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Commentary

Dual roles, targeting dilemmas, and future priorities: Rethinking METTL-mediated m6A modification in head and neck cancer

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With the recently published review in Cellular Signaling, we highlight the importance of Methyltransferase-like (METTL) family-mediated N6-methyladenosine (m6A) modification in head and neck cancer (HNC) progression, providing a theoretical foundation for their potential use as therapeutic targets.

Head and neck cancers (HNC) constitute a diverse group of highly aggressive malignancies [1,2]. Although treatment of HNC has evolved significantly over the past half century with improvements in surgical technique as well as advancements in medical and radiation oncology, overall survival rates remain stagnant due to the absence of effective early detection markers [3,4]. Epigenetic modifications of RNA have emerged as a prominent focus in oncology research. Among these, N6-methyladenosine (m6A) RNA methylation is one of the most prevalent chemical modifications in eukaryotic messenger RNA (mRNA). It plays a crucial role in mRNA translation, splicing, and stability, thereby regulating the progression of various tumors types [5,6]. METTL proteins function as m6A "writers" by catalyzing substrate methylation. The roles and mechanisms of the METTL family in diverse tumors are increasingly subjects of intense research interest, underscoring their significance in tumorigenesis and disease progression [7,8]. The published review systematically summarizes, for the first time, the roles of the METTL family (with particular focus on METTL3 and METTL14) as m6A writers in HNC, covering their regulatory effects on processes such as tumor proliferation, metastasis, and metabolic reprogramming [9]. However, several critical questions remain unresolved, particularly concerning the mechanisms underlying the functional duality of METTL proteins, the regulatory influence of the tumor microenvironment, and the impact of viral infection status on METTL activity. This commentary seeks to address these knowledge gaps and outline key directions for future research.

Focus on "Functional Duality": Mechanism Elucidation and Controversy Resolution

The original review explicitly proposed, for the first time, that the METTL family (with particular emphasis on METTL3) exhibits "oncogene-tumor suppressor" functional duality in HNC, a phenomenon especially prominent in thyroid cancer (TC) [10–12]. However, this duality was attributed merely to "differences in tumor tissue origin, tumor heterogeneity, and research methodologies" [13]. To further explore the molecular mechanisms underlying this duality, we addressed these controversies by integrating data from the original review with cutting-edge research findings.

First, the functions of the METTL family are not exerted independently; rather, they rely on specific interactions with m6A reader proteins (e.g., *YTHDF1*/2/3, insulin-like growth factor 2 mRNA-binding proteins [IGF2BP1/2]) [10,14–19]. We hypothesize that the tissue- and cell-specific nature of these interactions can directly account for functional divergence. Advances in bioinformatics tools enabling rapid analysis of large-scale datasets from sources such as The Cancer Genome Atlas (TCGA) can help elucidate the relationship between patient prognosis and the expression of these proteins [20]. The gene expression profile of m6A RNA methylation regulators and the corresponding clinical information were downloaded from TCGA HNC dataset. The differentially expressed m6A RNA methylation regulators between tumor samples and normal control samples, as well as the interaction and correlation of m6A RNA methylation regulators were evaluated. The results showed that in tumor samples, multiple m6A methylation regulators, such as METTL3, METTL14, *YTHDF1*, and YTHDF2, exhibit significantly upregulated expression levels [21,22]. This demonstrates that m6A RNA methylation regulators function as key hub genes in HNC.

Second, the METTL family dynamically regulates the tumor microenvironment (TME) through reprogramming effect on hypoxia, inflammation, and metabolism [23–27]. Nevertheless, the original review did not explore how the TME reciprocally regulates METTL functions—a critical factor contributing to the observed functional duality.

Third, HNC heterogeneity (e.g., HPV-positive vs. -negative, EBV-associated vs. non-associated) provides an essential context for METTL family duality [28]. Although existing studies have addressed different HNC subtypes (e.g., nasopharyngeal carcinoma (NPC), oral squamous cell carcinoma (OSCC), few have focused on the impact of infectious status. Specifically, whether viral genes are targeted represents a core reason for the functional divergence of METTL3 between HPV-positive and HPV-negative HNC. These factors can induce epigenetic alterations, such as changes in DNA methylation patterns or histone modifications, which subsequently affect gene expression and tumor behavior [12,29,30].

Fourth, METTL3 exhibits dual oncogenic and tumor-suppressive roles in TC, whereas it primarily functions as an oncogene in most other HNC. This functional duality may be attributed to tissue-of-origin specificity. TC originates from the endocrine system, whose signaling pathways fundamentally differences from those of HNCs arising from squamous epithelium. Similarly, in other endocrine-related malignancies, the role of METTL3 also demonstrates variability—it promotes tumor invasion in pituitary adenomas, while exhibiting tumor-suppressive effects in a subset of pancreatic ductal adenocarcinoma (PDAC) [31–34].

In HNC, METTL3 predominantly functions as an oncogenic driver. Given its tumor-suppressive role in TC, we propose the following alternative strategies: First, METTL3 could be indirectly activated through modulation of its upstream signaling pathways or by enhancing its interaction with functional cofactors. Second, rather than globally inhibiting m6A-dependent reader proteins, selective targeting of the oncogenic effectors *YTHDF2* and IGF2BPs may represent a more precise approach. Third, in subsets of TC with high METTL3 expression, a combinatorial strategy incorporating immune checkpoint inhibitors and METTL3 activators could be implemented to enable more target and effective therapy.

"Translational Challenges" in Targeted Therapy: Barriers from Basic Research to Clinical Practice

STM2457, the first-class METTL3 inhibitor, encounters technical limitations that impede its clinical translation, representing a critical and immediate bottleneck in therapeutic development [35,36]. STM2457 specifically targets the S-adenosylmethionine (SAM)-binding domain of METTL3. Although other METTL family members, such as METTL14, lack an active SAM-binding site, METTL14 may still be indirectly affected through its association with METTL3 in protein complexes [37]. Additional experimental investigations are required to comprehensively assess this potential off-target effect. STM2457 was initially validated in acute myeloid leukemia (AML), where it can directly access the hematopoietic system via circulation [38]. In contrast, HNC is a solid tumor characterized by dense stroma (e.g., collagen, fibroblasts). While current targeted delivery strategies may partially improve drug penetration, the variability in treatment responses across patient subgroups or tumor subtypes—referred to as stratified efficacy—remains poorly understood.

METTL3 expression in HNC cancer stem cells (CSCs) is 3.5-fold higher than that in ordinary cancer cells, and the 3'-untranslated region (3'-UTR) of *METTL3* mRNA contains relatively few m6A modification sites [14,39]. Consequently, CSCs possess a robust "drug resistance reservoir," posing significant challenges for targeted therapy. In mouse models, STM2457 induces dose-dependent myelosuppression[38]. Moreover, as METTL3 is expressed in normal oral mucosa, local administration may trigger oral mucositis [40,41]. These toxicities are particularly concerning for HNC patients, who often undergo radiotherapy and are already prone to mucositis; inhibitor-induced toxicity could lead to treatment interruption. Currently, dose-escalation data specific to HNC patients are lacking, representing a major gap in clinical translation.

Combination therapies targeting both METTLs and m6A readers (e.g., *YTHDF2*) are under consideration. However, avoiding overlapping toxicities and accounting for differential responses among HNC subtypes (e.g., HPV-positive vs. Negative- OSCC) remain challenging [20]. Furthermore, while METTLs show promise as prognostic biomarkers, most studies are limited by single-center, small-sample designs. Thus, validating the correlation between METTL expression and clinicopathological features (e.g., lymph node metastasis, chemoradiotherapy sensitivity) in multicenter cohorts is imperative.

"Priority Agenda" for Future Research

Based on the aforementioned analysis, we propose the following research priorities:

First, at the mechanistic level: Employ single-cell sequencing to dissect METTL family expression differences in the context of HNC heterogeneity (e.g., CSCs vs. ordinary cancer cells) [42,43]. Spatial transcriptomics can map their distribution within the TME, facilitating analysis of METTL3/14 expression across tumor cells, cancer-associated fibroblasts (CAFs), and T cells, providing novel targets for disrupting tumor-stroma crosstalk [44,45]. CRISPR screening can identify which eraser or reader proteins, when depleted following METTL3 inhibition, enhance therapeutic efficacy [46]. This will help elucidate the dynamic "writers-erasers-readers" equilibrium and provide a mechanistic basis for combination

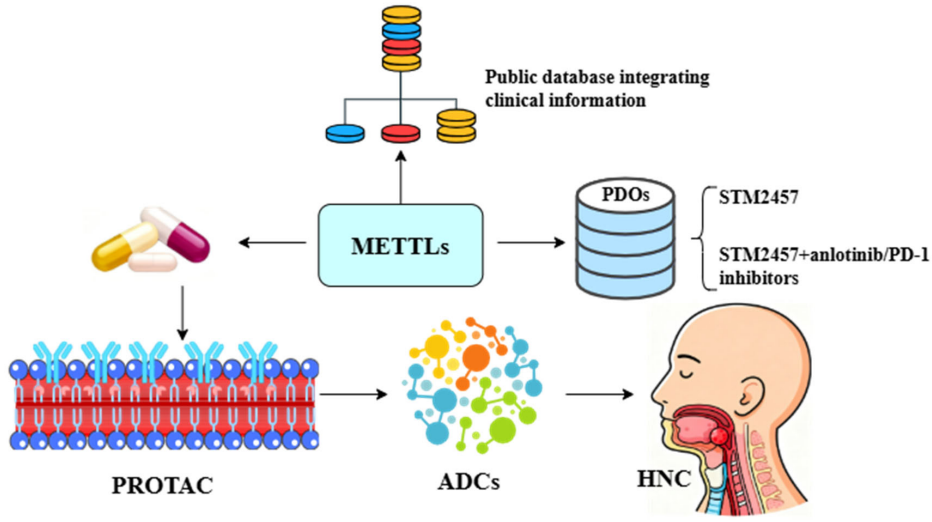

Figure 1. METTLs-based therapeutic strategies.

targeting. Additionally, investigate interactions between the METTL family and non-coding RNAs (e.g., lncRNA LINC00313, circCUX1) to clarify the "m6A modification - non-coding RNA stability - signaling pathway" regulatory axis.

Second, at the technical level: Current inhibitors (e.g., STM2457) exhibit off-target effects due to the conserved SAM-binding domain structure. Improving specificity for METTL3 is essential. Develop proteolysis-targeting chimeras (PROTACs), for instance, by fusing a METTL3 antibody with an E3 ubiquitin ligase (e.g., CRBN) [47]. This approach degrades METTL3 via the proteasome rather than inhibiting its enzymatic activity, potentially avoiding off-target effects (as PROTACs rely on protein-specific epitopes) and offering safer inhibitors for HNC solid tumors. We propose an antibody-based delivery system, as opposed to direct utilization of the METTL3 antibody as the targeting moiety in PROTACs, to improve tumor-specific targeting via antibody–drug conjugates (ADCs) or antibody-modified nanoparticles. For PROTACs, alternative delivery strategies, such as penetration-enhancing peptides or activatable cell-penetrating peptides, will be explored to enable more precise delivery of STM2457 to solid tumor cells and thereby enhance therapeutic efficacy. Existing cell lines poorly recapitulate HNC heterogeneity, limiting accurate efficacy prediction. Establish patient-derived organoids (PDOs) from surgical specimens covering subtypes such as OSCC, NPC, and hypopharyngeal squamous cell carcinoma (HSCC), and detect METTL3/14 and readers expression profiles. Test STM2457 efficacy alone or combined with anlotinib/PD-1 inhibitors in PDOs, and construct an "expression profile - efficacy" correlation model (e.g., high METTL3 + low YTHDF2 = sensitive) to serve as a personalized tool for clinical stratification.

Third, at the translational level: Develop a treatment response prediction model based on METTLs (e.g., combining METTL3 expression and PD-L1 levels to predict immunotherapeutic response) to advance clinical trial design (e.g., STM2457 combined with PD-1 inhibitors in recurrent/metastatic HNC). Systemic STM2457 administration causes myelosuppression, while local administration induces oral mucositis. Address this by developing a nanocarrier drug delivery system—e.g., encapsulating STM2457 in poly (lactic-co-glycolic acid) (PLGA) nanoparticles surface-modified with an EGFR antibody (highly expressed in HNC)—to enable tumor-targeted delivery and reduce normal tissue toxicity [48]. For locally advanced HNC, explore radiotherapy-synchronized local administration (e.g., mouthwash formulation) to minimize systemic exposure while enhancing radiosensitivity, thereby customizing regimen for HNC patients. Most current studies are limited by single-center, small-sample designs. Collaborate with domestic and international HNC research centers to establish a public database integrating clinical information (stage, treatment, prognosis) and tissue samples (METTL expression, m6A profile). By integrating multicenter clinical data from HNC patients with METTL expression profiles and m6A epitranscriptomic data—generated under standardized sample processing and sequencing protocols—a robust "expression profile–efficacy" correlation model can be established to support biomarker validation, subtype-specific analyses, and prediction of therapeutic response. Conduct retrospective studies to validate METTL3/14 as prognostic biomarkers and clarify expression characteristics across HNC subtypes (HPV-/EBV-positive). Integrate scattered data from various cancer types (e.g., NPC, OSCC, TC) to construct a panoramic METTL-HNC atlas, providing foundational data for subsequent research.

Conclusion

This review establishes a conceptual framework for deciphering the mechanisms by which METTL-mediated m6A modification influences HNC biology and therapeutic responses. The functional duality of METTL proteins represents a key characteristic that requires further mechanistic investigation. Current inhibitors face significant but surmountable challenges, and the proposed multi-faceted research agenda offers a clear path forward for translating basic discoveries into improved clinical outcomes for HNC patients. By elucidating the roles of METTL family members and associated m6A modifications in HNC progression and treatment resistance, clinicians may achieve more accurate assessments of disease aggressiveness and tailor therapeutic strategies, ultimately enhancing pharmacological treatments efficacy for HNC patients.

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