</td>
</tr>
</tbody>
</table>

ELAVL1, ELAV-like protein 1; KIAA1429, Protein virilizer homolog; YTHDF; YTH domain-containing family protein; METTL, methyltransferase like; ALKBH5, RNA demethylase ALKBH5; WTAP, WT1 associated protein; FTO, alpha-ketoglutarate-dependent dioxygenase FTO.

Association between the upregulation of gene expression and the m 6A.index-high group in mantle cell lymphoma. The m6A.index-high and the m6A.index-low groups were identified to be two different classes of mantle cell lymphoma. Therefore, the expression profiles of the m6A.index-high and the m6A.index-low groups in mantle cell lymphoma were compared (Fig. 5A). A total of 280 upregulated genes and 54 downregulated genes were identified between the m6A. index-high and the m6A.index-low groups in mantle cell lymphoma (Fig. 5B; P<0.05). The m6A.index-high mantle cell lymphoma group exhibited an increased number of upregulated genes compared with the m6A.index-low group, which suggested that the m6A.index-high mantle cell lymphoma type had a different RNA metabolism process from the m6A. index-low mantle cell lymphoma type. The cumulative distribution of the expression of RNA molecules corresponding to different genes with regard to the m6A.index-high and m6A. index-low mantle cell lymphoma types additionally demonstrated that the m6A.index-high mantle cell lymphoma type exhibited high RNA levels compared with the total transcript profile in the GSE93291 dataset (Fig. 5C; P<0.001). This result was also validated in the secondary GSE21452 dataset (n=64).

Cell division and RNA metabolism pathways are significantly enriched pathways of m 6A in mantle cell lymphoma. A characteristic difference between the m6A.index-high and m6A. index-low mantle cell lymphoma types was evident. WHSC1, which encodes for a histone-lysine N-methyltransferase, was the top downregulated gene in the m6A.index-high group compared with the m6A.index-low group (Fig. 5D; P=4.81x10^-9). Metastasis associated in lung adenocarcinoma transcript 1 (MALAT1) was the top upregulated gene in the m6A.index-high group compared with the m6A.index-low group (Fig. 5D; P=1.98x10^-9). The differential expression of WHSC1 and MALAT1 was also validated in the GSE21452 dataset (n=64). A pathway analysis of the differentially
Figure 5. Different expression of the genes in the m^A.index-high and m^A.index-low groups of patients with mantle cell lymphoma. (A) The heatmap indicates the different expression of the genes in the m^A.index-high and m^A.index-low groups of patients with mantle cell lymphoma. Red, high expression; green, low expression; white, moderate expression. Only the top 12 upregulated and downregulated genes were noted. The two bar plots in the left of the heatmap refer to the fold-change (log2, left; green and red) difference and the P-value (-log10, right; blue), respectively. (B) The total number of the upregulated (280 genes) and the downregulated genes (54 genes) between the m^A.index-high and m^A.index-low mantle cell lymphoma types. (C) Cumulative distribution of RNA levels (log2-fold) of the differentially expressed genes between the m^A.index-high (red) and the m^A.index-low (green) mantle cell lymphoma groups. The left plot represents the GSE93291 dataset (n=123), and the right plot represents the GSE21452 dataset (n=64). (D) The different expression levels of the MALAT1 and the WHSC1 genes between the m^A.index-high and the m^A.index-low mantle cell lymphoma groups. The left plot corresponds to the GSE93291 dataset (n=123), and the right plot corresponds to the GSE21452 dataset (n=64). A two sided unpaired Student's t-test was used. *P<0.05 and **P<0.001. m^A, N^6-methyladenosine.
expressed genes between the m^6A.index-high and the m^6A.index-low mantle cell lymphoma types was conducted. The cell division and RNA metabolism pathways were demonstrated to be the most significantly enriched pathways based on the differential expression of specific genes (Fig. 6A). The RB transcriptional corepressor 1, cell division cycle 25A and kinesin family member C1 genes were included in the cell division pathways group, and were demonstrated to be differentially expressed, out of a total of 9 genes (Fig. 6B). Therefore, the m^6A regulators may regulate the cell division pathways, contributing to poor patient survival in mantle cell lymphoma.

Discussion

Recent studies have indicated that m^6A mRNA methylation controls T-cell homeostasis and modulates hematopoietic stem and progenitor cell differentiation (36,37). However, the role of m^6A during B-cell development and B-cell tumorigenesis remains poorly understood (38). The present study demonstrated that the imbalanced expression of m^6A regulators may be used for the prediction of patient survival in mantle cell lymphoma. A previous study indicated that m^6A regulator participates in the innate immunity via the RNA helicase probable ATP-dependent RNA helicase DDX46. Therefore, the m^6A gene and the m^6A regulators are involved in B-cell lymphoma development, T-cell homeostasis and innate immunity.

Mantle cell lymphoma is an aggressive type of B cell lymphoma with a short median patient survival time. The identification of novel biomarkers for the prediction of patient survival in mantle cell lymphoma is considered a challenging task (43). The mantle cell lymphoma international prognostic index (MIPI) score is currently the most common prognostic model for mantle cell lymphoma in clinical practice (44). MIPI includes the age, Eastern cooperative oncology group
performance status, leukocyte count and lactate dehydrogenase activity (45). However, these models lack a component that incorporates gene expression analysis. The present study demonstrated that the expression levels of 5 m^6^A regulators were significantly associated with the survival of patients with mantle cell lymphoma. In addition, a comprehensive m^6^A index was constructed to predict the survival of mantle cell lymphoma. The m^6^A index was better compared with each individual m^6^A regulator for survival prediction with a hazard ratio of 0.39 (95% CI, 0.24-0.65).

It was surprising that half (5 of 10) of the m^6^A regulators were able to predict patient survival in mantle cell lymphoma (P<0.05). It appeared that the m^6^A regulators were commonly associated with mantle cell lymphoma patient survival. In addition, the m^6^A index was a better survival predictor compared with the single m^6^A regulator, which suggested that the imbalanced expression of m^6^A regulators may predict poor patient survival in mantle cell lymphoma. Furthermore, the data from the present study provided evidence to support a marked association between m^6^A expression and mantle cell lymphoma incidence: i) The expression of m^6^A regulators was a good classifier in mantle cell lymphoma; ii) the samples of mantle cell lymphoma were divided into two groups according to the m^6^A index (m^6^A.index-high and m^6^A.index-low groups), with the m^6^A index-high group exhibiting high RNA levels compared with the total transcript profile; and iii) the differentially expressed genes were associated with the cell division and RNA metabolism pathways in the m^6^A-index-high group that may result in poor patient survival.

The m^6^A index was correlated with enhanced proliferation. Ki-67 is clinically important for risk stratification and clinical management of mantle cell lymphoma (45-47). The m^6^A index demonstrated a highly negative correlation with gene expressions of Ki-67 and DNA polymerases. A total of 17 proliferation-associated genes were defined as a proliferation ‘signature’ and associated with overall survival in mantle cell lymphoma (39). The present study further correlated the m^6^A index with the expression of 17 proliferation-associated genes in 123 mantle cell lymphoma samples; 16 of these 17 proliferation-associated genes were highly correlated with m^6^A index, which suggested that the m^6^A index was associated with proliferation in mantle cell lymphoma.

Mammalian KIAA1429 is the largest known component within the m^6^A methyltransferase complex and serves as a scaffold of the methyltransferase complex, while METTL3/METTL14/WTAP serve as the catalytic core components (24). In the results from the present study, the majority of the m^6^A writer molecules, including METTL3, METTL14 and WTAP, were classified as ‘favorable genes’, while the remaining m^6^A writer (KIAA1429) was categorized into the group of ‘harmful genes’. Therefore, within the group of 4 m^6^A writers, KIAA1429 appeared to be the most significant in terms of its biological function and clinical implications.

In summary, the results from the present study demonstrated that the expression levels of m^6^A regulators were associated with the survival of patients with mantle cell lymphoma and may serve as potential biomarkers for prognosis.

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Availability of data and materials

The data included in the present study have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession numbers GSE93291 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE93291) and GSE21452 (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE21452). The datasets used in the present study are available from the corresponding author upon reasonable requests.

Authors’ contributions

HJ and XZ conceived the project. WZ and XH analyzed the data. WZ, XH, JH, PY, CL, JW, RA, JZ, MP, KH, XK, XZ and HJ contributed towards the interpretation of the data. All authors wrote and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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