METTL3 in esophageal cancer: Current insights into molecular mechanisms, subtype heterogeneity and targeted therapy prospects (Review)

CHUNLAN PU[1*], HUAN HU[1*], HENGRUI FAN[1], TAO CHEN[2] and JIAO TANG[2]

[1]Medical Research Center, The Affiliated Hospital of Southwest Jiaotong University, The Third People's Hospital of Chengdu, Chengdu, Sichuan 610031, P.R. China; [2]Department of Laboratory Medicine, Xindu District People's Hospital, Chengdu, Sichuan 610500, P.R. China

Received January 22, 2026; Accepted April 7, 2026

DOI: 10.3892/ijo.2026.5884

Abstract. Esophageal cancer (EC), comprising esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), urgently requires novel targeted therapies. The m^{6}A methyltransferase METTL3 has emerged as a critical epitranscriptomic regulator in gastrointestinal malignancies. In ESCC, METTL3 functions predominantly as an oncogene, driving tumor progression via m^{6}A-dependent modulation of RNA stability, splicing, and translation across key networks, including NOTCH1, EGR1/Snail and Wnt/β-catenin. Conversely, hypotheses regarding m^{6}A-independent functions or direct immune-checkpoint regulation remain unvalidated in EC. Crucially, METTL3 actively modulates DNA damage repair and radiotherapy resistance, exposing a promising therapeutic vulnerability, although clinical pharmacological development remains nascent. Furthermore, METTL3 biology in EAC remains conspicuously uncharacterized. By strictly stratifying evidence by EC subtype, the present review distinguishes empirically validated mechanisms from premature cross-cancer extrapolations. Ultimately, a novel conceptual framework that redefines METTL3 not merely as a static oncogene, but as a dynamic, context-dependent regulatory hub, is proposed. Under therapeutic stress, METTL3 amplifies cellular phenotypic plasticity, systematically orchestrating tumor adaptation and treatment resistance.

Correspondence to: Dr Chunlan Pu, Medical Research Center, The Affiliated Hospital of Southwest Jiaotong University, The Third People's Hospital of Chengdu, 82 Qinglong Street, Qingyang, Chengdu, Sichuan 610031, P.R. China
E-mail: chunlanpu@swjtu.edu.cn

Dr Jiao Tang, Department of Laboratory Medicine, Xindu District People's Hospital, Xindu District People's Hospital, 199 Yuying Road, Xindu, Chengdu, Sichuan 610500, P.R. China
E-mail: tjsyfmm123@163.com

*Contributed equally

Key words: methyltransferase-like 3, N^6-methyladenosine, esophageal cancer, esophageal squamous cell carcinoma, esophageal adenocarcinoma, epitranscriptomics, targeted therapy

Contents

1. Introduction

Esophageal cancer (EC) is a highly aggressive malignancy, ranking among the leading causes of cancer-related mortality worldwide, with over 600,000 new cases and 500,000 deaths estimated annually (1). EC comprises two major histological subtypes, esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC), which differ substantially in geographic distribution, etiologic factors, molecular features and clinical behaviors. ESCC predominates in East Asia, East Africa and Central Asia, whereas the incidence of EAC continues to increase in numerous Western countries (2-4). Because early-stage EC is frequently asymptomatic, most patients present with advanced disease, resulting in dismal prognoses despite multimodal interventions (5,6). Current standard-of-care relies heavily on surgery, chemotherapy, radiotherapy, and, in selected settings, immune checkpoint blockade (7,8). Nevertheless, the high frequency of therapeutic resistance and the paucity of robust predictive biomarkers underscore an urgent clinical need to elucidate novel molecular dependencies and actionable therapeutic targets in EC (9,10).

Recently, epitranscriptomic regulation has emerged as a crucial regulatory layer in cancer biology (11,12). Among the over 170 identified RNA modifications, N^6-methyladenosine (m^6A) is the most abundant internal modification in eukaryotic messenger RNA (13,14). The m^6A landscape is dynamically governed by a complex of methyltransferases ('writers'), demethylases ('erasers') and m^6A-binding proteins ('readers') (15). Through coordinated control of RNA splicing, export, stability, degradation and translation, m^6A influences multiple physiological and pathological processes, including stem cell differentiation, immune regulation and tumor progression (16-19). Increasing evidence indicates that dysregulated m^6A signaling contributes to malignant transformation and treatment resistance by reshaping post-transcriptional gene expression programs (20-22).

Methyltransferase-like 3 (METTL3) serves as the indispensable catalytic core of the m^6A writer complex (23). Encoded on chromosome 14q11.2, METTL3 encodes a 795-amino-acid S-adenosylmethionine-dependent methyltransferase. Its catalytic activity, localized to a conserved C-terminal domain, is markedly enhanced upon heterodimerization with METTL14, which facilitates RNA recognition and binding capacity (24,25). Through canonical m^6A deposition, METTL3 regulates multiple steps of RNA metabolism, including splicing, nuclear export, stability, decay and translation (26,27). While studies in lung cancer (LC), gastric cancer (GC) and leukemia models further indicated non-canonical functions of cytoplasmic METTL3, including translation enhancement through direct interactions with components of the translation-initiation machinery or with poly(A)-binding protein cytoplasmic 1 (PABPC1) (28-31). However, whether such modification-independent or catalysis-independent functions operate in EC has not yet been directly demonstrated (32-34) (Fig. 1). This knowledge gap is particularly pronounced in ESCC. Consequently, canonical m^6A-dependent signaling currently provides the most robust mechanistic framework for delineating METTL3 function in EC.

Recent work has established METTL3 as an important regulator in EC; however, the most compelling evidence to date arising from ESCC models, whereas relevant data regarding EAC remain limited (35). Accordingly, rather than merely cataloging reported METTL3-associated pathways, the present review aims to critically reorganize the current knowledge base utilizing an evidence-stratified and subtype-aware framework. Mechanisms directly validated in ESCC from those observed in generalized, unstratified EC cohorts, as well as from hypotheses extrapolated from other malignancies, were meticulously delineated. Furthermore, it was highlighted why such cross-cancer extrapolations may be fundamentally inappropriate given the profound biological divergence between ESCC and EAC. Particular emphasis is placed on therapy-induced vulnerabilities, explicitly focusing on radiotherapy response, DNA damage repair, and the translational prospects of emerging METTL3-targeted modalities. Integrating currently available evidence, a novel conceptual model is proposed, wherein METTL3 functions not merely as a static oncogene, but as a state-dependent amplifier of ESCC plasticity under therapeutic stress.

2. Expression profiles and clinical significance of METTL3 in EC

Expression patterns in EC. Available evidence indicates that METTL3 is upregulated in EC tissues, with the clearest and most consistent data coming from ESCC (35-37). Both immunohistochemistry and reverse transcription-quantitative polymerase chain reaction (RT-qPCR) analyses demonstrate that METTL3 mRNA and protein levels are significantly elevated in ESCC tumors compared with matched adjacent non-tumorous mucosa (38-40). Moreover, elevated METTL3 expression is significantly associated with lymph node metastasis and more advanced tumor-node-metastasis (TNM) stage in patients with ESCC (41,42). Public database analyses further support this observation: Studies based on Gene Expression Omnibus (GEO; https://www.ncbi.nlm.nih.gov/geo/) microarray datasets and The Cancer Genome Atlas (TCGA; https://www.cancer.gov/ccg/research/genome-sequencing/tcga) transcriptomic data consistently demonstrate that METTL3 is broadly upregulated in ESCC and is closely associated with aggressive malignant phenotypes, including deeper invasion, metastasis and poor prognosis (38,42-44). By contrast, direct evidence regarding the expression profile of METTL3 in EAC remains far more limited. Current clues are derived mainly from mixed EC cohorts or stratified database analyses, which suggest that aberrant METTL3 expression may also be present in EAC (45). However, large-scale clinical tissue-based studies in EAC, particularly those providing systematic validation at the protein level, are still lacking. Therefore, the precise expression landscape of METTL3 in EAC, as a distinct histological subtype, remains to be further clarified.

Potential upstream regulation of METTL3. Despite METTL3 is frequently upregulated in ESCC and is closely associated with adverse clinicopathological features, including lymph node metastasis, advanced TNM stage, and poor prognosis, its upstream regulatory mechanisms in EC remain insufficiently characterized (42,46). Current evidence suggests that the widespread epigenetic reprogramming observed in ESCC, together with m^6A-dependent post-transcriptional regulation, may collectively contribute to the development of METTL3-associated aberrant phenotypes (47-49). Nevertheless, direct experimental evidence obtained in rigorously subtype-defined ESCC models remains insufficient to determine whether histone acetylation/deacetylation directly regulates METTL3 expression, or whether non-coding RNAs act as stable upstream regulators of METTL3 (50). Therefore, the upstream regulation of METTL3 should presently be regarded as an evolving frontier in EC research rather than a mechanistically fully resolved component of EC biology.

Clinical correlations. Current clinical and translational evidence consistently supports the pathological and clinical relevance of METTL3 in ESCC. Elevated METTL3 expression has been significantly associated with adverse clinicopathological features, including advanced TNM stage, lymph node metastasis, deeper invasion and unfavorable survival outcomes across multiple cohorts and public

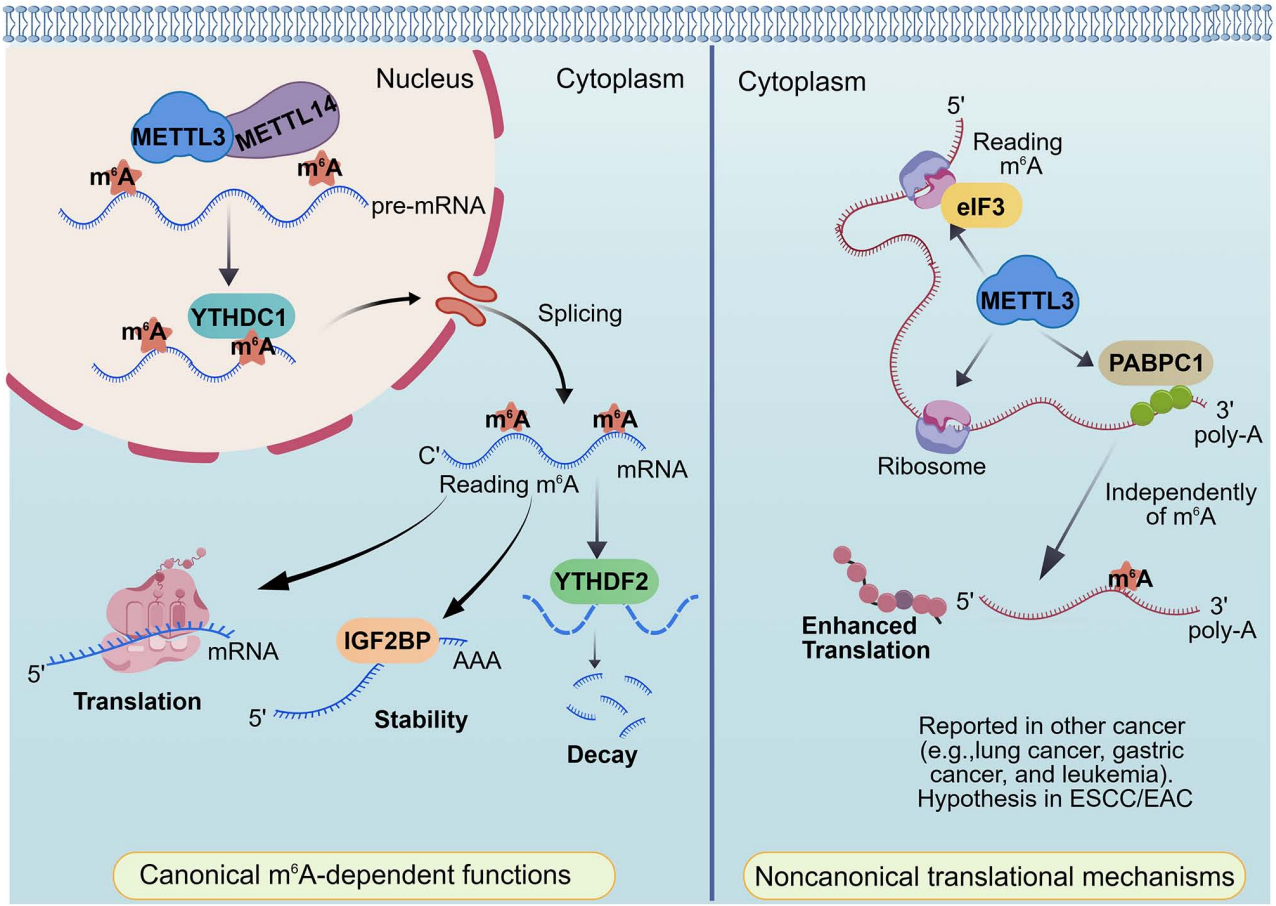

Figure 1. Schematic overview of the canonical and non-canonical mechanisms by which METTL3-mediated m^{6}A modification regulates RNA processing and translation. The left panel shows the canonical m^{6}A-dependent mode of regulation. In the nucleus, the METTL3/METTL14 methyltransferase complex catalyzes m^{6}A deposition on pre-mRNA, which is subsequently recognized by the reader protein YTHDC1 to regulate mRNA splicing. After nuclear export, m^{6}A-modified transcripts in the cytoplasm are recognized by distinct reader proteins, resulting in different functional outcomes, including increased mRNA stability mediated by IGF2BP, mRNA decay mediated by YTHDF2, and enhanced translation. The right panel illustrates the non-canonical function of cytoplasmic METTL3. METTL3 may cooperate with eIF3 and PABPC1 to promote translation of target mRNAs in an m^{6}A-dependent or m^{6}A-independent manner. These non-canonical mechanisms have been reported in other tumor types, whereas their role in ESCC/EAC remains to be fully elucidated. m^{6}A, N^6-methyladenosine; pre-mRNA, precursor mRNA; mRNA, messenger RNA; YTHDC1, YTH domain containing 1; YTHDF2, YTH N^6-methyladenosine RNA binding protein 2; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; eIF3, eukaryotic translation initiation factor 3; PABPC1, poly(A)-binding protein cytoplasmic 1; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma.

datasets (38,42-44). Several studies have further suggested that METTL3 may serve as an independent adverse prognostic factor in ESCC; however, this interpretation should be made with caution because of differences in cohort size, analytical methodology and multivariable adjustment strategies among available studies (40,51). Beyond its prognostic significance, emerging preclinical evidence indicates that METTL3 may also participate in the regulation of treatment response, particularly in the context of radiotherapy resistance, whereas its value as a clinically actionable predictive biomarker remains to be established (52-54). By contrast, the clinical significance of METTL3 in EAC remains insufficiently characterized. At present, the available evidence is inadequate to determine whether METTL3 has prognostic or predictive relevance comparable to that observed in ESCC, or whether its biological functions are largely histological subtype-dependent (55). Therefore, future studies using well-annotated EAC clinical specimens are required to define the clinical and biological significance of METTL3 in this distinct subtype.

3. METTL3-mediated regulatory mechanisms

A pervasive limitation in the current literature is the frequent use of the umbrella term 'esophageal carcinoma' without rigorous histological subtype resolution. To prevent the overstatement of subtype-specific conclusions, it is imperative to critically stratify the existing evidence. Consequently, this review categorizes METTL3-associated molecular mechanisms into three distinct tiers: (i) Mechanisms directly validated in authenticated ESCC models; (ii) pathways reported in unstratified EC cohorts lacking explicit subtyping; and (iii) cross-cancer mechanisms that, while biologically plausible, remain empirically unproven in either ESCC or EAC (Table I).

Directly validated mechanisms in ESCC. To date, the most convincing mechanistic evidence in EC comes from ESCC models, predominantly highlighting the canonical m^{6}A-dependent functions of METTL3 (56-58). Rather than operating through a singular universal downstream pathway, METTL3

Table I. Summary of METTL3-mediated molecular mechanisms in EC.

Mechanism/Axis	Biological Effect	ESCC	EAC	Experimental Model	Research Significance	Key limitations
METTL3-NOTCH1	Promotes tumor growth and progression	√[a]	x[b]	ESCC cell lines, xenografts	Supports oncogenic dependency in ESCC	Lacks direct validation in EAC
METTL3-EGR1/ Snail	Enhances EMT and metastatic potential	√	x	ESCC functional models	Supports invasion/metastasis-targeted strategies	Inconsistent reader dependency across studies
METTL3-APC/β-catenin/c-Myc/ PKM2	Drives glycolytic reprogramming	√	x	ESCC cell lines and mechanistic assays	Identifies metabolic vulnerabilities for intervention	Broader metabolic outputs (for example, glucose uptake) not fully clarified
METTL3-AMIGO2	Promotes proliferation and migration	√	x	Subtype-specific ESCC models	Supports plasticity-related phenotypes in ESCC	Relevance in EAC remains unknown
METTL3-IFIT2	Facilitates malignant progression	√	x	ESCC mechanistic studies	Potential pathogenic pathway	Integration with wider signaling networks incomplete
METTL3-IFI27	Enhances survival and mammosphere formation	√	x	*In vitro* and *in vivo* ESCC studies	Supports stemness/ plasticity models	Lack of EAC-specific evidence
METTL3-FAM135B/ Wnt/β-catenin	Promotes invasion and plasticity	√	x	ESCC models	Reinforces Wnt-related vulnerability	Hierarchical signaling crosstalk requires refinement
METTL3-DUXAP8/ PI 3K/AKT	Accelerates malignant progression	√	x	ESCC functional models	Convergence with canonical oncogenic signaling	PI3K/AKT is a common pan-cancer pathway
METTL3-COL12A1/ MAPK or WASF3/ p38 MAPK	Activates invasive signaling	√	x	ESCC mechanistic studies	Provides basis for increased disease invasiveness	Variation in pathway hierarchy between studies
METTL3-CASP9/ BIRC3	Inhibits apoptosis and promotes chemoresistance	√	x	Paclitaxel-associated ESCC models	Supports combinatorial intervention strategies	Evidence primarily restricted to preclinical stage
METTL3-LNCAROD/PARP1	Enhances DDR and radioresistance	√	x	Radioresistant ESCC models	Strong rationale forradio-sensitization/ DDR therapy	Limited clinical validation
METTL3-circCREBBP/MYC	Modulates radiosensitivity	√	x	ESCC radiotherapy models	Linked to plasticity under therapeutic stress	Requires broader validation
METTL3-TINAGL1 (translational)	Promotes malignant phenotype	-[c]	-	Undifferentiated EC models	Potential relevance to EC biology	Histological specificity remains unclear
METTL3-PIK3CA/ AKT	Facilitates oncogenic signaling	-	-	Undifferentiated EC/cell models	Suggests pathway convergence	Not yet identified as ESCC-specific

Table I. Continued.

Mechanism/ Axis	Biological Effect	ESCC	EAC	Experimental Model	Research Significance	Key limitations
METTL3-mediated PD-L1 regulation	Potential immune evasion	x	x	Non-EC cancer models	Hypothesis-generating only	Lacks direct evidence in ESCC or EAC

[a]Validated in specified EC subtype; [b]No direct validation in specified subtype; [c]Models did not distinguish between ESCC and EAC subtypes. AKT, protein kinase B; AMIGO2, adhesion molecule with Ig-like domain 2; BIRC3, Baculoviral IAP repeat containing; 3 EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; EGR1, early growth response 1; EMT, epithelial-mesenchymal transition; DDR, DNA damage response; DUXAP8, double homeobox A pseudogene 8; IFI27, interferon alpha-inducible protein 27; IFIT2, interferon-induced protein with tetratricopeptide repeats 2; FAM135B, family with sequence similarity 135 member B; MAPK, mitogen-activated protein kinase; METTL3, methyltransferase-like 3; MYC, MYC proto-oncogene; PARP1, poly(ADP-ribose) polymerase 1; PD-L1, programmed death-ligand 1; PKM2, pyruvate kinase M2; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TINAGL1, tubulointerstitial nephritis antigen-like 1; WASF3, WAS protein family member 3.

drives malignant progression via transcript-specific modulation of RNA stability, splicing and translation (35). Several critical molecular axes have been unequivocally established. For instance, METTL3-mediated m^{6}A deposition upregulates *NOTCH1* expression, triggering Notch signaling to facilitate tumor proliferation and progression (38). In parallel, METTL3 stabilizes early growth response 1 (EGR1) transcripts in a YTH domain family protein (YTHDF) 3-dependent manner, activating the EGR1/Snail pathway to promote epithelial-mesenchymal transition (EMT) and metastatic dissemination (37,59). Regarding metabolic reprogramming, METTL3 induces the m^{6}A-dependent, YTHDF2-mediated decay of adenomatous polyposis coli (APC) transcripts; this suppresses APC expression, prompting β-catenin accumulation and the subsequent hyperactivation of c-Myc- and pyruvate kinase M2 (PKM2)-driven glycolysis (48).

Recent ESCC-specific studies have further expanded this intricate mechanistic landscape (Fig. 2). Notable discoveries include the YTH domain-containing protein 1 (YTHDC1)-dependent regulation of adhesion molecule with Ig-like domain 2 (AMIGO2) pre-mRNA splicing, the direct transcriptional modulation of interferon-induced protein with tetratricopeptide repeats 2 (IFIT2), and the insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2)-mediated stabilization of interferon alpha-inducible protein 27 (IFI27) (46,60,61). Additional validated networks encompass family with sequence similarity 135 member B (FAM135B) -associated Wnt/β-catenin hyperactivation (62), double homeobox A pseudogene 8 (DUXAP8)-mediated phosphoinositide 3-kinase (PI3K)/Protein Kinase B (AKT) signaling (63) and mitogen-activated protein kinase (MAPK)-linked cascades involving collagen type XII alpha 1 chain (COL12A1) and WAS protein family member 3 (WASF3) (40). Collectively, these empirical findings substantiate a model wherein METTL3 orchestrates ESCC progression by integrating multiple, parallel RNA-centric regulatory networks that synergistically govern proliferation, invasion, metabolic adaptation and therapeutic response.

Mechanisms reported in EC without clear histologic resolution. A subset of studies has delineated METTL3 regulatory mechanisms using generalized EC cohorts that lack explicit ESCC or EAC annotation. Prominent examples include the broad hyperactivation of AKT signaling, the YTHDF1-dependent translational enhancement of tubulointerstitial nephritis antigen-like 1 (TINAGL1), and the IGF2BP2-mediated stabilization of PIK3CA transcripts (64-66). While these molecular events may ultimately prove relevant to specific EC subtypes, the absence of stringent histological stratification fundamentally limits the validity of any subtype-specific inferences. Consequently, these pathways must be strictly classified as 'EC-associated' rather than 'ESCC-established'. This rigorous distinction is critical in a research landscape disproportionately skewed toward ESCC, where an unwarranted assumption of biological equivalence across fundamentally divergent subtypes could severely misguide future translational efforts (Fig. 2).

Cross-cancer mechanisms with possible relevance but insufficient proof in ESCC/EAC. Conversely, numerous

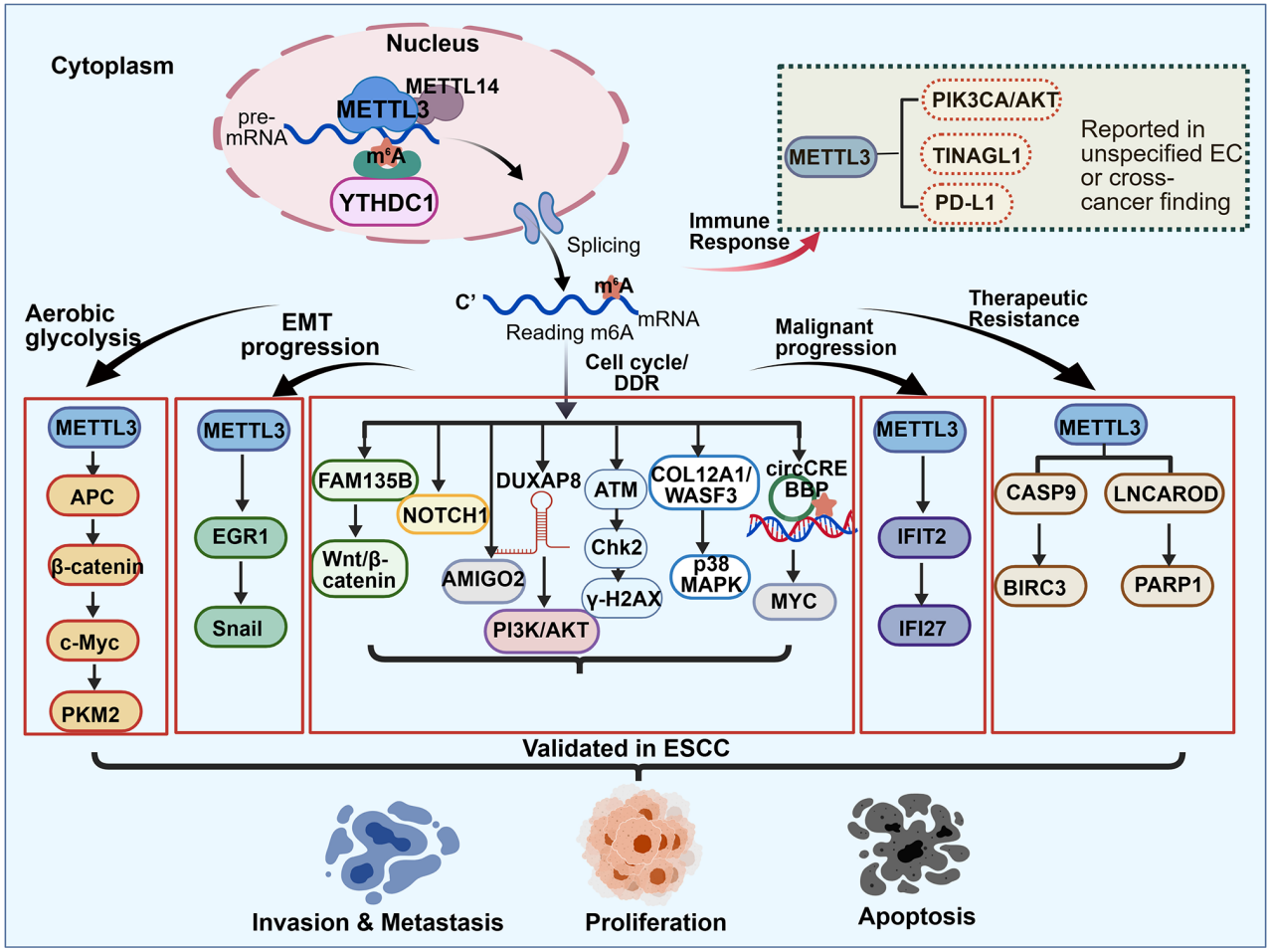

Figure 2. Schematic overview of the downstream molecular network and biological functions regulated by METTL3 in EC. In the nucleus, the METTL3/METTL14 complex catalyzes m^{6}A deposition on pre-mRNA, which is recognized by YTHDC1 to regulate mRNA splicing. After export to the cytoplasm, m^{6}A-modified transcripts participate in multiple signaling pathways associated with tumor progression. In ESCC, METTL3 has been implicated in aerobic glycolysis, EMT, cell cycle/DDR, malignant progression and therapeutic resistance through APC/β-catenin/c-Myc/PKM2, EGR1/Snail, FAM135B/Wnt/β-catenin, NOTCH1, DUXAP8, AMIGO2, ATM/Chk2/γ-H2AX, COL12A1/WASF3/p38 MAPK, circCREBBP/MYC, PI3K/AKT, IFIT2/IFI27, CASP9/BIRC3 and LNCAROD/PARP1. The figure also summarizes putative METTL3-associated immune response-related molecules, including PIK3CA/AKT, TINAGL1 and PD-L1. Collectively, these METTL3-regulated pathways contribute to the control of proliferation, apoptosis, invasion and metastasis in EC cells. m^{6}A, N^6-methyladenosine; pre-mRNA, precursor mRNA; mRNA, messenger RNA; YTHDC1, YTH domain containing 1; EMT, epithelial-mesenchymal transition; DDR, DNA damage response; ESCC, esophageal squamous cell carcinoma; EC, esophageal cancer; DUXAP8, double homeobox A pseudogene 8; IFI27, interferon alpha-inducible protein 27; IFIT2, interferon-induced protein with tetratricopeptide repeats 2; FAM135B, family with sequence similarity 135 member B; MAPK, mitogen-activated protein kinase; METTL3, methyltransferase-like 3; MYC, MYC proto-oncogene; PARP1, poly(ADP-ribose) polymerase 1; PD-L1, programmed death-ligand 1; PKM2, pyruvate kinase M2; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TINAGL1, tubulointerstitial nephritis antigen-like 1; WASF3, WAS protein family member 3.

METTL3-associated mechanisms frequently cited in contemporary EC reviews rely heavily on evidence extrapolated from other malignancies and remain wholly unverified within the esophageal context (21,67,68). Prominent among these are the cytoplasmic, m^{6}A-independent (or catalysis-independent) functions of METTL3, which reportedly enhance translation via direct physical interactions with ribosomes, eukaryotic translation initiation factor 3 (eIF3), or PABPC1 (69,70). Additional highly discussed but unvalidated paradigms in EC encompass specific long non-coding RNA (lncRNA) sponge networks, the direct transcriptional upregulation of programmed death-ligand 1 (PD-L1), the chemokine-driven recruitment of immunosuppressive macrophages, and the exosomal transfer of METTL3 derived from cancer-associated fibroblasts (71-74). Although the existence of analogous pathways in LC (75), GC (76), leukemia (77) and colorectal cancer (78) renders these mechanisms biologically plausible in EC, theoretical plausibility must not be conflated with empirical proof. Until definitive causality is established using authenticated, subtype-defined ESCC or EAC models, these molecular pathways must be rigorously framed as theoretical cross-cancer extrapolations rather than established drivers of esophageal carcinogenesis (Fig. 2).

4. METTL3-driven malignant phenotypes in ESCC

Given that direct mechanistic evidence remains most robustly established in ESCC, the phenotypic consequences delineated in this section center exclusively on this specific histological subtype, unless explicitly noted otherwise.

Regulation of metabolic reprogramming. Available evidence links METTL3 to metabolic adaptation in ESCC via at least

two distinct mechanistic avenues. First, METTL3-mediated m^{6}A deposition accelerates the decay of APC transcripts, consequently hyperactivating the β-catenin/c-Myc/PKM2 axis to drive glycolytic reprogramming (48). Second, METTL3 reportedly upregulates glutaminase 2 (GLS2) expression, further sustaining migratory and invasive phenotypes in ESCC cells (44). While these findings highlight METTL3's contribution to metabolic flexibility, several clinically relevant observations remain purely correlative. For instance, statistical associations between METTL3 expression and ^{18}F-fluorodeoxyglucose uptake, glucose transporter 1 (GLUT1) expression, or hexokinase 2 (HK2) abundance are compelling (45). However, they do not inherently prove direct, transcript-level control of glucose or lactate metabolism. Therefore, while a role for METTL3 in ESCC metabolic reprogramming is strongly supported, the comprehensive network of its downstream effectors awaits definitive characterization.

Chemotherapy resistance and apoptosis control. Acquired chemoresistance remains a primary cause of treatment failure in ESCC (79,80). Within this context, METTL3 has emerged as a pivotal regulator of apoptosis and therapeutic response (81-83). Direct functional evidence demonstrates that METTL3 attenuates paclitaxel sensitivity by modulating the caspase 9 (CASP9) and baculoviral IAP repeat containing 3 (BIRC3) pathways, mechanistically linking m^{6}A epitranscriptomic rewiring to the suppression of treatment-induced apoptosis (54). Consistently, the pharmacological inhibition of METTL3 profoundly sensitizes preclinical ESCC models to paclitaxel. These observations underscore that METTL3 functions not solely as a classical oncogenic driver, but actively dictates treatment tolerance (84). This paradigm shift is conceptually critical, situating METTL3 at the crucial nexus of oncogenic signaling and adaptive resistance, thereby providing a strong biological rationale for synergistic combination therapies.

Radiotherapy response and DNA damage response (DDR). Radiotherapy constitutes a cornerstone of ESCC management, and emerging data have begun to elucidate the critical role of METTL3 in governing radiosensitivity and DDR (85-88). Direct mechanistic evidence has shown that, in radioresistant ESCC models, METTL3-mediated m^{6}A modification stabilizes the lncRNA activating regulator of DKK1 (LNCAROD) in a YTHDC1-dependent manner (89). Upregulated LNCAROD subsequently maintains poly(ADP-ribose) polymerase 1 (PARP1) protein stability by facilitating the PARP1-nucleophosmin 1 interaction, thereby enhancing homologous recombination repair and promoting radioresistance (89). In parallel, m^{6}A-modified circular RNAs have also been implicated in the regulation of radiotherapeutic response in ESCC. For example, circular RNA derived from CREB binding lysine acetyltransferase (circCREBBP) enhances radiosensitivity by reducing MYC mRNA stability through an IGF2BP3-related mechanism (90). On the other hand, the METTL3 inhibitor STM2457 has been shown to activate ataxia-telangiectasia mutated (ATM)/checkpoint kinase 2 (Chk2)/phosphorylated histone H2AX (γ-H2AX)-associated DDR signaling and suppress tumor cell growth in ESCC cells, suggesting that METTL3 may participate in balancing DNA damage tolerance and treatment response (91). However, current evidence supporting the combination of METTL3 inhibitors with radiotherapy or DNA damage repair-targeted agents remains largely confined to preclinical inference, and further direct studies are required to validate this therapeutic strategy. Collectively, these findings establish METTL3 as a central arbiter balancing DNA damage tolerance with treatment-induced cytotoxicity, fortifying the translational rationale for integrating METTL3 inhibitors with radiotherapy or DNA damage repair-targeted agents (Fig. 2).

EMT, stemness and cellular plasticity. The involvement of METTL3 in EMT, invasion and stemness-associated traits in ESCC is most rigorously supported when contextualized within subtype-validated pathways (35). Specifically, METTL3 orchestrates metastatic dissemination via the EGR1/Snail axis, amplifies proliferative and migratory capacities through AMIGO2 regulation, and sustains sphere-forming potential by stabilizing IFI27 transcripts (59-61,92). Additionally, FAM135B-dependent Wnt/β-catenin hyperactivation further potentiates plasticity-related phenotypes in ESCC (62). At the same time, broader claims that METTL3 universally regulates EMT or cancer stemness through classical mediators such as transforming growth factor beta, zinc finger E-box binding homeobox 1, SRY-box transcription factor 2, octamer-binding transcription factor 4 and Nanog homeobox are derived mainly from other cancer types (93-95). While conceptually relevant, these canonical pathways currently lack rigorous validation in authenticated ESCC models. From a strictly evidence-based perspective, METTL3 is most accurately defined not as an indiscriminate driver of EMT, but as a context-dependent amplifier of phenotypic plasticity, uniquely poised to drive tumor adaptation under conditions of therapeutic stress.

Association with the tumor immune microenvironment (TIME). Although the TIME plays a central role in immune evasion in ESCC, current evidence linking METTL3 to the ESCC TIME is still derived predominantly from TCGA/GEO-based bioinformatic analyses and correlative clinical observations (96-98). Available studies suggest that METTL3 expression, or m^{6}A regulator-associated signatures, is statistically associated with immune cell infiltration, PD-L1-related phenotypic states, and immune scoring parameters, thereby indicating its potential value as an immune-associated biomarker (99,100). However, direct functional evidence in rigorously defined ESCC models remains limited and is still insufficient to establish METTL3 as a stable driver of immune escape, checkpoint regulation, M2 macrophage polarization, or fibroblast-dependent intercellular transfer in this subtype (101). Notably, recent studies at the level of EC have suggested that METTL3 may participate in M2 macrophage polarization and PD-L1-associated regulation, although whether these findings are directly applicable to strictly defined ESCC systems requires further validation. Therefore, at present, METTL3 is more appropriately regarded as a candidate immune-associated biomarker in ESCC rather than a mechanistically established immunoregulatory driver, and its immunological functions still require more systematic functional investigation.

5. Therapeutic targeting of METTL3 in EC

Antitumor effects of METTL3 inhibition in cellular and animal models. At present, direct evidence supporting the therapeutic potential of METTL3 is derived predominantly from preclinical models of ESCC, whereas EAC-specific data remain markedly limited. Available studies have shown with reasonable consistency that genetic depletion or pharmacological inhibition of METTL3 significantly suppresses ESCC cell proliferation, migration, invasion and *in vivo* tumorigenicity. Mechanistically, the most solid evidence in ESCC supports the involvement of METTL3 in Notch pathway activation (38), APC/β-catenin-associated glycolytic reprogramming (48), and the regulation of downstream effectors such as IFIT2. In addition, the proposed involvement of EGR1/Snail (35), AMIGO2, IFI27, and several more recently described effector axes has further expanded the downstream network governed by METTL3 (44,46,63). Nevertheless, these findings should still be interpreted with appropriate caution from an evidence-based perspective (102). Several frequently cited mechanisms, including broad immune-checkpoint regulation or certain receptor tyrosine kinase/AKT-associated translational control pathways, are currently supported far more strongly in other cancer types than in ESCC, where an equally robust mechanistic framework has not yet been established (26,72). Therefore, although METTL3 represents a highly promising candidate therapeutic target in ESCC, its actionable dependency is likely to remain strongly context-dependent and pathway-specific (Table II).

Enhancing chemosensitivity and reversing drug resistance. Among the pharmacological studies reported to date, the catalytic METTL3 inhibitor STM2457 and the repurposed drug elvitegravir represent the most representative ESCC-specific pharmacological evidence currently available (59,91). Existing studies have shown that STM2457 significantly suppresses ESCC cell proliferation and migration, induces G0/G1 cell-cycle arrest and apoptosis, and activates the ATM-Chk2-associated DDR (91). Moreover, when combined with paclitaxel, STM2457 exhibits enhanced antitumor activity in both *in vitro* and *in vivo* models. By contrast, elvitegravir inhibits ESCC metastasis by promoting STUB1-dependent proteasomal degradation of METTL3. Taken together with recent mechanistic studies involving the CASP9/BIRC3, LNCAROD/PARP1 and circCREBBP/MYC regulatory axes, the available evidence suggests that METTL3-targeted therapy may be of particular value in paclitaxel-treated or radioresistant ESCC (54,89,90). Nevertheless, evidence supporting combination strategies integrating METTL3 inhibition with radiotherapy or DDR-targeted agents remains largely confined to the preclinical setting, and further direct studies are required to validate these therapeutic approaches. These critical observations support the development of combination strategies which strategically integrate METTL3 inhibition with taxanes, conventional radiotherapy, or DDR-directed pharmacological agents.

Emerging targeted therapeutic strategies

Small-molecule inhibitors. The development of small-molecule METTL3 inhibitors is advancing rapidly, although substantial differences remain among individual compounds with respect to the level of supporting evidence and translational maturity (103,104). STM2457 is a well-characterized catalytic METTL3 inhibitor in ESCC. Available studies have shown that STM2457 suppresses ESCC cell proliferation and migration, induces G0/G1 cell-cycle arrest and apoptosis, and activates the ATM-Chk2-associated DDR (91). While UZH1a and UZH2 function as invaluable chemical probes for interrogating basic METTL3 biology, their therapeutic efficacy has not yet been validated in ESCC-specific models (105). In terms of clinical translation, STC-15 is the most advanced candidate to date, having entered a first-in-human phase I monotherapy study in advanced solid tumors, followed by a phase Ib/II trial in combination with the PD-1 inhibitor toripalimab (106) (Fig. 3). However, these clinical trials are not exclusive to ESCC, and publicly available data have yet to define the precise pharmacological activity of STC-15 in esophageal malignancies. Therefore, although research on METTL3 inhibitors has clearly progressed beyond the earliest *in vitro* proof-of-concept stage, their clinical translation in ESCC remains at an early stage of development.

RNA interference (RNAi) and antisense oligonucleotides (ASOs). RNAi-based METTL3 silencing strategies reproducibly exert potent antitumor effects in ESCC models and remain highly valuable for preclinical target validation (54,107,108). Conversely, METTL3-directed ASO therapy in EC remains a purely conceptual approach rather than an experimentally mature platform (35,109). To avoid overstating the translational readiness of oligonucleotide-based therapeutics, the literature must explicitly delineate this distinction. Thus, while RNAi provides definitive proof-of-target engagement in ESCC, ASO-based METTL3 inhibition must be discussed strictly as a technically plausible but fundamentally unvalidated avenue for future investigation.

Targeted protein degradation (TPD). TPD strategies offer an exceptionally attractive paradigm to overcome the intrinsic limitations of pure catalytic inhibition, particularly if the non-canonical or scaffold-like functions of METTL3 prove biologically critical in solid tumors (110-112). Nevertheless, current empirical data evaluating METTL3-directed proteolysis-targeting chimeras (PROTACs) originate predominantly from acute myeloid leukemia models, with only limited extension into GC research (77,113,114) (Fig. 4). At present, no study has directly validated a METTL3 degrader in ESCC. Consequently, academic discourse must frame PROTACs as an emerging technological platform which holds strong conceptual relevance to ESCC, rather than presenting them as an already established therapeutic option for this specific malignancy. Future preclinical endeavors will need to prioritize rigorous degrader testing within subtype-defined ESCC models and precisely determine whether TPD confers distinct therapeutic advantages over catalytic inhibition within therapy-resistant microenvironments.

6. Rationale against the extrapolation of ESCC-derived METTL3 biology to EAC

The current preponderance of ESCC-based evidence should not be misconstrued as evidence of biological equivalence across EC subtypes (109,115). This profound evidentiary imbalance

Table II. METTL3-targeted therapeutic strategies in EC.

Strategy/Agent	Type	Mechanism of action	Validated in ESCC	Validated in EAC	Other cancers	Primary antitumor effect	Development stage	Preliminary evaluation
STM2457	Catalytic inhibitor	Inhibits METTL3 catalytic activity	Yes	No	Yes	Inhibits malignant phenotype and perturbs DDR	Preclinical	Strongest ESCC-specific pharmacological evidence to date
Elvitegravir	Repurposed drug	Inhibits METTL3-mediated oncogenic behavior	Ltd	No	Ltd	Attenuates malignant phenotype in ESCC	Preclinical/ repurposing	Promising, but lacks the selectivity of dedicated inhibitors
UZH1a	Inhibitor/probe	Inhibits METTL3 methyltransferase activity	No	No	Yes	Used for METTL3 functional characterization	Chemical probe	Suitable as a mechanistic tool rather than an ESCC therapeutic
UZH2	Inhibitor/Probe	Inhibits METTL3 methyltransferase activity	No	No	Yes	Suppresses METTL3 at probe level	Chemical probe	Supports target druggability; lacks ESCC-specific validation
STC-15	Small molecule inhibitor	Targeted METTL3 inhibition	No	No	Yes	Undergoing clinical pharmacological assessment	Early clinical	Most advanced clinically, but EC-specific activity is unclear
METTL3 RNA interference	RNA interference	Knockdown of METTL3 expression	Yes	No	Yes	Inhibits proliferation, migration, and growth	Preclinical	Strongly supports ESCC dependency on METTL3
METTL3 ASO	Antisense oligo	Reduces METTL3 transcript abundance	No	No	Concept	Potential gene silencing strategy	Conceptual	Rational approach, but currently unvalidated in EC
PROTACs/ degraders	Targeted protein degradation	Induces METTL3/14 degradation	No	No	Yes	Inhibits catalytic and potential scaffold functions	Preclinical	High potential once non-canonical functions are confirmed
METTL3 inhibition + paclitaxel	Combination Therapy	Enhances chemosensitivity via apoptosis	Yes	No	Ltd	Improved therapeutic response in ESCC models	Preclinical	Highly relevant to therapy-induced vulnerabilities
METTL3 inhibition + RT/DDR inhibitors	Combination therapy	Sensitizes to RT and disrupts DNA repair	Yes	No	Concept	Radio-sensitization and DDR synergy	Preclinical	One of the most promising directions for clinical translation

EC, esophageal cancer; ESCC, esophageal squamous cell carcinoma; EAC, esophageal adenocarcinoma; EMT, epithelial-mesenchymal transition; DDR, DNA damage response; RT, radiotherapy; Ltd, limited; ASO, antisense oligonucleotide; PROTAC, proteolysis targeting chimera.

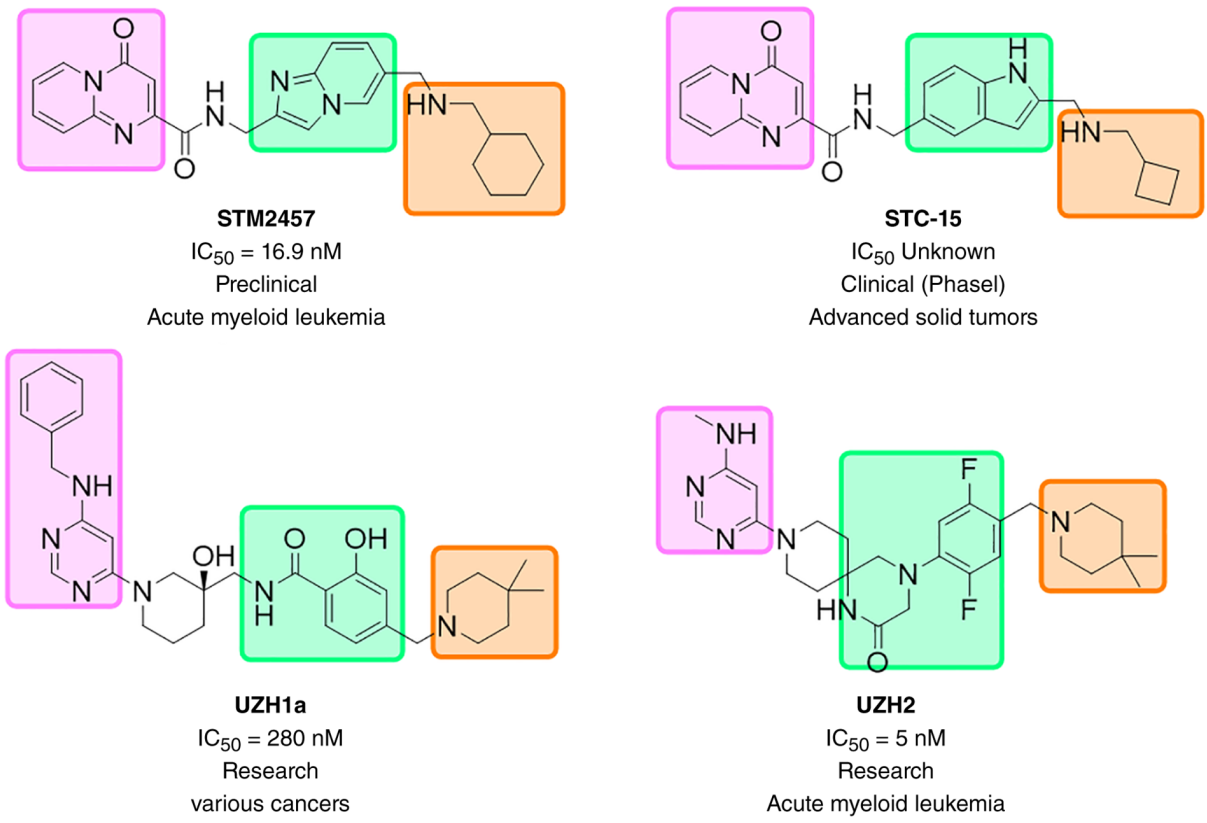

Figure 3. Representative small-molecule METTL3 inhibitors and their reported potency and development status. The colored boxes in the figure indicate the key binding regions of the inhibitors to METTL3/14. METTL, methyltransferase-like.

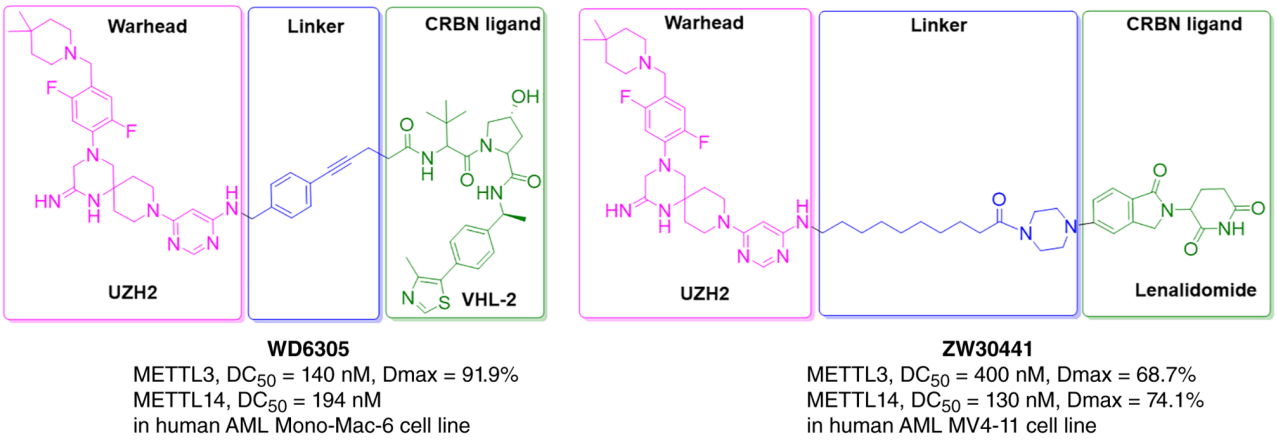

Figure 4. Chemical structures of representative METTL3/14-targeting proteolysis-targeting chimeras' degraders. AML, acute myeloid leukemia; METTL, methyltransferase-like.

transcends mere quantitative disparities and carries significant conceptual implications for the field. Comprehensive comparative analyses of m^{6}A regulatory networks indicate that ESCC and EAC diverge substantially regarding baseline expression patterns, genomic alterations, molecular pathway associations and TIME correlations (115,116). Furthermore, these two distinct malignancies exhibit divergent prognostic trajectories for specific epitranscriptomic regulators, which notably include vir-like m^{6}A methyltransferase associated (115). Collectively, these fundamental molecular discrepancies strongly challenge any premature assumption that METTL3 oncogenic dependency operates independently of histological subtype.

Direct functional evidence elucidating METTL3 biology in EAC remains conspicuously limited. Fundamentally, the underlying biological and etiologic contexts of EAC are entirely distinct from those of ESCC (35,109). EAC typically develops through the well-characterized Barrett's esophagus metaplasia-dysplasia sequence (117,118). Importantly, transcriptome-wide m^{6}A mapping within Barrett's esophagus tissues has already revealed extensive epitranscriptomic remodeling which directly regulates EAC-associated oncogenic

pathways (119-121). Furthermore, the inherent imperfections of current EAC *in vitro* systems severely exacerbate this evidentiary deficit (122). Recent critical reviews emphasize substantial limitations within currently available experimental models, particularly highlighting historical instances where widely utilized EAC cell lines were ultimately proven misidentified or cross-contaminated (123,124). Consequently, the scientific community must strictly treat the glaring absence of robust, EAC-specific METTL3 data as a critical knowledge gap, rather than improperly bridging this void through automatic extrapolation from established ESCC paradigms.

Accordingly, this section does not seek to impose a forced mechanistic equivalency between ESCC and EAC but rather aims to delineate a rigorous future research agenda. Investigators must urgently address several high-priority questions to advance the epitranscriptomic understanding of EAC. Primary inquiries should determine whether METTL3 protein expression is consistently dysregulated across well-annotated clinical EAC cohorts and whether this specific methyltransferase actively dictates m^{6}A transcriptional programs during Barrett's-associated carcinogenesis. Additional critical investigations must ascertain if EAC tumors harbor fundamentally distinct m^{6}A reader dependencies and whether the functional status of METTL3 accurately predicts therapeutic responses to EAC-specific clinical regimens. Ultimately, resolving these fundamental molecular questions will strictly necessitate the utilization of subtype-authenticated cell lines, advanced three-dimensional organoids, patient-derived xenograft models, and highly integrated multi-omic m^{6}A-mapping methodologies (116,125,126).

7. Challenges and future directions

Although METTL3 represents a highly appealing therapeutic target, several critical translational challenges currently impede its broad clinical application (102,127). First, because METTL3 is indispensable for maintaining normal tissue homeostasis, systemic pharmacological inhibition inevitably raises significant concerns regarding on-target, off-tumor toxicity (128,129). Second, pure catalytic inhibition may fail to sufficiently abrogate the potential non-canonical or scaffold-like functions of METTL3, particularly in tumors where specific cytoplasmic localization and protein-protein interactions prove biologically critical (70,130). Third, the oncology field currently lacks validated predictive biomarkers which can reliably identify the specific ESCC patient populations most likely to derive clinical benefit from METTL3-directed interventions (35). Finally, as emphasized throughout the present review, the existing evidence base remains profoundly skewed toward the ESCC subtype, strictly precluding the broad generalization of these mechanistic paradigms to EAC (131-133).

Future investigations must therefore progress beyond the mere cataloging of additional downstream transcript targets. Instead, researchers should instead focus on rigorously defining specific METTL3 dependency states within the dynamically evolving tumor microenvironments (134,135). High-priority research objectives must include comprehensive, subtype-resolved proteogenomic mapping across both ESCC and EAC cohorts (136). Additionally, integrating high-resolution single-cell and spatial transcriptomic analyses will be crucial for deciphering intricate METTL3-associated tumor-stroma interactions and immune states (137,138). Furthermore, biomarker development strategies must actively incorporate METTL3 subcellular localization, specific m^{6}A reader contexts, and dynamic therapy-exposed transcriptomic signatures (70,134). These translational efforts should proceed alongside rational preclinical and clinical testing that strategically pairs METTL3 inhibition with conventional radiotherapy, taxanes, DDR-targeted agents (such as PARP, ATR, or DNA-PK inhibitors) and contemporary immunotherapies (35,72). In parallel, the scientific community must systematically benchmark classical catalytic inhibitors against emerging protein degraders (for example, PROTACs) and nucleic acid-based strategies (139,140). This comparative evaluation will ultimately dictate which therapeutic modality most effectively suppresses both the canonical and the potential noncanonical oncogenic functions of METTL3 within the complex milieu of solid tumors.

8. Conclusion

In summary, current evidence most strongly supports METTL3 as an oncogenic and potentially actionable epitranscriptomic regulator in ESCC, rather than as a uniformly validated driver across all forms of EC. Within ESCC, the best-supported mechanisms involve an m^{6}A-dependent regulation of transcript stability, splicing and translation, subsequently governing pathways integral to tumor growth, invasion, metabolic adaptation, apoptosis evasion and radiotherapy-associated DNA damage repair. Conversely, several widely discussed mechanisms, including m^{6}A-independent translational activation and direct immune-checkpoint regulation, remain unproven in EC and should be interpreted cautiously. Through the integration of evidence-stratified and subtype-aware analyses, METTL3 is better understood not simply as a generic RNA methyltransferase, but as a dynamic, context-dependent regulatory factor. Notably, under therapeutic stress, METTL3 markedly enhances the phenotypic plasticity of ESCC cells, systematically propelling tumor adaptation and evolution. This perspective has direct translational implications for biomarker discovery and the rational design of synergistic combination strategies incorporating chemotherapy, radiotherapy and DDR-targeted agents. Moving forward, a paramount priority for the field is to ascertain whether comparable METTL3 dependencies operate in EAC, an endeavor that strictly demands the utilization of subtype-authenticated experimental models and extensively annotated clinical cohorts.

Acknowledgements

Not applicable.

Funding

The present study was supported by Medical Science and Technology Program of the Sichuan Provincial Health Commission (grant no. 24QNMP009), the Medical Research Project of Chengdu (grant nos. 2023080 and 2024172), the Sichuan Medical Association Oncology (Hengrui-Yihang)

Special Scientific Research Project (grant no. 2024HR38), The Third People's Hospital of Chengdu Scientific Research Project (grant no. 2023PI25) and the Clinical Research Program (grant no. CSY-YN-03-2024-016).

Availability of data and materials

Not applicable.

Authors' contributions

CP conceived the study, acquired funding, and prepared the initial draft of the manuscript, including the figures. HH and JT assisted with literature retrieval and manuscript revision. HH, JT, TC and HF provided overall supervision and were responsible for critical review and editing of the manuscript. Data authentication is not applicable. All authors read 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.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
2. Zhang X, Wang Y and Meng L: Comparative genomic analysis of esophageal squamous cell carcinoma and adenocarcinoma: New opportunities towards molecularly targeted therapy. Acta Pharm Sin B 12: 1054-1067, 2022.
3. Rubenstein JH and Shaheen NJ: Epidemiology, diagnosis, and management of esophageal adenocarcinoma. Gastroenterology 149: 302-317.e1, 2015.
4. Xia C, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N and Chen W: Cancer statistics in China and United States, 2022: Profiles, trends, and determinants. Chin Med J (Engl) 135: 584-590, 2022.
5. Mansour NM, Groth SS and Anandasabapathy S: Esophageal adenocarcinoma: Screening, surveillance, and management. Annu Rev Med 68: 213-227, 2017.
6. Acharya R, Mahapatra A, Verma HK and Bhaskar LVKS: Unveiling therapeutic targets for esophageal cancer: A comprehensive review. Curr Oncol 30: 9542-9568, 2023.
7. He S, Xu J, Liu X and Zhen Y: Advances and challenges in the treatment of esophageal cancer. Acta Pharm Sin B 11: 3379-3392, 2021.
8. Fatehi Hassanabad A, Chehade R, Breadner D and Raphael J: Esophageal carcinoma: Towards targeted therapies. Cell Oncol 43: 195-209, 2020.
9. Liu K, Zhao T, Wang J, Chen Y, Zhang R, Lan X and Que J: Etiology, cancer stem cells and potential diagnostic biomarkers for esophageal cancer. Cancer Lett 458: 21-28, 2019.
10. Luan S, Zeng X, Zhang C, Qiu J, Yang Y, Mao C, Xiao X, Zhou J, Zhang Y and Yuan Y: Advances in Drug Resistance of Esophageal Cancer: From the perspective of tumor microenvironment. Front Cell Dev Biol 9: 664816, 2021.
11. Ye C, Yan X and Gao Y: Advances in epigenetic therapy for esophageal cancer. Clin Epigenetics 18: 42, 2026.
12. Recillas-Targa F: Cancer epigenetics: An overview. Arch Med Res 53: 732-740, 2022.
13. He PC and He C: m6A RNA methylation: From mechanisms to therapeutic potential. EMBO J 40: e105977, 2021.
14. Jain S, Koziej L, Poulis P, Kaczmarczyk I, Gaik M, Rawski M, Ranjan N, Glatt S and Rodnina MV: Modulation of translational decoding by m6A modification of mRNA. Nat Commun 14: 4784, 2023.
15. Zhang H, Shi X, Huang T, Zhao X, Chen W, Gu N and Zhang R: Dynamic landscape and evolution of m6A methylation in human. Nucleic Acids Res 48: 6251-6264, 2020.
16. Han SH and Choe J: Diverse molecular functions of m6A mRNA modification in cancer. Exp Mol Med 52: 738-749, 2020.
17. Hong J, Xu K and Lee JH: Biological roles of the RNA m6A modification and its implications in cancer. Exp Mol Med 54: 1822-1832, 2022.
18. Quan C, Belaydi O, Hu J, Li H, Yu A, Liu P, Yi Z, Qiu D, Ren W, Ma H, *et al*: N6-Methyladenosine in cancer immunotherapy: An undervalued therapeutic target. Front Immunol 12: 697026, 2021.
19. Brewer G: METTL3 inhibition enhances antitumour immunity. Nat Rev Cancer 23: 654, 2023.
20. Wang L, Yang Q, Zhou Q, Fang F, Lei K, Liu Z, Zheng G, Zhu L, Huo J, Li X, *et al*: METTL3-m6A-EGFR-axis drives lenvatinib resistance in hepatocellular carcinoma. Cancer Lett 559: 216122, 2023.
21. Deng X, Qing Y, Horne D, Huang H and Chen J: The roles and implications of RNA m6A modification in cancer. Nat Rev Clin Oncol 20: 507-526, 2023.
22. Wang Y, Hong Z, Song J, Zhong P and Lin L: METTL3 promotes drug resistance to oxaliplatin in gastric cancer cells through DNA repair pathway. Front Pharmacol 14: 1257410, 2023.
23. Zhang Y, Quan M, Chen Q, Han H, Zhang X, Xu X and Wang Z: Recent progress of METTL3 inhibitors for cancer therapeutics: Design, optimization and potential applications. RSC Med Chem 17: 1289-1298, 2026.
24. Wang X, Feng J, Xue Y, Guan Z, Zhang D, Liu Z, Gong Z, Wang Q, Huang J, Tang C, *et al*: Structural basis of N6-adenosine methylation by the METTL3-METTL14 complex. Nature 534: 575-578, 2016.
25. Yu D, Horton JR, Yang J, Hajian T, Vedadi M, Sagum CA, Bedford MT, Blumenthal RM, Zhang X and Cheng X: Human MettL3-MettL14 RNA adenine methyltransferase complex is active on double-stranded DNA containing lesions. Nucleic Acids Res 49: 11629-11642, 2021.
26. Lin S, Choe J, Du P, Triboulet R and Gregory RI: The m6A methyltransferase METTL3 promotes translation in human cancer cells. Mol Cell 62: 335-345, 2016.
27. Lee JH, Hong J, Zhang Z, de la Peña Avalos B, Proietti CJ, Deamicis AR, Guzmán G P, Lam HM, Garcia J, Roudier MP, *et al*: Regulation of telomere homeostasis and genomic stability in cancer by N6-adenosine methylation (m6A). Sci Adv 7: eabg7073, 2021.
28. Li Y, He X, Lu X, Gong Z, Li Q, Zhang L, Yang R, Wu C, Huang J, Ding J, *et al*: METTL3 acetylation impedes cancer metastasis via fine-tuning its nuclear and cytosolic functions. Nat Commun 13: 6350, 2022.
29. Zheng W, Dong X, Zhao Y, Wang S, Jiang H, Zhang M, Zheng X and Gu M: Multiple functions and mechanisms underlying the role of METTL3 in human cancers. Front Oncol 9: 01403, 2019.
30. Xu J, Chen Q, Tian K, Liang R, Chen T, Gong A, Mathy NW, Yu T and Chen X: m6A methyltransferase METTL3 maintains colon cancer tumorigenicity by suppressing SOCS2 to promote cell proliferation. Oncol Rep 44: 973-986, 2020.
31. Peng K, Chen X, Lin A, Tong Z and Lin W: PolyC-RNA-binding protein 1 (PCBP1) enhances tropomyosin 3 (TPM3) mRNA stability to promote the progression of esophageal squamous cell carcinoma. Bioengineered 13: 8581-8592, 2022.
32. Delaunay S and Frye M: Localization-dictated function for METTL3. Nat Cell Biol 24: 1188-1189, 2022.
33. Dai Z, Lin B, Qin M, Lin Y, Wang L, Liao K, Xie G, Wang F and Zhang J: METTL3-mediated m6A modification of SLC7A11 enhances nasopharyngeal carcinoma radioresistance by inhibiting ferroptosis. Int J Biol Sci 21: 1837-1851, 2025.
34. Mao W, Jiang Q, Feng Y, Peng C, Peng H, Li X, Jiao L, Zhang L, Ma L and Sun T: TRIM21-mediated METTL3 degradation promotes PDAC ferroptosis and enhances the efficacy of Anti-PD-1 immunotherapy. Cell Death Dis 16: 240, 2025.
35. Chun H and Baima K: METTL3-driven m6A modifications in esophageal squamous cell Carcinoma: Emerging mechanisms, biomarker potential, and therapeutic innovations. Eur J Pharmacol 1002: 177785, 2025.

36. Yang L, Ding C, Tuo M, Chu T and Liu P: METTL3 enhances esophageal squamous cell carcinoma progression by suppressing ferroptosis through the PBX3/CA9 cascade. Pathol Res Pract 269: 155865, 2025.
37. Liang X, Zhang Z, Wang L, Zhang S, Ren L, Li S, Xu J and Lv S: Mechanism of methyltransferase like 3 in epithelial-mesenchymal transition process, invasion, and metastasis in esophageal cancer. Bioengineered 12: 10023-10036, 2021.
38. Han H, Yang C, Zhang S, Cheng M, Guo S, Zhu Y, Ma J, Liang Y, Wang L, Zheng S, *et al*: METTL3-mediated m6A mRNA modification promotes esophageal cancer initiation and progression via Notch signaling pathway. Mol Ther Nucleic Acids 26: 333-346, 2021.
39. Wang H, Zhang Y, Chen L, Liu Y, Xu C, Jiang D, Song Q, Wang H, Wang L, Lin Y, *et al*: Identification of clinical prognostic features of esophageal cancer based on m6A regulators. Front Immunol 13: 950365, 2022.
40. Li J, Li Z, Xu Y, Huang C and Shan B: METTL3 facilitates tumor progression by COL12A1/MAPK signaling pathway in esophageal squamous cell carcinoma. J Cancer 13: 1972-1984, 2022.
41. Li Y, Niu C, Wang N, Huang X, Cao S, Cui S, Chen T, Huo X and Zhou R: The role of m6A Modification and m6A regulators in esophageal cancer. Cancers (Basel) 14: 5139, 2022.
42. Xia TL, Yan SM, Yuan L and Zeng MS: Upregulation of METTL3 expression predicts poor prognosis in patients with esophageal squamous cell carcinoma. Cancer Manag Res 12: 5729-5737, 2020.
43. Zhou Y, Guo S, Li Y, Chen F, Wu Y, Xiao Y and An J: METTL3 is associated with the malignancy of esophageal squamous cell carcinoma and serves as a potential immunotherapy biomarker. Front Oncol 12: 824190, 2022.
44. Chen X, Huang L, Yang T, Xu J, Zhang C, Deng Z, Yang X, Liu N, Chen S and Lin S: METTL3 promotes esophageal squamous cell carcinoma metastasis through enhancing GLS2 expression. Front Oncol 11: 667451, 2021.
45. Liu XS, Yuan LL, Gao Y, Zhou LM, Yang JW and Pei ZJ: Overexpression of METTL3 associated with the metabolic status on 18F-FDG PET/CT in patients with Esophageal Carcinoma. J Cancer 11: 4851-4860, 2020.
46. Ge F, Li Z, Hu J, Pu Y, Zhao F and Kong L: METTL3/m6A/IFIT2 regulates proliferation, invasion and immunity in esophageal squamous cell carcinoma. Front Pharmacol 13: 1002565, 2022.
47. Teng C, Kong F, Mo J, Lin W, Jin C, Wang K and Wang Y: The roles of RNA N6-methyladenosine in esophageal cancer. Heliyon 8: e11430, 2022.
48. Wang W, Shao F, Yang X, Wang J, Zhu R, Yang Y, Zhao G, Guo D, Sun Y, Wang J, *et al*: METTL3 promotes tumour development by decreasing APC expression mediated by APC mRNA N6-methyladenosine-dependent YTHDF binding. Nat Commun 12: 3803, 2021.
49. Chen Z, Li C, Zhou Y, Li P, Cao G, Qiao Y, Yao Y and Su J: Histone 3 lysine 9 acetylation-specific reprogramming regulates esophageal squamous cell carcinoma progression and metastasis. Cancer Gene Ther 31: 612-626, 2024.
50. Jin Q, Qu H and Quan C: New insights into the regulation of METTL3 and its role in tumors. Cell Commun Signal 21: 334, 2023.
51. Chen J, Zhu ZX, Yang PJ, Deng F, Li PF, Zhu ZF, Xu X, Wu WJ and Shen WG: The dysregulation of UPP1 incurred by METTL3 regulates the malignancy of esophageal squamous cell carcinoma in an m6A-YTHDC1-KLF5-mediated manner. Cell Signal 137: 112201, 2026.
52. Ma R and Zhao L: The role and mechanism of ferroptosis mediated by METTL3-m6A modification in regulating radioresistance of esophageal cancer. Int J Radiat Oncol Biol Phys 117: e248-e249, 2023.
53. Chen X, Zhang L, He Y, Huang S, Chen S, Zhao W and Yu D: Regulation of m6A modification on ferroptosis and its potential significance in radiosensitization. Cell Death Discov 9: 343, 2023.
54. Ji P, Wan B, Gao M, Yin S, Wu H, Wang J, Ma Y, Xu W and Wang M: METTL3 promotes esophageal squamous cell carcinoma progression and reduces chemosensitivity to paclitaxel through the CASP9/BIRC3-dependent apoptosis pathway. Genes Dis 13: 101693, 2025.
55. Liu XS, Zhang Y, Liu ZY, Gao Y, Yuan LL, Zeng DB, Tan F, Wan HB and Pei ZJ: METTL3 as a novel diagnosis and treatment biomarker and its association with glycolysis, cuproptosis and ceRNA in oesophageal carcinoma. J Cell Mol Med 28: e18195, 2024.
56. Zou J, Zhong X, Zhou X, Xie Q, Zhao Z, Guo X and Duan Y: The M6A methyltransferase METTL3 regulates proliferation in esophageal squamous cell carcinoma. Biochem Biophys Res Commun 580: 48-55, 2021.
57. Chen J, Li S, Huang Z, Cao C, Wang A and He Q: METTL3 suppresses anlotinib sensitivity by regulating m6A modification of FGFR3 in oral squamous cell carcinoma. Cancer Cell Int 22: 295, 2022.
58. Huang T, You Q, Liu J, Shen X, Huang D, Tao X, He Z, Wu C, Xi X, Yu S, *et al*: WTAP Mediated m6A modification stabilizes PDIA3P1 and promotes tumor progression driven by histone lactylation in esophageal squamous cell carcinoma. Adv Sci (Weinh) 12: e06529, 2025.
59. Liao L, He Y, Li SJ, Zhang GG, Yu W, Yang J, Huang ZJ, Zheng CC, He QY, Li Y and Li B: Anti-HIV drug elvitegravir suppresses cancer metastasis via increased proteasomal degradation of m6A methyltransferase METTL3. Cancer Res 82: 2444-2457, 2022.
60. Qiu Y, Tian Z, Miao TY, Shen L, Chen J, Li PF, Zhu ZX, Zhu ZF, Wu WJ, Xu X and Shen WG: The METTL3-m6A-YTHDC1-AMIGO2 axis contributes to cell proliferation and migration in esophageal squamous cell carcinoma. Gene 908: 148281, 2024.
61. Zhang X, Bai Y, Shang L, Wang Y, Yao W and Wu S: METTL3-Mediated m6A Methylation Stabilizes IFI27 to drive esophageal squamous cell carcinoma progression through an IGF2BP2-Dependent Mechanism. J Biochem Mol Toxicol 39: e70167, 2025.
62. Zhang TT, Yi W, Dong DZ, Ren ZY, Zhang Y and Du F: METTL3-mediated upregulation of FAM135B promotes EMT of esophageal squamous cell carcinoma via regulating the Wnt/β-catenin pathway. Am J Physiol Cell Physiol 327: C329-C340, 2024.
63. Wang P, Chen S, Lei M, Chen Y, He H, Chen P, Chen W, Zhou H, Wang F and Zhang D: METTL3-mediated m6A methylation of LncRNA DUXAP8 promoted esophageal squamous cell carcinoma progression by activating the PI3K/AKT signaling pathway. Cell Div 21: 1, 2025.
64. Hou H, Zhao H, Yu X, Cong P, Zhou Y, Jiang Y and Cheng Y: METTL3 promotes the proliferation and invasion of esophageal cancer cells partly through AKT signaling pathway. Pathol Res Pract 216: 153087, 2020.
65. Zhang L, Cai E, Xu Y, Liu Z, Zheng M, Sun Z, Pei D and Wang Q: YTHDF1 facilitates esophageal cancer progression via augmenting m6A-dependent TINAGL1 translation. Cell Signal 122: 111332, 2024.
66. Guo X, Huang A, Qi Y, Chen J, Yang M and Jin M: METTL3/IGF2BP2 Promotes the Malignant Progression of Esophageal Cancer by Activating the PIK3CA/AKT Pathway. Thorac Cancer 16: e70022, 2025.
67. Han Y, Sun J, Yao M, Miao L and Li M: Biological roles of enhancer RNA m6A modification and its implications in cancer. Cell Commun Signal 23: 254, 2025.
68. Huang C, Zhang K, Guo Y, Shen C, Liu X, Huang H, Dou X and Yu B: The crucial roles of m^6A RNA modifications in cutaneous cancers: Implications in pathogenesis, metastasis, drug resistance, and targeted therapies. Genes Dis 10: 2320-2330, 2022.
69. Choe J, Lin S, Zhang W, Liu Q, Wang L, Ramirez-Moya J, Du P, Kim W, Tang S, Sliz P, *et al*: mRNA circularization by METTL3-eIF3h enhances translation and promotes oncogenesis. Nature 561: 556-560, 2018.
70. Wei X, Huo Y, Pi J, Gao Y, Rao S, He M, Wei Q, Song P, Chen Y, Lu D, *et al*: METTL3 preferentially enhances non-m6A translation of epigenetic factors and promotes tumourigenesis. Nat Cell Biol 24: 1278-1290, 2022.
71. Song Z, Wang X, Chen F, Chen Q, Liu W, Yang X, Zhu X, Liu X and Wang P: LncRNA MALAT1 regulates METTL3-mediated PD-L1 expression and immune infiltrates in pancreatic cancer. Front Oncol 12: 1004212, 2022.
72. Brichkina A, Suezov R and Huber M: Methyltransferase-like 3 (METTL3) inhibition potentiates antitumor immunity: A novel strategy for improving anti-PD1 therapy. Signal Transduct Target Ther 8: 448, 2023.
73. Yu H, Liu J, Bu X, Ma Z, Yao Y, Li J, Zhang T, Song W, Xiao X, Sun Y, *et al*: Targeting METTL3 reprograms the tumor microenvironment to improve cancer immunotherapy. Cell Chem Biol 31: 776-791.e7, 2024.
74. Peng L, Wang D, Han Y, Huang T, He X, Wang J and Ou C: emerging role of cancer-associated fibroblasts-derived exosomes in tumorigenesis. Front Immunol 12: 795372, 2022.

75. Sun Y, Shen W, Hu S, Lyu Q, Wang Q, Wei T, Zhu W and Zhang J: METTL3 promotes chemoresistance in small cell lung cancer by inducing mitophagy. J Exp Clin Cancer Res 42: 65, 2023.
76. Hu F, Zhang S and Chai J: METTL3 promotes gastric cancer progression via modulation of FNTA-Mediated KRAS/ERK signaling activation. Mol Cancer Res 23: 724-738, 2025.
77. Hwang K, Bae J, Jhe YL, Kim J, Cheong JH, Choi HS and Sim T: Targeted degradation of METTL3 against acute myeloid leukemia and gastric cancer. Eur J Med Chem 279: 116843, 2024.
78. Zhang L, Mao Z, Yin K and Wang S: Review of METTL3 in colorectal cancer: From mechanisms to the therapeutic potential. Int J Biol Macromol 277: 134212, 2024.
79. Li B, Hong P, Zheng CC, Dai W, Chen WY, Yang QS, Han L, Tsao SW, Chan KT, Lee NPY, *et al*: Identification of miR-29c and its Target FBXO31 as a key regulatory mechanism in esophageal cancer chemoresistance: Functional validation and clinical significance. Theranostics 9: 1599-1613, 2019.
80. Zhang HF, Wu C, Alshareef A, Gupta N, Zhao Q, Xu XE, Jiao JW, Li EM, Xu LY and Lai R: The PI3K/AKT/c-MYC axis promotes the acquisition of cancer stem-like features in esophageal squamous cell carcinoma. Stem Cells 34: 2040-2051, 2016.
81. Liao X, Cai D, Liu J, Hu H, You R, Pan Z, Chen S, Xu K, Dai W, Zhang S, *et al*: Deletion of Mettl3 in mesenchymal stem cells promotes acute myeloid leukemia resistance to chemotherapy. Cell Death Dis 14: 796, 2023.
82. Li M, Xia M, Zhang Z, Tan Y, Li E, Guo Z, Fang M, Zhu Y and Hu Z: METTL3 antagonizes 5-FU chemotherapy and confers drug resistance in colorectal carcinoma. Int J Oncol 61: 106, 2022.
83. He X, Li Y, Li J, Li Y, Chen S, Yan X, Xie Z, Du J, Chen G, Song J and Mei Q: HDAC2-Mediated METTL3 delactylation promotes DNA damage repair and chemotherapy resistance in triple-negative breast cancer. Adv Sci (Weinh) 12: e2413121, 2025.
84. Li N, Wei X, Dai J, Yang J and Xiong S: METTL3: A multifunctional regulator in diseases. Mol Cell Biochem 480: 3429-3454, 2025.
85. Puhr HC, Prager GW and Ilhan-Mutlu A: How we treat esophageal squamous cell carcinoma. ESMO Open 8: 100789, 2023.
86. Korpan M, Puhr HC, Prager GW and Ilhan-Mutlu A: State-of-the-art therapy and innovative treatment strategies in esophageal squamous cell cancer. Memo 17: 274-279, 2024.
87. Sun X, Bai C, Li H, Xie D, Chen S, Han Y, Luo J, Li Y, Ye Y and Jia J, *et al*: PARP1 modulates METTL3 promoter chromatin accessibility and associated LPAR5 RNA m6A methylation to control cancer cell radiosensitivity. Mol Ther 31: 2633-2650, 2023.
88. Zhang C, Yang T, Chen H, Ding X, Chen H, Liang Z, Zhao Y, Ma S and Liu X: METTL3 inhibition promotes radiosensitivity in hepatocellular carcinoma through regulation of SLC7A11 expression. Cell Death Dis 16: 9, 2025.
89. Shi X, Zhang X, Huang X, Zhang R, Pan S, Huang S, Wang Y, Ke Y, Guo W, Liu X, *et al*: N6-methyladenosine-mediated upregulation of LNCAROD confers radioresistance in esophageal squamous cell carcinoma through stabilizing PARP1. Clin Transl Med 14: e70039, 2024.
90. Sun H, Liu F, Song X, Sun R, Zhang M, Huang J, Gu W and Shao Y: m6A-modified circCREBBP enhances radiosensitivity of esophageal squamous cell carcinoma by reducing the stability of MYC through interaction with IGF2BP3. Int J Biol Macromol 286: 138534, 2025.
91. Gao C, Yang H, Cheng J, He S, Yang Y, Xu L, Ma Q, Guo X and Zhong X: STM2457 impairs the proliferation of esophageal squamous cell carcinoma by activating DNA damage response through ATM-Chk2 axis. Med Oncol 42: 82, 2025.
92. Bian Y, Bi G, Shan G, Liang J, Yao G, Sui Q, Hu Z, Zhan C, Chen Z and Wang Q: Identification of the relationship between single-cell N6-methyladenosine regulators and the infiltrating immune cells in esophageal carcinoma. Heliyon 9: e18132, 2023.
93. Gong Y, Wu J and Hu Y: m6A epitranscriptomic regulation of KRAS by METTL3 promotes EMT and stromal remodeling through TGF-β/SMAD signaling in cervical cancer. Cancer Gene Ther 33: 198-211, 2026.
94. Li T, Hu PS, Zuo Z, Lin JF, Li X, Wu QN, Chen ZH, Zeng ZL, Wang F, Zheng J, *et al*: METTL3 facilitates tumor progression via an m6A-IGF2BP2-dependent mechanism in colorectal carcinoma. Mol Cancer 18: 112, 2019.
95. Lin X, Hong Y, You S, Li P, Lv Y, Zheng J and Sun P: METTL3-mediated m6A modification of LINC00857 enhances stemness and metastasis of ovarian cancer cells by activating the YAP-TEAD pathway. Sci Rep 15: 41132, 2025.
96. Wu HX, Chen YK, Wang YN, Chen JY, Xiang SJ, Jin Y, Wang ZX, Huang CY, Yang LP, He Y, *et al*: Dissecting small cell carcinoma of the esophagus ecosystem by single-cell transcriptomic analysis. Mol Cancer 24: 142, 2025.
97. Zhang X, Peng L, Luo Y, Zhang S, Pu Y, Chen Y, Guo W, Yao J, Shao M, Fan W, *et al*: Dissecting esophageal squamous-cell carcinoma ecosystem by single-cell transcriptomic analysis. Nat Commun 12: 5291, 2021.
98. Jia Y, Zhang B, Zhang C, Kwong DL, Chang Z, Li S, Wang Z, Han H, Li J, Zhong Y, *et al*: Single-cell transcriptomic analysis of primary and metastatic tumor ecosystems in esophageal squamous cell carcinoma. Adv Sci (Weinh) 10: e2204565, 2023.
99. Li R, Huang B, Tian H and Sun Z: Immune evasion in esophageal squamous cell cancer: From the perspective of tumor microenvironment. Front Oncol 12: 1096717, 2023.
100. Guo W, Tan F, Huai Q, Wang Z, Shao F, Zhang G, Yang Z, Li R, Xue Q, Gao S and He J: Comprehensive Analysis of PD-L1 expression, immune infiltrates, and m6A RNA methylation regulators in esophageal squamous cell carcinoma. Front Immunol 12: 669750, 2021.
101. Sun Y and Huang S: METTL3-mediated m6A modification of CXCR4 drives M2 macrophage polarization and suppresses antitumor immunity in esophageal cancer. J Clin Biochem Nutr 78: 136-141, 2026.
102. Yuan F, Zhang W, Xia Y, Zhou X and Gao H: The role and mechanism of METTL3 in cancer: Emerging insights into m6A methylation and therapeutic potential. Eur J Med Res 30: 1017, 2025.
103. Fiorentino F, Menna M, Rotili D, Valente S and Mai A: METTL3 from target validation to the first small-molecule inhibitors: A medicinal chemistry journey. J Med Chem 66: 1654-1677, 2023.
104. Tang H, Zhang R and Zhang A: Small-molecule inhibitors targeting RNA m6A modifiers for cancer therapeutics: Latest advances and future perspectives. J Med Chem 68: 18114-18142, 2025.
105. Moroz-Omori EV, Huang D, Kumar Bedi R, Cheriyamkunnel SJ, Bochenkova E, Dolbois A, Rzeczkowski MD, Li Y, Wiedmer L and Caflisch A: METTL3 inhibitors for epitranscriptomic modulation of cellular processes. ChemMedChem 16: 3035-3043, 2021.
106. Moser JC, Papadopoulos KP, Rodon Ahnert J, Ofir-Rosenfeld Y, Holz J-B and null n: Phase 1 dose escalation and cohort expansion study evaluating safety, PK, PD and clinical activity of STC-15, a METTL-3 inhibitor, in patients with advanced malignancies. J Clin Oncol 42: 2586-2586, 2024.
107. Bennett CF: Therapeutic antisense oligonucleotides are coming of age. Annu Rev Med 70: 307-321, 2019.
108. Collotta D, Bertocchi I, Chiapello E and Collino M: Antisense oligonucleotides: A novel Frontier in pharmacological strategy. Front Pharmacol 14: 1304342, 2023.
109. Wen L, Fu J, Wang Z, Xie R, Tang S, Yu L and Zhou H: Regulatory mechanisms of m6A RNA methylation in esophageal cancer: A comprehensive review. Front Genet 16: 1531799, 2025.
110. Du W, Huang Y, Chen X, Deng Y, Sun Y, Yang H, Shi Q, Wu F, Liu G, Huang H, *et al*: Discovery of a PROTAC degrader for METTL3-METTL14 complex. Cell Chem Biol 31: 177-183.e17, 2024.
111. Dai XJ, Ji SK, Fu MJ, Liu GZ, Liu HM, Wang SP, Shen L, Wang N, Herdewijn P, Zheng YC, *et al*: Degraders in epigenetic therapy: PROTACs and beyond. Theranostics 14: 1464-1499, 2024.
112. Esteva-Socias M and Aguilo F: METTL3 as a master regulator of translation in cancer: Mechanisms and implications. NAR Cancer 6: zcae009, 2024.
113. Nar R, Wu Z, Li Y, Smith A, Zhang Y, Wang J, Yu F, Gao S, Yu C, Huo Z, *et al*: Targeting METTL3 protein by proteolysis-targeting chimeras: A novel therapeutic approach for acute myeloid leukemia. Genes Dis 12: 101452, 2024.
114. Smith AR, Nar R, Li Y, Gour A, Sharma A, Qian Z, Zheng G and Wu Z: Discovery of CRBN-recruiting PROTAC degraders of the METTL3-METTL14 complex. Med Chem Res 34: 2299-2308, 2025.
115. Li Z, Zheng C, Huang L, Yin X, Wang Z, Liu C and Li B: The landscape of m6A regulators in esophageal cancer: molecular characteristics, immuno-oncology features, and clinical relevance. Ann Transl Med 10: 1347, 2022.
116. Lyu Q, Chai Y, Chen W, Chen Y and Li Y: Integrated bioinformatics analysis of differences between EAC and ESCC. BMC Cancer 25: 1668, 2025.

117. Yin F, Hernandez Gonzalo D, Lai J and Liu X: Histopathology of barrett's esophagus and early-stage esophageal adenocarcinoma: An updated review. Gastrointest Disord 1: 147-163, 2019.
118. Grady WM, Yu M, Markowitz SD and Chak A: Barrett's esophagus and esophageal adenocarcinoma biomarkers. Cancer Epidemiol Biomarkers Prev 29: 2486-2494, 2020.
119. Maslenkina K, Mikhaleva L, Naumenko M, Vandysheva R, Gushchin M, Atiakshin D, Buchwalow I and Tiemann M: Signaling pathways in the pathogenesis of barrett's esophagus and esophageal adenocarcinoma. Int J Mol Sci 24: 9304, 2023.
120. Zou K, Dong H, Li M, Zhang Y, Zhang K, Song D and Chu C: Comprehensive analysis of transcriptome-wide N6-methyladenosine methylomes in the Barrett's esophagus in rats. Genomics 115: 110687, 2023.
121. Dilworth MP, Nieto T, Stockton JD, Whalley CM, Tee L, James JD, Noble F, Underwood TJ, Hallissey MT, Hejmadi R, *et al*: Whole Genome Methylation Analysis of Nondysplastic Barrett Esophagus that Progresses to Invasive Cancer. Ann Surg 269: 479-485, 2019.
122. Martinez-Uribe O, Becker TC and Garman KS: Promises and limitations of current models for understanding Barrett's Esophagus and esophageal adenocarcinoma. Cell Mol Gastroenterol Hepatol 17: 1025-1038, 2024.
123. Boonstra JJ, van der Velden AW, Beerens EC, van Marion R, Morita-Fujimura Y, Matsui Y, Nishihira T, Tselepis C, Hainaut P, Lowe AW, *et al*: Mistaken identity of widely used esophageal adenocarcinoma Cell Line TE-7. Cancer Res 67: 7996-8001, 2007.
124. Capes-Davis A, Theodosopoulos G, Atkin I, Drexler HG, Kohara A, MacLeod RA, Masters JR, Nakamura Y, Reid YA, Reddel RR and Freshney RI: Check your cultures! A list of cross-contaminated or misidentified cell lines. Int J Cancer 127: 1-8, 2010.
125. Hu L, Liu S, Peng Y, Ge R, Su R, Senevirathne C, Harada BT, Dai Q, Wei J, Zhang L, *et al*: m(6)A RNA modifications are measured at single-base resolution across the mammalian transcriptome. Nat Biotechnol 40: 1210-1219, 2022.
126. Johnson A, Ali SM, Yelensky R, Chmielecki J, Elvin JA, Lipson D, Miller VA, Stephens PJ, Ross JS and Wang K: Comprehensive genomic profiling of advanced stage esophageal squamous cell carcinomas (ESCC) and esophageal adenocarcinomas (EAC). J Clin Oncol 33: 1535-1535, 2015.
127. Zheng G, Bi J, Yan Y, Yu B and Fu Y: Emerging role of RNA m6A modifications in laryngeal squamous cell carcinoma: Insights into tumorigenesis and therapeutic potential. Apoptosis 30: 2077-2089, 2025.
128. Huang M, Wang X, Zhang M, Liu Y and Chen YG: METTL3 restricts RIPK1-dependent cell death via the ATF3-cFLIP axis in the intestinal epithelium. Cell Regen 13: 14, 2024.
129. Kansal R, Sharma V, Potraje P and Datta M: m6A RNA modification and its emerging roles in diseases: Recent advances and therapeutic implications. J Transl Med 24: 433, 2026.
130. Errani F, Invernizzi A, Herok M, Bochenkova E, Stamm F, Corbeski I, Romanucci V, Di Fabio G, Zálešák F and Caflisch A: Proteolysis Targeting Chimera Degraders of the METTL3-14 m^{6}A-RNA Methyltransferase. JACS Au 4: 713-729, 2024.
131. Xing L, Jiang Z, Xu R, Dang T, Wu J, Chai J and Meng X: CCN1 promotes APRIL/BAFF signaling in esophageal squamous cell carcinoma but attenuates it in esophageal adenocarcinoma. Sci Rep 15: 1808, 2025.
132. Wu H, Yu J, Li Y, Hou Q, Zhou R, Zhang N, Jing Z, Jiang M, Li Z, Hua Y, *et al*: Single-cell RNA sequencing reveals diverse intratumoral heterogeneities and gene signatures of two types of esophageal cancers. Cancer Lett 438: 133-143, 2018.
133. Liu M, Huang Y, Tian H, Guo C, Liu Z, Liu A, Yang H, Li F, Duan L, Shen L, *et al*: Absolute Risk Prediction for Esophageal Squamous Cell Carcinoma Adaptable to Regional Disease Burden across Diverse Regions. Cancer Epidemiol Biomarkers Prev 34: 510-517, 2025.
134. Su W, Che L, Liao W and Huang H: The RNA m^{6}A writer METTL3 in tumor microenvironment: Emerging roles and therapeutic implications. Front Immunol 15: 1335774, 2024.
135. Gu Y, Fang Y, Wu X, Xu T, Hu T, Xu Y, Ma P, Wang Q and Shu Y: The emerging roles of SUMOylation in the tumor microenvironment and therapeutic implications. Exp Hematol Oncol 12: 58, 2023.
136. Li L, Jiang D, Zhang Q, Liu H, Xu F, Guo C, Qin Z, Wang H, Feng J, Liu Y, *et al*: Integrative proteogenomic characterization of early esophageal cancer. Nat Commun 14: 1666, 2023.
137. Pei X, Liu Z, Tang L, Zhang J, He Y, Zhuang X, Song Y, Peng S, He Y, Zhao Y, *et al*: Single-cell multi-omic and spatial profiling of esophageal squamous cell carcinoma reveals the immunosuppressive role of GPR116+ pericytes in cancer metastasis. Nat Genet 57: 2494-2508, 2025.
138. Sinha UK, Park YM and Lin DC: A high-power spatial, single-cell view of pericytes in esophageal cancer metastasis. Nat Genet 57: 2350-2351, 2025.
139. Li G, Chen W, Liu D and Tang S: Recent advances in medicinal chemistry strategies for the development of METTL3 inhibitors. Eur J Med Chem 290: 117560, 2025.
140. Li H, Zhang Q, Feng Q, You Q and Guo X: The development of small molecules targeting methyltransferase-like 3. Drug Discov Today 28: 103513, 2023.