

REVIEW

Open Access



IGF2BP2: an m⁶A reader that affects cellular function and disease progression

Siyi Liu^{1,2}, Shan Liao³, Junyu He⁴, Yanhong Zhou^{2*}  and Qian He^{1*}

*Correspondence:
zhouyanhong@csu.edu.cn;
heqian1162@hnca.org.cn

¹ Department of Radiation Oncology, The Affiliated Cancer Hospital of Xiangya School of Medicine Central South University/Hunan Cancer Hospital, Changsha 410013, Hunan, China

² Cancer Research Institute, Basic School of Medicine, Central South University, Changsha 410011, Hunan, China

³ Department of Pathology, The Third Xiangya Hospital of Central South University, Changsha 410013, Hunan, China

⁴ Department of Clinical Laboratory, Brain Hospital of Hunan Province (The Second People's Hospital of Hunan Province), Changsha 410007, Hunan, People's Republic of China

Abstract

Insulin-like growth factor 2 messenger RNA (mRNA)-binding protein 2 (IGF2BP2) is a widely studied N⁶-methyladenosine (m⁶A) modification reader, primarily functioning to recognize and bind to m⁶A modification sites on the mRNA of downstream target genes, thereby enhancing their stability. Previous studies have suggested that the IGF2BP2-m⁶A modification plays an essential role in cellular functions and the progression of various diseases. In this review, we focus on summarizing the molecular mechanisms by which IGF2BP2 enhances the mRNA stability of downstream target genes through m⁶A modification, thereby regulating cell ferroptosis, epithelial–mesenchymal transition (EMT), stemness, angiogenesis, inflammatory responses, and lipid metabolism, ultimately affecting disease progression. Additionally, we update the related research progress on IGF2BP2. This article aims to elucidate the effects of IGF2BP2 on cell ferroptosis, EMT, stemness, angiogenesis, inflammatory responses, and lipid metabolism, providing a new perspective for a comprehensive understanding of the relationship between IGF2BP2 and cell functions such as ferroptosis and EMT, as well as the potential for targeted IGF2BP2 therapy for tumors and other diseases.

Keywords: IGF2BP2, Ferroptosis, Epithelial–mesenchymal transition, Cell stemness, Angiogenesis

Introduction

m⁶A is one of the most common reversible modification forms of eukaryotic messenger RNA (mRNA) [1]. As a key epigenetic mechanism, m⁶A modification directly controls RNA metabolic processes, including mRNA processing, mRNA export, translation initiation, mRNA stability, and lncRNA (long noncoding RNA) biogenesis, thereby regulating various processes from cell differentiation and apoptosis to treatment resistance, immune response, and ultimately cell function [2, 3].

There are three types of proteins involved in the biological process of m⁶A modification: m⁶A methyltransferases (the “writers”), m⁶A demethylases (the “erasers”), and m⁶A recognition factors (the “readers”) [4]. The m⁶A writer, composed of the catalytic subunit MAC and the regulatory subunit MACOM, is primarily responsible for m⁶A deposition on specific substrate RNAs [5]. The deposition of m⁶A on RNA can



alter the secondary structure of local RNA, creating one or more binding sites for m⁶A effectors, thereby affecting the interaction between RNA and RNA-binding proteins (RBPs) [6, 7]. m⁶A modification mediates alternative splicing by influencing the binding of small nuclear RNAs (snRNAs), key components of spliceosomes, or splicing factors to pre-mRNAs [8–10]. m⁶A erasers, such as fat mass and obesity-associated protein (FTO) and alkB homolog 5 (ALKBH5), can effectively mediate the removal of RNA m⁶A modifications and maintain the reversibility of the m⁶A regulatory system [11]. The m⁶A readers are RBPs that recognize and selectively bind to m⁶A sites (with the exception of YTHDC2), guiding the fate of target RNAs [12, 13]. These three types of proteins play an irreplaceable role in the m⁶A modification process.

The insulin-like growth factor 2 mRNA-binding protein family (IGF2BPs) is a recently identified class of RBP with m⁶A reader function [14]. As m⁶A-binding proteins, IGF2BPs possess six characteristic RNA-binding domains, including two RNA recognition motifs (RRM1 and RRM2) and four K-homology (KH) domains (KH1 to KH4) [15]. IGF2BPs preferentially bind to the consensus sequence of “UGGAC” (containing the m⁶A core motif of “GGAC”) [16]. Most IGF2BP binding sites (92%) are located in protein-coding transcripts (mRNA) and are highly enriched in the 3′-untranslated region (3′-UTR) and near stop codons [16]. Additionally, the KH3-4 di-domain is essential for m⁶A recognition and binding, while KH1-2 may play an auxiliary role. Meanwhile, posttranslational modifications of the regions flanking KH3–4 may also be important for the selectivity of IGF2BPs [15, 17].

IGF2BP2 is a member of the IGF2BP family [3]. Huang et al. found that high-confidence targets of IGF2BP2 often have longer half-lives than their nontarget counterparts and play a crucial role in enhancing the stability of target mRNA [16]. During the process of exerting its mRNA-stabilizing function, IGF2BP2 relies on RNA stabilizers such as ELAV-like RNA-binding protein 1 (HuR) and matrin 3 (MATR3) [18, 19]. Specifically, IGF2BP2 can recruit HuR to protect m⁶A-containing mRNA from degradation and promote its translation [16]. Additionally, during heat shock and recovery, IGF2BP2 colocalizes with stress granules and shuttles between ribosomal and nonribosomal components, revealing its role in mRNA stability and storage under stress conditions [16]. Numerous studies have shown that IGF2BP2 is involved in the development and progression of various biological processes and malignant tumors, such as cancer metabolism, cell apoptosis, invasion, and metastasis, by regulating different types of RNA in various cell types and pathways.

Today, m⁶A modification is a subject of widespread interest. An increasing number of researchers recognize that the interactions of IGF2BP2, as an m⁶A reader, with m⁶A writers or erasers play a significant role in the progression of human metabolic disease and tumors. For example, Wang et al. primarily reviewed the role of IGF2BP2 in metabolic diseases such as diabetes, nonalcoholic steatohepatitis, obesity, and fatty liver. They also elucidated the mechanisms by which IGF2BP2 regulates breast, pancreatic, and esophageal cancers through miRNA and lncRNA [20]. However, with further research into cellular functions such as ferroptosis, angiogenesis, and cellular inflammation, IGF2BP2 has been found to play an important role in these processes as well. In this article, we focus on summarizing the specific molecular mechanisms by which IGF2BP2 affects ferroptosis, epithelial–mesenchymal transition (EMT), stemness,

angiogenesis, inflammatory responses, and lipid metabolism. We also update recent research on the impact of IGF2BP2 on disease prognosis and treatment, providing a theoretical basis for a comprehensive understanding of IGF2BP2-m⁶A modifications.

IGF2BP2 affects cell ferroptosis

Ferroptosis, an iron-dependent cell death program, is characterized by redox imbalance and subsequent toxic lipid peroxidation, showing great potential in cancer therapy [21, 22]. Biochemically, cells undergoing ferroptosis exhibit decreased levels of glutathione (GSH) and glutathione peroxidase 4 (GPX4), as well as an accumulation of lipid peroxidation [23]. In the past 3 years, a multitude of studies have found that, in tumor cells such as esophageal squamous cell carcinoma (ESCC) and hypopharyngeal squamous cell carcinoma (HPSCC), as well as in normal cells such as human colon epithelial cells, alveolar epithelial cells, and primary microvascular endothelial cells, IGF2BP2 can regulate the stability of ferroptosis-related proteins such as GPX4, solute carrier family 7, member 11 (SLC7A11), and hypoxia-inducible factor (HIF-1) alpha mRNA stability, or accelerate the degradation of downstream target gene activating transcription factor 3 (ATF3) in an m⁶A modification-dependent manner, thereby affecting ferroptosis and playing a more critical role in disease progression [24–29].

IGF2BP2 enhances mRNA stability of downstream target genes and inhibits cell ferroptosis through an m⁶A modification-dependent mechanism

GPX4, an antioxidant enzyme, is a downstream mediator of the amino acid antiporter system xc⁻ and can participate in the reduction of phospholipid hydroperoxides in the membrane [30]. Concurrently, GPX4 inhibition and the accumulation of reactive oxygen species (ROS) are closely related to the key feature of iron-dependent lipid peroxidation (LPO) in the process of cell ferroptosis [31]. Currently, a multitude of studies have confirmed that GPX4 plays a significant role in the regulation of cell ferroptosis by IGF2BP2; indeed, IGF2BP2 can directly or indirectly upregulate the expression of GPX4 through m⁶A modification [24–26]. For instance, Liu and colleagues found that IGF2BP2 enhances GPX4 expression through m⁶A modification, thereby inhibiting ferroptosis and attenuating the progression of ulcerative colitis (UC). IGF2BP2 and GPX4 are downregulated in UC treated with dextran sulfate sodium (DSS). Overexpression of IGF2BP2 can enhance the stability of GPX4 mRNA in human normal colon epithelial NCM460 cells stimulated by DSS, thereby inhibiting ROS, malondialdehyde (MDA), and iron levels, ultimately improving UC symptoms, disease activity index scores, inflammatory responses, and ferroptosis [24]. Yang et al. also revealed that lncRNA TMEM44 antisense RNA 1 (TMEM44-AS1) is extremely expressed in ESCC tissues and cells. Mechanistically, TMEM44-AS1 is positively correlated with GPX4 expression. TMEM44-AS1 can bind to the RNA-binding protein IGF2BP2, enhancing the stability of GPX4 mRNA, thereby inhibiting ferroptosis in ESCC cells and accelerating their proliferation, invasion, and metastasis [25]. In addition, Ye et al. found that ALKBH5-mediated m⁶A demethylation inhibits the transcription of nuclear factor erythroid 2-related factor 2 (NRF2). In HPSCC cells, ALKBH5 is poorly expressed, and IGF2BP2 can enhance the stability of NRF2 mRNA through m⁶A modification. Meanwhile, there is a positive correlation between GPX4 levels and NRF2 expression levels. After the

expression of NRF2 increases, GPX4 is upregulated, ultimately inhibiting ferroptosis in HPSCC cells and promoting the development of HPSCC [26] (Fig. 1).

In summary, in NCM460 cells stimulated by DSS and tumor cells such as ESCC cells and hypopharyngeal squamous cell carcinoma (HPSCC) cells, IGF2BP2 can directly enhance the stability of GPX4 mRNA through m⁶A modification or indirectly upregulate GPX4 expression by stabilizing NRF2 mRNA, thereby inhibiting cell ferroptosis, improving symptoms of ulcerative colitis (UC), or accelerating the progression of ESCC and hypopharyngeal squamous cell carcinoma. In the gene expression network, long noncoding RNA (lncRNA) serves as an important regulatory factor that can regulate mRNA stability, translation, and posttranslational modifications in the cytoplasm, as well as control nuclear structure and transcription in the nucleus [32]. In the aforementioned study by Yang et al., they found that TMEM44-AS1 can interact with IGF2BP2 by acting as a molecular scaffold between IGF2BP2 and GPX4, ultimately affecting ferroptosis [25]. However, the precise molecular mechanisms by which TMEM44-AS1 functions as a molecular scaffold during this process require further exploration.

IGF2BP2 enhances mRNA stability of downstream target genes and promotes cell ferroptosis through an m⁶A-modification-dependent mechanism

At the same time, a multitude of studies have also found that, in addition to upregulating the expression of GPX4 and inhibiting cell ferroptosis, IGF2BP2 can also promote ferroptosis in alveolar epithelial cells and mouse pancreatic cells AR42J

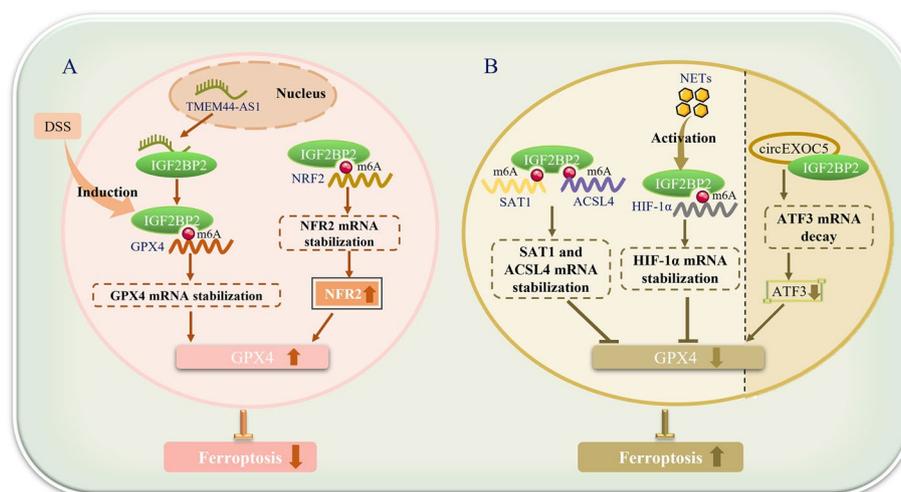


Fig. 1 IGF2BP2 affects cell ferroptosis. **A** IGF2BP2 can directly enhance the stability of GPX4 mRNA or indirectly upregulate GPX4 expression by stabilizing NRF2 mRNA through m⁶A modification in human normal colon epithelial cells, ESCC, and HPSCC cells stimulated by sodium dextran sulfate (DSS), thereby inhibiting cell ferroptosis. **B** IGF2BP2 can also downregulate GPX4 expression and promote ferroptosis in alveolar epithelial cells, mouse pancreatic cells, and pulmonary microvascular endothelial cells by enhancing the stability of HIF-1 α , SAT1, and ACSL4 mRNA, or promoting the degradation of ATF3 mRNA through non-m⁶A-modification-dependent mechanisms. DSS dextran sulfate sodium salt, GPX4 glutathione peroxidase 4, TMEM44-AS1 transmembrane protein 44 antisense RNA 1, NRF2 nuclear factor erythroid 2-related factor 2, SAT1 spermidine/spermine N1-acetyltransferase 1, ACSL4 acyl-CoA synthetase long chain family member 4, NETs neutrophil extracellular traps, HIF-1 α hypoxia-inducible factor 1 subunit alpha, circEXOC5 circular RNA exocyst complex component 5, ATF3 activating transcription factor 3. Microsoft PowerPoint was used to create this graphic

by enhancing the stability of HIF-1 α , spermidine/spermine N1-acetyltransferase 1 (SAT1), and acyl-CoA synthetase long-chain family member 4 (ACSL4) mRNA, than downregulating GPX4 expression, and ultimately exacerbating the inflammatory response in acute lung injury or acute pancreatitis [27–29]. As is well known, during disease progression, polymorphonuclear neutrophils (PMNs) are the first line of immune defense against pathogens [33]. In addition to phagocytosis and degranulation, neutrophils can also release neutrophil extracellular traps (NETs)—DNA material webs decorated with bactericidal proteins—effectively trapping microorganisms in circulation [34]. Zhang et al.'s study showed that, in alveolar epithelial cells of sepsis-induced acute lung injury (SI-ALI) patients, NETs can activate the m⁶A-IGF2BP2-dependent mechanism mediated by methyltransferase-like 3 (METTL3), inducing upregulation of HIF-1 α . Subsequently, the level of GPX4 was downregulated, glycolysis was enhanced, and oxidative phosphorylation was reduced, thereby promoting ferroptosis and metabolic reprogramming of alveolar epithelial cells, playing a key role in the progression of SI-ALI [28]. In addition, Chen and colleagues' research also revealed that, in AR42J cells of severe acute pancreatitis (SAP) mouse pancreas, IGF2BP2 can recognize m⁶A-modified SAT1 and ACSL4 mRNA and enhance their stability. Overexpression of SAT1 or ACSL4 further reduces the levels of GSH, SLC7A11, and GPX4, and upregulates intracellular Fe²⁺ levels, ultimately exacerbating SAP inflammation by promoting cell ferroptosis [29] (Fig. 1).

IGF2BP2 accelerates ATF3 mRNA degradation and promotes cell ferroptosis through a non-m⁶A-modification-dependent mechanism

Numerous studies have shown that IGF2BP2, as an m⁶A reader, primarily functions by enhancing the mRNA stability of downstream target genes. However, Wang et al. found that IGF2BP2 can also affect the degradation of target gene mRNA through mechanisms that are independent of m⁶A modification. In primary microvascular endothelial cells (PMVECs), the demethylase ALKBH5 can stabilize the expression of circular RNA exocyst complex component 5 (circEXOC5) through demethylation, which in turn recruits IGF2BP2 to promote the degradation and shorten the half-life of ATF3 mRNA, ultimately promoting ferroptosis in PMVECs and exacerbating sepsis-induced acute lung injury (ALI) [27] (Fig. 1).

Today, with m⁶A modification becoming a hot topic, IGF2BP2 has received considerable attention as an m⁶A reader whose primary function is to enhance the stability of downstream target gene mRNA. However, in the aforementioned studies, IGF2BP2 also played a crucial role in the degradation of ATF3 mRNA. In addition, recent studies have found that, in triple-negative breast cancer (TNBC) cells, IGF2BP2 can upregulate the protein level of cyclin-dependent kinase 6 (CDK6) by regulating the shift in translation rate during the initiation of CDK6 translation, rather than the stability of mRNA [35]. This suggests that, in addition to its impact on downstream target gene mRNA stability, IGF2BP2 also has many potential roles that need to be explored, such as its effects on mRNA translation rates or protein levels.

IGF2BP2 promotes EMT in tumor cells

EMT is a cellular process by which epithelial cells lose some of their epithelial characteristics and acquire a mesenchymal phenotype to facilitate cell movement [36]. An increasing body of evidence suggests that the abnormal activation of the EMT developmental program contributes to the occurrence, invasion, metastasis, and acquisition of treatment resistance in tumors [37, 38]. In tumor cells, various signals from the tumor microenvironment can trigger the activation of EMT, such as Wnt, Notch, growth factor receptor signaling, and inflammatory cytokines [39, 40]. The induction of EMT is coordinated by numerous core EMT transcription factors (TFs), including snail family transcriptional repressors 1 and 2 (SNAI1/2), twist family bHLH transcription factors 1 and 2 (TWIST1/2), and zinc finger E-box binding homeobox 1 and 2 (ZEB1/2) [37]. Wang et al. summarized that IGF2BP2 can disrupt TGF- β -induced EMT in lung cancer cells, and miR-138 inhibits EMT in glioma cells by targeting IGF2BP2 at the 3'-UTR level [30, 31]. However, in recent years, research on the impact of IGF2BP2 on the EMT process has been continuously reported. Here, we update the relevant research showing that IGF2BP2 promotes EMT in tumor cells and accelerates disease progression by affecting the mRNA stability of genes related to the EMT process. In addition, we provide a detailed review of the molecular mechanisms by which IGF2BP2 promotes EMT in tumor cells under the influence of upstream regulatory factors [32–38].

IGF2BP2 promotes the EMT process of tumor cells by affecting the mRNA stability of its downstream target genes

Slug belongs to the snail family of zinc finger transcription inhibitors, and its most studied functions include regulating epithelial cell plasticity and EMT [41]. It is indispensable for tissue maintenance and tumor progression [42–45]. High mobility group A1 (HMGA1) protein is a small nuclear protein that can serve as a structural transcription factor [46]. It has been shown to activate multiple genes involved in tumorigenesis, tumor proliferation, migration, invasion, and EMT [47]. There is currently evidence to suggest that IGF2BP2 can enhance the stability of Slug and HMGA1 mRNA through m⁶A-modification-dependent mechanisms and play a role in the EMT process of tumor cells such as head and neck squamous cell carcinoma (HNSCC) and gastric cancer (GC) [48–50]. For example, Yu et al. confirmed that Slug is a key EMT-related transcription factor in HNSCC tissue and a direct target of IGF2BP2. IGF2BP2 can bind to the m⁶A site in the Slug coding sequence (CDS) region, promoting the stability of its mRNA and ultimately facilitating lymph node metastasis, lymphangiogenesis, as well as HNSCC cell migration and invasion through the EMT process in vivo [48]. Ouyang et al.'s experiment also found that the expression of IGF2BP2 was significantly upregulated in GC tissues. IGF2BP2 enhances its stability by directly interacting with HMGA1 mRNA, thereby increasing its expression, promoting GC cell migration and invasion, as well as EMT [49]. In addition, Hou et al.'s study also revealed that IGF2BP2 can interact with DExH-box helicase 9 (DHX9) and long intergenic non-protein-coding RNA 460 (LINC00460) in colorectal cancer (CRC) cells, thereby binding to the 3'-UTR of HMGA1 mRNA, enhancing its mRNA stability, and ultimately inducing the EMT of CRC cells, promoting their proliferation, migration, and invasion [50] (Fig. 2).

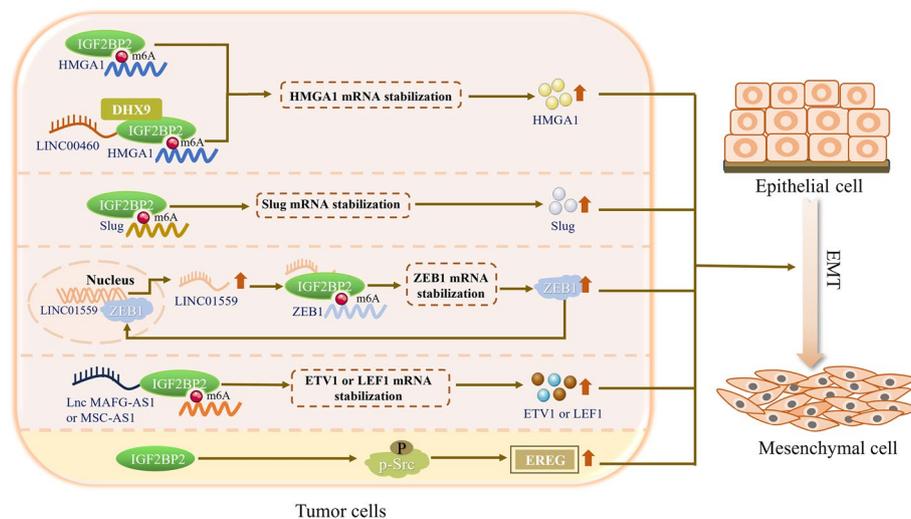


Fig. 2 IGF2BP2 promotes EMT process in tumor cells. In tumor cells such as gastric cancer and colorectal cancer, IGF2BP2 can promote the stability of Slug, HMGA1, and ZEB1 mRNA by directly recognizing and binding to their m⁶A site or being recruited by upstream regulatory factors, ultimately promoting the EMT process of tumor cells. In addition, IGF2BP2 can also upregulate EREG genes and trigger EMT in head and neck cancer by promoting phosphorylation levels of Src and other genes instead of m⁶A modification dependence. *HMGA1* high mobility group A1, *DHX9* DExH-box helicase 9, *LINC00460* long intergenic non-protein-coding RNA 460, *LINC01559* long intergenic non-protein-coding RNA 1559, *ZEB1* zinc finger E-box binding homeobox 1, *Lnc MAFG-AS1* MAF BZIP transcription factor G antisense RNA 1, *MSC-AS1* musculin antisense RNA 1, *ETV1* ETS translocation variant 1, *LEF1* lymphoid enhancer binding factor 1, *Src* nonreceptor tyrosine kinase gene, *EREG* epiregulin. Microsoft PowerPoint was used to create this graphic

Overall, in HNSCC, GC, and CRC cells, IGF2BP2 can directly recognize and bind to the m⁶A sites of Slug and HMGA1 mRNAs, or interact with DHX9 and LINC00460 to promote the stability of Slug and HMGA1 mRNA, ultimately facilitating the EMT of tumor cells and accelerating their invasion and migration [48–50].

The upstream regulatory factors of IGF2BP2 affect its function, thereby accelerating the EMT process of tumor cells

In addition to directly or indirectly acting on Slug and HMGA1, IGF2BP2 may also be recruited by various noncoding RNAs, thereby stabilizing downstream target gene mRNAs such as ZEB1 and Cell division cycle 27 (CDC27), and playing a role in the EMT process of tumor cells [51–54]. For example, Shen et al. confirmed that, in GC cells, ZEB1 acts as a transcription factor that binds to the long intergenic non-protein-coding RNA 1559 (LINC01559) promoter, activating the expression of LINC01559. Meanwhile, LINC01559 can recruit IGF2BP2 to stabilize ZEB1 mRNA and upregulate ZEB1 expression in GC cells. The formation of the ZEB1/LINC01559/IGF2BP2 positive feedback loop ultimately accelerates GC cell proliferation, migration, and EMT processes [51]. Zhao et al. also found that, in hepatocellular carcinoma (HCC) cells, transcription factor 7-like 2 (TCF7L2) promotes the transcription of circ_0000775 and induces its high expression. Subsequently, circ_0000775 maintains the stability of CDC27 mRNA by recruiting IGF2BP2, thereby positively regulating the expression of CDC27 and ultimately promoting HCC cell migration, invasion, and EMT [52]. At the same time, the research results of Weng et al. and Ma et al. also showed that, in

pancreatic cancer (PC) and melanoma cells, lncRNA MAF BZIP transcription factor G antisense RNA 1 (MAFG-AS1) and musclin antisense RNA 1 (MSC-AS1) can also stabilize ETS translocation variant 1 (ETV1) and lymphoid enhancer binding factor 1 (LEF1) mRNA, respectively, by recruiting IGF2BP2, and ultimately promote tumor cell migration, invasion, proliferation, and EMT [53, 54]. In summary, in GC, HCC, PC, and melanoma cells, IGF2BP2 can be recruited by upstream regulatory factors LINC01559, circ_0000775, lncRNA MAFG-AS1, and MSC-AS1 to stabilize ZEB1, CDC27, ETV1, and LEF1 mRNA, respectively. Ultimately, this promotes EMT of tumor cells and accelerates their migration and invasion (Fig. 2).

At the same time, researchers have revealed that, in HNSCC, IGF2BP2 can also activate the nonreceptor tyrosine kinase Src signaling pathway by promoting the phosphorylation levels of focal adhesion kinase (FAK), Raf, Src, and mitogen-activated protein kinase kinase (MEK), thereby mediating the upregulation of the epiregulin (EREG) gene. Ultimately, this triggers EMT, promoting the migration and invasion response of oral squamous cell carcinoma (OSCC) cells [55] (Fig. 2). This study expands our understanding of the role of IGF2BP2 in phosphorylation, which is beneficial for a comprehensive understanding of the role and molecular mechanisms of IGF2BP2. However, this study also has limitations. For instance, in the process of IGF2BP2 regulating EMT in HNSCC cells, how does IGF2BP2 promote the phosphorylation level of downstream target genes, and what is the specific molecular mechanism? Besides promoting the phosphorylation levels of genes such as FAK and Raf, is the m⁶A modification-dependent mechanism involved in regulating the expression of EREG? These issues warrant further exploration.

IGF2BP2 promotes the stemness characteristics of tumor cells and hematopoietic stem cells

Stem cells are a unique type of cell that can not only divide to produce more cells with stemness but also differentiate into other types of cells [56, 57]. Compared with terminally differentiated cells, stem cells retain the ability to reenter the cell cycle and proliferate [58]. Moreover, the sustained existence of stem cell states may also lead to the production of cancer stem cells (CSCs). CSCs exhibit preferential invasiveness and are closely related to the occurrence, spread, and treatment resistance of cancer [59–61]. In recent years, the relationship between IGF2BP2 and cell stemness has also attracted widespread attention. Wang et al. mentioned that IGF2BP2 can promote stem cell-like characteristics of pancreatic cancer (PC) cells by binding to and stabilizing m⁶A-modified DANCR RNA [53]. On this basis, we have updated and summarized the specific molecular mechanisms by which IGF2BP2 stabilizes mRNA of downstream target genes such as SOX2 and CCAR1, enhances the stemness characteristics of colorectal cancer (CRC) cells and hematopoietic stem cells, and ultimately affects disease progression [53–59].

IGF2BP2 regulates the mRNA stability of its downstream target genes, thereby promoting the stemness of tumor cells

In many types of tumors, fundamental tumor characteristics such as proliferation and invasion are related to cell stemness [62–65]. Currently, there is evidence suggesting

that IGF2BP2 plays a role in the development of various tumor cell stemness through m⁶A-modification-dependent mechanisms, ultimately affecting disease progression [66–71]. For example, Weng et al. also observed that IGF2BP2 plays an important role in the self-renewal of leukemia stem cells/initiating cells (LSCs/LICs). IGF2BP2 is highly expressed in LSCs/LICs, and silencing of IGF2BP2 or depletion of METTL3 and METTL14 can lead to significant reprogramming of cellular metabolites, especially those involved in glutamine (Gln) and glutamate (Glu) metabolism. Mechanistically, IGF2BP2 interacts with the components of the eukaryotic translation initiation factor (eIF) complex. It recruits eIF proteins to its target mRNA and regulates the expression of key targets V-myc avian myelocytomatosis viral oncogene homolog (MYC), glutamic-pyruvic transaminase 2 (GPT2), and solute carrier family 1 member 5 (SLC1A5) in the glutamine metabolism pathway in an m⁶A-modification-dependent manner, ultimately promoting the development of acute myeloid leukemia (AML) and self-renewal of leukemia stem cells/initiating cells [67]. Li et al. also confirmed that the expression of sex-determining region Y-box 2 (SOX2) is positively correlated with METTL3 and IGF2BP2 in CRC tissues. Methylated SOX2 transcripts, especially the CDS region, are specifically recognized by IGF2BP2 to enhance their stability, ultimately promoting self-renewal and cell stemness in CRC [68]. In addition, Huang et al. also discovered m⁶A modification of circABCC4 mediated by METTL3 in prostatic carcinoma (PCa). Subsequently, m⁶A-circABCC4 recruited IGF2BP2 protein to cell division cycle and apoptosis regulator 1 (CCAR1) mRNA, thereby enhancing the stability of CCAR1 mRNA and activating the Wnt/ β -catenin pathway, ultimately promoting the stemness and metastasis of PCa cells [69]. Overexpression of IGF2BP2 in HCC and ESCC cells can also respectively stabilize cell division cycle 45 (CDC45) and octamer-binding transcription factor 4 (OCT4) mRNA through m⁶A modification, ultimately promoting tumor cell stemness and exerting tumorigenic effects [70, 71]. In summary, in tumor cells such as PC, leukemia, CRC, and PCa, IGF2BP2 enhances cellular stemness by stabilizing specific mRNAs, including SOX2, and CCAR1, among others. This stabilization promotes tumor cell proliferation and migration, ultimately accelerating cancer progression.

It is well established that IGF2BP2 functions in recognizing and binding to the m⁶A site, without engaging in editing. Therefore, during the process where m⁶A levels rise and mRNA fate is influenced, there often exists a “cooperative” relationship between the m⁶A reader and writer. The collaboration between IGF2BP2 and m⁶A writers (e.g., METTL3) has been described in the studies by Weng, Li, and Huang et al., as mentioned above [67–69]. The nuclear translocation of METTL3 is crucial for m⁶A modification, and its subcellular distribution serves as a fundamental factor in determining its physiological functions [72]. Li et al. discovered that a positive feedback loop dependent on IL-6 m⁶A modification promotes the function of nuclear METTL3. This loop also influences the subcellular localization of METTL3, ultimately contributing to breast cancer (BC) metastasis [73]. The mRNA transcript of IL-6 is modified by m⁶A mediated by METTL3, which enhances the stability of IL-6 mRNA. Subsequently, IL-6 induced deacetylation of K177-METTL3 promotes nuclear transfer of METTL3 through the AMPK/SIRT1 axis, which plays a crucial role in its m⁶A modification. In conclusion, this positive feedback loop, which depends on METTL3-mediated IL-6 m⁶A modification, enhances the migration and invasion potential of BC cells. Typically, IGF2BP2 enhances

the stability of specific mRNAs by recognizing their m⁶A modifications. An intriguing question then arises: does IGF2BP2 play a role in the process by which IL-6 promotes the nuclear translocation of METTL3? The answer likely hinges on whether IGF2BP2 assists in enhancing the stability of IL-6 mRNA that is mediated by METTL3-m⁶A. Presently, this remains an open question.

As another set of crucial proteins involved in m⁶A biological processes, the demethylases—referred to as “erasers”—are another important group of proteins involved in m⁶A biological processes, with ALKBH5 and FTO being the most well-known examples. In recent years, the relationship between IGF2BP2 and m⁶A erasers has been extensively studied. A multitude of studies have revealed that m⁶A erasers exhibit low expression levels in tumor cells such as HNSCC, CRC, and papillary thyroid cancer (PTC). This downregulation appears to enhance the ability of m⁶A readers such as IGF2BP2 to recognize m⁶A modifications [74, 75]. For instance, downregulation of FTO and ALKBH5 collaboratively activate FOXO signaling through m⁶A modification of HK2 mRNA mediated by IGF2BP2. As a result, glycolysis in CRC is enhanced, thereby accelerating the malignant biological behavior of tumor cells [74]. Additionally, FTO inhibits glycolysis and growth in PTC cells by blocking IGF2BP2 recognition of m⁶A modifications and reducing the stability of APOE mRNA [75]. Nevertheless, in the aforementioned studies exploring the effect of IGF2BP2 on the stemness of tumor cells, it remains unclear whether FTO and ALKBH5 are consistently downregulated to support the function of IGF2BP2. Furthermore, it is an open question whether FTO and ALKBH5 can regulate IGF2BP2 function through other potential mechanisms beyond m⁶A modification. These questions highlight the need for further in-depth research to elucidate the complex interactions between m⁶A erasers and IGF2BP2 in cancer progression. These issues still warrant further in-depth research.

IGF2BP2 regulates the mRNA stability of downstream target genes, promotes self-renewal of hematopoietic stem cells, and maintains their function

Hematopoietic stem cells (HSCs) possess extensive self-renewal capabilities and multilineage differentiation potential, which are essential for the continuous production of blood cells [76]. In adults, HSCs reside within a specialized bone marrow microenvironment that comprises various hematopoietic and non-hematopoietic cell types, including mesenchymal stem cells and endothelial cells [77, 78]. Research by Yin et al. has demonstrated that elevated expression of m⁶A-IGF2BP2 regulates the transcriptional state and sustains the maintenance of HSCs, with IGF2BP2 being crucial for preserving HSC function. Mechanistically, a deficiency in IGF2BP2 significantly reduces the stability of Bmi1 mRNA within HSCs. Bmi1 is vital for modulating mitochondrial function and sustaining HSCs [79, 80]. The accelerated degradation of Bmi1 mRNA results in increased expression of mitochondrial-related genes, indicating heightened mitochondrial activity in HSCs. This, in turn, leads to the loss of HSC quiescence and a subsequent impairment of their function [81]. From a certain perspective, m⁶A can be regarded as a quality control mechanism for maintaining HSC integrity. This study provides the first clear evidence that the m⁶A reader IGF2BP2 is a pivotal factor in safeguarding hematopoietic stem cell stemness and elucidates its role and molecular mechanisms in the maintenance of HSCs and hematopoiesis.

IGF2BP2 promotes angiogenesis

Angiogenesis, which is the process of forming new blood vessels, is a complex and dynamic process. It is regulated by a variety of pro-angiogenic and anti-angiogenic molecules and plays a pivotal role in tumor growth, invasion, and metastasis [82]. With the advancement of molecular and cellular biology, various biomolecules involved in tumor angiogenesis, including growth factors, chemokines, and adhesion molecules, have been progressively identified [69–71]. For nearly 3 years, a large number of studies have revealed that IGF2BP2 also exerts a significant influence on angiogenesis in diseases such as tumors and retinopathy [72–79]. Therefore, it is necessary to timely summarize the effects and molecular mechanisms of IGF2BP2 on angiogenesis.

IGF2BP2 enhances the mRNA stability of downstream target genes

through an m⁶A-modification-dependent mechanism, thereby promoting angiogenesis

Research has demonstrated that IGF2BP2 plays a role in regulating tumor development by modulating the proliferation, invasion, and migration of various human cancer cells, including colorectal and lung cancer cell lines. As the significance of angiogenesis in tumor growth becomes increasingly recognized, IGF2BP2 has garnered considerable interest from researchers owing to its potential to promote tumor angiogenesis and accelerate cancer progression [83, 84]. For instance, Li et al. confirmed that IGF2BP2 can enhance the stability of the opa interacting protein 5 antisense RNA 1 (OIP5-AS1) mRNA in glioma tissues and cells. This enhancement increases the binding of OIP5-AS1 to MicroRNA-495-3p (miR-495-3p), ultimately promoting the formation of vasculogenic mimicry (VM) in glioma [83]. Concurrently, Fang et al. discovered that IGF2BP2 is specifically expressed in subsets of lung adenocarcinoma (LUAD) cells (referred to as LUAD_SGF2BP2) and endothelial cells (referred to as En_SGF2BP2). IGF2BP2 is preferentially secreted by exosomes from the LUAD_SGF2BP2 subset and taken up by the En_SGF2BP2 subset within the tumor microenvironment. Subsequently, IGF2BP2 enhances the stability of Fms-related receptor tyrosine kinase 4 (FLT4) mRNA through m⁶A modification, thereby activating the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) signaling pathway. This activation ultimately promotes LUAD angiogenesis and metastasis [84] (Fig. 3).

In addition to its role in tumor angiogenesis, IGF2BP2 has also been identified as a promoter of angiogenesis in trophoblast and wound healing contexts [85, 86]. Zhang et al. have shown that IGF2BP2 can modulate the stability of the long intergenic non-protein-coding RNA 1116 (lnc01166) mRNA through m⁶A methylation in trophoblast cells. This regulation leads to an upregulation of the angio-associated migratory cell protein (AAMP) expression by sequestering microRNA-210-3p (miR-210-3p), which in turn promotes trophoblast angiogenesis and may inhibit the development of preeclampsia [85]. Furthermore, research by Zhi and colleagues suggests that IGF2BP2 could emerge as a novel therapeutic target for conditions such as diabetes, aging, and vascular diseases. In keratinocytes (HaCaT), IGF2BP2 can bind to the 3'-UTR of heparinase (HPSE) mRNA, thereby stabilizing it and ultimately promoting the proliferation and migration of HaCaT cells. This process accelerates wound healing and angiogenesis [86]. In summary, IGF2BP2 can enhance the stability of various

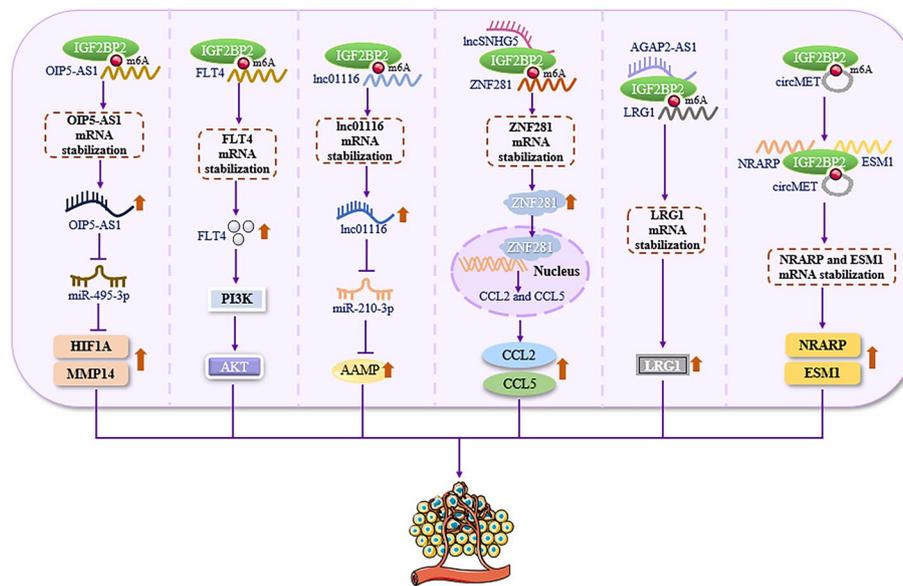


Fig. 3 IGF2BP2 promotes angiogenesis. IGF2BP2 can enhance the stability of OIP5-AS1, FLT4, and lnc01116 mRNA in an m⁶A-modification-dependent manner or bind to lncSNHG5, AGAP2-AS1, and circMET, respectively, to enhance the stability of ZNF281, LRG1, and NRARP/ESM1 mRNA in nourishing cells and tumor cells such as lung adenocarcinoma and glioma, ultimately promoting angiogenesis. *OIP5-AS1* opa interacting protein 5 antisense RNA 1, *miR-495-3p* microRNA-495-3p, *HIF1A* hypoxia-inducible factor 1 subunit alpha, *MMP14* matrix metalloproteinase 14, *FLT4* Fms-related receptor tyrosine kinase 4, *PI3K* phosphatidylinositol-3-kinase, *AKT* protein kinase B, *lnc01116* long intergenic non-protein-coding RNA 1116, *miR-210-3p* microRNA-210-3p, *AAMP* angio-associated migratory cell protein, *lncSNHG5* long noncoding RNA small nucleolar RNA host gene 5, *ZNF281* zinc finger protein 281, *CCL2* C–C motif chemokine ligand 2, *CCL5* C–C motif chemokine ligand 5, *AGAP2-AS1* AGAP2 antisense RNA 1, *LRG1* leucine-rich α -2 glycoprotein 1, *circMET* circular RNA MET, *NRARP* Notch regulated ankyrin repeat protein, *ESM1* endothelial cell specific molecule 1. Microsoft PowerPoint was used to create this graphic

mRNAs, including lnc01116, HPSE, FLT4, and OIP5-AS1, in different cell types such as keratinocytes, trophoblasts, lung adenocarcinoma, and glioma. This enhancement promotes angiogenesis, potentially inhibits preeclampsia, accelerates wound healing, and contributes to the development of LUAD, glioma, and other tumors, respectively. However, the *in vivo* data from Zhi et al. are lacking, and further *in vivo* studies are needed to explore the expression pattern of IGF2BP2 and its role in promoting angiogenesis (Fig. 3).

IGF2BP2 upstream regulators affect its function and promote angiogenesis

As an RBP, IGF2BP2 has been shown to interact with long noncoding RNAs (lncRNAs) such as Notch regulated ankyrin repeat protein (NRARP) and endothelial cell specific molecule 1 (ESM1). This interaction modulates the posttranscriptional fate of downstream genes, enhances mRNA stability, and promotes angiogenesis in conditions such as bladder cancer (BCa), breast cancer (BC), and retinopathy [87–89]. For instance, Zhao et al. discovered that IGF2BP2 and AGAP2 antisense RNA 1 (AGAP2-AS1) are highly upregulated in BCa. AGAP2-AS1, predominantly found in the cytoplasm, can bind directly to IGF2BP2, thereby stabilizing leucine-rich α -2 glycoprotein 1 (LRG1) mRNA and promoting tumor proliferation, migration, invasion, and angiogenesis

in vitro, as well as tumor growth and metastasis in vivo [87]. Zeng and colleagues confirmed that IGF2BP2 can stabilize zinc finger protein 281 (ZNF281) mRNA by binding to the long noncoding RNA small nucleolar RNA host gene 5 (lncSNHG5). This interaction leads to the upregulation of C–C motif chemokine ligand 2 (CCL2) and C–C motif chemokine ligand 5 (CCL5), activating the p38 mitogen-activated protein kinase (P38 MAPK) signaling in endothelial cells and promoting angiogenesis and vascular leakage, which can accelerate tumor metastasis and lead to poor prognosis in BC patients [88]. Additionally, Yao et al. found that, in diabetic retinopathy, circular RNA MET (circMET) interacts with IGF2BP2 in endothelial cells. Overexpression of IGF2BP2 significantly increases the expression of m⁶A-modified circMET. Subsequently, circMET forms a complex with IGF2BP2 and either NRARP or ESM1, enhancing their mRNA stability and promoting retinal angiogenesis and accelerating retinal lesions [89] (Fig. 3). In summary, by binding to AGAP2-AS1, lncSNHG5, and circMET, IGF2BP2 enhances the stability of ZNF281, NRARP, and ESM1 mRNA in a manner dependent on m⁶A modification. This enhancement promotes angiogenesis in BCa, BC, and retinopathy, respectively, and can accelerate disease progression.

IGF2BP2 affects inflammatory response

Tumor-associated inflammation (TAI) is a hallmark of most cancers, exerting both promoting and inhibiting effects on tumorigenesis. Inflammatory cytokines and cells are implicated in the development and progression of tumors across various body sites. Monocytes, the precursors of macrophages, are derived from hematopoietic stem cells, enter the bloodstream, and migrate to peripheral tissues, where they differentiate into macrophages and dendritic cells [90]. As key immune cells in the tumor microenvironment, macrophages play a pivotal role in TAI development [91, 92]. Influenced by the local microenvironment and pathophysiological factors, macrophages can polarize into two distinct phenotypes: pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2) [93]. Inflammatory cytokines are vital in normal cellular inflammation, host immune responses, and cell growth regulation, and they are central mediators in many autoimmune and chronic inflammatory diseases [94]. A multitude of inflammatory cytokines are also linked to cancers such as BC, GC, and LUAD [95]. Over the past 3 years, IGF2BP2 has been widely reported to influence macrophage polarization and regulate cytokine secretion, thereby modulating the inflammatory response and promoting disease progression. Consequently, we have summarized the relevant studies showing that IGF2BP2 affects the inflammatory response by enhancing the stability of mRNA from downstream target genes [86–94].

IGF2BP2 affects inflammatory response by influencing macrophage polarization or regulating cytokine secretion

IGF2BP2 inhibits inflammatory response by promoting polarization of M2 macrophages

M2 macrophages predominantly secrete anti-inflammatory cytokines, such as interleukin-10 (IL-10), which aid in clearing receptors and various remodeling factors. This process helps to reduce inflammation, dampen the immune response, and facilitate tissue repair and remodeling [96, 97]. In the context of tumors, tumor-associated macrophages (TAMs) are often induced by environmental cues to adopt

the M2 macrophage phenotype. This adoption contributes to the establishment of an immunosuppressive tumor niche, which can promote tumor progression and resistance to therapy [98, 99].

The notion that IGF2BP2-m⁶A in tumor cells promotes the polarization of M2 macrophages, thereby accelerating cancer and inflammatory diseases, has been substantiated by numerous studies [100–103]. For instance, Li and Zhang and their teams discovered that circular RNA integrin subunit beta 6 (circITGB6) and circular RNA aspartate beta-hydroxylase (circASPH) can directly interact with IGF2BP2 in ovarian cancer (OC) and CRC cells, stabilizing IGF2BP2 protein. IGF2BP2 then enhances the stability of fibroblast growth factor 9 (FGF9) and stimulator of interferon genes (STING) mRNA, inducing TAM polarization toward M2 macrophages. This process promotes M2 macrophage-dependent cisplatin (CDDP) resistance in OC and accelerates CRC progression [102, 103]. Furthermore, Liu, Zhu, and colleagues confirmed that IGF2BP2, when bound to lncRNA PTGS2 antisense NFKB1 complex-mediated expression regulator RNA (PACERR) and long intergenic non-protein-coding RNA 1232 (LINC01232), can enhance the stability of Krüppel-like factor 12 (KLF12), transcriptional regulator Myc-like (c-myc), and transforming growth factor beta receptor 1 (TGFB1) mRNA in the cytoplasm through m⁶A modification. This enhancement promotes M2 macrophage polarization and accelerates the progression of pancreatic ductal adenocarcinoma (PDAC) and NSCLC, respectively [100, 101] (Fig. 4).

Studies have also shown that IGF2BP2 in macrophages can regulate their own gene expression, promote M2 macrophage polarization, and accelerate disease progression [99, 104]. For example, Liu et al. demonstrated that exosomes derived from non-small cell lung cancer (NSCLC) can transfer circular RNA Parkin coregulated-like (circPACRGL) to human monocytic leukemia cells (THP-1). CircPACRGL then binds to IGF2BP2, enhancing the stability of Yes1-associated transcriptional regulator (YAP1) mRNA. This interaction modulates Hippo signaling in THP-1 cells, promotes M2 macrophage polarization, and ultimately accelerates the proliferation, migration, and invasion of NSCLC cells [104] (Fig. 4). Similarly, Wang et al. found that IGF2BP2 expression is higher in bone marrow-derived macrophages and peritoneal macrophages. During cockroach allergen (CRE)-induced allergic inflammation, IGF2BP2 directly binds to tuberous sclerosis complex 1 (TSC1) and peroxisome proliferator-activated receptor γ (PPAR γ). This binding enhances the stability of TSC1 and PPAR γ , activating the TSC1/mechanistic target of rapamycin complex 1 (mTORC1) pathway and PPAR γ -mediated fatty acid uptake. These actions shift M0 macrophages toward M2 activation, exacerbating pulmonary inflammation [99]. Additionally, Lin et al. confirmed that, in macrophages, circADAMTS6 stabilizes CAMK2A mRNA by forming a ternary complex with IGF2BP2 and CAMK2A. This interaction leads to CREB activation, driving M2 macrophage polarization and accelerating emphysema progression [105].

In the current literature, the primary mechanism for regulating IGF2BP2 is through modulating its expression levels, which in turn affects IGF2BP2's ability to recognize and bind to its target gene mRNAs. Future research may focus on the efficiency of upstream regulatory factors that directly influence IGF2BP2's recognition and binding to these mRNAs, which could garner significant interest. Additionally, Wang et al. discovered that the autophagy lysosome pathway (ALP), which is involved in the degradation of

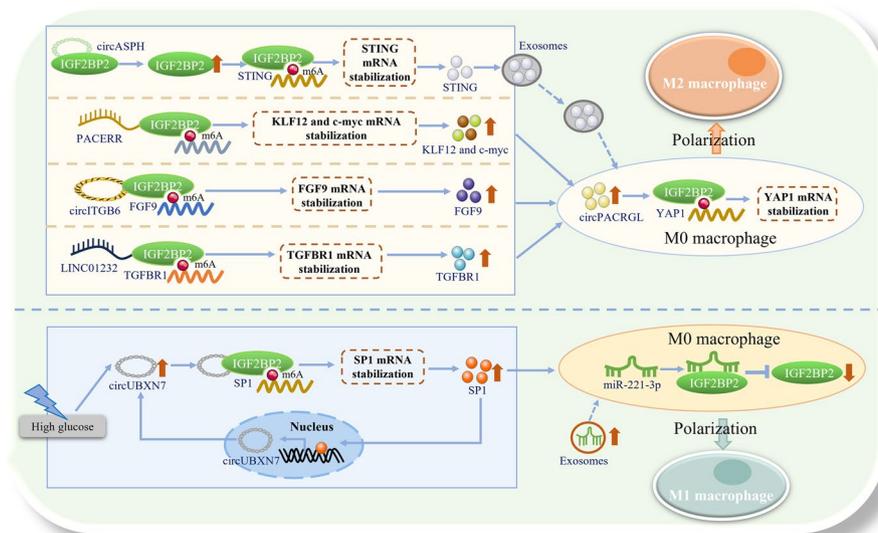


Fig. 4 IGF2BP2 affects macrophage polarization. Under the action of circASPH, LncRNA PACERR, circITGB6, and LINC01232 in tumor cells such as CRC, PDAC, OC, and non-small cell lung cancer (NSCLC), IGF2BP2 enhances the stability of STING, KLF12, c-myc, FGF9, and TGFBRI mRNA, ultimately promoting polarization of M2 macrophages. Meanwhile, IGF2BP2 in macrophages can enhance the stability of YAP1 mRNA and promote polarization of M2 macrophages under the action of circPACRGL. In addition, in human renal tubular epithelial cells, the binding of IGF2BP2 to circUBXN7 can enhance the stability of SP1 mRNA and promote polarization of M1 macrophages through m⁶A modification. At the same time, IGF2BP2 in macrophages is downregulated by miR-221-3p, ultimately promoting polarization of M1 macrophages. *circASPH* circular RNA aspartate beta-hydroxylase, *STING* stimulator of interferon genes, *PACERR* PTGS2 antisense NFKB1 complex-mediated expression regulator RNA, *KLF12* Krüppel-like factor 12, *c-myc* transcriptional regulator Myc-like, *circITGB6* circular RNA integrin subunit beta 6, *FGF9* fibroblast growth factor 9, *LINC01232* long intergenic non-protein-coding RNA 1232, *TGFBRI* transforming growth factor beta receptor 1, *circPACRGL* circular RNA Parkin coregulated like, *YAP1* Yes1-associated transcriptional regulator, *circUBXN7* circular RNA UBX domain protein 7, *SP1* Sp1 transcription factor, *miR-221-3p* microRNA-221-3p. Microsoft PowerPoint was used to create this graphic

IGF2BP2, can be inhibited by *LINRIS* (Long Intergenic Noncoding RNA for IGF2BP2 Stability) [106]. This finding not only clarifies the degradation pathway of IGF2BP2 but also establishes a link between the lncRNA epigenetic network and m⁶A modification. However, it is important to note that, aside from the ALP, ubiquitinated cellular proteins are also degraded through the ubiquitin proteasome system (UPS) [107]. Given this, a pertinent question for future research is whether there exists a molecular mechanism that mediates the degradation of IGF2BP2 via the UPS, thereby potentially altering its expression levels. Answering this question could significantly expand our understanding of the regulatory pathways for IGF2BP2.

In summary, the action of lncRNAs such as LINC01232, circPACRGL, PACERR, circITGB6, and circASPH enables IGF2BP2 to enhance the stability of mRNAs for TGFBRI, YAP1, c-myc, and FGF9. This stabilization facilitates the polarization of M2 macrophages, potentially accelerating the onset and progression of NSCLC, OC, CRC, and pulmonary inflammation. However, the research has some limitations. M2 macrophages can be classified into three subgroups—M2a, M2b, and M2c—which exhibit distinct phenotypes and secreted substances, and thus have varying effects on diseases and tissue damage [108]. M2a macrophages are induced by IL-4 or IL-13, while

M2b macrophages are activated by immune complexes, Toll-like receptors, or IL-1R agonists. Both M2a and M2b subgroups exert immunomodulatory functions and drive type II immune responses. In contrast, M2c macrophages, which are induced by IL-10, are more closely associated with immune suppression and tissue remodeling [108, 109]. Notably, it remains unclear which specific subgroups of M2 macrophages are regulated by IGF2BP2 during the process of promoting M2 macrophage polarization. Uncovering the answer to this question could be of great significance. It may enable us to gain a more profound understanding of the mechanism by which IGF2BP2 mediates tumor immune escape through the modulation of M2 macrophage polarization.

IGF2BP2 promotes inflammation by promoting polarization of M1 macrophages

M1 macrophages represent the primary phenotype in normal immune responses, engaging in TH1 (type I T helper cell) responses to various pathogens and producing pro-inflammatory cytokines that can eliminate tumor cells and inhibit microbial activity [110, 111]. M1 macrophages are classically activated by interferon-gamma (IFN- γ) or lipopolysaccharide (LPS), leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and IL-1 β . These cytokines facilitate microbial phagocytosis and initiate immune responses [112]. IGF2BP2 in tumor cells has also been identified as playing a crucial role in the polarization of M1 macrophages [113]. For instance, Lin et al. confirmed that circular RNA UB domain protein 7 (CircUBXN7) promotes macrophage infiltration and renal fibrosis in diabetic nephropathy (DKD), a process related to IGF2BP2-mediated stabilization of the Sp1 transcription factor (SP1) mRNA. CircUBXN7 is significantly upregulated in the plasma of DKD patients. By binding directly to IGF2BP2, it enhances the stability and activation of SP1 mRNA, ultimately promoting M1 macrophage polarization, inhibiting M2 macrophage polarization, and increasing macrophage infiltration, EMT, fibrosis, and proteinuria in vivo [113].

Similarly, IGF2BP2 in macrophages has been found to promote M1 macrophage polarization [114, 115]. Ji et al. reported that, after miR-221-3p, which is carried by exosomes derived from breast epithelial cells, enters macrophages, this microRNA can promote the polarization of M1 macrophages by targeting IGF2BP2, playing a crucial role in the development of mastitis [114] (Fig. 4). Following treatment with LPS or LPS-derived exosomes (LPS-exo), miR-221-3p enhances macrophage migration and chemotaxis toward breast tissue by targeting IGF2BP2. However, the mechanism by which IGF2BP2 contributes to this phenotype remains to be elucidated, and the specific molecular mechanism by which miR-221-3p regulates IGF2BP2 expression is still unclear [114]. Further exploration is needed to address these issues. Additionally, Du et al. confirmed that, in THP-1-derived M0 macrophages, the METTL3/IGF2BP2 complex promotes M1 macrophage polarization by stabilizing the mRNA encoding T cell immunoglobulin mucin 1 (TIM1) [115]. When the polarization of macrophages is abnormal, it exacerbates inflammatory responses, thereby affecting the occurrence of sepsis and related organ damage [115].

In summary, the interaction between IGF2BP2 and circUBXN7 can enhance the stability of SP1 mRNA through m⁶A modification, or this interaction can be regulated

by miR-221-3p. This enhancement subsequently promotes the polarization of M1 macrophages and accelerates the progression of DKD or mastitis.

IGF2BP2 enhances the secretion of various pro-inflammatory cytokines in a non-macrophage-dependent manner, promoting inflammatory responses
IGF2BP2 stabilizes the mRNA of downstream target genes through m⁶A modification, enhances the secretion of various pro-inflammatory cytokines, and promotes inflammatory response

In recent years, numerous studies have demonstrated that IGF2BP2 can stabilize the mRNA of downstream target genes through m⁶A modification, leading to an increase in the secretion of various pro-inflammatory cytokines in a non-macrophage-dependent manner. This enhancement of inflammatory responses ultimately affects disease progression [116–119]. As a key enzyme in catalyzing m⁶A modification of RNA, METTL3 has been shown by Wang et al. to modulate programmed cell death and renal inflammation in tubular epithelial cells (TECs) stimulated by TNF- α , cisplatin (CDDP), and LPS. Silencing METTL3 alleviates these effects, while its overexpression has the opposite impact [116]. METTL3 promotes m⁶A modification of TGF-beta activated kinase 1 binding protein 3 (TAB3), increasing TAB3 mRNA stability by binding IGF2BP2 to its m⁶A-modified stop codon region. This process ultimately promotes the production of pro-inflammatory cytokines (TNF- α and IL-6), chemokines (MCP-1), and adhesion molecules (ICAM-1), accelerating kidney injury and inflammatory responses [116]. Jiang et al. discovered that METTL3 enhances the stability of TIMP metalloproteinase inhibitor 2 (TIMP2) mRNA in podocytes from kidney biopsies of DKD patients in an IGF2BP2-dependent manner. Subsequently, TIMP2 upregulates the expression of Notch3 and Notch4, increasing the secretion of pro-inflammatory factors such as TNF- α and IL-1 β . This leads to pro-inflammatory and pro-apoptotic effects, accelerating podocyte injury in DKD [117]. Zhou et al. also revealed that IGF2BP2 enhances the stability of stromal interaction molecule 1 (STIM1) mRNA in LPS-induced A549 cells. Inhibition of STIM1 expression regulated by IGF2BP2 reduces LPS-induced endoplasmic reticulum stress (ERS) and inflammatory responses in A549 cells, mitigating cell damage in pneumonia cell models [118]. Furthermore, IGF2BP2 plays a significant role in the secretion of pro-inflammatory cytokines by tumor cells. Ji et al. found that the expression and m⁶A modification level of colony-stimulating factor 2 (CSF2) were significantly increased in gastric cancer mesenchymal stem cells (MSCs). Mechanistically, IGF2BP2 binds and stabilizes CSF2 mRNA in GC MSCs, inducing normal MSCs to reprogram into pro-cancer MSCs. This reprogramming enhances the proliferation, migration, and drug resistance of gastric cancer cells through the secretion of multiple pro-inflammatory factors [119].

In summary, IGF2BP2 plays a significant role in stabilizing the mRNA of TAB3, TIMP2, STIM1, and CSF2 through m⁶A modification. This stabilization enhances the secretion of pro-inflammatory cytokines, such as TNF- α , IL-1 β , and IL-6, which in turn accelerates kidney injury, DKD podocyte injury, and cell damage in pneumonia cell models. It also promotes inflammatory responses or accelerates GC progression. However, there are limitations in the study by Zhou et al. They did not validate the role of IGF2BP2 in stabilizing STIM1 mRNA through in vitro experiments. Furthermore,

while they found that inhibiting STIM1 expression regulated by IGF2BP2 can affect tumor cells, it remains unclear whether downregulation of IGF2BP2 indirectly affects STIM1 expression. These questions warrant further exploration in future experimental studies.

The upstream regulatory factors of IGF2BP2 affect its function, thereby enhancing the secretion of pro-inflammatory cytokines and exacerbating cellular inflammatory responses

Furthermore, IGF2BP2 can augment the secretion of IL-6 and MCP-1 by activating signaling pathways such as Toll-like receptor 4 (TLR4)/nuclear factor kappa-B (NF- κ B), thereby exacerbating inflammation and damage to adipocytes and trophoblasts [120, 121]. For instance, You et al. demonstrated that, in mature 3T3-L1 adipocytes stimulated by TNF- α , lncRNA MGE3 can activate the TLR4/NF- κ B signaling pathway by increasing the protein expression of IGF2BP2. This activation subsequently leads to elevated secretion levels of inflammatory factors IL-6 and MCP-1, enhanced cell apoptosis, and increased caspase-3 activity, ultimately worsening adipocyte inflammatory damage and insulin sensitivity imbalance [120]. Concurrently, Huang et al. discovered that circSESN2 can exacerbate high glucose (HG)-induced trophoblast damage by binding to IGF2BP2 and upregulating its protein expression. The inhibition of circSESN2 or IGF2BP2 not only promotes the invasion and migration of HTR-8/SVneo cells but also reduces cell apoptosis, pro-inflammatory cytokine release, and oxidative stress damage [121]. However, the precise mechanism by which IGF2BP2 influences the secretion of pro-inflammatory cytokines following upregulation by circSESN2 remains unclear, and additional experimental evidence is required to clarify this relationship. In summary, lncRNA MGE3 or circSESN2 can upregulate the expression of IGF2BP2, activating the TLR4/NF- κ B signaling pathway or other related pathways, and enhancing the secretion of pro-inflammatory cytokines such as IL-6 and MCP-1. This leads to increased inflammatory damage to adipocytes and trophoblasts and accelerates cell apoptosis.

IGF2BP2 regulates cellular lipid metabolism

The regulation of lipid metabolism, including lipid uptake, synthesis, and hydrolysis, is essential for maintaining cellular homeostasis [122]. Cancer cells within the tumor microenvironment can exploit lipid metabolism to fuel their rapid proliferation, survival, migration, invasion, and metastasis [123]. Numerous studies have indicated that m⁶A modification is associated with the progression of lipid metabolism disorders in humans [124, 125]. As the most abundant epigenetic modification of mRNA, m⁶A modification is crucial for regulating mRNA levels of genes related to lipid metabolism [126, 127]. Consequently, in recent years, researchers have observed that IGF2BP2 can enhance the stability or translation of mRNAs encoding lipid metabolism-related proteins such as platelet glycoprotein 4 (CD36), fatty acid binding protein 5 (FABP5), EBF transcription factor 2 (EBF2), and peroxisome proliferator-activated receptor γ (PPAR γ). This enhancement affects lipid metabolism and accelerates the progression of nonalcoholic fatty liver disease (NAFLD), obesity, and obesity-related diseases.

IGF2BP2 enhances the mRNA stability of downstream target genes through m⁶A modification, promoting lipid accumulation

Over the past decades, the global prevalence of metabolic diseases such as steatohepatitis, type 2 diabetes, and myocardial infarction has risen significantly [128, 129]. These obesity-related diseases are partly attributed to the abnormal accumulation of harmful lipid metabolites in tissues not designed for lipid storage, such as the liver, vascular system, and pancreatic beta cells [129]. Research has confirmed that IGF2BP2-m⁶A modification promotes lipid accumulation by regulating the levels of proteins involved in lipid metabolism. For instance, Wang et al. demonstrated that AK142643 can interact with IGF2BP2 in the livers of mice fed a high-fat diet (HFD). This interaction subsequently enhances the stability of CD36 mRNA, leading to increased hepatic lipid accumulation both in vivo and in vitro, ultimately impacting hepatic lipid metabolism and accelerating the progression of NAFLD [130]. Furthermore, Jiang et al. revealed the pivotal role of the Hilnc-IGF2BP2 signaling axis in lipid metabolism. Hilnc can directly interact with IGF2BP2, enhancing the stability of PPAR γ mRNA and thereby promoting diet-induced obesity and hepatic steatosis [131]. Additionally, Chen et al. uncovered a mechanism by which abnormal m⁶A modifications in the ALKBH5/IGF2BP2/FABP5/mTOR axis affect lipid metabolism, offering a new molecular basis for the development of therapeutic strategies for pancreatic neuroendocrine tumors (pNENs). Mechanistically, overexpression of ALKBH5 increases the stability of FABP5 mRNA in a manner dependent on m⁶A-IGF2BP2, thereby promoting fatty acid synthesis through the phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) signaling pathway [132] (Fig. 5).

In summary, IGF2BP2, by recognizing m⁶A modification sites, can enhance the stability of mRNAs encoding CD36, PPAR γ , and FABP5, which promotes lipid accumulation in

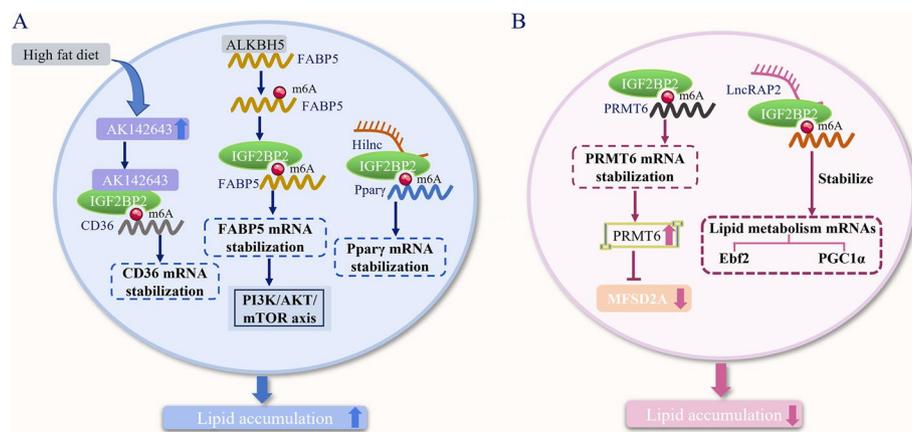


Fig. 5 IGF2BP2 regulates cellular lipid metabolism. **A** IGF2BP2 can enhance the stability of CD36, PPAR γ , and FABP5 mRNA through m⁶A-modification-dependent mechanisms when interacting with AK142643 and Hilnc, as well as being influenced by ALKBH5, promoting lipid accumulation in liver and pancreatic neuroendocrine tumor cells. **B** IGF2BP2 can enhance the stability of thermogenic factors Ebf2, PPAR γ , and PRMT6 mRNA in white adipocytes, ultimately reducing lipid accumulation. CD36 platelet glycoprotein 4, ALKBH5 human Alk B homolog 5, FABP5 fatty acid binding protein 5, PI3K/AKT/mTOR phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin, PPAR γ peroxisome proliferator-activated receptor γ , PRMT6 protein arginine N-methyltransferase 6, MFSD2A major facilitator superfamily domain-containing protein 2A, Ebf2 EBF transcription factor 2, PGC1 α peroxisome proliferator-activated receptor γ coactivator 1alpha. Microsoft PowerPoint was used to create this graphic

the liver and pancreatic neuroendocrine tumor cells. This enhancement accelerates the progression of NAFLD, obesity, hepatic steatosis, and pancreatic neuroendocrine tumors. In the study by Jiang et al., Hilnc was found to directly interact with IGF2BP2, thereby enhancing the stability of PPAR γ mRNA. However, it remains unclear whether Hilnc, like AK142643, stabilizes PPAR γ mRNA by facilitating the binding of IGF2BP2 to downstream target gene mRNA. The specific molecular mechanisms at play need further investigation to be fully understood.

IGF2BP2 enhances the mRNA stability of downstream target genes through m⁶A modification, reducing lipid accumulation

Adipose cells are rich in mitochondria and play a crucial role in energy homeostasis by dissipating energy in the form of heat or through metabolic processes [133]. Alvarez Dominguez et al. demonstrated that the levels of lncRAP2 and IGF2BP2 in adipocytes decrease during the development of obesity and diabetes. IGF2BP2 not only promotes lipid accumulation but also regulates the stability or translation of downstream target gene mRNAs, which subsequently affects the energy consumption of adipocytes, promotes lipolysis, and reduces lipid accumulation. Mechanistically, in mature white adipocytes, lncRAP2 can form a complex with IGF2BP2. This lncRAP2–IGF2BP2 complex supports the energy expenditure of mature adipocytes by binding to and stabilizing numerous mRNAs encoding metabolic effectors, including EBF2 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1 α) [134] (Fig. 5). However, it is not entirely clear whether lncRAP2, similar to Hilnc, regulates the affinity of IGF2BP2 for downstream target gene mRNAs. Further exploration is needed to elucidate this aspect of their interaction.

In addition to influencing the energy consumption of adipocytes, IGF2BP2 has also been found to affect the levels of docosahexaenoic acid (DHA), which is crucial for maintaining the function of human and mouse LSCs. IGF2BP2 stabilizes the mRNA of protein arginine methyltransferase 6 (PRMT6) through m⁶A modification, inhibiting the expression of the lipid transporter MFSD2A. This reduction in DHA levels helps maintain LSC function and ultimately promotes the development of AML [135] (Fig. 5). While this study suggests that the IGF2BP2–PRMT6–MFSD2A pathway influences DHA levels and plays a role in AML, the specific mechanisms underlying LSC-related fatty acid metabolism remain unclear. Furthermore, although IGF2BP2 can impact the metabolism of DHA and fatty acids in AML cells through the PRMT6–MFSD2A signaling axis, it is yet to be determined whether IGF2BP2 can directly regulate DHA levels.

In summary, IGF2BP2 plays a significant role in white adipocytes by enhancing the stability of thermogenic factor mRNAs, such as EBF2, PPAR γ , and PRMT6, in an m⁶A-modification-dependent manner. This enhancement of mRNA stability ultimately leads to reduced lipid accumulation and decreased docosahexaenoic acid (DHA) levels, which in turn can influence the development of various diseases [134, 135].

The relationship between IGF2BP2 and the prognosis or treatment of diseases **IGF2BP2 is associated with poor prognosis in various diseases**

Prognosis is a vital aspect of cancer diagnosis, influencing treatment decisions and the intensity of therapy [136]. Identifying prognostic biomarkers is crucial as it offers new prognostic insights and aids in pinpointing effective treatment targets. Studies

indicate that IGF2BP2 is overexpressed in HNSCC tissues, playing a significant role in cellular processes such as synthesis, metabolism, growth, death, and motility [137]. Its association with lymph node metastasis and poor prognosis makes it a critical independent adverse prognostic factor in HNSCC [48, 138]. Similarly, in OSCC, elevated IGF2BP2 expression correlates with poorer overall survival, suggesting its potential as a prognostic biomarker [139, 140]. IGF2BP2 impacts on biological functions and pathways, such as EMT, glycolysis, cell cycle, and immune responses, and contributes to a poor prognosis in OSCC [141, 142]. In PDAC, IGF2BP2 upregulation is linked to poor prognosis and the immunosuppressive tumor microenvironment [143, 144]. In glioblastoma, IGF2BP2's interaction with lncRNA CACS9 to enhance its stability suggests a poor prognosis for glioblastoma multiforme (GBM) [145]. This interaction stabilizes human kallikrein 2 (HK2) mRNA, and the disruption of this complex by CACS9 depletion affects IGF2BP2's function. The reliance on CACS9 in GBM cells and the uniqueness of this complex warrant further investigation. The prognostic significance of IGF2BP2 extends to other cancers, including pancreatic cancer [66, 146], AML [67], HCC [147], LUAD [148], and CRC [149, 150], where its upregulation is associated with poor outcomes and serves as a potential diagnostic and therapeutic target. In summary, understanding the prognostic implications of IGF2BP2 is essential for disease diagnosis and may offer novel approaches to treatment.

IGF2BP2 can promote chemoradiotherapy resistance in various diseases

Radiotherapy, which utilizes high-energy photon radiation such as X-rays and gamma rays, is a crucial method for treating cancer by directly and indirectly targeting cancer cells and tumor tissue to destroy them [151, 152]. Since its discovery by Nobel laureate Marie Curie, radiation has been recognized as a significant and effective tool in oncology for killing or controlling tumor growth [153]. Recently, Zhou et al. discovered that overexpression of IGF2BP2 in lung cancer cells can promote radiation resistance, while its inhibition can impair this resistance both in vitro and in vivo [154]. IGF2BP2 enhances the stability and translation of L-type amino acid transporter 1 (SLC7A5) mRNA through m⁶A modification, which in turn boosts SLC7A5-mediated methionine transport to produce S-adenosylmethionine. This leads to an increase in the trimethylation of histone H3 lysine 4 (H3K4me3), providing a positive feedback loop to the IGF2BP2 promoter region and upregulating its expression. This loop, through the AKT/mTOR pathway, enhances LUAD radiation resistance, potentially hindering the effectiveness of LUAD radiotherapy [154]. Additionally, research has indicated that circular RNA circEYA3 can decrease the radiosensitivity of HCC cells through the IGF2BP2/DTX3L axis. CircEYA3 binds to IGF2BP2, enhancing its ability to stabilize DTX3L mRNA, which specifically reduces radiation-induced DNA damage in HCC cells and increases their resistance to ¹²⁵I radiation seeds and external irradiation.

Chemotherapy is a central treatment strategy for the majority of cancer patients, and drug resistance can lead to treatment failure, making the understanding and study of chemotherapy resistance a significant challenge in cancer biology [155]. Research has shown that IGF2BP2 can stabilize the mRNA of downstream target genes, such as dipeptidyl peptidase-4 (DPP4), DANCR, hydroxy-3-methylglutaryl-CoA synthase 1 (HMGCS1), and ATPase copper transporting alpha (ATP7A), in

an m⁶A-modification-dependent manner in various tumor cells, including those from papillary thyroid carcinoma, glioblastoma, prostate, and OC. This stabilization enhances resistance to drugs such as cisplatin, selumetinib, etoposide, docetaxel, and temozolomide, ultimately promoting disease progression [156–163]. Furthermore, evidence suggests that, in glioblastoma and cervical cancer cells, lncRNAs OIP5-AS1 and miR-96-5p upregulate IGF2BP2 expression through interactions with microRNA-129-5p and lncRNA TRIM52-AS1, respectively. This upregulation promotes tumor cell resistance to temozolomide and cisplatin, inhibits tumor cell apoptosis, and accelerates tumor progression [164, 165].

In summary, IGF2BP2 plays a significant role in tumor radiotherapy and chemotherapy, with its impact mediated through m⁶A-modification-dependent mechanisms. Recent findings have highlighted the potential of IGF2BP2 small-molecule inhibitors in treating certain cancers, such as T-cell acute lymphoblastic leukemia and colorectal cancer [161, 166]. However, for many tumor types, including lung cancer, small-molecule inhibitors targeting IGF2BP2 have yet to be discovered. Consequently, the development of IGF2BP2 small-molecule inhibitors as targeted therapies for a range of diseases is likely to garner considerable interest from the research community.

Conclusions

As a well-studied m⁶A reader, IGF2BP2 has been confirmed by numerous studies to participate in a variety of biological and pathogenic processes. It achieves this by regulating the stability of downstream target gene mRNAs and is intimately linked to the onset and progression of cancer. The key roles played by ferroptosis, EMT, cell stemness, angiogenesis, inflammatory response, and lipid metabolism in physiological and pathological processes such as tumors, immunity, and development have always been the focus of researchers' attention. Understanding the regulatory interplay between IGF2BP2 and these processes, along with the specific molecular mechanisms involved, is anticipated to yield valuable new strategies for targeting IGF2BP2 in cancer treatment and drug development. Currently, research on IGF2BP2 predominantly focuses on its role in regulating mRNA stability through m⁶A modification. In contrast, there is a relative dearth of research on other molecular mechanisms that IGF2BP2 might employ. Next, a deeper understanding of the specific molecular mechanisms by which IGF2BP2 regulates downstream target gene expression may improve this situation, and may provide fresh insights and potentially therapeutic approaches.

Outstanding questions

1. In addition to regulating macrophage polarization, can IGF2BP2 also influence the differentiation of other immune cells associated with tumors, thereby exerting a more profound effect on the tumor microenvironment?
2. In the same RNA molecule, there are typically multiple N⁶-methyladenosine (m⁶A) modification sites and several m⁶A readers. Is there a specific sequence that m⁶A readers recognize at m⁶A sites? Is there a competitive relationship between other m⁶A readers and IGF2BP2?

3. Besides recruiting EIF4A1 to enhance the translation rate of CDK6, can IGF2BP2 also upregulate the translation rates of other downstream target genes? Furthermore, does IGF2BP2 possess other regulatory mechanisms that affect the expression of these downstream target genes?

Abbreviations

IGF2BP2	Insulin like growth factor 2 messenger RNA binding protein 2
snRNA	Small nuclear RNA
APA	Alternative polyadenylation
FTO	Obesity-associated protein
HuR	ELAV-like RNA-binding protein 1
MATR3	Matrin 3
m ⁶ A	N ⁶ -methyladenosine
EMT	Epithelial–mesenchymal transition
IGF2BPs	Insulin-like growth factor 2-messenger RNA binding proteins family
RBP	RNA-binding proteins
KH	K-homology
LncRNA	Long noncoding RNA
GSH	Glutathione
GPX4	Glutathione peroxidase 4
PTC	Papillary thyroid cancer
ESCC	Esophageal squamous cell carcinoma
HPSCC	Hypopharyngeal squamous cell carcinoma
SLC7A11	Solute carrier family 7, membrane 11
HIF-1	Hypoxia-inducible factor
ATF3	Activating transcription factor 3
ROS	Reactive oxygen species
LPO	Lipid peroxidation
UC	Ulcerative colitis
DSS	Dextran sulfate sodium
MDA	Malondialdehyde
TMEM44-AS1	TMEM44 antisense RNA 1
ALKBH5	AlkB homolog 5
NRF2	Nuclear factor erythroid 2-related factor 2
SAT1	Spermidine/spermine N1-acetyltransferase 1
ACSL4	Acyl-CoA synthetase long-chain family 4
PMNs	Polymorphonuclear neutrophils
NETs	Neutrophil extracellular traps
SI-ALI	Sepsis-induced acute lung injury
METTL3	Methyltransferase-like 3
SAP	Severe acute pancreatitis
PMVECs	Primary microvascular endothelial cells
circEXOC5	Circular RNA exocyst complex component 5
TNBC	Triple-negative breast cancer
CDK6	Cyclin-dependent kinase 6
TFs	Transcription factors
SNAI1/2	Snail family transcriptional repressor 1/2
TWIST1/2	Twist family bHLH transcription factor 1/2
ZEB1/2	Zinc finger E-box binding homeobox 1/2
TIM1	Mucin 1
HMGA1	High mobility group A1
HNSCC	Head and neck squamous cell carcinoma
GC	Gastric cancer
CDS	Coding sequence
DHX9	DExH-box helicase 9
LINC00460	Long intergenic non-protein-coding RNA 460
CRC	Colorectal cancer
UTR	Untranslated region
CDC27	Cell division cycle 27
LINC01559	Long intergenic non-protein-coding RNA 1559
HCC	Hepatocellular carcinoma
TCF7L2	Transcription factor 7-like 2
PC	Pancreatic cancer
MAFG-AS1	MAF BZIP transcription factor G antisense RNA 1
MSC-AS1	Musculin antisense RNA 1

ETV1	ETS translocation variant 1
LEF1	Lymphoid enhancer binding factor 1
Src	Nonreceptor tyrosine kinase gene
FAK	Focal adhesion kinase
MEK	Mitogen-activated protein kinase kinase
EREG	Epiregulin
OSCC	Oral squamous cell carcinoma
CSCs	Cancer stem cells
DANCR	Differentiation antagonizing non-protein-coding RNA
LSCs/LIC	Leukemia stem cells/initiating cells
Gln	Glutamine
Glu	Glutamate
eIF	Eukaryotic translation initiation factor
MYC	V-Myc avian myelocytomatosis viral oncogene homolog
SLC1A5	Solute carrier family 1 member 5
GPT2	Glutamic-pyruvic transaminase 2
AML	Acute myeloid leukemia
SOX2	Sex determining region Y-Box 2
PCa	Prostatic carcinoma
CCAR1	Cell division cycle and apoptosis regulator 1
CDC45	Cell division cycle 45
OCT4	Octamer-binding transcription factor 4
HSCs	Hematopoietic stem cells
OIP5-AS1	Opa interacting protein 5 antisense RNA 1
miR-495-3p	MicroRNA-495-3p
VM	Vasculogenic mimicry
LUAD	Lung adenocarcinoma
FLT4	Fms-related receptor tyrosine kinase 4
PI3K	Phosphatidylinositol-3-kinase
Akt	Protein kinase B
Lnc01166	Long intergenic non-protein-coding RNA 1116
AAMP	Angio-associated migratory cell protein
miR-210-3p	MicroRNA-210-3p
HPSE	Heparinase
NRARP	NOTCH regulated ankyrin repeat protein
ESM1	Endothelial cell specific molecule 1
BCa	Bladder cancer
AGAP2-AS1	AGAP2 antisense RNA 1
LRG1	Leucine-rich α -2 glycoprotein 1
ZNF281	Zinc finger protein 281
LncSNHG5	Long noncoding RNA small nucleolar RNA host gene 5
CCL2	C-C motif chemokine ligand 2
CCL5	C-C motif chemokine ligand 5
P38 MAPK	P38 mitogen-activated protein kinase
circMET	Circular RNA MET
TAI	Tumor-associated inflammation
LAUD	Lung adenocarcinoma
TAMs	Tumor-associated macrophage
NSCLC	Non-small cell lung cancer
THP-1	Human monocytic-leukemia cells
circPACRGL	Circular RNA Parkin coregulated like
YAP1	Yes1 associated transcriptional regulator
circITGB6	Circular RNA integrin subunit beta 6
circASPH	Circular RNA aspartate beta-hydroxylase
OC	Ovarian cancer
FGF9	Fibroblast growth factor 9
STING	Stimulator of interferon genes
CDDP	Cisplatin
PACERR	PTGS2 antisense NFKB1 complex-mediated expression regulator RNA
LINC01232	Long intergenic non-protein coding RNA 1232
KLF12	Kruppel-like factor 12
c-myc	Transcriptional regulator Myc-like
TGFBR1	Transforming growth factor beta receptor 1
PDAC	Pancreatic ductal adenocarcinoma
TSC1	Tuberous sclerosis complex 1
PPAR γ	Peroxisome proliferator-activated receptor γ
CRE	Cockroach allergen
mTORC1	Mechanistic target of rapamycin complex 1
ALP	Autophagy lysosome pathway
UPS	Ubiquitin proteasome system
TH1	Type I T helper cells

IFN – γ	Interferon-gamma
LPS	Lipopolysaccharide
TNF- α	Tumor necrosis factor- α
IL-6	Interleukin-6
DKD	Diabetes nephropathy
SP1	Sp1 transcription factor
LTA	Lipoteichoic acid
TECs	Tubular epithelial cells
TAB3	TGF-beta activated kinase 1 binding protein 3
MCP-1	Monocyte chemoattractant protein-1
ICAM-1	Intercellular adhesion molecule 1
TIMP2	TIMP metalloproteinase inhibitor 2
STIM1	Stromal interaction molecule 1
ERS	Endoplasmic reticulum stress
CSF2	Colony-stimulating factor 2
MSCs	Mesenchymalstem cells
TLR4	Toll-like receptor 4
NF - κ B	Nuclear factor kappa-B
HG	High glucose
CD36	Platelet glycoprotein 4
FABP5	Fatty acid binding protein 5
EBF2	EBF transcription factor 2
NAFLD	Nonalcoholic fatty liver disease
HFD	High-fat diet
pNENs	Pancreatic neuroendocrine tumors
PI3K/AKT/mTOR	Phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin
PGC1 α	PPAR gamma coactivator factor 1 alpha
DHA	Docosahexaenoic acid
PRMT6	Protein arginine methyltransferase 6
GBM	Glioblastoma multiforme
HK2	Human kallikrein 2
SLC7A5	L-type amino acid transporter 1
H3K4me3	Histone H3 lysine 4
DPP4	Dipeptidyl peptidase-4
HMGCS1	Hydroxy-3-methylglutaryl-CoA synthase 1
ATP7A	ATPase copper transporting alpha

Acknowledgements

Not applicable.

Author contributions

Siyi Liu wrote the manuscript and drew the figures. Shan Liao and Junyu He collected the related papers and helped to revise the manuscript. Yanhong Zhou and Qian He designed and revised the manuscript. All authors reviewed the manuscript and approved the submitted version.

Funding

The present study was supported by the Hunan Provincial Natural Science Foundation (2024JJ6623, 2022JJ30328, 2025JJ50488, and 2025JJ80826), Scientific Research Project of Hunan Provincial Health Commission (D202307016531), and independent exploration and innovation project of Central South University (2024ZZTS0865).

Availability of data and materials

Not applicable.

Declarations**Ethics approval and consent to participate**

Not applicable.

Consent for publication

Not applicable.

Competing interests

Not applicable.

Received: 30 November 2024 Accepted: 27 March 2025

Published online: 09 April 2025

References

- Wiener D, Schwartz S. The epitranscriptome beyond m(6)A. *Nat Rev Genet.* 2021;22:119–31. <https://doi.org/10.1038/s41576-020-00295-8>.
- He L, Li H, Wu A, Peng Y, Shu G, Yin G. Functions of N6-methyladenosine and its role in cancer. *Mol Cancer.* 2019;18:176. <https://doi.org/10.1186/s12943-019-1109-9>.
- Panneerdoss S, Eedunuri VK, Yadav P, Timilsina S, Rajamanickam S, Viswanadhappalli S, Abdelfattah N, Onyeagucha BC, Cui X, Lai Z, et al. Cross-talk among writers, readers, and erasers of m(6)A regulates cancer growth and progression. *Sci Adv.* 2018;4:eaat8263. <https://doi.org/10.1126/sciadv.aar8263>.
- Liu J, Yue Y, Han D, Wang X, Fu Y, Zhang L, Jia G, Yu M, Lu Z, Deng X, et al. A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation. *Nat Chem Biol.* 2014;10:93–5. <https://doi.org/10.1038/nchembio.1432>.
- van Tran N, Ernst FGM, Hawley BR, Zorbas C, Ulryck N, Hackert P, Bohnsack KE, Bohnsack MT, Jaffrey SR, Graille M, Lafontaine DLJ. The human 18S rRNA m6A methyltransferase METTL5 is stabilized by TRMT112. *Nucleic Acids Res.* 2019;47:7719–33. <https://doi.org/10.1093/nar/gkz619>.
- Liu N, Zhou Kl, Parisien M, Dai Q, Diatchenko L, Pan T. N6-methyladenosine alters RNA structure to regulate binding of a low-complexity protein. *Nucleic Acids Res.* 2017;45:6051–63. <https://doi.org/10.1093/nar/gkx141>.
- Liu N, Dai Q, Zheng G, He C, Parisien M, Pan T. N(6)-methyladenosine-dependent RNA structural switches regulate RNA-protein interactions. *Nature.* 2015;518:560–4. <https://doi.org/10.1038/nature14234>.
- Wei G, Almeida M, Pintacuda G, Coker H, Bowness JS, Ule J, Brockdorff N. Acute depletion of METTL3 implicates N(6)-methyladenosine in alternative intron/exon inclusion in the nascent transcriptome. *Genome Res.* 2021;31:1395–408. <https://doi.org/10.1101/gr.271635.120>.
- Mendel M, Delaney K, Pandey RR, Chen KM, Wenda JM, Vagbo CB, Steiner FA, Homolka D, Pillai RS. Splice site m(6)A methylation prevents binding of U2AF35 to inhibit RNA splicing. *Cell.* 2021;184(3125–3142):e3125. <https://doi.org/10.1016/j.cell.2021.03.062>.
- Liu Y, Yang D, Liu T, Chen J, Yu J, Yi P. N6-methyladenosine-mediated gene regulation and therapeutic implications. *Trends Mol Med.* 2023;29:454–67. <https://doi.org/10.1016/j.molmed.2023.03.005>.
- Li Y, Su R, Deng X, Chen Y, Chen J. FTO in cancer: functions, molecular mechanisms, and therapeutic implications. *Trends Cancer.* 2022;8:598–614. <https://doi.org/10.1016/j.trecan.2022.02.010>.
- Larivera S, Meister G. Domain confusion 2: m(6)A-independent role of YTHDC2. *Mol Cell.* 2022;82:1608–9. <https://doi.org/10.1016/j.molcel.2022.04.012>.
- Xu X, Cui J, Wang H, Ma L, Zhang X, Guo W, Xue X, Wang Y, Qiu S, Tian X, et al. IGF2BP3 is an essential N(6)-methyladenosine biotarget for suppressing ferroptosis in lung adenocarcinoma cells. *Mater Today Bio.* 2022;17:100503. <https://doi.org/10.1016/j.mtbio.2022.100503>.
- Dai XY, Shi L, Li Z, Yang HY, Wei JF, Ding Q. Main N6-methyladenosine readers: YTH family proteins in cancers. *Front Oncol.* 2021;11:635329. <https://doi.org/10.3389/fonc.2021.635329>.
- Dai N, Rapley J, Angel M, Yanik MF, Blower MD, Avruch J. mTOR phosphorylates IMP2 to promote IGF2 mRNA translation by internal ribosomal entry. *Genes Dev.* 2011;25:1159–72. <https://doi.org/10.1101/gad.204231.1>.
- Huang H, Weng H, Sun W, Qin X, Shi H, Wu H, Zhao BS, Mesquita A, Liu C, Yuan CL, et al. Recognition of RNA N(6)-methyladenosine by IGF2BP proteins enhances mRNA stability and translation. *Nat Cell Biol.* 2018;20:285–95. <https://doi.org/10.1038/s41556-018-0045-z>.
- Bell JL, Wachter K, Muhleck B, Pazaitis N, Kohn M, Lederer M, Huttelmaier S. Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression? *Cell Mol Life Sci.* 2013;70:2657–75. <https://doi.org/10.1007/s00018-012-1186-z>.
- Salton M, Elkon R, Borodina T, Davydov A, Yaspo ML, Halperin E, Shiloh Y. MatrIn 3 binds and stabilizes mRNA. *PLoS ONE.* 2011;6:e23882. <https://doi.org/10.1371/journal.pone.0023882>.
- Wang Y, Li Y, Toth JI, Petroski MD, Zhang Z, Zhao JC. N6-methyladenosine modification destabilizes developmental regulators in embryonic stem cells. *Nat Cell Biol.* 2014;16:191–8. <https://doi.org/10.1038/ncb2902>.
- Wang JY, Chen LJ, Qiang P. The role of IGF2BP2, an m6A reader gene, in human metabolic diseases and cancers. *Cancer Cell Int.* 2021. <https://doi.org/10.1186/s12935-021-01799-x>.
- Chen X, Yu C, Kang R, Kroemer G, Tang D. Cellular degradation systems in ferroptosis. *Cell Death Differ.* 2021;28:1135–48. <https://doi.org/10.1038/s41418-020-00728-1>.
- Dodson M, Castro-Portuguez R, Zhang DD. NRF2 plays a critical role in mitigating lipid peroxidation and ferroptosis. *Redox Biol.* 2019;23:101107. <https://doi.org/10.1016/j.redox.2019.101107>.
- Li J, Cao F, Yin HL, Huang ZJ, Lin ZT, Mao N, Sun B, Wang G. Ferroptosis: past, present and future. *Cell Death Dis.* 2020;11:88. <https://doi.org/10.1038/s41419-020-2298-2>.
- Liu W, Zeng H. IGF2BP2 attenuates intestinal epithelial cell ferroptosis in colitis by stabilizing m(6)A-modified GPX4 mRNA. *Cytokine.* 2024;173:156388. <https://doi.org/10.1016/j.cyto.2023.156388>.
- Yang R, Wan J, Ma L, Zhou F, Yang Z, Li Z, Zhang M, Ming L. TMEM44-AS1 promotes esophageal squamous cell carcinoma progression by regulating the IGF2BP2-GPX4 axis in modulating ferroptosis. *Cell Death Discov.* 2023;9:431. <https://doi.org/10.1038/s41420-023-01727-0>.
- Ye J, Chen X, Jiang X, Dong Z, Hu S, Xiao M. RNA demethylase ALKBH5 regulates hypopharyngeal squamous cell carcinoma ferroptosis by posttranscriptionally activating NFE2L2/NRF2 in an m(6)A-IGF2BP2-dependent manner. *J Clin Lab Anal.* 2022;36:e24514. <https://doi.org/10.1002/jcla.24514>.
- Wang W, Xu R, He P, Xiong Y, Zhao H, Fu X, Lin J, Ye L. CircEXOC5 aggravates sepsis-induced acute lung injury by promoting ferroptosis through the IGF2BP2/ATF3 axis. *J Infect Dis.* 2024;229:522–34. <https://doi.org/10.1093/infdis/jiad337>.
- Zhang H, Wu D, Wang Y, Guo K, Spencer CB, Ortoga L, Qu M, Shi Y, Shao Y, Wang Z, et al. METTL3-mediated N6-methyladenosine exacerbates ferroptosis via m6A-IGF2BP2-dependent mitochondrial metabolic reprogramming in sepsis-induced acute lung injury. *Clin Transl Med.* 2023;13:e1389. <https://doi.org/10.1002/ctm2.1389>.

29. Chen F, Su M, Han D, Wang Y, Song M. METTL14 depletion ameliorates ferroptosis in severe acute pancreatitis by increasing the N6-methyladenosine modification of ACSL4 and STA1. *Int Immunopharmacol*. 2024;128:111495. <https://doi.org/10.1016/j.intimp.2024.111495>.
30. Yang WS, SriRamaratnam R, Welsch ME, Shimada K, Skouta R, Viswanathan VS, Cheah JH, Clemons PA, Shamji AF, Clish CB, et al. Regulation of ferroptotic cancer cell death by GPX4. *Cell*. 2014;156:317–31. <https://doi.org/10.1016/j.cell.2013.12.010>.
31. Dixon SJ, Lemberg KM, Lamprecht MR, Skouta R, Zaitsev EM, Gleason CE, Patel DN, Bauer AJ, Cantley AM, Yang WS, et al. Ferroptosis: an iron-dependent form of nonapoptotic cell death. *Cell*. 2012;149:1060–72. <https://doi.org/10.1016/j.cell.2012.03.042>.
32. Yao RW, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. *Nat Cell Biol*. 2019;21:542–51. <https://doi.org/10.1038/s41556-019-0311-8>.
33. Hou L, Voit RA, Shibamura-Fujiogi M, Koutsogiannaki S, Li Y, Chen Y, Luo H, Sankaran VG, Yuki K. CD11c regulates neutrophil maturation. *Blood Adv*. 2023;7:1312–25. <https://doi.org/10.1182/bloodadvances.2022007719>.
34. Suzuki M, Ikari J, Anazawa R, Tanaka N, Katsumata Y, Shimada A, Suzuki E, Tatsumi K. PAD4 deficiency improves bleomycin-induced neutrophil extracellular traps and fibrosis in mouse lung. *Am J Respir Cell Mol Biol*. 2020;63:806–18. <https://doi.org/10.1165/rcmb.2019-0433OC>.
35. Xia T, Dai XY, Sang MY, Zhang X, Xu F, Wu J, Shi L, Wei JF, Ding Q. IGF2BP2 drives cell cycle progression in triple-negative breast cancer by recruiting EIF4A1 to promote the m6A-modified CDK6 translation initiation process. *Adv Sci*. 2024;11:e2305142. <https://doi.org/10.1002/advs.202305142>.
36. Fontana R, Mestre-Farrera A, Yang J. Update on epithelial-mesenchymal plasticity in cancer progression. *Annu Rev Pathol*. 2024;19:133–56. <https://doi.org/10.1146/annurev-pathmechdis-051222-122423>.
37. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. *Nat Rev Mol Cell Biol*. 2019;20:69–84. <https://doi.org/10.1038/s41580-018-0080-4>.
38. Pastushenko I, Blanpain C. EMT transition states during tumor progression and metastasis. *Trends Cell Biol*. 2019;29:212–26. <https://doi.org/10.1016/j.tcb.2018.12.001>.
39. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell*. 2009;139:871–90. <https://doi.org/10.1016/j.cell.2009.11.007>.
40. Xie M, Zhang L, He CS, Xu F, Liu JL, Hu ZH, Zhao LP, Tian Y. Activation of Notch-1 enhances epithelial-mesenchymal transition in gefitinib-acquired resistant lung cancer cells. *J Cell Biochem*. 2012;113:1501–13. <https://doi.org/10.1002/jcb.24019>.
41. Dai X, Xin Y, Xu W, Tian X, Wei X, Zhang H. CBP-mediated Slug acetylation stabilizes slug and promotes EMT and migration of breast cancer cells. *Sci China Life Sci*. 2021;64:563–74. <https://doi.org/10.1007/s11427-020-1736-5>.
42. Hajra KM, Chen DY, Fearon ER. The SLUG zinc-finger protein represses E-cadherin in breast cancer. *Cancer Res*. 2002;62:1613–8.
43. DiMeo TA, Anderson K, Phadke P, Fan C, Perou CM, Naber S, Kuperwasser C. A novel lung metastasis signature links Wnt signaling with cancer cell self-renewal and epithelial-mesenchymal transition in basal-like breast cancer. *Cancer Res*. 2009;69:5364–73. <https://doi.org/10.1158/0008-5472.CAN-08-4135>.
44. Perez-Losada J, Sanchez-Martin M, Rodriguez-Garcia A, Sanchez ML, Orfao A, Flores T, Sanchez-Garcia I. Zinc-finger transcription factor Slug contributes to the function of the stem cell factor c-kit signaling pathway. *Blood*. 2002;100:1274–86.
45. Yao B, Zhang Q, Yang Z, An F, Nie H, Wang H, Yang C, Sun J, Chen K, Zhou J, et al. CircEZH2/miR-133b/IGF2BP2 aggravates colorectal cancer progression via enhancing the stability of m(6)A-modified CREB1 mRNA. *Mol Cancer*. 2022;21:140. <https://doi.org/10.1186/s12943-022-01608-7>.
46. Fusco A, Fedele M. Roles of HMGA proteins in cancer. *Nat Rev Cancer*. 2007;7:899–910. <https://doi.org/10.1038/nrc2271>.
47. Resar LM. The high mobility group A1 gene: transforming inflammatory signals into cancer? *Cancer Res*. 2010;70:436–9. <https://doi.org/10.1158/0008-5472.CAN-09-1212>.
48. Yu D, Pan M, Li Y, Lu T, Wang Z, Liu C, Hu G. RNA N6-methyladenosine reader IGF2BP2 promotes lymphatic metastasis and epithelial-mesenchymal transition of head and neck squamous carcinoma cells via stabilizing slug mRNA in an m6A-dependent manner. *J Exp Clin Cancer Res*. 2022;41:6. <https://doi.org/10.1186/s13046-021-02212-1>.
49. Ouyang J, Li J, Li D, Jiang J, Hao T, Xia Y, Lu X, Zhang C, He Y. IGF2BP2 promotes epithelial to mesenchymal transition and metastasis through stabilizing HMGA1 mRNA in gastric cancer. *Cancers*. 2022. <https://doi.org/10.3390/cancers14215381>.
50. Hou P, Meng S, Li M, Lin T, Chu S, Li Z, Zheng J, Gu Y, Bai J. LINC00460/DHX9/IGF2BP2 complex promotes colorectal cancer proliferation and metastasis by mediating HMGA1 mRNA stability depending on m6A modification. *J Exp Clin Cancer Res*. 2021;40:52. <https://doi.org/10.1186/s13046-021-01857-2>.
51. Shen H, Zhu H, Chen Y, Shen Z, Qiu W, Qian C, Zhang J. ZEB1-induced LINC01559 expedites cell proliferation, migration and EMT process in gastric cancer through recruiting IGF2BP2 to stabilize ZEB1 expression. *Cell Death Dis*. 2021;12:349. <https://doi.org/10.1038/s41419-021-03571-5>.
52. Zhao C, Sun J, Dang Z, Su Q, Yang J. Circ_0000775 promotes the migration, invasion and EMT of hepatic carcinoma cells by recruiting IGF2BP2 to stabilize CDC27. *Pathol Res Pract*. 2022;235:153908. <https://doi.org/10.1016/j.prp.2022.153908>.
53. Weng H, Feng W, Li F, Huang D, Lin L, Wang Z. Transcription factor ETV1-induced lncRNA MAFG-AS1 promotes migration, invasion, and epithelial-mesenchymal transition of pancreatic cancer cells by recruiting IGF2BP2 to stabilize ETV1 expression. *Growth Factors*. 2023;41:152–64. <https://doi.org/10.1080/08977194.2023.2227272>.
54. Ma Y, Jin Y, Li C, Liu Y, Wang D. LncRNA MSC-AS1 motivates the development of melanoma by binding to miR-302a-3p and recruiting IGF2BP2 to elevate LEF1 expression. *Exp Dermatol*. 2021;30:1764–74. <https://doi.org/10.1111/exd.14427>.

55. Lin CW, Yang WE, Su CW, Lu HJ, Su SC, Yang SF. IGF2BP2 promotes cell invasion and epithelial-mesenchymal transition through Src-mediated upregulation of EREG in oral cancer. *Int J Biol Sci.* 2024;20:818–30. <https://doi.org/10.7150/ijbs.91786>.
56. Yin MX, Zhang L. Hippo signaling in epithelial stem cells. *Acta Biochim Biophys Sin.* 2015;47:39–45. <https://doi.org/10.1093/abbs/gmu111>.
57. Mo JS, Park HW, Guan KL. The hippo signaling pathway in stem cell biology and cancer. *EMBO Rep.* 2014;15:642–56. <https://doi.org/10.1525/embr.201438638>.
58. Rossi F, Noren H, Jove R, Beljanski V, Grinnemo KH. Differences and similarities between cancer and somatic stem cells: therapeutic implications. *Stem Cell Res Ther.* 2020;11:489. <https://doi.org/10.1186/s13287-020-02018-6>.
59. Barker N, Ridgway RA, van Es JH, van de Wetering M, Begthel H, van den Born M, Danenberg E, Clarke AR, Sansom OJ, Clevers H. Crypt stem cells as the cells-of-origin of intestinal cancer. *Nature.* 2009;457:608–11. <https://doi.org/10.1038/nature07602>.
60. Xu X, Rock JR, Lu Y, Futtner C, Schwab B, Guinney J, Hogan BL, Onaitis MW. Evidence for type II cells as cells of origin of K-Ras-induced distal lung adenocarcinoma. *Proc Natl Acad Sci USA.* 2012;109:4910–5. <https://doi.org/10.1073/pnas.1112499109>.
61. Gebhardt T, Park SL, Parish IA. Stem-like exhausted and memory CD8(+) T cells in cancer. *Nat Rev Cancer.* 2023;23:780–98. <https://doi.org/10.1038/s41568-023-00615-0>.
62. Jordan CT, Guzman ML, Noble M. Cancer stem cells. *N Engl J Med.* 2006;355:1253–61. <https://doi.org/10.1056/NEJMra061808>.
63. Clevers H. The cancer stem cell: premises, promises and challenges. *Nat Med.* 2011;17:313–9. <https://doi.org/10.1038/nm.2304>.
64. La Porta CAM, Zapperi S. Complexity in cancer stem cells and tumor evolution: toward precision medicine. *Semin Cancer Biol.* 2017;44:3–9. <https://doi.org/10.1016/j.semcancer.2017.02.007>.
65. Matteucci C, Balestrieri E, Argaw-Denboba A, Sinibaldi-Vallebona P. Human endogenous retroviruses role in cancer cell stemness. *Semin Cancer Biol.* 2018;53:17–30. <https://doi.org/10.1016/j.semcancer.2018.10.001>.
66. Hu X, Peng WX, Zhou H, Jiang J, Zhou X, Huang D, Mo YY, Yang L. IGF2BP2 regulates DANCR by serving as an N6-methyladenosine reader. *Cell Death Differ.* 2020;27:1782–94. <https://doi.org/10.1038/s41418-019-0461-z>.
67. Weng H, Huang F, Yu Z, Chen Z, Prince E, Kang Y, Zhou K, Li W, Hu J, Fu C, et al. The m(6)A reader IGF2BP2 regulates glutamine metabolism and represents a therapeutic target in acute myeloid leukemia. *Cancer Cell.* 2022;40(1566–1582):e1510. <https://doi.org/10.1016/j.ccell.2022.10.004>.
68. Li T, Hu PS, Zuo Z, Lin JF, Li X, Wu QN, Chen ZH, Zeng ZL, Wang F, Zheng J, et al. METTL3 facilitates tumor progression via an m(6)A-IGF2BP2-dependent mechanism in colorectal carcinoma. *Mol Cancer.* 2019;18:112. <https://doi.org/10.1186/s12943-019-1038-7>.
69. Huang C, Xu R, Zhu X, Jiang H. m6A-modified circABCC4 promotes stemness and metastasis of prostate cancer by recruiting IGF2BP2 to increase stability of CCAR1. *Cancer Gene Ther.* 2023;30:1426–40. <https://doi.org/10.1038/s41417-023-00650-x>.
70. Wu T, Liao L, Wu T, Chen S, Yi Q, Xu M. IGF2BP2 promotes glycolysis and hepatocellular carcinoma stemness by stabilizing CDC45 mRNA via m6A modification. *Cell Cycle.* 2023;22:2245–63. <https://doi.org/10.1080/15384101.2023.2283328>.
71. Zhao R, Li T, Zhao X, Yang Z, Ma L, Wang X. The m6A reader IGF2BP2 promotes the progression of esophageal squamous cell carcinoma cells by increasing the stability of OCT4 mRNA. *Biochem Cell Biol.* 2024;102:169–78. <https://doi.org/10.1139/bcb-2023-0067>.
72. Xiang Y, Laurent B, Hsu CH, Nachtergaele S, Lu Z, Sheng W, Xu C, Chen H, Ouyang J, Wang S, et al. RNA m(6)A methylation regulates the ultraviolet-induced DNA damage response. *Nature.* 2017;543:573–6. <https://doi.org/10.1038/nature21671>.
73. Li Y, He X, Lu X, Gong Z, Li Q, Zhang L, Yang R, Wu C, Huang J, Ding J, et al. METTL3 acetylation impedes cancer metastasis via fine-tuning its nuclear and cytosolic functions. *Nat Commun.* 2022;13:6350. <https://doi.org/10.1038/s41467-022-34209-5>.
74. Ye M, Chen J, Lu F, Zhao M, Wu S, Hu C, Yu P, Kan J, Bai J, Tian Y, Tang Q. Down-regulated FTO and ALKBH5 co-operatively activates FOXO signaling through m6A methylation modification in HK2 mRNA mediated by IGF2BP2 to enhance glycolysis in colorectal cancer. *Cell Biosci.* 2023;13:148. <https://doi.org/10.1186/s13578-023-01100-9>.
75. Huang J, Sun W, Wang Z, Lv C, Zhang T, Zhang D, Dong W, Shao L, He L, Ji X, et al. FTO suppresses glycolysis and growth of papillary thyroid cancer via decreasing stability of APOE mRNA in an N6-methyladenosine-dependent manner. *J Exp Clin Cancer Res.* 2022;41:42. <https://doi.org/10.1186/s13046-022-02254-z>.
76. Spangrude GJ, Heimfeld S, Weissman IL. Purification and characterization of mouse hematopoietic stem cells. *Science.* 1988;241:58–62. <https://doi.org/10.1126/science.2898810>.
77. Eaves CJ. Hematopoietic stem cells: concepts, definitions, and the new reality. *Blood.* 2015;125:2605–13. <https://doi.org/10.1182/blood-2014-12-570200>.
78. Wilkinson AC, Ishida R, Kikuchi M, Sudo K, Morita M, Crisostomo RV, Yamamoto R, Loh KM, Nakamura Y, Watanabe M, et al. Long-term ex vivo haematopoietic-stem-cell expansion allows nonconditioned transplantation. *Nature.* 2019;571:117–21. <https://doi.org/10.1038/s41586-019-1244-x>.
79. Liu J, Cao L, Chen J, Song S, Lee IH, Quijano C, Liu H, Keyvanfar K, Chen H, Cao LY, et al. Bmi1 regulates mitochondrial function and the DNA damage response pathway. *Nature.* 2009;459:387–92. <https://doi.org/10.1038/nature08040>.
80. Park IK, Qian D, Kiel M, Becker MW, Pihalja M, Weissman IL, Morrison SJ, Clarke MF. Bmi-1 is required for maintenance of adult self-renewing haematopoietic stem cells. *Nature.* 2003;423:302–5. <https://doi.org/10.1038/nature01587>.
81. Yin R, Chang J, Li Y, Gao Z, Qiu Q, Wang Q, Han G, Chai J, Feng M, Wang P, et al. Differential m(6)A RNA landscapes across hematopoiesis reveal a role for IGF2BP2 in preserving hematopoietic stem cell function. *Cell Stem Cell.* 2022;29(149–159):e147. <https://doi.org/10.1016/j.stem.2021.09.014>.

82. Liu ZL, Chen HH, Zheng LL, Sun LP, Shi L. Angiogenic signaling pathways and anti-angiogenic therapy for cancer. *Signal Transduct Target Ther.* 2023;8:198. <https://doi.org/10.1038/s41392-023-01460-1>.
83. Li H, Wang D, Yi B, Cai H, Wang Y, Lou X, Xi Z, Li Z. SUMOylation of IGF2BP2 promotes vasculogenic mimicry of glioma via regulating OIP5-AS1/miR-495-3p axis. *Int J Biol Sci.* 2021;17:2912–30. <https://doi.org/10.7150/ijbs.58035>.
84. Fang H, Sun Q, Zhou J, Zhang H, Song Q, Zhang H, Yu G, Guo Y, Huang C, Mou Y, et al. m(6)A methylation reader IGF2BP2 activates endothelial cells to promote angiogenesis and metastasis of lung adenocarcinoma. *Mol Cancer.* 2023;22:99. <https://doi.org/10.1186/s12943-023-01791-1>.
85. Zhang T, Tang X, Zhu Y, Wang C, Jiang Z, Yang N, Wang T, Shu L, Xu Y, Sun L. IGF2BP2 enhances LincRNA01116 stability via m(6) A: a potential biomarker and therapeutic target for patients with pre-eclampsia. *J Cell Biochem.* 2023;124:239–53. <https://doi.org/10.1002/jcb.30358>.
86. Zhi S, Li J, Kong X, Xie X, Zhang Q, Fang G. Insulin-like growth factor 2 mRNA binding protein 2 regulates proliferation, migration, and angiogenesis of keratinocytes by modulating heparanase stability. *Bioengineered.* 2021;12:11267–76. <https://doi.org/10.1080/21655979.2021.2002495>.
87. Zhao X, Chen J, Zhang C, Xie G, Othmane B, Kuang X, Liu B. LncRNA AGAP2-AS1 interacts with IGF2BP2 to promote bladder cancer progression via regulating LRG1 mRNA stability. *Cell Signal.* 2023;111:110839. <https://doi.org/10.1016/j.cellsig.2023.110839>.
88. Zeng H, Hou Y, Zhou X, Lang L, Luo H, Sun Y, Wan X, Yuan T, Wang R, Liu Y, et al. Cancer-associated fibroblasts facilitate premetastatic niche formation through lncRNA SNHG5-mediated angiogenesis and vascular permeability in breast cancer. *Theranostics.* 2022;12:7351–70. <https://doi.org/10.7150/thno.74753>.
89. Yao MD, Jiang Q, Ma Y, Zhu Y, Zhang QY, Shi ZH, Zhao C, Yan B. Targeting circular RNA-MET for anti-angiogenesis treatment via inhibiting endothelial tip cell specialization. *Mol Ther.* 2022;30:1252–64. <https://doi.org/10.1016/j.ymthe.2022.01.012>.
90. DeNardo DG, Ruffell B. Macrophages as regulators of tumour immunity and immunotherapy. *Nat Rev Immunol.* 2019;19:369–82. <https://doi.org/10.1038/s41577-019-0127-6>.
91. Shen Y, Xu LR, Tang X, Lin CP, Yan D, Xue S, Qian RZ, Guo DQ. Identification of potential therapeutic targets for atherosclerosis by analysing the gene signature related to different immune cells and immune regulators in atherosclerotic plaques. *BMC Med Genomics.* 2021;14:145. <https://doi.org/10.1186/s12920-021-00991-2>.
92. Mohapatra S, Pioppini C, Ozpolat B, Calin GA. Non-coding RNAs regulation of macrophage polarization in cancer. *Mol Cancer.* 2021;20:24. <https://doi.org/10.1186/s12943-021-01313-x>.
93. Wang Y, Shi R, Zhai R, Yang S, Peng T, Zheng F, Shen Y, Li M, Li L. Matrix stiffness regulates macrophage polarization in atherosclerosis. *Pharmacol Res.* 2022;179:106236. <https://doi.org/10.1016/j.phrs.2022.106236>.
94. Neurath MF, Finotto S. IL-6 signaling in autoimmunity, chronic inflammation and inflammation-associated cancer. *Cytokine Growth Factor Rev.* 2011;22:83–9. <https://doi.org/10.1016/j.cytogfr.2011.02.003>.
95. Grivnennikov SI, Karin M. Inflammatory cytokines in cancer: tumour necrosis factor and interleukin 6 take the stage. *Ann Rheum Dis.* 2011;70(Suppl 1):i104–108. <https://doi.org/10.1136/ard.2010.140145>.
96. Chen D, Nemazanyy I, Peulen O, Shostak K, Xu X, Tang SC, Wathieu C, Turchetto S, Tielens S, Nguyen L, et al. Elp3-mediated codon-dependent translation promotes mTORC2 activation and regulates macrophage polarization. *EMBO J.* 2022;41:e109353. <https://doi.org/10.1525/embj.2021109353>.
97. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity.* 2010;32:593–604. <https://doi.org/10.1016/j.immuni.2010.05.007>.
98. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity.* 2014;41:49–61. <https://doi.org/10.1016/j.immuni.2014.06.010>.
99. Wang X, Ji Y, Feng P, Liu R, Li G, Zheng J, Xue Y, Wei Y, Ji C, Chen D, Li J. The m6A reader IGF2BP2 regulates macrophage phenotypic activation and inflammatory diseases by stabilizing TSC1 and PPARgamma. *Adv Sci.* 2021;8:2100209. <https://doi.org/10.1002/advs.202100209>.
100. Zhu L, Liu Y, Tang H, Wang P. FOXP3 activated-LINC01232 accelerates the stemness of non-small cell lung carcinoma by activating TGF-beta signaling pathway and recruiting IGF2BP2 to stabilize TGFBR1. *Exp Cell Res.* 2022;413:113024. <https://doi.org/10.1016/j.yexcr.2022.113024>.
101. Liu Y, Shi M, He X, Cao Y, Liu P, Li F, Zou S, Wen C, Zhan Q, Xu Z, et al. LncRNA-PACERR induces pro-tumour macrophages via interacting with miR-671-3p and m6A-reader IGF2BP2 in pancreatic ductal adenocarcinoma. *J Hematol Oncol.* 2022;15:52. <https://doi.org/10.1186/s13045-022-01272-w>.
102. Li H, Luo F, Jiang X, Zhang W, Xiang T, Pan Q, Cai L, Zhao J, Weng D, Li Y, et al. CircITGB6 promotes ovarian cancer cisplatin resistance by resetting tumor-associated macrophage polarization toward the M2 phenotype. *J Immunother Cancer.* 2022. <https://doi.org/10.1136/jitc-2021-004029>.
103. Zhang Y, Guo J, Zhang L, Li Y, Sheng K, Zhang Y, Liu L, Gong W, Guo K. CircASPH enhances exosomal STING to facilitate M2 macrophage polarization in colorectal cancer. *Inflamm Bowel Dis.* 2023;29:1941–56. <https://doi.org/10.1093/ibd/izad113>.
104. Liu X, Xiong H, Lu M, Liu B, Hu C, Liu P. Trans-3, 5, 4'-trimethoxystilbene restrains non-small-cell lung carcinoma progression via suppressing M2 polarization through inhibition of m6A modified circPACRGL-mediated Hippo signaling. *Phytomedicine.* 2024;126:155436. <https://doi.org/10.1016/j.phymed.2024.155436>.
105. Lin J, Xia H, Yu J, Wang Y, Wang H, Xie D, Cheng C, Lu L, Bian T, Wu Y, Liu Q. circADAMTS6 via stabilizing CAMK2A is involved in smoking-induced emphysema through driving M2 macrophage polarization. *Environ Int.* 2024;190:108832. <https://doi.org/10.1016/j.envint.2024.108832>.
106. Wang Y, Lu JH, Wu QN, Jin Y, Wang DS, Chen YX, Liu J, Luo XJ, Meng Q, Pu HY, et al. LncRNA L1NRIS stabilizes IGF2BP2 and promotes the aerobic glycolysis in colorectal cancer. *Mol Cancer.* 2019. <https://doi.org/10.1186/s12943-019-1105-0>.
107. Heo AJ, Ji CH, Kwon YT. The Cys/N-degron pathway in the ubiquitin-proteasome system and autophagy. *Trends Cell Biol.* 2023;33:247–59. <https://doi.org/10.1016/j.tcb.2022.07.005>.

108. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.* 2004;25:677–86. <https://doi.org/10.1016/j.it.2004.09.015>.
109. Mosser DM. The many faces of macrophage activation. *J Leukoc Biol.* 2003;73:209–12. <https://doi.org/10.1189/jlb.0602325>.
110. Lafuse WP, Wozniak DJ, Rajaram MVS. Role of cardiac macrophages on cardiac inflammation, fibrosis and tissue repair. *Cells.* 2020. <https://doi.org/10.3390/cells10010051>.
111. Munjal A, Khandia R. Atherosclerosis: orchestrating cells and biomolecules involved in its activation and inhibition. *Adv Protein Chem Struct Biol.* 2020;120:85–122. <https://doi.org/10.1016/bs.apcsb.2019.11.002>.
112. Essandoh K, Li Y, Huo J, Fan GC. MiRNA-mediated macrophage polarization and its potential role in the regulation of inflammatory response. *Shock.* 2016;46:122–31. <https://doi.org/10.1097/SHK.0000000000000604>.
113. Lin Z, Lv D, Liao X, Peng R, Liu H, Wu T, Wu K, Sun Y, Zhang Z. CircUBXN7 promotes macrophage infiltration and renal fibrosis associated with the IGF2BP2-dependent SP1 mRNA stability in diabetic kidney disease. *Front Immunol.* 2023;14:1226962. <https://doi.org/10.3389/fimmu.2023.1226962>.
114. Ji ZH, Gao F, Xie WY, Wu HY, Ren WZ, Yuan B. Mammary epithelial cell-derived exosomal miR-221-3p regulates macrophage polarization by targeting Igf2bp2 during mastitis. *J Agric Food Chem.* 2023;71:14742–57. <https://doi.org/10.1021/acs.jafc.3c03350>.
115. Du X, Guo Y, Zhao X, Zhang L, Fan R, Li Y. METTL3-mediated TIM1 promotes macrophage M1 polarization and inflammation through IGF2BP2-dependent manner. *J Biochem Mol Toxicol.* 2024;38:e23845. <https://doi.org/10.1002/jbt.23845>.
116. Wang JN, Wang F, Ke J, Li Z, Xu CH, Yang Q, Chen X, He XY, He Y, Suo XG, et al. Inhibition of METTL3 attenuates renal injury and inflammation by alleviating TAB3 m6A modifications via IGF2BP2-dependent mechanisms. *Sci Transl Med.* 2022;14:eabk2709. <https://doi.org/10.1126/scitranslmed.abk2709>.
117. Jiang L, Liu X, Hu X, Gao L, Zeng H, Wang X, Huang Y, Zhu W, Wang J, Wen J, et al. METTL3-mediated m(6)A modification of TIMP2 mRNA promotes podocyte injury in diabetic nephropathy. *Mol Ther.* 2022;30:1721–40. <https://doi.org/10.1016/j.jymthe.2022.01.002>.
118. Zhou W, Dai Q, Su N, Liu Z, Hu J. IGF2BP2-dependent STIM1 inhibition protects against LPS-induced pneumonia in vitro by alleviating endoplasmic reticulum stress and the inflammatory response. *Exp Ther Med.* 2023;26:575. <https://doi.org/10.3892/etm.2023.12273>.
119. Ji R, Wu C, Yao J, Xu J, Lin J, Gu H, Fu M, Zhang X, Li Y, Zhang X. IGF2BP2-mediated m(6)A modification of CSF2 reprograms MSC to promote gastric cancer progression. *Cell Death Dis.* 2023;14:693. <https://doi.org/10.1038/s41419-023-06163-7>.
120. Lu Y, Qie D, Yang F, Wu J. LncRNA MEG3 aggravates adipocyte inflammation and insulin resistance by targeting IGF2BP2 to activate TLR4/NF-kappaB signaling pathway. *Int Immunopharmacol.* 2023;121:110467. <https://doi.org/10.1016/j.intimp.2023.110467>.
121. Huang X, Guo L. Circular RNA SESN2 aggravates gestational trophoblast cell damage induced by high glucose by binding to IGF2BP2. *Mol Reprod Dev.* 2023;90:73–86. <https://doi.org/10.1002/mrd.23667>.
122. Petrenko V, Sinturel F, Riezman H, Dibner C. Lipid metabolism around the body clocks. *Prog Lipid Res.* 2023;91:101235. <https://doi.org/10.1016/j.plipres.2023.101235>.
123. Bian X, Liu R, Meng Y, Xing D, Xu D, Lu Z. Lipid metabolism and cancer. *J Exp Med.* 2021. <https://doi.org/10.1084/jem.20201606>.
124. Xie W, Ma LL, Xu YQ, Wang BH, Li SM. METTL3 inhibits hepatic insulin sensitivity via N6-methyladenosine modification of Fasn mRNA and promoting fatty acid metabolism. *Biochem Biophys Res Commun.* 2019;518:120–6. <https://doi.org/10.1016/j.bbrc.2019.08.018>.
125. Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. *Science.* 2007;318:1469–72. <https://doi.org/10.1126/science.1151710>.
126. Bi Z, Liu Y, Zhao Y, Yao Y, Wu R, Liu Q, Wang Y, Wang X. A dynamic reversible RNA N(6)-methyladenosine modification: current status and perspectives. *J Cell Physiol.* 2019;234:7948–56. <https://doi.org/10.1002/jcp.28014>.
127. Yang Z, Yu GL, Zhu X, Peng TH, Lv YC. Critical roles of FTO-mediated mRNA m6A demethylation in regulating adipogenesis and lipid metabolism: implications in lipid metabolic disorders. *Genes Dis.* 2022;9:51–61. <https://doi.org/10.1016/j.gendis.2021.01.005>.
128. Spengler EK, Loomba R. Recommendations for diagnosis, referral for liver biopsy, and treatment of nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Mayo Clin Proc.* 2015;90:1233–46. <https://doi.org/10.1016/j.mayocp.2015.06.013>.
129. Chaurasia B, Summers SA. Ceramides in metabolism: key lipotoxic players. *Annu Rev Physiol.* 2021;83:303–30. <https://doi.org/10.1146/annurev-physiol-031620-093815>.
130. Wang P, Wang X, He D, Zhuang C. LncRNA AK142643 promotes hepatic lipid accumulation by upregulating CD36 via interacting with IGF2BP2. *Gene.* 2023;887:147747. <https://doi.org/10.1016/j.gene.2023.147747>.
131. Jiang Y, Peng J, Song J, He J, Jiang M, Wang J, Ma L, Wang Y, Lin M, Wu H, et al. Loss of Hlinc prevents diet-induced hepatic steatosis through binding of IGF2BP2. *Nat Metab.* 2021;3:1569–84. <https://doi.org/10.1038/s42255-021-00488-3>.
132. Chen J, Ye M, Bai J, Gong Z, Yan L, Gu D, Hu C, Lu F, Yu P, Xu L, et al. ALKBH5 enhances lipid metabolism reprogramming by increasing stability of FABP5 to promote pancreatic neuroendocrine neoplasms progression in an m6A-IGF2BP2-dependent manner. *J Transl Med.* 2023;21:741. <https://doi.org/10.1186/s12967-023-04578-6>.
133. Cohen P, Kajimura S. The cellular and functional complexity of thermogenic fat. *Nat Rev Mol Cell Biol.* 2021;22:393–409. <https://doi.org/10.1038/s41580-021-00350-0>.
134. Alvarez-Dominguez JR, Winther S, Hansen JB, Lodish HF, Knoll M. An adipose lncRAP2-Igf2bp2 complex enhances adipogenesis and energy expenditure by stabilizing target mRNAs. *iScience.* 2022;25:103680. <https://doi.org/10.1016/j.isci.2021.103680>.

135. Cheng Y, Gao Z, Zhang T, Wang Y, Xie X, Han G, Li Y, Yin R, Chen Y, Wang P, et al. Decoding m(6)A RNA methylome identifies PRMT6-regulated lipid transport promoting AML stem cell maintenance. *Cell Stem Cell*. 2023;30(69–85):e67. <https://doi.org/10.1016/j.stem.2022.12.003>.
136. Paulsson J, Micke P. Prognostic relevance of cancer-associated fibroblasts in human cancer. *Semin Cancer Biol*. 2014;25:61–8. <https://doi.org/10.1016/j.semcancer.2014.02.006>.
137. Deng X, Jiang Q, Liu Z, Chen W. Clinical significance of an m6A reader gene, IGF2BP2, in head and neck squamous cell carcinoma. *Front Mol Biosci*. 2020;7:68. <https://doi.org/10.3389/fmolb.2020.00068>.
138. Hu Y, Chen J, Liu M, Feng Q, Peng H. IGF2BP2 serves as a core m6A regulator in head and neck squamous cell carcinoma. 2022. *Biosci Rep*. <https://doi.org/10.1042/BSR20221311>.
139. Wang X, Xu H, Zhou Z, Guo S, Chen R. IGF2BP2 maybe a novel prognostic biomarker in oral squamous cell carcinoma. 2022. *Biosci Rep*. <https://doi.org/10.1042/BSR20212119>.
140. Xu K, Dai X, Wu J, Wen K. N(6)-methyladenosine (m(6)A) reader IGF2BP2 stabilizes HK2 stability to accelerate the Warburg effect of oral squamous cell carcinoma progression. *J Cancer Res Clin Oncol*. 2022;148:3375–84. <https://doi.org/10.1007/s00432-022-04093-z>.
141. Lin SH, Lin CW, Lu JW, Yang WE, Lin YM, Lu HJ, Yang SF. Cytoplasmic IGF2BP2 protein expression in human patients with oral squamous cell carcinoma: prognostic and clinical implications. *Int J Med Sci*. 2022;19:1198–204. <https://doi.org/10.7150/ijms.74751>.
142. Zhou L, Li H, Cai H, Liu W, Pan E, Yu D, He S. Upregulation of IGF2BP2 promotes oral squamous cell carcinoma progression that is related to cell proliferation, metastasis and tumor-infiltrating immune cells. *Front Oncol*. 2022;12:809589. <https://doi.org/10.3389/fonc.2022.809589>.
143. Deng H, Yao H, Zhou S, He C, Huang Y, Li Y, Chen H, Shu J. Pancancer analysis uncovers an immunological role and prognostic value of the m6A reader IGF2BP2 in pancreatic cancer. *Mol Cell Probes*. 2024;73:101948. <https://doi.org/10.1016/j.mcp.2023.101948>.
144. Huang S, Wu Z, Cheng Y, Wei W, Hao L. Insulin-like growth factor 2 mRNA binding protein 2 promotes aerobic glycolysis and cell proliferation in pancreatic ductal adenocarcinoma via stabilizing GLUT1 mRNA. *Acta Biochim Biophys Sin*. 2019;51:743–52. <https://doi.org/10.1093/abbs/gmz048>.
145. Liu H, Qin S, Liu C, Jiang L, Li C, Yang J, Zhang S, Yan Z, Liu X, Yang J, Sun X. m(6)A reader IGF2BP2-stabilized CAS9 accelerates glioblastoma aerobic glycolysis by enhancing HK2 mRNA stability. *Cell Death Discov*. 2021;7:292. <https://doi.org/10.1038/s41420-021-00674-y>.
146. Cao P, Wu Y, Sun D, Zhang W, Qiu J, Tang Z, Xue X, Qin L. IGF2BP2 promotes pancreatic carcinoma progression by enhancing the stability of B3GNT6 mRNA via m6A methylation. *Cancer Med*. 2023;12:4405–20. <https://doi.org/10.1002/cam4.5096>.
147. Pu J, Wang J, Qin Z, Wang A, Zhang Y, Wu X, Wu Y, Li W, Xu Z, Lu Y, et al. IGF2BP2 promotes liver cancer growth through an m6a-FEN1-dependent mechanism. *Front Oncol*. 2020;10:578816. <https://doi.org/10.3389/fonc.2020.578816>.
148. Jia M, Shi Y, Xie Y, Li W, Deng J, Fu D, Bai J, Ma Y, Zuberi Z, Li J, Li Z. WT1-AS/IGF2BP2 axis is a potential diagnostic and prognostic biomarker for lung adenocarcinoma according to ceRNA network comprehensive analysis combined with experiments. *Cells*. 2021. <https://doi.org/10.3390/cells11010025>.
149. Liu X, He H, Zhang F, Hu X, Bi F, Li K, Yu H, Zhao Y, Teng X, Li J, et al. m6A methylated EphA2 and VEGFA through IGF2BP2/3 regulation promotes vasculogenic mimicry in colorectal cancer via PI3K/AKT and ERK1/2 signaling. *Cell Death Dis*. 2022;13:483. <https://doi.org/10.1038/s41419-022-04950-2>.
150. Wang J, Zhu M, Zhu J, Li J, Zhu X, Wang K, Shen K, Yang K, Ni X, Liu X, et al. HES1 promotes aerobic glycolysis and cancer progression of colorectal cancer via IGF2BP2-mediated GLUT1 m6A modification. *Cell Death Discov*. 2023;9:411. <https://doi.org/10.1038/s41420-023-01707-4>.
151. Franzone P, Fiorentino A, Barra S, Cante D, Masini L, Cazzulo E, Todisco L, Gabriele P, Garibaldi E, Merlotti A, et al. Image-guided radiation therapy (IGRT): practical recommendations of Italian association of radiation oncology (AIRO). *Radiol Med*. 2016;121:958–65. <https://doi.org/10.1007/s11547-016-0674-x>.
152. Gong L, Zhang Y, Liu C, Zhang M, Han S. Application of radiosensitizers in cancer radiotherapy. *Int J Nanomed*. 2021;16:1083–102. <https://doi.org/10.2147/IJN.S290438>.
153. Kulakowski A. The contribution of Marie Skłodowska-Curie to the development of modern oncology. *Anal Bioanal Chem*. 2011;400:1583–6. <https://doi.org/10.1007/s00216-011-4712-1>.
154. Zhou Z, Zhang B, Deng Y, Deng S, Li J, Wei W, Wang Y, Wang J, Feng Z, Che M, et al. FBW7/GSK3beta mediated degradation of IGF2BP2 inhibits IGF2BP2-SLC7A5 positive feedback loop and radioresistance in lung cancer. *J Exp Clin Cancer Res*. 2024;43:34. <https://doi.org/10.1186/s13046-024-02959-3>.
155. Ippolito MR, Martis V, Martin S, Tjhuis AE, Hong C, Wardenaar R, Dumont M, Zerbib J, Spierings DCJ, Fachinetti D, et al. Gene copy-number changes and chromosomal instability induced by aneuploidy confer resistance to chemotherapy. *Dev Cell*. 2021;56(2440–2454):e2446. <https://doi.org/10.1016/j.devcel.2021.07.006>.
156. Wang W, Ding Y, Zhao Y, Li X. m6A reader IGF2BP2 promotes lymphatic metastasis by stabilizing DPP4 in papillary thyroid carcinoma. *Cancer Gene Ther*. 2024;31:285–99. <https://doi.org/10.1038/s41417-023-00702-2>.
157. Han J, Yu X, Wang S, Wang Y, Liu Q, Xu H, Wang X. IGF2BP2 Induces U251 glioblastoma cell chemoresistance by inhibiting FOXO1-mediated PID1 expression through stabilizing lncRNA DANCR. *Front Cell Dev Biol*. 2021;9:659228. <https://doi.org/10.3389/fcell.2021.659228>.
158. Shi SJ, Han DH, Zhang JL, Li Y, Yang AG, Zhang R. VIM-AS1 promotes proliferation and drives enzalutamide resistance in prostate cancer via IGF2BP2-mediated HMGC51 mRNA stabilization. *Int J Oncol*. 2023. <https://doi.org/10.3892/ijo.2023.5482>.
159. Fu L, Zhang D, Yi N, Cao Y, Wei Y, Wang W, Li L. Circular RNA circPBX3 promotes cisplatin resistance of ovarian cancer cells via interacting with IGF2BP2 to stabilize ATP7A mRNA expression. *Hum Cell*. 2022;35:1560–76. <https://doi.org/10.1007/s13577-022-00748-8>.
160. Zhang M, Wang Q, Ke Z, Liu Y, Guo H, Fang S, Lu K. LINC01001 promotes progression of crizotinib-resistant NSCLC by modulating IGF2BP2/MYC axis. *Front Pharmacol*. 2021;12:759267. <https://doi.org/10.3389/fphar.2021.759267>.

161. Feng P, Chen D, Wang X, Li Y, Li Z, Li B, Zhang Y, Li W, Zhang J, Ye J, et al. Inhibition of the m(6)A reader IGF2BP2 as a strategy against T-cell acute lymphoblastic leukemia. *Leukemia*. 2022;36:2180–8. <https://doi.org/10.1038/s41375-022-01651-9>.
162. Wang J, Xu J, Zheng J. A1BG-AS1 promotes adriamycin resistance of breast cancer by recruiting IGF2BP2 to upregulate ABCB1 in an m6A-dependent manner. *Sci Rep*. 2023;13:20730. <https://doi.org/10.1038/s41598-023-47956-2>.
163. Jiang X, Guo S, Wang S, Zhang Y, Chen H, Wang Y, Liu R, Niu Y, Xu Y. EIF4A3-induced circARHGAP29 promotes aerobic glycolysis in docetaxel-resistant prostate cancer through IGF2BP2/c-Myc/LDHA signaling. *Cancer Res*. 2022;82:831–45. <https://doi.org/10.1158/0008-5472.CAN-21-2988>.
164. Wang X, Li X, Zhou Y, Huang X, Jiang X. Long non-coding RNA OIP5-AS1 inhibition upregulates microRNA-129-5p to repress resistance to temozolomide in glioblastoma cells via downregulating IGF2BP2. *Cell Biol Toxicol*. 2022;38:963–77. <https://doi.org/10.1007/s10565-021-09614-z>.
165. Wu EY, Huang LP, Bao JH. miR-96-5p regulates cervical cancer cell resistance to cisplatin by inhibiting lncRNA TRIM52-AS1 and promoting IGF2BP2. *Kaohsiung J Med Sci*. 2022;38:1178–89. <https://doi.org/10.1002/kjm2.12593>.
166. Dahlem C, Abuhaliema A, Kessler SM, Krohler T, Zoller BGE, Chanda S, Wu Y, Both S, Muller F, Lepikhov K, et al. First small-molecule inhibitors targeting the RNA-binding protein IGF2BP2/IMP2 for cancer therapy. *ACS Chem Biol*. 2022;17:361–75. <https://doi.org/10.1021/acscchembio.1c00833>.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.