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INTEGRATIVE TRANSCRIPTOMIC AND PROTEOMIC EXPLORATION OF METTL25 EXPRESSION PATTERNS IN HUMAN TISSUES AND CANCERS

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ABSTRACT

Background: Although recent studies have established the critical roles of methyltransferases in epigenetic regulation and cellular homeostasis, the biological function of METTL25, a member of this enzyme family, is not well known. Current clinical research has identified various methyltransferases as key regulators of gene expression, yet METTL25 remains functionally uncharacterized, representing a significant knowledge gap in our understanding of methyltransferase biology. **Objective:** This study examines the expression patterns of METTL25 across normal human tissues and cancer contexts to identify its potential physiological and pathological roles and to understand its regulatory mechanisms in health and disease. **Methods:** We conducted a systematic computational analysis using large-scale publicly available transcriptomic and proteomic datasets. Expression patterns were analyzed across normal human tissues and cancer cell lines. Correlation analysis between mRNA and protein levels was performed, followed by differential gene expression analysis comparing thyroid carcinoma to normal thyroid tissue. Functional enrichment analysis was applied to identify biological pathways associated with METTL25 expression. **Results:** METTL25 exhibited tissue-specific expression patterns with highest expression observed in endocrine organs (thyroid, adrenal glands) and immune compartments (lymphoid tissues). Moderate correlation between mRNA and protein levels was identified ($r=0.404$; $p=0.001$), indicating transcriptional control of protein abundance. METTL25 expression was significantly downregulated in thyroid carcinoma compared to normal thyroid tissue ($p<0.01$). Higher METTL25 expression in tumors was statistically significant and positively correlated with gene signatures related to wound healing, coagulation, and hemostasis pathways. **Conclusion:** METTL25 functions as a tissue-restricted methyltransferase with tumor suppressor characteristics in thyroid cancer. The positive correlation between METTL25 expression and wound healing pathways was statistically significant, suggesting its involvement in tissue repair mechanisms. These findings provide the foundation for future mechanistic studies investigating METTL25's role in cancer biology and its potential as a therapeutic target.

BACKGROUND

Methylation is a fundamental biochemical modification that regulates diverse cellular processes, including gene expression, RNA stability, protein function, and signal transduction[1,2]. This process involves the enzymatic transfer of a methyl group from the universal methyl donor, S-adenosylmethionine (SAM), to DNA, RNA, or protein substrates, leading to their methylation and the conversion of SAM into S-adenosylhomocysteine (SAH) and resulting in structural and functional changes that impact gene regulation and cellular behavior to various biological substrates[3]. The enzymes that catalyze these reactions, methyltransferases, are broadly categorized by substrate specificity into DNA, RNA, and protein methyltransferases, each contributing to the maintenance of cellular homeostasis in. Each group plays a distinct role in maintaining cellular homeostasis and is implicated both normal and disease context[2, 4-6].

In addition to their well-known roles in epigenetic regulation, methyltransferases have emerged as key modulators of post-translational modification in non-histone proteins such as TP53, PTEN, c-Fos, AKT, and STAT3[1,7]. These modifications influence cellular events such as tumor suppression, differentiation, and immune response. Notably, several protein methyltransferases within the methyltransferase-like (METTL) family have been associated with cancer development and progression. Our finding uncovered EEF1AKMT3 (METTL21B) as a critical regulator of tumor invasiveness and metastasis in gastric cancer through its interaction with the MAP2K7/TP53 signaling axis[1]. In addition, we also reported PRMT1 methylates c-Fos, protecting it from autophagic degradation and thereby promoting gastric cancer cell growth and invasiveness[8]. In hepatocellular carcinoma (HCC), multiple METTL family members, including METTL6 and METTL21A, have been associated with tumor progression and prognosis, highlighting their potential as biomarkers and therapeutic targets[4]. Furthermore, METTL3, a widely studied RNA methyltransferase, regulates m6A RNA modifications and has been implicated in cancer progression and therapy resistance, reinforcing the significance of methylation beyond DNA and histone modifications[9, 10].

Despite increasing interest in the METTL family, many of its members remain poorly characterized. Among them, METTL25, a member of this family, stands out as one of the least explored, with limited reports describing its function and biological significance. While other METTL enzymes have been associated with oncogenic and physiological processes, the role of METTL25 remains largely unexplored[4,11]. To date, only two publications indexed in PubMed (as of early 2024) specifically mention METTL25. One included METTL25 in a multi-gene expression analysis of METTL family members in hepatocellular carcinoma (HCC), although METTL25 itself was not significantly associated with clinical parameters or survival outcomes[4], and another referenced the gene in a genome-wide association study related to digital dermatitis[12]. The lack of focused investigations underscores a significant knowledge gap and highlights the importance of preliminary exploratory studies to understand its potential biological functions.

Recent advancements in high-throughput transcriptomic and proteomic profiling have enabled researchers to examine gene expression patterns across normal and diseased tissues. Publicly available resources such as the Genotype-Tissue Expression (GTEx) project, the Gene Expression Omnibus (GEO), and the Cancer Cell Line Encyclopedia (CCLE) provide large-scale datasets that allow for systematic gene characterization across diverse tissue types, developmental stages, and pathological conditions[11, 13]. The integration of these datasets has proven essential for prioritizing candidate genes for functional validation and predicting gene-disease associations, thereby facilitating the characterization of understudied genes such as METTL25.

In this study, transcriptomic and proteomic data from GTEx, GEO, and CCLE were utilized to comprehensively assess the expression patterns of METTL25 in human tissues and cancer cell lines. The aim was to establish an initial biological profile of METTL25, identify tissues and systems where it may play a functional role, and generate hypotheses regarding its potential relevance in human physiology and disease. These findings would contribute to a better understanding of the methyltransferase family and help guide future experimental studies aimed at uncovering the potential roles of METTL25 in cellular physiology and disease.

METHODS

Study Design and Data Sources

This study employed a cross-sectional exploratory design to examine the expression profile of METTL25 in normal human tissues, cancer tissues, and cancer cell lines using publicly available transcriptomic and proteomic datasets. The analysis focused on identifying tissue-specific expression patterns and exploring the relationship between METTL25 RNA and protein levels, and functional annotation of METTL25 using R programming language.

METTL25 Expression in Normal Human Tissues

To evaluate METTL25 expression in normal tissues, data were retrieved from the Genotype-Tissue Expression (GTEx) project and the Gene Expression Omnibus (GEO). Median gene-level transcript per million (TPM) values for METTL25 were retrieved from the GTEx Portal. The dataset, derived from GTEx_Analysis_v10, included normalized expression profiles across a broad range of adult human tissues and the median expression was already calculated. The data used for the analyses in this manuscript were obtained from the GTEx Portal (https://www.gtexportal.org/home/downloads/adult-gtex/bulk_tissue_expression) on February 18, 2025.

In addition, raw RNA-sequencing data from dataset GSE120795 were downloaded from the Gene Expression Omnibus (GEO) and processed to complement the analysis. Raw counts were processed by filtering out low-expression genes and the expression data was log-transformed for normalization. Relevant sample metadata, including information on tissue origin, was extracted and integrated with the expression dataset. Gene annotation files were used to locate and extract METTL25 expression values across the tissue types represented in the dataset.

METTL25 Expression and RNA-Protein Correlation in Cancer Cell Lines

Expression profiling of METTL25 in cancer cell lines was performed using transcriptomic and proteomic datasets obtained from the Cancer Cell Line Encyclopedia (CCLE) through the DepMap portal. These datasets were accessed using the "depmap" R package. METTL25 RNA-seq data were retrieved using the depmap_TPM() function, while protein expression levels were extracted via the depmap_proteomic() function. The datasets were filtered to remove missing values and grouped by tissue or lineage based on cell line annotations.

To assess the concordance between transcript and protein expression, METTL25 RNA and protein data were matched using unique cell line identifiers. Samples with missing values were excluded to ensure completeness. This allowed for direct comparison of METTL25 transcript and protein levels within the same cellular context, offering insight into the post-transcriptional regulation of METTL25 in cancer cells.

METTL25 Expression Analysis in Normal and Tumor Tissues

To investigate the expression pattern of METTL25 across normal and tumor tissues, we utilized a unified RNA-seq dataset published by Wang et al. (2018) (14). This dataset combines transcriptomic data from GTEx (healthy tissues) and TCGA (tumor and adjacent normal tissues), and has been preprocessed with quantile normalization and batch effect correction using the ComBat method, allowing for cross-cohort comparison.

Expression values for METTL25 (measured in FPKM) were extracted from individual organ-specific files. For each cancer type, samples were categorized into three groups: (1) GTEx-derived normal tissues, (2) TCGA adjacent normal tissues (NAT), and (3) TCGA tumor tissues. All FPKM values were transformed using log2(FPKM + 1) to reduce skewness and stabilize variance. To assess differences in METTL25 expression across the three groups, we performed Kruskal-Wallis tests followed by pairwise Wilcoxon rank-sum tests with Benjamini-Hochberg correction for multiple comparisons. This pipeline was applied consistently across multiple cancer types and matched normal tissues available in the dataset

Differential Expression and Functional Enrichment Based on METTL25 Expression in Thyroid Cancer

To investigate the transcriptomic changes associated with METTL25 expression in thyroid carcinoma (TCGA-THCA), we retrieved RNA-seq raw count data from the Genomic Data Commons (GDC) using the TCGAbiolinks R package. Gene expression data were filtered to include only primary tumor samples, followed by preprocessing (TCGAanalyze_Preprocessing), normalization based on GC content (TCGAanalyze_Normalization), and low-expression gene filtering (TCGAanalyze_Filtering). Expression of METTL25 was then extracted using its Ensembl gene ID, and tumor samples were stratified into High (top 10%) and Low (bottom 10%) expression groups based on quantile cutoffs.

Differential expression analysis (DEA) between High and Low METTL25 groups was performed using the TCGAanalyze_DEA function with the edgeR pipeline and generalized linear model (glmLRT) approach. Genes were considered significantly differentially expressed if they met an absolute log2 fold change > 1 and FDR < 0.05.

To explore the biological functions associated with METTL25-associated transcriptional changes, we selected strongly upregulated genes (log2FC > 2, FDR < 0.05) and submitted their gene symbols to WebGestalt (http://www.webgestalt.org/) for over-representation analysis (ORA) using the Gene Ontology (GO) categories (15). The reference gene list was set to the genome-wide protein-coding background (Homo sapiens), and significance thresholds were defined by FDR-adjusted p-values (< 0.05). This enrichment analysis provided insights into the biological processes potentially regulated in the context of high METTL25 expression in thyroid cancer.

Statistical Analysis and Data Visualization

All statistical analyses were performed using R version 4.2.1 in RStudio. To assess the correlation between METTL25 RNA and protein expression levels across cancer cell lines, Pearson correlation analysis was conducted using only samples with matched transcriptomic and proteomic data. Correlation coefficients and corresponding p-values were computed to evaluate the strength and statistical significance of RNA-protein concordance. To compare METTL25 expression across tissue groups (e.g., tumor vs. normal), the Wilcoxon rank-sum test was applied for two-group comparisons, while comparisons involving three groups (GTEx normal, TCGA adjacent normal, and TCGA tumor) were analyzed using the Kruskal-Wallis test, followed by pairwise Wilcoxon rank-sum tests with Benjamini-Hochberg correction for multiple testing.

For differential expression analysis (DEA) between high and low METTL25 expression groups in thyroid cancer (TCGA-THCA), the edgeR pipeline was used with the generalized linear model likelihood ratio test (glmLRT) method. Genes were considered significantly differentially expressed if they met the thresholds of $|\log_2 \text{fold change}| > 1$ and FDR < 0.05. Functional enrichment of upregulated genes was performed using WebGestalt for over-representation analysis (ORA) in Gene Ontology (GO) categories. Significance was determined based on FDR-adjusted p-values < 0.05, using all protein-coding genes in the human genome as the reference background.

RESULTS

RNA Expression of METTL25 across Human Tissues

To characterize the physiological expression profile of METTL25, RNA-sequencing data from the GSE120795 dataset were analysed. This dataset includes RNA sequencing data from multiple solid tissue samples representing 20 different organs, collected from post-mortem healthy donors who died in road accidents within 36 hours. Additionally, blood samples were obtained from 17 healthy volunteers, as previously described[16]. After variance-stabilizing transformation (VST) normalization of the raw counts, METTL25 expression was compared across a wide range of tissues representing at various anatomical sites.

The analysis revealed that METTL25 expression remained relatively consistent across tissues, with no strong tissue specificity. However, within the dataset of 135 samples, as shown in **Figure 1**, the thyroid gland exhibited the highest median METTL25 expression among all tissues, followed by the adrenal gland, small intestine, and tonsils. These tissues showed relatively elevated expression compared to other organ systems. In contrast, METTL25 expression was comparatively lower in gastrointestinal tissues such as the colon and liver. The liver showed one of the lowest levels of METTL25 expression.

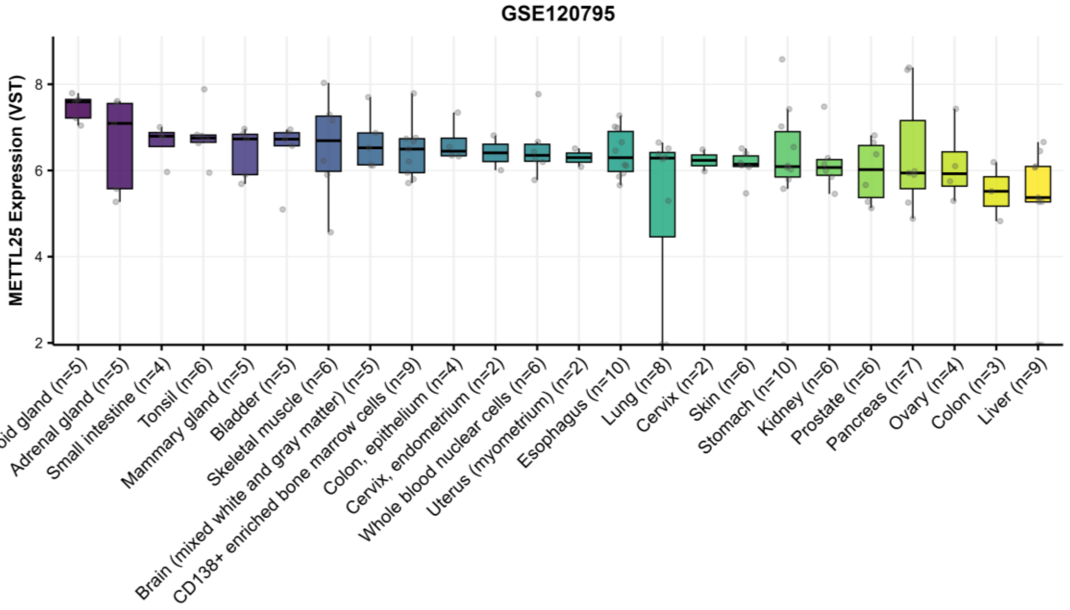
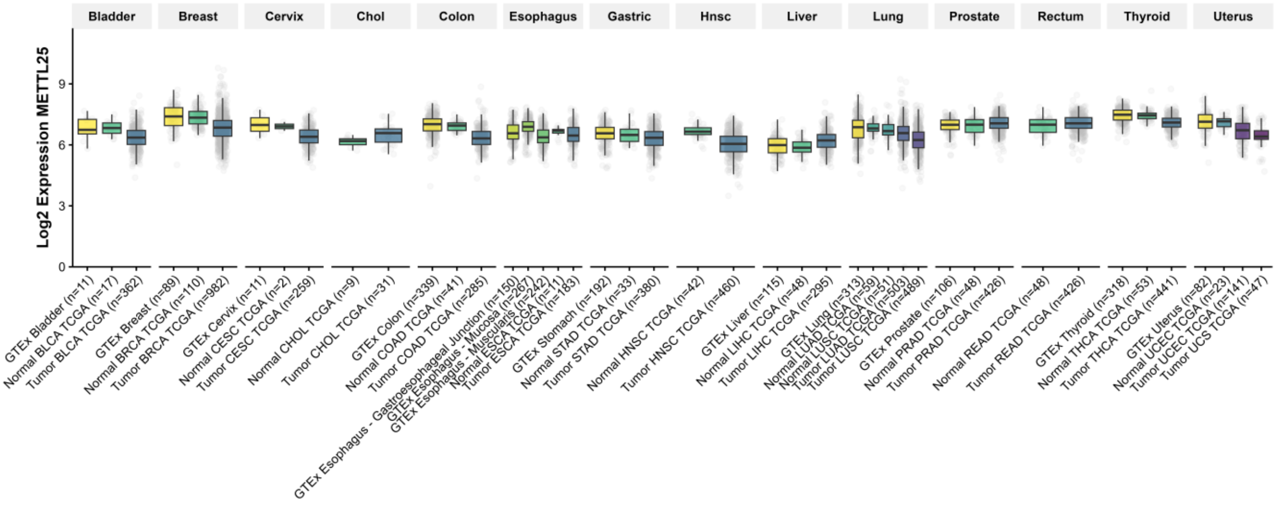


Figure 1. Normalized METTL25 RNA expression (VST) across different human tissues in the GSE120795 dataset



Interestingly, hematopoietic and lymphoid tissues such as whole blood and CD138+ enriched bone marrow cells exhibited intermediate levels of expression, suggesting a potential but modest role for METTL25 in immune-related functions. The distribution of expressions across samples within each tissue type also varied, such as the lung showing higher variability (wider interquartile ranges), possibly reflecting heterogeneity in sample composition or donor-specific expression patterns. Overall, the data indicate that although METTL25 is expressed across many tissues, its activity appears to be more pronounced in certain endocrine and mucosal tissues. This pattern may reflect unique regulatory mechanisms or specific functional roles that are particularly important in these tissue types.

To further investigate tissue-specific transcriptional patterns of METTL25, expression data were analysed from the Adult Genotype-Tissue Expression (GTEx) project, which provides a comprehensive public resource for studying gene expression and regulation across a broad range of non-diseased human tissues. In this study, median TPM values of METTL25 mRNA were extracted across 68 distinct tissues. To emphasize the most divergent expression levels, the ten tissues with the highest and the ten with the lowest METTL25 median expression were visualized in **Figure 2**.

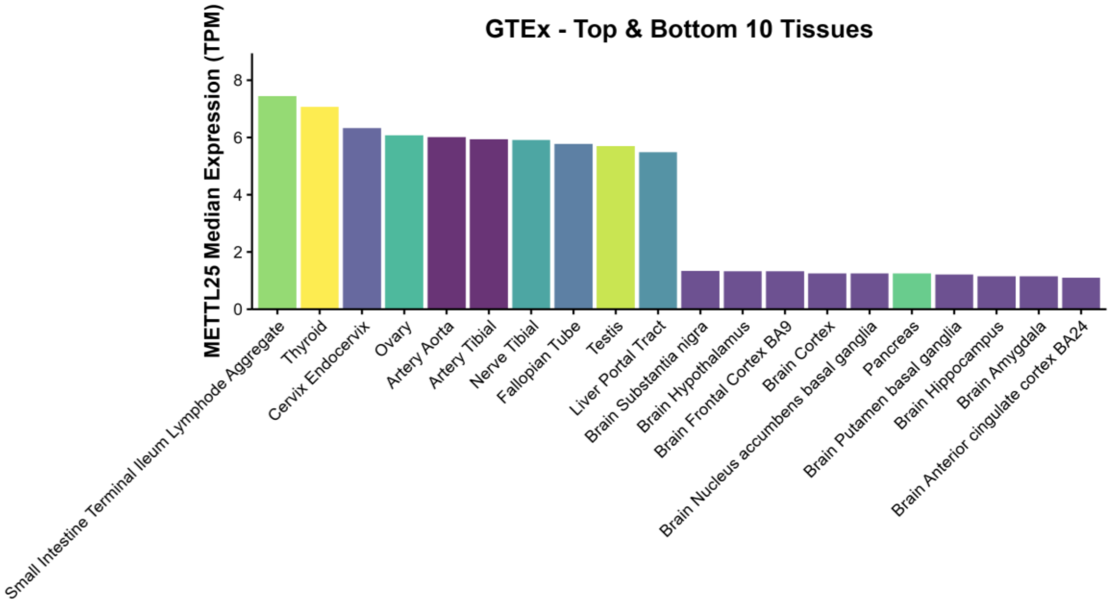


Figure 2. Top 10 tissues with the highest and lowest METTL25 expression, ranked by median TPM values from the GTEx dataset.

Consistent with findings from the GSE120795 dataset, METTL25 exhibited relatively higher expression in the thyroid, small intestine (terminal ileum), with additional high expression noted in lymph node aggregates. On the other hand, notably lower expression was observed in the pancreas and multiple brain regions, such as anterior cingulate cortex, amygdala, basal ganglia, hypothalamus.

These observations provide converging evidence from two independent transcriptomic datasets that METTL25 is broadly distributed across human tissues, albeit with modest tissue-specific variation. Higher expression in endocrine-related tissues such as the thyroid and adrenal gland, along with mucosal and immune-associated organs such as the small intestine and lymphoid tissues (tonsils, lymph nodes) suggests a potential regulatory role in endocrine signalling, immune function, and epithelial maintenance. Conversely, the uniformly low expression in neural tissues may reflect a more limited role in brain-specific cellular processes.

METTL25 RNA and Protein Expression Correlation

To further characterize the expression pattern of METTL25 and its correlation with protein expression, transcriptomic and proteomic data from the Cancer Cell Line Encyclopedia (CCLE) were analyzed. RNA and protein expression data for various cancer cell lines were obtained using the depmap R package. A total of 63 cancer cell lines were included in the correlation analysis after filtering for samples with both RNA and protein expression data available. This integrated dataset provides a valuable resource for evaluating the relationship between transcriptional and translational regulation of METTL25 across diverse cancer types.

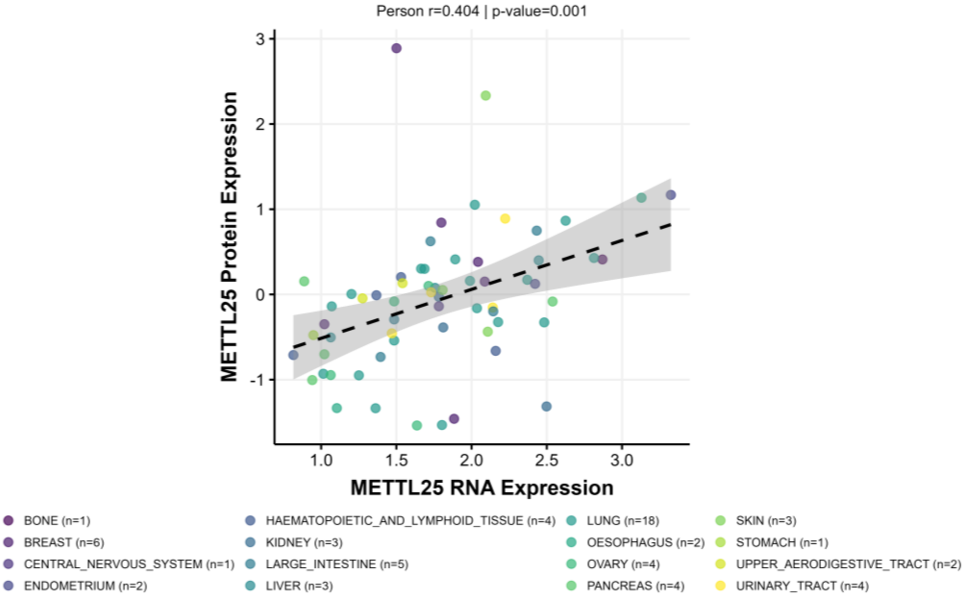


Figure 3. The correlation analysis between RNA and protein expression levels of METTL25 across various tissues in the CCLE dataset.

As shown in **Figure 3**, Pearson correlation analysis revealed a moderate, statistically significant positive correlation between METTL25 RNA and protein expression (r = 0.404, p = 0.00102), indicating that higher RNA expression is generally associated with increased protein expression of METTL25. However, the moderate correlation coefficient implies that while RNA expression levels contribute to protein abundance, other post-transcriptional and translational regulatory mechanisms are likely to influence protein expression of METTL25.

METTL25 Expression Across Normal and Tumor Tissues

To gain insights into the potential clinical relevance of METTL25, its RNA expression was compared between cancer and normal tissues across various organ systems. RNA expression analysis of unified transcriptomic dataset consisting of TCGA tumor, TCGA adjacent normal tissues, and GTEx-derived healthy tissues revealed METTL25 expression was significantly downregulated in several cancer types, including bladder cancer (BLCA), breast cancer (BRCA), colon adenocarcinoma (COAD), thyroid carcinoma (THCA), uterine corpus endometrial carcinoma (UCEC), and head and neck squamous cell carcinoma (HNSC) (**Figure 4**). These patterns were observed consistently when comparing both adjacent non-tumor tissues from TCGA and GTEx-derived normal tissues, when available. The downregulation observed in several digestive tract malignancies such as colon and rectal cancer align with prior results demonstrating relatively high METTL25 expression in normal small intestinal tissues (**Figure 1** and **Figure 2**).

Conversely, a significant upregulation of METTL25 was detected in cholangiocarcinoma and liver hepatocellular carcinoma, suggesting a distinct regulatory landscape in hepatobiliary tumors. Interestingly, in cervical and gastric cancers, significant differences were noted between GTEx and TCGA cancer samples, whereas no statistically significant change was observed when comparing adjacent normal and cancer samples within TCGA. This discrepancy may stem from limited adjacent normal samples, biological heterogeneity, or platform-related variation between datasets. Taken together, these results underscore the context-dependent regulation of METTL25 in human cancers.

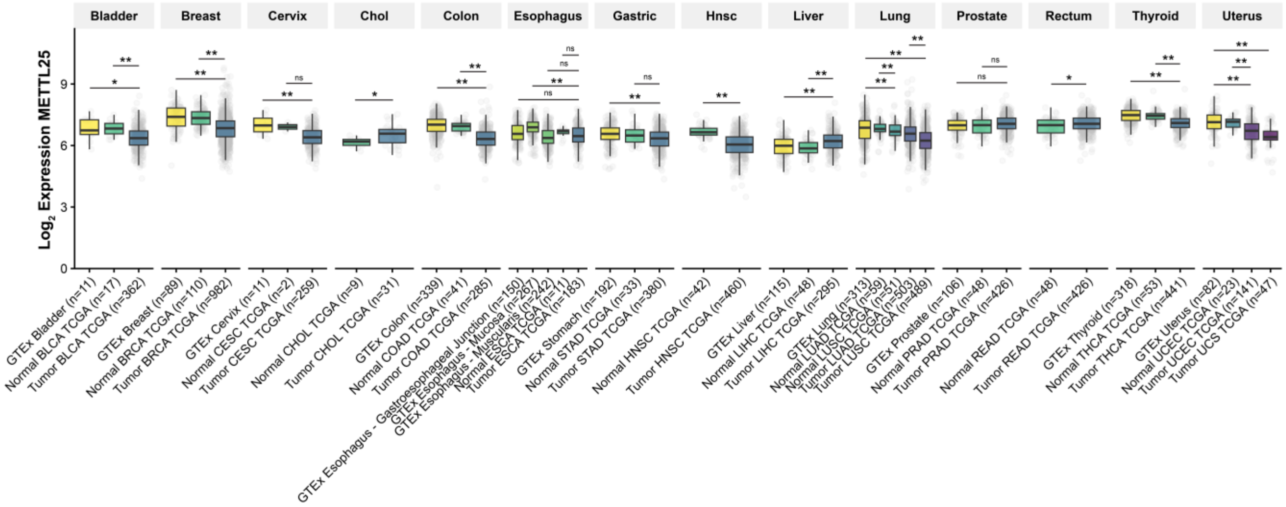


Figure 4. METTL25 expression comparison between normal and tumor tissues across major cancer types. Expression levels were obtained from TCGA and GTEx datasets. Box plots display median and interquartile ranges with individual data points overlaid. Statistical significance was determined using Wilcoxon rank-sum tests ($p < 0.05$ = *, $p < 0.01$ = **, ns = not significant).

Enrichment of Biological Processes in High METTL25-Expressing Thyroid Tumors

Among the cancer types showing significant downregulation of METTL25 in tumors, thyroid carcinoma (THCA) demonstrated one of the most notable expression gaps, with consistently high expression observed in normal thyroid tissues based on both GTEx and GSE120795 datasets (**Figure 1** and **Figure 2**). Given this striking physiological expression and its marked suppression in tumor samples, THCA was selected for further investigation. To explore the functional implications of METTL25 activity within tumors, we performed differential expression analysis (DEA) between tumor samples with high and low METTL25 expression (top and bottom 10%), identifying genes significantly upregulated in the high-expression group. The clinical characteristics of patients with high and low METTL25 expression are summarized in **Table 1**. Applying a stringent cutoff of log2 fold change > 2 and FDR < 0.05, a total of 374 upregulated genes were selected and submitted to over-representation analysis (ORA) using the WebGestalt platform.

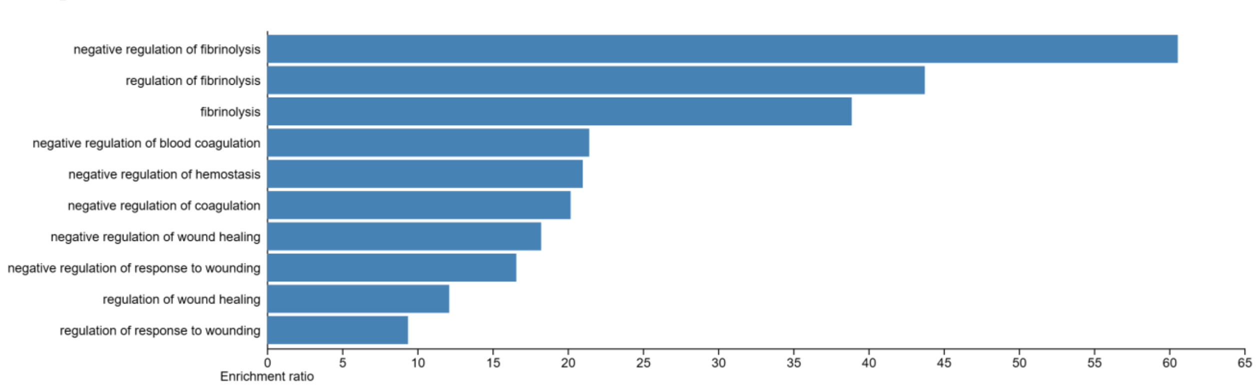


Figure 5. Gene Ontology (GO) enrichment analysis of upregulated genes in the high METTL25-expressing group in TCGA-THCA

Table 1. The clinical characteristics of patients with high and low METTL25 expression in TCGA-THCA

Clinical Variable	**METTL25 Expression Group**	
	High[1] (n = 51)	**Low[1] (n = 50)**
Age at diagnosis	46 [34, 52]	47 [37, 63]
Gender		
Female	39 (76%)	28 (56%)
Male	12 (24%)	22 (44%)
Race		
Asian	6 (12%)	4 (8.0%)
Black/african american	2 (3.9%)	2 (4.0%)
White	38 (75%)	35 (70%)
Unknown	5 (9.8%)	9 (18%)
AJCC Pathologic Stage		
Stage I	27 (53%)	25 (50%)
Stage II	4 (7.8%)	3 (6.0%)
Stage III	19 (37%)	15 (30%)
Stage IV	1 (2.0%)	7 (14%)
Tumor (T) Stage		
T1	9 (18%)	15 (30%)
T2	23 (45%)	10 (20%)
T3	19 (37%)	19 (38%)
T4	0 (0%)	5 (10%)
TX	0 (0%)	1 (2.0%)
Node (N) Stage		
N0	24 (47%)	21 (42%)
N1	21 (41%)	28 (56%)
NX	6 (12%)	1 (2.0%)
Metastasis (M) Stage		
M0	29 (57%)	32 (64%)
MX	22 (43%)	18 (36%)
Vital Status		
Alive	51 (100%)	46 (92%)
Dead	0 (0%)	4 (8.0%)

[1] Median [Q1, Q3]; n (%)

The top-enriched GO term was "negative regulation of response to wounding" (GO:1903035), with a 22.6-fold enrichment and a false discovery rate (FDR) of 0.0026 (**Figure 5**). Closely related terms, including "negative regulation of wound healing" and "regulation of wound healing", were also significantly enriched, suggesting a role for METTL25-associated gene expression in controlling tissue repair mechanisms. In addition, processes linked to coagulation and fibrinolysis, such as "negative regulation of blood coagulation" and "negative regulation of fibrinolysis" were prominently represented, with enrichment ratios exceeding 25 and highly significant FDR-adjusted p-values (< 0.02).

DISCUSSION

The findings of this study provide a deeper understanding of METTL25 expression patterns in human tissues and cancer cell lines. Analysis of multiple independent datasets consistently demonstrated that METTL25 is broadly expressed, albeit with variations across different tissues. Notably, higher expression levels were observed in the thyroid, adrenal glands, small intestine, and lymphoid tissues, while lower levels were found in the brain and pancreas. This tissue-specific distribution suggests that METTL25 may have functional relevance in endocrine regulation, immune function, and epithelial maintenance. The relatively low expression in neural and pancreatic tissues raises intriguing questions about its potential regulatory constraints or compensatory mechanisms in these organs, which could be explored in future research.

Methyltransferase-like (METTL) proteins have been implicated in diverse physiological and pathological contexts[7, 17-21]. For example, METTL3 and METTL14 play essential roles in RNA methylation and have been linked to immune responses and cancer progression[9,19,21,22]. Similarly, METTL18 has been shown to be upregulated in tumors compared to normal tissues in the TCGA-BRCA cohort, with high expression correlating with lower survival rates in breast cancer patients [4, 23]. These findings align with our results, suggest that METTL25, like other METTL family members, may have a role in cellular regulation and disease. However, unlike other methyltransferases, whose functions have been extensively characterized [4, 11], the biological significance of METTL25 remains largely unexplored.

The immune system might be associated important context for METTL25 function. Given METTL25's relatively high expression in lymphoid tissues, it is worth exploring whether it contributes to immune responses or hematopoiesis. Methyltransferases have been implicated in diverse stages of immune cell activation, differentiation, and cytokine production[18,24-26]. Notably, protein methylation can modulate immune system development by influencing epigenetic reprogramming, transcription factor activity, and receptor signaling [5, 18]. This raises the possibility that METTL25 may participate in immune regulation via methylation-dependent pathways, a hypothesis that warrants further exploration through functional immunological studies.

Furthermore, the endocrine implications of METTL25 expression align with findings on other methyltransferases [17, 22]. For instance, METTL3, which has been extensively studied for its role in endocrine dysfunction and metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), and pancreatic cancer[22]. The regulation of RNA modifications by methyltransferases like METTL3 suggests a broader role for these enzymes in modulating endocrine pathways, including those potentially influenced by METTL25. Additionally, methyltransferases have been implicated in pancreatic progenitor differentiation, as seen in studies on AMI-5, a protein methyltransferase inhibitor that affects endocrine specification in the pancreas by downregulating Ngn3[27]. These findings suggest that METTL25, as part of the broader methyltransferase family, may contribute to endocrine tissue homeostasis and disease susceptibility, warranting further investigation.

A recent study by Wang et al. further supports the notion that METTL25 may be relevant in cancer biology. Among the 33 METTL family members, 11 METTLs including METTL25, were found to be significantly upregulated in HCC compared to normal tissues in hepatocellular carcinoma[4]. Interestingly, METTL25 was the only member not significantly associated with tumor stage or invasion depth, suggesting that it may follow a distinct regulatory mechanism or have a non-canonical function in liver cancer. These findings underscore the need for further exploration of METTL25's context-dependent roles in cancer.

In the cancer cell line analysis, METTL25 RNA expression exhibited a moderate positive correlation with protein levels, indicating that transcriptional activity influences protein abundance. However, additional post-transcriptional and post-translational mechanisms likely regulate METTL25 protein levels, including mRNA stability, protein degradation, and potential modifications such as phosphorylation or ubiquitination. Such regulatory complexity has been observed in other METTL family members. For instance, METTL21B undergoes ubiquitination-mediated degradation in response to specific cellular signals, affecting its stability and function[1].

Moreover, the observed variability in METTL25 expression across different cancer cell lines suggests that its regulation may be influenced by tumor-specific factors. A similar phenomenon has been described for METTL21A, where expression differences across cancer types correlated with tumor aggressiveness and patient prognosis[4]. Given that several METTL proteins are involved in oncogenic signaling pathways, it is plausible that METTL25 plays a role in tumor progression, either as a tumor suppressor or an oncogene, depending on the cellular context. Recent studies have demonstrated that methyltransferases play a role in regulating ribosome biosynthesis, translation elongation, and cytoskeletal remodeling[23]. Specifically, METTL18 has been identified as an oncogenic factor in HER2-negative breast cancer, where it influences Src phosphorylation through RPL3 methylation. This process, in turn, promotes metastasis by modulating interactions with HSP90 and actin polymerization[23], highlighting its potential as a therapeutic target. Given the structural and functional similarities among METTL family proteins, METTL25 may exert similar regulatory effects in different cancer subtypes, particularly in relation to tumor microenvironment interactions and metastatic potential.

Our results suggest that METTL25 may play a physiological role in regulating genes involved in wound healing and hemostasis in the thyroid, as these processes were enriched among genes upregulated in tumors that retained relatively higher METTL25 expression. Given that METTL25 is normally highly expressed in healthy thyroid tissue but significantly downregulated in thyroid carcinoma, the loss of METTL25 expression in tumors may lead to dysregulation of these biological pathways. Thus, rather than being tumor-promoting, the functions associated with METTL25, such as negative regulation of tissue repair and coagulation, may be disrupted in its absence, potentially contributing to the altered microenvironment and behavior of thyroid tumors. This highlights a putative tumor-suppressive function of METTL25 that warrants further functional validation.

Also, the potential role of METTL25 in tumor suppression should be considered, given that some protein lysine methyltransferases (PKMTs) function as tumor suppressors by stabilizing p53, regulating β-catenin, and maintaining genomic stability[28]. While most research focuses on their oncogenic functions, emerging evidence suggests that PKMTs can also suppress tumorigenesis through the regulation of tumor suppressor networks. Whether METTL25 exerts pro- or anti-tumorigenic effects may depend on cell type, signaling context, and the presence of interacting proteins.

This study has limitations, as it relies solely on publicly available secondary datasets without independent or experimental validation, which may introduce data heterogeneity and limit causal interpretation. Despite these limitations, our integrative multi-omics approach offers valuable preliminary insights into METTL25's tissue-specific expression and potential biological roles, providing a solid basis for future experimental studies.

CONCLUSION

This study reveals that METTL25 exhibits tissue-specific expression, with notably high levels in the thyroid and consistent downregulation in thyroid carcinoma. Functional enrichment analysis suggests that METTL25 may regulate genes involved in wound healing and hemostasis, indicating a potential tumor-suppressive role. These findings provide initial insights into METTL25's biological relevance and highlight its potential as a target for further investigation in cancer research.

ETHICAL APPROVAL

Ethical approval was not required for this study as it exclusively used publicly available, de-identified datasets from established repositories (GTEx, TCGA, etc.). No direct human subjects were involved in this research.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Nur Aziz: Conceptualization, Methodology, Investigation, Software, Formal Analysis, Writing - Original Draft, Writing - Review & Editing. **Laily Rahmawati**: Conceptualization, Methodology, Software, Formal Analysis, Validation, Writing - Review & Editing. **Nurinanda Prisky Qomaladewi**: Conceptualization, Writing - Original Draft.

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