Molecular Therapy
Review

Targeting RNA adenosine editing and modification enzymes for RNA therapeutics

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Adenosine-to-inosine (A-to-I) RNA editing, and N6 methyladenosine (m6A) are among the most abundant modifications in eukaryotic messenger RNA, affecting various aspects of RNA metabolism and cellular function, including proliferation, differentiation, responses to stressors, and cell death. Recent preclinical evidence suggests that both modifications play a significant role in multiple disorders, including infections, chronic inflammatory diseases, and cancer, sparking great interest in their therapeutic potential. Structural characterization of ADARs (adenosine deaminases acting on RNA) and key m6A enzymes has enabled the development of small molecule inhibitors modulating their expression, enzymatic activity, or binding to target RNAs. Herein, we review preclinical evidence supporting the therapeutic benefits of targeting ADARs and m6A enzymes in diverse disease contexts. Small molecule inhibitors of RNA modification enzymes have shown potent anti-proliferative and pro-apoptotic effects in cancer cells, and have successfully inhibited tumor growth *in vivo*, without evident toxicity, while their combination with immuno-/chemotherapeutics displayed synergistic anti-neoplastic action. Adenosine RNA editing via recruitment of endogenous ADARs and usage of guide RNAs showed remarkable efficacy in correcting G-to-A point mutations and restoring the associated protein expression with limited off-target activity. Future studies are warranted to evaluate the safety and clinical efficacy of RNA editing or modification-targeting therapeutics in patients.

INTRODUCTION

RNA molecules are dynamically regulated in response to microenvironmental signals, enabling the rapid adaptation of gene function and fundamental cellular functions to environmental changes. The discovery of RNA modifications, which occur co- or post-transcriptionally and expand the RNA alphabet from the four canonical bases to more than 170 individual nucleotides,[1] has revealed an additional layer of gene regulation, paving the way for new developments in the field of RNA-based therapeutics, precision medicine, and drug development. In this review, we focus on two of the most prevalent and functionally significant modifications found in eukaryotic messenger RNA, adenosine-to-inosine (A-to-I) RNA editing and N6-methyladenosine (m6A).[2] Recent technological advances enabling detection of RNA modifications, including direct long-read RNA sequencing[3] and antibody-based immunoprecipitation of methylated RNA followed by sequencing (MeRIP-seq and m6A-seq),[4,5] have provided unprecedented insights into the regulation and role of these modifications in both physiology and disease. A-to-I RNA editing and m6A affect multiple aspects of RNA metabolism including transcript stability,[6–8] processing,[9] and splicing,[10] as well as translational control.[11–14] Consequently, they are essential for the control of numerous homeostatic processes,[15] including cellular proliferation, cell death,[16,17] DNA damage response,[18–20] senescence,[18–20] differentiation,[21] metabolism,[22] and stress adaptation.[23] This dynamic adaptability is particularly critical during injury, where precise responses to an evolving microenvironment are essential for proper cell fate decisions. Dysregulated RNA modification levels, loss-of-function mutations in genes encoding RNA editing or modifying enzymes and RNA modification reader proteins, as well as point mutations that disrupt RNA modifications, have therefore been linked to several human diseases, such as infections, chronic inflammatory conditions, cardiometabolic disorders, neurological diseases, and cancer.[24–28] Notably, both deamination and m6A have emerged as critical regulators of disease development, progression, and response to therapy.

Given their widespread presence and central role in the regulation of gene function, these mRNA modifications represent promising therapeutic targets across a broad spectrum of diseases. Small enzymatic

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inhibitors against methyltransferase 3 (METTL3), which is part of the m6A writing complex, or against fat mass and obesity-associated protein (FTO), which removes m6A, have been tested in numerous preclinical disease models. The METTL3 inhibitor STC-15 is currently under investigation in a phase 1 clinical trial for acute myeloid leukemia (AML) and other advanced cancers (NCT05584111). Small molecule inhibitors targeting adenosine deaminases acting on RNA (ADARs), the enzymes mediating A-to-I RNA editing, are currently under development, while target-specific RNA base editing to correct point mutations and treat genetic disorders caused by G-to-A pathogenic mutations has entered phase 1 and phase 2 clinical trials (NCT06405633, NCT06677307). The high specificity and reversibility of small molecule inhibitors against RNA modification enzymes, together with high speed and low cost of their production, make these therapeutics a promising option for widespread use in the near future. Here, we review experimental evidence supporting the therapeutic efficacy of therapeutics targeting m6A or A-to-I RNA editing in a wide range of human diseases.

THERAPEUTIC TARGETING ON m6A

m6A methylation function in health and disease

The reversible methylation of N6-adenosine is dynamically regulated by a multicomponent complex comprising two methyltransferases (METTLs) or "writers," namely METTL3 and METTL14, along with the auxiliary protein Wilms tumor-associated protein-1 (WTAP), as well as m6A "erasers" (FTO and ALKBH5) and "readers" (the YTHDF family, YTHDC1, YTHDC2, and others).[29,30] Additional components of the m6A methyltransferase complex play a role in this process. RBM15/RBM15b facilitates the recruitment of the writers to specific RNA-binding sites, while VIRMA directs this complex to the 3′-UTR near stop codons, influencing site-specific methylation.[31] Moreover, CBLL1 and ZC3H13 stabilize the complex in nuclear speckles, enhancing its catalytic activity.[32] Recently, other m6A regulators, like METTL4, METTL5, and METTL16, have been shown to play a role in the methylation of non-coding RNAs, suggesting that they may contribute to disease progression.[33]

The m6A methylome is evolutionarily conserved, and its importance is highlighted by the fact that global genetic deletion of METTL3, METTL14, or WTAP in mice results in early embryonic lethality due to severe developmental defects, including defective embryonic stem cell differentiation, ineffective hematopoiesis, and widespread cell apoptosis.[34–36] m6A methylation driven by Mettl3 and Mettl14 orchestrates normal embryonic hematopoiesis by controlling endothelial-to-hematopoietic transition,[37] as well as proliferation, self-renewal capability, and differentiation of human stem and progenitor cells (HSPCs).[38–40] m6A also regulates the development of the reproductive system affecting both oocyte maturation and spermatogenesis.[41] Alkbh5-inactivation leads to aberrant splicing in spermatocytes and male infertility,[42] while deletion of the m6A reader Ythdf2 in mice results in defective oocyte maturation and female-specific infertility.[43] Moreover, cell-specific knockout of m6A methyltransferases or demethylases has revealed the essential role of m6A for the physiological development and maintenance of multiple organs, including the brain,[44] liver,[45,46] and skeletal muscle.[47] These findings, highlight that the dynamic and strict regulation of m6A is essential for cellular and organismal homeostasis.

Although m6A is classified as a non-substitutional RNA modification, since it does not drastically alter the structural identity of adenosine residues, it influences many aspects of RNA metabolism (Figure 1). m6A methylation is essential for the maintenance of normal cellular functions and homeostasis by regulating key cellular processes such as cell cycle, proliferation, and apoptosis, and is therefore centrally implicated in the development and progression of several diseases (Figure 2; Table 1; Tables S1 and S2). For example, METTL3 knockout in human AML cell lines inhibits the translation of the transcription factor SP1[306] and of the oncogenes c-MYC, BCL2, and PTEN,[38] thereby restricting tumor progression *in vivo*. Conversely, the m6A eraser FTO enhances tumor cell proliferation and survival by demethylating pro-apoptotic transcripts, such as *ASB2* and *RARA*, and reducing their stability in AML cells.[307] In glioblastoma, METTL3-mediated m6A modification of *SOX2* mRNA increases the transcript's stability and promotes self-renewal and tumorigenicity of glioma stem-like cells, while depletion of Mettl3 leads to cell-cycle arrest and reduced tumor growth.[308] FTO has also been linked to cancer progression as it promotes the degradation of the pro-apoptotic *BNIP3* transcript in an m6A-dependent manner, preventing cancer cell apoptosis.[309] Likewise, the m6A reader YTHDF2 promotes cancer cell survival by degrading the pro-apoptotic transcripts *TNFRSF2* and *BMF*, thereby suppressing cancer cell apoptosis.[310,311] Therefore, targeting the m6A machinery may provide therapeutic benefits in multiple types of cancer by restoring the balance of pro-apoptotic factors in cancer cells.

Beyond its central role in the regulation of cell cycle, m6A is involved in modulating immune responses.[312] Mettl3 or m6A depletion led to the formation of endogenous double-stranded RNA (dsRNA) in murine fetal liver cells, which in turn activated the innate immune sensors MDA5 and RIG-I promoting type I interferon signaling, as well as the PKR-eIF2α pathway, inducing cell apoptosis.[40] METTL3-mediated m6A methylation is essential for dendritic cell activation and function, as it promotes the translation of key co-stimulatory molecules, such as CD40 and CD80, as well as cytokine expression such as interleukin (IL)-12.[313] This process facilitates dendritic cell-induced activation of T cells and serves as a "bridge" between innate and adaptive immune responses.[313] Moreover, Mettl3-mediated m6A modification promotes the homeostatic expansion and differentiation of naive T cells by inducing the decay of SOCS family transcripts encoding STAT-signaling inhibitory proteins. Thereby, Mettl3 enhances the IL-7/STAT5/SOCS signaling pathway, which is crucial for T cell homeostasis and function.[314] On the other hand, the m6A reader YTHDF1 affects T cell activation by regulating the translation of immune checkpoint proteins, such as PD-L1, a function with important consequences for the response of cancer cells to immune checkpoint blockade.[315] m6A fine-tunes multiple aspects of innate and adaptive immune responses, making

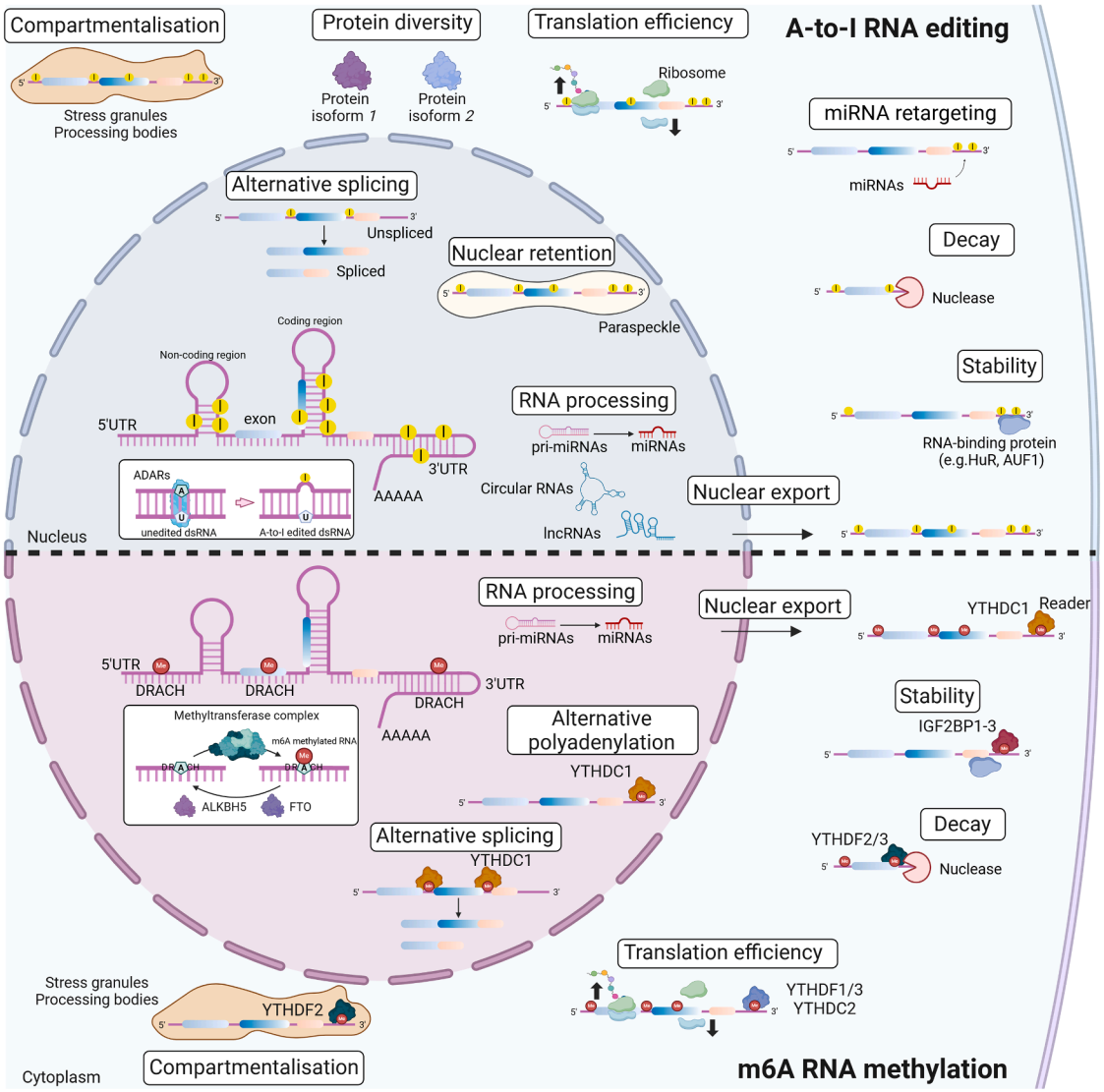

Figure 1. Role of A-to-I RNA editing and m6A in RNA metabolism

A-to-I RNA editing is induced by ADARs, which act on dsRNA to catalyze the site-specific deamination of adenosine to inosine. Due to their chemical similarity, inosine is recognized by the cellular machinery as guanosine, leading to the disruption of dsRNA structures and thereby modulating RNA metabolism. A-to-I RNA editing can affect multiple aspects of RNA metabolism depending on the site where it takes place in the transcript and the cellular localization of the transcript. A-to-I editing of RNAs in the nucleus controls nuclear retention or export of transcripts, as well as processing of non-coding RNAs such as microRNAs (miRNAs). A-to-I RNA editing in the cytoplasm can affect transcript stability and decay, as well as translation efficiency, while RNA editing in exons can lead to protein diversity.

The reversible methylation of N6-adenosine is dynamically regulated by a multicomponent complex comprising two methyltransferases (METTLs) or "writers," along with the auxiliary protein Wilms tumor-associated protein-1 (WTAP), as well as m6A "erasers" (FTO and ALKBH5), and "readers" (the YTHDF family, YTHDC1, YTHDC2, and others). Methylation of transcripts in the nucleus can lead to alternative polyadenylation and splicing, as well as affect miRNA processing and nuclear export. The fate of methylated transcripts in the cytoplasm depends on competitive binding of m6A reader proteins, which can either increase or decrease transcript stability, but also affect translation efficiency of mRNAs.

m6A enzymes attractive therapeutic targets not only in cancer immunotherapy, but also in chronic immune-mediated inflammatory disorders.

A large number of studies highlight the central role of m6A in regulating key mechanistic pathways and processes that affect disease progression in of diverse prevalent diseases (Tables 1 and S1; Figure 2), making it an attractive therapeutic target. Beyond its central role in cell-cycle progression and cell survival/apoptosis, as well as immune responses described above, m6A has been shown to control, among others, autophagy in age-related disorders such as osteoarthritis,[73] vascular endothelial growth factor (VEGF)-induced

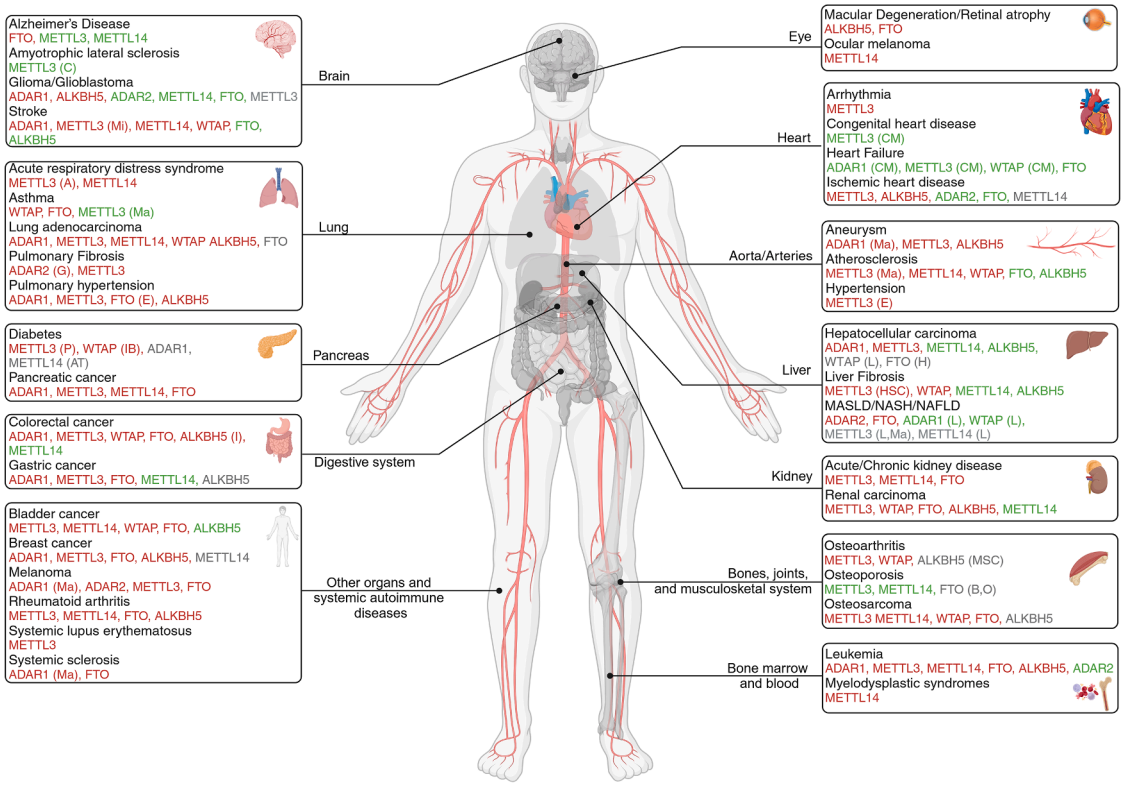

Figure 2. Role of A-to-I RNA editing and m6A in disease progression

ADAR and m6A enzymes have been implicated in the development and progression of multiple diseases, affecting all human organ systems. The studies included in the figure provide *in vivo* evidence that genetic or pharmacological modulation of enzymes may affect disease outcome. References for this figure can be found in Table S1. Letters in parentheses correspond to a cell-specific or tissue-specific deletion or overexpression of the corresponding enzyme (A: alveolar epithelial; AT: adipose tissue; B: bone; C: cholinergic; CM: cardiomyocyte; E: endothelial G: germline cell; H: hepatocyte; HSC: Hepatic stellate cell; I: intestine; IB: islet beta; L: liver; Ma: macrophage; Mi: microglia; MSC: mesenchymal stem cell; O: osteoblast; P: pericyte). Green color corresponds to improvement of disease outcome, while red color means aggravation of disease after either deletion or overexpression of the corresponding enzymes. We must emphasize that cell-specific or tissue-specific deletion may not represent the overall role of the enzyme in the disease.

neo-angiogenesis in tumors,[118,119] Hippo signaling-induced liver fibrosis,[200] and extracellular matrix remodeling—fibrosis in ischemic heart disease,[161,164–166] insulin signaling and sensitivity in the liver, and adipose tissue in metabolic disorder.[207,208,282–284]

Small molecules targeting METTL3

Since METTL3 is the main catalytic subunit of the methyltransferase complex,[316,317] targeting METTL3 is an effective approach to modulate m6A levels.[318,319] STM2457 is the most potent, selective inhibitor of METTL3 described to date. It was identified through a high-throughput screen of 250,000 drug-like compounds followed by chemical optimization.[320] This compound exhibited over 1,000-fold selectivity for METTL3 compared with 45 other methyltransferases, while it did not affect the enzymatic activity of 468 kinases.[320] Since its development in 2021, STM2457 has been used in multiple *in vivo* models spanning a wide range of hematopoietic and solid tumors, as well as metabolic, inflammatory, and fibrotic disorders (Table 2; Figure S1). Treatment of multiple cancer cell lines with STM2457 *in vitro* consistently showed impairment of proliferation, induction of cell-cycle arrest, and apoptosis, as well as functional inhibition of cancer cells including reduced colony formation, migration, and invasion,[326,334,337,338] underlining the potential of this compound as a novel anti-neoplastic drug. Of note, treatment with STM2457 did not affect the proliferation and survival of healthy cells, showing an overall safe therapeutic profile.

STM2457 treatment has also been shown to inhibit tumor growth *in vivo* in multiple disease models, including colorectal cancer (CRC),[322] primary hepatocellular carcinoma (HCC),[326,329] and HCC associated with non-alcoholic fatty liver disease (NAFLD-HCC),[327] intrahepatic cholangiocarcinoma,[323] oral squamous cell carcinoma (OSCC),[325] osteosarcoma,[321] renal cell carcinoma,[182] and small cell-[328] and non-small cell lung cancer.[332] From a mechanistic point of view, enzymatic inhibition of METTL3 in cancer cells led to the formation of endogenous dsRNA and upregulation of cell-intrinsic type I and II interferon responses, as well as of classical proinflammatory mediators such as tumor necrosis factor (TNF) and IL-6, boosting immune surveillance of tumor cells *in vivo*.[339] STM2457 treatment also

Table 1. Effect of METTL3/METTL14/WTAP in disease

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
Brain						
Alzheimer's disease	METTL3	↑ mitochondrial dysfunction ↓ macrophage migration, Aβ clearance	*MFN2, PSD95,* *CCN2, circRIMS2* *DNMT3A*	stability, decay translation	glial cell (H), hippocampal neuronal cell (M) BMDM (M)	Chen et al.[48], Zhao et al.[49], and Wang et al.[50] Yin et al.[51]
	METTL14	↓ neuronal injury ↓ ferroptosis	*CBLN4* *TUG1*	stability stability	neuroblastoma cell line (H) neuroblastoma cell line (H), hippocampal tissues (M)	Mu et al.[52] Gu et al.[53]
Amyotrophic lateral sclerosis	METTL3	↑ motor neuron survival ↑ stress granule formation	*TDP-43* *FUS*	splicing localization	embryonic stem cell-derived motor neuron (M) neuroblastoma (H), Primary fibroblasts (H)	Dermentzaki et al.[54] Di Timoteo et al.[55]
Glioma/Glioblastoma	METTL3	↑ DNA repair ↑ proliferation, self-renewal ↓ proliferation, self-renewal	*MGMT, ANPG* *OPTN circDLC1, ADAM19*	expression decay stability, expression	glioblastoma cell line (H) glioblastoma stem cells (H) Primary glioma (H), glioma cell line (H)	Shi et al.[56] Lv et al.[57] Wu et al.[58]
	METTL14	↓ proliferation self-renewal	*ADAM19, circRNA_103239*	expression, sponging	primary glioma (H), glioma cell line (H)	Cui et al.[59], Zhang et al.[60]
	WTAP	↑ proliferation, migration, invasion ↑ chemoresistance, DNA repair signaling	*PI3K/AKT, LOXL2, FLOT1* *UBE2D3*	stability, expression stability	glioma cell lines (H), primary glioma (H) glioblastoma cell lines (H)	Qiu et al.[61], Ji et al.[62] Bao et al.[63]
Parkinson's Disease	METTL3	↑ neuron degeneration	*GLX*	stability	brain tissue of Parkinson's disease model (M)	Gong et al.[64]
	METTL14	↓ ferroptosis, mitochondrial dysfunction	*TRAF6*	expression	neuronal cell line (M)	Shao et al.[65]
Stroke	METTL3	↑ neutrophil recruitment, neuronal loss ↑ apoptosis, cell-cycle arrest, oxidative stress	*BATF* *ABHD11-AS1*	stability stability	microglia (H) primary astrocytes (M)	Wu et al.[66] Huang et al.[67]
	METTL14	↑ microglial polarization	*PAX6, KAT3B, HDAC3*	stability	microglia cell line (M), microglial cell line (R)	Zhang et al.[68], Li et al.[69], Liang et al.[70]
	WTAP	↑ microglial polarization	*PTGS2*	stability	microglia cell line (M)	Sui et al.[71]
Bones, joints, and musculoskeletal system						
Osteoarthritis	METTL3	↑ ferroptosis ↑ senescence ↓ autophagy	*HMGB1* *ATG7*	stability stability	primary chondrocytes (R) fibroblast-like synoviocytes (H) (M)	Bao et al.[72] Chen et al.[73]
	METTL14	↑ matrix degradation, ↑ ferroptosis	*FAS-S1, GPX4*	expression	immortalized chondrocytes (H), osteoarthritis cartilage (R), primary chondrocytes (M), chondrogenic cell line (M)	Liu et al.[74], Zhang et al.[75]
	WTAP	↑ apoptosis, matrix degradation ↓ proliferation	*CA12, FRZB, TIMP4*	stability	articular cartilages (H), chondrocytes cell line (H), primary chondrocyte (H)	Lin et al.[76], An et al.[77], and Deng et al.[78]
Osteoporosis	METTL3					

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
		↓ angiogenesis ↑ senescence ↑ proliferation ↓ senescence ↑ osteogenic differentiation	*SLIT3* *SLC1A5* *HSPA1A* *YAP, SOX4, CHI3L1*	expression stability stability stability	bone marrow mesenchymal stem cells (M) osteoblast from cranial bone (R) primary osteoblast (M), preosteoblast cell (M) periodontal ligament cell (H), osteoblast (M), BMDM (M)	Wei et al.[79] Liu et al.[80] Wang et al.[81] Wang et al.[82], Feng et al.[83], and Sun et al.[84]
	METTL14	↑ osteogenic differentiation ↓ pyroptosis ↓ mitochondrial damage	*USP7, GLUT3, SIRT1* *HOXA5* *SLC25A3*	stability stability stability	bone marrow mesenchymal cells (H), osteoblastic cell line (M), BMDM (M) macrophage cell line (M), BMDM (M) osteoblastic cell line (M)	Leng et al.[85], Wang et al.[86], and Wang et al.[87] Tang et al.[88] Wang et al.[89]
	WTAP	↑ osteogenic differentiation ↓ senescence	*SP1*	stability	preosteoblast cell line (M), primary osteoblasts (M)	Yue et al.[90]
Osteosarcoma	METTL3	↑ proliferation, migration, invasion ↑ chemoresistance	*MCAM, HDAC5, LEF1* *LINC00520, TRIM7*	stability stability, translation	osteosarcoma cell line (H) osteosarcoma cell line (H)	Song et al.[91], Jiang et al.[92], and Miao et al.[93] Wei et al.[94] and Zhou et al.[95]
	METTL14	↑ proliferation, migration, invasion ↓ proliferation, migration, invasion	*MN1* *NA*	stability, translation NA	osteosarcoma cell line (H) osteosarcoma cell line (H)	Li et al.[96] Liu et al.[97]
	WTAP	↑ proliferation, migration, invasion	*HMBOX1, USP7*	stability	osteosarcoma cell line (H)	Chen et al.[98] and Yang et al.[99]
Bone marrow and blood						
Leukemia	METTL3	↑ proliferation ↓ cell differentiation, apoptosis ↑ chemoresistance, ↓ autophagy ↑ leukemogenesis	*c-MYC, BCL2, PTEN, NEAT1* *PTEN* *MDM2*	translation, expression stability stability	myeloid leukemia cell line (H) myeloid leukemia cell line (H) myeloid leukemia cell line (H)	Vu et al.[38] and Yao et al.[100] Lai et al.[101] Sang et al.[102]
	METTL14	↑ leukemogenesis	*MYB, MYC, TCP1, CYP1B1, CXCR4*	stability, translation, expression	leukemia mononuclear cell (H), myeloid leukemia cell line (H), bone marrow progenitor cell (M)	Weng et al.[103], Zhang et al.[104], and Li et al.[105]
	WTAP	↑ proliferation, migration, invasion ↓ apoptosis	*KDM4B, SUCLG2-AS1*	stability	myeloid leukemia cell line (H)	Shao et al.[106] and Liu et al.[107]
Myelodysplastic syndrome	METTL14	↑ proliferation	*SETBP1*	stability	bone marrow mononuclear cells (H)	Jiang et al.[108]
Digestive system						
Colorectal cancer	METTL3	↑ proliferation, invasion, migration ↑ glycolytic pathway ↑ angiogenesis ↑ chemoresistance	*CCNE, MYC, SOX2, CRB3* *SLC2A1, REG1α* *VEGFA* *RAD51, TRAF5*	stability stability stability expression, stability	colorectal cancer cell line (H) colorectal cancer cell line (H) colorectal cancer cell line (H) colorectal cancer cell line (H)	Zhu et al.[109], Xiang et al.[110], Li et al.[111], and Pan et al.[112] Shen et al.[113], Chen et al.[114], and Zhou et al.[115] Zhang et al.[116] and Liu et al.[117]

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
						Li et al.[118] and Lan et al.[119]
	METTL14	↓ proliferation, invasion, migration ↓ glycolysis ↓ chemoresistance	*NANOG, SCD1, ARRDC4* *pri-miR-6769b, pri-miR-499a* *pri-miR-17*	stability processing stability	colorectal cancer cell line (H) colorectal cancer cell line (H) colorectal cancer cell line (H)	Sun et al.[120], Xu et al.[121], and Wang et al.[122] Hou et al.[123] Sun et al.[124]
	WTAP	↑ proliferation, invasion, migration ↑ PANoptosis	*SNAI1, SOX1, VEGFA* *NLRP3, NRF2*	expression, stability expression, stability	colorectal cancer cell line (H) colorectal cancer cell line (H)	Han et al.[125], Tang et al.[126], and Ye et al.[127] Mo et al.[128] and Tan et al.[129]
Gastric cancer	METTL3	↑ proliferation, invasion, migration ↑ chemoresistance	*YAP1, HDGF, HBXIP, SMAD3* *PARP1, SUV39H2*	expression, stability stability	gastric cancer cell line (H), gastric cancer tissue (H, M) gastric cancer cell line (H)	Zhou et al.[130], Wang et al.[131], Yang et al.[132], and Yuan et al.[133] Li et al.[134] and Yang et al.[135]
	METTL14	↓ proliferation, invasion, migration ↓ chemoresistance	*LHPP, circORC5, TAF10* *circUGTT2*	expression, stability, sponging expression, sponging	gastric cancer cell line (H) gastric cancer cell line (H)	Lin et al.[136], Fan et al.[137], and Zhao et al.[138] Chen et al.[139]
	WTAP	↑ chemoresistance	*TGF-β*	stability	gastric cancer cell line (H)	Liu and Da[140]
Eye						
Macular degeneration	METTL3	↑ fibrosis	*HMGA2*	stability	retinal pigment epithelial cell (M)	Wang et al.[141]
Ocular melanoma	METTL14	↑ cell growth	*FAT4*	stability	ocular melanoma cell line (M)	Zhuang et al.[142]
Heart and blood vessels						
Aneurysm	METTL3	↑ matrix degradation, macrophage infiltration	*miR-34a*	miRNA processing	aortic smooth muscle cell (H)	Zhong et al.[143]
	METTL14	↑ ferroptosis	*ACSL4*	stability, translation	aortic smooth muscle cells (H, M)	Wang et al.[144]
	WTAP	↓ proliferation	*NA*	NA	brain microvascular endothelial cell	Yuan et al.[145]
Arrhythmia	METTL3	↑ sympathetic hyperactivity and remodeling	*TRAF6*	localization, expression	primary microglia (R), macrophage (R)	Yang et al.[146] and Qi et al.[147]
Atherosclerosis	METTL3	↑ cytokine signaling, pyroptosis ↑ proliferation, migration	*BRAF, H19, NLRP3, KLF4* *JAK2/STAT3*	stability, translation stability	primary macrophage (M), macrophage cell line (M), monocyte cell line (H), aortic endothelial cell (H, M) umbilical vein endothelial cell (H)	Li et al.[148], Xu et al.[149], and Chien et al.[150] Dong et al.[151]
	METTL14	↑ oxidative stress ↑ macrophage activation, foam cell formation ↓ cell viability, ↑ apoptosis	*circARHGAP12* *MYD88* *p65*	stability, expression stability stability	umbilical vein endothelial cell (H) macrophage cell line (H), BMDM (M) umbilical vein endothelial cell (H)	Min et al.[152] Zheng et al.[153] Liu et al.[154]

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
	WTAP	↑ pyroptosis	*NLRP3*	stability	macrophage cell line (M)	Luo et al.[155]
Cardiac valve degeneration	METTL3	↑ cytokine signaling	*TRPM4*	stability	monocyte cell line (H)	Wu et al.[156]
Congenital heart disease	METTL3	↓ apoptosis	*SH3BGR*	stability	cardiomyocyte cell line (H)	Shi et al.[157]
Heart Failure	METTL3	↑ cardiomyocyte hypertrophy ↑ fibrosis	*OTUD1* *TNC*	stability, translation stability	primary neonatal cardiac myocyte (R) cardiomyocyte cell line (H), cardiomyocyte (M)	Dorn et al.[158], Huang et al.[159], and Lu et al.[160] Cheng et al.[161]
	WTAP	↑ chromatin accessibility	*MEF2A, MEF2C*	transcription	cardiomyocyte (M)	Shi et al.[162]
Hypertension	METTL3	↑ endothelial dysfunction	*RUNX1*	stability	endothelial cell (M)	Zhang et al.[163]
Ischemic heart disease	METTL3	↑ fibrosis, apoptosis ↑ SMCs switching	*TNC, MetBil, DNA-PKcs* *PFN1*	stability, expression, post-transcriptional phosphorylation translation	cardiomyocyte (M), cardiomyocyte cell line (M), neonatal cardiac fibroblast (M) aorta smooth muscle cell (M, R)	Lu et al.[161], Zhuang et al.[164], Ma et al.[165], and Li et al.[166] Gao et al.[167]
	METTL14	↑ cell viability ↑ oxidative stress, apoptosis	*WNT1* *AKT/mTOR*	translation post-transcriptional phosphorylation	ventricular cardiomyocyte (M) primary neonatal cardiac myocyte (R), cardiomyocyte cell line (R)	Pang et al.[168] Wu et al.[169] and Wang et al.[170]
	WTAP	↑ apoptosis, ROS production	*ATF4, KLF6, SNHG1*	stability	cardiomyocyte cell line (H)	Wang et al.[171], Liu et al.[172], and Fang et al.[173]
Kidney						
Acute/chronic kidney disease	METTL3	↑ ferroptosis	*HO-1*	stability	renal tubular epithelial cell (M)	Lv et al.[174]
	METTL14	↑ ferroptosis	*LPCAT3, PPARγ*	stability	primary tubular epithelial cell (M)	Xu et al.[175] and Liu et al.[176]
	WTAP	↑ apoptosis, ferroptosis, mitochondrial dysfunction	*LMNB1*	stability, expression	renal proximal tubule cell line (H)	Huang et al.[177]
Kidney fibrosis	METTL3	↑ fibrosis, inflammation	*cGAS, STING1, TAB3, EVL*	stability, expression	primary kidney tubular cell (H), kidney tubular cell line (H)	Jung et al.[178], Tsai et al.[179], Wang et al.[180], and Ni et al.[181]
Renal cell carcinoma	METTL3	↑ proliferation, migration	*ACBD1, PLOD2*	translation	renal cell carcinoma cell line (H)	Chen et al.[182] and Shi et al.[183]
	METTL14	↑ glycolytic reprogramming ↑ proliferation, invasion, migration	*BPTF* *Lnc-LSG1*	stability LncRNA binding	renal cell carcinoma cell line (H, M) renal cell carcinoma cell line (H)	Zhang et al.[184] Shen et al.[185]
	WTAP	↑ proliferation	*TEX41, CDK2*	stability, decay	renal cell carcinoma cell line (H)	Zhou et al.[186] and Tang et al.[187]
Liver						
Hepatocellular carcinoma	METTL3	↑ proliferation, invasion, migration, stemness ↑ chemoresistance ↓ ferroptosis	*LIMA1, SOCS2* *SL7A11, USP15*	stability stability	hepatoma cell line (H) hepatoma cell line (H)	Zhang et al.[188] and Chen et al.[189] Zhang et al.[190] and Fang et al.[191]
	METTL14	↓ proliferation, invasion, migration ↓ glycolysis	*DGCR8* *USP48*	pri-miRNA processing stability	hepatoma cell line (H) hepatoma cell line (H), primary	Ma et al.[192] Du et al.[193]

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
		↓ chemoresistance ↑ ferroptosis	*CHOP* *SL7A11*	expression decay	hepatocyte (M) hepatoma cell line (H) hepatoma cell line (H)	Pan et al.[194] Fan et al.[195]
	WTAP	↑ immune evasion ↑ proliferation, migration, ferroptosis ↑ mitochondrial damage, lipid oxidation ↓ cancer progression	*PDL1* *ATG5* *NOA1, GPX4* *PSMB4, PSMB6*	stability translation expression expression	hepatoma cell line (H) hepatoma cell line (H) hepatoma cell line (H) primary hepatocyte (M)	Yu et al.[196] Li et al.[197] Liu et al.[198] Li et al.[199]
Liver Fibrosis	METTL3	↑ fibrosis	*LATS2*	stability, expression	hepatic stellate cell (M)	Li et al.[200]
	METTL14	↓ fibrosis	*NOVA2*	stability	hepatic stellate cell (H, M)	Hou et al.[201]
	WTAP	↑ lipid oxidation, proliferation, migration ↑ apoptosis	*ENPP1* *PTCH1*	translation stability	hepatic stellate cell (M) hepatic stellate cell (R)	Sun et al.[202] Wei et al.[203]
MASLD/NASH/NAFLD	METTL3	↑ macrophage metabolic reprogramming ↓ autophagy, clearance of lipid droplets ↓ hepatic free fatty acid uptake	*DDIT4* *RUBICON* *CD36, CCL2*	stability stability transcription	macrophage (M) hepatoma cell line (M) primary hepatocyte (M)	Qin et al.[204] Peng et al.[205] Li et al.[206]
	METTL14	↑ lipid production, insulin resistance ↑ mitochondrial dysfunction ↓ lipid accumulation, liver injury, and fibrosis	*SIRT1, ACLY, SCD1* *DGCR8* *GLS2*	expression pri-miRNA processing translation	primary hepatocyte (M), hepatocellular carcinoma tissue (H) primary hepatocyte (M) primary hepatocyte (M)	Zhou et al.[207] and Yang et al.[208] Wang et al.[209] Wang et al.[210]
	WTAP	↓ lipolysis, hepatic free fatty acid uptake	*IGFBP1, CD36, CCL2*	transcription	primary hepatocyte (M)	Li et al.[211]
Lung and respiratory system						
Acute respiratory distress syndrome	METTL3	↑ apoptosis ↓cytokine signaling	*MME* *TRIM59*	expression stability	alveolar epithelial cell (M), lung epithelial cell (M) lung microvascular endothelial cell (H)	Jia et al.[212] Chen et al.[213]
	METTL14	↑ inflammasome activation ↑ autophagy	*NRLP3* *THRIL*	decay stability	macrophage (M) alveolar epithelial cell (H)	Cao et al.[214] Shi et al.[215]
Asthma	METTL3	↓ autophagy	*PTX3*	stability, decay	monocyte cell line (H), BMDM (M)	Han et al.[216]
	METTL14	↓ proliferation, migration	*NA*	NA	bronchial epithelial cell (H)	Chen et al.[217]
	WTAP	↑ proliferation, migration	*AXIN1*	stability	airway smooth muscle cell (H)	Chen et al.[218]
Lung adenocarcinoma	METTL3	↑ proliferation ↓ ferroptosis ↑ autophagy	*PI3/AKT, SLC7A11, YAP1* *ATG5, ATG7*	stability, translation expression	NSCLC cell line (H), lung adenocarcinoma cell line (H) NSCLC cell line (H)	Xu et al.[219], Gao et al.[220], and Ni et al.[221] Liu et al.[222]
	METTL14	↑ glycolytic activity ↑ invasion, migration, proliferation	*G6PD* *CDC5L, AC026356.1*	stability expression	lung adenocarcinoma cell line (H) lung adenocarcinoma cell line (H)	Wu et al.[223] Yu et al.[224] and Zhang et al.[225]

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
	WTAP	↑ cell growth	*circEEF2, CANT1*	stability	lung adenocarcinoma cell line (H)	Zheng et al.[226]
Pulmonary fibrosis	METTL3	↑ fibroblast-to-myofibroblast transition	*KCNH6*	translation	normal fibroblast cell line (H)	Zheng et al.[227]
Pulmonary hypertension	METTL3	↑ proliferation, migration ↓ pyroptosis	*PTEN, RBPJ* *PTEN*	stability stability	pulmonary artery smooth muscle cell (M, R) pulmonary artery smooth muscle cell (M)	Du et al.[228] and Jiang et al.[229] Jiang et al.[229]
	METTL14	↑ proliferation, migration	*GRAP, MEIS1*	stability, decay, expression	pulmonary artery smooth muscle cell (H, R)	Liu et al.[230] and Yao et al.[231]
	WTAP	↑ proliferation ↑ apoptosis	*eIF2α* *IFI16*	expression stability	pulmonary artery smooth muscle cell (R) pulmonary artery smooth muscle cell (H)	Zhang et al.[232] Rao et al.[233]
Other organs and systemic autoimmune diseases						
Bladder cancer	METTL3	↑ proliferation, invasion, migration	*P3H4, SETD7, KLF4, CDCP1, ITGA6*	stability, decay, expression	bladder cancer cell line (H)	Liu et al.[234], Xie et al.[235], Ying et al.[236], and Jin et al.[237]
	METTL14	↑ proliferation, invasion, migration ↑ lipid metabolism	*USP38* *lncDBET*	stability stability	bladder cancer cell line (H) bladder cancer cell line (H)	Huang et al.[238] and Guimarães-Teixeira et al.[239] Liu et al.[240]
	WTAP	↑ proliferation, invasion, migration, ↓ ferroptosis ↑ chemoresistance	*PIGT, NRF2* *SYTL1, TNFAIP3*	stability decay	bladder cancer cell line (H) bladder cancer cell line (H)	Tan et al.[241] and Wang et al.[242] Wang et al.[243] and Wei et al.[244]
Breast cancer	METTL3	↑ proliferation, invasion, migration ↑ chemoresistance	*PD-L1, PRM7, BCL-2* *AK4, MALAT1, EGF*	stability, expression stability, expression, translation	breast cancer cell line (H, M) breast cancer cell line (H)	Wan et al.[245], Lu et al.[246], and Wang et al.[247] Liu et al.[248], Li et al.[249], and Li et al.[250]
	METTL14	↓ proliferation, invasion, migration ↑ proliferation, invasion, migration ↑ chemoresistance	*YAP1* *miR-146a-5p, USP22, Erα, LINC00882, miR-29c-3p* *E2F1*	decay expression, stability, miRNA processing stability	breast cancer cell line (H) breast cancer cell line (H), triple-negative breast cancer cell line (H) breast cancer cell line (H)	Bai et al.[251] and Gong et al.[252] Yi et al.[253], Zhuang et al.[254], Gao et al.[255], and Wu et al.[256] Liu et al.[257]
	WTAP	↑ proliferation, invasion, migration, ↓ ferroptosis	*MALAT1, EXOSC2, NUPR1, DLGAP1-AS1*	stability, expression	breast cancer cell line (H), triple-negative breast cancer cell line (H)	Zhao et al.[258], Lv et al.[259]. Tan et al.[260], and Huang et al.[261]
Melanoma	METTL3	↑ proliferation, invasion, migration ↑ chemoresistance	*SNHG3, UCK2, TXNDC5, MMP2* *EGFR*	stability, expression translation	malignant melanoma cell line (H) malignant melanoma cell line (H)	Chu et al.[262], Wu et al.[263], Yue et al.[264], and Dahal et al.[265] Bhattarai et al.[266]
Rheumatoid arthritis	METTL3		*AMIGO2, ICAM2*	stability, expression		

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Table 1. *Continued*

	RNA enzyme	Pathway	Target gene	Effect on target gene	Cell or tissue model	References
		↑ proliferation, migration, inflammation			primary fibroblast-like synoviocyte (H), fibroblast-like synoviocyte cell line (H)	Su et al.[267], Miao et al.[268], Chen et al.[269], and Shi et al.[270]
	METTL14	↓ cytokine signaling ↓ apoptosis, ↑ cell migration and invasion	*TNFAIP3* *LASP1*	decay, translocation stability	peripheral blood mononuclear cell (H) primary fibroblast-like synoviocyte (H)	Tang et al.[271] Li et al.[272]
	WTAP	↑ PANoptosis ↑ macrophage polarization	*TRAIL-DR4, NLRP3, MK5-AS1* *ETS1*	stability expression	fibroblast-like synoviocyte cell line (H) fibroblast-like synoviocyte cell line (H)	Cui et al.[273], Liu et al.[274], and Wen et al.[275] Wan et al.[276]
Systemic lupus erythematosus	METTL3	↑ immune cell infiltration	*IRF4*	expression	B lymphocyte cell line (H)	Liu et al.[277] and Lu et al.[278]
Pancreas						
Diabetes	METTL3	↑ proliferation, migration ↑ autophagy, senescence ↑ β cells dysfunction	*EGR1, PKC-η, FAT4, PDGFRA* *SIRT1* *GSIS, HDAC1*	expression, stability, decay expression, decay decay	umbilical vein endothelial cell (H), retinal pericyte (H), lens epithelial cell line (H) insulinoma β-cell line (M), pancreatic endocrine cell (M)	Tao et al.[279] and Suo et al.[280] Dong et al.[281] Cheng et al.[282], Wang et al.[283], and Sun et al.[284]
	METTL14	↓ insulin sensitivity in BAT ↑ cell viability ↑ cell differentiation ↑ renal lesions and renal fibrosis	*PTGSE2, CBR1, TRAIL, TNFR1* *NA* *FZD2* *TUG1*	stability, decay NA stability stability, expression	immortalized preadipocyte (H) pancreatic beta-cell line (M) intestinal epithelial stem cell (M) renal tubular epithelial cell (H)	Xiao et al.[285] and Xiao et al.[286] Zhou et al.[287] and Liu et al.[288] Kahraman et al.[289] and Shan et al.[290] Zheng et al.[291]
	WTAP	↑ mitochondrial dysfunction, PANoptosis, inflammasome ↑ hyperglycemia	*TRIM22, NEAT1, NLRP3* *PDX1*	stability, expression expression	renal tubular epithelial cell (H, M), corneal epithelial cell (H) insulinoma cell line (R), islet beta cell (M)	Zhang et al.[292], Guo et al.[293], and Lan et al.[294] Li et al.[295]
Pancreatic cancer	METTL3	↑ cell viability, proliferation, migration, invasion	*E2F5, DDX3, FBXO31, AREG, ID2*	stability	Pancreatic cancer cell line (H), hepatocellular carcinoma cell line (H), pancreatic duct epithelial cell line (H)	Tang et al.[296], Lin et al.[297], Chen et al.[298], Su et al.[299], and Chen et al.[300]
	METTL14	↑ proliferation, invasion, migration ↑ chemoresistance	*MYC, circSTX6, PERP* *CDA*	stability, expression stability	pancreatic cancer cell line (H), hepatocellular carcinoma cell line (H) pancreatic cancer cell line (H), hepatocellular carcinoma cell line (H)	Li et al.[301], Lu et al.[302], and Wang et al.[303] Zhang et al.[304]
	WTAP	↑ proliferation, stemness	*GBE1*	stability, expression	pancreatic cancer cell line (H), hepatocellular carcinoma cell line (H)	Jin et al.[305]

This table was created using the MESH term {"enzyme" and "disease"} in PubMed, last accessed February 7, 2025.
BMDM, bone marrow mononuclear macrophages; H, human; M, mouse; R, rat.

Table 2. Small molecule inhibitor against METTL3 (STM2457)

Disease	Model	Effect of STM2457 on disease outcome	Pathways affected by Mettl3 inhibition	Effect of Mettl3 inhibition on target transcript	Reference
Osteosarcoma	human osteosarcoma (MNNG/HOS) cell line primary human osteosarcoma cells MNNG/HOS cells implant in BALB/c nude mice	↑ cell death/apoptosis in *vitro* ↓ tumor growth in xenografted mice no systemic toxicity, ↔body weight	↑ apoptosis	↑ BAX, Cl.cas3, CASP1 expression ↓ BCL2 expression ↓ ZBTB7C expression	An et al.[321]
Colorectal cancer	murine CRC cell lines (CT26, MC38) male immunocompetent C57BL/6 mice engrafted with MC38/CT26 cells	↓ tumor growth synergy with anti-pd1: ↓tumor growth ↑ t cell infiltration of the tumors ↓ circulating myeloid-derived suppressor cells	n/a	↓BHLHE41 translation efficiency	Chen et al.[322]
Renal cell carcinoma	renal cell carcinoma (ACHN cell) xenograft mouse model	↓tumor growth	n/a	↓ PLOD2 translation efficiency	
Intrahepatic cholangiocarcinoma	HCCC-9810 and HuCC-T1 cells HuCC-T1 mouse allografts	*in vitro*: ↓proliferation, ↑ apoptosis and synergy with gemcitabine *in vitro* *in vivo*: ↓ tumor growth, ↓cell proliferation and angiogenesis, synergy with gemcitabine	↓ glycolysis	↓ NFAT5 transcript stability through decreased IGF2BP1 -binding	Gao et al.[323]
Acute lung injury (LPS-induced)	MLE-12 cells mice treated with intratracheal LPS	↓ LPS-induced cell apoptosis *in vitro* ↓inflammatory cell infiltration, intra-alveolar edema, alveolar hemorrhage, and cell apoptosis	n/a	↑ neprilysin mRNA stability	Jia et al.[212]
Kidney fibrosis	HK-2 cells, NRK49F cells unilateral ureteral obstruction mouse model	↓ cellular mesenchymal transition/ECM gene expression *in vitro* ↓extent of fibrosis *in vivo*	↓TGF-b pathway	↓*NET1* transcript stability	Jung et al.[178]
Insulin resistance	HepG2 cells high fat diet-fed C57BL/6 mice	↓high fat diet-induced insulin resistance	↑insulin signaling (p-IRS)	↓CYP2B6 expression	Li et al.[324]
Oral squamous cell carcinoma	HSC3, SCC9, SCC15, and SCC25 cell lines Huh-7 xenografts in BALB/c nude mice	↑ cell-cycle blockade and apoptosis, and ↓ migration of oscc cells synergistic effect with anlotinib: ↓ migration, ↓ colony formation, ↓ stemness and ↑ apoptosis of oscc cells *in vitro* ↓ tumor cell proliferation and growth *in vivo* synergy with anlotinib *in vivo*	↓EMT	↓EGFR protein levels	Liu et al.[325]
Hepatocellular carcinoma	Huh-7, HepG2, Hep3B, PLC/PRF5 and BEL-7404cells Huh7 xenografts in Balb/c nude mice	↓cell viability, ↑ cell-cycle arrest and ↑apoptosis *in vitro* ↓ spheroid formation and ↑cell death *in vitro* ↓tumor growth *in vivo*	↓MAPK-ERK signaling	↑ DUSP5 and SPRY2 expression	Liu et al.[326]
Non-alcoholic fatty liver disease-associated	HKCI2 cells orthotopic Hepa1-6 cells incubated in NASH liver of C57BL/6 mice	↓tumor growth *in vivo* ↑ percentage of IFN-γ^+ and GZMB$^+$ CD8$^+$ T cells in NAFLD-HCC tumors synergistic effect with anti-PD1 *in vivo*	↓ cholesterol biosynthesis	↓SCAP translation efficiency through ↓ YTHDC1-binding	Pan et al.[327]
Small cell lung cancer	H69, H69AR, H446 and H446DDP cell lines SCLC xenografts in BALB/C nude mice	↑apoptosis *in vitro* additive effect on chemotherapy leading to ↓tumor growth rate and ↓ tumor size *in vivo*	↓ mitophagy	↓ *DCP2* degradation	Sun et al.[328]
Hepatocellular carcinoma	MHCC97H and Huh7-LR cells MHCC97H cell xenografts in nude mice	↓cell growth and colony formation and ↑ apoptosis *in vitro* synergistic effect with lenvatinib (VEGFR	n/a	↓ EGFR translation efficiency	Wang et al.[329]

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Table 2. *Continued*

Disease	Model	Effect of STM2457 on disease outcome	Pathways affected by Mettl3 inhibition	Effect of Mettl3 inhibition on target transcript	Reference
	Hepa1-6 cells injected into left lobes of the livers of male C57BL/6 mice	inhibitor) *in vitro* synergistic effect with lenvatinib:↓ tumor cell proliferation and ↑ apoptosis leading to ↓tumor volume and weight in xenografts *in vivo* ↑sensitivity of Hepa1-6 orthotopic mouse HCC model to lenvatinib			
Corneal neovascularization	HUVECs, 3 T3 cells and HSV-1 F strain BALB/c mice	↓tube formation and migration of HSV-1-infected HUVECs ↓corneal neovascular length *in vivo*	↓ Wnt pathway and angiogenesis	↓ LRP6 expression	Wang et al.[330]
Doxorubicin-induced cardiotoxicity	HL-1 cardiomyocytes C57BL/6J mice treated with doxorubicin	↓ DOX-evoked cell death and LDH release *in vitro* ↓DOX-evoked adverse cardiac remodeling (LVEF, LVSF, interstitial fibrosis, plasma *c*TnT levels, heart size and weight) *in vivo*	↓ferroptosis	↓ *TFRC* transcript stability (IGF2BP2-dependent)	Wu et al.[331]
Non-small cell lung cancer	A549 & H1975 cells A549 xenografts in nude mice	↓ proliferation, migration, invasion and ↑ apoptosis in A549 & H1975 cells ↓colonization and progression of cancer *in vivo*	n/a	↑ translation efficiency of PD-L1	Xiao et al.[332]
Intrahepatic cholangiocarcinoma	HuCC-T1 and HCCC-9810 cells	↓proliferation, cell invasion, ↑cell-cycle arrest & apoptosis in ICC cells	n/a	↑ *IFIT2* transcript stability (YTHDF2-dependent)	Xu et al.[333]
Acute myeloid leukemia	primary murine acute myeloid leukemia, MOLM-13 cells human acute myeloid leukemia patient-derived xenografts primary murine MLL-AF9/Flt3$^{Itd/+}$ AML model	↓clonogenic potential of primary murine acute myeloid leukemia cells but no effect on normal human cord blood CD34+ cells or HSPCs ↑myeloid differentiation and cell-cycle arrest in MOLM-13 & primary murine AML cells ↑ apoptosis in mouse & human AML cells, no effect on normal cells ↓AML engraftment and expansion, ↑survival in an AML patient-derived xenografts and in the primary murine MLL-AF9/Flt3Itd/+ AML model ↓ self-renewal of leukemic stem cells *in vivo* ↑mouse survival and ↓presence of AML cells in peripheral blood in re-transplantation experiments no effect on mouse body weight	n/a	↓SP1 and BRD4 protein levels	Yankova et al.[320]
Medulloblastoma	Daoy and ONS-76 cell lines patient-derived SHH-MB cell line	↓ cell viability of cancer cells, smaller effect on normal cerebellar neurons	↓ Sonic Hedgehog signaling	↑ PTCH1 transcript stability ↓ GLI2 translation efficiency	Zhang et al.[334]
Epstein-Barr virus (EBV)	BJAB cells Primary B and T cells (isolated from PBMCs)	↑EBV copy numbers in BJAB cells ↓TLR-9-agonist-induced B cell proliferation, immunoglobulin & IL-6/IL-8 secretion ↓CD107a and IFN-γ expression in CD4+ and CD8+ T cells ↓ apoptosis of BJAB cells co-cultured with T cells	↓ TLR-9 pathway	↓TLR9 transcript stability	Zhang et al.[335]
Human cytomegalovirus (HCMV) infection	HAECs and HUVECs Female C57BL/6 mice	↓ pyroptosis of HCMV-infected endothelial cells *in vitro* ↓ endothelial damage in HCMV-infected mice *in vivo*	↓ AIM-2 inflammasome activation & pyroptosis	↑ UCHL1 transcript stability (HNRNPD-dependent)	Zhu et al.[336]

affected key signaling cascades and cellular processes including, among others, STAT3 translation,[340] MAPK signaling,[326] Hedgehog signaling,[334] TNF and Hippo signaling,[332] as well as mitophagy,[328] pyroptosis[336] and ferroptosis.[331]

Beyond its effects in multiple types of cancer, STM2457 has also shown promise in ameliorating metabolic, inflammatory and fibrotic tissue damage across a wide range of diseases, including metabolic syndrome-associated insulin resistance,[324] acute respiratory distress syndrome,[212] and kidney fibrosis,[178] as well as endothelial damage[336] and pathological neoangiogenesis[330] induced by viral infections. Additionally, STM2457 treatment showed immunoregulatory functions since it limited aberrant T cell activation and polarization toward a proinflammatory Th1 phenotype in experimental models of allograft rejection.[341]

Finally, preclinical studies have established an important role of METTL3 in the development and persistence of AML.[38,306,342] Treatment with STM2457 resulted in dose-dependent growth inhibition of multiple AML cells, accompanied by cell-cycle arrest and induction of apoptosis, while it reduced their clonogenic potential, and promoted cell differentiation.[320] In contrast, STM2457 treatment had no effect on normal hematopoietic cells.[320] More importantly, STM2457 showed clinical efficacy in human AML patient-derived xenografts and in the primary murine *MLL-AF9/Flt3*$^{Itd/+}$ AML model, where it impaired the engraftment and expansion of AML and prolonged the mouse lifespan, while showing no systematic toxicity.[320] Initial STM2457 treatment decreased the number of circulating AML cells in re-transplantation experiments, suggesting a potential effect of the drug in preventing relapse,[320] an observation with potential clinical significance for the achievement of prolonged disease remission in the clinical setting, that remains to be validated in longer-term follow-up in clinical studies. Moreover, STM2457 treatment was also able to restore sensitivity to Adriamycin in human AML cells.[343] These promising preclinical results, along with a thorough toxicity screening,[320] have supported the development of a phase 1 clinical trial in AML and other advanced malignancies using a chemically modified, more potent version of STM2457, namely STC-15 (NCT05584111).

Small molecules targeting METTL14

METTL14 lacks a functional catalytic domain, and is an allosteric activator of the enzymatic activity of METTL3.[30,317] Its role is largely non-enzymatic, making it difficult to target with small molecule inhibitors, as drug development typically focuses on enzymatic active sites.[317] The tight interaction and interdependence between METTL14 and METTL3 further complicate the development of specific inhibitors that target METTL14 without affecting METTL3, as disrupting this interaction could destabilize the entire complex, leading to off-target effects.[316] This functional redundancy reduces the incentive to develop METTL14-specific inhibitors, as inhibitors of METTL3 indirectly affect the entire METTL3-METTL14 complex.[320] Given its structural role, targeting METTL14 may require innovative approaches, such as disrupting its interaction with METTL3 through allosteric strategy,[344] proteolysis targeting chimeras,[345] or using RNA-based therapeutics to modulate its function indirectly.

Small molecules targeting FTO

The discovery of the demethylating activity of fat mass and obesity-associated protein (FTO) in 2011[346] followed by the discovery of the second m6A demethylase, ALKBH5, underlined the reversibility and fine-tuning of m6A in the human organism[30,347] (Table S2). Structure-based virtual screening and biochemical analyses allowed the identification of multiple chemical FTO inhibitors.[348] Rhein, a competitive inhibitor of substrate binding, has been shown to limit viability of multiple leukemia cell lines *in vitro*, as well as inhibit tumor growth *in vivo*, without showing toxicity, while it also restored sensitivity to the kinase inhibitor nilotinib.[349] Of interest, the widely used non-steroidal anti-inflammatory drug meclofenamic acid was also later shown to inhibit FTO's activity through competitive substrate binding[350] enabling the development of multiple derivatives with much higher efficacy in FTO inhibition, including FB23-2 and Dac51.[351] Both compounds have been utilized in multiple *in vivo* studies showing anti-tumoral activity in models of AML,[352] melanoma,[353] and different types of solid tumors, such as uterine leiomyosarcoma,[354] nasopharyngeal carcinoma,[355] glioblastoma,[59] and clear cell renal cell carcinoma[356] (Table 3; Figure S2), without showing systemic toxicity. Overall, FB23-2 and Dac51 promoted cell-cycle arrest and apoptosis of cancer cells, which was often accompanied by increased DNA damage accumulation (Table 3). Functionally, FTO inhibitors limited the invasion and migration of cancer cells (Table 3). Moreover, FB23-2-treated AML cell lines and primary patient-derived cells showed reduced self-renewal and were skewed toward more differentiated cell states.[352] Similar effects were observed when AML cells were treated with R-2HG,[361] a small molecule that competes both 2-oxoglutarate (2OG) and substrate binding to FTO,[351] as well as by treatment with CS1 and CS2,[357] two newly identified FTO inhibitors. These cellular effects led to the delay of tumor growth *in vivo* and prolonged the survival of different cancer mouse models (Table 3). Of interest, Dac51 treatment of melanoma cells also led to increased tumor infiltration by T lymphocytes and enhanced cytokine release,[353] offering another mechanistic aspect. More importantly, FB23-2 or Dac51 treatment showed synergistic action with anti-PD1 in melanoma[353] and sensitized cells to radiotherapy in nasopharyngeal carcinoma,[355] while CS1/CS2 treatment sensitized AML cells to demethylating agents,[357] highlighting the additive value of FTO inhibitors when combined with currently approved therapies. Beyond cancer, FB23-2 has been shown to reduce glucose-induced activation of endothelial cells which may affect diabetic retinopathy,[358] and other diabetic complications, as well as to limit osteoclast differentiation and reduce bone loss in models of periodontitis.[359] On the contrary, FB23-2 treatment increased intra-orbital inflammation and aggravated autoimmune anterior uveitis.[360] FTO inhibitors, either alone or in combination with standard chemotherapeutic agents, hold promise as effective treatments for multiple types of cancer, particularly in cases with high FTO expression. However, none of the currently known FTO inhibitors appear to be

Table 3. Small molecule inhibitors of m6A demethylases

FTO inhibitors

Compound	Disease	Model	Effect of m6A demethylase inhibitors on disease outcome	Pathways affected by m6A demethylase inhibition	Effect of m6A demethylase inhibition on target transcript	Reference
CS1, CS2	acute myeloid leukemia	primary human acute myeloid leukemia cells patient-derived xenotransplantation (PDX) AML model	↓viability of primary human leukemia cells, no effect on normal cells *in vitro* ↑ cell-cycle arrest & apoptosis, ↑ myeloid differentiation in human AML cells *in vitro* ↓leukemia infiltration and ↑ mouse survival *in vivo* synergistic effect with T cell treatment or demethylating agents *in vivo*	↓ immune checkpoint inhibition (PD-L1, PD-L2, LILRB4)	↓ LILRB4 transcript stability (YTHDF2-dependent)	Su et al.[357]
Dac51	melanoma	mouse T cells, B16-OVA melanoma cells B16-OVA and MC38 xenografts in C57BL/6 mice	↑ cytokine release and cytotoxic capacity of T cells co-cultured with Dac51-pretreated B16-OVA melanoma cells ↓ tumor growth, ↑ tumor infiltrating $CD8^+$ T cells and IFN-γ *in vivo* synergistic effect with anti-PD1 *in vivo* (↓ tumor growth, ↓ cancer relapse, ↑ survival)	↓ glycolysis	↓Jun, Junb, and Cebpb transcript stability (YTHDF2-dependent)	Liu et al.[353]
Dac51	uterine leiomyosarcoma	SK-UT-1 cells	↓ proliferation, cell-cycle arrest	n/a	n/a	Yang et al.[354]
FB23-2	diabetic retinopathy	HUVECs oxygen-induced retinopathy mouse model	↓ high glucose-induced proliferation, migration and tube formation in HUVECs. ↓ neovascular tufts formation *in vivo* without signs of systemic toxicity.		↓ CDK2 transcript stability (YTHDF2-dependent)	Chen et al.[358]
FB23-2	periodontitis	RAW 264.7 & mouse bone marrow cells differentiated toward osteoclast experimental periodontitis mouse model	↑ markers of DNA damage, cell-cycle arrest, ↓proliferation and ↑ apoptosis *in vitro* prevention of the transformation of osteoclast precursor cells into osteoclasts and ↓bone-resorbing capacity. ↓osteoclastogenesis and bone resorption *in vivo*	↑ DNA damage response (↑ *p*-Chk2, p-p53, ↑ γ-H2Ax)	↓ CDK2 and Cyclin A2 transcript stability (YTHDF2-dependent)	He et al.[359]
FB23-2	uveitis	HMC3 & primary mouse microglial cells experimental autoimmune uveitis mouse model	↑ migration of primary microglial cells *in vitro* ↑ clinical & histological severity of uveitis by intravitreal injection	↑ GPC4/TLR-4/NF-kB pathway activation	↑ GPC4 transcript stability	He et al.[360]
FB23-2	Acute myeloid leukemia	multiple murine & human acute myeloid leukemia cell lines MONOMAC6 and patient-derived acute myeloid	↓ proliferation of murine acute myeloid leukemia cells, no effect on proliferation of healthy bone marrow cells ↑ cell-cycle arrest & apoptosis of	n/a	↓ MYC and CEBPA expression	Huang et al.[352]

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Table 3. *Continued*

FTO inhibitors						
Compound	Disease	Model	Effect of m6A demethylase inhibitors on disease outcome	Pathways affected by m6A demethylase inhibition	Effect of m6A demethylase inhibition on target transcript	Reference
		leukemia xenotransplantation in NSGS mice	acute myeloid leukemia cells ↑ myeloid differentiation of acute myeloid leukemia cells *in vitro* & *in vivo* delayed disease progression, ↑ survival in acute myeloid leukemia mice ↓ liver/spleen enlargement and leukemia stem cell number prevented re-implantation no systemic toxic effects			
FB23-2	nasopharyngeal carcinoma	C666-1R and HONE1R cell lines HONE1R xenografts in BALB/C nude mice	↑ DNA damage and sensitization to irradiation *in vitro* ↑ DNA damage & ↓ proliferation of irradiated cancer cells *in vivo* ↓tumor growth and ↑ sensitivity to radiotherapy *in vivo*	↑lipid peroxidation and ferroptosis	↓ OTUB1 expression	Huang et al.[355]
FB23-2	clear cell renal cell carcinoma (ccRCC)	clear cell renal cell carcinoma cell lines patient-derived xenograft mouse model	↓ tumor growth, ↓ cancer cell proliferation and ↑ survival *in vivo*	↑ autophagy	↑SIK2 mRNA stability (IGF2BP2-dependent)	Xu et al.[356]
MA2	glioblastoma	multiple GSC cell lines PBT003 xeno-transplants in NSG mice	↓ growth and self-renewal of multiple glioblastoma stem cell lines *in vitro*, no effect on normal neural stem cells, brain astrocytes, or HeLa cells ↓ glioblastoma stem cell-induced tumorigenesis (↓ tumor size) and ↑ survival *in vivo*	n/a	n/a	Cui et al.[59]
R-2HG	acute myeloid leukemia	multiple human leukemia cell lines primary human acute myeloid leukemia cells human acute myeloid leukemia cell xenotransplantation in NSGS mice	↓ proliferation and viability,↑ cell-cycle arrest and apoptosis *in vitro* ↓colony formation and viability of primary human AML cells ↓ acute myeloid leukemia progression and burden and ↑ survival *in vivo* synergy with chemotherapeutics *in vivo*	n/a	↓MYC & CEBPA transcript stability (YTHDF2-dependent)	Su et al.[361]
Rhein	acute myeloid leukemia/ chronic myelogenous leukemia	K562, KU812 cells patient-derived acute/ chronic myeloid leukemia cells nilotinib-resistant K562 xenografts in nude mice	synergy with nilotinib and PKC412 *in vitro* (↓ cell viability and colony formation) synergy with nilotinib *in vivo* (↓ tumor growth, ↓ cancer cell proliferation)	n/a	↓ transcript stability (YTHDF2-dependent) and ↓ translation efficiency of MERTK and BCL2	Yan et al.[349]

(*Continued on next page*)

Table 3. *Continued*

FTO inhibitors						
Compound	Disease	Model	Effect of m6A demethylase inhibitors on disease outcome	Pathways affected by m6A demethylase inhibition	Effect of m6A demethylase inhibition on target transcript	Reference
			restoration of sensitivity to nilotinib in primary patient cells *ex vivo*			
Rhein	coronavirus infection	Vero cells	dose-dependent inhibition of cell infectivity	n/a	n/a	Zannella et al.[362]
ALKBH5 inhibitors						
DDO-2728	acute myeloid leukemia	MV4-11, MOLM-13 cells MV4-11 xenograft tumor mouse model	cell-cycle arrest, ↓ proliferation and ↑ apoptosis of AML cells *in vitro* ↓ tumor growth, no systemic toxicity	n/a	↓ TACC3 transcript stability (AML-specific)	Wang et al.[363]
ALK-04	Melanoma	CT26 (colorectal cancer) cells B16 melanoma cells B16 mouse xenografts	↓ tumor growth synergy with anti-PD-1 and GVAX immunotherapy *in vivo*	↓ lactate	↓ Mct4 transcript stability	Li et al.[364]
IOX1	Glioblastoma	U251 cells GL261 xenografts in NOD-SCID or C57BL/6J mice	↓ tumor growth, ↑ survival *in vivo* synergy with anti-PD1 immunotherapy *in vivo* (↑ survival)	n/a	↓ ZDHHC3 transcript stability (YTHDF2-dependent)	Tang et al.[365]
IOX1	acute kidney injury	ischemia-reperfusion (I/R)-induced acute kidney injury mouse model	↓ I/R-induced kidney injury (↓ creatinine, BUN, tissue damage) reprogramming of renal leukocyte infiltrate toward anti-inflammatory profile (↑ Tregs, ↓ neutrophils and macrophages)	n/a	↑Ccl28 transcript stability (IGF2BP2-dependent)	Chen et al.[366]

clinically viable due to their limited efficacy. Therefore, there is a need to develop more potent FTO inhibitors that can serve as valuable tools for studying the biological roles of FTO in both normal and cancer cells, as well as in other diseases driven by FTO activity.

Small molecules targeting ALKBH5

ALKBH5, like FTO, is a member of the 2OG and ferrous iron-dependent nucleic acid oxygenase superfamily.[367] Several inhibitors of ALKBH5 have been identified through high-throughput screening, virtual screening, and structure-based drug design (Table 3).[368–370] Broad-spectrum 2OG-dependent oxygenase inhibitors, such as NOG, PDCA, and IOX3, weakly inhibit ALKBH5 activity by competing with 2OG at the active site.[371] IOX1, a competitive 2OG inhibitor, has demonstrated protective effects against ischemic injury in kidney[366] and the heart tissue,[372] partly through regulating inflammatory cell infiltration.[366] Furthermore, pharmacological inhibition of ALKBH5 with IOX1 enhances the therapeutic efficacy of anti-PD-1 treatment in preclinical glioma mouse models.[365] ALK-04 has also been shown to enhance immunotherapy efficacy when combined with GVAX and PD-1 antibodies,[364] by inhibiting the infiltration of Treg cells and myeloid-derived suppressor cells in tumor tissue.[364] Alternative strategies to specifically inhibit the demethylation activity of ALKBH5 are being developed. DDO-2728 binds to ALKBH5 by occupying the m6A-binding pocket. It suppresses tumor growth in the MV4-11 xenograft mouse model of AML and demonstrates a favorable safety profile.[363] TD19, a covalent inhibitor targeting specific cysteine residues in ALKBH5 without affecting FTO, exhibits strong anti-oncogenic efficacy in AML and glioblastoma multiforme cell lines.[373] Ena15 and Ena21 are two additional ALKBH5 inhibitors. Ena21 acts as a selective competitive inhibitor by competing with 2OG at the active site, while Ena15 is a non-competitive inhibitor. Both compounds have demonstrated the ability to inhibit proliferation of glioblastoma multiforme-derived cell lines.[374] Although these inhibitors exhibit good *in vitro* activity against ALKBH5, they generally lack high selectivity compared with FTO and potency *in vivo* since cancer cells treated with ALKBH5 inhibitors do not recapitulate the phenotype of ALKBH5-silenced cells, highlighting the challenges in designing potent and selective inhibitors for this enzyme.

Small molecules targeting m6A readers

The development of small molecule inhibitors targeting m6A readers is emerging as a promising strategy for treating various malignancies (Table S3). IGF2BP is a family of RNA-binding proteins highly expressed in cancerous tissues, playing a pivotal role in tumor initiation and progression.[375] As a result, IGF2BPs represent promising candidates for clinical applications. BTYNB, an IGF2BP1 inhibitor, reduced colony formation in ovarian cancer and melanoma cells by downregulating oncogenic targets such as c-Myc and eEF2.[376] Cucurbitacin B, an allosteric IGF2BP1 regulator, reduced tumor volume in hepatocellular carcinoma models while enhancing $CD4^+$/$CD8^+$ T cell infiltration and reducing PD-L1 expression, potentially alleviating immunosuppression.[377] Other IGF2BP family inhibitors have also shown antitumor activity. JX5, a novel IGF2BP2 inhibitor that binds to the KH3-4 domains, exhibited strong cytotoxic effects in Jurkat cells overexpressing IGF2BP2 while sparing those with normal expression, indicating a selective effect.[378] In T cell acute lymphoblastic leukemia xenograft mouse models, intraperitoneal JX5 administration reduced leukemia burden by decreasing $CD45^+$ cell engraftment in bone marrow and spleen without showing gastrointestinal or systemic toxicity.[378] Similarly, CWI1-2, another IGF2BP2 inhibitor, demonstrated significant anti-leukemic effects in AML, particularly in $CD34^+$ hematopoietic progenitor cells with high IGF2BP2 expression.[379] CWI1-2 promoted differentiation and apoptosis by downregulating glutamine metabolism genes, and reducing ATP production, while it showed good therapeutic efficacy and no systemic toxicity *in vivo*.[379] YTHDF is a class of proteins abnormally expressed in several cancers, acting generally as an oncogenic factor by driving cancer cell proliferation and drug resistance.[380] Tegaserod, targeting YTHDF1, induced G1-phase arrest and apoptosis in AML-derived $CD34^+$ cells while impairing leukemia stem cell renewal with promising results in AML xenograft models.[381] DC-Y13-27, a selective YTHDF2 inhibitor, showed efficacy in *in vivo* models of melanoma and colorectal carcinoma[382] and synergistic action with ionizing radiation and anti-PD-L1 immunotherapy through increased $CD8^+$ T cell infiltration of tumor tissues.[382] While promising preclinical results are emerging, small molecules targeting m6A readers are still in early development and face challenges in activity and selectivity. Considering the significant role of readers in regulating the effect of m6A on target transcripts, they hold strong therapeutic potential and require deeper investigation.

CRISPR-based tools for targeted m6A methylation and demethylation

Given that m6A modifications at different sites within the same transcript can have opposing effects, i.e., m6A in the 5′ untranslated region (UTR) suppresses transcription while m6A in the 3′ UTR enhances transcript stability, global inhibition or activation of m6A enzymes may lead to unpredictable outcomes.[383] Moreover, factors such as the local secondary structure of the transcript, subcellular localization, and the availability of reader proteins might influence m6A reader binding and consequently affect transcript stability and translation efficiency of the methylated transcript. Therefore, developing methods for precise, temporal, and transcript/locus-specific m6A editing is crucial for understanding its dynamic and context-dependent functions. CRISPR-based tools have been engineered to edit mRNA m6A modifications at single-base resolution. dCas13 fusions with a truncated METTL3 methyltransferase domain localized in the nucleus, as well as dCas13 fusions with a modified METTL3:METTL14 methyltransferase complex localized in the cytoplasm have been created.[384] These tools enable site-specific m6A incorporation in distinct cellular compartments. *In vitro* studies have demonstrated their high specificity, minimal off-target effects, and ability to induce m6A-mediated changes in transcript abundance and alternative splicing.[384] Further advancements have led to chemically and light-inducible, reversible m6A editing platforms that allow transient, site-specific m6A modifications.[385] Given the dynamic and reversible nature of m6A, CRISPR-based tools for targeted m6A demethylation of specific transcripts or even specific m6A sites have also been developed. The

dm6ACRISPR system, a fusion of a catalytically inactive Type VI-B Cas13 enzyme with ALKBH5, enables precise demethylation of m6A sites in specific mRNAs such as *CYB5A* and *CTNNB1*, leading to transcript stabilization and enhanced translation with minimal off-target effects.[386] An important clinical application of this technology is the demethylation of oncogenic transcripts, such as *EGFR* and *MYC*, resulting in suppressed cancer cell proliferation.[386] Similarly, a dCas13b-FTO demethylation system has been designed, which specifically demethylated the *Tgfb1* 5′ UTR, stabilizing the transcript and enhancing Tgfb1-Smad2 signaling in goat primary myoblasts.[387] To mitigate potential issues associated with constitutively expressed CRISPR-RNA editing enzymes, an inducible m6A demethylation platform (FKBP*-dCas13b-ALK) was developed, allowing time-specific and transient m6A demethylation via the addition or removal of the Shield-1 molecule.[388]

THERAPEUTIC MANIPULATION OF THE A-TO-I RNA EDITING MACHINERY

RNA editing function in health and disease

A-to-I RNA editing is induced by ADARs, which act on dsRNA to catalyze the site-specific deamination of adenosine to inosine.[389] Due to their chemical similarity, inosine is recognized by the cellular machinery as guanosine, leading to the disruption of dsRNA structures and thereby modulating RNA metabolism (Figure 1).[8,390–394] Three mammal ADAR enzymes have been described. ADAR1 and ADAR2 are responsible for catalyzing A-to-I RNA editing in various target RNAs and are highly conserved across nearly all metazoans.[395] ADAR3, on the other hand, lacks enzymatic editing activity and is exclusively expressed in the brain, where it competes with ADAR2 for binding to *GRIA2* pre-mRNA.[396]

ADAR1 is essential for life, as its global deletion in mice results in embryonic lethality marked by widespread apoptosis, defective hematopoiesis, and a strong induction of type I interferon signaling.[397–399] Similarly, ADAR1 is essential for the maintenance of homeostasis as its cell-specific deletion in vascular beds in adult animals leads to sudden death.[400,401] ADAR1 has two isoforms: the nuclear ADAR1p110 and the primarily cytoplasmic, interferon-inducible ADAR1p150.[402] The two ADAR1 isoforms exhibit distinct, complementary roles during embryonic development. ADAR1p110 is essential for the normal development of multiple organs including the kidneys and brain, while the longer ADAR1p150 isoform is essential for normal intestinal homeostasis and B cell development.[403] In the absence of ADAR1, the innate immune sensor MDA5 senses endogenous dsRNA and activates the adaptor protein MAVS, leading to the phosphorylation of the transcription factor IRF3 and increasing the expression of type I interferons and interferon-stimulated genes.[403–405] In parallel, the dsRNA sensor PKR mediates the phosphorylation of eIF2α, resulting in translational inhibition and the activation of the ATF4-mediated integrated stress response.[406,407] Moreover, accumulation of endogenous Z-DNA-RNA hybrids may activate Z-DNA binding protein 1 (ZBP1). ZBP1 binds to endogenous Z-RNA, a left-handed dsRNA conformation, leading to RIPK1–FADD–caspase 8-dependent apoptosis, MLKL-dependent necroptosis, and NLRP3–GSDMD-dependent pyroptosis.[408–410] While ADAR1 has been established as a key suppressor of autoinflammatory interferonopathy, there are still outstanding questions regarding the role played by endogenous dsRNAs and their editing in this process.[411]

Loss-of-function mutations in ADAR1 are associated with Aicardi-Goutières syndrome, a severe autoinflammatory disorder, characterized by increased type I interferon signaling.[412] On the other hand, ADAR1 tends to be overexpressed in several diseases affecting tissue-specific gene expression and disease progression (Table 4). Increased ADAR1 expression and enhanced RNA editing activity have shown promise as prognostic biomarkers in multiple types of cancer, being inversely associated with the long-term survival of patients.[394,486–489] For instance, ADAR1 hyper-editing of *AZIN1* mRNA in HCC, leads to its nuclear translocation, promoting cancer cell proliferation and tumor progression by neutralizing antizyme-mediated degradation of ODC and CCND1.[450,490,491] Several preclinical models have shown that cell-specific genetic knockout of *Adar* protects against tumor growth and metastasis, in solid tumors and multiple types of leukemia (Figure 2; Table S1). From a mechanistic aspect, innate immune activation in the absence of ADAR1 makes cancer cells more vulnerable to immune checkpoint inhibition, chemotherapy, and irradiation.[492] Therefore, targeted inhibition of ADAR1 enhances the efficacy of tumor immunotherapy by increasing MDA5/PKR-mediated dsRNA sensing or improving ZBP1-dependent necrosis.[493,494] ADAR1-mediated RNA editing is also involved in the pathogenesis of prevalent non-communicable diseases beyond cancer, controlling immune responses in chronic inflammatory diseases (Table 4). In contrast, ADAR1 exerts a protective role in aging through HuR-mediated stabilization of the anti-aging sirtuin SIRT1 and subsequent suppression of the translation of p16INK4a mRNA, ultimately preventing cellular senescence.[19] The multifaceted role of ADAR1 in disease suggests that its modulation could serve as a promising therapeutic strategy across various malignancies and immune-related disorders.

To date, most studies have focused on the role of ADAR1 in homeostasis and disease, because it is responsible for the vast majority of RNA editing events. The second member of the ADAR family, ADAR2, was initially thought to function only in the central nervous system, where it catalyzes exonic RNA editing of the glutamate receptor (GluR), a process that is indispensable for neuronal homeostasis and life, since even heterozygous mice bearing one unedited allele of the GluR exhibit severe seizures and early postnatal lethality.[495] ADAR2-mediated RNA editing beyond the central nervous system has been described. While ADAR2 is dispensable for immune and vascular system homeostasis, it controls IL-6-dependent immune cell trafficking in acute and chronic ischemic heart disease,[447] highlighting the therapeutic potential of targeting ADAR2 in IL-6-driven pathologies including coronary artery disease, systemic rheumatic disorders, hyperinflammatory syndrome associated with various infections such as COVID-19, or even cancer.[496,497]

Table 4. Effect of A-to-I RNA editing (ADAR1/ADAR2) in disease

	Enzyme	Molecular pathway	Target gene	Effect on target gene	Cell or tissue model	Reference
Brain						
Alzheimer's disease	ADAR1	↓ interferon signaling	NA	expression	glial cell (H)	McEntee et al.[413]
	ADAR2	↑ editing of GluA2 Q/R site	GRIA2	NA	brain tissue (H)	Gaisler-Salomon et al.[414]
Glioma/Glioblastoma	ADAR1	↑ autophagy ↑ proliferation ↑ self-renewal and stemness	p62 CDK2 GM2A	expression stability expression	glioma cell line (H) glioblastoma cell line (H) glioblastoma stem cell (H)	Zhang et al.[415] [416,417] Jiang et al.[418]
	ADAR2	↑ migration, invasion, cell resistance ↓ proliferation, migration, glycolipid metabolism	miR-589-3p PHKA2, PTX3	expression decay	glioblastoma cell line (H) glioblastoma cell line (H)	[419,420] [421,422]
Parkinson's Disease	ADAR2	↑ hyperammonemia	5-HT2B receptors	Expression	astrocyte (M)	Yue et al.[423]
Stroke	ADAR1	↑ apoptosis, reactive oxygen species	NA	NA	astrocytes, cortical neuron (M)	Cai et al.[424]
	ADAR2	↑ editing of GluR1/GluR2	GRIA2	expression	brain of Sprague-Dawley rat (R)	Montori et al.[425]
Bones, joints, and musculoskeletal system						
Osteosarcoma	ADAR1	↓ proliferation, migration	circRBMS3	expression	osteosarcoma cell (H)	Gong et al.[426]
Bone marrow and blood						
Leukemia	ADAR1	↑ proliferation, ↓ apoptosis ↑ self-renewal, survival ↑ cytokine signaling	pri-miR-766 NA STAT3	miRNA processing editing splicing	leukemia cell line (H) leukemia cell line (H) leukemia cell line (H)	[427,428] [429] [430]
	ADAR2	↓ leukemogenesis	COPA, COG3	localization	leukemia cell line (H)	[431]
Digestive system						
Colorectal cancer	ADAR1	↑ proliferation, invasion, migration ↓ ferroptosis	AZIN1 FAK/AKT	hyper-editing expression	colon carcinoma cell line (H) colon carcinoma cell line (H)	[432,433] [434]
	ADAR2	↓ migration, invasion	miR-200, COPA	Expression	colon carcinoma cell line (H)	[435]
Gastric cancer	ADAR1	↑ proliferation, invasion, and migration ↑ chemoresistance ↓ interferon signaling	AZIN1, mTOR, CALR SCD1 miR-302a	expression stability processing, maturation	gastric adenocarcinoma cell line (H) patient-derived organoid (H) gastric adenocarcinoma cell line (H)	[436–438] [394] [439]
Heart and blood vessels						
Aneurysm	ADAR1	↑ cytokine signaling ↑ matrix degradation	Drosha MMP2, MMP9	decay stability	bone marrow-derived macrophage (M) Aortic SMC (M)	[440] [441]
Atherosclerosis	ADAR1	↑ innate immune response to TNFα ↑ matrix degradation	NEAT1 CTSS	stability stability	HUVEC (H) HUVEC (H)	[392] [8]
Congenital heart disease	ADAR2	↑ cardiac fibrosis	FLNB	hypo-editing	ADAR2$^{-/-}$ heart tissue (M)	[442]
Heart Failure	ADAR1	↓ immune activation ↑ cardiomyocyte survival	IRF7 miR-199a-5p	expression expression		[443] [444]

(*Continued on next page*)

Table 4. *Continued*

	Enzyme	Molecular pathway	Target gene	Effect on target gene	Cell or tissue model	Reference
					cardiomyocyte (M) ADAR1$^{fl/fl}$ αMHC-Cre heart tissue (M)	
	ADAR2	↑ sarcomere regularity	circAKAP13	stability	cardiomyocyte (H)	445
Ischemic heart disease	ADAR2	↑ proliferation, ↓ apoptosis ↑ immune cell trafficking	miR-34a pri-mir-199a-1, pri-mir-199a-2, pri-mir-335	expression miRNA processing	cardiomyocyte (M) HUVEC (H), lung endothelial cell (M)	446 447
Liver						
Hepatocellular carcinoma	ADAR1	↑ survival, oxidative stress ↑ mitophagy ↑ proliferation	KEAP1/NRF2 GLI1 AZIN1, ITGA2, CircARSP91	expression, translocation stability expression, translocation	hepatocellular carcinoma cell line (H) hepatocellular carcinoma cell line (H) hepatocellular carcinoma cell line (H)	448 449 450–452
	ADAR2	↑ tumorigenesis	COPA, pri-miR-214 and miR-214	stability, processing	hepatocellular carcinoma cell line (H)	453,454
MASLD/NASH/NAFLD	ADAR1	↓ steatosis, fibrosis, ferroptosis ↓ inflammasome activation	ACSL4, GPX4 c-jun	expression expression	liver tissue (M), hepatocyte (M) liver tissue (M), Monocyte (H)	455 456
	ADAR2	↑ gluconeogenesis, glycogen synthesis ↑ dyslipidemia	AMPK/CREB SAA1	expression expression	liver tissue (M) liver tissue and plasma (M)	457 458
Lung and respiratory system						
Asthma	ADAR1	↑ type I interferon-stimulated genes	Interferon-stimulated genes	Expression	lung tissue (M)	459
Lung adenocarcinoma	ADAR1	↑ invasion, migration, proliferation	miR-1251-5p, F-circEA1, miR-4673	Expression	non-small-cell lung cancer line (H)	460,461
		↑ DNA damage repair, radiotherapeutic resistance	RAD18, E2F3	expression, stability	non-small-cell lung cancer line (H)	462
Pulmonary Fibrosis	ADAR1	↑ fibrosis	Let-7d, miRNA-21, PELI1, SPRY2	Expression	pulmonary fibroblasts (H)	463,464
		↑ fibrosis	CTGF, miR-21, PELI1, SPRY2	expression, stability	pulmonary fibroblasts (H), lung tissue (M)	464,465
Pulmonary hypertension	ADAR1	↑ proliferation	circCDK17	Stability	pulmonary artery smooth muscle cell (H)	466
Other organs and systemic autoimmune diseases						
Bladder cancer	ADAR2	↑ invasion, chemoresistance	circFNTA, circ0001005	expression, circularization	bladder carcinoma cell (H)	467,468
Breast cancer	ADAR1	↑ proliferation, migration ↓ ferroptosis	LINC0062, FLNB, PKR miR-335-5p	hyper-editing, expression expression	breast carcinoma cell (H) breast carcinoma cell (H)	469–471 472
	ADAR2	↑ chemoresistance	circHIF1	back-splicing	breast carcinoma cell (M)	473

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Table 4. *Continued*

	Enzyme	Molecular pathway	Target gene	Effect on target gene	Cell or tissue model	Reference
Melanoma	ADAR1	↑ proliferation, migration ↓ PANoptosis	miR-30a, miR-30d ZBP-1	expression nuclear export	melanoma cell line (H) melanoma cell line (H)	474–476 477
	ADAR2	↑ stemness, ↓ apoptosis	DOCK2	Stability	melanoma cell line (H)	478
Rheumatoid arthritis	ADAR1	↑ proinflammatory gene expression	CTSS	stability	HUVEC (H)	479
Systemic lupus erythematosus	ADAR2	↑ immune function	NA	NA	T cell (H)	480
Systemic sclerosis	ADAR1	↑ type I interferon response ↑ macrophage activation	CTSS NF-κB	stability expression	HUVEC (H) bone marrow-derived macrophage (M)	481 482
Pancreas						
Diabetes	ADAR1	↑ dyslipidemia, insulin resistance ↓ adipogenesis	ghrelin, peptide YY Dicer	expression binding, processing	Adar1$^{+/-}$ stomach tissue and serum (M) embryonic fibroblasts (M)	483 484
Pancreatic cancer	ADAR1	↑ proliferation, invasion, cancer cell resistance	c-Myc	stability	pancreatic cancer cell line (H)	485

This table was created using the MESH term {"enzyme" and "disease"} in PubMed, last accessed 7/2/25.

Precise RNA base editing using endogenous ADARs

Base editing has gained significant attention in the past decade and CRISPR-Cas9-based therapies, aimed at correcting point mutations at the DNA level, are currently being tested in advanced stages of clinical trials.[498] However, off-target events and toxicity caused by the introduction of DNA double-strand breaks limit their use in larger scale.[498] RNA editing presents a novel category of therapeutic applications, with the correction of pathogenic G-to-A mutations as a logical first step. Currently, more than 24,000 pathogenic G-to-A mutations have been reported in ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/). Additionally, A-to-I RNA editing can result in 17 different amino acid substitutions, offering a means to modulate protein amino acid content, structure, function, and protein-protein or protein-RNA interactions. Unlike DNA editing, RNA editing provides a reversible and tunable alternative, which makes it a safer and potentially more efficient approach.[499] Initial efforts relied on overexpression of exogenous RNA editing enzymes, but this approach led to approximately 10,000–100,000 off-target events across the transcriptome.[500] Newer approaches focused on designing guide RNAs with higher specificity to the target transcript to recruit endogenous ADARs.[501–503] The RNA editing for programmable A-to-I (G) replacement (REPAIR) system was created by fusion of the ADAR2 deaminase domain with the E488Q hyperactivating mutation to enhance catalytic activity (ADAR2DD) with the catalytically inactive PspCas13b[501] (Table 5). The first version, REPAIRv1, could correct two disease-associated mutations (878G→A, AVPR2W293X; associated with X-linked nephrogenic diabetes insipidus, and 1517G→A, FANCC W506X; associated with Fanconi anemia) and 33/34 more sites tested.[501] However, off-target events were observed within the guide RNA-target RNA duplex.[501] Through structure-guided protein engineering of ADAR2DD, the REPAIRv2 system was developed, which showed dramatic reduction of off-target events in both guide-target duplexes and transcriptome-wide positions.[501] The LEAPER system (leveraging endogenous ADAR for programmable editing of RNA), which used short engineered ADAR-recruiting RNAs, was highly efficient (up to 80% editing) in multiple cell lines without showing significant off-target activity and could restore α-l-iduronidase catalytic activity in primary fibroblasts derived from individuals with Hurler syndrome without evoking innate immune responses.[502] Another approach using chemically optimized antisense oligonucleotides to recruit endogenous ADARs to edit endogenous transcripts, termed RESTORE (recruiting endogenous ADAR to specific transcripts for oligonucleotide-mediated RNA editing) was developed. RESTORE showed minimal off-target editing, all in non-coding regions, and did not disturb physiological editing activity in multiple cell lines and human primary cells from different tissues.[503] Editing efficiency was highest in the presence of ADAR1p150, or after treatment with interferon (IFN)-α, which could have clinical repercussions for editing activity in situations characterized by innate immune activation. Importantly, RESTORE was able to increase a1-antithrypsin secretion by 2-fold.[503] In a similar approach, the design of circular ADAR recruiting guide RNAs and delivery via adeno-associated viruses enabled the *in vivo* RNA editing of mouse *Pcsk9* transcript in the liver of

Table 5. CRISPR-Cas13 with adenosine deaminating activity and small molecule inhibitors of Adar enzymes

Therapeutic	Disease	Model	Effect on disease outcome	Effect on pathways/ target transcript	Reference
A-to-I RNA editing					
REPAIRv2, minixABE	cystic fibrosis	CFTR mutant human bronchial cells	restored CFTR protein by correcting nonsense mutations (UGA) by sequence-specific RNA editing in	restored CFTR protein expression	Chiavetta et al.[504]
Recruitment of endogenous ADARs (cadRNA)	hyperlipidemia mucopolysaccharidosis type I-Hurler	C57BL/6J, IDUA-W392X mice	53% RNA editing of the mPCSK9 transcript in C57BL/6J mice livers 12% UAG-to-UGG RNA correction of the amber nonsense mutation in the IDUA-W392X	edit transcript	Katrekar et al.[505]
RESTORE (recruiting endogenous ADAR to specific transcripts for oligonucleotide-mediated RNA editing)	A1-antithrypsin deficiency	multiple immortalized and primary human cell lines	STAT1 transcript editing affecting phosphotyrosine 701 site PiZZ mutation (E342K) in SERPINA1 (serpin family A member 1) resulting in 2-fold increased secretion of a1-antithrypsin	2-fold increased AAT-1 expression	Merkle et al.[503]
REPAIR (RNA Editing for Programmable A-to-I Replacement)	nephrogenic diabetes insipidus, Fanconi anemia.	human embryonic kidney 293 cell line	correction of 878G→A (AVPR2W293X; X-linked nephrogenic diabetes insipidus), 1517G→A (FANCC W506X; Fanconi anemia) and 33 more sites	edit transcript	Cox et al.[501]
ADAR inhibitor					
Rebecsinib: inhibition of ADAR1p110 to ADAR1p150 splice isoform switching	Leukemia	humanized LSC mouse model serial transplantation assays	↓leukemia stem cell self-renewal and survival *in vitro*. ↓ leukemia stem cell self-renewal *in vivo* in the bone marrow, peripheral blood and spleen in and prolonged survival. no effect on normal hematopoietic stem and progenitor cells no systemic toxic effects	splice isoform switching of MCL1-long (pro-survival) to MCL1-short (pro-apoptotic)	Crews et al.[506]
AVA-ADR-001: ADAR1p150 inhibitor (binding on the Zα domain)	melanoma	B16F10 syngeneic melanoma solid model	↓ tumor growth synergy with anti-PD1 *in vivo*	↑ interferon-stimulated genes and T cell activation markers	Goswami et al.[507]
ZYS-1: ADAR1 deaminase inhibitor (binding within ADAR1 catalytic pocket)	prostate cancer	multiple prostate cancer cell lines, DU-145 xenotransplantation mouse model	↓ cell proliferation, cell-cycle arrest and ↑ apoptosis *in vitro* ↓ colony formation *in vitro* ↓ tumor growth *in vivo* (↑ human IFN-γ, ↑CD8+ T cells and ↓ myeloid-derived suppressor cells in tumor)	n/a	Wang et al.[508]

C57BL/6J mice.[505] Cluster guide RNAs are an alternative approach showing on-target editing of endogenous transcripts (up to 45%) without off-target events *in vitro* and up to 10% of reporter constructs in mouse liver *in vivo*.[509] In contrast to the current DNA editing approaches, A-to-I RNA editing does not induce potentially toxic DNA double-strand breaks. Furthermore, because RNA editing events are transient in nature, they pose a lower risk of long-lasting side effects. However, guide RNA efficiency and specificity remain significant challenges in RNA editing therapeutics. While newer approaches that recruit endogenous ADARs have reduced transcriptome-wide off-target effects, editing of nearby adenosines within the guide RNA-target RNA duplex remains a limitation. Since site-specific and highly selective RNA editing occurs predominantly in nascent RNAs, an in-depth study of local secondary structures and the 3D conformation of guide RNA-target RNA duplexes may help to develop more specific and efficient RNA editing platforms.

Novel small molecule inhibitors of ADAR1

In parallel with advances in *in vivo* adenosine-based RNA editing techniques to correct point mutations and treat hereditable diseases, novel small molecule inhibitors against ADAR1 are currently being tested in preclinical models. The interferon-inducible ADAR1p150 isoform has a distinct role in regulating innate immune responses.[403–405,407] It is involved in the regulation of proinflammatory gene expression in chronic inflammatory disorders[8,392,479] and has recently been shown to mediate resistance to immune checkpoint blockade in various forms of cancer.[493] Therefore, the design of ADAR1p150-specific inhibitors, sparing the constitutively expressed ADAR1p110 isoform, has gained significant attention[506,507,510] (Table 4). Rebecsinib is a novel small molecule that binds to the spliceosome core complex and inhibits isoform switching from ADAR1p110 to ADAR1p150, AVA-ADR-001 targets ADAR1p150 Z-DNA binding domain, while ZYS-1 selectively inhibits the deaminase activity of ADAR1.[508] Treatment of different types of cancer cells (leukemia, melanoma, prostate cancer) with any of the above-mentioned ADAR1 inhibitors resulted in lower cell proliferation, cell-cycle arrest, and increased cell death *in vitro*, leading to slower tumor growth and prolonged survival *in vivo*,[506–508] while AVA-ADR-001 also showed a synergistic effect with anti-PD1 therapy *in vivo*.[507]

Synergistic effects of targeting adenosine RNA editing and modification enzymes with established treatment modalities

Silencing of m6A methylation enzymes can significantly impact cancer cell sensitivity to immune checkpoint inhibitors and chemotherapy. Enzymatic inhibitors of METTL3 induce the formation of endogenous dsRNA in cancer cells, leading to activation of the type I interferon pathway and enhanced antigen presentation, thereby "priming" cancer cells to respond to treatment.[511] *In vivo* treatment of breast cancer cell xenografts with STM2457 in combination with PD-1 inhibitors eliminated immune-escaped cancer cells resistant to each monotherapy.[339] In orthotopic NAFLD-HCC models, combination therapy of STM2457 with anti-PD1 was more effective at inhibiting tumor growth compared with either monotherapy, increasing the percentage of IFN-γ^+ and GZMB$^+$ CD8$^+$ cytotoxic T cells in the tumors.[327] Similarly, combination of STM2457 with anti-PD1 in a model of CRC allografts showed superior effects to either monotherapy, and increased T cell infiltration of the tumors.[322] STM2457 also increased sensitivity of HCC tumors to the vascular endothelial growth factor receptor (VEGFR)-inhibitor Lenvatinib[329] and showed synergistic effects with the chemotherapeutic agent gemcitabine in a mouse model of intrahepatic cholangiocarcinoma allografts.[333] Similarly, STM2457 demonstrated synergy with the tyrosine kinase inhibitor Anlotinib in an OSCC model in nude mice,[325] as well as with various chemotherapeutic agents in mouse models using xenografts of small cell lung cancer in nude mice.[328] This synergy was partly attributed to the downregulation of mitophagy.[328] Similarly, METTL3 knockdown in mice bearing Lewis lung carcinoma tumors sensitized them to anti-PD-1 treatment, leading to increased CD8$^+$ T cell and natural killer (NK) cell tumor infiltration and reduced tumor growth.[512] Similar effects were observed in another model of lung tumorigenesis, as well as in experiments using STM2457.[512] The central role of METTL3 in DNA damage response and repair has also been leveraged in preclinical studies examining its potential synergy with genotoxic agents. Indeed, METTL3 silencing significantly enhanced the sensitivity of HCC tumors to oxaliplatin, leading to significantly smaller tumor sizes compared with monotherapy alone. This effect was partly due to increased oxidative stress and DNA damage accumulation in cancer cells.[513] Furthermore, genetic knockout of Mettl3 restored the sensitivity of melanoma cells to BRAF kinase inhibitors both in human cell lines *in vitro* and in xenograft mouse models *in vivo* leading to reduced tumor growth.[266] Given that METTL3 inhibitors have reached clinical trials and have demonstrated an overall safe profile to date, these promising preclinical findings highlight potential areas for future clinical applications.

ADAR1 inhibition has also shown *in vivo* synergistic effects with immune checkpoint inhibitors, chemotherapeutics, and irradiation against multiple types of cancer. A central mechanism for this synergistic action appears to be the induction of type I interferon signaling by dsRNA sensing by MDA5 and PKR.[403,406,407,493] Activation of RNA immunity leads to the production of proinflammatory and growth-inhibitory signals, affecting tumor growth while also "priming" cancer cells to respond to additional treatments.[493] Loss of ADAR1 was shown to overcome resistance to PD-1 checkpoint blockade and significantly inhibited tumor growth in models of melanoma and CRC.[493] This resistance is typically caused by the inactivation of antigen presentation by tumor cells.[493] Silencing of ADAR1 in mouse tumor cells resulted in the production of type I and type II interferons, which primed cancer cells to respond to a secondary "hit," such as PD-1/PD-L1 blockade, chemotherapy, or radiotherapy, bypassing the need for CD8$^+$ T cell recognition of cancer cells.[493] Future studies are warranted to show the reproducibility of these significant findings in large animal models and patients.

A more recent approach involved engineered nanovesicles combining small interfering RNA (siRNA) against ADAR1 packaged in lipid

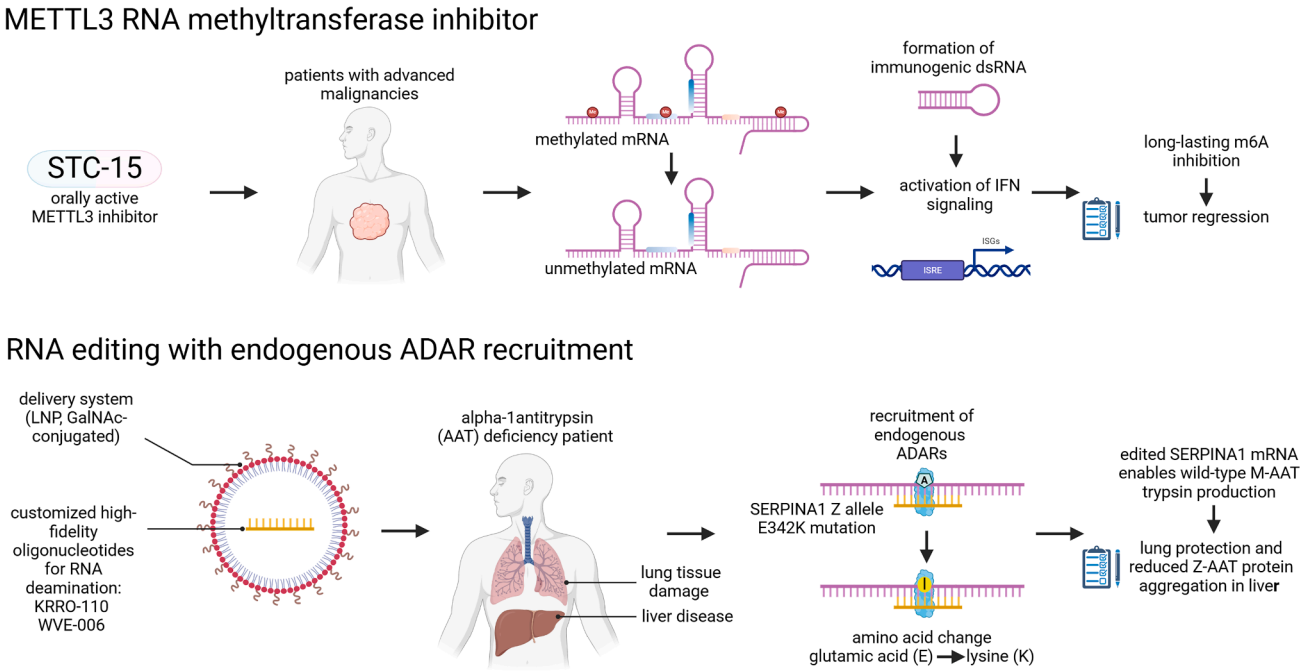

Figure 3. Clinical trials targeting RNA adenosine editing and modification enzymes

STC-15, a selective enzymatic inhibitor of METTL3, is currently being tested in phase 1 clinical trials in individuals with multiple types of advanced cancer. Inhibition of METTL3 in cancer cells leads to the formation of double-stranded RNA, which in turn activates interferon signaling and boosts host immune responses against tumor cells and stops tumor progression.

Adenosine deaminase-induced molecularly targeted editing oligonucleotides (AIMer) approaches for targeted A-to-I editing of SERPINA1 gene, which is associated with alpha-1 antitrypsin (AAT) deficiency, are currently being tested in phase 1 and 2 clinical trials with preliminary results showing effective restoration of wild-type AAT protein expression, which is expected to ameliorate liver and lung damage in patients.

nanoparticles that were coated with the plasma membrane of genetically engineered PD-1-overexpressing cells.[514] This construct could disrupt the PD-1/PD-L1 immune inhibitory axis by presenting the PD1 protein on the coating membranes and deliver the siRNA against ADAR1 in cancer cells. The engineered nanovesicles were administered to 4T1 tumor-bearing mice, a model of metastatic mammary cancer used to simulate human metastatic triple-negative breast cancer, and the combination treatment significantly reduced tumor growth.[514] This approach also effectively prevented abscopal tumor development and lung metastasis compared with each monotherapy, and the synergistic effect was partly mediated by the upregulation of both type I and type II interferons, which made the cancer cells more susceptible to other secreted cytokines.[514] ADAR1 deletion in organoids derived from patients with gastric cancer resistant to 5-fluorouracil and cisplatin restored sensitivity to the combination treatment, leading to reduced tumor size in mouse xenografts.[394] This effect was partly mediated by the reduction of *SCD1* transcript stability, a molecule that facilitates lipid droplet formation and mitigates chemotherapy-induced ER stress, thereby promoting cancer cell self-renewal.[394] Consistent with this, silencing Adar1 restored sensitivity to temozolomide in human glioma cells *in vitro* and led to reduced tumor growth in an orthotopic glioblastoma mouse model.[415] Moreover, Adar1 silencing has been shown to enhance the sensitivity of both mouse and human ovarian cancer cells to DNA methyltransferase inhibitors *in vitro* and *in vivo*, reducing tumor burden and prolonging survival in immunocompetent mouse models injected intraperitoneally with ovarian cancer cells. This effect was partly attributed to increased proinflammatory responses, leading to enhanced $CD8^+$ T cell infiltration into tumors.[515] ADAR1 deletion may also promote telomere instability and DNA damage accumulation as shown in HeLa cells *in vitro* and validated in numerous mouse and human cell lines with non-canonical telomeric repeats, making ADAR1 an attractive therapeutic target in telomerase-positive cancers.[20]

Clinical trials targeting RNA adenosine editing and modification enzymes

STC-15, a modified version of STM-2457 developed by STORM Therapeutics, is currently being evaluated in a phase 1 clinical trial (NCT05584111) for patients with advanced solid malignancies (Figure 3; Table S4). Preliminary results from 42 patients indicated that STC-15 was efficient in reducing m6A levels in blood cells by 63% within 24 h from administration. Tumor regressions were observed in all dose levels, while STC-15 treatment led to the activation of innate immune pathways, including type I and type II interferon signaling. Disease control rate (defined as the percentage of patients with partial response, complete response, or stable disease) was 78%, while the observed adverse effects were manageable and more

commonly involved thrombocytopenia, gastrointestinal distress and skin rashes, while no treatment limiting adverse effects were observed.[516–518] These promising preliminary results suggest that STC-15 has the potential to become a valuable addition to cancer treatment options.

CRISPR- and adenosine deaminase-induced molecularly targeted editing oligonucleotides (AIMer) approaches for targeted A-to-I editing of specific transcripts have also advanced to clinical trials, yielding promising results and demonstrating an overall favorable safety profile (Figure 3; Table S4). Alpha-1 antitrypsin (AAT) deficiency, a genetic disease often caused by a point mutation in the *SERPINA1* gene, leads to misfolding and aggregation of AAT protein in hepatocytes, reducing functional AAT in circulation and increasing the risk of liver and lung disease.[519] WVE-006, developed by Wave Life Sciences, is a GalNAc-conjugated oligonucleotide that drives targeted A-to-I RNA editing of the *SERPINA1* transcript by recruiting endogenous ADAR enzymes to restore levels of the wild-type AAT protein. Preclinical studies in mice showed that WVE-006 increased wild-type AAT serum levels, reduced liver inflammation, and cleared AAT aggregates, with similar effects observed in human-derived hepatocytes.[520] RestorAATion-1 (NCT06186492) a phase 1 study conducted on healthy volunteers showed a well-tolerated and favorable safety profile. Initial results from the RestorAATion-2 clinical trial (NCT06405633) demonstrated successful RNA editing of the *SERPINA1* transcript in two patients *in vivo*, restoring wild-type AAT levels and increasing neutrophil elastase inhibition, marking the first clinical proof of therapeutic A-to-I RNA editing in humans. The therapy was well-tolerated, with no serious adverse events reported, and early increases in AAT levels were observed as early as 3 days post-treatment.[521] Similarly, the REWRITE study (NCT06677307) investigating KRRO-110, another AIMer encapsulated in a lipid nanoparticle developed by Korro Bio aiming at restoring functional AAT levels, recently announced the initiation of dosing in up to 64 participants.[522]

While the first-in-human data from clinical trials of RNA-modifying therapeutics support an overall safe and well-tolerable profile, increased awareness of late-onset off-target or adverse events is warranted. Further clinical studies involving a larger number of individuals and extended follow-up periods are necessary to more accurately assess the safety and efficacy of these promising novel compounds. These studies should evaluate key factors such as the number needed to treat per condition, long-term efficacy, the potential need for recurrent therapy, and the monitoring of any long-term adverse reactions or off-target effects. Furthermore, deeper phenotyping and closer monitoring of preclinical models could help identify potential adverse effects associated with these novel drug compounds before reaching the clinic. For instance, performing a complete blood count, including white blood cell counts and their subtypes, hemoglobin levels, and platelet numbers, would provide insights into potential bone marrow toxicity. Furthermore, since m6A inhibitors are likely to be co-administered with other drugs, conducting comprehensive safety studies on co-administration in various disease models would be highly valuable.

LIMITATIONS OF CURRENT RNA MODIFICATION THERAPEUTICS AND FUTURE PERSPECTIVES

Post-translational modifications of RNA modification enzymes may affect the efficacy of RNA-modifying therapeutics

Post-translational modification of m6A methyltransferases, demethylases, and reader proteins

Post-translational modifications of m6A writer enzymes affect their structure, cellular localization, interactions with other m6A machinery components, and enzymatic activity, thereby significantly impacting global m6A levels and the transcriptome.[523] Methylation of METTL14 protein by PRMT1 enhances the interaction of the METTL3-METTL14 complex with WTAP, thereby increasing global m6A levels.[524] Similarly, methylation of METTL14 protein increases its interaction with RNA-polymerase II-bound RNA substrates with important repercussions for m6A-induced DNA repair in stem cells that is crucial for their self-renewal and maintenance.[525] Adding to the complexity of post-translational control of protein function, the same post-translational modification may exert opposite effects in different disease contexts. Acetylation of METTL3 can both affect its cellular localization and increase its stability, modulating the migration and invasion of several cancer cells.[526–528] For example, IL-6-induced deacetylation of METTL3 promotes its nuclear localization, leading to the stabilization of breast cancer metastasis-promoting transcripts,[527] potentially conferring resistance to therapies targeting these transcripts. Conversely, increased METTL3 protein acetylation reduces methylation and increases *MTF1* expression, a transcription factor driving hepatocellular carcinoma progression,[528] suggesting that acetyltransferase inhibitors could synergize with METTL3-targeted therapies in hepatocellular carcinoma but not in breast cancer. Acetylation of METTL14 also increases its stability leading to inactivation of the NF-κB pathway in macrophages.[529] SUMOylation of METTL3 promotes tumorigenesis by repressing its m6A methyltransferase activity without affecting its stability, localization, or interactions with METTL14 and WTAP.[530] TAK-981, a first-in-class SUMOylation inhibitor currently under clinical trials for solid tumors,[531] could restore METTL3 activity and sensitize cells to m6A-modulating drugs. METTL3 and WTAP phosphorylation by ERK allow the USP5-mediated deubiquitination of METTL3 and WTAP to stabilize the m6A writer complex and increase m6A methylation of oncogenic transcripts, which may contribute to tumorigenesis.[532] Tumors with constitutive ERK activation, as found in BRAF-mutated melanomas, may therefore resist METTL3 inhibition unless combined with ERK pathway inhibitors such as trametinib.

Post-translational modifications also affect m6A demethylases with variable effects on their activity and substrate binding capacity. For example, dynamic and reversible acetylation of ALKBH5 increases its demethylase activity by increasing its affinity to bind on m6A-methylated RNA substrates, a regulatory mechanism that is enhanced in cancer cells.[533] On the other hand, increased SUMOylation of ALKBH5 under oxidative stress conditions reduces its binding

capacity to multiple target transcripts leading to increased expression of genes involved in DNA damage response and repair, and thus plays a key role in hematopoietic stem cell maintenance.[534] Whether antioxidants used in immune-oncology such as N-acetyl cysteine[535] could alter the efficacy of ALKBH5 inhibitors remains under investigation.

Post-translational modifications also affect binding of m6A reader proteins on their target RNAs or their cellular localization, thereby affecting protein expression. For example, PRMT1-mediated methylation of hnRNP m6A reader proteins is essential for their nuclear localization,[536] while it can also affect their binding capacity to multiple target RNAs, with functional implications for the development of inflammatory disorders.[537] PRMT inhibitors, such as GSK3368715 tested in clinical trials in patients with advanced solid tumors,[538] may thus enhance the response to m6A-targeted therapies in chronic inflammatory disorders. In the absence of the deacetylase SIRT1, as observed in breast cancer cells, increased IGF2BP2 acetylation leads to increased transcript degradation and abnormal lysosome function promoting cancer cell proliferation and survival.[539] By targeting both tumor suppressors and oncogenic proteins, SIRT1 has a bifunctional role at different stages of tumorigenesis. Therefore, the investigation of SIRT1 inhibitors and activators for cancer treatments should consider the effect on methylated transcripts. Given these regulatory complexities, studying the effects of m6A inhibitors under various *in vitro* and *in vivo* conditions is essential to determine whether such modifications influence their efficacy and clinical translatability.

Post-translational modification of ADAR enzymes

The stability, cellular localization, and enzymatic activity of ADARs are greatly affected by post-translational modifications. AKT-mediated phosphorylation of ADAR1p110 on T738 and ADAR2 on T553 has been shown to suppress their enzymatic activity,[540] which suggests that tumors with high AKT activity may exhibit different sensitivity to ADAR-targeted therapies. Similarly, SUMOylation of ADAR1 by SUMO-1 has been shown to reduce its RNA editing activity *in vitro*.[541] Ubiquitination of ADAR1p110 at Lys48, which is induced by type I interferon, leads to its degradation, a regulatory mechanism to achieve efficient antiviral activity.[542] The presence or absence of such post-translational modifications may influence the sensitivity to ADAR1 inhibitors. The nuclear localization of ADAR2 depends on its phosphorylation, which is regulated by a phosphatase that has not yet been identified. In the absence of this phosphorylation, ADAR2 relocates to the cytoplasm, where it undergoes rapid degradation.[543] While the exact structural implications, including conformational changes and changes in substrate binding, of the different post-translational modifications on ADAR1 and ADAR2 have not been delineated to date, their study is warranted to understand how RNA editing enzymatic activity will be affected in diverse disease contexts.

Post-translational modification in the therapeutic context

Post-translational modifications can affect resistance or sensitivity to RNA-modifying therapies by directly controlling enzymatic activity, protein-protein interactions, and substrate binding of the RNA-modifying enzymes. Indeed, enhanced methyltransferase activity due to post-translational modifications could stabilize mRNAs of target survival genes like MYC or increase m6A on transcripts encoding immune checkpoints like PD-L1 (Tables 1 and S2) promoting resistance to chemotherapy and immune checkpoint inhibitors. Some lessons can be drawn from cancer chemotherapy, where post-translational modifications have been shown to affect binding of the drugs to their target molecules, speed of drug efflux from target cells, as well as inactivation of the therapeutic compounds per se.[544] For example, post-translational modifications of EGFR can directly affect chemotherapy resistance in NSCLC,[545] breast,[546] and colorectal cancer.[547] Given that METTL3 inhibition has been shown to affect the progression of multiples types of cancer, such as HCC and oral squamous cell carcinoma, through modification of EGFR protein levels,[266,329] it is worth studying whether post-translational modifications of EGFR could also indirectly affect the efficacy of METTL3 inhibitors. Several clinical takeaways must be taken into consideration. Post-translational modification status (e.g., METTL3 acetylation, ADAR1 ubiquitination) could be used to stratify patients for targeted therapies. However, post-translational modifications may have opposing roles across cancers, necessitating disease-specific therapeutic designs. Furthermore, several inhibitors that target post-translational modification regulators have been approved for cancer treatment.[548] Such drugs may also affect RNA-modifying enzymes leading to unwanted effects in compensatory cellular pathways. Therefore, combined strategies targeting post-translational modification regulators may overcome resistance to RNA-modifying enzyme inhibitors. By integrating post-translational modification profiling into preclinical and clinical studies, the translational potential of RNA-modifying therapeutics can be optimized to address resistance mechanisms and improve patient outcomes.

Structural characterization of m6A reader binding to RNA substrates to inform m6A-based RNA editing therapeutics

While CRISPR-based m6A editing seems to be efficient and specific, the fate of the newly methylated transcript depends on the competitive binding of the m6A reader proteins. Factors such as the local secondary structure of the transcript, subcellular localization, and the availability of reader proteins might influence m6A reader binding and consequently affect transcript stability and translation efficiency. Thus, a better understanding of the specificity or selectivity of readers in relation to their binding to mRNA modified at different sites based on structural biology studies is necessary to inform and enhance m6A-based RNA editing research. m6A readers recognize m6A through a specific, well-characterized YTH domain that binds m6A with several-fold higher affinity than adenosine.[549] Vertebrate YTH domain-containing proteins can be classified into three categories: YTHDF (YTH domain-containing family protein) family that has three members YTHDF1-3, as well as YTHDC1 and YTHDC2 that are not paralogs despite having a similar name.[550] Binding of m6A to YTH proteins has been well-characterized through crystallography and involves an aromatic cage comprising three tryptophan

residues similarly recognizing the N6-methyl group.[550] While YTH domain does not selectively interact with neighboring bases besides m6A, it selectively recognizes neighboring phosphate and sugars at the −2, −1, +1, and +2 positions.[551,552] YTHDF family proteins, as well as YTHDC2, mostly reside in the cytoplasm, thus affecting transcript stability and translation, while YTHDC1 is located in the nucleus and thus primarily involved in nuclear processing of the transcripts, including splicing and nuclear export.[6,12,14,553–555] Transcriptome-wide studies have revealed an almost identical binding profile of the YTHDF proteins,[31,550] suggesting that no m6A site is uniquely bound by a single YTHDF protein. Given that YTHDF2 is mostly associated with enhanced degradation of the target transcript,[6] YTHDF1 mostly leads to increased translation of the methylated transcript,[14] while YTHDF3 shares both properties,[553,554] the competitive binding of the reader proteins will determine the fate of the methylated transcripts. On the other hand, YTHDC1 protein has been shown to mostly bind to nuclear RNAs, thus having a mostly distinct m6A targetome.[31] Moreover, in contrast to YTHDF1-3 and YTHDC1, iCLIP studies did not reveal any specific binding profile of YTHDC2 on m6A, suggesting that this reader may operate under certain circumstances or in specific cell types.[31] Future studies should focus on elucidating the precise structural determinants of m6A reader binding to RNA substrates, particularly in the context of transcript-specific influences such as local secondary structures and cellular localization. These investigations will be essential for improving the efficiency and specificity of m6A-based RNA editing therapeutics, by providing deeper insights into how competitive binding and reader protein interactions impact RNA metabolism.

A-to-I RNA editing and m6A: Friends or foes?

While most studies have examined A-to-I RNA editing and m6A modifications independently, emerging evidence suggests that these two adenosine modifications may interact to shape transcript fate. m6A-negative transcripts undergo more extensive A-to-I editing compared with m6A-positive ones in human embryonic stem cells.[556] Furthermore, an inverse correlation between m6A and A-to-I editing rates on the same transcript suggests a competitive relationship, likely mediated by the binding competition between ADAR enzymes and m6A methyltransferases.[556] Supporting this antagonistic interaction, METTL3 knockdown in HEK cells resulted in increased global A-to-I RNA editing, whereas FTO knockdown led to decreased A-to-I editing, independent of ADAR expression levels.[556] Conversely, ADAR1 transcripts are methylated by METTL3, enhancing their stability and increasing ADAR1 protein levels implying that m6A may affect RNA editing levels through disruption of the binding of ADAR to each substrate, rather than affecting its expression levels.[416] Moreover, ADAR1 degradation may occur through an m6A-YTHDF1-dependent mechanism, underlying the complex interplay between these enzymes.[508] Both m6A and A-to-I RNA editing are involved in the progression of common diseases, such as leukemia and solid tumors, and influence the response to current treatment modalities, such as immune checkpoint inhibition. As a result, inhibiting an adenosine RNA modification enzyme could have varying outcomes, depending on how these modifications interact within a given disease context. For instance, if both modifications drive similar cellular behaviors, inhibition might yield a synergistic effect. Conversely, if they exert opposing effects within the same pathway, the outcome could be antagonistic. Alternatively, a cascading effect could lead to unpredictable consequences by altering both RNA editing and m6A modifications across multiple transcripts. These possibilities underscore the need for detailed mechanistic studies to fully understand their therapeutic implications.

Translating RNA modification therapeutics into effective clinical drugs

While targeting RNA adenosine editing and modification enzymes has shown promise in diverse preclinical models, certain issues remain to be investigated before they reach clinical practice. As shown in Figure 2 and Table S1, both m6A methylases and demethylases can exert similar effects on the progression of certain diseases. AML constitutes the best-studied example to date. Both METTL3 and FTO inhibitors have been shown to decrease the tumorigenic capacity of AML cells *in vitro* and to halt disease progression in mouse models. One possible explanation could be that m6A methylases and demethylases may control the methylation of different sites on key disease-driving transcripts and different aspects of transcript processing, therefore collaborating in an oncogenic role. For example, METTL3 has been shown to increase translation efficiency of MYC mRNA,[38] while FTO increases its expression through demethylation of sites in 5′ UTR.[361] One can wonder if these effects are truly independent, or if they represent complementary modifications on distinct transcripts. Overall, m6A methylation seems to subtly fine-tune the balance between essential homeostatic functions and pathogenic functions. It is therefore evident that a detailed mapping of the m6A methylome and its regulation by the m6A methylases and demethylases in diverse clinical contexts is necessary to tailor therapeutics. Depending on the dynamic methylome landscape, both an increase or decrease in global m6A levels may be beneficial, or detrimental, for disease progression, making a personalized medicine approach necessary.

Moreover, there are highly context-dependent and even sometimes contradictory effects of RNA adenosine editing and modification enzymes across various diseases, reflecting the complexity of RNA post-transcriptional regulation. While these enzymes influence several aspects of RNA metabolism, their function varies based on cell type, disease subtype, and specific RNA targets. For instance, ADAR1, METTL3, METTL14, FTO, or ALKBH5 may promote tumor survival by stabilizing oncogenic transcripts, yet in other contexts, their activity may enhance immune recognition and suppression of tumor growth (Tables 1 and 4; Table S2). Similarly, Mettl3 and Mettl14 knockdown in hepatic stellate cells *in vitro* lead to opposing effects, with Mettl3-inhibtion ameliorating HSC activation in a Lats2-dependent mechanism,[200] while Mettl14-inhibtion aggravating HSC activation through NOVA2.[201] Furthermore, FTO and ALKBH5 demonstrate opposing roles in bone homeostasis based on the balance of transcript-specific effects on osteogenesis or extracellular matrix degradation (Table S2). Additionally, FTO and ALKBH5 might target

different RNA molecules depending on the cancer type or the specific cellular environment. FTO and ALKBH5 both demethylate m6A-modified RNA, but they may do so in distinct ways or influence different sets of RNA targets (Table S2). These seemingly conflicting findings illustrate how different study models (cells, animals, human tissues) yield complementary but divergent insights. It also underlines the critical need for precise characterization of RNA adenosine editing and modification enzymes in cell-specific, tissue-specific, and transcript-specific roles to guide targeted and effective therapeutic strategies.

Another issue for the effective translation of RNA modification therapeutics in effective clinical drugs are potential sex-specific effects. While the effects of sex on the transcriptome are relatively small, they are genome-wide and mostly mediated through transcription factor binding,[557] a process partly regulated by m6A and RNA editing. Indeed, RNA editing has been suggested as a sex-dependent prognostic factor in glioma, since hyper-editing of PKR, which mediates the activation of transcription factors involved in immune response, was associated with poor survival in female patients but a better outcome in male patients.[558] However, most preclinical studies use explicitly male or female mice, limiting the generalizability of their results, given the sex-specific effects of m6A methylation and RNA editing in certain disease contexts.[558,559] The complex interaction of how m6A methylation and RNA editing alter the physiology of each tissue in a sex-specific manner should be systematically investigated.

Similarly, aging-related changes could also greatly affect the efficacy of small molecules against RNA-modifying enzymes in the clinic. While most preclinical models use young mice (6–10 weeks old), most non-communicable human diseases manifest with increased age, while aging is a major risk factor for prevalent diseases such as cardiovascular, neurological, autoimmune diseases, and cancer.[560] Importantly, the m6A landscape is drastically altered in the tissues of aging primates,[561] while polymorphisms in the RNA editing genes are associated with extreme old age.[562] This shifting landscape of aged RNA methylome and editome highlights a previously unmapped dimension of aging. RNA adenosine editing and modification enzymes may act as molecular switches capable of delaying age-related disorders and extending health span. Understanding how these enzymes influence aging could pave the way for therapeutic strategies targeting these pathways. To bridge preclinical research with clinical applications, studies on small molecule inhibitors of RNA-modifying enzymes in preclinical aging models are crucial for enhancing translatability and therapeutic potential.

Despite the growing interest in targeting RNA editing and modification enzymes, several methodological and conceptual gaps remain that limit the translatability of findings into clinical applications. Current studies often focus on the stability of specific RNA targets without precisely mapping the modified sites. A comprehensive approach involving site-directed mutagenesis could elucidate functional consequences across various overlooked RNA processes, including splicing, nuclear export, translation efficiency, and interactions with RNA-binding proteins, beyond RNA stability. Implementing CRISPR-Cas or site-specific nucleotide modification tools to mutate sites and comparing impacts across different RNA processes in the study design will enhance our understanding of RNA adenosine editing and methylation in disease progression, advancing targeted therapy development.

CONCLUSIONS

Recent advances in RNA modification research have shed light on their regulation and roles in diverse diseases. RNA modification therapies offer a groundbreaking approach to treat diseases by targeting the modifications of RNA, rather than the gene itself. This distinction is essential because many disease-associated genes also have significant homeostatic functions. Directly targeting these genes risks disrupting essential processes such as immune regulation, cell proliferation, and tissue repair. Instead, by focusing on disease-specific RNA modifications, therapies can selectively block harmful gene activity, while preserving its normal function. Small molecule inhibitors targeting modification and editing enzymes like METTL3 and ADAR1 have shown encouraging preclinical and early clinical results, demonstrating the potential to suppress oncogenes or restore normal protein function in genetic diseases. However, the widespread role of these modifications in maintaining normal cellular processes presents a challenge. Broad inhibition of RNA-modifying enzymes can unintentionally disrupt immune responses, stem cell maintenance, or stress adaptation. To address this, emerging technologies like CRISPR-based RNA editing systems enable site-specific editing of pathogenic transcripts without affecting healthy ones. Additionally, disease-associated RNA structures, localization patterns, or RNA-protein interactions can be leveraged to design context-dependent therapies that selectively target dysregulated transcripts. A deeper mechanistic understanding of RNA modifications is essential to unlock their full therapeutic potential. By unraveling how these modifications regulate gene expression, protein synthesis, and cellular behavior, we can design more precise therapies that target pathogenic changes without disrupting essential homeostatic functions. Considering this rapidly evolving and emerging field, future research should prioritize replicating key findings and critically reassessing conclusions across independent studies to strengthen the reliability of RNA editing and RNA modification-related discoveries and their therapeutic potential. This knowledge is the key to transforming RNA modification therapies from promising innovations into powerful, safe, and widely applicable treatments.

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AUTHOR CONTRIBUTIONS

Conceptualization: K.S.; data curation: N.I.V., M.P.-S., A.-P.A., S.T.-C., K.S.; supervision: S.T.-C., K.S.; visualization: A.-P.A., S.T.-C.; writing-original draft: N.I.V., S.T.-C.; writing-review & editing: N.I.V., M.P.-S., A.-P.A., S.T.-C., K.S.

DECLARATION OF INTERESTS

The authors declare no competing interests.

SUPPLEMENTAL INFORMATION

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