

A novel small molecule METTL3 inhibitor exerts promising antitumor effects on oral squamous cell carcinoma

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Introduction

- Oral squamous cell carcinoma (OSCC) is an aggressive disease that has substantial impacts on global health.
- RNA N6-Methyladenosine (m6A) modification is an emerging player in the posttranscriptional regulation of gene expression.
- m6A is a reversible modification and regulated by specific enzymes.
- METTL3 is a master regulator enzyme of m6A modification and its dysregulation is strongly associated with different types of cancer including OSCC.

Objective

- To describe the development of STM2457, a new class of highly potent and selective, small-molecule inhibitor of METTL3 for OSCC treatment.

Methods

- The expression and clinical implication of METTL3 were investigated in OSCC patients.
- OSCC patient-derived organoids (PDOs) and the corresponding 2D cell lines were established from the patients who have increased expression of METTL3.
- The pharmacological activity of STM2457 was extensively studied with organoids and primary OSCC cells.
- m6A level of mRNA was measured by an m6A-RNA methylation quantification kit.
- Real-time quantitative PCR was used for gene expression and western blot was used for protein expression analysis.

Results

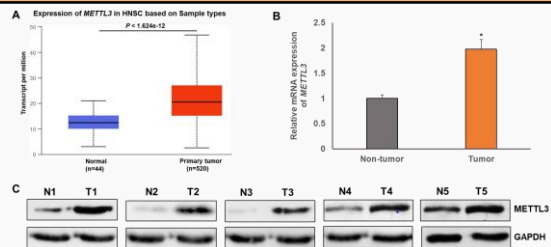


Figure 1. METTL3 mRNA (A, TCGA dataset and B, tissues from tumor and non-tumor) and protein (C) expressions were increased in OSCC patient tissues. T, cancer tissue; N, paired normal tissue

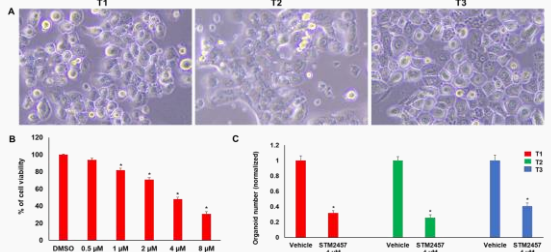


Figure 2. A) 2D OSCC cell lines established from OSCC organoids (OSCC organoids established from patient tissues T1, T2, and T3 with increased expression of METTL3). B) STM2457 treatment reduced OSCC cell viability in different concentration over 24 h. STM2457 IC50 was determined for 2D OSCC cell lines (~4 μM). C) STM2457 treatment reduced organoid forming efficiency.

Results

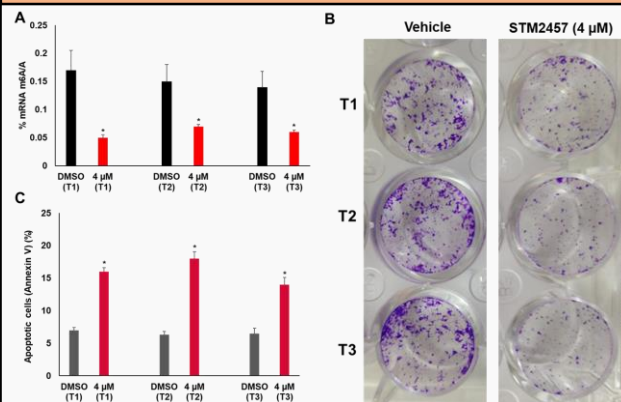


Figure 3. STM2457 treatment reduced m6A level (A), colony formation (B) and induced apoptosis (C) in 2D OSCC cell lines by blocking METTL3 activity.

Conclusion

METTL3 inhibition as a novel and potent therapeutic option for OSCC.

The authors were fully responsible for all content and editorial decisions, were involved in all stages of poster development and have approved the final version.

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