MedScience 2026, 20(1): 59−77
https://doi.org/10.1007/s11684-026-1203-5

REVIEW

Emerging role of RNA modification reader YTHDF2 in hematopoiesis, immunity, and cancer

Xin Liu[1,2,*], Sai Xiao[1,2,*], Songqi Duan[1,2], Jianjun Chen[3,4,5], Shoubao Ma (✉)[1,2,4,5]

[1]Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Los Angeles, CA 91010, USA; [2]Hematologic Malignancies Research Institute, City of Hope National Medical Center, Los Angeles, CA 91010, USA; [3]Department of Systems Biology, Beckman Research Institute of City of Hope, Duarte, CA 91010, USA; [4]Center for RNA Biology and Therapeutics, Beckman Research Institute of City of Hope, Duarte, CA 91010, USA; [5]City of Hope Comprehensive Cancer Center, Los Angeles, CA 91010, USA

Abstract **N^6-methyladenosine (m^6A) RNA modification has emerged as a pivotal epitranscriptomic mark shaping RNA metabolism and cellular programs. Among the diverse m^6A reader proteins, YTHDF2 has garnered significant attention as a key regulator of RNA stability. Recent studies highlight the multifaceted roles of YTHDF2 in orchestrating hematopoietic stem cell self-renewal and differentiation, fine-tuning immune cell development and function, and modulating tumor-immune interactions within the tumor microenvironment. YTHDF2 has also been shown to function as a reader for RNA 5-methylcytosine (m^5C) modification. By linking m^6A- and/or m^5C-dependent RNA dynamics to hemato-immune homeostasis, YTHDF2 functions as a central epitranscriptomic integrator linking intrinsic genetic programs to developmental and environmental cues. Here, we summarize current advances in understanding YTHDF2-mediated RNA regulation across physiological and pathological contexts, discuss its potential as a therapeutic target in immune-related diseases and cancers, and highlight future directions in the field.**

Keywords m^6A RNA modification; YTHDF2; RNA metabolism; hematopoiesis; immune regulation; tumor immunity

Introduction

Post-transcriptional regulation plays a critical role in shaping gene expression programs essential for cellular homeostasis and disease progression. Among the diverse chemical modifications on RNA, N^6-methyladenosine (m^6A) is the most abundant internal modification in eukaryotic mRNAs, influencing RNA stability, splicing, translation, and localization [1,2]. The biological effects of m^6A are mediated by a dynamic interplay between methyltransferases ("writers", e.g., METTL3, METTL14, WTAP, KIAA1429, RBM15/RBM15B, ZC3H13, and METTL16), demethylases ("erasers", e.g., FTO and ALKBH5), and m^6A binding proteins ("readers", e.g., YTHDF1/2/3 and IGF2BP1/2/3), which collectively orchestrate RNA fate in response to developmental and environmental cues [3–6]. The broad role of m^6A modification in gene regulation [7], hematological malignancies [8–10], as well as cancer and cancer immunotherapy [11–15] has been extensively reviewed by us and others. In this review, we specifically focus on YTHDF2, given its critical role and the breadth of studies highlighting its involvement in hematopoiesis, immunity, and cancer.

YTHDF2, a prototypical m^6A reader, primarily functions to promote mRNA degradation by recognizing m^6A-modified transcripts and recruiting decay machinery [16,17]. Beyond its canonical role in m^6A recognition, emerging evidence suggests that YTHDF2 may also engage with other RNA modifications, such as 5-methylcytosine (m^5C) [18], reflecting a broader functional versatility within the epitranscriptomic landscape. YTHDF2 exerts widespread regulatory effects on multiple biological processes, including hematopoietic stem cell (HSC) self-renewal, immune cell differentiation and activation, inflammatory response modulation, and tumor-immune interactions [19–22]. Building on these findings, YTHDF2 has emerged as a pivotal post-transcriptional regulator that integrates intrinsic genetic programs with extrinsic environmental cues to fine-tune

Received August 23, 2025; accepted November 26, 2025
Correspondence: Shoubao Ma, shma@coh.org

*These authors contributed equally to this work.

cellular homeostasis [4]. In the hematopoietic system, YTHDF2 safeguards HSC integrity by facilitating the clearance of pro-differentiation transcripts, thus maintaining stemness and supporting stress-induced regeneration [21,23]. In the immune system, YTHDF2 orchestrates lineage specification and functional programming of diverse immune cell subsets [24]. Emerging evidence also links YTHDF2 to the dynamic crosstalk between immune cells and the tumor microenvironment (TME) [17,25]. Thus, by shaping the transcriptomic landscape of both immune effectors and tumor cells, YTHDF2 influences the antitumor immunity, immune evasion, and therapeutic responses.

In this review, we summarize the current understanding of YTHDF2-mediated RNA regulation and its implications for cellular and organismal physiology, including HSC maintenance, immune cell development, functional programming, and the modulation of tumor-immune interactions within the TME. Finally, we discuss the emerging therapeutic potential of targeting YTHDF2 and highlight future directions to guide research in this rapidly evolving field.

Literature search strategy

References for this review were identified through searches of PubMed and Web of Science, with additional articles obtained via Google Scholar and reference mining from key original studies and recent reviews. The search covered literature published between 2014 and 2025, using combinations of the terms "YTHDF2" (or "YTH domain-containing protein 2"), "m^{6}A", "m^{5}C", "hematopoiesis", "immune regulation", "tumor immunity", "cancer", and "inhibitor". Only English-language, peer-reviewed original research and review articles providing mechanistic or functional insights into YTHDF2 were included, whereas conference abstracts, preprints, and correlation-only studies without experimental validation were excluded. Foundational papers in immunology and hematopoiesis were additionally reviewed to provide essential conceptual context.

RNA-stability-dependent and independent role of YTHDF2 in gene expression regulation

The YTHDF family proteins (YTHDF1, YTHDF2, and YTHDF3) share a conserved YTH domain that recognizes m^{6}A-modified transcripts, yet they execute distinct regulatory functions on these targets. YTHDF1 primarily promotes translation of m^{6}A-modified mRNAs through interaction with the translation initiation factor complex 3 (eIF3) [26]. YTHDF3 cooperates with YTHDF1 and YTHDF2 to support either translation or mRNA decay and may show partial functional overlap with YTHDF2 in certain contexts [27,28]. By contrast, YTHDF2 is distinctive for its dual recognition capacity, mediating m^{6}A-mediated RNA decay and m^{5}C-associated stabilization, which underlies its unique and non-redundant function in post-transcriptional regulation [2,17].

As a major m^{6}A reader, YTHDF2 recognizes methylated transcripts and typically promotes their degradation, thereby shaping gene expression post-transcriptionally in an RNA-stability-dependent manner [16,29,30]. Mechanistically, YTHDF2 interacts with the superfamily homology (SH) domain of CNOT1, the scaffolding subunit of the CCR4-NOT deadenylase complex, to recruit this complex, initiating poly(A) tail shortening and subsequent decay of m^{6}A-modified mRNAs by the CAF1 and CCR4 subunits [29]. Besides deadenylation-dependent decay, YTHDF2 can also promote m^{6}A RNA degradation through an endoribonucleolytic pathway. In this process, HRSP12 binds to the GGUUC motif within target transcripts and bridges YTHDF2 to the RNase P/MRP endoribonuclease complex, thereby facilitating site-specific cleavage and rapid degradation of the bound RNAs [30]. m^{5}C is another post-transcriptional modification implicated in the regulation of mRNA metabolism, including transcript stability, export, and translation efficiency [31,32]. Recent evidence indicates that YTHDF2 also acts as a reader of m^{5}C, contributing to mRNA stabilization and enhanced gene expression via recruiting poly(A)-binding protein cytoplasmic 1 (PABPC1) [18,33]. Beyond its canonical role in promoting mRNA decay, a recent study has revealed that YTHDF2 can also facilitate mRNA translation in an RNA-stability-independent manner [34]. In ovarian cancer (OC), YTHDF2 physically interacts with the RNA helicase DDX1 and the eukaryotic translation initiation factor eIF3F to promote the translation of m^{6}A-modified transcripts encoding microtubule-associated proteins such as cytoskeleton-associated protein 2 (CKAP2) [34]. This highlights a previously unrecognized, RNA-stability-independent role of YTHDF2 in promoting protein translation. Together, these findings underscore the multifaceted regulatory functions of YTHDF2 in shaping gene expression through both RNA-stability-dependent decay and RNA-stability-independent translational enhancement (Fig. 1).

Role of YTHDF2 in hematopoiesis

Emerging evidence has highlighted the critical role of m^{6}A RNA modification in regulating hematopoiesis. As a principal m^{6}A reader, YTHDF2 selectively mediates the degradation of methylated transcripts and serves as a pivotal regulator of HSC fate decisions. Early evidence from a zebrafish model by Zhang *et al*. demonstrated that

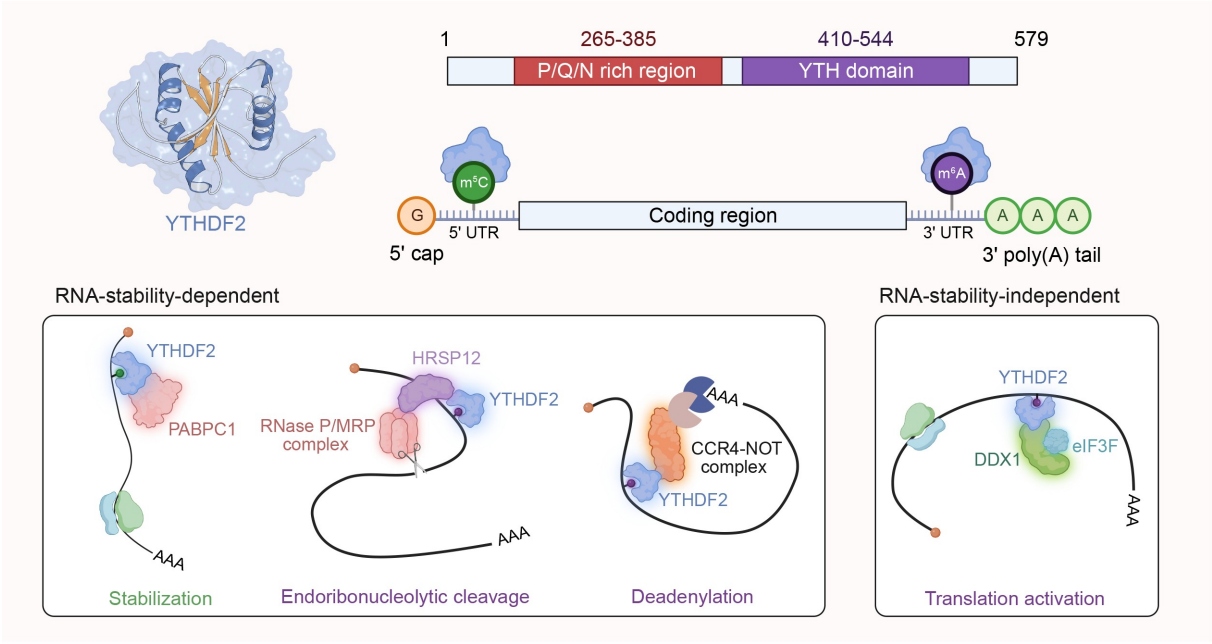

Fig. 1 Molecular mechanisms underlying YTHDF2-mediated RNA fate decisions. YTHDF2 modulates gene expression via RNA-stability-dependent and -independent mechanisms. In the RNA-stability-dependent pathway, YTHDF2 recruits the CCR4-NOT deadenylase complex or mediates endoribonucleolytic cleavage through the HRSP12 and RNase P/MRP to promote m^{6}A RNA degradation. YTHDF2 also acts as an m^{5}C reader, recruiting PABPC1 to stabilize target mRNAs. In the RNA-stability-independent pathway, YTHDF2 interacts with DDX1 and eIF3F to enhance the translation of specific m^{6}A-modified transcripts.

YTHDF2 plays an essential role in hematopoiesis through m^{6}A-dependent mRNA decay, primarily by modulating the Notch signaling pathway required for hematopoietic stem and progenitor cell (HSPC) specification [21]. A critical step of this process is the endothelial-to-hematopoietic transition (EHT), during which HSPCs derive from hemogenic endothelium and acquire hematopoietic identity during embryogenesis [35,36]. Depletion of either METTL3 or YTHDF2 disrupts this transition, resulting in markedly reduced expression of HSPC markers (*runx1*, *cmyb*) and a significant loss of hemogenic endothelial cells and emerging HSPCs [21]. Mechanistically, this phenotype results from impaired YTHDF2-mediated m^{6}A-dependent degradation of arterial transcripts such as *notch1a* and *rhoca*, leading to sustained Notch1 signaling during EHT that maintains endothelial identity and represses HSPC programming [21,37–39]. Under physiologic conditions, m^{6}A methylation enables YTHDF2 to recognize and promote the decay of *notch1a* mRNA, thereby limiting Notch signaling activity to permit the EHT. In the absence of functional m^{6}A modification or YTHDF2 recognition, *notch1a* transcripts exhibit increased stability, resulting in persistent Notch1 activity that preserves endothelial characteristics and ultimately blocks HSPC specification [21]. This finding first reveals a unifying mechanism by which m^{6}A modification, through YTHDF2-dependent mRNA decay, acts as a critical modulator of cell fate decisions in pluripotent and multipotent stem cells during early hematopoietic development.

In the adult hematopoietic system, Li *et al.* first reported that YTHDF2 recognizes m^{6}A-modified transcripts encoding key self-renewal transcription factors, including *Tal1, Gata2, Runx1,* and *Stat5a*, facilitating their degradation and consequently limiting HSC expansion [40]. Conditional deletion of *Ythdf2* in hematopoietic cells markedly increases the number of functional HSCs without affecting lineage differentiation or inducing hematologic malignancies [40]. Similarly, knockdown (KD) of YTHDF2 in human umbilical cord blood (hUCB) HSCs significantly enhances *ex vivo* HSC expansion, colony-forming capacity, and serial transplantation potential [40]. Complementing this finding, Wang *et al.* reported that hematopoietic-specific deletion of *Ythdf2* in mice not only expands HSC numbers but also enhances their regenerative capacity under stress conditions [41]. Mechanistically, YTHDF2 deficiency prevents the degradation of mRNAs encoding Wnt signaling targets, such as *Myc*, *Ccnd1,* and *Axin2*, as well as pro-survival factors, including *Mcl-1* and *Bcl2*, during hematopoietic stress; these combined effects synergistically promote HSC regeneration [41]. Further extending these observations, Mapperley *et al.* demonstrated that YTHDF2 plays an essential role in maintaining long-term HSC function by restraining proinflammatory signaling [42]. While *Ythdf2* deficiency

initially led to HSC expansion, its loss ultimately impaired HSC self-renewal and multilineage hematopoiesis in mice, particularly under serial transplantation or aging conditions [42]. Mechanistically, loss of YTHDF2 in HSCs results in the accumulation of m^{6}A-modified transcripts associated with inflammatory signaling, such as *Stat1*, *Il6ra,* and *Gadd45g*, due to their prolonged half-life [42]. This accumulation of proinflammatory transcripts sustains activation of multiple inflammatory signaling pathways, including IFN-α and IFN-γ responses, TNF-α signaling, and IL6/JAK/STAT3 cascades, thereby driving chronic inflammation that compromises HSC function [42]. Furthermore, YTHDF2 expression was upregulated in response to experimentally induced inflammation and was required to protect HSCs from inflammatory stress [42].

Taken together, these studies collectively establish YTHDF2 as a key regulator of HSC homeostasis, with essential roles in early embryonic HSPC specification, adult HSC expansion, stress-induced regeneration, and the suppression of inflammatory stress responses (Fig. 2). Notably, YTHDF2 plays stage-specific yet evolutionarily conserved roles across hematopoiesis: during embryogenesis, it facilitates the EHT by limiting Notch1 signaling through m^{6}A-dependent mRNA decay, whereas in adult hematopoiesis, it maintains HSC homeostasis by controlling the stability of transcripts involved in self-renewal and inflammatory regulation.

Role of YTHDF2 in immune cell development and function

To provide a comprehensive overview of the multifaceted roles of YTHDF2 in immune regulation, we summarize current mechanistic insights across distinct immune cell subsets (Table 1). YTHDF2 orchestrates the

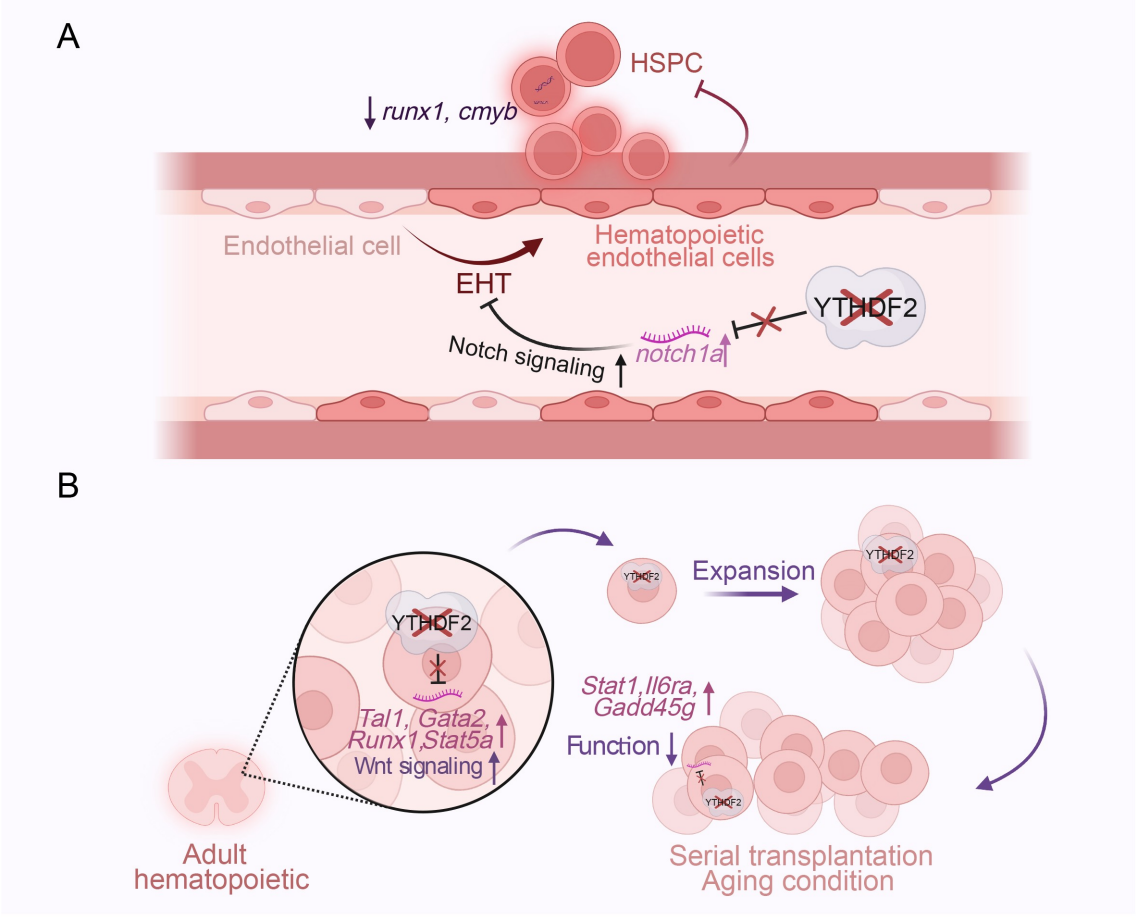

Fig. 2 Multifaceted roles of YTHDF2 in embryonic and adult hematopoiesis. (A) In the zebrafish model, YTHDF2 promotes HSPC specification during the EHT by mediating m^{6}A-dependent decay of arterial endothelial transcripts such as *notch1a*. Loss of YTHDF2 stabilizes *notch1a* mRNA, leading to sustained Notch signaling, maintenance of endothelial identity, and impaired HSPC emergence. (B) In the adult hematopoietic system, loss of YTHDF2 leads to accumulation of m^{6}A-modified transcripts encoding self-renewal factors (*Tal1*, *Gata2*, *Runx1*, and *Stat5a*) and Wnt signaling targets, thereby promoting HSC expansion and enhancing regenerative capacity. In parallel, YTHDF2 deficiency stabilizes inflammatory transcripts (*Stat1*, *Il6ra*, *Gadd45g*), leading to sustained inflammatory signaling that ultimately impairs long-term HSC function.

Table 1 YTHDF2-mediated immune regulation across different immune cell types

Immune cell type	Role of YTHDF2	Mechanistic basis	References
B cells	Developmental and fate commitment regulator	Promotes pro-B proliferation by degrading *Foxo1* and *Rag1*; directs GC fate by repressing PB/PC-associated genes (*Irf4*, *Xbp1*, *Prdm1*, *Sdc1*) at the pre-GC stage	[46,47]
NK cells	Homeostasis and effector regulator	Maintains NK cell homeostasis and maturation via Eomes regulation and m^{6}A-dependent *Tardbp* mRNA decay; essential for IL-15-mediated survival, proliferation, and cytotoxicity; promotes antitumor and antiviral function by sustaining perforin expression and Ly49D$^+$Ly49H$^+$ effector subsets; regulated by SMAD4 to enhance NKG2D expression in CRC; suppressed by lncRNA LINC00707-mediated degradation in HCC	[56–58]
Macrophages	Immunosuppressive	Suppresses M1 polarization via IFN-γ–STAT1 inhibition; regulated by IL-10–STAT3 axis and CX3CL1-CX3CR1-mediated recruitment; promotes M2 polarization through *p53* mRNA decay and NF-κB/MAPK suppression; controls inflammation/ROS via Mettl3-dependent *Pyk2* mRNA decay; drives pro-tumoral polarization in TNBC with reduced antigen presentation	[19,20,61–64]
MDSCs	Immunosuppressive	Degrades *Adrb2*, *Metrnl*, and *Smpdl3b* to sustain NF-κB activity; promotes TGF-β signaling by degrading *Bambi* mRNA under irradiation; promotes *RXRα* mRNA degradation to restrain PMN-MDSCs expansion, chemotaxis, and suppressive function in AIH	[69–71]
CD8$^+$ T cells	Effector and mitochondrial homeostasis regulator	Promotes nuclear RNA synthesis upon activation; maintains mitochondrial fitness by degrading *Coa3*, *Mrpl16*, *Mrps12*, and *Tefm*; cooperates with IKZF1/3 to support open chromatin and effector gene expression	[78]
Treg cells	Immunosuppressive	Forms a TNF–NF-κB–YTHDF2 regulatory loop that sustains intratumoral Treg survival and immunosuppressive activity via degradation of *Nlrc3*, *Nfkbie*, and *Traf3*	[80]
Th9 cells	Immunosuppressive	Restrains Th9 cell differentiation by degrading m^{6}A-modified *Gata3* and *Smad3* transcripts; reduces IL-9, IL-21, and IL-2 production; deletion enhances Th9 cell-mediated antitumor immunity by promoting infiltration and activation of DCs, CD8$^+$ T cells, and NK cells in the TME	[81]

development, homeostasis, and effector functions of B cells, natural killer (NK) cells, macrophages, myeloid-derived suppressor cells (MDSCs), CD8$^+$ T cells, and CD4$^+$ T cell subsets, including regulatory T (Treg) cells and T helper 9 (Th9) cells. These effects are highly context-dependent, highlighting YTHDF2 as a multifaceted regulator of immune responses (Fig. 3).

YTHDF2 directs early B cell proliferation and germinal center fate commitment

B cells are central to adaptive immunity, responsible for antibody production, antigen presentation, and long-term immunological memory. Their development proceeds through defined stages in the bone marrow, beginning with HSCs and progressing through pro-B, pre-B, immature, and mature B cell stages [43]. Upon antigen encounter in secondary lymphoid organs, mature B cells can further differentiate into either antibody-secreting plasmablasts or germinal center B (GC B) cells, the latter undergoing clonal expansion, somatic hypermutation, and affinity maturation to generate high-affinity antibodies and memory B cells [44]. During early B cell development in the bone marrow, IL-7 signaling plays a pivotal role in supporting the proliferation and survival of pro-B cells [45]. Recent evidence reveals that YTHDF2 facilitates this process by promoting the decay of m^{6}A-modified transcripts that would otherwise restrain cell cycle progression [46]. In large pre-B cells, a subset of transcripts bearing high levels of m^{6}A modifications, including *Foxo1* and *Rag1*, which negatively regulate cell cycle progression, is selectively bound and destabilized by YTHDF2 [46]. Functionally, conditional deletion of *Ythdf2* in B-lineage cells leads to a moderate developmental block between the pro-B and late large pre-B stages and results in reduced total B cell numbers in the spleen [46]. *In vitro* proliferation assays further confirm that *Ythdf2*-deficient pro-B cells display a markedly impaired proliferative response to IL-7 stimulation [46]. Notably, the subsequent transition from large pre-B to small pre-B cells remains unaffected by YTHDF2 loss, highlighting a stage-specific requirement for YTHDF2-mediated RNA decay during early B lymphopoiesis [46].

Beyond early development, YTHDF2 also plays a pivotal role in B cell differentiation during adaptive immune responses. Upon antigen stimulation, B cell precursors at the pre-GC stage upregulate YTHDF2 expression, which promotes the degradation of m^{6}A-modified transcripts involved in the plasmablast (PB) genetic program [47]. This post-transcriptional repression prevents premature commitment to the PB lineage and facilitates the establishment of the GC B cell fate. Loss of *Ythdf2* in B cells selectively impairs GC B cell formation

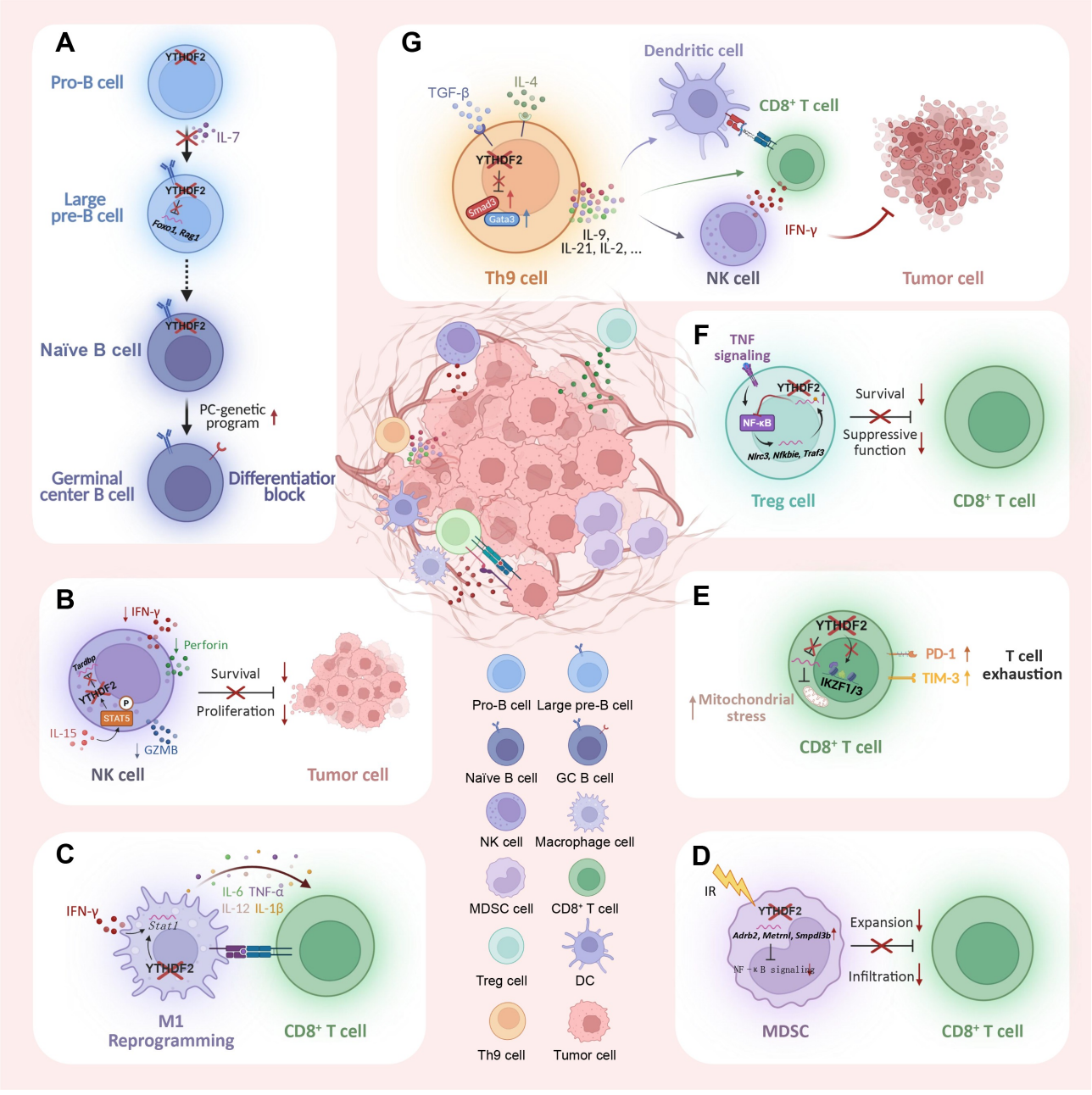

Fig. 3 Overview of YTHDF2 functions in immune cell differentiation and effector function. (A) YTHDF2 promotes pro-B cell proliferation by degrading m^{6}A-modified transcripts such as *Foxo1* and *Rag1*, thereby facilitating IL-7-driven cell cycle progression. (B) YTHDF2 is transcriptionally induced by IL-15-activated STAT5 and sustains NK cell survival, proliferation, and effector functions by degrading m^{6}A-modified *Tardbp* mRNA. Loss of YTHDF2 impairs IFN-γ, perforin, and granzyme B production, thereby weakening antitumor activity. (C) YTHDF2 restrains M1-type macrophage polarization by promoting *Stat1* mRNA decay and limiting IFN-γ-STAT1 signaling. YTHDF2 deficiency increases proinflammatory cytokines (IL-6, TNF-α, IL-12, IL-1β) and enhances CD8$^+$ T cell-mediated antitumor immunity. (D) YTHDF2 promotes the degradation of *Adrb2*, *Metrnl*, and *Smpdl3b* mRNAs, sustaining NF-κB signaling and driving MDSC expansion and tumor infiltration, thereby suppressing antitumor immunity. (E) YTHDF2 depletion in CD8$^+$ T cells leads to accumulation of m^{6}A-modified mitochondrial transcripts, causing mitochondrial stress and permitting IKZF1/3-mediated repression, which in turn increases PD-1 and TIM-3 expression and promotes T cell exhaustion. (F) TNF-driven NF-κB activation in intratumoral Treg cells induces YTHDF2 expression, which promotes the decay of m^{6}A-modified transcripts encoding NF-κB negative regulators (*Nlrc3*, *Nfkbie*, and *Traf3*), sustaining NF-κB activity, supporting Treg survival and suppressive function in the TME. (G) YTHDF2 deficiency in Th9/Tc9 cells stabilizes m^{6}A-modified *Gata3* and *Smad3* transcripts, enhancing IL-2, IL-9, and IL-21 production, reprogramming the TME, and promoting DC, CD8$^+$ T, and NK cell infiltration and activation to amplify antitumor immunity.

while leaving antigen-induced proliferation and activation largely intact, indicating that YTHDF2 is dispensable for early activation but essential for directing lineage commitment toward the GC program [47]. Transcriptomic analysis further revealed that *Ythdf2*-deficient GC-phenotype ($GL7^+$ FAS^+) B cells aberrantly upregulate expression of genes typically expressed in PBs and plasma cells, including *Irf4*, *Xbp1*, *Sdc1*, and *Prdm1*, indicating a failure to suppress the PB/PC differentiation program [47]. Together, these observations support that post-transcriptional suppression of PB-associated gene expression by YTHDF2 is essential for directing appropriate B cell fate commitment during the early stages of adaptive immune responses.

YTHDF2 orchestrates NK cell development and antitumor/antiviral function

NK cells are cytotoxic innate lymphoid cells that constitute a critical component of the innate immune system. They exert potent antitumor and antiviral effects by inducing target cell apoptosis through perforin/granzyme release and death receptor pathways, and by secreting cytokines such as IFN-γ and TNF-α [48–51]. The development, maturation, and effector functions of NK cells are tightly controlled by cytokine signaling (notably IL-15), transcriptional regulators such as Eomes and T-bet, and post-transcriptional mechanisms, including RNA modifications [52–55].

A recent study uncovered the multifaceted regulatory roles of YTHDF2-mediated m^6A methylation in NK cell immunity [56]. YTHDF2 regulates NK cell homeostasis and terminal maturation by modulating cell trafficking and controlling the expression of Eomes, a key transcription factor for NK cell differentiation [56]. Moreover, YTHDF2 is transcriptionally upregulated by STAT5 downstream of IL-15 signaling and is essential for IL-15-mediated NK cell survival, proliferation, and effector functions [56]. Mechanistically, YTHDF2 maintains NK cell homeostasis and effector function by selectively binding to m^6A-modified *Tardbp* mRNA and promoting its degradation [56]. Consistent with a broader role in host defense, YTHDF2 is constitutively expressed at high levels in NK cells and is further induced by IL-15 stimulation, murine cytomegalovirus (MCMV) infection, and tumor challenge [56]. In the B16F10 melanoma lung-metastasis model, NK cell-specific deletion of *Ythdf2* (*Ythdf2*$^{\Delta NK}$ mice) results in reduced NK cell infiltration into tumor sites and diminished expression of IFN-γ, granzyme B, and perforin, leading to increased metastatic burden, a phenotype further validated by adoptive transfer of *Ythdf2*$^{\Delta NK}$ or *Ythdf2*^{WT} NK cells into NK/T/B cell-deficient (*Rag2*$^{-/-}$*Il2rg*$^{-/-}$) mice [56]. During MCMV infection, *Ythdf2*-deficient NK cells show impaired expansion, reduced proliferation, and decreased percentages of $Ly49D^+$ $Ly49H^+$ effector NK cell subsets, accompanied by a marked reduction in perforin but not IFN-γ or granzyme B production, suggesting a predominant role for perforin-mediated antiviral activity [56]. Recent studies have identified a SMAD4–YTHDF2 regulatory axis in NK cells that is critical for sustaining antitumor function within the TME of colorectal cancer (CRC) [57]. SMAD4 expression is markedly reduced in NK cells infiltrated in CRC tumors, correlating with impaired cytotoxicity. Enforced overexpression of SMAD4 significantly enhanced NK cell cytotoxicity against CRC cells, highlighting its functional importance [57]. Mechanistically, YTHDF2 acts as a downstream effector of SMAD4, mediating the post-transcriptional control of m^6A-modified RNAs involved in NK cell activation and cytotoxicity [57]. Elevated SMAD4 expression increased YTHDF2 abundance, which in turn promoted the activating receptor NKG2D, thereby amplifying NK cell cytotoxicity toward CRC cells [57]. Conversely, another study demonstrated that the lncRNA LINC00707 facilitates the ubiquitin-dependent degradation of YTHDF2, impairing NK cell cytotoxicity and promoting hepatocellular carcinoma (HCC) progression [58]. LINC00707 was identified as the most significantly upregulated lncRNA in HCC tissues and acts as an oncogene by driving HCC cell proliferation, migration, and invasion [58]. Mechanistic investigations revealed that LINC00707 directly binds to YTHDF2 and promotes its ubiquitination-mediated proteasomal degradation, thereby reducing YTHDF2 protein levels and compromising NK cell cytotoxicity [58]. Overall, YTHDF2 emerges as a central regulator of NK cell development and antitumor function, whose activity is finely tuned by transcriptional programs and lncRNA-mediated pathways, with significant implications for immune surveillance and tumor progression.

YTHDF2 deficiency promotes antitumoral macrophage differentiation

Macrophages are highly plastic immune cells that play central roles in orchestrating inflammatory responses and shaping the TME. Depending on environmental cues, they can adopt distinct functional phenotypes, ranging from pro-inflammatory, antitumoral M1 macrophages to anti-inflammatory, tumor-promoting M2 macrophages [59]. Tumor-associated macrophages (TAMs) predominantly exhibit an M2-like phenotype, which supports tumor progression, angiogenesis, and immune suppression [60]. Reprogramming TAMs toward an M1 phenotype represents a promising strategy to enhance antitumor immunity.

An early study showed that YTHDF2 knockdown promotes antitumoral (M1) macrophage polarization by enhancing LPS-induced production of proinflammatory

cytokines, including IL-6, TNF-α, IL-1β, and IL-12, indicating that YTHDF2 functions as a negative regulator of M1-type macrophage polarization [61]. Subsequent studies further demonstrated that YTHDF2 deficiency promotes the reprogramming of TAMs toward an antitumoral M1 phenotype. Knockout of *Ythdf2* in TAMs significantly inhibits tumor growth in both ovalbumin (OVA)-expressing B16 (B16-OVA) melanoma and MC38 colon carcinoma mouse models [19]. Mechanistically, YTHDF2 deficiency stabilizes *Stat1* mRNA and further activates the IFN-γ–STAT1 signaling pathway to promote M1 reprogramming [19]. Notably, YTHDF2 expression is regulated by the IL-10–STAT3 signaling axis, and targeting YTHDF2 in TAMs has been shown to enhance $CD8^+$ T cell-mediated antitumor immunity and improve the efficacy of PD-L1 blockade therapy [19]. In addition, tumoral YTHDF2 plays a crucial role in shaping the tumor immune microenvironment by modulating macrophage polarization [20]. Specifically, YTHDF2 deficiency within tumor cells promotes the recruitment of macrophages via CX3CL1–CX3CR1 axis and drives their polarization toward an inflammatory, antitumoral M1 phenotype in the presence of $CD8^+$ T cell-associated IFN-γ, thereby enhancing antigen presentation and antitumor immune responses [20]. Consistently, independent studies have further highlighted the multifaceted role of YTHDF2 in macrophage immunity. YTHDF2 regulates macrophage polarization via distinct mechanisms in M1 and M2 subsets, promoting M2 polarization by facilitating *p53* mRNA degradation while suppressing M1 polarization through inhibition of NF-κB, p38, and JNK signaling pathways [62]. The Mettl3–YTHDF2–*Pyk2* axis has been identified as a key post-transcriptional pathway controlling macrophage inflammatory responses and ROS production, with YTHDF2 directly binding *Pyk2* mRNA in a *Mettl3*-dependent manner to modulate MAPK/AKT signaling and NADPH oxidase activity [63]. In triple-negative breast cancer (TNBC), YTHDF2 promotes the polarization of intra-tumoral macrophages toward a pro-tumoral, immunosuppressive phenotype, which is associated with reduced antigen presentation and SPI1-driven transcriptional programs [64]. Collectively, these findings establish YTHDF2 as a pivotal regulator of macrophage functional programming, integrating cytokine signaling, post-transcriptional control, and tumor-derived cues to shape immune polarization and antitumor immunity.

YTHDF2 regulates the expansion and function of MDSCs

MDSCs are a heterogeneous population of immature myeloid cells that expand in cancer, autoimmune diseases, and other conditions associated with chronic or persistent inflammation. They inhibit T cell activation, promote regulatory T cell differentiation, and remodel the TME to favor immune evasion and tumor progression [65–67]. Based on their lineage origin, MDSCs are classified into two major subsets in both humans and mice: granulocytic/polymorphonuclear MDSCs (PMN-MDSCs), which derive from the granulocytic lineage, and monocytic MDSCs (M-MDSCs), which originate from the monocytic lineage [68]. Owing to their critical role in maintaining an immunosuppressive milieu, MDSCs have emerged as key targets for improving antitumor immunity.

A recent study found the significance of YTHDF2 in modulating antitumor immunity during radiotherapy (RT). Ionizing radiation (IR) induces YTHDF2 expression in MDSCs through NF-κB activation, which in turn promotes their expansion, tumor infiltration, and immunosuppressive function in both murine and human tumors [69]. Myeloid-specific *Ythdf2* deficiency remodels the MDSC compartment by altering their differentiation and limiting accumulation, ultimately enhancing the antitumor efficacy of RT [69]. Mechanistically, YTHDF2 directly degrades transcripts such as *Adrb2*, *Metrnl*, and *Smpdl3b*, which encode negative regulators of NF-κB signaling, thereby forming an IR–YTHDF2–NF-κB regulatory circuit that sustains immunosuppressive activity in irradiated MDSCs [69]. Another independent mechanism involves the TGF-β pathway, controlled by YTHDF2 through bone morphogenetic protein and activin membrane-bound inhibitor (*Bambi*) transcript degradation. IR specifically downregulates BAMBI in MDSCs in both murine models and humans via YTHDF2-mediated, m^6A-dependent mRNA decay, a process dependent on NF-κB signaling [70]. Decreased BAMBI expression activates TGF-β signaling in MDSCs, initiating a positive feedback loop that reinforces their immunosuppressive activity. Restoring BAMBI using adeno-associated viral delivery (AAV-Bambi) reverses these effects, improving antitumor immunity and synergizing with RT to suppress local tumors and distant metastasis [70]. However, a recent study demonstrated that the role of YTHDF2 in MDSCs is context dependent. In a model of ConA-induced hepatitis, *Ythdf2*-deficient MDSCs exhibit increased expansive and suppressive function, resulting in reduced immune-mediated liver injury [71]. Mechanistically, suppression of YTHDF2 promotes the proliferation and function of MDSCs through upregulation of RXRα transcripts, a key transcription factor governing the expression of lipid metabolism-related genes [71]. Therefore, these findings underscore the dualistic nature of YTHDF2 in immune regulation; therapeutic targeting of YTHDF2 must be highly context-specific, with careful consideration of disease type, immune landscape, and treatment modality.

YTHDF2 maintains CD8$^+$ T cell antitumor activity

CD8$^+$ T cells are pivotal mediators of adaptive antitumor immunity, distinguished by their antigen-specific recognition of tumor-derived peptides presented by MHC class I molecules. Upon activation, they undergo clonal expansion and differentiate into cytotoxic T lymphocytes (CTLs) capable of eliminating malignant or infected cells through antigen-directed killing and transcriptionally regulated effector functions [72,73]. However, under chronic antigen exposure and/or sustained inflammatory signaling, CD8$^+$ T cells may enter an exhausted state. These exhausted CD8$^+$ T cells are characterized by a progressive loss of effector functions, reduced memory recall and maintenance capacity, and sustained upregulation of multiple inhibitory receptors such as PD-1, TIM-3, and LAG-3 [74,75]. To overcome T cell exhaustion and restore antitumor immunity, immune checkpoint blockade (ICB) therapies have been developed to target inhibitory pathways such as the PD-1/PD-L1 axis. Blockade of the PD-1 pathway can partially reverse T cell exhaustion and enhance immune responses in both chronic infections and cancer [76,77].

Recent studies have revealed that YTHDF2 is a critical mediator of CD8$^+$ T cell antitumor immunity by integrating m^{6}A-dependent RNA metabolism with transcriptional and epigenetic regulation. Although predominantly cytoplasmic under homeostatic conditions, YTHDF2 translocates to the nucleus in an m^{6}A-dependent manner upon early activation or reactivation of T cells, where it facilitates nascent RNA synthesis [78]. In the cytoplasm, YTHDF2 maintains mitochondrial homeostasis by promoting the m^{6}A-dependent decay of transcripts such as *Coa3*, *Mrpl16*, *Mrps12*, and *Tefm*, which would otherwise accumulate and disrupt metabolic fitness in CD8$^+$ T cells [78]. In addition, YTHDF2 interacts with the transcriptional repressors IKZF1 and IKZF3, contributing to the maintenance of an open chromatin state and supporting the sustained transcription of effector genes required for CD8$^+$ T cell polyfunctionality [78]. Therapeutically, the impaired effector function and PD-1 resistance observed upon conditional knockout of *Ythdf2* in T cells can be partially rescued by pharmacologic inhibition of IKZF1/3 using lenalidomide. In MC38-bearing murine tumor models, combination treatment with lenalidomide and PD-1 blockade markedly restored cytokine production and tumor control in *Ythdf2*-deficient mice, nearly eradicating tumors in some cases [78].

YTHDF2 regulates CD4$^+$ T cell differentiation and antitumor function

CD4$^+$ T cells are a heterogeneous population of lymphocytes essential for orchestrating adaptive immune responses and shaping the tumor immune landscape. Upon activation, naïve CD4$^+$ T cells differentiate into multiple effector subsets, including Th1, Th2, Th17, Tfh, Th9, and Treg cells, each characterized by distinct cytokine profiles and transcriptional programs [79]. In general, the dynamic balance between effector and regulatory CD4$^+$ T cell subsets plays a pivotal role in shaping antitumor immunity. Recent studies have revealed that YTHDF2 modulates this balance by restraining Treg-mediated immunosuppression and promoting the differentiation and effector function of antitumor Th9 cells [80,81]. YTHDF2 plays a context-specific role in sustaining the survival and suppressive function of Treg cells within the TME. Conditional deletion of *Ythdf2* in Treg cells significantly reduces tumor growth in murine models, including B16F10 melanoma and MC38 colon carcinoma, without perturbing peripheral immune homeostasis [80]. Mechanistically, intratumoral Treg cells upregulate YTHDF2 in response to TNF-driven NF-κB activation. YTHDF2, in turn, promotes the degradation of m^{6}A-modified transcripts encoding negative regulators of NF-κB signaling, including *Nlrc3*, *Nfkbie*, and *Traf3*, thereby sustaining NF-κB activity [80]. This positive feedback loop enhances Treg survival and immunosuppressive function within tumors. In the absence of YTHDF2, Tregs undergo increased apoptosis, reduced intratumoral accumulation, and impaired ability to suppress local immune responses [80]. Targeting YTHDF2 in Treg cells may therefore represent a viable strategy to relieve immunosuppression within tumors and selectively enhance antitumor immunity, while preserving peripheral immune homeostasis.

Tumor necrosis factor (TNF) is a rapidly induced proinflammatory cytokine produced by multiple immune cell types, including CD4$^+$ T cells, and must be tightly regulated to prevent excessive inflammation [82,83]. A recent study demonstrated that activation of human primary CD4$^+$ T cells leads to increased m^{6}A methylation of *TNF* mRNA, predominantly in the 3′ untranslated region [84]. YTHDF2 directly binds m^{6}A-modified *TNF* transcripts and promotes their degradation, functioning as a negative feedback mechanism to rapidly downregulate TNF production during early immune responses [84]. Pharmacologic modulation of m^{6}A levels confirmed its functional relevance, as inhibition of the demethylase FTO with entacapone reduced TNF protein and mRNA expression, whereas inhibition of METTL3 with STM2457 or CRISPR/Cas9-mediated METTL3 knockout reduced m^{6}A levels and increased TNF expression [84]. A recent study from our group uncovered a pivotal role for YTHDF2 in T helper cell differentiation [81]. Genetic ablation of *Ythdf2* in naïve CD4$^+$ T cells did not affect differentiation into Th1, Th2, Th17, or Treg subsets, but significantly enhanced Th9 cell differentiation in both

mice and humans [81]. Mechanistically, YTHDF2 deficiency promotes Th9 polarization by stabilizing *Gata3* mRNA in the presence of IL-4 signaling [85] and *Smad3* mRNA downstream of TGF-β signaling [86], two transcription factors known to directly regulate Th9 differentiation [87–89]. Th9 cells possess unique properties that stimulate robust antitumor responses by engaging both adaptive and innate immunity [81,90–94]. Our findings demonstrate that YTHDF2-deficient, antigen-specific Th9 cells produce elevated levels of IL-9 and IL-21, which enhance the infiltration and cytotoxic activity of NK cells and $CD8^+$ T cells, thereby suppressing tumor growth in three distinct murine tumor models [81]. Building on these insights, we engineered YTHDF2-disrupted human chimeric antigen receptor (CAR) Th9 cells targeting epidermal growth factor receptor (EGFR) or prostate stem cell antigen (PSCA) [81]. These modified CAR Th9 cells secreted higher levels of IL-9 and IL-21 compared to their wild-type counterparts [81]. *In vivo*, YTHDF2-deficient CAR Th9 cells exhibited superior antitumor efficacy in both lung and pancreatic cancer xenograft models [81]. Collectively, these findings identify YTHDF2 as a key regulator of Th9 cell differentiation and effector function and suggest that targeting YTHDF2 may enhance the therapeutic potential of CAR T cell immunotherapies.

YTHDF2 in cancer progression and tumor immunity

Dual roles of YTHDF2 in cancer progression

In solid tumors, YTHDF2 predominantly acts as an oncogenic factor through diverse mechanisms. In lung adenocarcinoma (LUAD), YTHDF2 facilitates tumor proliferation and metastasis by degrading *AXIN1* and activating the Wnt/β-catenin pathway [95]. In HCC, multiple studies reveal its multifaceted roles: it promotes cancer stemness and metastasis via stabilizing OCT4 expression [96], enhances immune evasion and angiogenesis by upregulating the ETV5/PD-L1/VEGFA axis [97], and its oncogenic function is further potentiated by O-GlcNAcylation, sustaining tumor growth in HBV-related HCC [98]. Additionally, YTHDF2 forms co-condensates with CRTC2 to boost translation of oncogenic m^6A-modified transcripts such as *LRP5* and *c-Jun*, driving HCC development and contributing to lenvatinib resistance [99]. In other malignant solid tumors, YTHDF2 promotes prostate cancer (PCa) progression through multiple m^6A-dependent mechanisms. One study revealed that elevated levels of METTL3 and YTHDF2 correlate with poor prognosis in PCa patients [100]. Mechanistically, YTHDF2 directly binds to m^6A-modified transcripts of *LHPP* and *NKX3-1*, promoting their degradation and thereby enhancing AKT phosphorylation and downstream oncogenic signaling. Functionally, knockdown of either METTL3 or YTHDF2, or overexpression of LHPP and NKX3-1, suppresses tumor cell proliferation and migration through inhibition of AKT signaling [100]. Another study further demonstrated that YTHDF2 facilitates PCa invasion and metastasis by recognizing METTL3-mediated m^6A modification of *USP4* mRNA and inducing its degradation via HNRNPD recruitment, thereby triggering downstream signaling alterations [101]. In glioblastoma (GBM), PRMT6 and CDK9 co-regulate YTHDF2 expression, and elevated YTHDF2 promotes migration, invasion, and epithelial-mesenchymal transition (EMT) by degrading *APC* and *GSK3β* mRNAs, thereby activating the Wnt/β-catenin pathway and driving GBM progression [102]. In ocular melanoma, a study provided the first evidence of a mechanistic crosstalk between histone lactylation and m^6A methylation in tumorigenesis [103]. Elevated histone lactylation was observed in ocular melanoma tissues and correlated with poor prognosis [103]. Mechanistically, increased histone lactylation promotes YTHDF2 transcription, which in turn recognizes m^6A-modified *PER1* and *TP53* mRNAs and leads to their degradation, thereby suppressing the expression of these tumor-suppressor genes and accelerating tumorigenesis [103]. Pharmacological inhibition of histone lactylation using the glycolysis inhibitors 2-deoxy-D-glucose (2-DG) and oxamate, or simultaneous silencing of LDHA and LDHB, effectively reduced YTHDF2 expression and suppressed ocular melanoma growth both *in vitro* and *in vivo*, identifying YTHDF2 as a novel oncogenic driver in ocular melanoma [103]. Notably, beyond its canonical mRNA decay function, YTHDF2 also exerts an RNA-stability-independent role in OC by promoting the translation of m^6A-modified transcripts, which contributes to tumor progression and chemotherapy resistance [34].

In hematological malignancies, YTHDF2 similarly exhibits pro-tumorigenic roles but through mechanisms distinct from those in solid tumors. In acute myeloid leukemia (AML), YTHDF2 is essential for the maintenance of leukemia stem cells (LSCs). Paris *et al*. demonstrated that YTHDF2 sustains the survival and self-renewal of LSCs by facilitating the degradation of multiple m^6A-modified transcripts, notably including *Tnfrsf2* (TNFR2), whose accumulation in *Ythdf2*-deficient LSCs sensitizes the cells to apoptosis [23]. In parallel, YTHDF2 also promotes AML progression by binding to m^6A-modified precursor microRNA-126 (pre-miR-126) and recruiting AGO2 to facilitate its maturation into oncogenic miR-126 [104], which further reinforces LSC self-renewal and leukemogenesis by targeting multiple downstream genes, including *ADAM9*, *ILK*, and *CDK3* [105–107]. Collectively, these studies indicate that YTHDF2 drives AML progression through both mRNA

degradation-dependent and microRNA maturation-dependent mechanisms. Importantly, YTHDF2 appears dispensable for normal HSC function, and its deletion may even enhance HSC activity, underscoring its potential as a selective therapeutic target in AML [21]. In multiple myeloma (MM), YTHDF2 has been shown to promote malignant cell proliferation by activating the STAT5A/MAP2K2/p-ERK axis and the EGR1/$p21^{cip1/waf1}$/CDK2-Cyclin E1 axis [108,109]. Extending these findings, a recent study by Chen *et al*. revealed that YTHDF2 plays a pivotal oncogenic role in B cell malignancies. Its overexpression alone was sufficient to drive B cell acute lymphoblastic leukemia (B-ALL) initiation [18]. Mechanistically, YTHDF2 functions as a dual RNA modification reader: as an m^5C reader, it stabilizes transcripts such as *ATP5PB*, *ATP5MG*, and *ATP5MF* by recruiting PABPC1, thereby enhancing mitochondrial ATP synthesis to fuel malignant proliferation; as an m^6A reader, it suppresses the expression of CD19 and HLA-DMA/B (major histocompatibility complex (MHC) class II molecules) and thereby promotes B-ALL cells escape from immune surveillance [18].

Despite its predominantly pro-tumorigenic roles, emerging evidence indicates that YTHDF2 can also function as a tumor suppressor in specific contexts, highlighting its dual role in cancer progression. In HCC, YTHDF2 suppresses tumor growth by promoting the m^6A-dependent degradation of *EGFR* mRNA, thereby inhibiting ERK/MEK signaling, cellular proliferation, and tumor growth potential [110]. Furthermore, YTHDF2 maintains vascular homeostasis and restrains inflammation-mediated malignancy by degrading *IL11* and *SERPINE2* transcripts, and its loss accelerates vascular remodeling and metastatic progression [22]. Similarly, in gastric cancer, YTHDF2 functions as a tumor suppressor by upregulating PPP2CA in an m^6A-independent manner and inhibiting the FOXC2 signaling pathway, while clinical evidence associates its expression with improved prognosis in patients [111–113].

Taken together, these findings underscore the dual, context-dependent roles of YTHDF2 in cancer progression. This context dependency, particularly evident in HCC, likely arises from tumor microenvironmental influences such as hypoxia, inflammation, and metabolic stress, which dynamically modulate YTHDF2 expression, post-translational modifications, and target specificity. While YTHDF2 predominantly acts as an oncogenic driver in both solid tumors and hematological malignancies, it can exert tumor-suppressive effects under specific molecular or microenvironmental contexts, such as in HCC and gastric cancer, reflecting the influence of cancer type, molecular signaling, and TME-derived cues (Table 2).

YTHDF2 orchestrates tumor immune evasion

Tumor immune evasion refers to the capacity of malignant cells to avoid recognition and elimination by the host immune system, despite the presence of tumor-associated antigens and active immune surveillance [114]. Among various immune escape strategies, suppressed antigen presentation and restricted immune cell infiltration are key processes regulated by YTHDF2.

Table 2 Dual roles of YTHDF2 in cancer progression across different tumor types

Cancer type	Role of YTHDF2	Mechanistic basis	References
Lung adenocarcinoma	Oncogenic	*AXIN1* degradation; Wnt/β-catenin pathway activation	[95]
Hepatocellular carcinoma	Oncogenic/Tumor-suppressive	*OCT4* stabilization; ETV5/PD-L1/VEGFA axis activation; O-GlcNAcylation; *LRP5*, *c-Jun* mRNA translation; *EGFR*, *IL11*, *SERPINE2* mRNA degradation	[22,96–99,110]
Prostate cancer	Oncogenic	*LHPP* and *NKX3-1* mRNA degradation; AKT phosphorylation; METTL3-mediated m^6A modification recognition; HNRNPD recruitment; *USP4* mRNA degradation	[100,101]
Glioblastoma	Oncogenic	PRMT6/CDK9-mediated YTHDF2 upregulation; *APC*, *GSK3β* mRNA degradation; Wnt/β-catenin pathway activation	[102]
Ocular melanoma	Oncogenic	Histone lactylation-induced YTHDF2 upregulation; degradation of m^6A-modified *PER1* and *TP53* mRNAs	[103]
Ovarian cancer	Oncogenic	RNA-stability-independent role: DDX1/eIF3F-mediated translation of m^6A-modified microtubule-associated mRNAs (e.g., *CKAP2*)	[34]
Acute myeloid leukemia	Oncogenic	LSC survival and self-renewal maintenance; degradation of m^6A-modified transcripts (e.g., *Tnfrsf2*)	[23]
Multiple myeloma	Oncogenic	STAT5A/MAP2K2/p-ERK axis activation; EGR1/$p21^{cip1/waf1}$/CDK2-Cyclin E1 axis activation	[108,109]
B cell acute lymphoblastic leukemia	Oncogenic	m^5C-driven stabilization of *ATP5PB*, *ATP5MG*, *ATP5MF* via PABPC1 recruitment; m^6A-driven degradation of immune recognition transcripts (*CD19*, *HLA-DMA/B*)	[18]
Gastric cancer	Tumor-suppressive	*PPP2CA* upregulation (m^6A-independent); *FOXC2* signaling inhibition	[111–113]

Through its control of RNA metabolism, YTHDF2 orchestrates critical steps of tumor immune evasion, shaping an immunosuppressive microenvironment and impairing antitumor immune responses (Fig. 4). Mechanistically, YTHDF2 accelerates the degradation of m^{6}A-modified *Cx3cl1* transcripts, thereby restricting the chemokine-driven recruitment of CX3CR1$^+$ inflammatory macrophages and cytotoxic CD8$^+$ T cells into the TME [20]. This suppression contributes to the establishment of an immune-excluded TME that limits antigen presentation and impairs effector T cell activation. In addition to blocking immune cell infiltration, YTHDF2

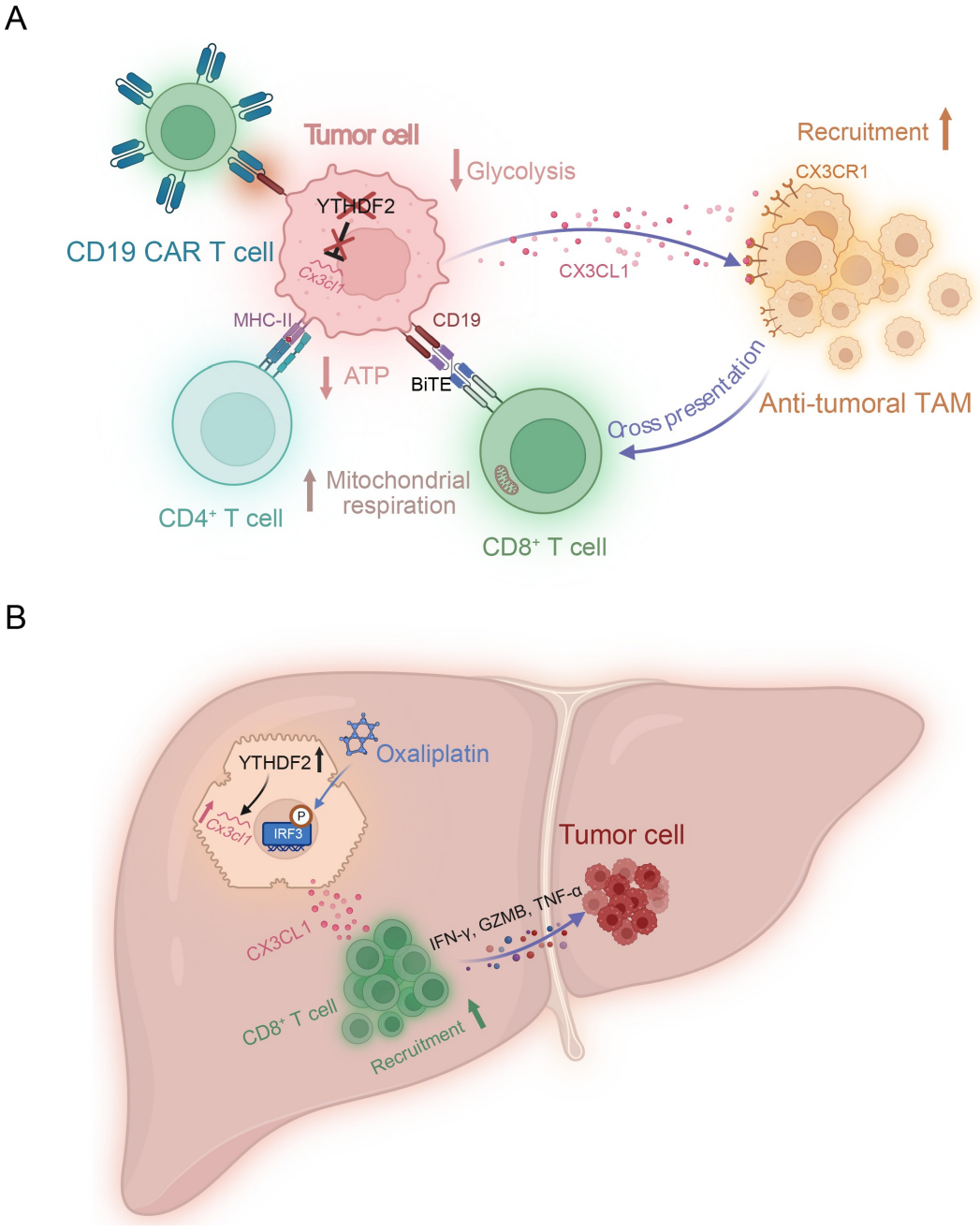

Fig. 4 YTHDF2 orchestrates tumor immune evasion or promotes antitumor immunity in a context-dependent manner. (A) In malignant cells, YTHDF2 drives immune evasion by degrading m^{6}A-modified *Cx3cl1* transcripts to suppress CX3CL1-mediated recruitment of CX3CR1$^+$ macrophages and CD8$^+$ T cells, sustaining glycolytic activity to metabolically restrain CD8$^+$ T cells, and destabilizing *CD19* and *HLA-DMA/B* transcripts to impair antigen presentation and recognition by CD4$^+$ T cells, CD8$^+$ T cells, and CD19-CAR-T cells. (B) In peritumoral hepatocytes, oxaliplatin induces YTHDF2 expression via the cGAS–STING–IRF3 axis, leading to m^{6}A-dependent stabilization of *Cx3cl1* transcripts and enhanced CD8$^+$ T cell recruitment, thereby promoting antitumor immunity.

suppresses the polarization of tumor-infiltrating macrophages toward an antitumoral M1-like phenotype and restrains their capacity for antigen cross-presentation, particularly under IFN-γ stimulation [20]. Loss of YTHDF2 in tumor cells enhances the accumulation and functionality of antitumoral macrophages, thereby facilitating $CD8^+$ T cell-mediated cytotoxic responses [20]. Furthermore, YTHDF2 sustains tumor glycolytic activity, which imposes metabolic constraints on infiltrating $CD8^+$ T cells. Deletion of YTHDF2 reduces glycolysis, promotes mitochondrial respiration in $CD8^+$ T cells, and restores their effector function and persistence within the TME [20]. Notably, IFN-γ produced by activated $CD8^+$ T cells contributes to the degradation of tumor-intrinsic YTHDF2, establishing a positive feedback loop that enhances $CD8^+$ T cell-mediated cytotoxicity [20].

In addition to immune cell exclusion, YTHDF2 further impairs antitumor immunity by reducing tumor cell immunogenicity through selective degradation of m^6A-modified transcripts [18]. Notably, YTHDF2 targets key components of the antigen-presentation machinery, including CD19 and HLA-DMA/B, whose expression is essential for B cell recognition by CAR-T cells and effective peptide loading onto MHC class II molecules [18]. By recruiting canonical RNA decay effectors such as CNOT1/6 and HRSP12 to these mRNAs, YTHDF2 facilitates their degradation and thereby limits surface antigen availability [18]. This process enables malignant B cells to evade T cell-mediated killing, including that elicited by CD19-targeted therapies such as blinatumomab and CD19-CAR-T cells [18]. Conversely, YTHDF2 depletion stabilizes these transcripts, restores antigen expression to functionally significant levels, enhances immune synapse formation, and sensitizes tumors to adoptive T cell therapy [18].

By contrast, the immunoregulatory role of YTHDF2 appears to be highly context dependent. While tumor-intrinsic YTHDF2 promotes immune evasion by limiting chemokine expression and impairing antigen presentation, recent findings have demonstrated that YTHDF2 in peritumoral hepatocytes plays an opposing role in liver cancer [115]. Oxaliplatin (OXA), a platinum-based chemotherapeutic agent commonly used in liver and colorectal cancers, induces YTHDF2 expression in hepatocytes via activation of the cGAS–STING–IRF3 signaling axis, leading to m^6A-dependent stabilization of *Cx3cl1* transcripts [115–117]. This, in turn, promotes the recruitment and activation of $CD8^+$ T cells, thereby facilitating effective antitumor immunity [115].

Together, these findings establish YTHDF2 as a context-dependent regulator of tumor immune dynamics. In malignant cells, YTHDF2 promotes immune evasion by restricting immune infiltration and destabilizing antigen-presentation machinery, thereby suppressing both innate and adaptive immune responses. In contrast, YTHDF2 enhances antitumor immunity in nonmalignant cells, such as peritumoral hepatocytes, by stabilizing chemokine transcripts and promoting $CD8^+$ T cell recruitment. These divergent roles underscore the importance of cell type-specific considerations when targeting m^6A regulators in cancer. Therapeutically, precision modulation of YTHDF2 offers a promising strategy to reshape the tumor immune microenvironment, enhance tumor immunogenicity, and improve responses to immunotherapies, including ICB and CD19-CAR-T cell therapy.

YTHDF2 inhibition as a therapeutic strategy

The concept of targeting YTHDF2 for cancer therapy is supported by accumulating preclinical evidence and the development of selective inhibitors. The first proof-of-concept was provided by a study demonstrating that pharmacologic inhibition of YTHDF2 with DC-Y13-27 effectively enhanced RT efficacy by counteracting IR-induced immunosuppression [69]. Screening an in-house compound library using fluorescence polarization (FP)-based high-throughput assays, researchers identified DC-Y13-27, a compound that blocks YTHDF2-m^6A interactions with an IC_{50} of 21.8 ± 1.8 μmol/L. Selectivity profiling revealed a marked preference for YTHDF2 over YTHDF1, which showed significantly weaker inhibition (IC_{50} of 165.2 ± 7.7 μmol/L) [69]. Mechanistically, YTHDF2 blockade disrupted the IR-NF-κB positive feedback loop, attenuated MDSC expansion and suppressive activity, and restored antitumor immunity. Notably, combining DC-Y13-27 with PD-L1 blockade produced synergistic effects, supporting the incorporation of YTHDF2 inhibitors into RT/immunotherapy regimens to overcome radioresistance [69].

Subsequently, DF-A7 was identified as a potent YTHDF2 degrader through a structure-based virtual screening followed by a fluorescent reporter assay [20]. DF-A7 mediated selective YTHDF2 degradation with an IC_{50} of approximately 50 nmol/L, while sparing YTHDF1 and YTHDF3 [20]. Functional studies confirmed that DF-A7 restored the expression of YTHDF2 targets such as *Cx3cl1* and *PRR5* and significantly inhibited tumor growth in both MC38 and B16-OVA tumor models. Importantly, the antitumor activity of DF-A7 was immune-dependent, as shown by increased infiltration of $CD8^+$ T cells and antitumoral macrophages, and was abrogated in immunodeficient mice [20]. DF-A7 exerted its antitumor effects by alleviating immunosuppressive signaling and reprogramming the TME to favor immune activation. Combining DF-A7 with PD-1/PD-L1 checkpoint blockade further enhanced therapeutic efficacy, providing a strong rationale for integrating

YTHDF2-targeting degraders into immunotherapy strategies, particularly in tumors refractory to current treatments [20].

In addition, CCI-38 was identified as a selective YTHDF2 inhibitor through structure-based virtual screening and validated by drug affinity responsive target stability (DARTS) and fluorescence thermal shift assays [18]. CCI-38 preferentially binds to YTHDF2 over YTHDF1 and YTHDF3, with a dissociation constant (K_D) of 10.1 ± 0.978 μmol/L [18]. Functional assays demonstrated that CCI-38 competitively blocks the binding of m^{6}A- and m^{5}C-modified RNA to YTHDF2, thereby restoring the expression of immune recognition molecules such as CD19 and HLA-DMA/B, reversing antigen escape in relapsed patient samples with low CD19 abundance and resensitizing these cells to CD19-CAR-T cytotoxicity [18]. In patient-derived xenograft models, CCI-38 treatment alone reduced malignant B cell burden, delayed leukemia progression, and prolonged survival, while its combination with CD19-CAR-T cells or blinatumomab produced synergistic therapeutic effects. This study provides preclinical evidence that targeting YTHDF2 with CCI-38, either alone or in combination with CAR-T or BiTE-based therapies, may offer a promising strategy for treating relapsed or refractory B cell malignancies by restoring immune recognition and overcoming antigen escape [18].

A recent study reported the identification of phenylpyrazole-based compounds as selective inhibitors of YTHDF2, with CK-75 emerging as a potent candidate [118]. Using a pipeline of orthogonal assays, including FP, Amplified Luminescent Proximity Homogeneous Assay Screen (AlphaScreen), and electrophoretic mobility shift assay (EMSA), CK-75 was shown to block YTHDF2-m^{6}A RNA interactions, achieving complete inhibition at 25 μmol/L [118]. Selectivity profiling demonstrated that CK-75 did not exhibit detectable inhibition of m^{6}A binding to YTHDF1, YTHDF3, YTHDC1, or YTHDC2, indicating high specificity for YTHDF2 [118]. Cellular assays further demonstrated that YTHDF2 inhibition by CK-75 induced cell cycle arrest, promoted apoptosis, and significantly reduced the viability of cancer cells [118].

Beyond selective inhibition of YTHDF2, N-7 was identified as a pan-YTH inhibitor through screening of a nucleoside analog library against the YTH domain of YTHDF1 [119]. Using FP competition assays, N-7 was shown to inhibit m^{6}A RNA binding across all five human YTH domains (YTHDF1, YTHDF2, YTHDF3, YTHDC1, and YTHDC2), with IC_{50} values ranging from 30 to 48 μmol/L [119]. Direct interaction between N-7 and YTH domains was further confirmed by a thermal shift assay [119]. As a pan-inhibitor, N-7 expands the chemical landscape of m^{6}A reader inhibitors and provides a valuable tool compound for probing YTH-dependent biology, while offering a potential starting point for next-generation inhibitors with improved potency and selectivity.

Among currently available YTHDF2 inhibitors (Table 3), the degrader DF-A7 shows the highest apparent potency (IC_{50} ≈ 50 nmol/L) with strong selectivity over YTHDF1/3 [20]. DC-Y13-27 blocks the YTHDF2-m^{6}A interaction with an IC_{50} of 21.8 ± 1.8 μmol/L [69]. CCI-38 preferentially binds to YTHDF2 (K_D = 10.1 ± 0.98 μmol/L) over YTHDF1/3 [18]. CK-75 achieves complete blockade of YTHDF2-m^{6}A binding at 25 μmol/L, with minimal activity toward other YTH readers [118]. N-7, a pan-YTH tool compound (IC_{50} 30–48 μmol/L across YTHDF1/2/3 and YTHDC1/2), is useful for probing YTH biology but is currently limited by selectivity and potency [119]. Collectively, these inhibitors represent a spectrum of YTHDF2-targeting strategies, with DF-A7 likely being the most potent and selective. DC-Y13-27 and CK-75 show distinct translational potential in RT sensitization and tumor-cell inhibition, CCI-38 functions as an immune-restoring agent in antigen-escape B cell malignancies, and N-7 serves as a broad pan-YTH probe, albeit with limited potency.

Overall, these preclinical studies highlight the translational potential of pharmacologic YTHDF2 inhibition in oncology. By disrupting YTHDF2-RNA

Table 3 Small-molecule inhibitors target YTHDF2

Inhibitor	Discovery/screening method	Potency (IC_{50}/K_D)	Selectivity	References
DC-Y13-27	FP-based HTS of in-house compound library	IC_{50} = 21.8 ± 1.8 μmol/L	Preferential for YTHDF2 over YTHDF1 (IC_{50} = 165.2 ± 7.7 μmol/L)	[69]
DF-A7	Structure-based virtual screening followed by fluorescent reporter assay	IC_{50} ≈ 50 nmol/L	Selective for YTHDF2 over YTHDF1/3	[20]
CCI-38	Structure-based virtual screening with DARTS and fluorescence thermal shift assays	K_D = 10.1 ± 0.978 μmol/L	Selective for YTHDF2 over YTHDF1/3	[18]
CK-75	FP, AlphaScreen, and EMSA	Complete inhibition at 25 μmol/L	High specificity for YTHDF2 (no inhibition of YTHDF1/3/DC1/DC2)	[118]
N-7	Nucleoside analog library screening with FP competition assay and thermal shift assay	IC_{50} = 30–48 μmol/L	Pan-inhibitor of YTHDF1/2/3/DC1/DC2	[119]

interactions or promoting targeted protein degradation, small-molecule inhibitors such as DC-Y13-27, DF-A7, CCI-38, CK-75, and N-7 have demonstrated the ability to restore immune recognition, overcome antigen escape, and reprogram the TME to favor antitumor immunity. These findings not only validate YTHDF2 as a druggable target but also provide a framework for its incorporation into multimodal cancer therapy, including RT, ICB, and adoptive cell therapies. Future efforts will be needed to optimize the potency, selectivity, and pharmacokinetic properties of YTHDF2 inhibitors, paving the way for their clinical translation and broad application in cancer treatment.

Conclusions and perspectives

YTHDF2 has emerged as a central regulator of RNA metabolism and tumor-immune interactions, exhibiting a highly context-dependent dual role. While it frequently promotes oncogenic signaling and facilitates immune evasion, it can, in certain settings, contribute to antitumor immunity through immune-regulatory mechanisms [18–20,69,80]. This complexity underscores both the therapeutic promise and the inherent challenges associated with targeting YTHDF2 in cancer.

Given the diverse roles of YTHDF2 in tumor progression and immune regulation, targeting YTHDF2 is most likely to achieve maximal benefit when integrated into rational combination strategies. Preclinical evidence suggests that YTHDF2 inhibition synergizes with ICB, RT, and adoptive T cell therapies by reversing immunosuppressive programs and restoring immune surveillance [18,20,69]. These findings provide a framework for clinical development in tumors resistant to standard immunotherapy. Within this broader framework, recent advances in m^5C methylation research further emphasize the therapeutic relevance of targeting RNA-modification readers in cancer and immune-related diseases, supporting the notion of YTHDF2 as a dual (m^6A/m^5C) reader with translational potential [120,121].

Beyond small-molecule inhibitors, RNA-based therapeutic approaches offer an alternative strategy to suppress YTHDF2 expression. siRNA-loaded nanoparticles and aptamer–liposome systems have demonstrated promising efficacy in HCC, reducing PD-L1 expression and angiogenesis while enhancing antitumor immunity [97]. Such delivery platforms may enable tumor-selective targeting and mitigate systemic toxicity, which remains a key challenge given the context-dependent role of YTHDF2 in normal immune and hematopoietic function.

Future research should prioritize the development of clinically viable YTHDF2 inhibitors with improved selectivity and pharmacokinetics, as well as biomarker-driven patient stratification to identify tumors most likely to respond. Comprehensive evaluation of safety profiles, particularly regarding HSC and T cell function, will be essential. Collectively, these strategies highlight the potential of YTHDF2 as an actionable epitranscriptomic target, paving the way for combination therapies that integrate epigenetic modulation with immunotherapy and conventional modalities.

Acknowledgements

This work was supported by the National Institutes of Health (NIH), the National Institute of Allergy and Infectious Diseases (NIAID) (No. 1R01AI192847, Shoubao Ma), and the New Investigator Research Grant Program of The Leukemia Research Foundation (Shoubao Ma).

Compliance with ethics guidelines

Conflicts of interest Xin Liu, Sai Xiao, Songqi Duan, Jianjun Chen, and Shoubao Ma declare that they have no conflict of interest.

This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

References

1. Roundtree IA, Evans ME, Pan T, He C. Dynamic RNA modifications in gene expression regulation. Cell 2017; 169(7): 1187–1200
2. Ma S, Barr T, Yu J. Recent advances of RNA m^6A modifications in cancer immunoediting and immunotherapy. Cancer Treat Res 2023; 190: 49–94
3. Shi H, Wei J, He C. Where, when, and how: context-dependent functions of RNA methylation writers, readers, and erasers. Mol Cell 2019; 74(4): 640–650
4. Zhao BS, Roundtree IA, He C. Post-transcriptional gene regulation by mRNA modifications. Nat Rev Mol Cell Biol 2017;

18(1): 31–42
5. Yang Y, Hsu PJ, Chen YS, Yang YG. Dynamic transcriptomic m^{6}A decoration: writers, erasers, readers and functions in RNA metabolism. Cell Res 2018; 28(6): 616–624
6. Li X, Zheng M, Ma S, Nie F, Yin Z, Liang Y, Yan X, Wen W, Yu J, Liang Y, Huang S, Han H. YTHDC1 is a therapeutic target for B-cell acute lymphoblastic leukemia by attenuating DNA damage response through the KMT2C-H3K4me1/me3 epigenetic axis. Leukemia 2025; 39(2): 308–322
7. Liu Y, Yang D, Liu T, Chen J, Yu J, Yi P. N6-methyladenosine-mediated gene regulation and therapeutic implications. Trends Mol Med 2023; 29(6): 454–467
8. Qing Y, Su R, Chen J. RNA modifications in hematopoietic malignancies: a new research frontier. Blood 2021; 138(8): 637–648
9. Chen M, Chen Y, Wang K, Deng X, Chen J. Non-m^{6}A RNA modifications in haematological malignancies. Clin Transl Med 2024; 14(6): e1666
10. Zhang L, Lou Y, Li W, Guo H, Truong Nguyen LX, Chen Z. RNA m^{6}A modification: a key regulator in normal and malignant processes. Cell Investig 2025; 1(2): 100023
11. Li W, Deng X, Chen J. RNA-binding proteins in regulating mRNA stability and translation: roles and mechanisms in cancer. Semin Cancer Biol 2022; 86(Pt 2): 664–677
12. Li X, Ma S, Deng Y, Yi P, Yu J. Targeting the RNA m^{6}A modification for cancer immunotherapy. Mol Cancer 2022; 21(1): 76
13. Deng X, Qing Y, Horne D, Huang H, Chen J. The roles and implications of RNA m^{6}A modification in cancer. Nat Rev Clin Oncol 2023; 20(8): 507–526
14. Li Y, Huang H, Wu S, Zhou Y, Huang T, Jiang J. The role of RNA m^{6}A modification in cancer glycolytic reprogramming. Curr Gene Ther 2023; 23(1): 51–59
15. Mehmood R. Ramifications of m^{6}A modification on ncRNAs in cancer. Curr Genomics 2024; 25(3): 158–170
16. Wang X, Lu Z, Gomez A, Hon GC, Yue Y, Han D, Fu Y, Parisien M, Dai Q, Jia G, Ren B, Pan T, He C. N6-methyladenosine-dependent regulation of messenger RNA stability. Nature 2014; 505(7481): 117–120
17. Xiao S, Duan S, Caligiuri MA, Ma S, Yu J. YTHDF2: a key RNA reader and antitumor target. Trends Immunol 2025; 46(6): 485–498
18. Chen Z, Zeng C, Yang L, Che Y, Chen M, Sau L, Wang B, Zhou K, Chen Y, Qing Y, Shen C, Zhang T, Wunderlich M, Wu D, Li W, Wang K, Leung K, Sun M, Tang T, He X, Zhang L, Swaminathan S, Mulloy JC, Müschen M, Huang H, Weng H, Xiao G, Deng X, Chen J. YTHDF2 promotes ATP synthesis and immune evasion in B cell malignancies. Cell 2025; 188(2): 331–351.e30
19. Ma S, Sun B, Duan S, Han J, Barr T, Zhang J, Bissonnette MB, Kortylewski M, He C, Chen J, Caligiuri MA, Yu J. YTHDF2 orchestrates tumor-associated macrophage reprogramming and controls antitumor immunity through CD8$^+$ T cells. Nat Immunol 2023; 24(2): 255–266
20. Xiao S, Ma S, Sun B, Pu W, Duan S, Han J, Hong Y, Zhang J, Peng Y, He C, Yi P, Caligiuri MA, Yu J. The tumor-intrinsic role of the m^{6}A reader YTHDF2 in regulating immune evasion. Sci Immunol 2024; 9(95): eadl2171
21. Zhang C, Chen Y, Sun B, Wang L, Yang Y, Ma D, Lv J, Heng J, Ding Y, Xue Y, Lu X, Xiao W, Yang YG, Liu F. m^{6}A modulates haematopoietic stem and progenitor cell specification. Nature 2017; 549(7671): 273–276
22. Hou J, Zhang H, Liu J, Zhao Z, Wang J, Lu Z, Hu B, Zhou J, Zhao Z, Feng M, Zhang H, Shen B, Huang X, Sun B, Smyth MJ, He C, Xia Q. YTHDF2 reduction fuels inflammation and vascular abnormalization in hepatocellular carcinoma. Mol Cancer 2019; 18(1): 163
23. Paris J, Morgan M, Campos J, Spencer GJ, Shmakova A, Ivanova I, Mapperley C, Lawson H, Wotherspoon DA, Sepulveda C, Vukovic M, Allen L, Sarapuu A, Tavosanis A, Guitart AV, Villacreces A, Much C, Choe J, Azar A, van de Lagemaat LN, Vernimmen D, Nehme A, Mazurier F, Somervaille TCP, Gregory RI, O'Carroll D, Kranc KR. Targeting the RNA m^{6}A reader YTHDF2 selectively compromises cancer stem cells in acute myeloid leukemia. Cell Stem Cell 2019; 25(1): 137–148.e6
24. Winkler R, Gillis E, Lasman L, Safra M, Geula S, Soyris C, Nachshon A, Tai-Schmiedel J, Friedman N, Le-Trilling VTK, Trilling M, Mandelboim M, Hanna JH, Schwartz S, Stern-Ginossar N. m^{6}A modification controls the innate immune response to infection by targeting type I interferons. Nat Immunol 2019; 20(2): 173–182
25. Zhang L, Chen C, Feng J, Zhang H, Nguyen LXT, Chen Z. The role of YTHDF2 in anti-tumor immunity. Cell Investig 2025; 1(1): 100008
26. Wang X, Zhao BS, Roundtree IA, Lu Z, Han D, Ma H, Weng X, Chen K, Shi H, He C. *N*^{6}-methyladenosine modulates messenger RNA translation efficiency. Cell 2015; 161(6): 1388–1399
27. Shi H, Wang X, Lu Z, Zhao BS, Ma H, Hsu PJ, Liu C, He C. YTHDF3 facilitates translation and decay of *N*^{6}-methyladenosine-modified RNA. Cell Res 2017; 27(3): 315–328
28. Lasman L, Krupalnik V, Viukov S, Mor N, Aguilera-Castrejon A, Schneir D, Bayerl J, Mizrahi O, Peles S, Tawil S, Sathe S, Nachshon A, Shani T, Zerbib M, Kilimnik I, Aigner S, Shankar A, Mueller JR, Schwartz S, Stern-Ginossar N, Yeo GW, Geula S, Novershtern N, Hanna JH. Context-dependent functional compensation between Ythdf m^{6}A reader proteins. Genes Dev 2020; 34(19-20): 1373–1391
29. Du H, Zhao Y, He J, Zhang Y, Xi H, Liu M, Ma J, Wu L. YTHDF2 destabilizes m^{6}A-containing RNA through direct recruitment of the CCR4-NOT deadenylase complex. Nat Commun 2016; 7(1): 12626
30. Park OH, Ha H, Lee Y, Boo SH, Kwon DH, Song HK, Kim YK. Endoribonucleolytic cleavage of m^{6}A-containing RNAs by RNase P/MRP complex. Mol Cell 2019; 74(3): 494–507.e8
31. Nombela P, Miguel-López B, Blanco S. The role of m^{6}A, m^{5}C and Ψ RNA modifications in cancer: novel therapeutic opportunities. Mol Cancer 2021; 20(1): 18
32. Guarnacci M, Preiss T. The *je ne sais quoi* of 5-methylcytosine in messenger RNA. RNA 2024; 30(5): 560–569
33. Yang Y, Wang L, Han X, Yang WL, Zhang M, Ma HL, Sun BF, Li A, Xia J, Chen J, Heng J, Wu B, Chen YS, Xu JW, Yang X, Yao H, Sun J, Lyu C, Wang HL, Huang Y, Sun YP, Zhao YL, Meng A, Ma J, Liu F, Yang YG. RNA 5-Methylcytosine facilitates the maternal-to-zygotic transition by preventing maternal mRNA decay. Mol Cell 2019; 75(6): 1188–1202.e11
34. Liu T, Yang D, Wei Q, Wang Y, Tian L, Liu X, Yang Y, Luo Q, Xu J, Liu Y, Yang C, Zuo X, Luo F, Luo X, Zhao H, Li L, Xu J, Yu J, Ma S, Yu J, Yi P. The RNA-stability-independent role of the RNA m^{6}A reader YTHDF2 in promoting protein translation to confer tumor chemotherapy resistance. Mol Cell 2025; 85(12):

2320–2336.e9
35. Kissa K, Herbomel P. Blood stem cells emerge from aortic endothelium by a novel type of cell transition. Nature 2010; 464(7285): 112–115
36. Bertrand JY, Chi NC, Santoso B, Teng S, Stainier DYR, Traver D. Haematopoietic stem cells derive directly from aortic endothelium during development. Nature 2010; 464(7285): 108–111
37. Lizama CO, Hawkins JS, Schmitt CE, Bos FL, Zape JP, Cautivo KM, Borges Pinto H, Rhyner AM, Yu H, Donohoe ME, Wythe JD, Zovein AC. Repression of arterial genes in hemogenic endothelium is sufficient for haematopoietic fate acquisition. Nat Commun 2015; 6(1): 7739
38. Gama-Norton L, Ferrando E, Ruiz-Herguido C, Liu Z, Guiu J, Islam ABMMK, Lee SU, Yan M, Guidos CJ, López-Bigas N, Maeda T, Espinosa L, Kopan R, Bigas A. Notch signal strength controls cell fate in the haemogenic endothelium. Nat Commun 2015; 6(1): 8510
39. Zhang P, He Q, Chen D, Liu W, Wang L, Zhang C, Ma D, Li W, Liu B, Liu F. G protein-coupled receptor 183 facilitates endothelial-to-hematopoietic transition via Notch1 inhibition. Cell Res 2015; 25(10): 1093–1107
40. Li Z, Qian P, Shao W, Shi H, He XC, Gogol M, Yu Z, Wang Y, Qi M, Zhu Y, Perry JM, Zhang K, Tao F, Zhou K, Hu D, Han Y, Zhao C, Alexander R, Xu H, Chen S, Peak A, Hall K, Peterson M, Perera A, Haug JS, Parmely T, Li H, Shen B, Zeitlinger J, He C, Li L. Suppression of m^{6}A reader Ythdf2 promotes hematopoietic stem cell expansion. Cell Res 2018; 28(9): 904–917
41. Wang H, Zuo H, Liu J, Wen F, Gao Y, Zhu X, Liu B, Xiao F, Wang W, Huang G, Shen B, Ju Z. Loss of YTHDF2-mediated m^{6}A-dependent mRNA clearance facilitates hematopoietic stem cell regeneration. Cell Res 2018; 28(10): 1035–1038
42. Mapperley C, van de Lagemaat LN, Lawson H, Tavosanis A, Paris J, Campos J, Wotherspoon D, Durko J, Sarapuu A, Choe J, Ivanova I, Krause DS, von Kriegsheim A, Much C, Morgan M, Gregory RI, Mead AJ, O'Carroll D, Kranc KR. The mRNA m^{6}A reader YTHDF2 suppresses proinflammatory pathways and sustains hematopoietic stem cell function. J Exp Med 2021; 218(3): e20200829
43. Hardy RR, Hayakawa K. B cell development pathways. Annu Rev Immunol 2001; 19(1): 595–621
44. Victora GD, Nussenzweig MC. Germinal centers. Annu Rev Immunol 2012; 30(1): 429–457
45. Ochiai K, Maienschein-Cline M, Mandal M, Triggs JR, Bertolino E, Sciammas R, Dinner AR, Clark MR, Singh H. A self-reinforcing regulatory network triggered by limiting IL-7 activates pre-BCR signaling and differentiation. Nat Immunol 2012; 13(3): 300–307
46. Zheng Z, Zhang L, Cui XL, Yu X, Hsu PJ, Lyu R, Tan H, Mandal M, Zhang M, Sun HL, Sanchez Castillo A, Peng J, Clark MR, He C, Huang H. Control of early B cell development by the RNA *N*^{6}-methyladenosine methylation. Cell Rep 2020; 31(13): 107819
47. Grenov A, Hezroni H, Lasman L, Hanna JH, Shulman Z. YTHDF2 suppresses the plasmablast genetic program and promotes germinal center formation. Cell Rep 2022; 39(5): 110778
48. Chiossone L, Dumas PY, Vienne M, Vivier E. Natural killer cells and other innate lymphoid cells in cancer. Nat Rev Immunol 2018; 18(11): 671–688
49. Vivier E, Raulet DH, Moretta A, Caligiuri MA, Zitvogel L, Lanier LL, Yokoyama WM, Ugolini S. Innate or adaptive immunity? The example of natural killer cells. Science 2011; 331(6013): 44–49
50. Ma S, Caligiuri MA, Yu J. Harnessing natural killer cells for lung cancer therapy. Cancer Res 2023; 83(20): 3327–3339
51. Ma S, Yu J, Caligiuri MA. Natural killer cell-based immunotherapy for cancer. J Immunol 2025; 214(7): 1444–1456
52. Huntington ND, Vosshenrich CAJ, Di Santo JP. Developmental pathways that generate natural-killer-cell diversity in mice and humans. Nat Rev Immunol 2007; 7(9): 703–714
53. Gordon SM, Chaix J, Rupp LJ, Wu J, Madera S, Sun JC, Lindsten T, Reiner SL. The transcription factors T-bet and Eomes control key checkpoints of natural killer cell maturation. Immunity 2012; 36(1): 55–67
54. Ma S, Caligiuri MA, Yu J. Harnessing IL-15 signaling to potentiate NK cell-mediated cancer immunotherapy. Trends Immunol 2022; 43(10): 833–847
55. Sayegh M, Ma S, Yu J. Application of natural killer immunotherapy in blood cancers and solid tumors. Curr Opin Oncol 2023; 35(5): 446–452
56. Ma S, Yan J, Barr T, Zhang J, Chen Z, Wang LS, Sun JC, Chen J, Caligiuri MA, Yu J. The RNA m^{6}A reader YTHDF2 controls NK cell antitumor and antiviral immunity. J Exp Med 2021; 218(8): e20210279
57. Li X, Wang Y, Cai L, Huang S. SMAD4 enhances the cytotoxic efficacy of human NK cells against colorectal cancer cells via the m^{6}A reader YTHDF2. Front Immunol 2024; 15: 1440308
58. Wei M, Lu L, Ma J, Luo Z, Tan X, Wang J. LINC00707 impairs the natural killer cell antitumour activity in hepatocellular carcinoma through decreasing YTHDF2 stability. J Cell Mol Med 2024; 28(5): e18106
59. Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 2011; 11(11): 723–737
60. Jaiswal S, Chao MP, Majeti R, Weissman IL. Macrophages as mediators of tumor immunosurveillance. Trends Immunol 2010; 31(6): 212–219
61. Yu R, Li Q, Feng Z, Cai L, Xu Q. m^{6}A reader YTHDF2 regulates LPS-induced inflammatory response. Int J Mol Sci 2019; 20(6): 1323
62. Cai L, Li D, Feng Z, Gu X, Xu Q, Li Q. YTHDF2 regulates macrophage polarization through NF-κB and MAPK signaling pathway inhibition or p53 degradation. Dis Markers 2022; 2022: 3153362
63. Cai Y, Yu R, Zhang Z, Li D, Yi B, Feng Z, Xu Q. Mettl3/Ythdf2 regulate macrophage inflammation and ROS generation by controlling Pyk2 mRNA stability. Immunol Lett 2023; 264: 64–73
64. Jin H, Chen Y, Zhang D, Lin J, Huang S, Wu X, Deng W, Huang J, Yao Y. YTHDF2 favors protumoral macrophage polarization and implies poor survival outcomes in triple negative breast cancer. iScience 2024; 27(6): 109902
65. Ma S, Cheng Q, Cai Y, Gong H, Wu Y, Yu X, Shi L, Wu D, Dong C, Liu H. IL-17A produced by γδ T cells promotes tumor growth in hepatocellular carcinoma. Cancer Res 2014; 74(7): 1969–1982
66. Kumar V, Patel S, Tcyganov E, Gabrilovich DI. The nature of myeloid-derived suppressor cells in the tumor microenvironment. Trends Immunol 2016; 37(3): 208–220
67. Gabrilovich DI. Myeloid-derived suppressor cells. Cancer

Immunol Res 2017; 5(1): 3–8
68. Veglia F, Sanseviero E, Gabrilovich DI. Myeloid-derived suppressor cells in the era of increasing myeloid cell diversity. Nat Rev Immunol 2021; 21(8): 485–498
69. Wang L, Dou X, Chen S, Yu X, Huang X, Zhang L, Chen Y, Wang J, Yang K, Bugno J, Pitroda S, Ding X, Piffko A, Si W, Chen C, Jiang H, Zhou B, Chmura SJ, Luo C, Liang HL, He C, Weichselbaum RR. YTHDF2 inhibition potentiates radiotherapy antitumor efficacy. Cancer Cell 2023; 41(7): 1294–1308.e8
70. Wang L, Si W, Yu X, Piffko A, Dou X, Ding X, Bugno J, Yang K, Wen C, Zhang L, Chen D, Huang X, Wang J, Arina A, Pitroda S, Chmura SJ, He C, Liang HL, Weichselbaum R. Epitranscriptional regulation of TGF-β pseudoreceptor BAMBI by m^{6}A/YTHDF2 drives extrinsic radioresistance. J Clin Invest 2023; 133(24): e172919
71. Lyu Z, Huang B, Zhang J, Qian Q, Pu X, Cui N, Ou Y, Li B, You Z, Lian M, Tang R, Chen W, Zhao Z, Hou J, Gershwin ME, Zhang H, Xia Q, Ma X. Suppression of YTHDF2 attenuates autoimmune hepatitis by expansion of myeloid-derived suppressor cells. J Autoimmun 2023; 135: 102993
72. Koh CH, Lee S, Kwak M, Kim BS, Chung Y. CD8 T-cell subsets: heterogeneity, functions, and therapeutic potential. Exp Mol Med 2023; 55(11): 2287–2299
73. Farhood B, Najafi M, Mortezaee K. CD8$^+$ cytotoxic T lymphocytes in cancer immunotherapy: a review. J Cell Physiol 2019; 234(6): 8509–8521
74. McLane LM, Abdel-Hakeem MS, Wherry EJ. CD8 T cell exhaustion during chronic viral infection and cancer. Annu Rev Immunol 2019; 37(1): 457–495
75. Wherry EJ, Kurachi M. Molecular and cellular insights into T cell exhaustion. Nat Rev Immunol 2015; 15(8): 486–499
76. Pauken KE, Wherry EJ. Overcoming T cell exhaustion in infection and cancer. Trends Immunol 2015; 36(4): 265–276
77. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science 2018; 359(6382): 1350–1355
78. Zhang H, Luo X, Yang W, Wu Z, Zhao Z, Pei X, Zhang X, Chen C, Lei JH, Shi Q, Zhao Q, Chen Y, Wu W, Zeng Z, Ju HQ, Qiu M, Liu J, Shen B, Chen M, Chen J, Deng CX, Xu RH, Hou J. YTHDF2 upregulation and subcellular localization dictate CD8 T cell polyfunctionality in anti-tumor immunity. Nat Commun 2024; 15(1): 9559
79. Zhu J, Yamane H, Paul WE. Differentiation of effector CD4 T cell populations (*). Annu Rev Immunol 2010; 28(1): 445–489
80. Zhang L, Dou X, Zheng Z, Ye C, Lu TX, Liang HL, Wang L, Weichselbaum RR, He C. YTHDF2/m^{6}A/NF-κB axis controls anti-tumor immunity by regulating intratumoral Tregs. EMBO J 2023; 42(15): e113126
81. Xiao S, Duan S, Hong Y, Zhang J, Ma S, Caligiuri MA, Yu J. Loss of YTHDF2 enhances Th9 programming and CAR-Th9 cell antitumor efficacy. Nat Immunol 2025; 26(9): 1501–1515
82. Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. Int J Mol Sci 2021; 22(5): 2719
83. Skartsis N, Ferreira LMR, Tang Q. The dichotomous outcomes of TNFα signaling in CD4$^+$ T cells. Front Immunol 2022; 13: 1042622
84. van Vroonhoven ECN, Picavet LW, Scholman RC, Sijbers LJPM, Kievit CRE, van den Dungen NAM, Mokry M, Evers A, Lebbink RJ, Mocholi E, Coffer PJ, Calis JJA, Vastert SJ, van Loosdregt J. N6-methyladenosine promotes TNF mRNA degradation in CD4$^+$ T lymphocytes. J Leukoc Biol 2024; 116(4): 807–815
85. Seki N, Miyazaki M, Suzuki W, Hayashi K, Arima K, Myburgh E, Izuhara K, Brombacher F, Kubo M. IL-4-induced GATA-3 expression is a time-restricted instruction switch for Th2 cell differentiation. J Immunol 2004; 172(10): 6158–6166
86. Nakao A, Imamura T, Souchelnytskyi S, Kawabata M, Ishisaki A, Oeda E, Tamaki K, Hanai J, Heldin CH, Miyazono K, ten Dijke P. TGF-β receptor-mediated signalling through Smad2, Smad3 and Smad4. EMBO J 1997; 16(17): 5353–5362
87. Elyaman W, Bassil R, Bradshaw EM, Orent W, Lahoud Y, Zhu B, Radtke F, Yagita H, Khoury SJ. Notch receptors and Smad3 signaling cooperate in the induction of interleukin-9-producing T cells. Immunity 2012; 36(4): 623–634
88. Tamiya T, Ichiyama K, Kotani H, Fukaya T, Sekiya T, Shichita T, Honma K, Yui K, Matsuyama T, Nakao T, Fukuyama S, Inoue H, Nomura M, Yoshimura A. Smad2/3 and IRF4 play a cooperative role in IL-9-producing T cell induction. J Immunol 2013; 191(5): 2360–2371
89. Nakatsukasa H, Zhang D, Maruyama T, Chen H, Cui K, Ishikawa M, Deng L, Zanvit P, Tu E, Jin W, Abbatiello B, Goldberg N, Chen Q, Sun L, Zhao K, Chen W. The DNA-binding inhibitor Id3 regulates IL-9 production in CD4$^+$ T cells. Nat Immunol 2015; 16(10): 1077–1084
90. Lu Y, Hong S, Li H, Park J, Hong B, Wang L, Zheng Y, Liu Z, Xu J, He J, Yang J, Qian J, Yi Q. Th9 cells promote antitumor immune responses *in vivo*. J Clin Invest 2012; 122(11): 4160–4171
91. Lu Y, Hong B, Li H, Zheng Y, Zhang M, Wang S, Qian J, Yi Q. Tumor-specific IL-9-producing CD8$^+$ Tc9 cells are superior effector than type-I cytotoxic Tc1 cells for adoptive immunotherapy of cancers. Proc Natl Acad Sci USA 2014; 111(6): 2265–2270
92. Lu Y, Wang Q, Xue G, Bi E, Ma X, Wang A, Qian J, Dong C, Yi Q. Th9 cells represent a unique subset of CD4$^+$ T cells endowed with the ability to eradicate advanced tumors. Cancer Cell 2018; 33(6): 1048–1060.e7
93. Liu L, Bi E, Ma X, Xiong W, Qian J, Ye L, Su P, Wang Q, Xiao L, Yang M, Lu Y, Yi Q. Enhanced CAR-T activity against established tumors by polarizing human T cells to secrete interleukin-9. Nat Commun 2020; 11(1): 5902
94. Xue G, Zheng N, Fang J, Jin G, Li X, Dotti G, Yi Q, Lu Y. Adoptive cell therapy with tumor-specific Th9 cells induces viral mimicry to eliminate antigen-loss-variant tumor cells. Cancer Cell 2021; 39(12): 1610–1622.e9
95. Li Y, Sheng H, Ma F, Wu Q, Huang J, Chen Q, Sheng L, Zhu X, Zhu X, Xu M. RNA m^{6}A reader YTHDF2 facilitates lung adenocarcinoma cell proliferation and metastasis by targeting the AXIN1/Wnt/β-catenin signaling. Cell Death Dis 2021; 12(5): 479
96. Zhang C, Huang S, Zhuang H, Ruan S, Zhou Z, Huang K, Ji F, Ma Z, Hou B, He X. YTHDF2 promotes the liver cancer stem cell phenotype and cancer metastasis by regulating OCT4 expression via m^{6}A RNA methylation. Oncogene 2020; 39(23): 4507–4518
97. Wen J, Xue L, Wei Y, Liang J, Jia W, Yong T, Chu L, Li H, Han S, Liao J, Chen Z, Liu Y, Liu Q, Ding Z, Liang H, Gan L, Chen X, Huang Z, Zhang B. YTHDF2 is a therapeutic target for HCC by suppressing immune evasion and angiogenesis through ETV5/PD-L1/VEGFA axis. Adv Sci (Weinh) 2024; 11(13): 2307242
98. Yang Y, Yan Y, Yin J, Tang N, Wang K, Huang L, Hu J, Feng Z,

Gao Q, Huang A. O-GlcNAcylation of YTHDF2 promotes HBV-related hepatocellular carcinoma progression in an *N*^{6}-methyladenosine-dependent manner. Signal Transduct Target Ther 2023; 8(1): 63

99. Wang M, Zou F, Wang S, Yang Y, Xia C, Chen L, Liu B, Li L, Li MJ, Li H, Song W, Niu R, Yuan Z, Yang J, Li X, Chen K, Wu Z, Mi Z. CRTC2 forms co-condensates with YTHDF2 that enhance translational efficiency of m^{6}A-modified mRNAs to drive hepatocarcinogenesis and lenvatinib resistance. Cancer Res 2025; 85(11): 2046–2066
100. Li J, Xie H, Ying Y, Chen H, Yan H, He L, Xu M, Xu X, Liang Z, Liu B, Wang X, Zheng X, Xie L. YTHDF2 mediates the mRNA degradation of the tumor suppressors to induce AKT phosphorylation in N6-methyladenosine-dependent way in prostate cancer. Mol Cancer 2020; 19(1): 152
101. Chen Y, Pan C, Wang X, Xu D, Ma Y, Hu J, Chen P, Xiang Z, Rao Q, Han X. Silencing of METTL3 effectively hinders invasion and metastasis of prostate cancer cells. Theranostics 2021; 11(16): 7640–7657
102. Yu P, Xu T, Ma W, Fang X, Bao Y, Xu C, Huang J, Sun Y, Li G. PRMT6-mediated transcriptional activation of ythdf2 promotes glioblastoma migration, invasion, and emt via the wnt-β-catenin pathway. J Exp Clin Cancer Res 2024; 43(1): 116
103. Yu J, Chai P, Xie M, Ge S, Ruan J, Fan X, Jia R. Histone lactylation drives oncogenesis by facilitating m^{6}A reader protein YTHDF2 expression in ocular melanoma. Genome Biol 2021; 22(1): 85
104. Zhang Z, Zhou K, Han L, Small A, Xue J, Huang H, Weng H, Su R, Tan B, Shen C, Li W, Zhao Z, Qing Y, Qin X, Wang K, Leung K, Boldin M, Chen CW, Ann D, Qian Z, Deng X, Chen J, Chen Z. RNA m^{6}A reader YTHDF2 facilitates precursor miR-126 maturation to promote acute myeloid leukemia progression. Genes Dis 2024; 11(1): 382–396
105. Li Z, Chen P, Su R, Li Y, Hu C, Wang Y, Arnovitz S, He M, Gurbuxani S, Zuo Z, Elkahloun AG, Li S, Weng H, Huang H, Neilly MB, Wang S, Olson EN, Larson RA, Le Beau MM, Zhang J, Jiang X, Wei M, Jin J, Liu PP, Chen J. Overexpression and knockout of miR-126 both promote leukemogenesis. Blood 2015; 126(17): 2005–2015
106. Lechman ER, Gentner B, Ng SWK, Schoof EM, van Galen P, Kennedy JA, Nucera S, Ciceri F, Kaufmann KB, Takayama N, Dobson SM, Trotman-Grant A, Krivdova G, Elzinga J, Mitchell A, Nilsson B, Hermans KG, Eppert K, Marke R, Isserlin R, Voisin V, Bader GD, Zandstra PW, Golub TR, Ebert BL, Lu J, Minden M, Wang JC, Naldini L, Dick JE. miR-126 Regulates Distinct Self-Renewal Outcomes in Normal and Malignant Hematopoietic Stem Cells. Cancer Cell 2016; 29(2): 214–228
107. Zhang L, Nguyen LXT, Chen YC, Wu D, Cook GJ, Hoang DH, Brewer CJ, He X, Dong H, Li S, Li M, Zhao D, Qi J, Hua WK, Cai Q, Carnahan E, Chen W, Wu X, Swiderski P, Rockne RC, Kortylewski M, Li L, Zhang B, Marcucci G, Kuo YH. Targeting miR-126 in inv(16) acute myeloid leukemia inhibits leukemia development and leukemia stem cell maintenance. Nat Commun 2021; 12(1): 6154
108. Hua Z, Wei R, Guo M, Lin Z, Yu X, Li X, Gu C, Yang Y. YTHDF2 promotes multiple myeloma cell proliferation via STAT5A/MAP2K2/p-ERK axis. Oncogene 2022; 41(10): 1482–1491
109. Liu R, Miao J, Jia Y, Kong G, Hong F, Li F, Zhai M, Zhang R, Liu J, Xu X, Wang T, Liu H, Hu J, Yang Y, He A. N6-methyladenosine reader YTHDF2 promotes multiple myeloma cell proliferation through EGR1/p21$^{cip1/waf1}$/CDK2-Cyclin E1 axis-mediated cell cycle transition. Oncogene 2023; 42(20): 1607–1619
110. Zhong L, Liao D, Zhang M, Zeng C, Li X, Zhang R, Ma H, Kang T. YTHDF2 suppresses cell proliferation and growth via destabilizing the EGFR mRNA in hepatocellular carcinoma. Cancer Lett 2019; 442: 252–261
111. Zheng J, Liang Y, Xu X, Zhou J, Jiang S, Yu J. N6-methyladenosine binding protein YTHDF2 inhibits gastric cancer cell growth and predicts better prognosis in patients with gastric cancer. Transl Oncol 2025; 56: 102395
112. Zhou Y, Fan K, Dou N, Li L, Wang J, Chen J, Li Y, Gao Y. YTHDF2 exerts tumor-suppressor roles in gastric cancer via up-regulating PPP2CA independently of m^{6}A modification. Biol Proced Online 2023; 25(1): 6
113. Shen X, Zhao K, Xu L, Cheng G, Zhu J, Gan L, Wu Y, Zhuang Z. YTHDF2 Inhibits Gastric Cancer Cell Growth by Regulating FOXC2 Signaling Pathway. Front Genet 2021; 11: 592042
114. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol 2004; 22(1): 329–360
115. Yang Z, Wang X, Fu Y, Wu W, Hu Z, Lin Q, Peng W, Pan Y, Wang J, Chen J, Hu D, Zhou Z, Xu L, Zhang Y, Hou J, Chen M. YTHDF2 in peritumoral hepatocytes mediates chemotherapy-induced antitumor immune responses through CX3CL1-mediated CD8$^+$ T cell recruitment. Mol Cancer 2024; 23(1): 186
116. Zhou J, Sun H, Wang Z, Cong W, Wang J, Zeng M, Zhou W, Bie P, Liu L, Wen T, Han G, Wang M, Liu R, Lu L, Ren Z, Chen M, Zeng Z, Liang P, Liang C, Chen M, Yan F, Wang W, Ji Y, Yun J, Cai D, Chen Y, Cheng W, Cheng S, Dai C, Guo W, Hua B, Huang X, Jia W, Li Y, Li Y, Liang J, Liu T, Lv G, Mao Y, Peng T, Ren W, Shi H, Shi G, Tao K, Wang W, Wang X, Wang Z, Xiang B, Xing B, Xu J, Yang J, Yang J, Yang Y, Yang Y, Ye S, Yin Z, Zhang B, Zhang B, Zhang L, Zhang S, Zhang T, Zhao Y, Zheng H, Zhu J, Zhu K, Liu R, Shi Y, Xiao Y, Dai Z, Teng G, Cai J, Wang W, Cai X, Li Q, Shen F, Qin S, Dong J, Fan J. Guidelines for the Diagnosis and Treatment of Hepatocellular Carcinoma (2019 Edition). Liver Cancer 2020; 9(6): 682–720
117. Tsilimigras DI, Brodt P, Clavien PA, Muschel RJ, D'Angelica MI, Endo I, Parks RW, Doyle M, de Santibañes E, Pawlik TM. Liver metastases. Nat Rev Dis Primers 2021; 7(1): 27
118. Qiu X, Kemker C, Goebel GL, Lampe P, Wallis N, Schiller D, Bigler K, Jiang M, Sievers S, Yeo GW, Wu P. Phenylpyrazoles as Inhibitors of the m^{6}A RNA-Binding Protein YTHDF2. JACS Au 2025; 5(2): 618–630
119. Wang CH, Zhou H. Discovery of a new inhibitor for YTH domain-containing m^{6}A RNA readers. RSC Chem Biol 2024; 5(9): 914–923
120. Xing H, Gu X, Liu Y, Xu L, He Y, Xue C. NSUN2 regulates Wnt signaling pathway depending on the m5C RNA modification to promote the progression of hepatocellular carcinoma. Oncogene 2024; 43(47): 3469–3482
121. Lou N, Gu X, Fu L, Li J, Xue C. Significant roles of RNA 5-methylcytosine methylation in cancer. Cell Signal 2025; 126: 111529