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REVIEW

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Novel insights into the interaction between IGF2BPs and ncRNAs in cancers

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Abstract

Insulin-like growth factor II mRNA-binding proteins (IGF2BPs), a family of RNA-binding proteins, are pivotal in regulating RNA dynamics, encompassing processes such as localization, metabolism, stability, and translation through the formation of ribonucleoprotein complexes. First identified in 1999 for their affinity to insulin-like growth factor II mRNA, IGF2BPs have been implicated in promoting tumor malignancy behaviors, including proliferation, metastasis, and the maintenance of stemness, which are associated with unfavorable outcomes in various cancers. Additionally, non-coding RNAs (ncRNAs), particularly long non-coding RNAs, circular RNAs, and microRNAs, play critical roles in cancer progression through intricate protein-RNA interactions. Recent studies, predominantly from 2018 onward, indicate that IGF2BPs can recognize and modulate ncRNAs via N6-methyladenosine (m6A) modifications, enriching the regulatory landscape of RNA–protein interactions in the context of cancer. This review explores the latest insights into the interplay between IGF2BPs and ncRNAs, emphasizing their potential influence on cancer biology.

Keywords IGF2BPs, NcRNAs, Cancer, Ribonucleoprotein complexes, Cancer biology

Introduction

Insulin-like growth factor II mRNA-binding proteins (IGF2BPs), including IGF2BP1, IGF2BP2, and IGF2BP3, are a family of RNA-binding proteins that were first identified in 1999 for their binding to the insulin-like growth factor II leader 3 mRNA [1]. These proteins are crucial in modulating RNA dynamics, primarily by forming ribonucleoprotein complexes (RNPs) with target RNAs, thereby governing their localization, metabolism, stability, and translation [2, 3]. The high expression of IGF2BPs showed a significant association with poor prognoses in most human cancers, such as colorectal cancer [4], gastric cancer [5], pancreatic cancer [6], lung cancer [7]. Furthermore, emerging research suggests that IGF2BPs are implicated in a multitude of tumor malignant behaviors, including proliferation [8, 9], metastasis [10, 11], angiogenesis [12], resistance to apoptosis and ferroptosis [13, 14], maintenance of cell stemness [15], immune evasion [16], and drug resistance [17].

Regulatory non-coding RNAs (ncRNAs), predominantly long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs), play pivotal roles in the development and progression of cancer [18–20]. These ncRNAs, with the exception of certain circRNAs, do not encode proteins but exert their functions through interactions with proteins and other RNAs [19, 21]. Recent investigations have elucidated that N6-methyladenosine (m6A) modification, which involves the methylation of the adenosine base at the nitrogen-6 position, is present not only on mRNA but also on ncRNAs [22, 23]. Since their discovery in 2018, it has been recognized that IGF2BPs can recognize m6A modifications and influence

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the fate of ncRNAs in an m6A-dependent manner [24], adding a layer of complexity to the interactions between IGF2BPs and ncRNAs. Accumulating evidence suggests that IGF2BPs can modulate the stability and metabolism of ncRNAs, and conversely, ncRNAs can also regulate the expression and function of IGF2BPs [25–27]. This review synthesizes the latest advancements in the interplay between IGF2BPs and ncRNAs in the context of cancer.

The structure of IGF2BPs

In human cells, IGF2BPs are predominantly localized in the cytoplasm, where they assemble into ribonucleoprotein complexes (RNPs) with RNAs, with a smaller fraction detectable in the nucleus [28, 29]. IGF2BPs bind not only to mRNA but also to ncRNAs such as circRNAs [30] and lncRNAs [31]. The IGF2BP family exhibits distinctive similarities in domain order and spacing, featuring two RNA recognition motifs (RRMs) in the N-terminal and four hnRNP K homology (KH) domains in the C-terminal region, with over 56% amino acid sequence similarity [32] (Fig. 1). The KH domains are primarily responsible for RNA binding, whereas the RRM domains contribute to the stabilization of RNPs, particularly those with a half-life exceeding 2 h, thereby enhancing their stability [33, 34]. The sequence homology suggests that IGF2BPs may perform common biological functions and likely target similar RNAs [3, 35]. However, research by Biswas et al. indicates that despite their overall similarity, variations in the amino acid composition of the variable loop regions in the KH3 and KH4 domains confer distinct RNA binding specificities among IGF2BPs [36].

Each IGF2BP protein possesses two adjacent tandem KH domains that contain a highly conserved GXXG motif and a variable loop, which are crucial for RNA-binding capacity and sequence-specific recognition, respectively [36–38]. During its engagement with RNA, the GXXG motif aligns with the phosphate backbone, while the variable loop confronts the nucleotide bases, together forming a clamp-like structure that securely fastens to the RNA [37, 39, 40]. The architecture of IGF2BP1 features KH1-2 and KH3-4 domains arranged as intramolecular pseudo-dimers, with the KH3-4 domains adopting an intramolecular antiparallel pseudo-dimeric conformation [41, 42]. The sequence recognition profiles of IGF2BP1's KH domains vary significantly: KH1 affiliate with CNG sequence, KH3 with CA or ACA sequence, KH4 with CGGAC or GGAC sequence, while KH2 shows minimal sequence specificity [41]. The KH3 and KH4 domains of IGF2BP2 mirror the structure of their counterparts in IGF2BP1, adopting the type I KH fold (βααββα) and positioning themselves in an antiparallel pseudo-dimeric configuration [36]. The KH3 domain of IGF2BP2 demonstrates greater specificity for the UCA sequence, while the KH4 domain shows flexibility, differing from the stringent specificity observed in IGF2BP1's KH4 domain [36, 42]. IGF2BP3's RRM domains follow a conventional RRM-fold (β1α1β2β3α2β4), positioning two α-helices above an anti-parallel four-stranded β-sheet [43]. The recognition sequences of RRM domains of IGF2BP3 typically feature a continuous stretch of at least three cytosines, which makes up the majority (80%) of these sequences, with the CCC sequence being predominant [43]. The KH1-2 domains of IGF2BP3 form a stable monomeric folding unit, where KH1 shows a marked affinity for the GGC motif and KH2 for the CA motif [44].

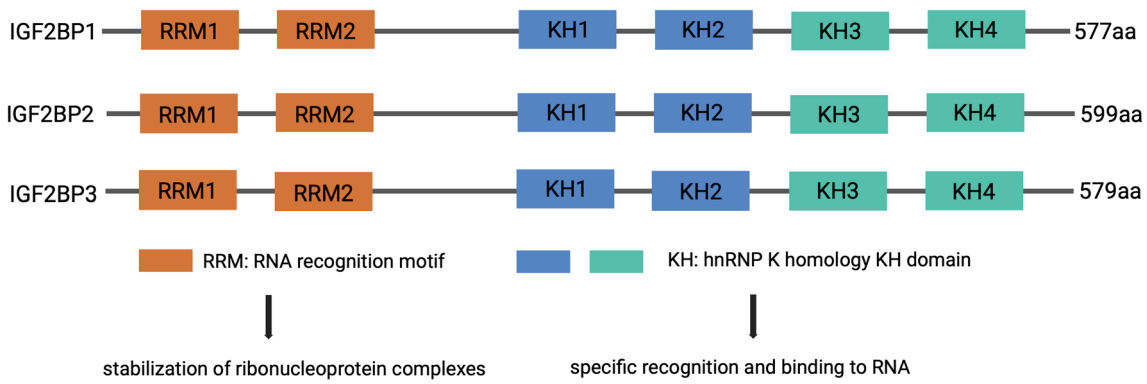

Fig. 1 Features and functions of domains in IGF2BPs. The IGF2BP family comprises two N-terminal RNA recognition motifs (RRMs) and four C-terminal hnRNP K homology (KH) domains. The KH domains are chiefly involved in specific recognition and binding to RNA, while the RRM domains contribute significantly to the stabilization of ribonucleoprotein complexes (RNPs). Created in BioRender. Sun, Y. (2024) https://BioRender.com/w47h805

The interaction between m6A modification and IGF2BPs

m6A modification is the predominant form of RNA modification in eukaryotes, dynamically influencing the post-transcriptional fate of modified RNA molecules under both physiological and pathological conditions [45, 46]. It is involved in various human diseases, including metabolic diseases, cardiovascular diseases, and particularly in human cancers [47]. This modification is catalyzed by methyltransferases such as methyltransferase-like protein 3 (METTL3) [48], METTL14 [49], and METTL16 [50], and can be reversed by demethylases like fat mass and obesity-associated protein (FTO) [51] and α-ketoglutarate-dependent dioxygenase alk B homolog 5 (ALKBH5) [52]. m6A-modified RNA is recognized by a group of proteins known as "readers," which include YT521-B homology domain family proteins (YTHDF1/2/3) [53], YT521-B homology domain containing 1 and 2 (YTHDC1/2) [54, 55], and IGF2BP1/2/3 [24]. The majority of m6A sites are located within the consensus motif DRACH (where D = G/A/U, R = G/A, H = A/U/C) [56], and are often found in the vicinity of stop codons [57, 58].

YTHDF2, the first identified m6A reader, facilitates mRNA degradation by recruiting the CCR4-NOT deadenylase complex [59]. In contrast, YTHDF1 promotes mRNA translation through its interaction with the translation initiation factor eIF3 [60]. YTHDF3 displays a dual role, participating in mRNA decay in conjunction with YTHDF2 and enhancing the translation of methylated RNA in partnership with YTHDF1 [61]. IGF2BPs, as single-stranded RNA-binding proteins, selectively recognize m6A sites via their third and fourth KH domains (KH3-4), markedly enhancing mRNA stability [24]. Mutations in the KH3-4 domains abrogate the m6A-reading function of IGF2BPs, highlighting the essential role of these domains in m6A recognition [24]. Additionally, IGF2BPs preferentially recognize m6A-modified mRNAs and further promote their stability and potential translation by recruiting other RNA stabilizers such as ELAV-like RNAbinding protein 1 (ELAVL1; also known as HuR), matrin 3 (MATR3) and poly(A)-binding protein cytoplasmic 1 (PABPC1) [24].

The interaction between IGF2BPs and ncRNAs

The interactions between IGF2BPs and ncRNAs manifest in several aspects as depicted in Fig. 2: (a) The IGF2BPS-ncRNA binary complexes modulate the degradation of target mRNA (Fig. 2A). On the one hand, lncRNAs/circRNAs act as scaffolds that facilitate the association between IGF2BPs and targeted mRNAs, thereby stabilizing the targeted mRNAs [27]. On the other hand, lncRNAs/circRNAs can interfere with the mRNA binding capability of IGF2BPs by competitively binding to these proteins, leading to destabilization of the target mRNAs [30]. (b) The IGF2BP-ncRNA binary complexes regulate their own metabolism through dynamic interplay (Fig. 2B). Generally, IGF2BPs enhance the stability of lncRNAs and circRNAs by binding to them [10], but they can also induce destabilization by recruiting the CCR4-NOT1 deadenylase complex [62]. Similarly, lncRNAs and circRNAs often prevent the degradation of IGF2BPs by inhibiting ubiquitination. Specifically, ncRNAs interact with IGF2BP proteins to suppress ubiquitination mediated by E3 ubiquitin ligases or to recruit deubiquitinating enzymes [63, 64]. However, in certain cases, these ncRNAs facilitate IGF2BP degradation by promoting ubiquitination through the recruitment of E3 ubiquitin ligases [65]. (c) The expression of IGF2BPs is modulated by miRNAs and the competing endogenous RNA (ceRNA) mechanism (Fig. 2C). The specific literature supporting these regulatory mechanisms will be discussed in detail later in the text, providing comprehensive references to studies that substantiate each mechanism.

The IGF2BPS-ncRNA binary complexes modulate the degradation of target mRNA

As detailed in Table 1, the formation of binary complexes between IGF2BPs and ncRNAs, particularly lncRNAs and circRNAs, is instrumental in the modulation of target mRNA degradation, thereby contributing to the regulation of malignant behaviors in cancer cells.

Enhancing the stability of target mRNA

In breast cancer, lncRNA KB-1980E6.3 and circCD44 have been shown to bind to IGF2BP1 and IGF2BP2, respectively, thereby enhancing breast cancer stem cell characteristics and promoting cell proliferation, migration, invasion, and tumorigenesis by stabilizing *c-Myc* mRNA [27, 66]. Similarly, IGF2BP2 also binds to lncRNA PACERR and circMYO1C in pancreatic ductal adenocarcinoma, modulating the tumor immune microenvironment by enhancing mRNA stability of *KLF12* and *PD-L1*, respectively [67, 68]. In gastric cancer, the pathways involving lncRNA GHET1/IGF2BP1/*c-Myc*, LINC01559/IGF2BP2/*ZEB1*, and circARID1A/IGF2BP3/*SLC7A5* promote cell proliferation by enhancing the mRNA stability of *c-Myc*, *ZEB1*, and *SLC7A5*, respectively [69–71]. In lung adenocarcinoma, circXPO1 and circMMP2 interact with IGF2BPs to augment the mRNA stability of CTNNB1 and FOXM1, thereby enhancing cell proliferation, invasion, and migration [72, 73]. In colorectal cancer (CRC), IGF2BP2 collaborates with LINC00460 and circNSUN2 to promote metastasis by stabilizing mRNA of *HMGA1* and *HMGA2*, enhancing their expression [74, 75]. Additionally, circITGB6

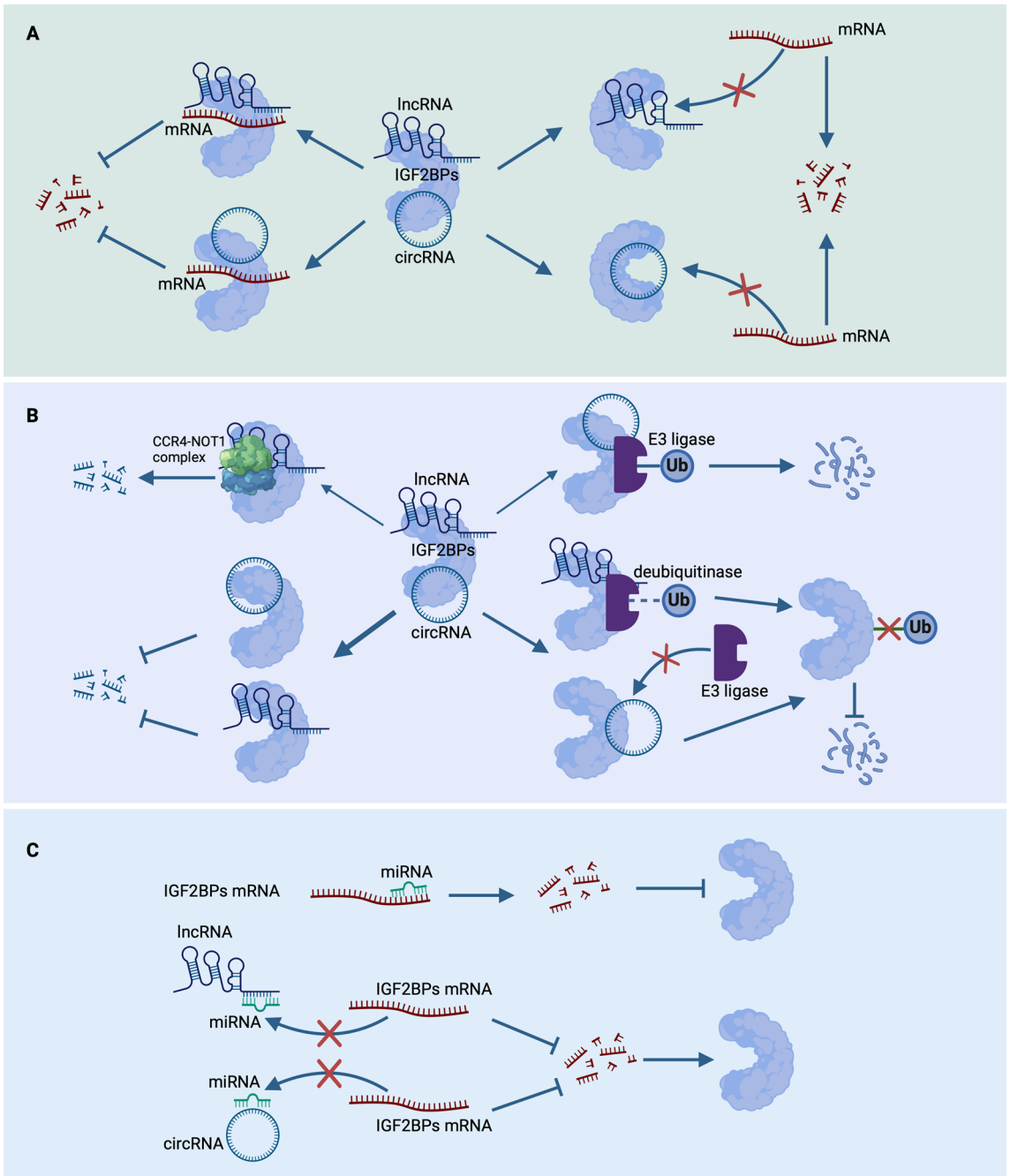

Fig. 2 The interaction between IGF2BPs and ncRNAs. **A** IGF2BPs-ncRNA binary complexes influence mRNA stability through two main pathways: lncRNAs/circRNAs can serve as scaffolds to stabilize target mRNAs by enhancing IGF2BPs association, or they may destabilize mRNAs by competitively binding to IGF2BPs, thereby reducing their mRNA affinity. **B** These complexes also regulate IGF2BP metabolism dynamically. IGF2BPs typically increase ncRNA stability by binding, though they can also recruit the CCR4-NOT1 complex to promote ncRNA degradation. In turn, lncRNAs and circRNAs often protect IGF2BPs from ubiquitination, but in certain scenarios, they facilitate IGF2BP degradation via E3 ligase-mediated ubiquitination. **C** miRNAs and the ceRNA mechanism further modulate IGF2BP expression. Created in BioRender. Sun, Y. (2024) https://BioRender.com/y07q007

promotes epithelial-mesenchymal transition (EMT) and metastasis in CRC by enhancing IGF2BP3-mediated *PDPN* mRNA stability [76]. In prostate cancer, lncRNA PCAT6 and circARHGAP29 increase the stability of *IGF1R* and *LDHA* mRNA, respectively, by reinforcing their interactions with IGF2BP2, contributing to bone

Table 1 Modulation of mRNA degradation by IGF2BPS-ncRNA binary complexes in cancers

lncRNAs/circRNAs	IGF2BPs	Target mRNA	mRNA outcome	Cancer type	Cellular function	Ref
KB-1980E6.3	IGF2BP1	*c-Myc*	Stable	Breast cancer	Maintenance of stem cells self-renewal	[66]
FGF13-AS1	IGF2BP1	*c-Myc*	Unstable	Breast cancer	Inhibition of glycolysis and stemness properties	[31]
GHET1	IGF2BP1	*c-Myc*	Stable	Gastric carcinoma	Promotion of proliferation	[69]
THOR	IGF2BP1	*c-Myc*	Stable	Retinoblastoma	Promotion of cell growth and migration, apoptosis resistance	[81]
LINC01093	IGF2BP1	*GLI1*	Unstable	Hepatocellular carcinoma	Suppression of proliferation and metastasis	[86]
LINC02428	IGF2BP1	*KDM5B*	Unstable	Hepatocellular carcinoma	Suppression of proliferation and metastasis	[87]
circCMTM3	IGF2BP1	*PARK7*	Stable	Hepatocellular carcinoma	Ferroptosis resistance	[82]
circXPO1	IGF2BP1	*CTNNB1*	Stable	Lung adenocarcinoma	Promotion of proliferation and invasion	[72]
circCRIM1	IGF2BP1	*HLA-F*	Unstable	Non-small cell lung cancer	Repression of immune evasion	[89]
circPTPRA	IGF2BP1	*MYC, FSCN1*	Unstable	Bladder cancer	Suppression of proliferation, migration and invasion	[88]
circFAM13B	IGF2BP1	*PKM2*	Unstable	Bladder cancer	Repression of immune evasion and glycolysis	[30]
PACERR	IGF2BP2	*KLF12* *c-Myc*	Stable	Pancreatic ductal adenocarcinoma	Promotion of proliferation, invasion and migration, increased M2-polarized cells	[67]
LINC00460	IGF2BP2	*HMGA1*	Stable	Colorectal cancer	Promotion of proliferation and metastasis	[74]
LINC01559	IGF2BP2	*ZEB1*	Stable	Gastric cancer	Promotion of proliferation, migration and EMT	[70]
PCAT6	IGF2BP2	*IGF1R*	Stable	Prostate cancer	Promotion of invasion, migration, proliferation and bone metastasis	[77]
circARHGAP29	IGF2BP2	*LDHA*	Stable	Prostate Cancer	Docetaxel resistance, enhancement of aerobic glycolysis	[78]
circMYO1C	IGF2BP2	*PD-L1*	Stable	Pancreatic ductal adenocarcinoma	Enhancement of immune escape	[68]
circITGB6	IGF2BP2	*FGF9*	Stable	Ovarian cancer	Enhancement of M2 polarization of TAMs, cisplatin resistance	[83]
circCD44	IGF2BP2	*c-Myc*	Stable	Triple-negative breast cancer	Promotion of proliferation, migration, invasion	[27]
circNSUN2	IGF2BP2	*HMGA2*	Stable	Colorectal cancer	Promotion of liver metastasis	[75]
circTNPO3	IGF2BP2	*SERPINH1*	Unstable	Clear cell renal cell carcinoma	Suppression of proliferation, migration and metastasis	[90]
DMDRMR	IGF2BP3	*CDK4*	Stable	Clear cell renal cell carcinoma	Promotion of tumor growth and metastasis	[79]
LINC00958	IGF2BP3	*E2F3*	Stable	Endometrial carcinoma	Promotion of proliferation, migration, invasion	[84]
ZNF674-AS1	IGF2BP3	*CA9*	Stable	Neuroblastoma	Cisplatin resistance, promotion of proliferation	[85]
MYO16-AS1	IGF2BP3	*HK2*	Unstable	Lung adenocarcinoma	Suppression of migration, invasion and glucose metabolism reprogramming	[91]
circMMP2	IGF2BP3	*FOXM1*	Stable	Lung adenocarcinoma	Promotion of proliferation and migration	[73]
circARID1A	IGF2BP3	*SLC7A5*	Stable	Gastric cancer	Promotion of proliferation	[71]
circZBTB44	IGF2BP3	*HK3*	Stable	Renal carcinoma	Promotion of proliferation and migration	[80]
circITGB6	IGF2BP3	*PDPN*	Stable	Colorectal cancer	Promotion of EMT and metastasis	[76]
circTNPO3	IGF2BP3	*MYC*	Unstable	Gastric cancer	Suppression of proliferation and metastasis	[92]

metastasis and enhanced aerobic glycolysis [77, 78]. In renal carcinoma, IGF2BP3 aids cell proliferation and metastasis by increasing mRNA stability of *CDK4* and *HK3* via interactions with lncRNA DMDRMR and circZ-BTB44, respectively [79, 80]. In retinoblastoma, lncRNA THOR promotes malignant transformation by enhancing cell growth, migration, and resistance to apoptosis, facilitated through the upregulation of *c-Myc* expression by IGF2BP1 [81]. In hepatocellular carcinoma (HCC), circC-MTM3 facilitates tumorigenesis by inhibiting ferroptosis, a process that involves recruiting IGF2BP1 to enhance the stability of *PARK7* [82]. In ovarian cancer, circITGB6 forms a ternary complex with IGF2BP2 and *FGF9*, stabilizing *FGF9* mRNA, which induces cisplatin resistance and M2 polarization in tumor-associated macrophages [83]. In endometrial carcinoma, IGF2BP3 upregulates *E2F3* expression by interacting with LINC00958, thereby promoting cell proliferation, migration and invasion [84]. In neuroblastoma, lncRNA ZNF674-AS1 increases cisplatin resistance and promotes cell proliferation by engaging IGF2BP3 to enhance *CA9* mRNA stability [85].

Reducing the stability of target mRNA

In breast cancer, lncRNA FGF13-AS1 disrupts the interaction of IGF2BP1 with *c-Myc* mRNA, thereby impairing glycolysis and stemness properties by reducing *c-Myc* mRNA stability [31]. In hepatocellular carcinoma, the mRNA-binding activity of IGF2BP1 is blocked by LINC01093 and LINC02428, preventing its association with *GLI1* and *KDM5B* mRNA, and thus inhibiting proliferation and metastasis [86, 87]. In bladder cancer, circFAM13B competitively binds to the KH3-4 domains of IGF2BP1, thereby diminishing its association with *PKM2*, leading to a decrease in the stability of *PKM2* mRNA and the subsequent inhibition of the glycolysis-driven acidic tumor microenvironment and improvement of immunotherapy (PD-1 antibodies) sensitivity [30]. In bladder cancer, circPTPRA competes with IGF2BP1 for binding to its K3-4 domains, disrupting the recognition of m6A-modified *MYC* and *FSCN1*, and subsequently inhibiting IGF2BP1-induced proliferation, migration, and invasion [88]. In non-small cell lung cancer (NSCLC), circCRIM1 hinders immune evasion by interfering with IGF2BP1, leading to the destabilization of *HLA-F* mRNA [89]. In clear cell renal cell carcinoma, circTNPO3 potently suppresses cell proliferation and migration by directly binding to IGF2BP2 and promoting the degradation of *SERPINH1* mRNA [90]. In lung adenocarcinoma, by competitively binding to IGF2BP3, lncRNA MYO16-AS1 compromises the protein's interaction with *HK2* mRNA, reducing *HK2* mRNA stability and subsequently suppressing migration and invasion through inhibition of glucose metabolism reprogramming [91]. In gastric cancer, circTNPO3 serves as a protein decoy for IGF2BP3 binding to its KH regions, competitively interfering with its stabilization of *MYC* mRNA and thereby suppressing cell proliferation and migration [92].

The IGF2BP-ncRNA binary complexes regulate their own metabolism through dynamic interplay

Regulating the stability of ncRNAs

IGF2BPs generally enhance the stability of lncRNAs/circRNAs by binding to them, although they can also lead to the degradation of these molecules under specific circumstances (Fig. 3). In hepatocellular carcinoma, IGF2BP1/3 stabilizes both lnc-CTHCC and LINC01138, thereby enhancing cell proliferation, migration, invasion, and metastasis [93, 94]. Furthermore, IGF2BP1 also stabilizes circMDK and lncRNA MIR4435-2HG via m6A modification, each contributing to HCC cell proliferation and stem-cell characteristics [95, 96]. IGF2BP2 participates in the stabilization of lncRNA ARHGAP5-AS1 through m6A modification, which facilitates the proliferation and metastasis of HCC [97]. IGF2BP3, by

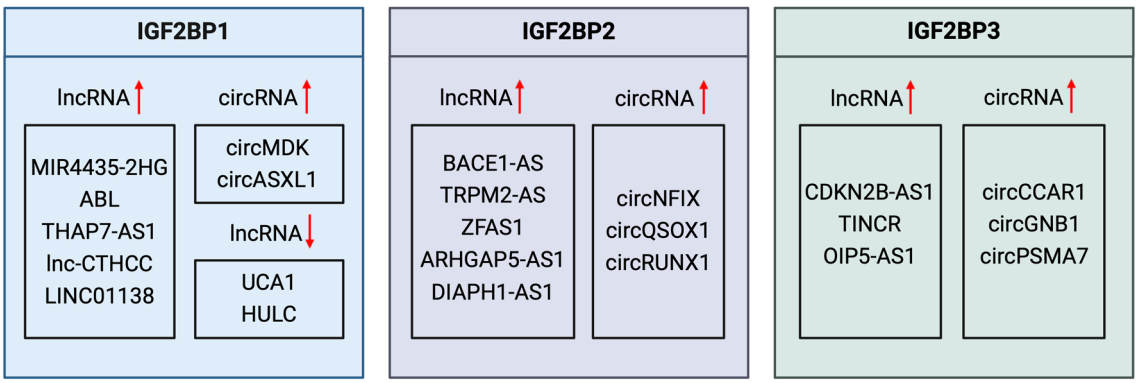

Fig. 3 The role of IGF2BPs in regulating the stability of lncRNAs/circRNAs. Created in BioRender. Sun, Y. (2024) https://BioRender.com/v35u511

stabilizing m6A-modified circCCAR1, not only accelerates tumor growth and metastasis but also facilitates resistance to anti-PD1 immunotherapy in HCC [98]. This occurs as circCCAR1 is internalized by CD8 + T cells and stabilizes the PD-1 protein, leading to T-cell dysfunction [98]. In gastric cancer, IGF2BP1 maintains the stability of lncRNA ABL, conferring resistance to apoptosis and multidrug resistance, and stabilizes lncRNA THAP7-AS1 to promote tumor growth, invasion, and metastasis [99, 100]. The binding of IGF2BP3 to lncRNA OIP5-AS1 through m6A modifications stabilizes OIP5-AS1, which in turn enhances gastric cancer cell proliferation, migration, invasion, EMT, and glycolysis [101]. In ovarian cancer, circASXL1, with its stability and expression enhanced by METTL3/IGF2BP1-mediated m6A modifications, promotes cell proliferation, migration, and invasion [102]. In addition, circNFIX promotes ovarian cancer cell proliferation, metastasis, and immune evasion, with its stability and expression dependent on IGF2BP2 recognition via m6A modification [103]. In colorectal cancer, IGF2BP2 binds and stabilizes lncRNA BACE1-AS and ZFAS1, as well as circQSOX1, enhancing the malignant properties of CRC cells along with resistance to apoptosis, aerobic glycolysis, and immune evasion [104–106]. In nasopharyngeal carcinoma, lncRNA TINCR is upregulated due to its interaction with IGF2BP3, which stabilizes its expression and promotes cell progression and resistance to cisplatin [107]. The m6A modification of lncRNA DIAPH1-AS1 confers enhanced stability by engaging IGF2BP2 recognition, which consequently fosters the growth and metastatic capabilities of nasopharyngeal carcinoma cells [108]. In gallbladder cancer, the m6A-modified lncRNA TRPM2-AS, recognized by IGF2BP2, exhibits high stability and expression, and its upregulation is linked to tumor angiogenesis [109]. In esophageal squamous cell carcinoma, circRUNX1 stimulates proliferation and metastasis, and its interaction with IGF2BP2 prevents its degradation, enhancing oncogenic effects [10]. In renal clear cell carcinoma, the interaction between lncRNA CDKN2B-AS1 and IGF2BP3 increases the stability of CDKN2B-AS1, thereby promoting cell proliferation, migration, and invasion [25]. In glioma, circGNB1 enhances stem cell proliferation, invasion, and neurosphere formation through its interaction with IGF2BP3, which stabilizes circGNB1 [110]. In bladder cancer, IGF2BP3 binds to the m6A-modified circPSMA7, increasing its expression and promoting proliferation and metastasis by regulating the cell cycle and EMT [111].

However, in hepatocellular carcinoma, IGF2BP1 facilitates the degradation of lncRNA HULC by serving as an adaptor to recruit the CCR4-NOT deadenylase complex, coordinated by CNOT1, a novel interaction partner of IGF2BP1 [112]. Similarly, in breast cancer, IGF2BP1 binds to lncRNA UCA1 through the "ACACCC" motifs present in UCA1 and facilitates its degradation by recruiting the CCR4-NOT deadenylase complex [62].

Regulating the degradation of IGF2BPs protein

LncRNAs and circRNAs predominantly maintain IGF2BPs protein levels by inhibiting ubiquitination-mediated degradation, although they can also occasionally decrease protein levels by facilitating degradation, as demonstrated in Table 2. In ovarian cancer, lncRNA MCF2L-AS1 confers cisplatin resistance by activating the IGF2/MEK/ERK pathway, primarily through upregulation of IGF2BP1 [113]. In leukemia, circ_0003420 targets

Table 2 lncRNAs/circRNAs-mediated regulation of IGF2BPs protein levels in cancers

lncRNA/circRNA	IGF2BPs	IGF2BPs outcome	Target mRNA	Cancer type	Mechanism	Ref
MCF2L-AS1	IGF2BP1	Upregulated	*IGF2*	Ovarian cancer	Unknown	[113]
circ_0003420	IGF2BP1	Downregulated	*HOXB4, MYB, ALDH1A1*	Acute myeloid leukemia	Unknown	[114]
LINRIS	IGF2BP2	Upregulated	*MYC*	Colorectal cancer	Blocks ubiquitination (K139)	[115]
circEZH2	IGF2BP2	Upregulated	*CREB1*	Colorectal cancer	Blocks ubiquitination	[116]
DGUOK-AS1	IGF2BP2	Upregulated	*TRPM7*	Non-small cell lung cancer	Unknown	[117]
circNDUFB2	IGF2BP2	Downregulated	-	Non-small cell lung cancer	Facilitates ubiquitination of IGF2BP2 by recruiting TRIM25	[65]
LINC00901	IGF2BP2	Upregulated	*MYC*	Pancreatic cancer	Unknown	[118]
MNX1-AS1	IGF2BP3	Upregulated	-	Gallbladder cancer	Prevents ubiquitination by recruiting USP16	[64]
circNEIL3	IGF2BP3	Upregulated	*CDK4/6, CD44, c-MYC*	Glioma	Prevents HECTD4-mediated ubiquitination (K450) by competitive binding mechanism	[119]
circNFATC3	IGF2BP3	Upregulated	*CCND1*	Gastric cancer	Prevents TRIM25-mediated ubiquitination by competitive binding mechanism	[63]

IGF2BP1, inducing cell death and suppressing leukemia stem cell characteristics by markedly reducing IGF2BP1 levels [114]. In colorectal cancer, lncRNA LINRIS promotes MYC-driven glycolysis by stabilizing IGF2BP2, achieved by inhibiting K139 ubiquitination and preventing IGF2BP2 degradation via the autophagy-lysosome pathway [115]. In addition, circEZH2 interacts with IGF2BP2 to prevent its ubiquitination-dependent degradation, thereby enhancing the stability of *CREB1* mRNA and exacerbating CRC cell proliferation and migration [116]. In non-small cell lung cancer, the positive regulation of IGF2BP2 by lncRNA DGUOK-AS1 promotes growth and metastasis by enhancing TRPM7 mRNA stability in an m6A-dependent manner [117]. Conversely, circNDUFB2 enhances the association between TRIM25 and IGF2BP2, promoting the ubiquitination and degradation of IGF2BP2 and contributing to the activation of anti-tumor immunity in NSCLC [65]. In pancreatic cancer, LINC00901 increases cell growth and invasion by upregulating *MYC* expression through IGF2BP2 [118]. In gallbladder cancer, lncRNA MNX1-AS1 promotes cell proliferation and metastasis by inhibiting IGF2BP3 degradation via recruitment of deubiquitinase USP16, suppressing the Hippo signaling pathway [64]. In glioma, circNEIL3 promotes IGF2BP3 upregulation by inhibiting HECTD4-mediated K450 ubiquitination, enabling glioma stem cells to enhance immunosuppressive properties in tumor-associated macrophages [119]. Finally, circNFATC3 binds to IGF2BP3, preventing its ubiquitination by TRIM25 and thereby enhancing IGF2BP3's stability, which consequently stabilizes *CCND1* mRNA and promotes gastric cancer cell proliferation [63].

The expression of IGF2BPs is modulated by miRNAs and ceRNA mechanism

This regulatory process involves miRNAs binding to specific sites within the 3' untranslated region (3'UTR) of IGF2BPs. The miRNA binding sites in the 3'UTR of IGF2BPs, which are critical for this interaction, are depicted in Fig. 4.

Regulating the expression of IGF2BPs by miRNA

In hepatocellular carcinoma, miR-625, miR-196b, and miR-186 potently suppress the aggressive characteristics HCC cells by blocking proliferation, migration, and invasion, all of which are achieved by targeting IGF2BP1 [26, 120, 121]. Additionally, miR-216b suppresses hepatocellular carcinoma cell proliferation, migration, and

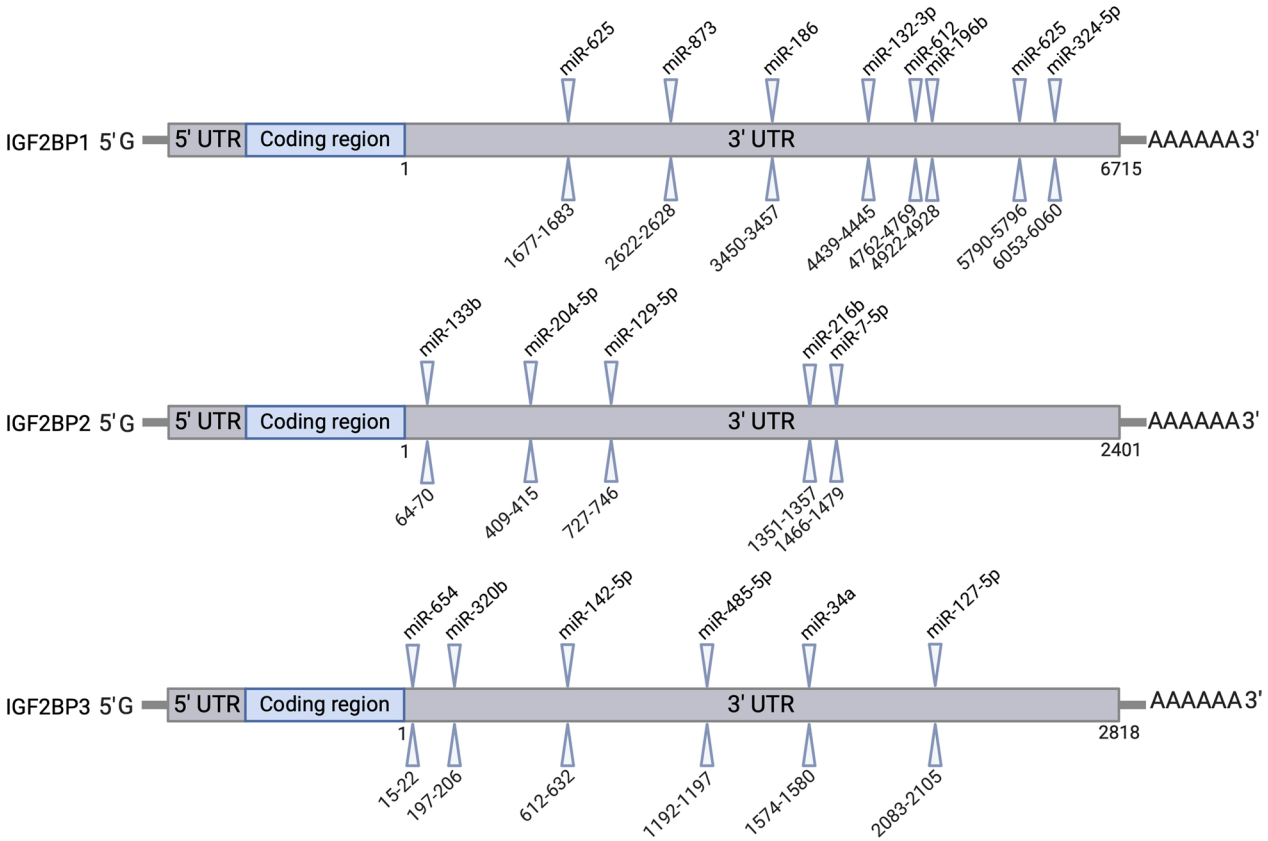

Fig. 4 The miRNA binding sites in the 3'UTR of IGF2BPs. Created in BioRender. Sun, Y. (2024) https://BioRender.com/c78l309

invasion by downregulating IGF2BP2 expression [122]. In glioblastoma, miR-873 effectively inhibits cell proliferation, migration, and invasion by suppressing IGF2BP1 expression [123]. In gastric cancer, the tumor-suppressive miRNA miR-34a negatively regulates IGF2BP3, and its depletion significantly decreases cell proliferation and invasion [124].

Regulating the expression of IGF2BPs by ceRNA mechanism

In gastric cancer, lncRNA TRPM2-AS promotes cell proliferation, metastasis, and radioresistance by functioning as a microRNA sponge for miR-612, thereby modulating the derepression of IGF2BP1 [125]. In colorectal cancer, circEZH2 facilitates cell proliferation and migration by sponging miR-133b to upregulate IGF2BP2, which stabilizes CREB1 mRNA and accelerates CRC progression [116]. LINC00858 promotes colorectal cancer cell progression, tumor growth, and hepatic metastasis by targeting miR-132-3p, which in turn regulates IGF2BP1 [126]. In hepatocellular carcinoma, the linc01134/miR-324-5p/IGF2BP1, lncRNA SNHG1/miR-7-5p/IGF2BP2 and circ_0026134/miR-127-5p/IGF2BP3 signaling pathways are identified to be involved in the regulation of the proliferation, migration, and metastatic properties of HCC cells [127–129]. In thyroid cancer, lncRNA MALAT1 has been shown to enhance IGF2BP2 expression by competitively interfering with miR-204, thereby fostering the proliferation, migration, and invasion capabilities of thyroid cancer cells [130]. lncRNA OIP5-AS1 in glioblastoma enhances chemoresistance to temozolomide and promotes cell proliferation and apoptosis inhibition by sponging miR-129-5p, relieving its inhibition on IGF2BP2 [131]. Additionally, CircHIPK3 promotes glioma cell proliferation, invasion, and tumor progression in vivo by enhancing IGF2BP3 expression through its interaction with miR-654 [132]. In head and neck squamous cell carcinoma, IGF2BP3 plays a crucial role, with its expression positively regulated by LINC00460, Linc01224, and circIGHG, each binding to respective miRNAs (miR-320b, miR-485-5p, and miR-142-5p) to modulate IGF2BP3 levels [133–135].

Conclusions and perspectives

The extensive study of IGF2BPs underscores their multifaceted roles in cancer biology, revealing significant implications for tumor progression, metastasis, angiogenesis, resistance to apoptosis, maintenance of stemness, and drug resistance. The oncogenic functions of IGF2BPs are well-established, and their upregulation is often associated with a poor prognosis in various cancer types [12, 13, 136]. The IGF2BP family of proteins is integral to RNA biology, engaging in intricate interactions with mRNA and a variety of ncRNAs, including circRNAs and lncRNAs. Their structural features, such as RNA recognition motifs and hnRNP K homology domains, endow them with specific RNA-binding capabilities that are crucial for their role in post-transcriptional gene regulation. Variations in their KH domains contribute to the differential RNA-binding specificities among family members, influencing their diverse roles in cancer progression and therapy response. The interaction between IGF2BPs and ncRNAs, particularly lncRNAs and circRNAs, adds a novel dimension to their regulatory functions. These ncRNAs can act as molecular scaffolds, competitive inhibitors, or regulatory targets of IGF2BPs, thereby modulating mRNA stability and impacting cancer cell behaviors. The regulatory mechanisms involving ceRNAs and miRNAs further complicate the control over IGF2BP expression, which is critical for cancer development.

The interaction between IGF2BPs and non-coding RNAs (ncRNAs) plays a critical role in the post-transcriptional regulation of target mRNA stability. However, there remains a fundamental question regarding the differential functional outcomes observed among various ncRNAs. Specifically, some ncRNAs act as scaffolds that stabilize mRNA by facilitating IGF2BPs binding, while others occupy the binding sites on IGF2BPs, thereby impeding their interaction with downstream target mRNAs. This dichotomy suggests that ncRNAs may possess structural or chemical modifications, such as m6A modifications, that govern their specificity as scaffolds or inhibitors. Investigating the role of specific sequences or structural regions within ncRNAs in determining their function as scaffolds or antagonists of IGF2BPs could provide insights into the mechanisms underlying mRNA stability regulation. Furthermore, the variability in ncRNAs' ability to recruit different protein modifiers, such as E3 ubiquitin ligases or deubiquitinases, hints at a potential sequence- or structure-specific determinant within the ncRNAs that selectively attracts these proteins. Future studies should aim to identify the specific sequence motifs or structural elements within ncRNAs that dictate the recruitment of particular protein modifiers. Such findings could significantly enhance our understanding of the role of ncRNAs in the broader regulatory landscape of protein stability and turnover.

In summary, our findings emphasize the complexity of the ncRNA-mediated regulatory networks involving IGF2BPs. The distinct mechanisms by which ncRNAs influence IGF2BPs' regulation of mRNA stability and their selective recruitment of protein modifiers point to a sophisticated layer of specificity likely driven by molecular features within ncRNAs. Future research should prioritize the elucidation of the contributions of specific sequences, structural motifs, and post-transcriptional

modifications, such as m6A, within ncRNAs, potentially paving the way for more targeted therapeutic strategies involving these regulatory interactions.

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Y.S. conceived the study and wrote the original draft. J.W. created the tables and drew the figures. W.S., C.L. and X.S. supervised the study and revised the manuscript. All authors read and approved the final manuscript.

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Declarations

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