Multifaceted roles of insulin-like growth factor 2 mRNA binding protein 2 in human cancer (Review)

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Abstract. Insulin-like growth factor 2 mRNA binding protein 2 (IGF2BP2) is an RNA binding protein that functions as an N^6-methyladenosine reader. It regulates various biological processes in human cancers by affecting the stability and expression of target RNA transcripts, including coding RNAs and non-coding RNAs (ncRNAs). Numerous studies have shown that IGF2BP2 expression is aberrantly increased in various types of cancer and plays multifaceted roles in the development and progression of human cancers. In the present review, the clinical importance of IGF2BP2 is summarized and its involvement in the regulation of biological processes, including proliferation, metastasis, chemoresistance, metabolism, tumor immunity, stemness and cell death, in human cancers is discussed. The chemical compounds that have been developed as IGF2BP2 inhibitors are also detailed. As ncRNAs are now important potential therapeutic agents for cancer treatment, the microRNAs that have been reported to directly target and inhibit IGF2BP2 expression in cancers are also described. In summary, by reviewing the latest literature, the present study aimed to highlight the clinical importance and physiological functions of IGF2BP2 in human cancer, with a focus on the great potential of IGF2BP2 as a target for inhibitor development. The present review may inspire new ideas for future studies on IGF2BP2, which may serve as a specific therapeutic target in cancer.

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Abbreviations: AML, acute myeloid leukemia; BC, breast cancer; CC, cervical cancer; CRC, colorectal cancer; DLB-CL, diffuse large B-cell lymphoma; EIF4A1, eukaryotic initiation factor 4A1; EMT, epithelial-mesenchymal transition; EphA2, ephrin type-A receptor 2; ESCC, esophageal squamous cell carcinoma; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HK2, hexokinase 2; HNSCC, head and neck squamous cell carcinoma; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; LSCC, laryngeal squamous cell carcinoma; LUAD, lung adenocarcinoma; lncRNA, long non-coding RNA; m^6A, N^6-methyladenosine; miRNA, microRNA; ncRNA, non-coding RNA; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; PDO, patient-derived organoid; PDX, patient-derived xenograft; PTC, papillary thyroid carcinoma; RBP, RNA binding protein; RRM, RNA recognition motif; RUNX2, runt-related transcription factor 2; T-ALL, T-cell acute lymphoblastic leukemia; TC, thyroid cancer; TME, tumor microenvironment; TNBC, triple-negative BC; OC, ovarian cancer; TCGA, The Cancer Genome Atlas; UTR, untranslated region; VM, vasculogenic mimicry; VEGFA, vascular endothelial growth factor

Key words: IGF2BP2, epitranscriptomic modification, m^6A methylation, cancer progression, therapeutical implication

Contents

1. Introduction

Numerous studies have demonstrated that epigenetic modifications regulate gene expression, thereby affecting cell growth and differentiation, and contributing to tumor growth (1).

Epigenetic modifications, which mainly include histone modification, RNA modification, DNA methylation, chromatin remodeling and non-coding RNA (ncRNA) regulation, are heritable and reversible mechanisms that regulate gene expression and contribute to cancer progression without inducing DNA sequence changes (2). RNA modification involves changing the chemical properties and structure of RNA by adding chemical groups to RNA molecules, which regulates RNA stability, translation efficiency and recognition by other molecules (3). The post-transcriptional modification of RNA, including capping, splicing and polyadenylation, is regarded as a key factor in the regulation of protein production in mammals (4). There are >100 distinct known chemical modifications that can be applied to RNA molecules post-transcriptionally, and among these, messenger RNA (mRNA) methylation has been recognized as an important mechanism of post-transcriptional gene regulation in eukaryotes; this includes the formation of N^6-methyladenosine (m^6A), N^1-methyladenosine and 5-methylcytosine (5-7). Among these modifications, m^6A RNA methylation refers to the methylation of adenosine bases at the nitrogen-6 position, particularly in the 3' untranslated region (UTR) near the stop codon and within long internal exons. This modification is dynamically reversible and important in the regulation of precursor mRNA stability, splicing, transport, localization, maturation, translation and degradation (8-10). As one of the most abundant internal modifications in eukaryotic mRNA, m^6A modification has been identified to play a critical role in various diseases, including cancer (11,12).

The insulin-like growth factor 2 mRNA binding protein (IGF2BP) family, also known as the IGF-mRNA binding protein (IMP) family was identified in 1999. These proteins attach to the 5'-UTR of mRNA and are involved in the localization, stability and translation of target RNAs. The IGF2BP family is a unique group of m^6A readers responsible for recognizing and binding to RNAs with m^6A modification, including IGF2BP1, IGF2BP2 and IGF2BP3, which are also known as IMP1, IMP2 and IMP3, respectively (13-16). As an RNA-binding protein, human IGF2BP2 interacts with various types of RNA, including mRNAs, microRNAs (miRNAs/miRs), and long ncRNAs (lncRNAs) (17). IGF2BP2 contains two N-terminal RNA recognition motifs (RRMs) and four C-terminal K homology (KH) domains, which bind to RNAs with very high affinity. It can bind to the 5'-UTR, 3'-UTR or coding region of target genes, and then assemble into granular ribonucleosomes to assist in mRNA localization, stabilization and translation (16,18,19). IGF2BP2 has been reported to participate in normal physiological functions, as well as in the development of diseases such as cancer. IGF2BP2 influences tumorigenesis and cancer progression by affecting various biological processes in cancer cells, such as proliferation, metastasis, angiogenesis, metabolism, cell death, stemness and tumor immunity.

Although Cao *et al* (14) and Wang *et al* (17) have reviewed the role of IGF2BP2 in various physiological activities, metabolic diseases and some types of cancers based on papers published prior to 2021, knowledge on IGF2BP2 in cancer has expanded rapidly since then. In the past several years, over >100 research articles reporting on IGF2BP2 in cancer have been published. In the present review, a more comprehensive overview of the multiple roles of IGF2BP2 in human cancer is provided, including an exhaustive description of the molecular mechanisms underlying the biological processes influenced by IGF2BP2 in cancer, including proliferation, metastasis, chemoresistance, tumor metabolism, tumor immunity, stemness and tumor cell death. In light of the notable effects of IGF2BP2 in different cancers, IGF2BP2 inhibitors and miRNAs that have been reported to directly regulate IGF2BP2 expression in cancers are discussed, to provide a theoretical foundation for potential therapies targeting IGF2BP2.

2. Structure and subcellular location of IGF2BP2

As shown in Fig. 1A, the genomic location of *IGF2BP2* is in the 3q27.2 chromosomal region. The IGF2BP2 protein comprises six known domains, including two RRMs and four KHs (Fig. 1B), which are consistent with those of the other two paralogs, IGF2BP1 and IGF2BP3. Among these domains, the KH domains are mainly responsible for RNA binding, while the RRM domains promote the stability of the IGF2BP2-RNA complex, thereby prolonging the RNA half-life of the target gene (20). Moreover, existing evidence indicates that IGF2BP2 is predominantly located and highly expressed in the cytoplasm of human cells, and not expressed in the cell nucleus or other specific organelles, such as the endoplasmic reticulum, golgi apparatus and mitochondria (Fig. 1C). Therefore, IGF2BP2 mainly promotes the stability and translation of target RNA transcripts by functioning as an m^6A reader in the cytoplasm.

3. IGF2BP2 expression and its clinical significance in different tumors

High IGF2BP2 expression has been reported to promote the progression of various solid and hematological tumors. As shown in Fig. 2, IGF2BP2 expression is widely upregulated in numerous types of human tumors and only downregulated in clear cell renal cell carcinoma (ccRCC). Thus, IGF2BP2 predominantly acts as an oncogene, and is associated with the tumorigenesis and development of various human cancers. Therefore, the clinical significance of IGF2BP2 and its association with patient survival and prognosis in different cancers are discussed in the present review.

Solid tumors. An association between IGF2BP2 expression and poor prognosis has been detected in most solid tumors that have been evaluated. For instance, IGF2BP2 expression is elevated in glioma and contributes to the poor survival of patients with low-grade glioma (21,22). In addition, IGF2BP2 was identified as the core regulator among all m^6A regulators in head and neck squamous cell carcinoma (HNSCC), in which it is highly expressed and independently predicts a poor prognosis in patients with HNSCC (23). Deng *et al* (24) were the first to evaluate the prognostic role of IGF2BP2 in HNSCC, via Kaplan-Meier and Cox regression analyses using public data from The Cancer Genome Atlas (TCGA), and immunohistochemistry results from HNSCC samples. The authors demonstrated that high expression of IGF2BP2 is associated with a poor prognosis and that IGF2BP2 has potential as a prognostic factor. IGF2BP2 has also been indicated to be an oncogenic factor in laryngeal squamous cell carcinoma (LSCC), and to promote the proliferation and invasion of LSCC

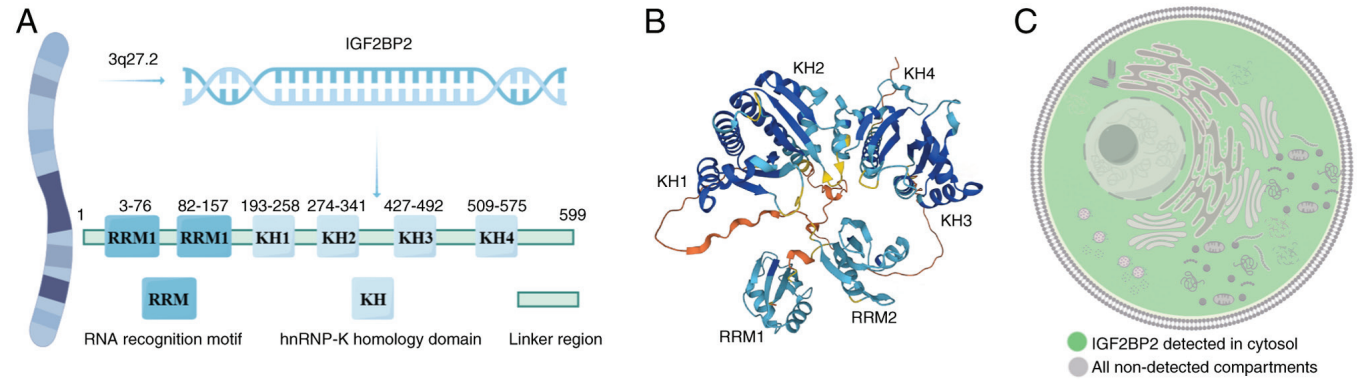

Figure 1. Structure and subcellular location of IGF2BP2. (A) Chromosome location and protein domains of *IGF2BP2*. (B) 3-Dimensional structure of IGF2BP2 according to the AlphaFold database (184). (C) Subcellular location and expression of IGF2BP2 in human cells. IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; hnRNP-K, heterogeneous nuclear ribonucleoprotein K.

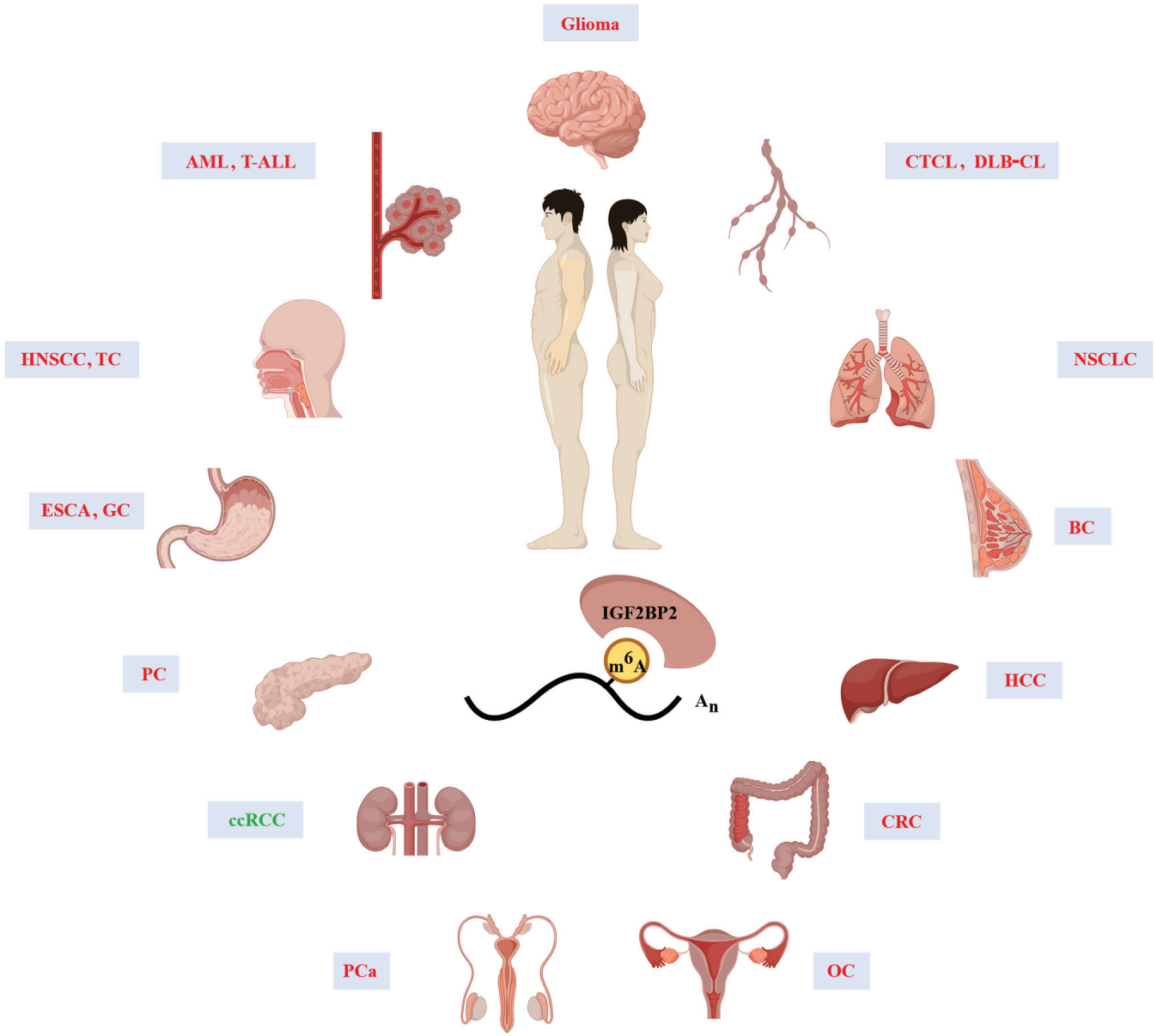

Figure 2. IGF2BP2 expression in various human cancers. Red typeface indicates IGF2BP2 upregulation while green typeface indicates IGF2BP2 downregulation. AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal cancer; CTCL, cutaneous T-cell lymphoma; ccRCC, clear cell renal cell carcinoma; DLB-CL, diffuse large B-cell lymphoma; ESCA, esophageal carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; m^6A, N^6-methyladenosine; NSCLC, non-small cell lung cancer; OC, ovarian cancer; PC, pancreatic cancer; PCa, prostate cancer; T-ALL, T-cell acute lymphoblastic leukemia; TC, thyroid cancer.

cells *in vitro* (25). Similarly, IGF2BP2 expression in oral squamous cell carcinoma (OSCC) exhibits a significant association with lymph node metastasis, tumor stage and patient survival, and IGF2BP2 protein is indicated to be a potent predictive marker in OSCC (26). Moreover, high IGF2BP2 expression was found to be associated with a shorter survival in patients with esophageal adenocarcinoma or esophageal squamous cell carcinoma (ESCC) (27). In addition, Barghash *et al* (27) suggested that IGF2BP2 might be a useful prognostic marker in Barrett's esophageal cancer and ESCC, while Lu *et al* (28) found that IGF2BP2 expression was significantly upregulated in ESCC tissues and that its expression was closely associated with the tumor-node-metastasis stage of ESCC.

Pancreatic ductal adenocarcinoma (PDAC) is one of the most malignant gastrointestinal tumors, with a poor prognosis and high relapse rate (15,29,30). IGF2BP2 is highly expressed in pancreatic intraepithelial neoplasia lesions, suggesting that it may serve as a marker for the early stages of PDAC (30). Moreover, an analysis of TCGA and Gene Expression Profiling Interaction Analysis databases revealed that IGF2BP2 is upregulated in pancreatic cancer (PC), and the expression level of IGF2BP2 correlates with the overall survival of patients with PC (30). Additionally, IGF2BP2 was identified as the IGF2BP family member with the greatest clinical relevance in PC, with high IGF2BP2 expression associated with a poor prognosis and an immunosuppressive microenvironment in PDAC (29).

IGF2BP2 has also been found to be associated with the development of hepatocellular carcinoma (HCC) and colorectal cancer (CRC). Zhang *et al* (31) originally isolated the autoantigen IGF2BP2 from a patient with HCC, and Lu *et al* (32) further demonstrated that IGF2BP2 expression is elevated in HCC and premalignant cirrhotic nodules. In addition, Shen *et al* (33) demonstrated that IGF2BP2 regulates glycolysis in CRC cells by controlling the expression of hexokinase and glucose transporters. Furthermore, IGF2BP2 expression was found to be upregulated in lung adenocarcinoma (LUAD) samples, as well as in patients with lung squamous cell carcinoma (34), while the downregulation of IGF2BP2 expression was indicated to be associated with improved survival in patients with LUAD (35). Almawi *et al* (36) investigated the association of rs4402960 and rs1470579 variants of *IGF2BP2* with breast cancer (BC) and triple-negative BC (TNBC). Although a positive association of rs440960 with BC was identified, both rs4402960 and rs1470579 showed negative associations with TNBC, suggesting that these genetic variants may have potential diagnostic and prognostic value in BC and its subtypes. In addition, IGF2BP2 expression was found to be upregulated in ovarian cancer (OC) and associated with a poor survival outcome in patients, and the knockdown of *IGF2BP2* inhibited OC cell proliferation *in vitro* (37,38). These findings indicate that IGF2BP2 plays a key role and may serve as a potential biomarker in most solid tumors.

Hematological tumors. IGF2BP2 has the potential to serve as a prognostic biomarker and therapeutic target in acute myelocytic leukemia (AML). He *et al* (39) found that the expression of IGF2BP2 was upregulated in patients with AML, negatively correlated with CCAAT/enhancer-binding protein a mutation status, and positively associated with poor prognostic factors. After analyzing gene expression datasets and performing genome enrichment analyses, the study found that genes regulated by IGF2BP2 were mainly enriched in pathways associated with cell proliferation. In addition, the study revealed that the knockdown of *IGF2BP2* by a short hairpin RNA vector significantly inhibited the growth of the KG-1a and Kasumi AML cell lines. Similarly, Feng *et al* (40) demonstrated that IGF2BP2 is highly expressed in T-cell acute lymphoblastic leukemia (T-ALL) and directly binds to the T-ALL oncogene *NOTCH1* in an m^{6}A-dependent manner. Another study, performed by Zhou *et al* (41), revealed that the rs4402960 polymorphism in the *IGF2BP2* gene was associated with an increased risk of developing diffuse large B-cell lymphoma (DLB-CL). These data demonstrate that IGF2BP2 plays a clinically important role in certain hematological tumors.

4. IGF2BP2 promotes tumor proliferation, metastasis, and progression

Sustained proliferation, along with invasion and metastasis, are hallmarks of human cancers that contribute to the poor prognosis of malignant tumors (42). As an m^{6}A modification reader, IGF2BP2 has been reported to promote tumor cell proliferation, metastasis and progression in a variety of cancers. Therefore, the latest evidence regarding the effects of IGF2BP2 on tumor proliferation, metastasis and progression is summarized in the present review (Table I).

In AML, IGF2BP2 has been indicated to promote cancer progression by stabilizing DEAD box helicase 21 and triggering the expression of Unc-51-like kinase 1 (43). In glioma, Song *et al* (44) revealed that IGF2BP2 mediates the upregulation of flotillin-1 via m^{6}A modification, thereby promoting tumor growth and metastasis. Yu *et al* (45) reported that IGF2BP2 is associated with lymphatic metastasis in patients with HNSCC promotes and promotes the epithelial-mesenchymal transition (EMT) of HNSCC cells by stabilizing *Slug* mRNA. In OSCC, IGF2BP2 has been reported to promote the expression of MYC and the autophagy-related gene RB1-inducible coiled-coil 1, thereby influencing the malignant progression of OSCC (46,47). IGF2BP2 also promotes OSCC progression by enhancing the stability of solute carrier family 7 member 11 (*SLC7A11*) mRNA (48). In addition, a recent study showed that epiregulin functions as a downstream modulator of IGF2BP2 and triggers EMT in OSCC, via a mechanism dependent on activation of the FAK/Src signaling pathway (49). IGF2BP2 has been indicated to influence the progression of thyroid cancer (TC) by regulating the expression of lncRNA *HAGLR* in an m^{6}A-dependent manner (50), and to promote lymphatic metastasis by the stabilization of dipeptidyl peptidase 4 mRNA in papillary thyroid carcinoma (PTC) (51). In LUAD, IGF2BP2 interacts with circular eukaryotic elongation factor 2 and calcium-activated nucleotidase 1 (*CANT1*), which stabilizes *CANT1* mRNA and promotes tumorigenesis and growth (52), while in NSCLC, IGF2BP2 promotes proliferation by regulating the expression of lncRNA *MALAT1* (53). In ESCC, IGF2BP2 promotes the stability of 5-hydroxytryptamine receptor 3A and circular runt-related transcription factor 1 RNA, which facilitates cell proliferation and metastasis (54,55). Moreover, IGF2BP2 also promotes

Table I. Roles of insulin-like growth factor 2 mRNA binding protein 2 in tumor proliferation, metastasis and progression.

Cancer type	Downstream RNA target	Cellular phenotype	(Refs.)
Acute myeloid leukemia	*DDX21*	Facilitates progression	(43)
Breast cancer	*UBE2D1*	Promotes progression	(79)
Breast cancer	*CDK6, QKI*	Promotes/suppresses proliferation	(80,97)
Breast cancer	*ATP6V1A, PR*	Promotes metastasis	(93,94)
Cervical cancer	*FOXM1*	Promotes progression	(84)
Colorectal cancer	*SOX2, STAG3, YAP, CCND1, TFRC*	Promotes progression	(62-65,67)
Colorectal cancer	*RAF1*	Promotes proliferation	(68)
Colorectal cancer	*HMGA1*	Promotes proliferation and metastasis	(66)
Cutaneous T-cell lymphoma	*CDKN2A*	Facilitates progression	(87)
Endometrial cancer	*PDGFRB*	Promotes progression	(83)
Esophageal squamous cell carcinoma	*HTR3A, circRUNX1*	Promotes proliferation and metastasis	(54,55)
Esophageal squamous cell carcinoma	*OCT4, EIF4A1*	Promotes progression	(56,57)
Gastric cancer	*SIRT1, IGF1R*	Promotes progression	(58,61)
Gastric cancer	*ZEB1*	Expedites proliferation, migration and EMT	(59)
Gastric cancer	*HMGA1*	Promotes metastasis and EMT	(60)
Glioma	*FLOT1*	Promotes proliferation and invasion	(44)
Glioma	*IGF2*	Promotes progression	(92)
Hepatocellular carcinoma	*CDC27*	Promotes migration, invasion and EMT	(75)
Hepatocellular carcinoma	lncRNA *TRPC7-AS1*	Promotes proliferation and invasion	(76)
Hepatocellular carcinoma	*DLK1, FEN1*	Induces proliferation	(77,78)
Head and neck squamous cell carcinoma	*Slug*	Promotes lymphatic metastasis and EMT	(45)
Laryngeal squamous cell carcinoma	*CPPED1*	Inhibits metastasis	(88)
Laryngeal squamous cell carcinoma	*TRIM59*	Promotes progression	(89)
Non-small cell lung cancer	*CANT1*	Promotes tumorigenesis	(52)
Non-small cell lung cancer	lncRNA *MALAT1, LATS1*	Promotes/inhibits proliferation	(53,95)
Ovarian cancer	*CKAP2L*	Promotes proliferation and metastasis	(82)
Ovarian	*SNAI1*	Inhibits progression	(96)
Oral squamous cell carcinoma	*RB1CC1, MYC, SLC7A11*	Inhibits/promotes proliferation	(46-48)
Oral squamous cell carcinoma	*EREG*	Promotes metastasis and EMT	(49)
Pancreatic cancer	*APLP2, B3GNT6, TLR4, MYC*	Promotes progression	(69-72)
Pancreatic cancer	*LINC00941*	Facilitates metastasis	(73)
Prostate cancer	*ETV1*	Promotes migration, invasion and EMT	(74)
Prostate cancer	*IGF1R*	Promotes metastasis	(85)
Prostate cancer	*HOXC6*	Facilitates progression	(86)
Renal cell carcinoma	*CKB, SERPINH1,* Netrin-4	Inhibits metastasis	(98-100)
Thyroid cancer	lncRNA *HAGLR*	Promotes progression	(50)
Thyroid cancer	*DPP4*	Promotes lymph node metastasis	(51)

APLP2, amyloid β precursor protein-like 2; ATP6V1A, ATPase H^+ transporting V1 subunit A; B3GNT6, β-1,3-N-acetylglucosaminyltransferase 6; CANT1, calcium-activated nucleotidase 1; CCND1, cyclin D1; CDC27, cell division cycle 27; CKB, creatine kinase B-type; CDKN2A, CDK inhibitor 2A; cirRUNX1, circular runt-related transcription factor 1; CKAP2L, cytoskeleton-associated protein 2-like; CPPED1, CDK5 regulatory subunit associated protein 1; DDX21, DEAD box helicase 21; DLK1, δ-like 1 homolog; DPP4, dipeptidyl peptidase 4; EIF4A1, eukaryotic initiation factor 4A1; EMT, epithelial-mesenchymal transition; EREG, epiregulin; ETV1, ETS transcription factor 1; FEN1, flap endonuclease 1; FLOT1, flotillin 1; FOXM1, forkhead box M1; HMGA1, high mobility group AT-hook 1; HOXC6, homeobox C6; HTR3A, 5-hydroxytryptamine receptor 3A; IGF1R, insulin-like growth factor 1 receptor; IGF2, insulin-like growth factor 2; lncRNA, long non-coding RNA; LATS1, large tumor suppressor 1; PDGFRB, platelet-derived growth factor β; OCT4, octamer-binding transcription factor 4; PR, progesterone receptor; QKI, quaking, RB1CC1, RB1-inducible coiled-coil 1; SERPINH1, serpin family H member 1; SIRT1, sirtuin 1; SLC7A11, solute carrier family 7 member 11; SNAI1, snail family transcriptional repressor 1; SOX2, SRY-box transcription factor 2; STAG3, stromal antigen 3; TFRC, transferrin receptor 1; TLR4, Toll-like receptor 4; TRIM59, tripartite motif containing 59; UBE2D1, ubiquitin conjugating enzyme E2 D1; YAP, yes-associated protein; ZEB1, zinc finger E-box binding homeobox 1.

the progression of ESCC by increasing the mRNA stability of octamer-binding transcription factor 4 and increasing eukaryotic initiation factor 4A1 (EIF4A1) translation in an m^{6}A-dependent manner (56,57).

IGF2BP2 regulates the proliferation and metastasis of gastric cancer (GC) via the recognition of m^{6}A modification sites in the mRNAs of sirtuin 1, zinc finger E-box binding homeobox 1 and high mobility group AT-hook 1 (*HMGA1*) (58-60). IGF2BP2 may also promote the progression of GC by regulating the insulin-like growth factor 1 receptor (IGF1R)-Ras homolog family member A-Rho-associated protein kinase signaling pathway (61). In CRC, IGF2BP2 promotes the mRNA stability and expression of SRY-box transcription factor 2, stromal antigen 3, yes-associated protein, cyclin D1 (*CCND1*) and *HMGA1* via an m^{6}A-dependent mechanism and promotes cancer progression (62-66). IGF2BP2 also contributes to CRC progression by regulating the methylation of transferrin receptor 1 mRNA via methyltransferase like 4, thereby influencing iron metabolism (67). Furthermore, IGF2BP2 regulates *RAF1* expression by blocking its degradation by *miR-195* in CRC, which promotes CRC cell proliferation (68). In PC, IGF2BP2 promotes cancer progression by stabilizing numerous mRNA transcripts, including those of amyloid β precursor protein-like 2, β-1,3-N-acetylglucosaminyltransferase 6, Toll-like receptor (TLR)4 and *MYC* (69-72). Furthermore, IGF2BP2 upregulates the mRNA stability of *LINC00941* and erythroblast variant transcription factor 1 in PC, which promotes cell metastasis (73,74). In HCC, IGF2BP2 maintains cell division cycle 27 mRNA stability, thereby promoting both proliferation and metastasis (75). Zhang *et al* (76) demonstrated that the IGF2BP2/lncRNA *TRPC7-AS1* axis promotes cell proliferation and invasion in HCC. Additionally, IGF2BP2 activates the small Rho GTPase RAC1 in a δ-like 1 homolog-dependent manner, which promotes hepatocarcinogenesis by amplifying inflammation (77). Furthermore, IGF2BP2 has been shown to facilitate the growth of liver cancer by increasing the mRNA stability of flap endonuclease 1 (78).

During the progression of BC, IGF2BP2 increases the stability of ubiquitin conjugating enzyme E2 D1 mRNA, which regulates the activation of TGF-β signaling by modulating the expression and phosphorylation levels of Smad2/3 (79). Xia *et al* (80) reported that IGF2BP2 drives tumor proliferation in TNBC by recruiting EIF4A1, which promotes the translation of m^{6}A-modified *CDK6*. Additionally, IGF2BP2 facilitates the metastasis of TNBC by promoting cell migration and reducing cell adhesion (81). Moreover, IGF2BP2 contributes to OC growth and metastasis by upregulating the expression of cytoskeleton-associated protein 2-like protein in an m^{6}A-dependent manner (82). In endometrial cancer, IGF2BP2 stabilizes platelet-derived growth factor b and activates JAK/STAT signaling, thereby inducing cancer progression (83). IGF2BP2 has also been shown to promote the mRNA stability of forkhead box M1 (*FOXM1*) and contribute to cervical cancer (CC) progression (84). In prostate cancer (PCa), IGF2BP2 promotes the mRNA stability of lncRNA *PCAT6* and *IGF1R* and facilitates the bone metastasis of cancer cells (85). In addition, IGF2BP2 stabilizes the methylated mRNA of homeobox C6 and enhances PCa progression (86). Furthermore, IGF2BP2 regulates the progression of cutaneous T-cell lymphoma by recognizing and stabilizing CDK inhibitor 2A mRNA (87). In particular, IGF2BP2 promotes tumor proliferation and metastasis by activating the PI3K/AKT signaling pathway in numerous human cancers, such as LSCC (88,89), HNSCC (90), PC (91) and glioblastoma (GBM) (92).

IGF2BP2 also promotes cancer progression via the degradation of RNA transcripts. For example, IGF2BP2 has been reported to promote the degradation of ATPase H$^+$ transporting V1 subunit A RNA, resulting in the production of a cellular secretome that increases tumor cell survival and invasiveness in BC (93). In TNBC, IGF2BP2 destabilizes the mRNA of the progesterone receptor and promotes cancer metastasis (94). However, several studies have suggested that IGF2BP2 inhibits cancer progression. One study indicated that IGF2BP2 interacts with lncRNA *HCG11* and large tumor suppressor kinase 1 mRNA, thereby mediating the methyltransferase like (METTL) 14-induced inhibition of LUAD (95). In addition, IGF2BP2 binds to the 3'-UTR region of snail family transcriptional repressor 1 (*SNAI1*) mRNA and mediates the fat mass and obesity-associated (FTO)-induced destabilization of *SNAI1*, thereby inhibiting OC progression (96). In BC, IGF2BP2 upregulates quaking protein expression, leading to the suppression of tumor growth (97). IGF2BP2 suppresses ccRCC metastasis by stabilizing the mRNA of creatine kinase B-type and serpin family H member 1, neuropilin and tolloid-like 1 (98,99). IGF2BP2 also binds to the m^{6}A site of the netrin-4 transcript and promotes its expression, which suppresses the invasion and migration of ccRCC (100). These findings suggest that IGF2BP2 plays multiple and conflicting roles in the promotion or inhibition of cancer cell proliferation, metastasis and progression.

5. IGF2BP2 confers tumor resistance to chemotherapy and radiotherapy

The development of chemoresistance and radioresistance markedly hinders the efficacy of radiochemotherapy in various cancers. However, the underlying mechanisms remain unclear. IGF2BP2 has been shown to regulate chemotherapy resistance, and also to lead to radiotherapy resistance. The existing literature on the role of IGF2BP2 in tumor resistance to chemotherapy and radiotherapy is summarized in the present review (Table II).

Chemotherapy resistance. Cisplatin (DDP) is the earliest and most effective platinum compound used to treat various cancers. However, several studies have shown that IGF2BP2 can contribute to DDP resistance in tumor cells. Wu *et al* (101) demonstrated that IGF2BP2 plays a role in mediating the *miR-96-5p*-induced resistance of CC cells to DDP. In addition, IGF2BP2 stabilizes ATPase copper transporting α mRNA and elevates its protein level, thereby facilitating circular PBX homeobox 3-promoted DDP resistance in OC cells (102). Furthermore, IGF2BP2 stabilizes lncRNA taurine upregulated gene 1 and promotes cell proliferation, migration, and autophagy via the *miR-195-5p*/hepatoma-derived growth factor/DEAD-box helicase 5/β-catenin axis, thereby promoting the resistance of CRC to DDP (103).

Table II. Associations of insulin-like growth factor 2 mRNA binding protein 2 with chemotherapy resistance in different cancers.

Cancer therapy	Cancer type	Target	Resistance mechanism	(Refs.)
Cisplatin	Cervical cancer	N/A	Inhibits cell apoptosis and increases cell proliferation	(101)
Cisplatin	Ovarian cancer	ATP7A	Reduces cell apoptosis	(102)
Cisplatin	Colorectal cancer	lncRNA *TUG1*	Activates autophagy	(103)
Etoposide	Glioma	lncRNA *DANCR*	Inhibits FOXO1 expression	(104)
Crizotinib	Non-small cell lung cancer	MYC	Inhibits cell apoptosis	(105)
Adriamycin	Breast cancer	ABCB1	Increases drug efflux	(106)
Tyrosine kinase inhibitor	Papillary thyroid carcinoma	ERBB2	Activates ERBB2 signaling	(107)
Temozolomide	Glioblastoma	N/A	Inhibits cell apoptosis	(108)
Enzalutamide	Castration-resistant prostate cancer	HMGCS1	Inhibits cell apoptosis and increases cell proliferation	(109)
Sorafenib	Hepatocellular carcinoma	SLC7A11	Decreases ferroptosis sensitivity	(110)

ABCB1, ATP binding cassette subfamily B member 1; ATPA7, ATPase copper transporting α; ERBB2, epidermal growth factor receptor 4; HMGCS1, 3-hydroxy-3-methylglutaryl-CoA synthase 1; lncRNA, long non-coding RNA; N/A, not applicable; SLC7A11, solute carrier family 7 member 11.

IGF2BP2 also mediates resistance to numerous other types of chemotherapeutic agents. In gliomas, IGF2BP2 stabilizes the lncRNA *DANCR*, which inhibits the FOXO1-induced transcriptional expression of phosphotyrosine interaction domain containing 1, thereby reducing the etoposide sensitivity of GBM cells (104). Zhang *et al* (105) elucidated the mechanism of crizotinib resistance in NSCLC, finding that IGF2BP2 modulates MYC expression and mediates *LINC01001*-induced chemoresistance. Wang *et al* (106) demonstrated that IGF2BP2 upregulates p-glycoprotein in an m^{6}A-dependent manner, thereby contributing to Adriamycin resistance in BC. Additionally, the IGF2BP2-dependent activation of epidermal growth factor receptor 4 (ERBB2) signaling contributes to the acquisition of resistance to tyrosine kinase inhibitors; the lapatinib-induced inhibition of IGF2BP2 and ERBB2 was able to reverse the resistance of a selumetinib-resistant PTC cell line (107). Moreover, the upregulation of *miRNA-129-5p* downregulates IGF2BP2, thereby repressing temozolomide resistance in GBM cells (108). Shi *et al* (109) found that IGF2BBP2 stabilizes 3-hydroxy-3-methylglutaryl-CoA synthase 1 mRNA to drive enzalutamide resistance in PCa. In addition, IGF2BP2 mediates sorafenib resistance in HCC by inhibiting ferroptosis via the promotion of *SLC7A11* mRNA stability (110).

Evaluation of the resistance to chemotherapeutics in patient-derived xenografts (PDXs) and patient-derived organoids (PDOs) revealed that IGF2BP2 expression in primary tumor tissue was associated with resistance to selumetinib, gefitinib and regorafenib in PDOs and to 5-fluorouracil and oxaliplatin in PDXs *in vivo* (111). These findings indicate that IGF2BP2 plays a key role in the development of chemoresistance in various cancers.

Radiotherapy resistance. In addition to chemoresistance, IGF2BP2 also modulates radiosensitivity in several cancers. For example, in lung cancer, IGF2BP2 promotes the stability and expression of *SLC7A5* mRNA, and SLC7A5 facilitates the transport of methionine into cells, which increases H3K4me3 enrichment and subsequently promotes IGF2BP2 expression. This IGF2BP2-SLC7A5 positive feedback loop promotes radioresistance through the AKT/mTOR pathway, suggesting that IGF2BP2 may be a potential therapeutic target to overcome radioresistance in lung cancer (112). In addition, IGF2BP2 has been shown to be involved in stabilizing deltex E3 ubiquitin ligase 3-like mRNA in HCC, thereby alleviating radiation-induced DNA damage and increasing the radiation resistance of cancer cells (113).

6. IGF2BP2 affects tumor metabolism

Aerobic glycolysis, also termed the Warburg effect, has been shown to play a key role in tumor cell proliferation and metastasis, and is an important distinguishing feature between normal cells and malignant tumor cells (114). As shown in Fig. 3, IGF2BP2 regulates aerobic glycolysis, glutamine metabolism and lipid synthesis by regulating the mRNA stability of its target transcripts. For instance, IGF2BP2 promotes AML progression by regulating the expression of lncRNA *DANCR* and upregulating glycolysis (115). In addition, the elevated expression of IGF2BP2 promotes AML development and the self-renewal of leukemia stem cells or initiation cells by regulating the expression of key targets, such as MYC, glutamate pyruvate transaminase 2 and solute carrier family 1 member 5, which are involved in glutamine metabolism pathways via m^{6}A modification. IGF2BP2 also increases the mRNA stability of the ribonucleotide reductase regulatory subunit M2B gene, which promotes the generation of glutathione in CRC cells (116).

IGF2BP2 has been reported to promote aerobic glycolysis and cell proliferation in CRC and PDAC by stabilizing glucose transporter 1 mRNA (117). IGF2BP2 also binds to

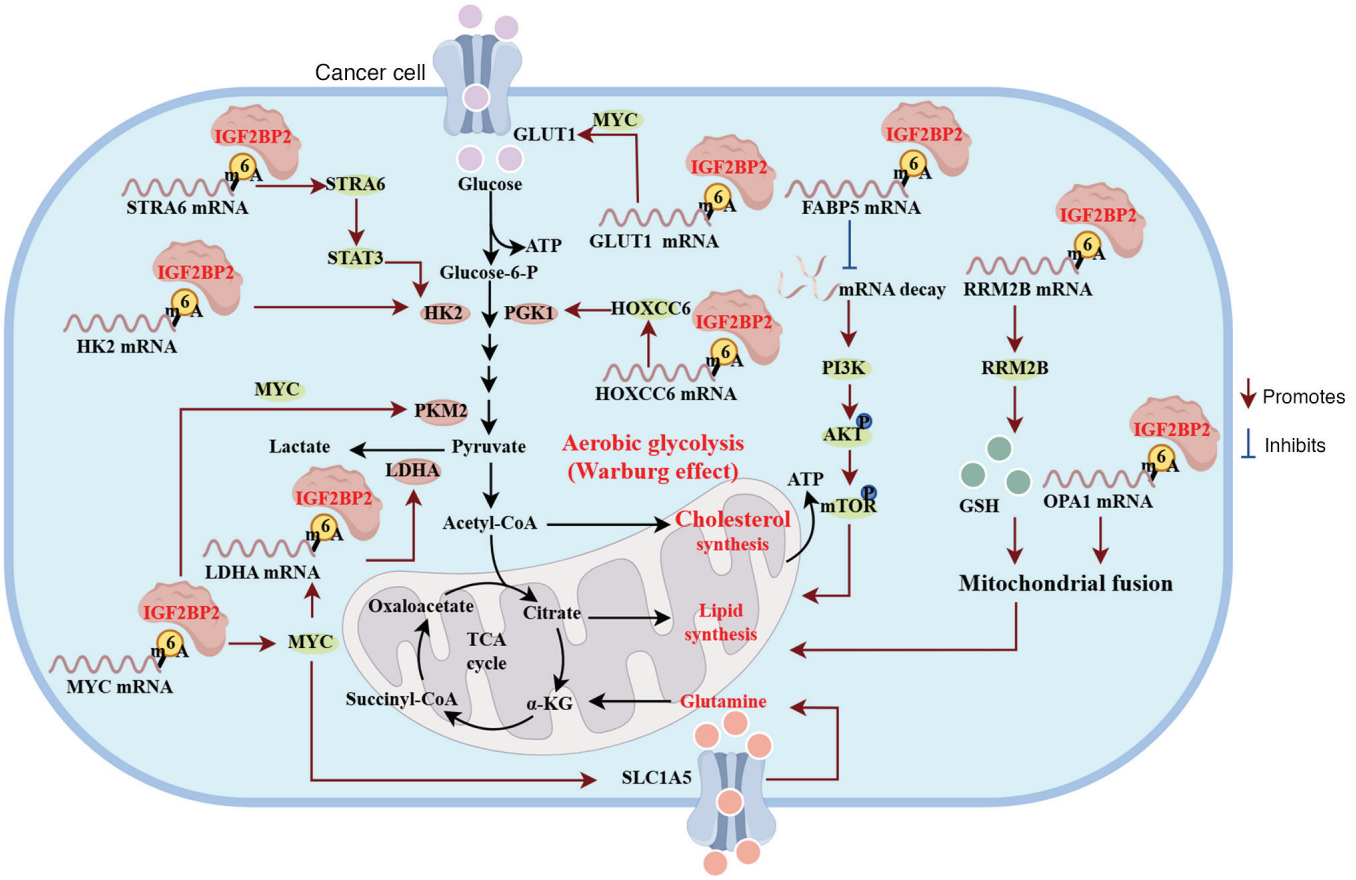

Figure 3. Association of IGF2BP2 with tumor metabolism. By binding to the m^{6}A modification site of target RNA transcripts, IGF2BP2 regulates the expression of certain key genes that are involved in tumor metabolism pathways, including aerobic glycolysis, glutamine metabolism and lipid synthesis. a-KG, a-ketoglutarate; CoA, coenzyme A; FABP5, fatty acid binding protein 5; glucose-6-P, glucose-6-phosphate; GLUT1, glucose transporter 1; GSH, glutathione; HK2, hexokinase 2; HOXCC6, homeobox C6; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; LDHA, lactate dehydrogenase A; m^{6}A, N^6-methyladenosine; OPA1, optic atrophy 1; PGK1, phosphoglycerate kinase 1; PKM2, pyruvate kinase M2; RRM2B, ribonucleotide reductase regulatory subunit M2B; SLC1A5, solute carrier family 1 member 5; STRA6, stimulated by retinoic acid 6; TCA, tricarboxylic acid.

MYC mRNA, improving its stability and expression, thereby maintaining MYC-mediated aerobic glycolysis and proliferation of CRC cells (118). In addition, IGF2BP2 contributes to the mRNA stability of stimulated by retinoic acid 6, leading to activation of the STAT3/hypoxia inducible factor 1 α axis and the subsequent upregulation of glycolysis in PDAC (119). IGF2BP2 also promotes *MYC* mRNA stability in an m^{6}A-dependent manner and promotes aerobic glycolysis during the progression of CC (120). Similarly, IGF2BP2 stabilizes *MYC* mRNA and promotes MYC protein expression, which further upregulates lactate dehydrogenase A expression and promotes aerobic glycolysis in PCa (121). Notably, the KH3-4 domains of the IGF2BP2 protein have been identified as the key RNA-binding domains responsible for the recognition of m^{6}A sites ('RGGAC/RRACH') within the lncRNA *ZFAS1*. In turn, *ZFAS1* directly binds to oxidative lethal 1 (OLA1), which promotes the ATPase activity of OLA1, thereby mediating mitochondrial energy metabolism, including ATP hydrolysis and glycolysis, in the progression of CRC (122).

Hexokinase 2 (HK2) is an enzyme that catalyzes the phosphorylation of glucose to form glucose-6-phosphate, which regulates the first committed step in glucose metabolism (123,124). The relationship between HK2 expression and tumor metabolism has been reported in numerous studies. For example, IGF2BP2 may directly interact with *HK2* mRNA by binding to the m^{6}A site in the 3'-UTR, thereby promoting the stability of *HK2* mRNA and increasing HK2 expression (125). IGF2BP2 recognizes the m^{6}A site of lncRNA *CASC9*, enhancing its stability. The resulting IGF2BP2/*CASC9* complex increases the stability of *HK2* mRNA, thereby promoting aerobic glycolysis in GBM cells (126). The FTO-AlkB homolog 5/IGF2BP2/HK2/FOXO1 axis is involved in the mechanism underlying the aberrant m^{6}A modification and regulation of glycolysis in CRC. Within this signaling pathway, IGF2BP2 regulates *HK2* mRNA expression in an m^{6}A-dependent manner, further promoting tumor metabolism and CRC progression (127). Additionally, IGF2BP2 increases the expression of fatty acid binding protein 5 in an m^{6}A-dependent manner in pancreatic neuroendocrine neoplasms, potentially leading to lipid metabolism disorders. This highlights a new molecular basis for the development of therapeutic strategies for pancreatic neuroendocrine neoplasms (128).

7. Association of IGF2BP2 with the tumor immune response

Immunotherapy acts against tumor cells that present new antigens and exhibit pro-inflammatory activity (129). However,

one feature of malignant tumors is their ability to avoid immune destruction (42). It has been shown that the IGF2BP family of RNA-binding proteins can regulate the innate and adaptive immune responses to cancer cells within the tumor microenvironment (TME). Among them, IGF2BP2 plays a crucial role in modulating the immune microenvironment of malignant tumors. As shown in Fig. 4, *IGF2BP2* knockout was found to increase major histocompatibility complex I (H-2) expression in mouse melanoma cells and induce intracellular IFNγ expression in syngeneic T-lymphocytes *in vitro* (130). Liu *et al* (131) reported that the knockdown of *IGF2BP2* inhibited CRC cell proliferation and migration, and also promoted tumor immunity by downregulation of the expression of MYC, TNFα and IL-10. In addition, IGF2BP2 has been shown to recognize and stabilize methylated programmed cell death ligand 1 (*PD-L1*) transcripts, thereby blocking T cell-mediated antitumor activity in CRC (132). In PDAC, IGF2BP2 increases the stability of Kruppel-like factor 12 and *MYC*, which induces the polarization of pro-tumor macrophages in the TME and promotes PC progression (133).

Using transcriptome data from TCGA and Gene Expression Omnibus datasets, Li *et al* (134) established an HNSCC immunophenotype based on m^{6}A regulatory genes and demonstrated that IGF2BP2 effectively promotes immunosuppression in HNSCC. The study indicated that IGF2BP2 inhibits the expression of effector T-cells involved in antigen recognition, signal transduction, proliferation and activation. Additionally, it suggested that IGF2BP2 increases the stability of tumorigenic genes, such as *EGFR* and *CD276*, thereby activating downstream signaling pathways. Furthermore, the study found that high IGF2BP2 expression is associated with a reduction in the number of tumor-infiltrating CD8$^+$ T cells. In another study, *in vitro* experiments demonstrated that high expression of IGF2BP2 promotes the progression of OSCC and is associated with tumor proliferation, metastasis and tumor-infiltrating immune cells (135). However, experimental validation, both *in vitro* and *in vivo*, is required to confirm the conclusions of the findings of the former study, which were based solely on bioinformatic approaches.

8. IGF2BP2 affects tumor stemness

Several reports have indicated that IGF2BP2 may affect cell stemness in various cancers. As shown in Fig. 5, IGF2BP2 stabilizes TGFb factor receptor 1 mRNA and participates in the forkhead box P3-promoted stemness of NSCLC cells (136). Additionally, IGF2BP2 increases the mRNA stability and expression of cell cycle and apoptosis regulator 1, which subsequently upregulates the expression levels of Wnt/β-catenin target genes, thereby promoting stemness and metastasis in PCa (137). Ji *et al* (138) found that the m^{6}A reader IGF2BP2 binds to and stabilizes colony-stimulating factor 2 (*CSF2*) mRNA in mesenchymal stem cells (MSCs). Consequently, IGF2BP2 overexpression simulates the effect of CSF2 on MSCs and promotes GC progression. In addition, the study revealed that IGF2BP2-regulated CSF2 induces Notch1 ubiquitination to reprogram MSCs into a tumor-promoting phenotype, including augmented tropism towards GC cells and elevated expression of FAP, α-SMA and inflammatory factors GM-CSF, FGF and PDGF-BB, providing a promising therapeutic target for GC. Furthermore, an early study found that IGF2BP2 regulates oxidative phosphorylation in primary GBM sphere cultures and contributes to the preservation of GBM cancer stem cells (139). Also, another study suggested that IGF2BP2 binds to *let-7* miRNA recognition elements and inhibits the silencing of *let-7* miRNA target genes such as *CCND1* and *HMGA2*, thereby promoting the clonality and tumor initiation ability of glioma stem cells (140).

9. IGF2BP2 regulates tumor cell death

As a key m^{6}A reader, IGF2BP2 has been demonstrated to affect different types of cell death, such as apoptosis and ferroptosis, in tumors by up- or downregulating the mRNA stability of target genes (Fig. 6). For instance, IGF2BP2 overexpression promotes the proliferation of DLB-CL cells and inhibits their apoptosis by regulating the p53 signaling pathway through the upregulation of 5'-nucleotidase domain containing 2 mRNA stability and expression (141). IGF2BP2 is also involved in recognizing and stabilizing *TLR2* mRNA, thereby promoting cell proliferation and inhibiting apoptosis in hypopharyngeal squamous cell carcinoma (142). Yang and Liu (143) reported that the inhibition of IGF2BP2 expression increases the apoptosis of hypopharyngeal cancer cells. Additionally, IGF2BP2 has been found to play an anti-apoptotic role in human HCC cells, with an anti-apoptotic mechanism that is independent of the PI3K signaling pathway but is regulated by extracellular signal-regulated kinases (ERK) 1/2 (144). Moreover, IGF2BP2 reduces the mRNA stability of acyl CoA synthetase medium-chain family member 3 (*ACSM3*), which functions as a tumor suppressor in AML, and IGF2BP2 overexpression reverses the ability of ACSM3 to promote apoptosis (145).

Ferroptosis was first proposed as a mechanism of cell death in 2012 (146). Ferroptosis is driven by iron-dependent phospholipid peroxidation and regulated by a variety of cellular metabolic events, including amino acid and lipid metabolism, redox homeostasis, mitochondrial activity and numerous disease-related signaling pathways (147,148). Yang *et al* (149) demonstrated that IGF2BP2 promotes the mRNA stability and expression of glutathione peroxidase 4, which inhibits ferroptosis, thereby promoting the malignant progression of ESCC. In addition, IGF2BP2 enhances the mRNA stability and expression of nuclear factor erythroid 2 like 2, also known as nuclear factor erythroid 2-related factor 2, consequently increasing cellular resistance to ferroptosis and reducing cell death (150). In CRC, IGF2BP2 stabilizes *FOXM1* mRNA and suppresses ferroptosis, thus promoting cell proliferation and migration (151). Furthermore, IGF2BP2 promotes the mRNA stability and expression of *SLC7A11*, which enhances the functions of system Xc- and confers ferroptosis resistance to HCC cells (110). These findings collectively suggest that IGF2BP2 promotes cancer progression via the inhibition of tumor cell death.

10. Association of IGF2BP2 expression with tumor angiogenesis and differentiation

The induction of angiogenesis is one of the characteristics of malignant tumors (42), as tumor growth relies on angiogenesis for the supply of nutrients and oxygen (152,153).

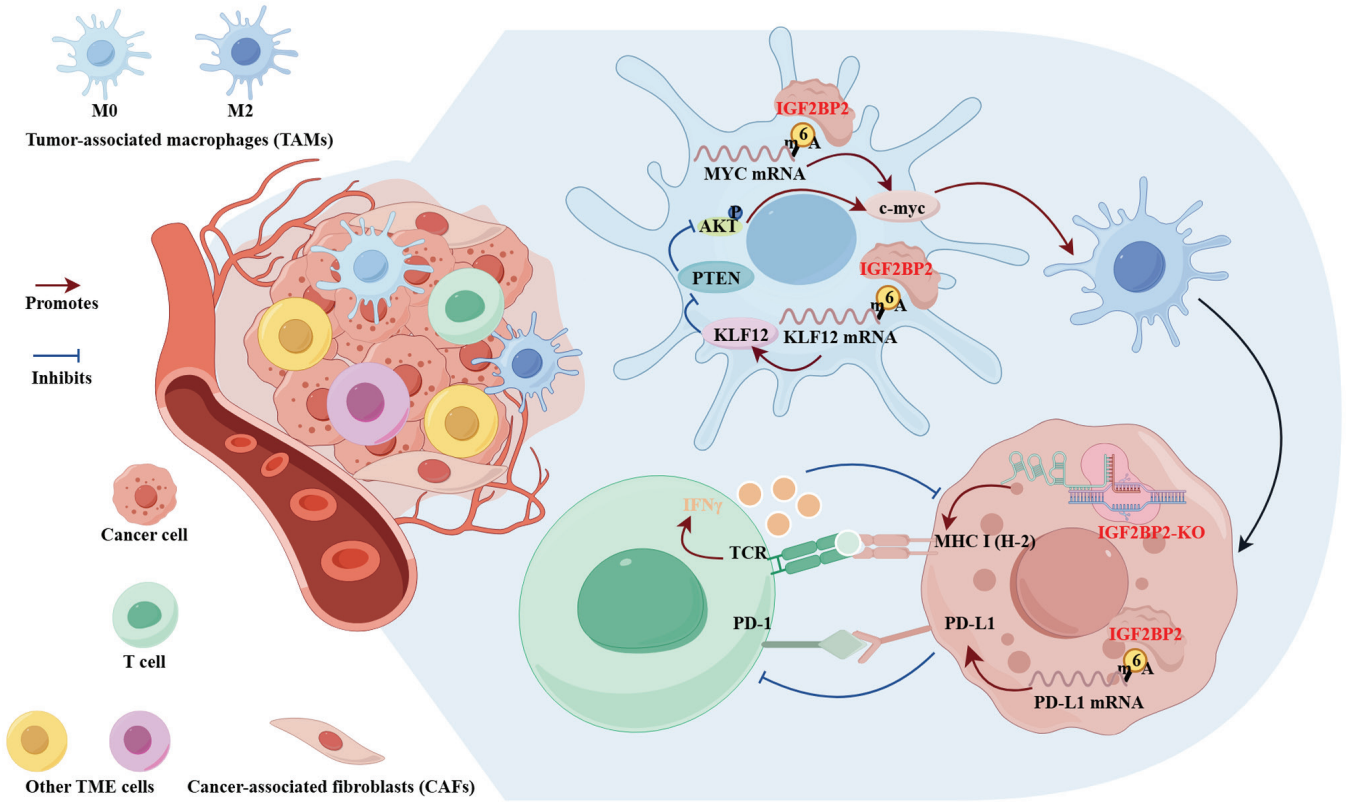

Figure 4. Effect of IGF2BP2 on the tumor immune microenvironment. IGF2BP2 affects the tumor immune microenvironment by regulating target gene expression in an m^{6}A-dependent manner. For example, it promotes the polarization of M0 macrophages to M2 macrophages, which facilitates cancer progression. Conversely, it also regulates the expression of PD-L1 and MHC 1, which attenuates antitumor immunity. IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; KLH12, Kruppel-like factor 12; m^{6}A, N^6-methyladenosine; KO, knockout; MHC 1, major histocompatibility complex 1; N^6-methyladenosine; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TCR, T-cell receptor; TME, tumor microenvironment.

IGF2BP2 increases the expression of thymidine kinase 1, thereby promoting angiogenesis and CD31 expression (154). In addition, IGF2BP2 activates endothelial cells and stabilizes fms-related tyrosine kinase 4 via m^{6}A modification, thereby activating the PI3K/AKT signaling pathway and promoting angiogenesis and metastasis in LUAD (155). In gallbladder cancer, IGF2BP2 recognizes the m^{6}A modification of transient receptor potential cation channel subfamily M member 2-antisense RNA, stabilizes its mRNA, and promotes angiogenesis by activating Notch1 signaling (156).

In addition to traditional tumor angiogenesis, vasculogenic mimicry (VM) is a tumor microcirculation model in which newly formed blood vessel-like structures transport nutrients and blood to support tumor growth (157). Both ephrin type-A receptor 2 (EphA2) and vascular endothelial growth factor (VEGFA) play crucial roles in VM in tumors (158-161). Liu *et al* (162) demonstrated that IGF2BP2 mediates the METTL3-regulated expression of EphA2 and VEGFA via an m^{6}A-dependent mechanism, thereby promoting VM via the PI3K/AKT/mTOR and ERK1/2 signaling pathways in CRC. In addition, the SUMOylation of IGF2BP2 regulates the opa-interacting protein-antisense RNA 1/*miR-495-3p* axis, which promotes VM and glioma cell growth (163). These findings highlight the diverse mechanisms by which IGF2BP2 influences tumor angiogenesis.

IGF2BP2 is also able to affect tumor differentiation. It recognizes the m^{6}A modification site in the 3'-UTR of runt-related transcription factor 2 (*RUNX2*) and increases its mRNA stability. Subsequently, RUNX2 binds to the promoter region of the sodium/iodine cotransporter and downregulates its expression to block the differentiation of radioiodine-refractory PTC (164). It has also been demonstrated that an aryl hydrocarbon receptor antagonist can promote the differentiation of PTC by inhibiting the circular SH2B adaptor protein 3/*miR-4640-5p*/IGF2BP2 axis. This provides a potential marker and novel therapeutic target for PTC differentiation (165).

11. Therapeutical implications of the role of IGF2BP2 in cancer

Considering the multifaceted roles of IGF2BP2 in the progression of various cancers, several IGF2BP2 inhibitors have been explored as potential therapeutic strategies (Table III). IGF2BP2 inhibitors were initially screened from various compound libraries using fluorescence polarization experiments, and the screening results were verified by thermal shift experiments and saturation transfer difference nuclear magnetic resonance. This identified 10 compounds in two categories, specifically 4-benzamidobenzoic acid and ureidothiophene derivatives, of which the three compounds with the strongest biological target-specific activities were tested and verified. These small-molecule inhibitors targeting IGF2BP2 were shown to have an inhibitory effect on the growth of

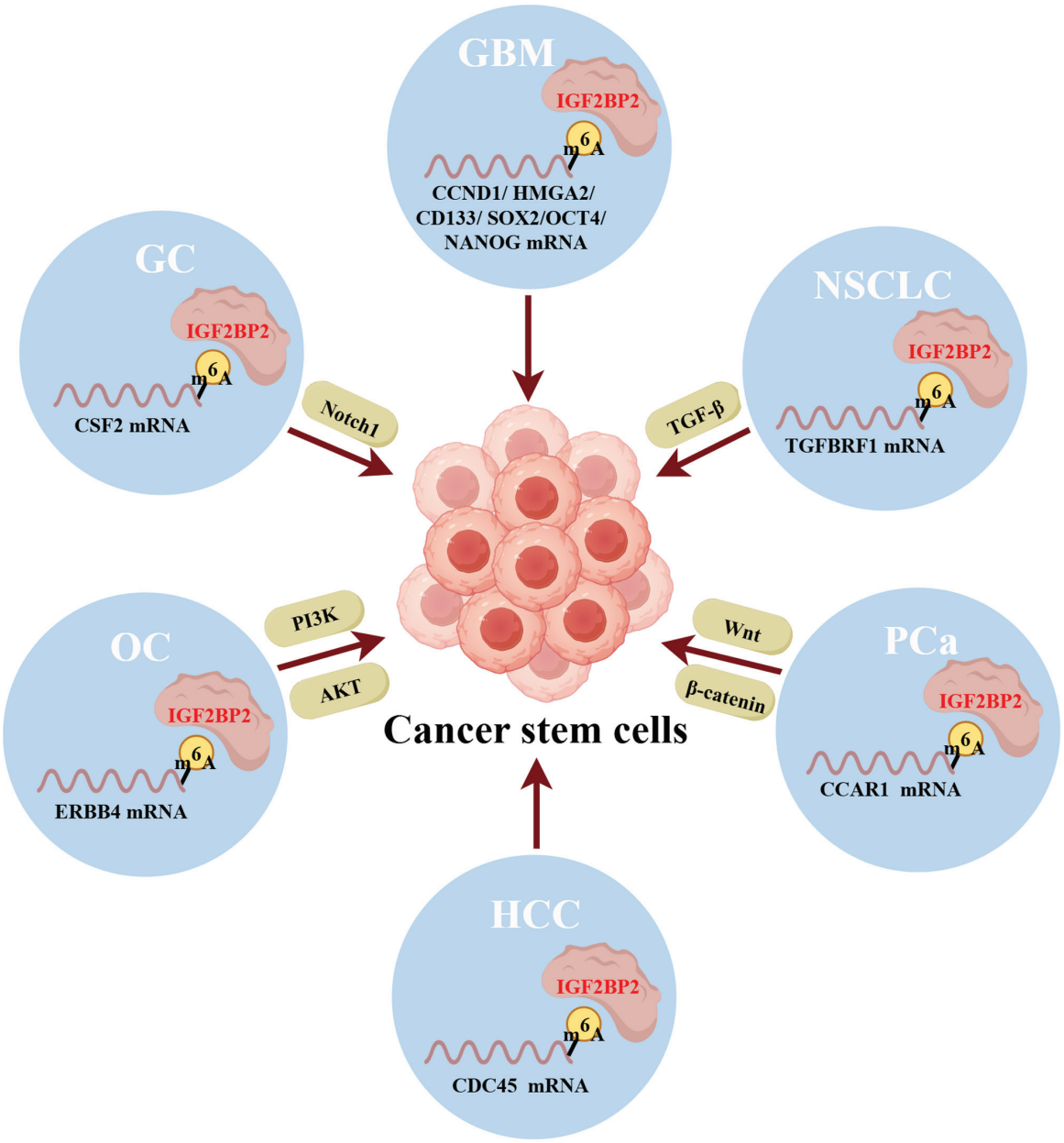

Figure 5. Effect of IGF2BP2 on cancer stem cells. IGF2BP2 regulates tumor stemness in several cancers by affecting various signaling pathways, including the Wnt/β-catenin, TGF-β, Notch1 and PI3K/AKT pathways. CCAR1, cell cycle and apoptosis regulator 1; CCND1, cyclin D1; CDC45, cell division cycle 45; CSF2, colony stimulating factor 2; ERBB4, epidermal growth factor receptor 4; GBM, glioblastoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HMGA2, high mobility group AT-hook 2; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; m^6A, N^6-methyladenosine; NSCLC, non-small cell lung cancer; OC, ovarian cancer; OCT4, octamer-binding transcription factor 4; PCa, prostate cancer; SOX2, SRY-box transcription factor 2; TGFBR1, TGFb factor receptor 1.

xenograft tumors in an *in vivo* experiment using zebrafish (166). Since then, CWI1-2 has been identified as another inhibitor of IGF2BP2. CWI1-2 binds to the K3-K4 domains of IGF2BP2 and inhibits its interaction with m^6A-modified target transcripts. Consequently, CWI1-2 induces apoptosis and differentiation and exerts an anti-leukemic effect (167). Similarly, Feng *et al* (40) identified another IGF2BP2 inhibitor, JX5, which targets the KH3-KH4 domains of IGF2BP2. JX5 treatment was demonstrated to inhibit T-ALL both *in vitro* and *in vivo*. Additionally, another study generated *IGF2BP2* knockout cells using the CRISPR/cas9-primer editing method and verified that IGF2BP2 has the potential to serve as an anticancer target (168).

Currently, miRNAs are used in treatment regimens to inhibit tumor progression due to their ability to directly regulate target genes (169-171). Numerous studies have demonstrated that ncRNAs, including miRNAs, can regulate the expression of IGF2BP2. As shown in Table IV, several miRNAs have been found to directly inhibit IGF2BP2 expression in different cancers. In TC, IGF2BP2 was identified as a target of *miR-204* and *miR-4640-5p*, which binds to the 3'-UTR of *IGF2BP2* to inhibit its expression (165,172). In HCC and ESCC, *miR-216b* was shown to bind to the 3'-UTR of *IGF2BP2* and decrease its expression (173,174). Similarly, *miR-200b* was found to inhibit IGF2BP2 expression in ESCC (175). Additionally, *miR-596* and *miR-7-5p* were confirmed to downregulate IGF2BP2

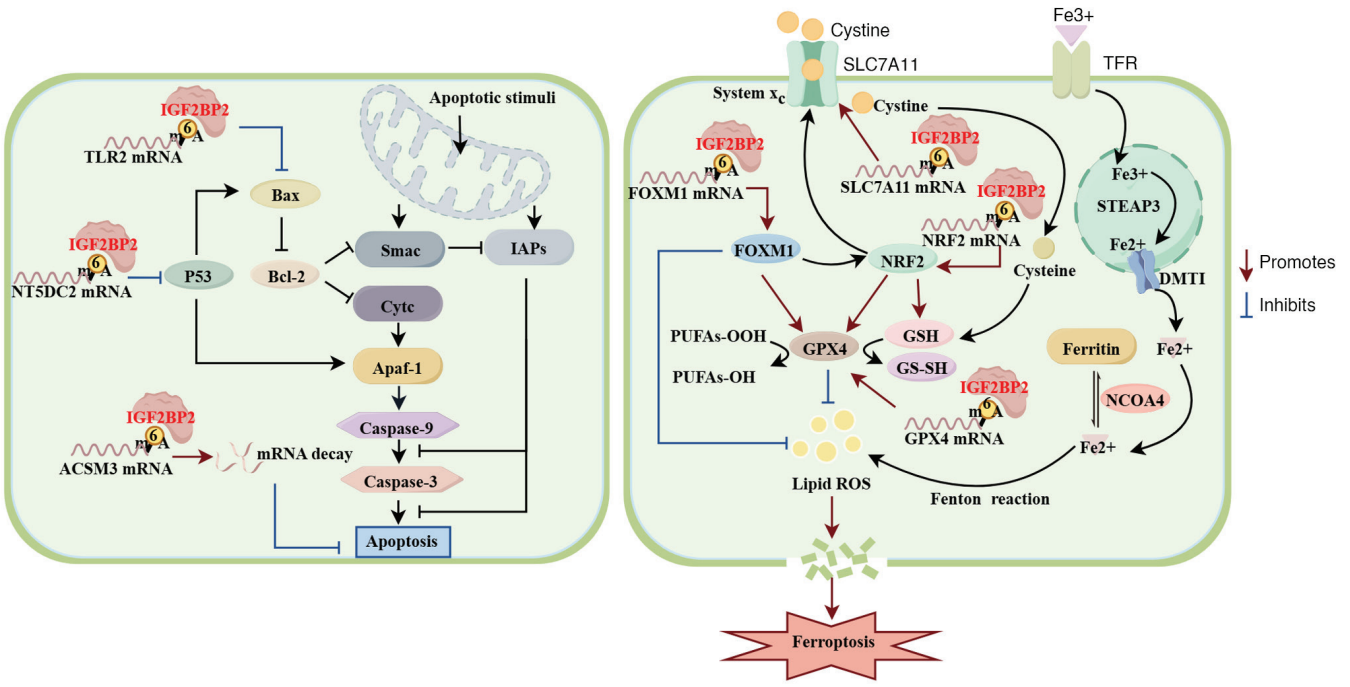

Figure 6. Association of IGF2BP2 with tumor cell death. IGF2BP2 regulates cell apoptosis and ferroptosis in numerous cancers by targeting various important molecules in the pathways of cell apoptosis and ferroptosis. ACSM3, acyl CoA synthetase medium-chain family member 3; Apaf-1, apoptotic protease activating factor 1; Cytc, cytochrome *c*; DMT1, divalent metal transporter 1; FOXM1, forkhead box M1; GPX4, glutathione peroxidase 4; GSH, glutathione; IAPS, inhibitor of apoptosis proteins; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; m^{6}A, N^6-methyladenosine; NCOA4, nuclear receptor coactivator 4; NRF2, nuclear factor erythroid 2-related factor 2; NT5DC2, 5'-nucleotidase domain containing 2'; PUFAs, polyunsaturated fatty acids; SLC7A11, solute carrier family 7 member 11; Smac, second mitochondria-derived activator of caspases; STEAP3, six-transmembrane epithelial antigen of the prostate 3; TFR, transferrin receptor; TLR2, Toll-like receptor 2.

expression in HCC (176,177). In CRC, IGF2BP2 was verified as a target of *miR-133b*, which directly inhibits the expression of IGF2BP2 (178). Several studies of gliomas demonstrated that *miR-138*, *miR-188* and *miR-129-5p* directly target and inhibit IGF2BP2 expression (108,179,180). Furthermore, *miR-98-5p*, *miR-485-5p*, *miR141* and *miR200a* were shown to inhibit IGF2BP2 expression in HNSCC (90), NSCLC (181), PC (91) and TNBC (94), respectively. These data suggest that the expression of IGF2BP2 can be inhibited by numerous miRNAs, which may offer a potential therapeutic approach for the targeting of IGF2BP2 in human cancers.

12. Conclusions and perspectives

m^{6}A readers regulate the fate of RNA transcripts by several mechanisms and influence cancer development by modulating gene expression. For instance, YTH domain containing 1 (YTHDC1) is involved in the splicing and nuclear export of m^{6}A-modified RNA transcripts, whereas YTHDC2 and YTH m^{6}A RNA binding proteins 1-3 promote the decay or translation of m^{6}A-modified RNAs (182). In contrast to other subfamilies of m^{6}A reader proteins, the IGF2BP family member IGF2BP2 stabilizes m^{6}A-modified RNA transcripts and promotes their translation (183). Consequently, IGF2BP2 plays a key role in the development and progression of various cancers via the upregulation of oncogene expression. As aforementioned, IGF2BP2 expression is upregulated in cancers compared with that in the corresponding normal tissues and is associated with a poor prognosis and shorter survival in patients with various tumors. IGF2BP2 has been shown to regulate numerous tumorigenic processes, including proliferation, metastasis, angiogenesis, metabolism, cell death, chemoresistance, tumor immunity and stemness. Therefore, IGF2BP2 is a potential biomarker and therapeutic target for malignant tumors. However, further research is necessary to elucidate the key roles of IGF2BP2 in tumorigenesis and progression, as well as to develop treatments targeting IGF2BP2 in cancer.

Although IGF2BP2 expression has been found to be upregulated in various tumors, the exact effects of IGF2BP2 on tumor development and progression, as well as the underlying molecular mechanisms, remain unclear in numerous cancers. Some studies have described the association of IGF2BP2 with tumor characteristics based solely on bioinformatic analyses using public databases, without experimental validation *in vitro* or *in vivo*. Therefore, further studies are necessary to understand the roles of IGF2BP2 in different tumors and uncover the underlying molecular mechanisms. Some studies have suggested that IGF2BP2 can influence tumor immunity, such as tumor-associated macrophage polarization and PD-L1 expression, by regulating the mRNA stability and expression of target genes. However, tumor immunity is extremely complex due to the involvement of multiple types of immune cells and other components of the TME. Accordingly, current knowledge of the effect of IGF2BP2 on tumor immunity is limited, and more research is needed to fully elucidate the participation of IGF2BP2 in TME regulation during tumorigenesis and tumor progression. In the future, novel immunotherapy regimens targeting IGF2BP2 may be developed to treat different tumors, particularly in patients who are insensitive or resistant to chemotherapy and radiotherapy.

Table III. Existing potential inhibitors of insulin-like growth factor 2 mRNA binding protein 2.

Inhibitor	Cancer type	Target site	Effect	(Refs.)
Benzamidobenzoic acid class	Colorectal cancer and liver cancer	RRM1 and KH3-KH4 domain	Inhibit tumor cell proliferation	(166)
Ureidothiophene class	Colorectal cancer and liver cancer	N/A	Inhibit tumor cell proliferation	(166)
CWI1-2	Leukemia	KH3-KH4 domain	Inhibits its binding to RNA targets	(167)
JX5	Leukemia	KH3-KH4 domain	Downregulates Notch1 expression	(40)

KH, RNA recognition motif; N/A, not applicable; RRM, RNA recognition motif.

Table IV. miRNAs that directly regulate IGF2BP2 expression in tumors.

Cancer type	MiRNAs	Effect on IGF2BP2	(Refs.)
Colorectal cancer	*miR-133b*	Downregulation	(178)
Esophageal squamous cell carcinoma	*miR-216b, miR-200b*	Downregulation	(174,175)
Glioma	*miR-138, miR-188, miR-129-5p*	Downregulation	(108,179,180)
Head and neck squamous carcinoma cell	*miR-98-5p*	Downregulation	(90)
Hepatocellular carcinoma	*miR-216b, miR-596, miR-7-5p*	Downregulation	(173,176,177)
Non-small cell lung cancer cell	*miR-485-5p*	Downregulation	(181)
Pancreatic cancer	*miR-141*	Downregulation	(91)
Thyroid cancer	*miR-204, miR-4640-5p*	Downregulation	(165,172)
Triple-negative breast cancer	*miR-200a*	Downregulation	(94)

IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; miR/miRNA, microRNA.

Given the notable involvement of IGF2BP2 in various human tumors, it is urgently necessary to develop specific inhibitors targeting this key molecule. However, studies on IGF2BP2 inhibitors remain limited. Currently, only CWI1-2 and JX5 are being evaluated for the treatment of AML in laboratory experiments. Another study focused on screening IGF2BP2 inhibitors and identified several candidate compounds. However, all existing compounds were investigated in preclinical experiments, but lack sufficient *in vivo* validation of their pharmacodynamics and drug toxicity. It is not known whether and when these compounds will be tested in clinical trials. All existing compounds target the KH3-4 domains of IGF2BP2; however, other members of the IGF2BP family, namely IGF2BP1 and IGF2BP3, also contain these domains, which may lead to off-target effects and resistance. By contrast, miRNAs can inhibit the expression of target genes with high specificity, and IGF2BP2 expression can also be inhibited by different miRNAs in cancer. Therefore, miRNAs are considered a promising approach for the specific inhibition of IGF2BP2 expression, which could help to overcome resistance and reduce off-target effects in human cancers. Overall, the study of IGF2BP2 inhibitors is in its early stages, but has great development potential for clinical application.

In summary, IGF2BP2 plays a key role in the development and progression of human cancers by regulating numerous oncogenic processes. Therefore, it has great potential as a target for cancer therapy. However, the effects of IGF2BP2 on certain physiological processes and the underlying molecular mechanisms remain poorly understood, particularly with regard to tumor immunity. Hence, these warrant further investigations in the future. In addition, the upstream molecular mechanisms, including post-translational modifications, specific transcription factors and epigenetic modifications, that regulate IGF2BP2 expression in cancers warrant further investigation, even though certain miRNAs have been found to regulate IGF2BP2 expression. Also, no specific inhibitor of IGF2BP2 has been clinically used to treat tumors, although several compounds have been identified and evaluated in laboratory research. Accordingly, another important topic for future research on IGF2BP2 is the development of small molecule inhibitors, which may be valuable for treating malignant tumors in which IGF2BP2 expression is abnormally upregulated.

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Authors' contributions

JS wrote the manuscript and drafted the figures. YD collected literature, provided guidance and revised the manuscript. Data authentication is not applicable. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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