METTL3 mediated protective immune modulation in low grade glioma patients

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INTRODUCTION

- Tumor immune microenvironment (TIME) determines the survival of cancer patients by maintaining an appropriate niche in the tumor cells.
- N6-methyladenosine (m6A) RNA methylation plays an influential role in immunoregulation, and immunotherapy evokes effective treatment responses in many tumors.
- Studies have shown that m6A modifier METTL3 induces the Production of IL6, IL12, and TNF-α in response to antigens.
- METTL3 promotes dendritic cell (DC) activation and function resulting in the initiation of immune response by activating T cells. Thus, forming a bridge between Cancer stem cells (CSCs) and the TIME.
- Our study aimed to investigate the regulatory role of Methyltransferase-like 3 (METTL3), a component of the complex m^6A methyltransferase effects on the prognosis of LGG, and correlation with tumor immune infiltration.

RATIONAL OF THE STUDY

To investigate the association of METTL3 expression with immune cell markers in LGG.

METHODS

The study was performed on the archived data available in the **TCGA** and **GEO**.

We comprehensively evaluated different m^6A modifiers and we screened immune genes associated with METTL3 by **TIMER database.**

The correlation between METTL3 and gene markers of immune cells and TAMs were analyzed using the **TIMER database.**

We used the **GEPIA database** and using the Spearman method, we analyzed the correlation between METTL3 and IDH1.

- The study was performed on the archived data available in the TCGA and GEO.
- Correlation between overall survival time and METTL3 expression was analyzed using Kaplan–Meier plot.
- Further, the correlation of METTL3 expression with the abundance of immune infiltrates was analyzed using the TIMER database (including B cell, Dendritic cell, CD4+ T cell, Neutrophil, CD8+ T cell, Macrophage) and screened for *METTL3*-related immune genes.
- In addition, we utilized TIMER database to understand the role of METTL3 in immune infiltration, especially with occurrence of isocitrate dehydrogenase 1 (IDH1) mutations in LGG patients.

RESULTS

- High METTL3 expression was found associated with improved overall survival in lower-grade glioma.
- We got a negative correlation between METTL3 and CD8+T cell infiltration, while CD4+T cell and macrophage infiltration was positively correlated with METTL3 expression.
- Majority of the immune markers were also negatively correlated with METTL3 expression. We also observed that METTL3 expression positively correlated with IDH1 expression in LGG. IDH1 mutation is significantly associated with tumor immune cell infiltration.

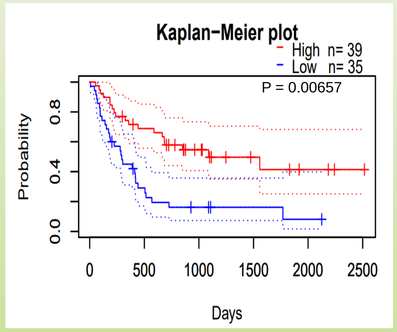

Figure 1. Kaplan-Meier survival curve showing high METTL3 expression found to be associated with improved overall survival in lower-grade glioma.

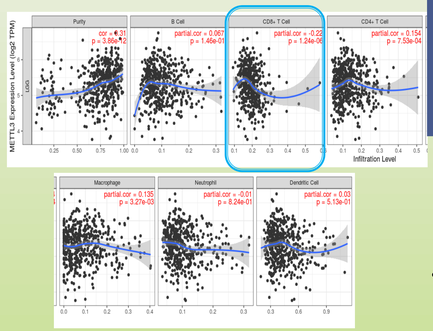

Figure 2. Correlation of METTL3 expression with immune infiltration level in LGG

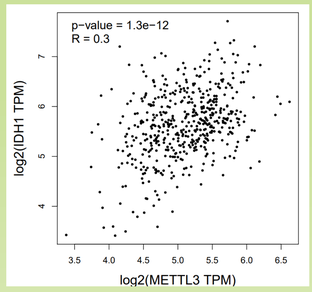

Figure 3. METTL3 expression has a positive relationship with IDH1 in LGG

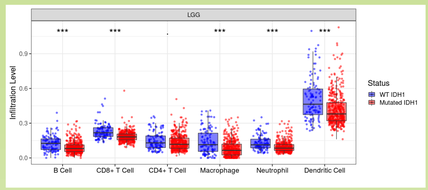

Figure 4: IDH1 mutation is significantly associated with tumor immune cell infiltration.

Table 1 Correlation analysis between METTL3 and gene markers of immune cells and TAMs

Description	Gene marker	LGG None cor	None p	Purity cor	Purity p
CD8+T cell	CD8A	-0.3478	***	-0.33995	***
	CD8B	-0.27276	***	-0.25334	***
M1 Macrophage	NOS2	-0.00589	0.893852	0.004356	0.924244
	IRF5	0.047859	0.277766	0.028903	0.527865
	PTGS2	-0.17926	***	-0.16466	***
M2 Macrophage	CD163	-0.03451	0.43393	-0.06041	0.186837
	VSIG4	0.063955	0.146813	0.034315	0.453556
	MS4A4A	0.038489	0.382804	0.007394	0.871733
Th1	TBX21	-0.02585	0.557926	-0.02008	0.661144
	STAT4	-0.30414	***	-0.2821	***
	STAT1	0.003465	0.937387	-0.01772	0.698757
	IFNG	-0.02712	0.53873	-0.01926	0.674094
	TNF	0.004591	0.91712	0.004051	0.929502
Th2	GATA3	-0.06693	0.128907	-0.08726	0.056349
	STAT6	-0.28227	***	-0.27031	***
	STAT5A	-0.01674	0.704466	-0.04482	0.3276
	IL13	0.179645	***	0.176351	***
Th17	STAT3	0.208187	***	0.184204	***
	IL17A	0.006364	0.885335	0.022246	0.62721
TAM's	CCL2	-0.13775	**	-0.13953	**
	CD274	-0.04931	0.263533	-0.04938	0.280789
	CD80	-0.0015	0.972836	-0.01605	0.726074
	CD86	-0.03932	0.372763	-0.06437	0.159524
	CSF1	0.196079	***	0.171926	***
	CSF1R	0.000943	0.982952	-0.0188	0.681328
	EGF	-0.02126	0.629899	-0.02642	0.563896
	IL10	-0.02784	0.528075	-0.04989	0.275824
	IL6	-0.1138	**	-0.13345	**
	LOX	0.04284	0.331323	0.036677	0.423058
	MFGE8	-0.02521	0.56768	-0.01494	0.744315
	PDCD1LG2	-0.06156	0.162558	-0.09463	*
	STAT3	0.208187	***	0.184204	***
	STAT6	-0.28227	***	-0.27031	***
	TGFB1	0.093606	*	0.069879	0.126666
	TLR4	0.074163	0.09239	0.071639	0.117366

CONCLUSION AND SUMMARY

- Our data provide a comprehensive bioinformatics analysis of METTL3 expression and shed light on the important role of METTL3 in LGG and provide an underlying mechanism between METTL3 and tumor-immune interactions.
- The Present study reveals the involvement of METTL3 in the cross-talk between CSC and TIME.
- Our findings suggest that METTL3 negatively correlates with the LGG immune infiltration and could be a potential biomarker for better prognosis

ACKNOWLEDGEMENT
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