



REVIEW ARTICLE

IGF2BPs as novel m⁶A readers: Diverse roles in regulating cancer cell biological functions, hypoxia adaptation, metabolism, and immunosuppressive tumor microenvironment

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Received 6 December 2022; received in revised form 24 March 2023; accepted 14 June 2023

Available online 20 July 2023

KEYWORDS

Cancer;
IGF2BP;
Immunosuppressive
TME;
m⁶A;
Molecular
mechanism;
Therapy

Abstract m⁶A methylation is the most frequent modification of mRNA in eukaryotes and plays a crucial role in cancer progression by regulating biological functions. Insulin-like growth factor 2 mRNA-binding proteins (IGF2BP) are newly identified m⁶A ‘readers’. They belong to a family of RNA-binding proteins, which bind to the m⁶A sites on different RNA sequences and stabilize them to promote cancer progression. In this review, we summarize the mechanisms by which different upstream factors regulate IGF2BP in cancer. The current literature analyzed here reveals that the IGF2BP family proteins promote cancer cell proliferation, survival, and chemoresistance, inhibit apoptosis, and are also associated with cancer glycolysis, angiogenesis, and the immune response in the tumor microenvironment. Therefore, with the discovery of their role as ‘readers’ of m⁶A and the characteristic re-expression of IGF2BPs in cancers, it is important to elucidate their mechanism of action in the immunosuppressive tumor microenvironment. We also describe in detail the regulatory and interaction network of the IGF2BP

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Peer review under responsibility of Chongqing Medical University.

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family in downstream target RNAs and discuss their potential clinical applications as diagnostic and prognostic markers, as well as recent advances in IGF2BP biology and associated therapeutic value.

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Introduction

Epigenetic mechanisms, mainly involving chromatin rearrangement, DNA methylation, RNA interference, RNA modification, and histone modification, refer to reversible and heritable phenotypes, which do not arise from altered DNA sequences.¹ There are over 170 types of RNA modifications, including N⁶-methyladenosine (m⁶A), N⁶,2'-O-dimethyladenosine (m⁶Am), 5-methylcytidine (m⁵C), 5-hydroxymethylcytidine (hm⁵C), and N¹-methyladenosine (m¹A). Among these, m⁶A methylation is the most abundant internal mRNA modification in eukaryotes, and m⁶A sites are enriched in 3' untranslated regions (UTR) especially located near stop codons.² The methylation of m⁶A sites regulates the post-transcriptional modifications of RNAs in several ways, including splicing, exporting, stabilization, translation, and decay. Recently, it has been demonstrated that m⁶A can participate in the regulation of biological processes through a variety of mechanisms, thus playing a key role in cancer.³

The methylation of m⁶A is regulated by regulators, consisting of 'writers', 'erasers', and 'readers'. Writers are methyltransferases, which install m⁶A methyl groups on RNA, while erasers are demethylases, which remove RNA m⁶A methylation reversibly. Readers are proteins that perform the biological functions of m⁶A methylation, and IGF2BPs are newly identified members of this group and include IGF2BP1, IGF2BP2, and IGF2BP3.⁴ However, as newly discovered m⁶A readers, the effects of IGF2BP in various malignancies and their associated mechanisms are still poorly understood.

Initially, researchers identified a protein with four K-homologous (KH) domains that is highly expressed in pancreatic cancer (PC) and named it KOC.⁵ With further research, the understanding of this protein grew, and was later named IGF2BP3. IGF2BP1, IGF2BP2, and IGF2BP3 belong to the family of RNA-binding proteins (RBPs), which participate in determining the fate of mRNAs transcripts by becoming a structural component of messenger ribonucleoprotein particles (mRNPs).^{6–8} Recently, a large number of studies have emerged investigating the function of IGF2BPs as m⁶A readers for recognizing m⁶A methylation. These studies provide evidence that IGF2BPs regulate gene expression by binding to the m⁶A binding sites of target mRNAs, thus intervening in various stages of RNA metabolism to influence many oncogenic processes, such as maintaining cancer stem cell stemness, promoting cancer proliferation, migration, glycolysis, cell cycle transition, and angiogenesis.^{4,9–14} Convincing evidence that IGF2BP mediates tumor bio-behavioral changes and regulates the progression of various malignant diseases including

pancreatic, hepatocellular, breast, and colorectal cancers through m⁶A methylation modifications.^{15–17} For example, IGF2BP2 promoted stem cell properties in breast cancer by stabilizing m⁶A-modified DROSHA mRNA.¹⁸ Herein, we propose that the role of IGF2BPs in the tumor microenvironment (TME) is multifactorial, not only promoting cancer biological properties but also their relationship with immune cells prompting us to further explore their role in the immunosuppressive TME.

The global incidence of malignant cancers is increasing and exploring their pathogenesis is of great significance for the early diagnosis and treatment of malignant cancers. Thus, it is particularly important to study the upstream regulatory mechanism of IGF2BPs. Understanding how these are expressed in malignant cancers will lead to a better understanding of the mechanisms responsible for tumorigenesis. In this review, we summarize various aspects involved in IGF2BP-mediated regulation of gene expression and the influence of different factors on their RNA binding capacity. Meanwhile, the specific mechanism of IGF2BPs in regulating RNA stability, localization, translation, and other processing in cancers is updated and the post-transcriptional regulatory network of its targeting noncoding RNAs (ncRNAs) is introduced. Finally, we discuss their potential value in cancer diagnosis, prognosis, and treatment, and track the development status of selective inhibitors of IGF2BPs to explore the possibility of their clinical application (Fig. 1).

The related structure of IGF2BPs protein for binding with the target RNAs

IGF2BPs are a family of insulin-like growth factor 2 mRNA-binding proteins that contain IGF2BP1–3. IGF2BPs' aliases include IMP1–3, VICKZ1–3 (based on the first letter of its founding members), CRD-BP (IGF2BP1), ZBP1 (IGF2BP1 homologue in chickens), Vg1RBP/Vera (homologue in *Xenopus*), or KOC (IGF2BP3),⁵ and are considered new m⁶A readers.⁴ However, it should be noted that Z-DNA binding protein 1 (ZBP1) should not be confused with IGF2BP1 and U3 small nucleolar ribonucleoprotein (IMP3) with IGF2BP3, as these share a common symbol/alias. IGF2BPs are highly conserved in many species, such as humans, chimpanzees, Rhesus monkeys, dogs, cows, rats, chickens, and zebrafish. IGF2BPs contain two RNA recognition motifs (RRM) at the N-terminal and four KH domains at the C-terminal¹⁹ (Fig. 2). From previous studies, we know that the four KH domains are essential for intracellular granule formation, trafficking of IGF2BP1, and RNA binding *in vitro*.²⁰ Further research has revealed that the KH1/2 domain may be necessary for



the stabilization of IGF2BP-RNA complexes,⁸ and the KH3/4 domain is essential for m⁶A recognition and binding with target RNAs.^{4,21} A recent study found that the high affinity of the KH1/2 domain for mRNA binding was achieved by interdomain coupling, which supported the role of IGF2BP1 recognition of known cancer targets.²² Different target RNAs require different KH domains for binding. For example, the KH1/2 domains of IGF2BP1 are necessary for

binding to long ncRNA (lncRNA) KB-1980E6.3.⁹ Although circNSUN2 binds to the KH3-4 didomain of IGF2BP2,²³ other studies have shown that all four KH domains of IGF2BP1 are essential for binding to KRAS or the microphthalmia-associated transcription factor (MITF) mRNA.^{24,25} Importantly, any single-point mutation in one of the four KH domains significantly affects the binding between IGF2BP1 and mRNA.²⁶

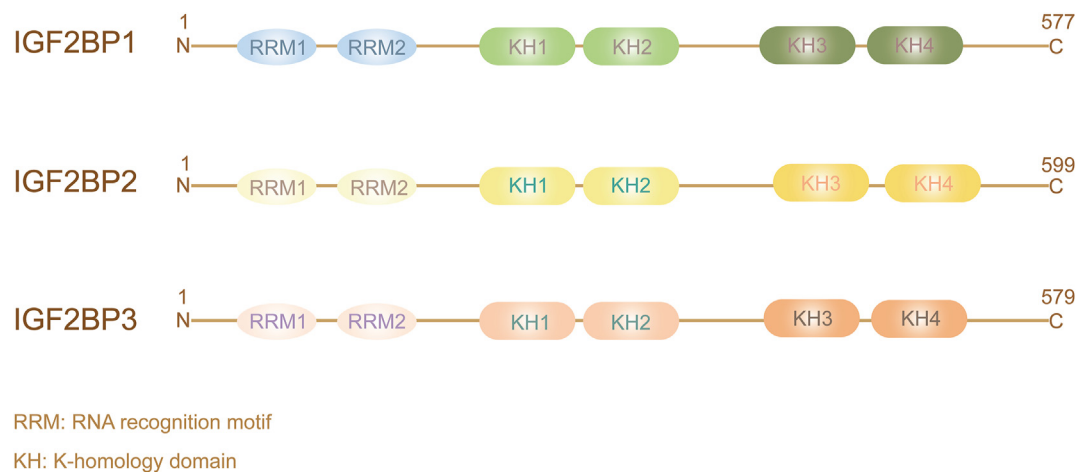


Figure 2 The structure of IGF2BPs. The three members of the IGF2BP family have similar structures: two RNA recognition motifs at the N-terminal and four K-homology domains at the C-terminal.

The regulation of IGF2BPs in cancers

The regulation process of IGF2BPs expression

IGF2BPs are expressed in the embryo and are also expressed in mature testicular germ cells and oocytes.^{27,28} In adult tissues, IGF2BPs except IGF2BP2 have low expression levels.²⁹ IGF2BPs are increased or re-expressed in some malignant cancers and are therefore considered a conserved post-transcriptional enhancer of pro-oncogenic factors.³⁰ The regulatory mechanisms of IGF2BP expression have not been fully elucidated, and therefore we will outline some regulatory modalities in cancers, including chromosomal rearrangements, epigenetic modifications, transcriptional control, post-translational modifications, degradation, and regulation.

Effect of chromosomal rearrangements on IGF2BPs expression

With the help of full transcriptome and whole genome sequencing, researchers have identified the chromosomal rearrangements occurring in thyroid cancer (TC), where the thyroid adenoma-associated (*THADA*) fusion to *LOC389473* (the upstream region of the *IGF2BP3* gene) and other regions in the vicinity increased the expression of full-length IGF2BP3 mRNA and protein.³¹ As we know, copy number alteration (CNA) is generally due to genomic rearrangements and is one of the mechanisms that lead to the overexpression of IGF2BP2 in hepatocellular carcinoma (HCC).³² However, CNAs are not the cause of the up-regulation of IGF2BP1 in anaplastic thyroid carcinomas (ATC),³³ indicating that the expression regulation of IGF2BP1/2/3 in cancers is diverse.

Epigenetic modifications affect IGF2BPs expression

Under the action of DNA methyltransferase or histone deacetylase inhibitors, the expression of IGF2BP3 increased significantly in mouse osteosarcoma, indicating that the expression of IGF2BP3 is partly attributable to epigenetic regulation such as DNA demethylation and histone acetylation.³⁴ Furthermore, researchers found that DNA methylation at the IGF2BP3 gene promoter contributed to its silencing in normal human tissues, in contrast to its

almost complete demethylation in intrahepatic cholangiocarcinoma.³⁵ In addition, histone acetylation on the promoter of IGF2BP1 promotes its transcriptional activation in melanoma cells.³⁶ In pancreatic islet cancers, it was also verified that IGF2BP2 is epigenetically regulated by menin–histone methyltransferase complexes in a time-dependent manner.³⁷ From this evidence, we know that one of the causes of IGF2BP re-expression in cancers is the alteration of epigenetic modifications.

Transcriptional and post-transcriptional control influence IGF2BPs expression

Exploring the regulation of gene transcription in the context of cancer helps to understand the occurrence and development of cancer. Some studies have identified the mechanism of IGF2BP transcriptional control in different cancers. In breast cancer, IGF2BP1 transactivation was shown to be associated with nuclear translocation of β -catenin, where a highly conserved element (CTTTG-TC) located near the IGF2BP1 promoter region was essential for IGF2BP1 transcriptional activity. Conversely, IGF2BP1 could also stabilize β -catenin mRNA, implying that there exists a positive feedback loop.³⁸ There is also evidence that IGF2BP2 transcription was regulated by the high mobility group AT-hook 2 (HMGA2) and its tumor-specific truncated form HMGA2Tr. In detail, HMGA2 binds directly to the AT-rich regulatory region located in the first intron of *IGF2BP2*, while a consensus binding site for NF- κ B adjacent to the AT-rich regulatory region can bind to NF- κ B. Ultimately, they synergistically promote the transcription of IGF2BP2 in human liposarcomas.³⁹ Nonetheless, MYC, a widely recognized oncogene, is not only a target mRNA for IGF2BP3 but it also effectively binds to the IGF2BP3 promoter in nasopharyngeal carcinoma (NPC) and increases its transcriptional activity, indicating that there may be a positive feedback loop between IGF2BP3 and MYC.^{4,40} In other cancers, such as triple-negative breast cancer (TNBC)⁴¹ and lung cancer,⁴² studies have explored their transcriptional regulation. Moreover, the positive feedback loops described above partially explain why IGF2BPs are highly expressed in malignant cancers, as these positive feedbacks may initiate cascade reactions that amplify their effects.

It has been shown that miRNAs can bind to IGF2BP to inhibit their expression.^{43–64} In contrast, in colorectal cancer (CRC), the short 3'UTR transcript of IGF2BP1 increases IGF2BP1 protein expression as it lacks miRNA sites.⁶⁵ Therefore, it can be speculated that competitive binding to miRNAs can also up-regulate IGF2BPs in cancers, and recent studies have confirmed this hypothesis.^{66–76} Interestingly, IGF2BP3 stabilizes the lncRNA KCNMB2-AS1 in an m⁶A methylation-dependent manner, while KCNMB2-AS1 sponges miR-130b-5p and miR-4294 can induce the up-regulation of IGF2BP3,⁷⁷ which then forms a positive feedback loop in cervical cancer. The mRNA of IGF2BP1 or IGF2BP3 is stabilized by the lncRNA THOR or DARS-AS1 in cancer cells.^{78,79} Therefore, the mechanisms by which ncRNAs regulate IGF2BP protein expression involve regulating gene transcription.

The influence of post-translational modifications on IGF2BPs

In post-translation and co-translation, mTOR can dually phosphorylate the Ser162 and Ser164 residue of IGF2BP2 located in the N-terminal linker region between RRM2 and KH1 in a rapamycin-sensitive manner.^{80,81} IGF2BP3 was also phosphorylated by mTOR at the Ser183 residue, and similarly, IGF2BP1 is co-translationally phosphorylated at Ser181 by mTOR in the mTOR complex 2 (mTORC2), and subsequently released from mTOR to bind target mRNAs, which protected the phosphorylation site from cellular protein phosphatases.⁸² Human embryonal rhabdomyosarcoma cells and mouse embryonic fibroblasts were used in these studies to demonstrate that phosphorylated IGF2BP could bind to downstream target RNAs, providing evidence for their role in cancer-promoting activity.

Regulation of IGF2BPs protein degradation

Regarding the degradation of IGF2BPs, researchers have recently reported that makorin ring finger protein 2 (MKRN2), an E3 ligase, acts as a cancer suppressor in neuroblastoma by mediating the ubiquitination of IGF2BP3.⁸³ Ubiquitin-specific protease 11 (USP11), a deubiquitinating enzyme, prevented the ubiquitination and degradation of IGF2BP3 in colorectal cancer.⁸⁴ Furthermore, SUMO1-mediated SUMOylation, a modification that regulates substrate protein expression and activity, prevents IGF2BP2 degradation in glioma through the ubiquitin proteasome pathway.⁸⁵

ncRNAs can also regulate IGF2BP degradation in different ways. For example, circNDUFB2 is down-regulated in non-small cell lung cancer (NSCLC), but its over-expression improves ubiquitination and degradation of IGF2BP1/2/3 mediated by TRIM25, a member of the tripartite motif (TRIM) family of E3 ubiquitin ligases.⁸⁶ LncRNA LINRIS prevented the degradation of IGF2BP2 via the autophagy-lysosome pathway in CRC by binding to the ubiquitination site K139 of IGF2BP2 in the absence of inhibition factors, such as GATA3.⁸⁷ circNEIL3 could inhibit HECTD4-mediated degradation of IGF2BP3 via the ubiquitin proteasome in glioma.⁸⁸ The differential regulation of IGF2BP degradation by ncRNAs also confirms that cancers have complex environments and regulatory mechanisms. In summary, preventing the degradation of IGF2BPs is another way to maintain their expression in cancers. In recent

years, the development of molecules that specifically degrade targeted proteins is an emerging cancer treatment strategy; therefore, drugs targeting IGF2BP degradation may be a viable therapeutic approach.

Various factors affecting the binding ability of IGF2BPs and RNA

IGF2BPs are required to bind to different RNAs to influence cancer progression; therefore, the RNA binding ability of IGF2BPs is very important and can be affected by many factors, including proteins, mRNAs, and ncRNAs. For instance, the Aurora kinase A (AURKA) oncogene enhanced the IGF2BP2 binding to m⁶A methylation-modified transcripts in breast cancer, rather than promoting its nuclear translocation.¹⁸ Although lncRNAs belong to ncRNAs, recently researchers have found that some lncRNAs can also encode proteins. Zhu et al.⁸⁹ confirmed in different cancer cell lines that LINC00266-1 encodes a peptide called RNA-binding regulatory peptide (RBRP), which binds to the KH3-4 domain of IGF2BP and promotes the ability of IGF2BP1 to recognize the m⁶A sites on c-MYC mRNA. YBX1 is important in promoting the recognition of m⁶A-modified RNAs by IGF2BP1/2/3 in myeloid leukemia.⁹⁰ Conversely, in Ewing sarcoma, ABCF1 mRNA acts as a sponge to bind to IGF2BP3 and limits its interaction with oncogenic target transcripts.⁹¹ Tyrosine protein phosphatase non-receptor type 13 (PTPN13) also inhibits the binding of IGF2BP1 to c-MYC to inhibit HCC cell proliferation and tumorigenesis.⁹² Although most ncRNAs are not translated into proteins, they have made great contributions to the regulation of genes, especially in the occurrence and development of cancers. Its regulatory effect on IGF2BPs could also manifest itself by affecting the binding ability of IGF2BPs and target RNAs. As shown in Table 1, some ncRNAs could promote binding processes to promote cancer progression,^{93–108} and some other ncRNAs could competitively bind to the KH domain of IGF2BP, thus interfering with the recognition of m⁶A modified RNAs by IGF2BP and inhibiting their expression to suppress cancers.^{109–114} The above results suggest that the effects of ncRNAs on the binding capacity of IGF2BPs are complex. Therefore, it is very interesting to investigate this mechanism in depth, which will help us to better understand the role of IGF2BPs in cancers and their mechanisms, and to find the molecules that can specifically inhibit the binding ability of IGF2BP with RNAs to treat cancers more effectively.

IGF2BPs-induced regulation of cancer

IGF2BPs regulate cancer progression by affecting RNAs

Despite being RNA-binding proteins with similar sequence homology, IGF2BP1, IGF2BP2, and IGF2BP3, the proteins exhibit different RNA-binding properties and may be related to different target transcripts. Each family member regulates a unique pool of RNAs.¹¹⁵ Thousands of transcripts have been identified as targets of each IGF2BP protein, but the exact molecular mechanism by which IGF2BPs control

Table 1 Upstream regulators of IGF2BPs in cancers.

Upstream regulators	IGF2BPs	Regulatory mechanisms of upstream factors on IGF2BPs	Effects on IGF2BPs expression	References
miR-98–5p, miR-625, miR-196b, miR-494, miR-21, miR-372, miR-708, miR-506, miR-873	1	Inhibit IGF2BP1 expression by binding with its 3'UTR	↓	43,44,46,53,55,56,58–60
miR-485–5p, miR-216b, miR-141, miR-188, miR-138	2	Inhibit IGF2BP2 expression by binding with its 3'UTR	↓	45,52,54,61,62
miR-34a, miR-129-1, miR-486	3	Inhibit IGF2BP3 expression by binding to its 3'UTR	↓	48,49,51
let-7 family	1/2/3	Bind to the 3'UTR	↓	57,63,64,232
miR-200a	2/3	Target the 3'UTR of IGF2BP2/3 mRNA to down-regulate its expression	↓	47
miR-1275	1/2/3	Inhibit IGF2BP1/2/3 expression by directly binding to their 3'UTR	↓	50
lncRNA THOR	1	Promote the mRNA stabilization activities of IGF2BP1	↑	79
linc01134	1	Function as ceRNA to up-regulate IGF2BP1 via sponging miR-324–5p	↑	71
lncRNA TRPM2-AS	1	Act as a microRNA sponge of miR-612 to up-regulate IGF2BP1	↑	72
lncRNA PCAT6	1	Function as ceRNA to up-regulate IGF2BP1 via sponging miR-513	↑	75
circBICD2	1	Regulate IGF2BP1 via miR-149–5p	↑	69
lncRNA MALAT1	2	Competitively binding to miR-204 to up-regulate IGF2BP2	↑	66
lncRNA RHPN1-AS1	2	Act as a sponge for miR-596 to up-regulate IGF2BP2	↑	76
circCD44	2	Function as a sponge for miR-502–5p to up-regulate IGF2BP2	↑	73
HBV-pgRNA	3	Function as a sponge for miR-let-7e-5p to up-regulate IGF2BP3	↑	67
LINC00460	3	Function as a sponge for miR-320b to up-regulate IGF2BP3	↑	70
lncRNA KCNMB2-AS1	3	Function as a sponge for miR-130b-5p and miR-4294 to up-regulate IGF2BP3	↑	77
circIGHG	3	Bind to miR-142–5p and consequently elevated IGF2BP3 activity	↑	68
circHIPK3	3	Promote IGF2BP3 expression via interacting with miR-654	↑	74
menin-histone methyltransferases	2	In a time-dependent manner	↑	37
β-catenin	1	The nuclear translocation of β-catenin promotes IGF2BP1 transactivation	↑	38

(continued on next page)

Table 1 (continued)

Upstream regulators	IGF2BPs	Regulatory mechanisms of upstream factors on IGF2BPs	Effects on IGF2BPs expression	References
HMGA2 and HMGA2Tr	2	Promote the transcription of IGF2BP2 together with NF- κ B	↑	39
HNH4G	2	Bind to the promoter region of IGF2BP2	↑	42
MYC	3	Bind to the promoter of IGF2BP3 and increase its transcriptional activity	↑	40
lncRNA DARS-AS1	3	Stabilize the mRNA of IGF2BP3	↑	78
mTOR	1/2/3	Phosphorylate IGF2BPs to promote their binding to downstream target mRNA	\	80–82
lncRNA LINRIS, SUMO1	2	Prevent IGF2BP2 degradation	↑	85,87
circNEIL3, USP11	3	Prevent ubiquitination and degradation of IGF2BP3	↑	84,88
MKRN2	3	Mediate the ubiquitination of IGF2BP3	↓	83
circNDUFB2	1/2/3	Overexpression of CIRCNDUFB2 promotes the ubiquitination and degradation of IGF2BPs	↓	86
estrogen receptor- β	3	Inhibit IGF2BP3 expression by repressing EGFR	↓	41
YBX1	1/2/3	Important for promoting the recognition of the m ⁶ A-modified RNAs	\	90
RBRP, lncRNA-GHET1, lncRNA NEAT1, circXOP1	1	Promote the recognition and interaction with target mRNA	\	89,97,99,101
AURKA, lncRNA SNHG12, linc01305, lncRNA PCAT6, LINC01559, LINC00460, circITGB6, circNSUN2, circARHGAP29, circARHGAP12	2	Strengthen IGF2BP2 interaction with target mRNA	\	18,23,93,94,96,100,104–107
HuR, BAG3, circ-0039,411, lncRNA DMDMR, lncRNA CERS6-AS1, LINC00467, linc01305, hsa_circ_0003258	3	Strengthen IGF2BP3 interaction with target mRNA	\	95,98,102,103,106,108,184,233
PTPN13, lncRNA FGF13-AS1, lncRNA NBAT1, LINC00261, circPTPRA	1	Inhibit the interaction between IGF2BP1 and c-MYC mRNA	\	92,109,110,113,114
LINC01093	1	Inhibit the interaction between IGF2BP1 and GLI1 mRNA	\	112
circ-TNPO3	3	Act as a protein decoy for IGF2BP3 to regulate the MYC-SNAIL axis	\	111
ABCF1 mRNA	3	Act as a sponge to limit the interaction with ABCG2, MMP9, and CD44	\	91

these transcripts and participate in biological processes has just begun to be elucidated. The most recent research indicates that the oncogenic function of IGF2BPs may depend on its role as m⁶A readers.⁴ Therefore, in this section, we review previous studies, combined with recent novel insights, to summarize the mechanism of action of IGF2BPs in the regulation of mRNA processing (Table 2) and the regulatory network of IGF2BPs and ncRNAs in cancers.

Modulation of mRNA by IGF2BPs in cancers

IGF2BPs could increase the stability of mRNA. Since the discovery of the IGF2BP protein family, its role as RBPs has been continuously updated. IGF2BP proteins can influence RNA stability through a variety of mechanisms in different cancers, including sequestering mRNAs in mRNP that did not contain the RNA-induced silencing complex (RISC),^{7,116,117} preventing miRNA-dependent degradation,^{118–121} and functioning as m⁶A readers that bind to m⁶A sites in RNA.^{4,11,18,122} Specifically, Huang et al⁴ identified three IGF2BPs that could preferentially bind to the “UGGAC” consensus sequence containing the “GGAC” m⁶A core motif and found that binding of IGF2BPs to the m⁶A methylation modification site in MYC mRNA could increase the stability of MYC mRNA as well as the translation efficiency in HCC and cervical cancer. Additionally, AURKA improved IGF2BP2 binding to the m⁶A-modified RNase III DROSHA transcript to stabilize DROSHA mRNA, which was further strengthened by binding of AURKA and the DROSHA transcript, thus promoting stem cell properties in breast cancer.¹⁸ Interestingly, in a recent study, Muller et al¹¹ verified that IGF2BP1 stabilized SRF mRNA in cancer by weakening miRNA-dependent decay and binding to its m⁶A sites. We know that ALKBH5 is an m⁶A demethylase, and its down-regulation increases the m⁶A methylation level of oncogene LY6/PLAUR domain containing 1 (LYPD1), which was recognized to be stabilized by IGF2BP1 and thus promoted HCC oncogenesis.¹²²

IGF2BPs can also destabilize RNAs. Ennajdaoui et al¹²³ found that in addition to stabilizing mRNAs by competing with miRNAs for common binding sites in target mRNAs, IGF2BP3 promoted mRNA binding to argonaute 2 (Ago2) (a RISC-component) and was believed to be a bimodal regulator of mRNA stability in pancreatic ductal adenocarcinoma (PDAC). However, it is not difficult to determine that although IGF2BPs have opposite effects on the regulation of target RNA stability, they play an oncogenic role in cancers. For example, by destabilizing stress-induced ligands ULBP2 they promote cancer immune escape,¹²⁴ or they destabilize eukaryotic translation initiation factor 4E binding protein 2 (EIF4E-BP2) to activate EIF4E, or they recruit CCR4-NOT transcription complex subunit 1 (CNOT1) to destabilize progesterone receptor (PR) mRNA, and these processes mediated by IGF2BP eventually promote cancer cell progression.^{47,125}

IGF2BPs could influence the localization of mRNA. In the cytoplasm, IGF2BP1 was found to be present in RNP granules 200–700 nm in size and was distributed along microtubules; it moved at an average speed of 0.12 μm/s in an ATP-dependent manner.²⁰ These granules were enriched in the perinuclear region but were also observed in neuronal

processes and growth cones.¹²⁶ Hence, these data supported the view that IGF2BP1 was associated with sub-cytoplasmic localization of the mRNA. Later, data from Jønson et al¹²⁷ determined that the RNP granules were 100–300 nm in diameter and contained 40S ribosomal subunits, shuttling heterologous nuclear RNPs, poly(A) binding proteins, and mRNAs, as well as CBP80 and factors belonging to the exon junction complex without EIF4E, EIF4G, and 60S ribosomal subunits. Therefore, mRNAs integrated into IGF2BP1 mRNP particles could not be translated and transported to the appropriate destinations to initiate protein synthesis.

In human breast cancer, IGF2BP1 promoted the localization of mRNAs related to cell adhesion and motility, such as E-cadherin, β-actin, α-actinin, and Arp2/3, to stabilize cell–cell junctions and focal adhesions, which eventually suppress cancer cell invasion.¹²⁸ However, this role of IGF2BP1 in stabilizing the cell junctions of breast cancer is contradictory to its role in cervical cancer, because Vikesaa et al¹²⁹ showed that the deletion of IGF2BP1/3 resulted in the altered formation of invasive pseudopodia in the HeLa cell line. Complex tumorigenesis and development mechanisms led to the regulation of IGF2BP1 by different factors and binding to different mRNAs is one possible explanation.

IGF2BPs could regulate the translation of mRNA. In malignant cancers, another important function of IGF2BPs in mRNA processing is to regulate mRNA translation.^{130,131} Phosphorylation of IGF2BP2 by mTOR promotes its translational activity, thereby regulating the translation initiation of IGF2 leader 3 mRNA through EIF4E and activation of the 5' cap-independent internal ribosome in human embryonic rhabdomyosarcoma.⁸⁰ After identifying IGF2BP as m⁶A readers, IGF2BP1 was also shown to reduce BMI1 protein levels in oral squamous cell carcinoma (OSCC) as BMI1 m⁶A methylation levels decreased.¹² Similarly, translational regulation of pancreatic and duodenal homeobox 1 (PDX1) in pancreatic β cells and V-Erb-B2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2) in radioiodine-refractory papillary thyroid cancer were also dependent on the recognition of m⁶A methylation by IGF2BP2.^{132,133} This evidence also provides strong evidence that IGF2BPs regulate mRNA translation through methylation of m⁶A.

However, just as the regulation of mRNA stability in malignant cancers by IGF2BP is twofold, so is the regulation of translation.^{134,135} As mentioned above, IGF2BPs participate in the cellular localization of β-actin. Hüttelmaier et al¹³⁵ further studied its translation mechanism in neuroma cells and found that β-actin translation would occur only when IGF2BP1 transported it to the endpoint of mRNA transport and phosphorylated tyrosine residues on IGF2BP1 by protein kinase Src, which had blocked the translation of β-actin.

Other modulation mechanisms of IGF2BPs to RNA. In addition to the above functions, nuclear localization of IGF2BPs is also important. Rivera Vargas et al¹³⁶ confirmed in six different cancer cell lines that the nucleocytoplasmic IGF2BP3–HNRNPM complex could regulate the expression of cyclins D1, D3, and G1 by shuttling to the nucleus and occupying the relevant binding sites before the export of

Table 2 Different mechanisms in regulating mRNA processes by IGF2BPs in cancers.

IGF2BPs	Cancer	Target mRNA	Mechanisms of IGF2BPs in RNA processes	Roles of mRNA in cancers	References
1	Breast cancer	KRT7	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote breast cancer lung metastasis	10
1	Lung adenocarcinoma	CTNNB1	Promote mRNA stabilization	Oncogene	101
1	GC	SEC62	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote GC proliferation and inhibit cell apoptosis	234
1	CRC	β-TrCP1	Prevent miRNA-dependent degradation	Serve as substrate recognition subunit of E3 ubiquitin ligase	120
1	CRC	LDHA	Bind to the 3'UTR of LDHA mRNA	Promote glycolysis	171
1	HCC	YES1	Serve as an m ⁶ A reader to promote mRNA stabilization	Oncogene	15
1	HCC	LYPD1	Stabilize mRNA in an m ⁶ A-dependent manner	Promote tumorigenesis	122
1	HCC	MKI67	Promote mRNA stabilization	Promote cell proliferation and inhibit cell apoptosis	235
1	HCC	GLI1	Promote mRNA stabilization	Promote cell proliferation and metastasis	112
1	HCC, ovarian cancer, lung cancer	SRF	Serve as an m ⁶ A reader and impair miRNA-dependent degradation	Enhance expression of genes that promote aggressive cancer phenotype	11
1	HCC, PC, ovarian cancer, melanoma, lung cancer,	E2F	Rely on 3'UTR-, miRNA-, and m ⁶ A-dependent to stabilize it	Promote G1/S cell cycle transition	13
1	Melanoma, ovarian cancer	eEF2	\	Enhance basal proliferation rates	223
1	Ovarian cancer	MDR1	Promote mRNA stabilization	Regulate chemoresistance	64
1	Ovarian cancer	SIRT1	Prevent miRNA-dependent degradation	Promote anoikis-resistance	118
1	Ovarian clear cell carcinoma	let-7 target mRNA (IGF2BP1, HMGA2, LIN28B)	Sequester mRNA into mRNP that do not contain RISC to stabilize it	Promote cancer cell growth and self-renewal	116
1	Endometrial cancer	SOX2	Serve as an m ⁶ A reader to promote mRNA stabilization	An oncogenic transcriptional factor	153
1	Endometrial cancer	PEG10	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cell cycle and cancer progression	159
1	Choriocarcinoma	RSK2, PPME1	Promote mRNA stabilization	Promote cell migration and invasion	236
1	Osteosarcoma	c-MYC	Sequester mRNA into mRNP that do not contain RISC to stabilize it	Promote cancer cell proliferation	7
1	Seminoma	TFAP2C	Serve as an m ⁶ A reader to promote mRNA stabilization	Increase resistance to cisplatin	163
1	Breast cancer	E-cadherin, β-actin, α-actinin, Arp2/3	Promote mRNA localization	Stabilize cell–cell connections and focal adhesions	128
1	Osteosarcoma, ovarian cancer	PTEN	Bind to a rare codon-comprising fragment of the PTEN ORF to stabilize it	Modulate cell polarization	134
1	Osteosarcoma, ovarian cancer,	MAPK4	Inhibit mRNA translation through binding to MAPK4	Promote cell adhesion and	134,237

1	tumor-derived cells		3'UTR	migration	
1	Rhabdomyosarcomas	cIAP1	Promote mRNA translation	Mediate apoptotic resistance	130
1	HCC	HCV	Promote mRNA translation	\	131
1	OSCC	BMI1	Promote mRNA translation in an m ⁶ A-dependent manner	Promote cell proliferation and metastasis	12
1/2/3	cervical cancer, HCC	MYC	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cancer proliferation, migration, and invasion	4
2	HNSCC	SLUG	Serve as an m ⁶ A reader to promote mRNA stabilization	Lymphatic metastasis and EMT	238
2	PTC	APOE	Serve as an m ⁶ A reader to promote mRNA stabilization	Mediate glycolysis	183
2	Radioiodine-refractory papillary thyroid cancer	RUNX2	Serve as an m ⁶ A reader to promote mRNA stabilization	Block the differentiation of radioiodine-refractory papillary thyroid cancer	239
2	Breast cancer	DROSHA	Serve as an m ⁶ A reader to promote mRNA stabilization	Maintain breast cancer stem-like cell stemness	18
2/3	LUAD	VANGL1	Serve as an m ⁶ A reader to promote mRNA stabilization	Mitigate the effects of radiation on LUAD by increasing genes about DNA repair after the damage	167
2	Lung cancer	TK1	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote angiogenesis	42
2	GC	ZEB1	LINC01559 recruits IGF2BP2 to stabilize ZEB1 mRNA	Serve as a transcription factor to combine with LINC01559, and promote cell proliferation, migration, and EMT	94
2	HCC	FEN1	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote HCC growth	32
2	PDAC	GLUT1	Bind to the middle of GLUT1 mRNA and promote mRNA stabilization	Promote glycolysis and proliferation	182
2	CRC	KLF4	Serve as an m ⁶ A reader to promote mRNA stabilization	A cancer suppressor gene; regulates intestinal epithelial homeostasis	240
2	CRC	SOX2	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote stemness features and metastatic	152
2	CRC	MTA1	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cancer migration and invasion	181
2	CRC	RAF-1	Prevent miRNA-dependent degradation	Promote cancer proliferation and survival	121
2	CRC	HK2	Bind to the 5'UTR/3'UTR of HK2 mRNA as an m ⁶ A reader to promote mRNA stabilization	Promote glycolysis and proliferation	185
2	CRC	MSX1, JARID2	LINC021 enhances its role as an m ⁶ A reader to promote mRNA stabilization	Promote tumorigenesis	241
2	Ovarian cancer	FGF9	Promote mRNA stabilization	Induce chemoresistance and the polarization of TAMs toward the	104

(continued on next page)

Table 2 (continued)

IGF2BPs	Cancer	Target mRNA	Mechanisms of IGF2BPs in RNA processes	Roles of mRNA in cancers	References
2	Prostate cancer	IGF1r	The mRNA stabilization may be related to m ⁶ A modification	M2 phenotype Promotes bone metastasis and cancer growth	96
2	Prostate cancer	LDHA	Bind to the 3'UTR of LDHA mRNA to promote mRNA stabilization	Promote glycolysis	93
2	Malignant embryonic rhabdoid tumor, cervical cancer, breast cancer, HCC, CRC, lung cancer	HMGA1	Bind to the 3'UTR of HMGA1 mRNA to promote mRNA stabilization and may be related to m ⁶ A modification	An oncogene; promote cancer proliferation, migration, and invasion	81,105
2	Glioblastoma	let-7 target mRNA (IGF2BP3, HMGA1, HMGA2, CCND1)	Prevent miRNA-dependent degradation	Preserve glioblastoma stem cell	119
2	Glioblastoma	CI/CIV	Promote the mRNA activity	Regulate OXPHOS	137
2	embryonic rhabdomyosarcoma	NRAS	Promote mRNA stabilization	oncogene	242
2	Embryonic rhabdomyosarcoma	IGF2	Promote mRNA translation	\	80
2	Radioiodine-refractory papillary thyroid cancer	ERBB2	Increase translation efficacy through binding to the m ⁶ A methylation site	Contribute to acquired resistance to TKI	133
3	NPC	KPNA2	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote proliferation and metastasis	40
1/3	Cervical cancer	CD44	Stabilize the 5.0 kb CD44 mRNA	Promote invadopodia formation	129
3	Breast cancer	CD44	Regulate CD44 promoter activity	Promote cell proliferation, maintain stemness, and induce chemotherapy resistance	179
3	Breast cancer	PD-L1	Serve as an m ⁶ A reader to promote mRNA stabilization	Inhibit cancer immune surveillance	174
3	Breast cancer	IGF2, MMP9, CD164	Bind to the mRNA and promote mRNA stabilization	Involve in migration and invasion	41
3	Breast cancer	CERS6	Promote mRNA stabilization	Promote cell proliferation, suppress cell apoptosis	102
3	Breast cancer	ABCG2	Bind to ABCG2 mRNA and regulate its expression	Promote cell invasion	243
3	Esophageal cancer	KIF18A	Stabilize KIF18A mRNA	Promote cancer proliferation and migration and is associated with radioresistance	244
3	GC	HDGF	Serve as an m ⁶ A reader to promote mRNA stabilization	Secrete HDGF promotes cancer angiogenesis; nuclear HDGF increases glycolysis	14
3	GC	HIF1A	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cell migration and angiogenesis	180
3	HCC	pgRNA	Promote mRNA stabilization in an m ⁶ A-independent manner	Promote HCC proliferation, stemness, and tumorigenicity	67
3	HCC	TRAF5	Promote mRNA stabilization	Promote cell proliferation and metastasis	103
3	CRC	KRAS, MAP2K1, TPR,	Promote mRNA stabilization with the help of ELAVL1	Promote cancer proliferation	245

3	CRC	CCNH ABCB1	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cancer chemoresistance	246
3	CRC	CCND1	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote cell cycle	160
3	CRC	VEGF	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote angiogenesis	160
2/3	CRC	GLUT1	Bind to 3'UTR of GLUT1 mRNA as an m ⁶ A reader	Promote glycolysis and proliferation	185
3	PDAC	HK2	Promote mRNA stabilization	Participate glycolysis	184
3	Hematopoietic progenitor cell	CDK6, MYC	Stabilize the mRNA and/or enhance translation	Oncogene	247
3	ccRCC	CDK4	Serve as an m ⁶ A reader to promote mRNA stabilization	Is associated with the G1/S transition	95
3	Cervical cancer, HCC	PKD4	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote glycolysis and ATP generation	186
3	Acute myeloid leukemia	COX2	Bind to the 3'UTR of mRNA to promote mRNA stabilization	Inhibit cell apoptosis	233
1/3	Myeloid leukemia	MYC, BCL2	Promote stability of m ⁶ A-modified mRNA with the help of YBX1	Maintain the myeloid leukemia cell survival	90
3	AML	RCC2	Serve as an m ⁶ A reader to promote mRNA stabilization	Promote AML progression	248
3	Human cancer cells	CCND1, CCND3, CCNG1	Cooperate with HNRNPM to regulate post-transcriptional expression	Accelerate cell proliferation	136
3	Ewing sarcoma	CD164	Bind to the mRNA to regulate its expression	Promote cancer invasion	249
3	Some kinds of solid cancers and fibrosarcoma	HMGA2, LIN28B	Sequester mRNA into mRNP that did not contain RISC	Oncogene	117
3	PDAC	164 direct target mRNA contained HMGA2, ZFP36L1, DCBLD2, CLDN1, CD44, ANTRX1, CLDN1, OLR1	Bind to Ago2 (a RISC component) and act as a bi-modal regulator of mRNA stability	Promote cell migration, proliferation, and remodel focal adhesion	123
3	HCC	ZO-1	Enhance Ago2-mRNA interactions to inhibit ZO-1 expression	Down-regulation of ZO-1 promotes cancer metastasis and invasion	250
3	LUAD	EIF4E-BP2	Serve as an RNA-destabilizing factor to promote EIF4E-BP2 mRNA degradation	Promote EIF4E-mediated translation activation	125
3	CRC	ULBP2	Bind to the 3'UTR of ULBP2 mRNA to destabilize it	Enable immune cells to recognize and destroy cells that express it	124
2/3	TNBC	PR	Recruit CNOT1 to destabilize PR mRNA	Promote the metastasis	47

AML: acute myeloid leukemia; CRC: colorectal cancer; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; LUAD: lung adenocarcinoma; NPC: nasopharyngeal carcinoma; OSCC, oral squamous cell carcinoma; PC, pancreatic cancer; PDAC: pancreatic ductal adenocarcinoma; PTC: papillary thyroid cancer; TNBC: triple-negative breast cancer.

mRNAs to the cytoplasm. In glioblastoma, IGF2BP2 could bind to oxidative phosphorylation-related mRNAs, such as NDUFS3 and COX7b, and deliver them to mitochondrial polysomes.¹³⁷ These findings reveal the functional diversity of IGF2BPs in RNA processing.

Modulation of IGF2BPs for ncRNA

IGF2BPs not only affect mRNAs but also interact with ncRNAs, which in turn modulate the expression of malignant cancer-related RNAs (Table 3). As we know, ncRNAs can affect mRNAs involved in the biological process of tumorigenesis and help identify potential targets for cancer treatment, which contribute to the discovery of cancer drugs. Just as IGF2BPs are identified as new m⁶A readers, how they regulate lncRNAs and circRNAs is also being updated, which has been shown to be associated with m⁶A binding sites in ncRNAs. Understanding the mechanism by which IGF2BP regulates RNAs remains to be further clarified, in that they can prevent miRNA-dependent

degradation of target RNAs; the only difference is that some RNA target RNAs have modified sites m⁶A that can be recognized and bound by IGF2BP.¹¹ Therefore, we will summarize below the regulation network between IGF2BPs and ncRNAs and describe the specific mechanism.

Interaction between IGF2BPs and miRNAs. One of the roles of miRNAs in cancers is to mediate mRNA silencing.¹³⁸ As mentioned above, IGF2BPs alter the ability to decay miRNA-dependent mRNA by binding to the binding sites and attenuating the interaction between miRNAs and Ago2 or acting as cytoplasmic safe houses in the context of cancer.^{117–121,139} Based on the presence of m⁶A methylation sites in miRNA-regulated mRNAs in HCC, ovarian cancer, and lung cancer,¹¹ we can continue to study whether most miRNA-targeted mRNAs have m⁶A sites, which can clarify the activity of IGF2BPs in cancers. Furthermore, combined activation of the IGF2BP family promoted oncogenic transformation through Dicer and was included in an

Table 3 The mechanism of IGF2BPs in regulating different ncRNAs in cancers.

IGF2BPs	Cancer	ncRNAs	Mechanism of IGF2BPs in regulating ncRNAs	References
1	CRC	miR-183	Prevent miR-183-dependent degradation of β -TrCP1	120
1	Ovarian cancer	miR-155–5p, miR-22–3p, miR-140–3P	Prevent miRNA-dependent degradation of SIRT1	118
1	HCC, ovarian cancer, lung cancer	miR-23a-3p, miR-125a-5p	Serve as an m ⁶ A reader and impair miRNA-dependent degradation of SRF	11
1	Breast cancer	lncRNA UCA1	Recruit CCR4-NOT deadenylase complex to destabilize it	148
1	HCC	lncRNA HULC	Recruit CCR4-NOT deadenylase complex to destabilize it	147
1	HCC	circMAP3K4	Promote translation	149
2	TC, NSCLC	lncRNA MALAT1	Positive feedback may exist between IGF2BP2 and lncRNA MALAT1	66,145
2	PC	lncRNA DANCR	Serve as an m ⁶ A reader to promote stabilization	16
2	CRC	lncRNA ZFAS1	Serve as an m ⁶ A reader to promote stabilization	144
2	CRC	miR-195	Prevent miRNA-dependent degradation of RAF-1	121
2	Renal cancer	lncRNA DUXAP9	Serve as an m ⁶ A reader to promote stabilization	142
2	Prostate cancer	lncRNA PCAT6	Serve as an m ⁶ A reader to promote stabilization	96
2	Cervical cancer	circARHGAP12	Serve as an m ⁶ A reader to promote stabilization	107
3	NPC	lncRNA TINCR	Slow its decay	146
3	Breast cancer	miR-3614	Blockade of miR-3614 maturation	139
3	Cervical cancer	lncRNA KCNMB2-AS1	Serve as an m ⁶ A reader to promote stabilization	77
1/3	HCC	LINC01138	Promote its stabilization	143
1/2/3	Ovarian clear cell carcinoma/ glioblastoma/some kinds of solid cancers and fibrosarcoma	let-7	Prevent miRNA-dependent degradation of let-7 target mRNA	116,117,119

CRC: colorectal cancer; HCC: hepatocellular carcinoma; NSCLC: non-small cell lung cancer; NPC: nasopharyngeal carcinoma; PC, pancreatic cancer; TC: thyroid cancer.

oncogenic network that included miRNAs and complex post-transcriptional regulation.¹⁴⁰ In this network, IGF2BPs regulated the interaction with miRNAs through a variety of complex mechanisms, thus affecting the expression of malignant cancer-related RNAs, and changing cell fate and behavior.

An important mechanism of IGF2BP1 affecting cancer was its complex regulation network with let-7 miRNA. Let-7 was a family of highly evolutionarily conserved miRNAs that suppressed cancer growth and is a key regulator of IGF2BP1 in post-transcriptional regulation. Although let-7 targets gene products, including LIN28A, LIN28B, and HMGA2, and displays oncogenic and self-renewal functions.¹⁴¹ The cancer suppressor role of the let-7 miRNA family was antagonized by the self-promoting oncogenic 'triangle' composed of HMGA2, IGF2BP1, and LIN28B.¹¹⁶ Similarly, IGF2BP2 protected let-7 miRNA family target genes from silencing to preserve glioblastoma stem cells.¹¹⁹ IGF2BP3 prevented the binding of Ago2/let-7 to LIN28B, thus increasing the expression of other let-7 target genes (such as HMGA2).¹¹⁷ The ultimate result of this complex regulation is to promote the occurrence and development of cancer.

Interaction between IGF2BPs and lncRNAs. lncRNAs are a subgroup of ncRNAs with a length of more than 200 nucleotides, which play an important role in various biological functions and disease processes. In the study of their cancer-promoting mechanisms, lncRNAs were found to be related to the methylation of m⁶A and could bind to IGF2BP to stabilize themselves.^{96,142,143} A representative example is the DANCER lncRNA regulated by IGF2BP2 in an m⁶A methylation-dependent manner, which promoted the stem cell-like properties of cancer, cell proliferation, and stabilization of PC pathogenesis.¹⁶ A recent study found that the crosstalk between IGF2BP2 and the ZFAS1 lncRNA promoted ATP hydrolysis and the Warburg effect and played an important role in mitochondrial energy metabolism in colon cancer.¹⁴⁴ More importantly, lncRNAs can form positive feedback regulation with IGF2BPs to better promote cancer progression,^{66,77,145} meaning that the regulatory mechanism of IGF2BPs on lncRNA expression is complex. However, there is a study that has not investigated whether IGF2BP and lncRNA binding sites were modified by m⁶A methylation and only concluded that IGF2BP3 could slow lncRNA TINCR decay and promote its stability.¹⁴⁶ However, IGF2BPs can also promote the destabilization of lncRNAs by recruiting the CCR4-NOT deadenylase complex, thus promoting the degradation of the lncRNA HULC in HCC and the lncRNA UCA1 in breast cancer.^{147,148} However, these data are also sufficient to demonstrate that one of the mechanisms of interaction between lncRNAs and IGF2BPs is through the m⁶A methylation, thus promoting cancer progression.

Interaction between IGF2BPs and circRNAs. Currently, there is little research on how IGF2BPs regulate circRNAs in cancer, and only a few articles have written that they function by recognizing and binding to the m⁶A site in circRNAs. For example, m⁶A methylation in circARHGAP12 is recognized by IGF2BP2, which then together promotes stabilization of the forkhead box M1 (FOXO1) mRNA in cervical cancer.¹⁰⁷ The Hsa_circ_0003258-IGF2BP3-HDAC4 complex can enhance the stability of histone deacetylase 4

(HDAC4) mRNA, and both hsa_circ_0003258 and HDAC4 contain m⁶A modification sites.¹⁰⁸ Interestingly, circMAP3K4 encodes a new peptide, and IGF2BP1 promotes its translation through m⁶A methylation.¹⁴⁹ Apart from that, the elimination of circCD44 or IGF2BP2 influences the level of m⁶A-modified c-MYC mRNA, and the combination between circCD44 and IGF2BP2 may improve the stabilization of c-MYC in TNBC.⁷³ Therefore, reasonable speculation is that IGF2BPs can bind to m⁶A-modified circRNAs, thus regulating the expression of downstream genes. However, that study also showed that IGF2BPs interact with circRNAs in more than one way. The KH3-4 di-domain of IGF2BP2 was also necessary for its interaction with circNSUN2 and HMGA2, which allowed IGF2BP2 to bind to the CAUCAU motif of circNSUN2, and then enhanced the stability of the HMGA2 mRNA. However, in this study, IGF2BP2 stabilized HMGA2 in a manner independent of m⁶A methylation.²³

IGF2BPs could regulate the biological functions of cancer cells

CSCs are cells with self-renewal ability and cloning capacity, which are associated with cancer recurrence, metastasis, and resistance. Therefore, the mechanism of various factors that maintain the stem of CSCs needs to be studied in depth to identify targets that can be used for cancer therapy. IGF2BPs are reported to be key regulators of stem-like tumorigenic features in HCC, glioblastoma, and osteosarcoma.^{34,67,119,137} In leukemia, IGF2BP1 maintained the stemness of leukemia stem cells by regulating the key regulators of self-renewal, HOXB4, and MYB, and the metabolism-related factor ALDH1A1.¹⁵⁰ Importantly, in a recent study, IGF2BP2 could recognize lncRNA DANCER and DROSHA mRNA through m⁶A methylation, thereby promoting the stemness of pancreatic or breast cancer stem cells.^{16,18} Disrupting the interaction between IGF2BP and MYC may suppress the stem properties of breast cancer cells.¹⁰⁹ SRY box transcription factor 2 (SOX2) is also an important factor involved in maintaining the self-renewal capacity of CSCs.¹⁵¹ For IGF2BPs, IGF2BP2 stabilizes SOX2 in an m⁶A methylation-dependent manner to maintain the stem-like properties of CRC.¹⁵² Although IGF2BP1 also stabilized SOX2 in endometrial cancer,¹⁵³ it remains to be explored whether IGF2BP1 promotes the maintenance of stemness. Unlike IGF2BP1/2, IGF2BP3 promoted cancer self-renewal and initiation by binding to SLUG and promoting its downstream target SOX2, rather than directly binding to SOX2 in TNBC.¹⁵⁴ This is also evidence to support differences in the target RNAs of the IGF2BP family. In addition, in the hypoxic TME, IGF2BP also can contribute to maintaining the stem capacity of CSCs and adaptation to hypoxia.^{9,155}

There is a period called the G1 phase between nuclear division (M phase) and DNA synthesis (S phase) of the cell cycle, allowing repair of DNA damage and replication errors.¹⁵⁶ Mistakes in this period can lead to the formation of cancer cells. The regulation of the cancer cell cycle by IGF2BPs is positive and can promote the G1/S transition to promote cell proliferation.^{110,136,157–159} Subsequently, it was confirmed that IGF2BP3 could bind to m⁶A sites in the coding sequence (CDS) region of cyclin D1 (CCND1, a checkpoint of

the G1/S phase of the cell cycle), increasing the proportion of cancer cells in phase S.¹⁶⁰ In addition, we know that E2F is a positive regulator of the G1/S phase checkpoint, and IGF2BP1 promotes the shortening of the G1 phase by stabilizing its mRNA in a 3'UTR/miRNA/m⁶A methylation-dependent manner, thus promoting cancer cell proliferation.¹³ Cyclin-dependent kinases (CDK) are also a factor that promotes cell cycle entry into the S phase and can be a therapeutic target for cancer.¹⁶¹ Although the lncRNA DMDRMR could cooperate with IGF2BP3 to promote the transition G1/S by binding to the CDK4 m⁶A binding site.⁹⁵

The generation of resistance to cancer drugs is a major challenge in cancer treatment. A review of the recent literature revealed that IGF2BPs can induce a variety of cancer cells to develop resistance to chemotherapeutic drugs, such as NPC,¹⁴⁶ NSCLC,¹⁶² CRC,¹⁷ seminoma,¹⁶³ leukemia,¹⁵⁰ glioblastoma,¹⁶⁴ and melanoma.¹⁶⁵ Importantly, in radioiodine-refractory papillary thyroid carcinoma, IGF2BP2 promoted the translation efficiency of target RNAs through m⁶A methylation, thereby resulting in cancer cells resistant to tyrosine kinase inhibitors.¹³³ Moreover, IGF2BPs are also factors that lead to cancer cells being resistant to radiotherapy.^{166,167}

IGF2BPs regulate cancers by altering the TME

The TME is a complex environment in which cancer cells grow and includes multiple components, such as cancer-associated cells, the extracellular matrix, and some cytokines. However, due to metabolic disorders of cancer cells and other factors, an immunosuppressive TME is often formed and promotes cancer cells to evade immune surveillance, which is an important cause of the poor efficacy of current cancer therapy. Reviewing previous studies, it is not difficult to find that although some studies have confirmed that IGF2BPs can inhibit cancers, most studies support their cancer-promoting effects, such as inhibiting the antitumor immune response, promoting the function of immunosuppressive cells, adapting to hypoxia, and promoting cancer metabolism, angiogenesis, drug resistance, metastasis, and cell cycle transition. In the following, we summarize the specific roles of IGF2BPs in modulating TME, especially immunosuppressive TME.

IGF2BPs inhibit the anti-tumor immune response

With increasing research efforts, it has been found that IGF2BPs may be related to the immune response in the TME, resulting in dynamic changes in their impact on cancer cells. For example, a restricted epitope peptide derived from IGF2BP3 was found to induce CD8⁺ T cells to produce powerful and specific immune responses against cancer cells,^{168,169} suggesting that IGF2BP3 can serve as an antigen for T-cell-mediated immunotherapy. Although IGF2BP1-depleted TME could induce the appearance of CRC,¹⁷⁰ which is inconsistent with the role of IGF2BP1 in the promotion of colon cancer found in other studies.^{89,171} This may be due to the different TME, but specific reasons still need to be further explored.

Given the few studies on IGF2BP and important cytokines in TME, and most are in inflammatory diseases,^{172,173} we next focus on the relationship between IGF2BP and tumor-

associated cells. For antitumor immune cells, IGF2BP3 can stabilize PD-L1 mRNA expression through m⁶A methylation, thus inhibiting the killing effect of cytotoxic T cells in the TME,¹⁷⁴ or inhibit NK cell-mediated cytotoxicity by promoting stress-induced ligand ULBP2 mRNA decay.¹²⁴ CircIGF2BP3, a circRNA derived from a back splicing event between exons 4 and 13 of IGF2BP3, suppressed CD8⁺ T cell infiltration in NSCLC TME by promoting PD-L1 deubiquitination.¹⁷⁵ In summary, IGF2BPs inhibit antitumor immune cells in the TME in various ways and ultimately promote tumor immune escape.

IGF2BPs promote the function of immunosuppressive cells

Immunosuppressive cells in the TME include tumor-associated macrophages (TAM), myeloid-derived suppressor cells (MDSC), regulatory T cells (Treg), and carcinoma-associated fibroblasts (CAF). TAMs are formed by the infiltration of peripheral blood immune cells into cancer tissue and are also important factors that mediate cancer immune escape in the immunosuppressive TME. Among IGF2BPs, IGF2BP2 was involved in the immune response of peripheral blood immune cells in CRC patients,¹⁷⁶ and the ternary complex composed of circITGB6/IGF2BP2/FGF9 can induce TAM polarization to the M2 phenotype (with tumor-promoting activity) in ovarian cancer.¹⁰⁴ Because cell communication mediated by extracellular vesicles (EVs) is also a key part of TME, Pan et al.⁸⁸ found that after EVs secreted by glioma cells were delivered to TAMs, the transported circNEIL3 cargo could stabilize IGF2BP3 and promote the polarization of its immunosuppressive phenotype. In addition, EVs secreted by IGF2BP1 knockdown melanoma cells inhibit cancer cell metastasis,¹⁷⁷ but it remains to be explored whether this process involves the regulation of immunosuppressive TME by IGF2BPs. In breast cancer, the co-culture of fibroblasts with cancer cells could promote the CAF phenotype, and under this condition, IGF2BP3 can promote the proliferation and survival of breast cancer cells by promoting CD44 expression in fibroblasts.^{178,179}

In conclusion, although there are no studies on the relationship of IGF2BPs with other immunosuppressive cells, such as MDSCs and Tregs, continuing to dig deeper into this field may also help us understand tumorigenesis and deepen our understanding of the immunosuppressive TME.

IGF2BPs promote the adapting to hypoxia of cancer cells

Hypoxia caused by rapid cancer growth is a common feature of the TME, leading to increased expression of hypoxia-inducible factor (HIF), which promotes cancer immune escape. It has been confirmed that hypoxia could induce the invasion of metastatic melanoma cells by regulating IGF2BP1 expression through HIF-1 α .³⁶ Currently, only a few studies mention that IGF2BPs regulate the biological behavior of cancer cells in a hypoxic environment through m⁶A methylation. For example, in gastric cancer, IGF2BP3 recognizes the m⁶A site on HIF-1 α mRNA and enhances its expression, thus promoting hypoxia-induced cell metastasis and angiogenesis.¹⁸⁰ Further, hypoxia-induced down-regulation of FTO promoted metastasis of CRC through an m⁶A-IGF2BP2-dependent mechanism.¹⁸¹ Whereas IGF2BP1 silencing in one study did not reverse hypoxia-induced

chemoresistance in HCC,⁴⁶ suggesting that IGF2BP1 was not the only gene involved in the regulation of chemoresistance. Importantly, binding of the lncRNA HIF1A-AS2 to IGF2BP2 promotes the adaptation of stem cells from glioblastoma multiforme to hypoxia.¹⁵⁵ This adaptive change can prevent hypoxia-induced cancer cell necrosis and forms an immunosuppressive TME.

IGF2BPs could affect the cancer metabolism

Cancer cells can also change their metabolism to regulate the adaptation to hypoxia. The use of glycolysis as a source of energy even in the presence of oxygen, known as the Warburg effect, is a unique way of glucose metabolism in cancer cells. Lactic acid produced by cancer cells accumulates in the TME, resulting in an immunosuppressive effect. IGF2BPs can promote cancer glycolysis by interacting with target RNAs related to glucose metabolism.^{87,93,171,182–184} In studies on glucose metabolism in CRC, it was found that m⁶A methylation in target genes (HK2 and GLUT1) could promote the activation of glycolysis and cell proliferation, while IGF2BP2/3 could bind to them to play its m⁶A reader role.¹⁸⁵ In addition, in gastric cancer (GC), HCC, and cervical cancer, there are similar findings that IGF2BP3 promotes the stability of target RNAs (HDGF, PDK4) through m⁶A methylation to regulate glycolysis and ATP production in cancer cells.^{14,186} In a recent study, Lu et al.¹⁴⁴ found that IGF2BP2 recognized and stabilized the lncRNA ZFAS1 through the m⁶A site, thus promoting ATP hydrolysis and the Warburg effect, providing a new mechanism for IGF2BP to promote cancer glycolysis. Although aerobic glycolysis is the main source for cancer cells to obtain energy, in recent years oxidative phosphorylation has also been found to be crucial in maintaining the stemness of some cancer stem cells (CSCs).¹⁸⁷ IGF2BPs also play a role in this form of energy metabolism. For instance, inhibition of IGF2BP2-mediated oxidative phosphorylation was detrimental to the clonogenicity of glioblastoma CSC.¹³⁷ However, because of the high energy demand of cancer cells, they often utilize lipid metabolism and amino acid metabolism to maintain their own growth needs. Current research on IGF2BP lipid metabolism has focused on its deletion which could make mice resistant to obesity and regulate glucose tolerance,^{188,189} but little is known about its mechanism of action in cancers. In NPC, IGF2BP3 could regulate acetyl-CoA-related metabolic processes by stabilizing the lncRNA TINCR, thus promoting lipid biosynthesis.¹⁴⁶ It is believed that with the deepening of the research, the mechanism of m⁶A methylation mediated by IGF2BPs to promote cancer metabolism will be elucidated and warrants further research.

IGF2BPs could promote cancer neovascularization

Cancer neovascularization is very important for nutrient and oxygen delivery and is essential for cancer growth and metastasis. IGF2BPs can also use their m⁶A reader function to stabilize related mRNAs to promote cancer angiogenesis.^{14,42} Vascular endothelial growth factor (VEGF) is also an important regulator of angiogenesis. In recent years, through in-depth research on m⁶A methylation, we have learned that there are m⁶A sites in the VEGF mRNA, which could be recognized and bound by IGF2BP3, thus promoting cancer angiogenesis.¹⁶⁰

In summary, the rapid growth of cancer cells leads to insufficient oxygen supply and the formation of a hypoxic environment, prompting cancer cells to alter their glucose metabolism and secrete a large amount of lactic acid into the TME, which inhibits the function of immune cells and enhances the activity of immunosuppressive cells. Moreover, the formation of cancer angiogenesis, cell cycle transition, and resistance to radiotherapy and chemotherapy, promote the cancer's adaptation to the adverse environment, which requires the joint efforts of all links. The role of IGF2BPs in the induction of immunosuppressive TME is very important. Due to the wide range of target RNAs of IGF2BPs, we can also find that they regulate many aspects of tumorigenesis and development, which may better explain the mechanism of IGF2BPs in the promotion of cancers. A better understanding of the mechanisms involved in IGF2BP regulation of immunosuppressive TME may contribute to avoiding cancer immune escape mechanisms.

The potential clinical application of IGF2BPs in cancers

Potential diagnosis values of IGF2BPs

The tumor-promoting effects of IGF2BPs have emerged from studies over the past few years. As we know, tissue biopsy is the gold standard for diagnosing cancer, and by studying the expression of IGF2BPs in tissues—using methods such as immunohistochemistry—it was found that they were rarely expressed in normal tissues. Therefore, whether IGF2BPs can be used as a cancer diagnostic marker is a question worthy of research (Table 4). For example, the detection of IGF2BP3 expression in samples obtained from a core needle biopsy or endoscopic biopsy could diagnose PC, CRC, *etc.*^{190–193} In the immunohistochemical staining analysis of pleural effusion cell block, IGF2BP3 could be used to distinguish metastatic gastric adenocarcinoma cells and reactive mesothelial cells in effusions.¹⁹⁴ However, IGF2BPs can not only distinguish between cancer and normal tissue but they can also differentiate between different types of cancers; IGF2BP1 can distinguish ATC from other follicular-derived thyroid cancers.³³ With the development of medicine, the requirements for less invasive diagnostic methods are increasing, so the examination of markers in the peripheral blood of patients has attracted greater attention. Some researchers have studied whether the presence of anti-IGF2BP2 autoantibody in peripheral blood could be used as a basis for diagnosing CRC, but the results obtained were not ideal, a result which may be attributed to the very low sensitivity (23.4%), although its specificity was very high, reaching 97.1%. Therefore, more studies are needed to determine whether it could be used as a complementary marker to diagnose CRC.¹⁹⁵

High specificity is a condition that can be used to define a cancer diagnostic marker, while the diagnostic utility of IGF2BPs in some cancers is still relatively low. The inability to differentiate salivary gland cancers,¹⁹⁶ in situ carcinoma, and invasive laryngeal squamous cell carcinoma (LSCC),¹⁹⁷ as well as benign lesions and malignant papillary thyroid cancer (PTC),¹⁹⁸ or low diagnostic sensitivity in

Table 4 The diagnosis value of IGF2BPs in different cancers.

Cancer type	IGF2BPs	Role of IGF2BPs in cancer diagnosis	Number of cases	References
Salivary gland tumors	3	Not a specific diagnostic marker for distinguishing salivary gland tumors	36	196
LSCC	3	Has good specificity and sensitivity for diagnosis of LSCC, but could not differentiate between carcinoma in situ and invasive carcinoma	238	197
ATC	1	Distinguishes ATC from another thyroid carcinoma of follicular origin	365	33
Follicular patterned thyroid tumors	3	Distinguishes malignant from benign follicular thyroid lesions	219	251
Papillary thyroid carcinoma	3	Inability to differentiate papillary carcinoma from benign lesions; sensitivity is 27% and specificity is 100%	84	198
Esophageal adenocarcinoma	3	Can diagnosis invasive esophageal adenocarcinoma and high-grade dysplasia	217 + 76	252,253
Extrapulmonary small cell carcinoma	3	Distinguishes small cell carcinoma from carcinoid tumor	75	254
Pancreatic carcinoma	3	A sensitive and specific marker for pancreatic ductal carcinoma and high-grade dysplastic lesions	72	255
PDAC	3	Distinguishes PDAC from chronic sclerosing pancreatitis and can be used in core needle biopsies; sensitivity is 88.4% and specificity is 94.6%	240	190
Malignant pancreatic cancers	3	Combined with IGF2BP3 immunostaining, the sensitivity, specificity, and accuracy of cytohistological analysis significantly increased to 87.9%, 100%, and 90.8%	215	191
Intraductal papillary mucinous neoplasm of the pancreas	3	Sensitivity for distinguishing cancerous from noncancerous lesions is 76.1% and specificity is 100%	205	192
Gastric adenocarcinoma	3	Distinguishes metastatic adenocarcinoma cells from reactive mesothelial cells in effusions; sensitivity is 78.4% and specificity is 92.5%	156	194
HCC	3	Seem to be of limited use as a single marker for the diagnosis; sensitivity is 52% and specificity is 97.1%	452	199
Cholangiocarcinoma	3	Distinguishes biliary cancer from the benign specimen (sensitivity is 76.4% and specificity is 80.9%); sensitivity is 89.7% and specificity is 91.7% when using IGF2BP3 and/or histology	119	256
Cholangiocarcinoma	3	Distinguishes biliary cancer from the benign specimen (sensitivity is 69.2% and accuracy is 80.0%); sensitivity is 80.8% and accuracy is 87.5% when combining IGF2BP3, EZH2, and p53	51	257
Cholangiocarcinoma	3	Diagnosing the presence of invasion in bile duct biopsies	37	258
Extrahepatic bile duct carcinoma	3	Useful in the diagnosis of extrahepatic bile duct carcinoma; sensitivity is 79.4% and specificity is 91.7%	80	259
CRC	2	The specificity of anti-IGF2BP2 autoantibodies in serum to detect colon cancer is 97.1%, but the sensitivity is only 23.4%	140	195
CRC	3	Combination of histological features and IGF2BP3 increase the sensitivity (95.7%) and negative predictive values (61.1%) for detecting CRC in biopsy specimens	1131	193
Pelvic serous carcinoma	3	Could serve as a latent precancer biomarker	316	260
Endometrial carcinoma	3	IGF2BP3 together with L1CAM represent the optimal combination for discrimination between low- and high-grade endometrial carcinoma compared	378	261

		with IGF2BP3 or L1CAM alone		
Teratoma	3	Might help diagnose metastatic mature teratoma and seminoma	178	262
Teratoma	3	Useful in the diagnosis of benign and malignant teratoma	37	263
Serous tubal carcinoma	3	Served as a complimentary biomarker to the diagnosis of serous tubal intraepithelial carcinoma	170	264
B-all	1	95% sensitivity and 86% specificity for the diagnosis of ETV6-RUNX1 translocation-positive B-ALL	143	265
Angiosarcoma	3	Distinguish between malignant and benign vascular lesions	71	266
Hodgkin lymphoma	3	Served as a supplemental diagnostic marker	81	267
Hodgkin lymphoma	3	The sensitivity of IGF2BP3 to distinguish Hodgkin lymphoma is 84.3%; CD30/IGF2BP3 differentiates Hodgkin lymphoma with the same sensitivity as CD15/CD30 (traditional markers)	51	268
Leiomyosarcoma	3	Distinguishes leiomyoma from leiomyosarcoma	216	269
Chondrosarcoma	3	Differentiates problematic cases of enchondroma from well-differentiated chondrosarcomas	78	270

ATC: anaplastic thyroid carcinomas; CRC: colorectal cancer; HCC: hepatocellular carcinoma; LSCC: laryngeal squamous cell carcinoma; PDAC: pancreatic ductal adenocarcinoma.

HCC,¹⁹⁹ were all IGF2BP defects as diagnostic markers in different cancers. Therefore, greater efforts are needed to apply IGF2BP as a potential cancer diagnostic marker, and studies of IGF2BP1/2 as diagnostic markers are far less than those of IGF2BP3, indicating that more representative studies with larger samples are needed.

The prognosis value of IGF2BPs

How to accurately estimate the prognosis of various malignancies is always of interest to clinicians. Over the past few decades, an increasing number of studies on IGF2BPs have found that they are tumor-promoting factors, and their qualified potential as prognostic markers can be confirmed in various large-sample studies or bioinformatic analyses. IGF2BP3 is currently the most studied, and there is much literature on its prediction of a poor prognosis in different cancers. In contrast, although IGF2BP1/2 have been poorly studied, they are known to be associated with a poor prognosis in some common cancers (Table 5).

As shown in Table 5, several large-sample studies have analyzed the expression of IGF2BPs in different cancers and correlated levels with clinical information and revealed that IGF2BP expression may be associated with metastasis, depth of invasion, early recurrence, and shorter overall survival (OS), and disease-free survival (DFS), which are independent prognostic factors predicting a poor prognosis.^{95,200–206} For example, in a retrospective study, it was found that the 5-year metastasis-free survival rate of IGF2BP3-positive patients with renal cell carcinoma was much lower than that of IGF2BP3-negative patients, concluding that IGF2BP3 could help identify patients with high metastatic potential and who may benefit from early systemic therapy.²⁰⁴ However, in stage 4 neuroblastoma, researchers found that IGF2BP1 had prognostic significance independent of that of the MYC family member, MYCN.²⁰⁶ With the development of high-throughput sequencing and bioinformatics, various clinical information data sets can be analyzed to identify whether a gene is associated with cancer prognosis and to establish cancer risk prognosis models. In recent studies, IGF2BPs, as m⁶A readers, were selected from different models of different cancers, which could predict cancer prognostic information.^{207–209} IGF2BP2 was the only m⁶A gene that was correlated with the DFS of PTC and had a strong correlation with clinical phenotypes.²¹⁰ In isocitrate dehydrogenase wild-type glioblastoma, Johnson et al²¹¹ established a nine-gene expression-based risk signature based on nine genes that included IGF2BP3, which predicted a poor prognosis.

However, evidence from some studies suggested that the prognosis of some cancers was not related to IGF2BP3 expression, such as urachal carcinoma of the bladder²¹² and prostate cancer.^{213,214} Even in several bioinformatics studies, IGF2BP2 was found to be a protective factor in neuroblastoma and TC,^{215,216} and deletion of IGF2BP1 led to poorer OS in soft tissue sarcomas.²¹⁷ The reasons for this phenomenon may be due to the different types of cancers studied on the one hand and may be related to limited sample size or limitations of bioinformatics methods on the other. But these results also suggest that IGF2BP can also estimate the prognosis of certain cancers.

Table 5 The prognosis value of IGF2BPs in cancers.

System	Cancer type	IGF2BPs	Role of IGF2BPs in prognosis	References
Head and neck	HNSCC	1	Antibody responses to IGF2BP1 have a poor prognosis	271
	HNSCC	2	Associated with T stage and poor prognosis	272
	OSCC, TSCC, NPC	3	Predicts poor outcome	40,273,274
Endocrine system	PTC	2	A four-m ⁶ A-regulator signature including IGF2BP2 predicts poor prognosis	210
	TC	2	A protective factor in the six-gene risk signature	216
	Poorly differentiate thyroid cancer	3	Associated with an increased risk of death, metastases, and DFS	275
Respiratory system	NSCLC	1	Associated with male, cancer size, non-adenocarcinoma, smoking history, and poor prognosis	200
	Lung cancer	1	A three-m ⁶ A-regulator signature including IGF2BP1 is related to OS, cancer status, and some clinical traits (gender, smoking history, etc.)	208
	LUAD	3	High expression of IGF2BPs predicts poorer OS and DFS	276,277
Breast	Breast cancer	1	An independent prognostic factor; associated with shorter OS	278
	Breast cancer	2/3	IGF2BP2/3, YTHDC2, and RBM15 could be used for the prognostic stratification of luminal A/B subtypes	279
	TNBC	3	Associated with a more aggressive phenotype and decreased OS	280
Digestive system	Malignant phyllodes tumor of the breast	3	Associated with shorter periods of metastasis-free and DFS	281
	Metaplastic breast carcinoma	3	Related to poor OS	282
	ESCC	3	Associated with adverse clinical outcomes in patients treated with surgery alone	283
	Esophageal adenocarcinoma	3	Associated with depth of cancer infiltration, lymph node metastases, and worse outcome	202
	Pancreatic cancer	1/2	Associated with poor prognosis	44,45
	Pancreatic ductal adenocarcinoma	3	Related to poor OS	284
	Intraductal papillary mucinous neoplasm	3	High expression of IGF2BP3 is related to shorter disease-specific survival	192
	Gastric adenocarcinoma	3	Predicts postoperative peritoneal dissemination and poor prognosis	285
	GC	1	High IGF2BP1 mRNA expression has poorer OS	201
	GC	2	Gene polymorphisms might be an independent predictor of chemotherapeutic response in patients with metastatic GC	286
	GC	3	Associated with poor disease-specific survival	48
	CRC	1/2	An independent poor prognostic marker	17,152
	HCC	2	Might be an independent risk factor	32
	HCC	3	Predicts early recurrence and poor prognosis	203

Reproductive system	Intrahepatic cholangiocarcinoma	3	Provides an independent prognostic value	35
	Gallbladder adenocarcinoma	3	Associated with high histological grade, advanced stage, lymphatic invasion, and worse OS	287
	Adenocarcinoma of the ampulla of Vater	3	Independently predicts shorter recurrence-free and OS	288
	Endometrial cancer	1	High expression is associated with poor prognosis	159
	Ovarian cancer	1	A three-m ⁶ A-regulator including IGF2BP1 signature predicts poor prognosis	207
	Ovarian clear cell carcinoma	3	Related to poor OS	289
	Uterine cancer	1	A pan-prognostic regulator	290
	Uterine corpus endometrial carcinoma	3	A three-m ⁶ A-regulator signature including IGF2BP3 predicts a poor prognosis	209
	Testicular germ cell tumor	1	A six-m ⁶ A-regulator signature including IGF2BP1 predicts a poor prognosis	291
	Prostate cancer	3	Has no independent prognostic value	213,214
Urinary system	Prostate cancer	3	High IGF2BP3 serum levels are related to patients' poor prognosis	292
	ccRCC	2	The six-gene signature including IGF2BP2 is an independent risk factor for OS	293
	ccRCC	3	An independent risk factor for localized CCRCC patients	205
	ccRCC	3	High co-expression of DMDMR and IGF2BP3 is associated with poor outcomes	95
	Primary papillary renal cell carcinoma and ccRCC	3	An independent prognostic biomarker for identifying patients with distant metastasis risk	294
	Renal cell carcinoma	3	An independent prognostic biomarker related to metastasis and reduced 5-year OS	204
	Bladder cancer	1/3	Significantly associated with poor prognosis	110,295
	Aggressive urothelial carcinoma of the bladder	3	An independent prognostic biomarker; can identify patients who may benefit from early aggressive therapy	296
	Upper tract urothelial carcinoma	3	Independently associated with disease recurrence, cancer-specific mortality, and all-cause mortality	297
	Urachal carcinoma of the bladder	3	Has no prognostic significance	212
Nervous system	Neuroblastoma	1/3	Predicts poorer prognosis	206,298
	Neuroblastoma	2	A protective factor in the five-gene signature	215
	Glioma	2	Associated with poor OS and DFS	62
	Glioblastoma	3	A nine-gene signature is an independent risk factor for OS	211
Hematopoietic system	AML, diffuse large b-cell lymphoma	1/2/3	Predicts poor OS	299
	B-ALL	3	Portends a favorable survival high-risk B-ALL	300
Skin	Melanoma	3	Predicts poor prognosis	301
Neuroendocrine tumor	Lung neuroendocrine tumor	3	Related to poor OS and DFS	302
Sarcoma	Osteosarcoma	1	Associated with high tumor grade, metastasis, recurrence, and	303

(continued on next page)

Table 5 (continued)

System	Cancer type	IGF2BPs	Role of IGF2BPs in prognosis	References
	Osteosarcoma	2	poor response to chemotherapy	304
	Soft-tissue sarcoma	1	An independent risk factor for OS and DFS	217
	Uterine leiomyosarcoma	3	Patients with loss of IGF2BP1 have poorer DFS	305
	Ewing sarcoma	3	An independent risk factor	91,249
			Associated with poor OS	

B-ALL: B cell-acute lymphoblastic leukemia; ccRCC: clear cell renal carcinoma; CRC: colorectal cancer; ESCC: esophageal squamous cell carcinoma; GC: gastric cancer; HCC: hepatocellular carcinoma; HNSCC: head and neck squamous cell carcinoma; LUAD: lung adenocarcinoma; NPC: nasopharyngeal carcinoma; NSCLC: non-small cell lung cancer; OSCC: oral squamous cell carcinoma; PTC: papillary thyroid cancer; TC: thyroid cancer; TNBC: triple-negative breast cancer.

Therefore, IGF2BPs have great potential to predict cancer prognosis, involving different systems for a wide range of cancers.

The potential treatment values of IGF2BPs

The treatment of malignant cancers poses a significant challenge in the development of modern medicine. Given that cytotoxic T lymphocytes (CTL) respond to cancer cells expressing IGF2BP3.^{168,169,218} In small-cell lung cancer, Zhang et al²¹⁹ constructed a prognostic signature based on m⁶A regulators, including IGF2BP3, the low score group had greater CD8⁺ T cell infiltration and better response to immunotherapy, so investigating immunotherapeutic approaches targeting IGF2BP3 in cancers is also an option. A recent phase I clinical trial demonstrated that a vaccine derived from IGF2BP3 and two other cancer peptides was effective against solid pediatric refractory cancers.²²⁰ As we know, antibody-based PD-1-PD-L1 inhibitors are an effective therapeutic approach for patients with various advanced cancers, but there are still many limitations and shortcomings. However, by further exploring the upstream regulatory mechanism of PD-L1, it was found that IGF2BP3 could stabilize its mRNA.¹⁷⁴ This may help improve the effect of anti-PD-1 immunotherapy on cancers.

Because IGF2BPs promote the development of various cancers, the identification of specific inhibitors of IGF2BPs is also a viable approach to cancer treatment. In a recent study, a fluorescence polarization-based screening platform identified some specific inhibitors targeting IGF2BP2 belonging to the benzamidobenzoic acid class and the ureidothiophene class, and achieved reduced cancer xenograft growth in zebrafish embryos.²²¹ This was the first description of a small-molecule inhibitor of IGF2BP2, facilitating the construction of RBP-specific inhibitors. Over the past few years, two inhibitors have been identified that specifically inhibit IGF2BP1. One is a newly identified small molecule inhibitor 7773, which binds directly to the hydrophobic surface of the KH3-4 domain of IGF2BP1 and acts by suppressing its binding to KRAS mRNA, thus specifically inhibiting its tumor-promoting activity.²²² Another is a small-molecule inhibitor BTYNB, which functions as a selective allosteric inhibitor of IGF2BP1 to decrease IGF2BP1 protein levels.²²³ Mechanistically, BTYNB impairs the interaction between IGF2BP1 and c-MYC or E2F1 mRNA. Its inhibitory effect on IGF2BP1 was demonstrated simultaneously in experimental cancer models, where cancer growth and peritoneal spread were inhibited.^{13,223}

In addition to these small-molecule inhibitors, many compounds play a role in inhibiting IGF2BPs. Confluentin, a compound isolated from *Albatrellus flettii*, inhibits the interaction between IGF2BP1 and KRAS mRNA.²²⁴ Furthermore, triptolide inhibits lnc-THOR-IGF2BP1 signaling, causing the inhibition of NPC cell growth.²²⁵ Berberine down-regulates IGF2BP3 expression to inhibit the proliferation of CRC cells,²²⁶ and IGF2BP3 expression is also inhibited by bromodomain and extraterminal domain inhibitor JQ1, which influences Ewing sarcoma anchorage-independent cell growth.⁹¹

Furthermore, oligonucleotides are also feasible as a new class of drugs, with several oligonucleotide therapies

already on the market.²²⁷ The development of oligonucleotides targeting IGF2BP as oncology drugs is also a strategic option, as it can inhibit IGF2BP1 binding to mRNA.^{228,229}

In conclusion, exploring the role of IGF2BPs in cancer immunotherapy and the development of drugs that specifically inhibit IGF2BPs, such as small molecule inhibitors, molecular compounds, and oligonucleotides, can help improve clinical therapeutic outcomes of different cancers, and therefore has great therapeutic potential.

Discussion

With the development of high-throughput sequencing and bioinformatics, an increasing number of studies have evaluated m⁶A methylation. We know that m⁶A methylation is inseparable from the occurrence and development of cancers and its mechanism is very complex. This review explored the role of m⁶A new readers IGF2BP1/2/3 in cancer immunosuppressive TME. Various functional *in vitro* and *in vivo* studies provide strong evidence for the regulation of cancer cell fate by IGF2BP, which act as oncogenes to promote cancer cell proliferation, survival, metastasis, and invasiveness in almost all cancers analyzed thus far. In contrast, a small number of studies report that IGF2BPs have an inhibitory effect on cancers.^{170,230,231} The different origins of cancer cells, differences in the TME, or the dissimilarity between nonmetastatic cells and metastatic cells are potential influencing factors. However, the detailed reasons for the contradictory functions of IGF2BP are still unclear and more research is needed to reveal the underlying causes. Additionally, we also reviewed the mechanisms by which IGF2BPs regulate cancers and find that IGF2BPs affect tumorigenesis by regulating the activity of different RNAs, including mRNAs, miRNAs, lncRNAs, and circRNAs. The consequence of this regulation is to inhibit the function of antitumor immune cells, influence cancer metabolism and the cancer cell cycle, and promote cancer angiogenesis and resistance to various treatments, thus inducing the formation of an immunosuppressive TME, which finally contributes to tumor-immune escape.

Currently, the research of various cancer markers has become an important direction for the development of oncology and other disciplines. More specific, sensitive, and minimally invasive markers discovered in these studies could help clinicians better diagnose and analyze the prognosis of malignant cancers earlier. At the same time, the discovery of different cancer suppressor genes and oncogenes, as well as an in-depth study of tumorigenesis, development, and malignant behavior, can help us better develop personalized cancer treatment strategies. Many studies indicate that further study of IGF2BP expression and its functions may meet the clinical requirements of new biomarkers for the diagnosis and prognosis of patients with malignant cancers. The search for inhibitors targeting the interaction between IGF2BP and its target RNAs may also be an effective strategy for cancer treatment. However, from the above discussion, it is not difficult to see that there are still several unanswered questions to be solved.

Although IGF2BPs can specifically recognize cancers with high specificity, their low sensitivity in some cancers is also of concern. Therefore, it may be more feasible to combine

IGF2BPs with other highly sensitive markers. At the same time, exploring whether IGF2BPs are promising biomarkers for the detection of different cancers or whether they may have a better diagnostic and prognostic value for a specific cancer type is also a factor to evaluate prior to clinical application. With the increase in the application of immunotherapy in recent years and the growing research on the relationship between IGF2BPs and PD-L1, it may be worthwhile to continue exploring this combination. Although specific small molecule inhibitors and clinical application of cancer vaccines have provided additional choices for patients with malignant cancers, the development of IGF2BP inhibitors and therapeutic cancer vaccines has just begun, and more evidence is needed to prove their efficacy and safety.

In conclusion, the complex relationship between IGF2BPs and their target RNAs is involved in the development of cancer, especially in the formation of the immunosuppressive TME, which is likely to be accomplished by m⁶A methylation. Therefore, it may be possible to explore further interconnections between IGF2BPs and their target RNAs in the context of specific cancers, which may open new frontiers for the diagnosis, prognosis, and treatment of cancers.

Author contributions

Meiqi Duan drafted this review; Haiyang Liu provided editorial assistance and gave some valuable suggestions; Shasha Xu provided the manuscript revision and figure drawing; Xiaofeng Jiang and Shan Zhao provided the design, guidance and revision of the manuscript; Xiaofeng Jiang, Haiyang Liu and Zhi Yang obtained funding supports. All authors provided substantial and useful assistance to this manuscript; All authors approved the final manuscript.

Conflict of interests

The authors declare that they have no competing interests.

Funding

This study was supported by grants from the Liaoning Nature Science Foundation of China (No. 2022JH2/101300042), The National Natural Science Foundation of China (No. 82173194, 81672877), the Key Research Project of Liaoning Provincial Department of Education of China (No. ZD2020004), and 2018 Youth Backbone Support Program of China Medical University (No. QGZ2018063).

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