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The IGF2BP family of RNA binding proteins links epitranscriptomics to cancer

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ABSTRACT

RNA binding proteins that act at the post-transcriptional level display a richness of mechanisms to modulate the transcriptional output and respond to changing cellular conditions. The family of IGF2BP proteins recognize mRNAs modified by methylation and lengthen their lifecycle in the context of stable ribonucleoprotein particles to promote cancer progression. They are emerging as key 'reader' proteins in the epitranscriptomic field, driving the fate of bound substrates under physiological and disease conditions. Recent developments in the field include the recognition that noncoding substrates play crucial roles in mediating the pro-growth features of IGF2BP family, not only as regulated targets, but also as modulators of IGF2BP function themselves. In this review, we summarize the regulatory roles of IGF2BP proteins and link their molecular role as m^{6}A modification readers to the cellular phenotype, thus providing a comprehensive insight into IGF2BP function.

1. Introduction

The insulin-like growth factor 2 (IGF2) mRNA binding protein family of proteins (IMPs/IGF2BPs, also labeled with different names derived from the different target mRNAs and contexts where they were identified (VICKZ, ZBP1, CRD-BP, KOC or Vg1RBP/Vera in Xenopus)), is involved in a variety of cellular processes, including development, growth, and stemness. In addition, mutations and overexpression of these proteins are associated with the appearance of a high number of human tumors. IGF2BP1 was the first family member to be characterized as a protein that stabilized *c-myc* mRNA in vitro through binding to the coding region stability determinant (CRD) [1]. After that, IGF2BP1 was also found to control *ACTB* mRNA localization through binding to a "zipcode" element in its 3′UTR [2], thereby ensuring localized translation of ß-actin at the cell periphery and neuronal outgrowth in a IGF2BP1 phosphorylation-dependent manner [3]. IGF2BP2 was first identified as binding to the 5′UTR of the IGF2 mRNA [4], and thereby promoting IGF2 translation by internal ribosomal entry [5]. The human IGF2BP3 was initially identified in a screen for highly expressed genes in pancreatic cancer [6]. Despite some specific RNA binding abilities and distinct affinities for particular targets, the canonical function for all three paralogs is the association to the 3′ untranslated region (3′UTR) of a number of target mRNAs to influence their localization, stability and translation. These RNA-binding proteins (RBPs) are highly expressed during development and in cancer, generally correlating with an aggressive malignant phenotype. They orchestrate the composition of RNA processing effector complexes by conferring sequence specificity and target mRNAs that are directly involved in the secretory pathway, the insulin/IGF pathway, the metabolic control of multiple tissues, or the ubiquitin-dependent protein degradation pathway, among other cellular axes. The evolution, structure and RNA binding affinity of this family of proteins have been excellently reviewed earlier [7,8], and so we overview these topics briefly here. This review's primary focus is on the current knowledge about the ability of IGF2BPs to sense RNA modifications and their consequences in downstream regulatory mechanisms and cell biology in general. We discuss the role of IGF2BPs as m^{6}A readers and how it might contribute to key roles of the proteins in tumorigenic settings. Remarkably, recent studies have highlighted their intense crosstalk with noncoding transcripts, and details of prominent examples of regulation are provided. Overall, the involvement of IGF2BPs as fine-tuners of RNA metabolism is far from being completely understood, as the variety of targets and mechanisms of regulation increase.

2. The IGF2BP protein family structure and binding affinity

IGF2BP1, 2 and 3 are the three members of a highly conserved RNA-binding protein (RBP) family that regulates a spectrum of processes in RNA lifecycle, including localization, translation control, stability, and

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Nomenclature

ABCF1	Binding Cassette Subfamily F Member 1
ALKBH	Alpha-ketoglutarate-dependent dioxygenase
ATF4	Activating Transcription Factor 4
CBX8	Chromobox protein homolog 8
eIF3h	Eukaryotic translation initiation factor 3 subunit h
eIF4E	Eukaryotic translation initiation factor 4E
FEN1	Flap endonuclease-1
FOXK1	Forkhead Box K1
FTO	FTO Alpha-Ketoglutarate Dependent Dioxygenase
GHET1	Gastric Carcinoma Proliferation Enhancing Transcript 1
HCG11	HLA Complex Group 11
HMGA2	High Mobility Group AT-Hook 2
hnRNP	Heterogeneous nuclear ribonucleoprotein
IGF2BP	Insulin-like growth factor-2 mRNA-binding proteins
IRES	Internal Ribosomal Entry Site
lncRNA	Long noncoding RNA
m^{6}A	N6-methyladenosine
MATR3	Matrin 3
METTL3	Methyltransferase 3, N6-Adenosine-Methyltransferase Complex Catalytic Subunit
miRNA	microRNA
mRNP	Messenger ribonucleoprotein
PABPC1	Poly(A) Binding Protein Cytoplasmic 1
PDLIM7	PDZ and LIM domain protein 7
PEG10	Paternally Expressed 10
RBP	RNA binding protein
RNP	Ribonucleoprotein
RPSAP52	Ribosomal Protein SA Pseudogene 52
RRM	RNA recognition motif
SG	Stress Granule
SNP	Single Nucleotide Polymorphisms
SOX2	SRY (Sex determining region Y)-box 2
tRNA	Transfer RNA
WTAP	WT1 Associated Protein
YBX1	Y-Box Binding Protein 1
YTHDC1–2	YTH Domain Containing Protein 1–2
YTHDF1–3	YTH Domain N6-Methyladenosine RNA Binding Protein 1–3
YTHDF3	YTH N6-Methyladenosine RNA Binding Protein 3

metabolism. IGF2BPs play a pivotal role in post-transcriptional regulation of RNAs in the context of ribonucleoprotein complexes (RNPs), which contain target mRNAs together with RNA-binding proteins, and may also include noncoding RNAs (ncRNAs), such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs). Although primarily observed in the cytoplasm, the presence of a nuclear export signal suggests that they associate with some of their target RNAs in the nucleus, and a minor fraction of the protein is certainly detected in the nucleus [3,9,10]. In the cytoplasm, IGF2BPs form granule-like mRNP structures often located in the perinuclear region that determine mRNA fate. Since IGF2BP-containing RNP may include exon-junction complex factors but not eIF4E or eIF4G [11,12], these IGF2BP-RNP targets were initially linked to non-translating cytoplasmic mRNPs, suggesting that IGF2BPs predominantly associate with mRNAs that enter the cytoplasm and have not yet undergone their first round of translation, thereby preventing their decay. Further research has provided a more complete picture, and although the exact molecular mechanism by which IGF2BPs recognize and regulate expression of their targets remains to be fully elucidated, their role has been broadened to include the regulation of mRNA stability, translation and localization (this latter aspect specially relevant in neuronal cells, where IGF2BPs are located at the edges of neurites in developing neurons) [13–15].

The three IGF2BP proteins' structures are notably similar in order and spacing of domains including a tandem of two RNA-recognition motifs (RRMs) and two tandems of two KH domains in the N- and C-terminal regions respectively [7] (Fig. 1). The overall amino acid sequence identity between all three proteins is 56 %, with greater degree of similarity within protein domains. IGF2BP1 and IGF2BP3 display the closest similarity, showing 73 % amino acid sequence identity with each other [16]. The three mammalian IMP paralogs belong to the family of zipcode-binding proteins, which include the *Vegetal-1* mRNA binding protein (Vg1RBP/Vera) in *Xenopus laevis*, and the zipcode-binding protein 1 in chickens. In *Drosophila*, a protein lacking the *N*-terminal RRM domain but comprising four KH-domains has been proposed to be *Drosophila* IGF2BP (*dIIMP*) [17].

All members of the IGF2BPs are shown to bind RNA, irrespective of the organism or tissue in which they are expressed [18]. In vitro studies have proved that the KH-domains are principally responsible for RNA-binding, whereas RRM-domains would contribute to the stabilization of the IGF2BP-RNA complexes with half-life greater than 2 h [19,20]. This reveals that IGF2BPs play a vital role in promoting the

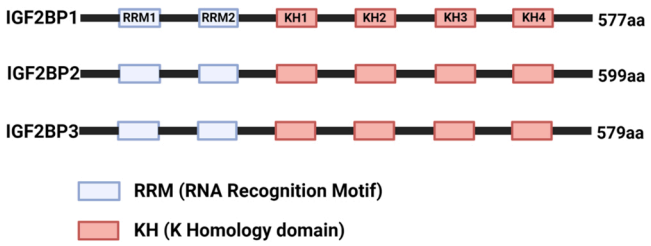

Fig. 1. Structure of IGF2BP family of proteins. The three IGF2BP paralogs are highly similar, with two N-terminal RRMs and four C-terminal hnRNPK Homology (KH) domains, which are characterized by a conserved αβ-topology that can be structurally and functionally included in two di-domains (KH1–2 and KH3–4) [195]. Association to single-stranded RNA is enhanced by the KH domains [14], whereas the RRMs are thought to stabilize the RNA-protein interactions [19]. In addition, KH domains are necessary for recognition of the m^{6}A mark [24] and recruitment to stress granules [20]. Created with BioRender.com.

formation of the protein-RNA complexes with high affinity [19]. When considering the binding affinities of each protein, it is not surprising that the complex array of RNA binding domains present in the IGF2BP paralogs might dictate a not completely overlapping preference for RNA binding motifs by each individual protein. Studies to address the binding affinity of each paralog have used both individual domains [21–23] as well as full-length proteins [24–28] for target RNA identification. This fact, together with the variety of techniques employed (mostly cross-linking and immunoprecipitation (CLIP)-related approaches for full-length protein:RNA interaction identification in living cells versus the use of systematic evolution of ligands by exponential enrichment (SELEX) experiments for single domain analysis in vitro), and possibly differences in context have rendered results that only partially overlap. KH domains recognize short (3–6 nucleotides) motifs through a characteristic flexible loop, often with cooperation between domains [29], and most studies with full-length proteins report a consensus sequence containing CA-rich motifs for all three paralogs (reviewed in [8]). In addition, a PAR-CLIP approach reported a common UGGAC motif [24]. By contrast, the study of truncated proteins has revealed a preference for bipartite motifs separated by a linker region of 10–25 nucleotides, similar to the zipcode element originally identified in the binding of

IGF2BP1 to *ACTINB* mRNA [2]. In this latter scenario, and despite specific preferences of each protein as revealed by SELEX approaches, the KH3 domain would bind to CA-rich motifs with weak nucleotide discrimination, whereas KH4 would bind to nearby motifs containing a central GG [22,23,30]. Compared to the fairly well-characterized KH3 and 4, the role of the KH1–2 and RRM1–2 domains in RNA recognition is unclear [8]. Finally, the relevance of protein-protein interactions in refining IGF2BPs affinity for specific RNA targets in varying cellular contexts is also incompletely understood [22,25], as is the role that formation of homo-and hetero-oligomers might have in protein function [19].

Of note, transcriptome-wide studies aiming at determining RNA preferences for IGF2BPs have helped uncover targets that mediate key functions of individual family members in different cellular environments, including carcinogenesis. For example, integrin *ITGB5* and *BCL2* mRNAs were identified in eCLIP experiments for IGF2BP1 and found to mediate the pro-survival and adhesion features linked to IGF2BP1 in human pluripotent stem cells [26]. iCLIP-seq experiments for IGF2BP3 uncovered the oncogenes MYC and CDK6 as direct targets mediating IGF2BP3-associated proliferation of hematopoietic progenitors and survival of B-ALL cells [27]. In pancreatic ductal adenocarcinoma cells, iCLIP-seq approaches revealed a potential synergistic function of IGF2BP3 with RISC complex to regulate targets involved in cancer-related pathways, including focal adhesions and cell migration [28].

Altogether, further work will be required to fully understand the specifics of RNA binding for each IGF2BP1–3, since their ability to regulate a different pool of target RNAs is the key feature that governs their related but distinct contributions to physiopathology.

3. The physiological role of IGF2BPs and their dysregulation in cancer

Evidence thus far indicates that the IGF2BPs are essential players of cell growth, stem cell maintenance, and differentiation during development. Their critical roles are highlighted by the fact that their dysregulation may lead to diseases such as diabetes [31], insulin resistance [32], obesity [33] or neurological disorders (reviewed in [34]). All members of the IGF2BP family are highly expressed in early development and carcinogenesis, the latter often related with poor prognosis, tumor progression and tumor cell hierarchy establishment [17]. IGF2BP1 and 3 are expressed at very low levels in adult tissues and are *bona fide* oncofetal proteins, whereas IGF2BP2 expression is maintained in most normal tissues into adulthood and is involved in metabolic processes (reviewed in [31,35]). Indeed, several loss-of-function and gain-of-function models have been used to investigate the physiological role of IGF2BPs and show their association with the regulation of cell metabolism. For example, *Igf2bp1*$^{-/-}$ mice are 40 % smaller, with small sized organs caused by hypoplasia, complete loss of villi and modification of the composition of the intestinal extracellular matrix [36]. This phenotype is similar to that seen in the transcription factor HMGA2-deficient mice, a major regulator of IGF2BP2 [37]. In the surviving adult mice, the histological changes become gradually normalized, indicating *Igf2bp1*$^{-/-}$ mice show delayed organ maturation. Interestingly, human genome-wide association studies (GWAS) proposed IGF2BP2 as a type-2 diabetes associated gene, emerging as a direct mammalian target of rapamycin (mTOR) substrate that coordinates cellular function and nutrient metabolism [38]. Collectively, the data collected from *Igf2bp2*$^{-/-}$ mice studies show that IGF2BP2 is involved in the metabolism of glucose, protein, lipid and energy by controlling the translation of *UCP1* mRNA, among other mitochondrial components [33]. Of note, single nucleotide polymorphisms (SNPs) located in the second intron of *IGF2BP2*gene are associated with impaired insulin secretion. IGF2BP2 deficient mice displayed better metabolic traits, increased insulin sensitivity, improved glucose tolerance and a longer life-span compared to the control animals [39,40]. However, the detailed mechanism of the molecular function of IGF2BP2 in response to glucose remains incomplete. More recently, *Imp2*$^{-/-}$ mice have been shown to display reduced levels of the *CCL2* chemokine (a direct mRNA target of IGF2BP2), which results in poor monocyte recruitment and Th17 cell polarization, protecting the animals from autoimmune neuroinflammation [41].

The impact of IGF2BPs dysregulation on cancer is illustrated by the fact that they are among the most upregulated RBPs across the TCGA [42]. For example, high levels of these proteins (and especially of IGF2BP3, possibly through its ability to regulate *CD44* [43]) associate with poorer prognosis in high-stage and high-grade ovarian carcinomas and lung cancers [44–46]. Similarly, their upregulation associates with worse outcomes of breast cancer [47], colorectal carcinoma [48], esophageal adenocarcinoma [49], glioma [50], hepatocellular carcinoma [51,52], pancreatic cancer [53–56], acute myelocyticleukemia (AML) [57], Ewing sarcoma [58] and head and neck squamous cell carcinoma [59]. Most of these studies are correlative in nature, and despite a large body of in vitro evidence generated over almost two decades indicating that IGF2BP proteins enhance the tumorigenic phenotype [7,60,61], in vivo results were scarce [62], and only in recent years a body of data regarding their causal roles in cancer etiology in vivo has been produced. For example, it has been shown in mouse genetic models that IGF2BP1 overexpression enhances *Kras* expression to synergistically contribute to the induction of lung adenocarcinoma, whereas its downregulation diminishes the formation of metastasis [46]. In melanoma models, high levels of IGF2BP1 increases metastasis [63], whereas its depletion decreases melanoma progression [63] and sensitizes melanoma cells to chemotherapy [64]. In mouse xenograft models of colorectal cancer, IGF2BP1 overexpression promotes tumor growth and cell dissemination into the blood by decreasing the expression of *E-cadherin* and other epithelial markers while promoting clonogenicity, suggesting a role in the early stages of CRC metastasis. By contrast, its knockdown in intestine cells reduces the number of tumors in a mouse model of intestinal tumorigenesis [65].

In a notable example, a recent study found that IGF2BP3 is overexpressed in MLL-translocated leukemia, being critical to the pathologic proliferative phenotype. Upon IGF2BP3 depletion, there is a delay in leukemia development, and the survival of mice with MLL-Af4-driven leukemia is significantly increased in a mechanism that involves the Ras signaling pathway [66]. In a related study, IGF2BP3 was seen specifically overexpressed in mixed lineage leukemia-rearranged (MLL-rearranged) B-acute lymphoblastic leukemia (B-ALL). IGF2BP3 overexpressing mice led to increased numbers of highly proliferating progenitor cells in the bone marrow, and skewing toward B cell/myeloid development, in a process involving the stabilization of the IGF2BP3 targets *MYC* and *CDK6* mRNAs [27]. Thus, understanding the mechanistic details of target regulation is key to understanding IGF2BPs function. For instance, IGF2BP1 plays a crucial role in shielding *MYC, PTEN* and *MDR1* mRNAs from endonucleolytic attack and *BTRC* mRNA from miRNA-mediated degradation in the cytoplasm [61,67–69]. Indeed, most mRNA targets of IGF2BP1 that are regulated by miRNAs and shielded from silencing by IGF2BP binding participate in the aggressive tumor cell phenotype, giving IGF2BP1 the most conserved oncogenic role within the family [70]. Another interesting aspect that mediates oncogenesis is the ability of IGF2BP1 to regulate the cargo of extracellular vesicles and promote melanoma metastasis [63]. A list of mRNA targets for each specific IGF2BP protein, together with the suggested mechanism of regulation and the impact of the regulation on physiopathology can be found in Table 1.

An additional layer of complexity was added by the realization that IGF2BPs are a distinct family of methyl-RNA binding proteins that protect m^{6}A-modified mRNAs from decay, promote mRNA stability and/or target mRNAs for storage (e.g., *MYC*) [24]. Given the impact of the m^{6}A mark on RNA metabolism and the involvement in the response to changing cellular conditions and specifically the cancer context, we will revise in the following sections some key aspects of this modification

Table 1
mRNA targets of IGF2BPs and impact of the regulation on physiopathology.

IGF2BP protein	Target mRNA	Cis-element	Regulation of target mRNA	Outcome of the regulation	References
IGF2BP1	*MDR1*	CDS	Inhibition of CRD-dependent mRNA decay	Antagonizes let-7-mediated sensitivity to chemotherapy in ovarian cancer	[68,182]
	KRAS	3´-UTR, CDS	Inhibition of mRNA decay	Promotes colon cancer cell proliferation, growth and survival	[183]
	BTRC	CDS	Inhibition of mRNA degradation	High levels of ßTrCP1 enhance ß-catenin/Tcf signalling, activate transcription factor NF-κB and suppress apoptosis in colorectal cancer cells	[61,67]
	HCV	5´-UTR, 3´-UTR	Enhancement of translation	not assessed	[184]
	PPP1R9B	3´-UTR	mRNA transport.	Required for distal dendritic RNA transport	[30]
	CD-44	3´-UTR	Transcript stabilization	Promotes formation of invadopodia in HeLa cells	[43]
	ACTB	3´-UTR	Inhibition of premature mRNA translation and enhanced mRNA transport	Ensures localized translation and regulates growth cone guidance.	[3,13,14,69, 185,186]
	MYC	CDS	Inhibition of CRD-dependent mRNA decay	Enhances tumor cell survival and proliferation	[1187]
	PTEN	CDS	Inhibition of CRD-dependent mRNA decay	Enhances the velocity and the directionality of tumor cell migration by sustaining cell polarization	[69]
	MAPK4	3´-UTR	Inhibition of mRNA translation	Enhances the velocity and the directionality of tumor cell migration by sustaining cell polarization	[69]
	IGF2	5´-UTR	Inhibition of mRNA translation	Not assessed	[4]
	CTNNB1	3´-UTR	Inhibition of mRNA decay	Not assessed	[188]
IGF2BP2	*IGF2*	5´-UTR	Enhancement of cap-independent translation following IGF2BP2 phosphorylation by mTOR	Enhanced IGF2 expression promotes tumor cell growth	[5,60]
	HMGA1	3′UTR	mRNA stabilization following IGF2BP2 phosphorylation by mTOR	Increased proliferation of cancer cell lines	[60]
	PINCH-2	3′-UTR	mRNA destabilization	Regulates adhesion structures and stabilizes microtubules in skeletal myoblasts	[144]
	UCP1	UTRs	Inhibition of mRNA translation	Limits longevity and modulates nutrient and energy metabolism in mouse models	[33]
	MURF3	5′-UTR and CDS	Enhancement of translation	Regulates adhesion structures and stabilizes microtubules in skeletal myoblasts	[144]
	GLUT1	3´-UTR	mRNA stabilization	Promotes aerobic glycolysis and proliferation of pancreatic ductal adenocarcinoma cells in vitro and in vivo	[54]
IGF2BP3	*IGF2*	5´-UTR	Enhancement of translation	Enhances tumor cell proliferation and survival in leukemia and glioblastoma models	[189–191]
	CD44	3´-UTR	mRNA destabilization	Promotes formation of invadopodia in HeLa cells	[43]
	ABCF1	n.a	ABCF1 mRNA acts as a decoy, thereby preventing the binding of IGF2BP3 to its oncogenic targets	High levels of ABCF1 counteract the oncogenic potential of IGF2BP3 in Ewing sarcoma	[58]

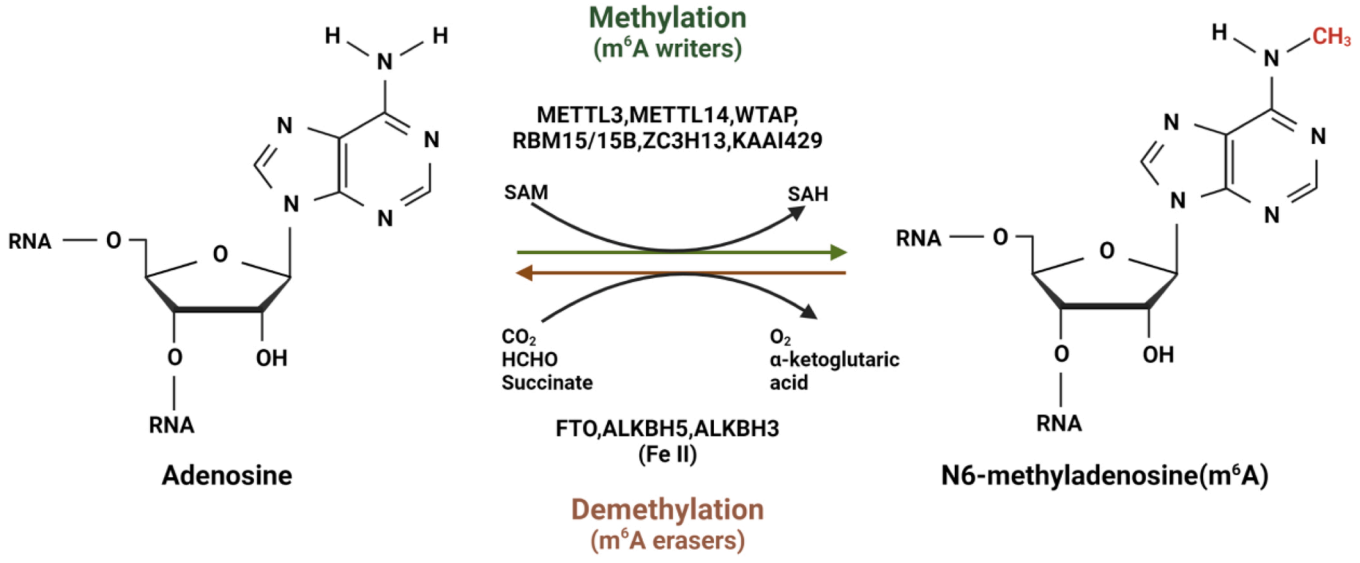

Fig. 2. Reversible m^6A modification. The dynamic homeostasis and reversible process of modification of m^6A is regulated by writers such as regulatory complex assisting METTL3-METTL14 core complex, known as MAC(m^6A-METTL complex), catalysing Adenosine(A) to N6-methyladenosine(m^6A) transformation, using S-adenosylmethionine(SAM) as the methyl donor; and its demethylation is catalysed by erasers FTO, ALKBH5 and ALKBH3, with co-substrates such as a-ketoglutaric acid (α-KG) and molecular oxygen(O_2) and co-factor ferrous iron(Fe II). Created with BioRender.com.

and its protein partners, to focus subsequently on IGF2BPs binding to (m^6A)-mRNAs in tumorigenesis.

4. The m^6A mark

The methylation of position N6 of adenosine (N6 -Methyladenosine, or m^6A), is one of the most abundant internal modifications in eukaryotic mRNAs [71], being found in approximately three to five sites in each mRNA molecule [72,73]. M^6A mark on RNA is post-transcriptionally catalyzed by a heterotrimeric methyltransferase complex present in nuclear speckles that includes the catalytic METTL3 and the allosteric activator METTL14 enzymes, and the WTAP RNA binding protein [74–76], whereas the RNA binding proteins RBM15 and RBM15B can bind to METTL3 and WTAP and direct the complex to specific RNA sites containing consensus motifs for methylation [77,78]. In mammals, mRNA methylation occurs within the consensus sequence RRACH (R = G or A; H = A, C or U), though only a portion of these putative methylation sites contain m^6A [79–81]. An alternative methylation pathway involves the splicing-related METTL16, which methylates U6 snRNA as well as some pre-mRNAs and ncRNAs [82,83]. The m^6A mark is reversible in nature: demethylating enzymes described to date (the fat mass and obesity-associated protein FTO [84] and the alpha-ketoglutarate-dependent dioxygenases ALKBH5 [81] and ALKBH3 [85] respond to stress signals and changing cellular conditions, and catalyze demethylation in an Fe (II) and α-ketoglutaric acid-dependent manner, which suggests the epigenetic feature of this RNA modification (Fig. 2).

Even though initially the m^6A mark was associated with promotion of mRNA degradation [71], subsequent studies have enriched this view by revealing that the location of this modification on the mRNA, together with the interplay between writer, eraser and reader complexes and the subcellular location of these binding proteins ultimately determine the impact in the lifecycle of target RNAs, revealing the multifaceted influence of methylation on mRNA metabolism [86]. Altogether, in addition to regulating the stability of the transcript, the presence of m^6A on RNA may also impact on its splicing, transport, localization and translation [81,87–89]. Noncoding RNAs can also be m^6A-modified; primary microRNA processing is modulated by m^6A presence [90], and long noncoding RNAs (lncRNAs), which are key regulators of epigenetic mechanisms and of gene expression [91,92], can also be modified by m^6A methylation, with consequences for their function. In one of the first described examples, the lncRNA *XIST*, essential for X-chromosome inactivation in female cells, is highly methylated with dozens of m^6A sites, which are necessary for its function as a transcriptional repressor [77].

The distribution of m^6A in tissue-specific sites has also been investigated, and the results revealed that this modification is most abundantly found in the heart, brain and kidney. Furthermore, the distribution of m^6A is richer in the adult than in the fetal brain [80]. N6-Methyladenosine plays a critical role in the development of an organism, and changes in the levels of m^6A have an impact on many life processes, including tissue development, stem cell self-renewal and differentiation [76,93]. M^6A can also control dynamic responses to extracellular stimuli, including the heat shock response [89], and circadian clock [94].

5. IGF2BPs, direct readers of m^6A-RNAs?

M^6A is most frequently found in the last exons near stop codons, allowing for 3′UTR regulation [80,95] and thus tightly tying the modification to the fate and function of RNAs. Changes in the mentioned "writers" and "erasers" of the modification affect the metabolism of the target RNA, but so do the changes in those RNA binding proteins with high affinity for m^6A-containing transcripts (the so-called "readers"). The YT521-B homology (YTH) domain-containing proteins YTHDC1–2 and YTHDF1–3 are the canonical readers of the m^6A mark, [71,79], but other proteins lacking this domain have also been shown to bind preferentially to m^6A-modified RNAs, including the IGF2BP1–3 family of proteins [24]. The selectivity for m^6A-containing RNAs by proteins without YTH domain is not completely understood but could be mediated by i) other domains capable of directly interacting with m^6A mark (this would be the case of the KH domains in IGF2BPs, possibly helped by flanking regions within the protein [24,96]) and/or ii) by binding to surrounding or overlapping RNA motifs that become more exposed and accessible to the RBPs following local structural changes facilitated by the presence of the m^6A modification (as has been seen, for example, for HNRNPC [97] or HNRNPG [98,99]. In this latter case, m^6A acts as a molecular 'switch' that may have a widespread effect on the binding of additional proteins to m^6A-modified RNAs. In some cases, the specific binding mechanism remains unclear: for example, HNRNPA2B1 protein was initially proposed to be a direct m^6A reader and interact through one of its RRMs to motifs that overlap with the m^6A consensus site, thereby regulating alternative splicing and microRNA processing in the nucleus [90]. However, subsequent studies suggested that HNRNPA2B1 action is helped by a "m^6A switch" type of mechanism, rather than functioning as a direct "reader" of m^6A modification [100]. It is possible that the IGF2BPs apparent direct affinity for m^6A is mediated by a similar mechanism, given the fact that the KH3 and 4 domains in IGF2BPs, necessary for m^6A binding, are actually not sufficient for the interaction, and that the IGF2BPs binding sites (despite the diversity of motifs found in different studies) may overlap with the m^6A consensus sequence DRACH (D, A/G/U; R, A/G; H, A/C/U) [79,80]. Other non-YTH-containing m^6A protein readers may remain to be uncovered, since some untargeted quantitative proteomics approaches have reported a variety of potential m^6A-RNA binding proteins, including RBPs with RRMs (such as HNRNPs or CPSF6) or with KH domains (such as FUBPS) [101,102]. In some cases, confirmation of the interaction has been reported by direct approaches (e.g., the KH domain-containing protein FMR1 and m^6A-RNA, where, again, sequence elements on the RNA surrounding the m^6A mark seem decisive in enhancing RNA-protein affinity [102]). The number of proteins whose binding to m^6A-containing or neighboring regions in a m^6A-dependent manner is likely to grow in the next years, as more transcriptomic-wide comparisons between m^6A RNA sets and individual Clip-seq studies in different pathophysiological settings are developed. Thus, as future studies clarify the specifics of m^6A-RNA recognition by non-YTH containing proteins such as IGF2BPs, it is likely that some mechanistic commonalities will appear.

6. M^6A and stress

There are a number of mechanisms through which stress signals globally reduce cap-dependent translation, a measure that helps conserve energy and nutrients while the cell promotes the expression of specific genes to cope with stress by using alternative mechanisms of translation initiation. This is especially relevant in the tumoral context, where cells face adverse conditions such as hypoxia or starvation, and where the use of internal ribosomal entry sites (IRES) in stress adaptive mRNAs is greatly enhanced [103,104]. In addition, under stress, most mRNAs stalled for translation are temporarily sequestered into cytosolic aggregates called stress granules (SGs), (reviewed in [105]), from which they will be eventually released and re-associated with polysomes once normal conditions resume. This is in contrast to RNAs recruited to the stress-induced P-bodies, which are targeted for degradation [106,107]. One key trigger of SG formation is the phosphorylation of eIF2α that happens upon several different types of stress such as oxidative, genotoxic or hypoxic conditions, and metabolic and proteotoxic stresses (such as endoplasmic reticulum stress) [108]. Some key proteins present in SG are small ribosomal subunits, miRNAs and Argonaute proteins, and a number of regulators of mRNA stability and translation, including the RNA binding proteins TIA-1, TIAR, RCK/p54, Y-box binding protein 1 (YB-1) and IGF2BPs [20,109]. SG play crucial roles in cancer biology,

by orchestrating stress signaling and providing the tumor with cell fitness and resistance to chemotherapy, and many SG components are overexpressed in human tumors [110,111]. Also, targeting SG formation induces apoptosis of tumoral cells (Takahashi et al., 2013) and inhibits metastasis [113].

It is becoming increasingly clear that the reshaping of the cellular RNA methylome enhances the shift towards cap-independent translation of certain transcripts and adds to the strategies included in the stress response pathways, so that the physiological roles of m^{6}A are linked in many cases to the response to changing cellular conditions, including stress stimuli. For example, during the response to heat shock, the generally m^{6}A-depleted 5′ untranslated regions (5′UTRs) are preferentially methylated as a result of stress-induced nuclear localization of the 'reader' YTHDF2, which protects the region from the m^{6}A demethylating action of FTO [89]. ALKBH5 also responds to hypoxia and targets the m^{6}A-modified *NANOG* mRNA in breast cancer cells [114]. Of note, the increase in 5′UTR methylation induces a widespread shift towards alternative, cap-independent translation initiation events, among others of the heat-shock protein *Hsp70* mRNA [88,89] and the activating transcription factor 4 (ATF4, a key effector of the integrated stress response) [115], which depends on a direct interaction between eIF3 and m^{6}A for ribosome recruitment. This cap-independent enhancement of translation may explain why certain circular RNAs may produce peptides in a m^{6}A-dependent manner (see below).

7. IGF2BPs as m^{6}A readers in normal and stress conditions?

One important recent development in IGF2BPs studies is their preferential binding for m^{6}A-modified RNAs: by using m^{6}A-modified single-stranded RNA as a bait, protein pull-down assays indicated that all three IGF2BP proteins were retrieved with a 3–4-fold higher affinity than with the compared unmethylated control, being among the top enriched proteins in the m^{6}A pull-downs [24]. This is mediated by the proteins' KH domains (specially domains 3 and 4, with KH domains 1 and 2 playing accessory roles). Albeit performed in a limited number of cell types, this study clarified the global picture of IGF2BP proteins affinity for their RNA targets; RNA-protein cross-linking experiments revealed that most target transcripts contain the UGGAC consensus sequence, which contains the GGAC m^{6}A core motif, and that > 80 % of the targets contain at least one m^{6}A site. As is generally typical for m^{6}A distribution, these sites are enriched in 3′UTRs and near stop codons, and, intriguingly, near 10 % of the targets correspond to non-protein-coding transcripts (see below). Crucially, binding to bona fide targets (including *MYC* mRNA) is impaired upon METTL14 knockdown, suggesting that the modification is the primary determinant for the interaction with IGF2BPs. Additionally, the same study showed that m^{6}A-RNA-IGF2BP binding enhances the stability and translation of m^{6}A-bearing mRNA targets by recruiting the mRNA stabilizers HuR, MATR3, and PABPC1. Colocalization with HuR seems to occur in P-bodies, whereas upon heat shock, IGF2BPs appear in stress granules and shift to non-ribosomal fractions in polysome profiles, underscoring their role as regulators of dynamic RNA metabolism to generally prevent degradation upon adverse cellular conditions [24] (Fig. 3). Even though evidence for colocalization of m^{6}A-RNAs and IGF2BP proteins in stress granules is still missing, the proposed mechanism would be in contrast to the general role of YTHDF2 as an m^{6}A-RNA destabilizer, and may be a consequence of different sequence affinity (ENCODE PAR-CLIP data indicates little overlap between IGF2BPs and YTHDF2-binding sites [24]) and/or location of binding sites (YTHDF2-binding sites being more abundant in CDS than 3′UTRs [71]). Given the abundance of growth-related targets, it is not surprising that knockdown of IGF2BPs and specifically KH3 and 4 mutants decreased proliferation and colony formation [24], although elucidating to what extent this is dependent on the roles as m^{6}A readers requires further studies.

The role of IGF2BP in ensuring the stability of stress granule-recruited mRNAs has been known for several years. For example, in response to oxidative stress or heat shock, IGF2BP1 relocalizes to SG, where it remains bound to its target mRNAs (including *MYC* and *IGF2*

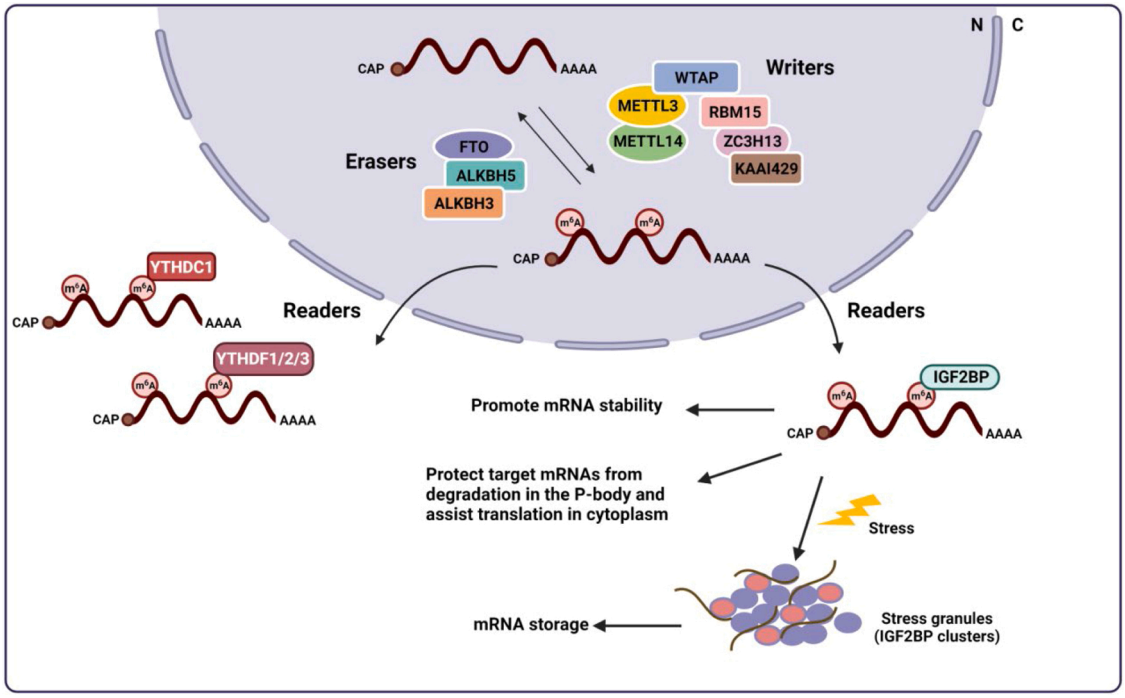

Fig. 3. Mechanism and function of IGF2BPs as m^{6}A readers. The modification of m^{6}A is regulated by writers, readers and erasers. Writers such as METTL3, METTL14, RBM15, ZCH13, WTAP and KAAI429 regulate m^{6}A methylation. FTO, ALKBH5 and ALKBH3 are erasers, which are identified to induce m^{6}A demethylation. Together with the YTHDF family, IGF2BPs are reported to be the main m^{6}A readers, and their functions are related to promoting mRNA stability, degradation, export and storage. In the cytoplasm, IGF2BPs protect RNA targets in the context of mRNPs under both physiological and stress conditions, under which these proteins and associated transcripts accumulate in stress granules for subsequent sorting. Created with BioRender.com.

mRNAs) and prevents their transfer to P bodies and subsequent decay, thereby determining the fate of target mRNAs during cellular stress [69,109]. The association of IGF2BPs with SG is stable, in contrast to the RBPs that are essential for SG assembly, which are highly mobile [116]. It was noted that the KH domains facilitate the recruitment of IGF2BP1 and 2 to the SG, whereas they play little role in the case of IGF2BP3 paralog [20]. Of note, while in non-stressed cells, IGF2BP may exert different types of regulation on transcripts (at the stability or the translation level), the proteins adopt a general stabilizing function in stress. Further studies have shown that the pivotal role of localization to SG to protect translationally-stalled mRNA targets from degradation might be an oversimplified picture [117,118]: in fact, depletion of IGF2BP1 may be the key event that destabilizes mRNA substrates, irrespective of SG integrity. Likewise, impairing SG formation does not affect the stress-induced stabilization of target mRNAs by IGF2BPs in intact mRNPs [116]. Rather, the maintenance of stable mRNP complexes seems key to preventing stress-induced mRNA degradation. Bearing this in mind, and given the growing number of studies pointing to the unequivocal relevance of m^{6}A modification for target recognition and function of IGF2BPs in tumorigenesis, future research shall elucidate the specific role that modifications on the RNA targets play in the response of IGF2BPs to stress.

8. M^{6}A-mRNA targets mediate tumorigenic functions of IGF2BPs

Aiming to understand the underlying mechanism(s) for IGF2BPs oncogenic features based on their ability to recognize m^{6}A modification, some recent studies have confirmed that the IGF2BP family of proteins recognizes mRNA in a highly m^{6}A-dependent manner, causing upregulation in oncogenic expression or downregulation in tumor suppressor gene expression. For instance, *PEG10* was shown to be bound by IGF2BP1 via m^{6}A modification. The polyadenylate-binding protein I (PABPC1) is then recruited by IGF2BP1 to enhance the stability of *PEG10* mRNA, upregulating *PEG10* expression and promoting endometrial cancer cell proliferation [119]. In colon cancer, it is demonstrated that IGF2BP1 promotes expression of the Polycomb protein CBX8 also in a m^{6}A-dependent manner. This results in the regulation of stemness and the suppression of chemosensitivity through induction of the CBX8 target LRG5 [120]. Through a novel mechanism, the lncRNA originally annotated as *LINC00266–1* produces a peptide that acts as a regulatory subunit of *IGF2BP1* and enhances its binding affinity for its target m^{6}A-*MYC* mRNA, promoting tumorigenesis by increasing the level and stability of *MYC* transcripts [121]. IGF2BP1 also binds and promotes the serum response factor *SRF* mRNA expression in a m^{6}A-dependent manner by preventing miRNA-mediated downregulation, enhancing tumor cell growth and invasion. Additionally, the functional link between the two genes and their oncogenic role in cancer cells is further reinforced by the observation that IGF2BP1 stabilizes the mRNAs of key downstream targets of SRF such as *FOXK1* and *PDLIM7* [96]. Perhaps the most compelling evidence linking the role of IGF2BP1 as an m^{6}A reader with an impact on oncogenesis is the finding that IGF2BP1 not only stabilizes cell cycle regulators like the transcription factors E2F transcripts in a m^{6}A-dependent manner, but also stabilizes E2F-driven oncogenic targets post-transcriptionally, robustly promoting cell cycle progression and proliferation across many solid cancers [122]. In a similar manner, the METTL3/IGF2BP2 axis is shown to promote tumorigenic features by stabilizing the Flap endonuclease-1 (*FEN1*) and SRY (sex determining region Y)-box 2 (*SOX2*) mRNAs in hepatocellular carcinoma and colorectal cancer, respectively [48,52]. The role of IGF2BP3 as m^{6}A reader has been studied in colon cancer, were IGF2BP3 expression is a predictor of progression and poor survival. IGF2BP3 binds to *Cyclin D1* and *VEGF* mRNAs, regulating both their stability and expression via m^{6}A modification. Through this mechanism, IGF2BP3 is associated with DNA replication, and IGF2BP3 knockdown consequently reduced the percentage of S phase in cell cycle, cell proliferation and angiogenesis [123]. In gastric cancer, IGF2BP3 contributes to tumor progression downstream of the elevated levels of METTL3 by binding to and stabilizing the m^{6}A-modified *HDGF* mRNA, which is involved in increased angiogenesis and glycolysis [124]. A list of reported m^{6}A-mRNA targets for each IGF2BP protein, and the relevance of the interaction for oncogenesis can be found in Table 2.

Table 2
Reported m^{6}A-mRNA targets of IGF2BPs and impact of the interaction on the oncogenic phenotype.

IGF2BP protein	m^{6}A-target	Tumor type	Regulation	References
IGF2BP1	*PEG10*	Endometrial cancer	Stabilizes *PEG10* mRNA and enhances expression	[119]
	MYC	Colorectal, ovarian, and other cancer types	Increases *MYC* mRNA stability and expression	[121]
	SRF	several	Enhances SRF-dependent transcriptional activity, resulting in tumor cell growth and invasion	[96]
	CBX8	Colon cancer	Enhances*CBX8*mRNA stability and expression, which regulates stemness and chemosensitivity in colon cancer	[120]
	E2F1–3	Across multiple tumor types	Promotes E2F-driven G1/S transition and cell growth	[122]
IGF2BP2	*FEN1*	Hepatocellular carcinoma	Enhances*FEN1* mRNA stability, promoting liver cancer growth	[52]
	MALAT1	Thyroid cancer	Elevates *MYC* expression, which consequently accelerates the proliferation, invasion and migration of TC cells	[142]
	SOX2	Colorectal cancer	Enhances*SOX2* mRNA stability and promotes CRC stemness	[48]
	GLUT1	Colorectal cancer	Activation of glycolysis and CRC progression	[192]
IGF2BP3	*VEGF*	Colon cancer	Represses angiogenesis	[123]
	CCND1	Colon cancer	Represses S phase and proliferation of colon cancer	[123]

It is expected that the number of bona fide m^{6}A-modified mRNA targets of the IGF2BP family will increase in the following years, as the preferential role as m^{6}A reader proteins is further established. There is an additional aspect in the substrates of the three paralogs that deserves attention, namely the fact that noncoding transcripts (including m^{6}A-marked ncRNAs) are in a more complex dialogue with IGF2BPs than mRNAs, both as regulated targets and also as regulatory cofactors of RBP function.

9. The emerging cross-regulation between IGF2BPs and (m^{6}A)-ncRNAs

In addition to the fairly well-characterized mRNA targets, an additional important aspect of the function and regulation of IGF2BPs in healthy and diseased tissues is provided by the noncoding transcriptome. It is increasingly clear that long noncoding RNAs are key regulatory players in diverse cellular processes, including growth, differentiation, apoptosis and cancer progression and metastasis [125,126]. Like m^{6}A-mRNAs, m^{6}A-marked noncoding transcripts are also bound and stabilized by IGF2BP proteins [56]. Conversely, many studies point to the role of ncRNAs as regulators of IGF2BPs function, and in

addition to the miRNAs that have been reported to target IGF2BP transcripts (among which, importantly, the tumor suppressor miRNA *let-7*) [127–130], a growing number of longer transcripts are known to interplay with IGF2BPs. Mechanistically, many studies have focused on the ability of lncRNAs to recruit, organize, or modulate the activity of RBPs, indicating that RNA is also able to regulate RBPs (recently reviewed in [131]. Therefore, similar to other RBPs, regulatory interactions that occur between IGF2BPs and RNA are bidirectional, particularly in the case of lncRNAs (Fig. 4).

9.1. LncRNAs that enhance IGF2BP function

A number of works have shown that binding to lncRNAs enhances the physical association between IGF2BPs and mRNA targets, through mechanisms that are generally not sufficiently understood but that may imply the formation of ternary complexes. For example, a study from our group showed that *RPSAP52* is a processed pseudogene that influences IGF2BP2 function through direct RNA—protein interaction and the enhancement of target mRNA recruitment to polysomes. In addition, *RPSAP52* impacts positively on the oncofetal *HMGA2* gene expression, with both regulatory mechanisms converging on the proliferative HMGA2/IGF2BP2/RAS axis to promote the growth of tumoral cells [132]. Although the spatial details of the interaction remain to be elucidated, one interesting possibility suggested by this study is that, by binding to more than one RNA through their multiple RNA binding domains, IGF2BPs may coordinate the function and fate of more than one target, and/or be themselves regulated by one RNA moiety to influence the protein ability to bind to other RNA substrates. Similarly, a highly conserved lncRNA, *THOR*, was seen to enhance the stability of IGF2BP targets through direct binding to IGF2BP1. Notably, this accelerates the onset of melanoma in human, mouse and zebrafish models [133]. Other examples of lncRNAs for which similar mechanisms have been suggested include *GHET1* in gastric carcinoma [134], *HCG11* in hepatocellular carcinoma [135], *LIN28B-AS1* in lung adenocarcinoma [136], and *linc01021* in colorectal cancer [137].

9.2. LncRNAs that hinder IGF2BP function

By contrast, interaction with other lncRNAs have been reported to impair IGF2BP function; such is the case for *FGF13-AS1* in breast cancer [138], the liver-specific *LINC01093* in hepatocellular carcinoma [139], or 91 H in colorectal cancer [140]: these lncRNAs display antitumoral effects via a potential competition with IGF2BP oncogenic targets for binding to the proteins. In view of the alternative regulatory modes, further work will be necessary to understand the specifics of the interactions that support the cooperative or competitive nature of lncRNA binding to IGF2BPs. For instance, it will be important to elucidate whether the affinity for the different RNA binding domains within

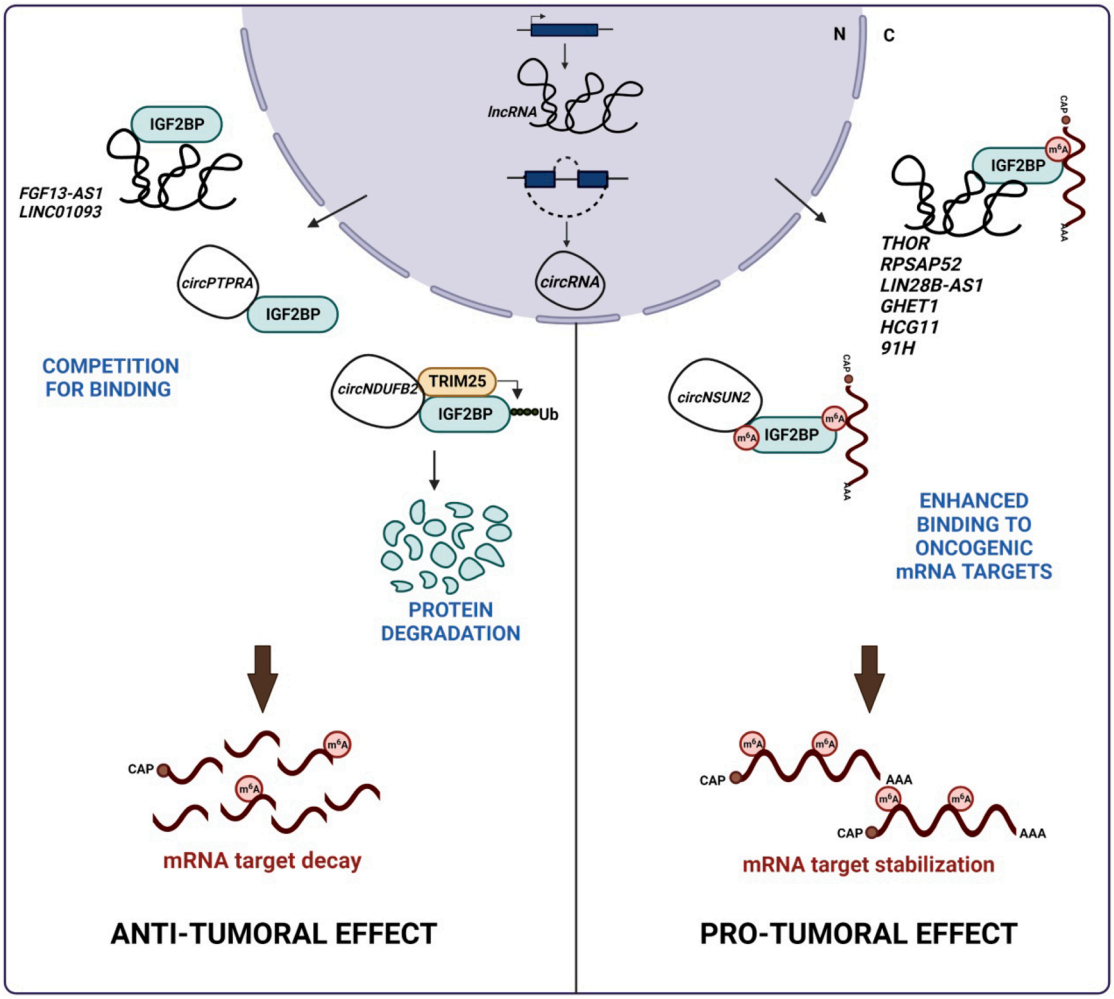

Fig. 4. (m^6A)-ncRNAs regulate IGF2BPs. A number of long noncoding RNAs and circRNAs modulate IGF2BP proteins, by impairing their function (through competition for the binding to the RNA targets or by decreasing protein levels), or conversely, by enhancing target recognition (through the establishment of ternary complexes). As a consequence, noncoding RNAs may promote or hinder the pro-tumoral features of the proteins, respectively. Specific examples are shown and listed in Table 3. Figure created with BioRender.com.

IGF2BPs is driving the ability to form ternary complexes with more than one RNA as substrate, or how the presence of m^{6}A sites influences the regulatory ability of lncRNAs.

9.3. Other mechanisms of IGF2BP regulation by lncRNAs

Besides impairing or enhancing target binding, lncRNAs may regulate IGF2BPs via additional mechanisms. For instance, *LINRIS* is a GATA3-controlled lncRNA upregulated in colorectal cancer that binds directly to and inhibits the ubiquitination and thus the degradation of IGF2BP2 protein in colorectal cancer [141]. In thyroid cancer, the highly abundant *MALAT1* lncRNA is able to upregulate IGF2BP2 expression by acting as a decoy for *miR-204* and preventing miRNA-mediated silencing of IGF2BP2. As a consequence, m^{6}A-modified *MYC* mRNA is stabilized and expression of the gene upregulated, enhancing the pro-growth phenotype [142].

9.4. LncRNAs regulated by IGF2BPs

On the other hand, although with only a few examples so far, lncRNAs may be themselves regulated by IGF2BPs: the liver-specific lncRNA *HULC* was shown to be destabilized by IGF2BP1 via recruitment of the CCR4-NOT deadenylase complex, in what was an unusual example of a IGF2BP protein inducing RNA decay [143]. Whether this is linked to the noncoding nature of the target is uncertain, since few examples of enhancement of mRNA decay have been reported for IGF2BP proteins [43,144], and further studies on the composition and subcellular location of the IGF2BP RNP complexes in the different contexts will be necessary to fully understand the regulatory mechanism taking place. Additionally, *HULC* is highly upregulated in liver cancer, where it induces tumor growth, but no clear correlation could be found between IGF2BP1 and the lncRNA levels in tumors, pointing to additional layers of control being present. In another recent study, IGF2BP2 was seen to act as a reader of the m^{6}A-modified *ZFAS1* lncRNA and stabilize the transcript. In turn, *ZFAS1* enhances the activity of the Obg-like ATPase 1 (OLA1), increasing ATP hydrolysis and the Warburg effect during colorectal cancer proliferation and progression. In addition, this study shows that IGF2BP2 is highly expressed in CRC cell lines and tumor tissues, positively correlating with the higher levels of *ZFAS1* lncRNA and m^{6}A mark [145].

Table 3 lists the best characterized examples to date of lncRNAs interacting with IGF2BPs.

However, for many of the reported examples, it is currently unknown whether these mechanisms also rely on modifications of the ncRNA molecules involved. Given recent evidence, though, one can foresee that m^{6}A modification on the lncRNA dictates the affinity for IGF2BP proteins. This is illustrated by the case of circRNAs (covalently closed RNA loops that generally derive from precursor mRNA back-splicing and display regulatory functions on other genes expression [146,147]), which are also reported to bind to IGF2BPs and are suggested to influence IGF2BPs function through a variety of mechanisms, in many cases mediated by the presence of the m^{6}A mark.

Table 3
lncRNAs and circRNAs binding partners of IGF2BPs.

ncRNA	IGF2BP protein	Regulation	References
THOR	IGF2BP1	Upregulates IGF2BP1 binding to mRNA targets and enhances cell proliferation, migration and invasion	[193]
GHET1	IGF2BP1	Enhances the gastric carcinoma cell proliferation and interaction between *MYC* mRNA and IGF2BP1, enhancing its stability and expression	[134]
HCG11	IGF2BP1	Interacts with IGF2BP1 and promotes cell proliferation and invasion in HCC cells	[135]
LIN28B-AS1	IGF2BP1	Upregulates IGF2BP1-dependent mRNA stability and promotes HCC cell progression	[194]
LINC01093	IGF2BP1	Affects expression of *GLI1*and downstream molecules in HCC progression	[139]
RPSAP52	IGF2BP2	Enhances target mRNA recruitment to polysomes	[174]
LINRIS	IGF2BP2	Prevents IGF2BP2 ubiquitinationin CRC	[141]
MALAT1	IGF2BP2	Promotes *MALAT1* stability, downstream target ATG12 expression and NSCLC proliferation	[142]
circNDUFB2	IGF2BP1–3	Enhances the interaction between TRIM25 and IGF2BPs, promoting protein degradation	[161]
circPTPRA	IGF2BP1	Inhibits tumor progression by blocking the recognition of mRNA tragets by IGF2BP1	[162]
circNSUN2	IGF2BP2	Enhances binding and stability of *HMGA2* mRNA and promotes CRC metastasis progression	[151]

10. IGF2BPs and (m^{6}A)-circRNAs

Recent literature points to circular RNAs as being prone to modification and interacting extensively with IGF2BPs. M^{6}A modification is widely present on circRNAs, with patterns that differ from those in the exons on linear mRNA they are related to. These patterns are cell-type specific, being specially present in human embryonic stem cells (hESCs) and enriched in circRNAs derived from long single exons [148]. In mRNAs, m^{6}A is most commonly found on final exons, whereas circularization of the last exon of genes is rare [149], suggesting distinct patterns of modification. M^{6}A-circRNAs are not especially unstable, but rather, high levels of modification correlate with high circRNA expression whereas, intriguingly, low levels of m^{6}A associate with lower circRNA expression (at least in some cell types). By contrast, m^{6}A mRNAs encoded by the parent genes of m^{6}A circRNAs have shorter half-lives among all m^{6}A mRNAs [148]. The presence of m^{6}A sites on circRNAs has been linked to several aspects of circRNA metabolism, including the back splicing that generates circRNAs [150], the export to the cytoplasm [151], the stability [152], and even the translation of circRNAs. Albeit generally considered noncoding RNAs, in some cases circRNAs are translated through cap-independent mechanisms [153–156], and m^{6}A modifications may influence this process: m^{6}A-modified regions may be used as internal ribosomal entry site (IRES) and promote translation initiation of circRNAs in a eIF4G2- and YTHDF3-dependent manner, which underscores the complex lives of this special class of transcripts. Importantly, this process is inhibited by the m^{6}A demethylase FTO protein, and increased by heat-shock, once more potentially linking m^{6}A-circRNA functions with the stress response [157]. Given the poor association of circRNAs with polysomes [158], the prevalence of this phenomenon remains to be assessed, but many m^{6}A-containing circRNAs were proposed to undergo similar cap-independent translation [157,159], and the presence of modified m^{6}A sites has been seen to enhance translation [160], while in other instances, circRNA translation seems to be unaffected by m^{6}A modification [159].

Future research will clarify the mechanisms by which m^{6}A regulates circRNA metabolism, and the impact of this regulation on disease progression, but their link with IGF2BP function is increasingly clear. For example, a report on the circRNA *circNDUFB2* describes its ability to downregulate IGF2BPs via scaffolding the interaction with the E3 ubiquitin ligase TRIM25, which induces protein degradation and contributes to inhibition of proliferation in non-small cell lung cancer. Of note, RNA-protein interaction is enhanced by the m^{6}A modification of *circNDUFB2* [161]. In another study, *circPTPRA* impairs the ability of IGF2BP1 to bind to m^{6}A-transcripts (including *MYC* mRNA) by interacting through the KH3 and 4 domains. This block in IGF2BP action

reduces the tumorigenic features of bladder cancer cells and xenografts models [162]. In this case, binding to circRNA does not affect protein stability or levels, and the impact on downstream targets seems to depend on the ability of the circRNA to outcompete the mRNA substrates for the binding to IGF2BP1. A similar example was seen in melanoma, where the circRNA *CDR1as* is able to bind to IGF2BP3 via several CA-rich sequences. Epigenetic silencing of *CDR1as* during tumor progression changes the levels of a subset of IGF2BP3-bound mRNA targets involved in cell invasion, presumably by unblocking IGF2BP function [163]. This is in contrast to what has been observed in the case of another circular RNA molecule: the modified m^{6}A-*circNSUN2* enhances IGF2BP2 function by interacting with this protein and *HMGA2* mRNA, forming a ternary complex that stabilizes the mRNA and promotes colorectal carcinoma metastasis progression [164]. The host gene of *circNSUN2*, *NSUN2*, is itself a 5-methylcytosine (m^{5}C) methyltransferase with a potential role in cancer and with tRNA molecules as main substrates [165], suggesting a complex crosstalk between the different epitranscriptomic modifications, and foreseeing further exciting developments in the research around IGF2BPs, ncRNAs and epitranscriptomics in cancer.

11. IGF2BPs as a therapeutic target in cancer

Given the ability of IGF2BPs to bind a wide range of prooncogenic mRNAs, and the growing evidence pointing to causal roles in the different aspects of tumorigenesis, their pharmaceutical inhibition could have an important therapeutic potential. High-throughput screenings that use fluorescence polarization to reveal small molecules capable of interfering with IGF2BP1 binding to key target mRNAs were developed [166], and a first small compound that inhibits the IGF2BP1-*MYC* mRNA interaction was reported a few years ago. The drug reduced proliferation of ovarian and melanoma cell lines in vitro [167]. More recently, a similar screening has produced a candidate compound that specifically binds the hydrophobic surface at the junction of KH3 and KH4 domains in IGF2BP1. Of note, the interaction hinders binding to *KRAS* mRNA (and possibly to other key targets) and results in diminished cellular migration and clonogenicity of colon and lung cancer cells in vitro, with no apparent effect on cell proliferation [168]. Another similar screening aimed at targeting IGF2BP2-RNA interactions has been developed with the use of generic IGF2BP2 binding motifs. In this case, candidate compounds inhibit cell proliferation in 2D and 3D cultures of human cells, and reduce tumor growth in zebrafish embryo xenograft models [169]. These preliminary findings suggest that at least IGF2BP1 and 2 are druggable targets to reduce tumor cell proliferation, but further studies are required to understand the different impact of each candidate drug on cell phenotypes, and to assess the selectivity and efficacy of these compounds in vivo.

By contrast, to date, no direct inhibitor of IGF2BP3 has been reported, but indirect strategies have been tested. For example, indirect pharmacological inhibition of IGF2BP3 via the bromodomain and extraterminal domain (BET) inhibitors has been described in megakaryocytes [170] and in B-ALL [27]. Similarly, in Ewing sarcoma, where high levels of IGF2BP3 are associated with worse patient outcome, the use of the BET inhibitor JQ1 in cell lines decreases IGF2BP3 expression and the levels of its key targets ABCF1, MMP9 or CD44, with a parallel reduction in cellular growth [58].

Altogether, the existence of these inhibitors indicates potential accessibility of IGF2BP proteins to exogenous manipulations, and warrants further exploration of their targeting by pharmacological compounds to counteract their oncogenic actions.

12. Final remarks

Around 7000 m^{6}A-modified RNAs are thought to be present in the cell. Since IGF2BPs target thousands of mRNAs, with large overlaps between the three IGF2BP1–3 proteins, and most of them bear the m^{6}A mark, these family is emerging as one key player in m^{6}A-dependent gene regulation. However, despite an increase in the number of studies that focus on this new angle, the contribution of m^{6}A reading activity to the well-established oncogenic properties of IGF2BP family is still unclear.

This is especially relevant for the ncRNA targets, which are emerging as key molecules that can be both regulated by and regulators of IGF2BPs activity; it remains to be elucidated to what extent modifications on these types of substrates influence the binding and the regulatory mechanisms taking place. When considering this type of regulation, the difference in concentration between ncRNAs and IGF2BPs poses difficulties. There are a few examples of highly abundant small ncRNAs bound by IGF2BPs: for instance, the nuclear RNA 7SK is stabilized by IGF2BP3 (which is able to undergo nuclear localization [171]), in a process that blocks P-TEFb activation and thus restricts megakaryocyte development [170]. Similarly, IGF2BP1 was seen to bind to the short Y3 RNA and enhance the cytoplasmic localization of the Ro60 ribonucleoprotein [172,173]. Regarding lncRNAs, it is easily conceivable that the extremely abundant *MALAT1* may compete for miRNA binding and thereby upregulate IGF2BP2 expression [142], but how the generally lowly expressed lncRNAs may influence the very abundant IGF2BPs in cancer cells remains unclear. Even though an accurate comparison of the relative levels of lncRNA targets and IGF2BPs is generally missing, studies that have addressed this aspect in a few cancer cells show a difference of several orders of magnitude between total lncRNA and IGF2BP protein levels [174]. This argues against the ability of the lncRNAs to enhance or compete for IGF2BPs function in an effective manner, even though other important variables that do not correlate with the measure of the average expression in a population of cells may be key in facilitating the regulation by ncRNAs. For instance, RNAs may be enriched or depleted neay key RBPs [175]. Also, if ternary complexes with more than one RNA bound by a given IGF2BP protein are formed, relative levels between the target RNAs, as well as the number of binding sites, the respective protein-RNA binding affinities and stability of the interactions could be decisive in the biological outcome. Also, liquid-liquid phase separation or local environments could justify the different stoichiometric abundance of ncRNA, mRNAs and IGF2BPs, presenting a scenario where mRNP function could be compartmentalized and represent sites of local high concentration of otherwise generally lowly present ncRNAs [176]. However, this is still speculative and more work is warranted to uncover mechanistic commonalities and solidly confirm the occurrence of the proposed regulation by lncRNAs. Recent technical developments that allow the spatial study of the transcriptome in subcellular and membrane-less compartments will likely shed valuable light to understand regulation by lncRNAs [177].

Recently, the presence of multiple m^{6}A on mRNAs has been shown to enhance liquid-liquid phase separation together with their bound proteins YTHDF1–3, suggesting that the diverse ways by which the cells interpret this modification are dictated by liquid-liquid phase separation principles [178–180]. For example, relocalization of mRNAs and RBPs to P bodies or stress granules upon stress may be driven not by the mere increase in the levels of m^{6}A per se, but rather, by the ability of the modification to scaffold the partition of the complexes in discrete intracellular condensates. Further work will clarify whether m^{6}A modification influences SG formation in general or just the fate of a particular subset of mRNAs within that structure. It is also unclear whether this feature of m^{6}A is key in enhancing the presence of IGF2BPs in granules under stress conditions, but other m^{6}A binding proteins have been reported to accumulate in stress granules linked to their “reader” ability [181]. Altogether, the detailed connection between target recognition and subcellular localization depending on post-transcriptional modification of the mRNAs/ncRNAs targets and how this determines RNA fate is still poorly understood, and future breakthroughs in the field will undoubtedly clarify our understanding of the role of IGF2BPs in cancer biology.

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References

[1] P.L. Bernstein, D.J. Herrick, R.D. Prokipcak, J. Ross, Control of c-myc mRNA half-life in vitro by a protein capable of binding to a coding region stability determinant, Genes Dev. vol. 6 (4) (1992) 642–654.
[2] A.F. Ross, Y. Oleynikov, E.H. Kislauskis, K.L. Taneja, R.H. Singer, Charact. a Actin. mRNA Zipcode-Bind. Protein vol. 17 (4) (1997) 2158–2165.
[3] S. Hüttelmaier, et al., Spatial regulation of β-actin translation by Src-dependent phosphorylation of ZBP1, Nature vol. 438 (7067) (2005) 512–515.
[4] J. Nielsen, J. Christiansen, J. Lykke-Andersen, A.H. Johnsen, U.M. Wewer, F. C. Nielsen, A family of insulin-like growth factor II mRNA-binding proteins represses translation in late development, Mol. Cell. Biol. vol. 19 (2) (1999) 1262–1270.
[5] N. Dai, J. Rapley, M. Ange, F.M. Yanik, M.D. Blower, J. Avruch, mTOR phosphorylates IMP2 to promote IGF2 mRNA translation by internal ribosomal entry, Genes Dev. vol. 25 (11) (2011) 1159–1172.
[6] F. Müeller-Pillasch, et al., Cloning of a gene highly overexpressed in cancer coding for a novel KH-domain containing protein, Oncogene vol. 14 (22) (1997) 2729–2733.
[7] N. Degrauwe, M.L. Suvà, M. Janiszewska, N. Riggi, I. Stamenkovic, Imps: an RNA-binding protein family that provides a link between stem cell maintenance in normal development and cancer, Genes Dev. vol. 30 (22) (2016) 2459–2474.
[8] S.M. Korn, C.J. Ulshöfer, T. Schneider, A. Schlundt, Structures and target RNA preferences of the RNA-binding protein family of IGF2BPs: an overview, Structure vol. 29 (8) (2021) 787–803.
[9] F. Pan, S. Hüttelmaier, R.H. Singer, W. Gu, ZBP2 facilitates binding of ZBP1 to β-Actin mRNA during transcription, Mol. Cell. Biol. vol. 27 (23) (2007) 8340–8351.
[10] Y. Oleynikov, R.H. Singer, Real-time visualization of ZBP1 association with beta-actin mRNA during transcription and localization, Curr. Biol. vol. 13 (3) (2003) 199–207.
[11] L. Jønson, et al., Molecular composition of IMP1 ribonucleoprotein granules, Mol. Cell. Proteom. vol. 6 (5) (2007) 798–811.
[12] D. Weidensdorfer, et al., Control of c-myc mRNA stability by IGF2BP1-associated cytoplasmic RNPs, Rna vol. 15 (1) (2009) 104–115.
[13] H.L. Zhang, et al., Neurotrophin-induced transport of a β-actin mRNP complex increases β-actin levels and stimulates growth cone motility, Neuron vol. 31 (2) (2001) 261–275.
[14] K.L. Farina, S. Hüttelmaier, K. Musunuru, R. Darnell, R.H. Singer, Two ZBP1 KH domains facilitate β-actin mRNA localization, granule formation, and cytoskeletal attachment, J. Cell Biol. vol. 160 (1) (2003) 77–87.
[15] D.M. Tiruchinapalli, et al., Activity-dependent trafficking and dynamic localization of zipcode binding protein 1 and β-actin mRNA in dendrites and spines of hippocampal neurons, J. Neurosci. vol. 23 (8) (2003) 3251–3261.
[16] J.L. Bell, et al., Insulin-like growth factor 2 mRNA-binding proteins (IGF2BPs): post-transcriptional drivers of cancer progression? Cell. Mol. Life Sci. vol. 70 (15) (2013) 2657–2675.
[17] K. Yaniv, J.K. Yisraeli, The involvement of a conserved family of RNA binding proteins in embryonic development and carcinogenesis, Gene vol. 287 (1–2) (2002) 49–54.
[18] D. Griffin, W.T. Penberthy, H. Lum, R.W. Stein, W.L. Taylor, Isolation of the B3 transcription factor of the Xenopus TFIIIA gene, Gene vol. 313 (1–2) (2003) 179–188.
[19] J. Nielsen, M.A. Kristensen, M. Willemoës, F.C. Nielsen, J. Christiansen, Sequential dimerization of human zipcode-binding protein IMP1 on RNA: A cooperative mechanism providing RNP stability, Nucleic Acids Res. vol. 32 (14) (2004) 4368–4376.
[20] K. Wächter, M. Köhn, N. Stöhr, S. Hüttelmaier, Subcellular localization and RNP formation of IGF2BPs (IGF2 mRNA-binding proteins) is modulated by distinct RNA-binding domains, Biol. Chem. vol. 394 (8) (2013) 1077–1090.
[21] R. Dagil, et al., IMP1 KH1 and KH2 domains create a structural platform with unique RNA recognition and re-modelling properties, Nucleic Acids Res. vol. 47 (8) (2019) 4334–4348.
[22] T. Schneider, et al., Combinatorial recognition of clustered RNA elements by the multidomain RNA-binding protein IMP3, Nat. Commun. vol. 10 (1) (2019) 1–18.
[23] J. Biswas, V.L. Patel, V. Bhaskar, J.A. Chao, R.H. Singer, C. Eliscovich, The structural basis for RNA selectivity by the IMP family of RNA-binding proteins, Nat. Commun. vol. 10 (1) (2019) 1–10.
[24] H. Huang, et al., Recognition of RNA N 6 -methyladenosine by IGF2BP proteins enhances mRNA stability and translation, Nat. Cell Biol. vol. 20 (3) (2018) 285–295.
[25] M. Hafner, et al., Transcriptome-wide Identification of RNA-binding protein and microRNA target sites by PAR-CLIP, Cell vol. 141 (1) (2010) 129–141.
[26] A.E. Conway, et al., Enhanced CLIP uncovers IMP Protein-RNA targets in human pluripotent stem cells important for cell adhesion and survival, Cell Rep. vol. 15 (3) (2016) 666–679.
[27] J.K. Palanichamy, et al., RNA-binding protein IGF2BP3 targeting of oncogenic transcripts promotes hematopoietic progenitor proliferation, J. Clin. Invest vol. 126 (4) (2016) 1495–1511.
[28] H. Ennajdaoui, et al., IGF2BP3 modulates the interaction of invasion-associated transcripts with RISC, Cell Rep. vol. 15 (9) (2016) 1876–1883.
[29] R. Valverde, L. Edwards, L. Regan, Structure and function of KH domains, FEBS J. vol. 275 (11) (2008) 2712–2726.
[30] V.L. Patel, et al., Spatial arrangement of an RNA zipcode identifies mRNAs under post-transcriptional control, Genes Dev. vol. 26 (1) (2012) 43–53.
[31] J. Christiansen, A.M. Kolte, T.V.O. Hansen, F.C. Nielsen, IGF2 mRNA-binding protein 2: biological function and putative role in type 2 diabetes, J. Mol. Endocrinol. vol. 43 (5) (2009) 187–195.
[32] X. Li, et al., Variation in IGF2BP2 interacts with adiposity to alter insulin sensitivity in Mexican Americans, Obesity vol. 17 (4) (2009) 729–736.
[33] N. Dai, et al., IGF2BP2/IMP2-deficient mice resist obesity through enhanced translation of Ucp1 mRNA and other mRNAs encoding mitochondrial proteins, Cell Metab. vol. 21 (4) (2015) 609–621.
[34] S. Ravanidis, F.G. Kattan, E. Doxakis, Unraveling the pathways to neuronal homeostasis and disease: Mechanistic insights into the role of RNA-binding proteins and associated factors, Int. J. Mol. Sci. vol. 19 (8) (2018) 1–49.
[35] J.K. Yisraeli, VICKZ proteins: a multi-talented family of regulatory RNA-binding proteins, Biol. Cell vol. 97 (1) (2005) 87–96.
[36] T.V.O. Hansen, et al., Dwarfism and impaired gut development in insulin-like growth factor II mRNA-binding protein 1-deficient mice, Mol. Cell. Biol. vol. 24 (10) (2004) 4448–4464.
[37] J.R. Brants, T.A.Y. Ayoubi, K. Chada, K. Marchal, W.J.M. Van De Ven, M.M. R. Petit, Differential regulation of the insulin-like growth factor II mRNA-binding protein genes by architectural transcription factor HMGA2, FEBS Lett. vol. 569 (1–3) (2004) 277–283.
[38] L.O. Huang, et al., Genome-wide discovery of genetic loci that uncouple excess adiposity from its comorbidities, Nat. Metab. vol. 3 (2) (2021) 228–243.
[39] L.J. Scott, et al., A genome-wide association study of type 2 diabetes in finns detects multiple susceptibility variants, Science vol. 316 (5829) (2007) 1341–1345.
[40] E. Zeggini, et al., Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes, Science vol. 316 (5829) (2007) 1336–1341.
[41] R. Bechara, et al., The RNA-binding protein IMP2 drives a stromal-Th17 cell circuit in autoimmune neuroinflammation, JCI Insight vol. 7 (3) (2022).
[42] Z.L. Wang, et al., Comprehensive genomic characterization of RNA-binding proteins across human cancers, Cell Rep. vol. 22 (1) (2018) 286–298.
[43] J. Vikesaa, et al., RNA-binding IMPs promote cell adhesion and invadopodia formation, EMBO J. vol. 25 (7) (2006) 1456–1468.
[44] M. Köbel, et al., Expression of the RNA-binding protein IMP1 correlates with poor prognosis in ovarian carcinoma, Oncogene vol. 26 (54) (2007) 7584–7589.
[45] T. Kato, et al., Increased expression of insulin-like growth factor-II messenger RNA-binding protein 1 is associated with tumor progression in patients with lung cancer, Clin. Cancer Res. vol. 13 (2 I) (2007) 434–442.
[46] Y.B. Rosenfeld, et al., VICKZ1 enhances tumor progression and metastasis in lung adenocarcinomas in mice, Oncogene (2019).
[47] A. Barghash, V. Helms, S.M. Kessler, Overexpression of IGF2 mRNA-Binding Protein 2 (IMP2/p62) as a Feature of Basal-like Breast Cancer Correlates with Short Survival, Scand. J. Immunol. vol. 82 (2) (2015) 142–143.
[48] T. Li, et al., METTL3 facilitates tumor progression via an m6A-IGF2BP2-dependent mechanism in colorectal carcinoma, Mol. Cancer vol. 18 (1) (2019) 1–15.
[49] A. Barghash, N. Golob-Schwarzl, V. Helms, J. Haybaeck, S.M. Kessler, Elevated expression of the IGF2 mRNA binding protein 2 (IGF2BP2/IMP2) is linked to short survival and metastasis in esophageal adenocarcinoma, Oncotarget vol. 7 (31) (2016) 49743–49750.
[50] Y. Yang, et al., Tumor suppressor microRNA-138 suppresses low-grade glioma development and metastasis via regulating IGF2BP2, Onco. Targets Ther. vol. 13 (2020) 2247–2260.
[51] A.A. Waly, et al., Methylation in MIRLET7A3 gene induces the expression of IGF-II and its mRNA binding proteins IGF2BP-2 and 3 in Hepatocellular carcinoma, Front. Physiol. vol. 10 (JAN) (2019) 1–10.
[52] J. Pu, et al., IGF2BP2 Promotes Liver Cancer Growth Through an m6A-FEN1-Dependent Mechanism, Front. Oncol. vol. 10 (November) (2020) 1–10.
[53] X. Xu, Y. Yu, K. Zong, P. Lv, Y. Gu, Up-regulation of IGF2BP2 by multiple mechanisms in pancreatic cancer promotes cancer proliferation by activating the PI3K/Akt signaling pathway, J. Exp. Clin. Cancer Res. vol. 38 (1) (2019) 1–14.
[54] S. Huang, Z. Wu, Y. Cheng, W. Wei, L. Hao, Insulin-like growth factor 2 mRNA binding protein 2 promotes aerobic glycolysis and cell proliferation in pancreatic ductal adenocarcinoma via stabilizing GLUT1 mRNA, Acta Biochim. Biophys. Sin. (Shanghai) vol. 51 (7) (2019) 743–752.
[55] C. Dahlem, A. Barghash, P. Puchas, J. Haybaeck, S.M. Kessler, The insulin-like growth factor 2 mRNA binding protein IMP2/IGF2BP2 is overexpressed and correlates with poor survival in pancreatic cancer, Int. J. Mol. Sci. vol. 20 (13) (2019) 1–8.
[56] X. Hu, et al., IGF2BP2 regulates DANCR by serving as an N6-methyladenosine reader, Cell Death Differ. vol. 27 (6) (2020) 1782–1794.

[57] X. He, et al., IGF2BP2 overexpression indicates poor survival in patients with acute myelocytic leukemia, Cell. Physiol. Biochem. vol. 51 (4) (2018) 1945–1956.
[58] C. Mancarella, et al., Insulin-like growth factor 2 mRNA-binding protein 3 is a novel post-transcriptional regulato of ewing sarcoma malignancy, Clin. Cancer Res. vol. 24 (15) (2018) 3704–3716.
[59] X. Deng, Q. Jiang, Z. Liu, W. Chen, Clinical Significance of an m6A Reader Gene, IGF2BP2, in Head and Neck Squamous Cell Carcinoma, Front. Mol. Biosci. vol. 7 (2020) 1–9.
[60] N. Dai, F. Ji, J. Wright, L. Minichiello, R. Sadreyev, J. Avruch, IGF2 mRNA binding Protein-2 is a tumor promoter that drives cancer proliferation through its client mRNAs IGF2 and HMGA1, Elife vol. 6 (2017) 1–21.
[61] F.K. Noubissi, et al., CRD-BP mediates stabilization of βTrCP1 and c-myc mRNA in response to β-catenin signalling, Nature vol. 441 (7095) (2006) 898–901.
[62] C.R. Tessier, G.A. Doyle, B.A. Clark, H.C. Pitot, J. Ross, Mammary tumor induction in transgenic mice expressing an RNA-binding protein, Cancer Res. vol. 64 (1) (2004) 209–214.
[63] A. Ghoshal, et al., Extracellular vesicle-dependent effect of RNA-binding protein IGF2BP1 on melanoma metastasis, Oncogene vol. 38 (21) (2019) 4182–4196.
[64] T.W. Kim, T. Havighurst, K.M. Kim, M. Albertini, Y.G. Xu, V.S. Spiegelman, Targeting insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in metastatic melanoma to increase efficacy of BRAFV600E inhibitors, Mol. Carcinog. vol. 57 (5) (2018) 678–683.
[65] K.E. Hamilton, et al., IMP1 promotes tumor growth, dissemination and a tumor-initiating cell phenotype in colorectal cancer cell xenografts, Carcinogenesis vol. 34 (11) (2013) 2647–2654.
[66] T.M. Tran, et al., The RNA-binding protein IGF2BP3 is critical for MLL-AF4-mediated leukemogenesis, Leukemia vol. 36 (1) (2022) 68–79.
[67] I. Elcheva, S. Goswami, F.K. Noubissi, V.S. Spiegelman, CRD-BP protects the coding region of βTrCP1 mRNA from miR-183-mediated degradation, Mol. Cell vol. 35 (2) (2009) 240–246.
[68] D. Sparanese, C.H. Lee, CRD-BP shields c-myc and MDR-1 RNA from endonucleolytic attack by a mammalian endoribonuclease, Nucleic Acids Res. vol. 35 (4) (2007) 1209–1221.
[69] N. Stöhr, et al., IGF2BP1 promotes cell migration by regulating MK5 and PTEN signaling, Genes Dev. vol. 26 (2) (2012) 176–189.
[70] S. Müller, et al., IGF2BP1 enhances an aggressive tumor cell phenotype by impairing miRNA-directed downregulation of oncogenic factors, Nucleic Acids Res. vol. 46 (12) (2018) 6285–6303.
[71] X. Wang, et al., N 6-methyladenosine-dependent regulation of messenger RNA stability, Nature vol. 505 (7481) (2014) 117–120.
[72] C.M. Wei, A. Gershowitz, B. Moss, Methylated nucleotides block 5′ terminus of HeLa cell messenger RNA, Cell vol. 4 (4) (1975) 379–386.
[73] M. Lee, B. Kim, V.N. Kim, Emerging roles of RNA modification: M6A and U-Tail, Cell vol. 158 (5) (2014) 980–987.
[74] J. Liu, et al., A METTL3-METTL14 complex mediates mammalian nuclear RNA N6-adenosine methylation, Nat. Chem. Biol. vol. 10 (2) (2014) 93–95.
[75] X.L. Ping, et al., Mammalian WTAP is a regulatory subunit of the RNA N6-methyladenosine methyltransferase, Cell Res. vol. 24 (2) (2014) 177–189.
[76] Y. Wang, Y. Li, J.I. Toth, M.D. Petroski, Z. Zhang, J.C. Zhao, N6 -methyladenosine modification destabilizes developmental regulators in embryonic stem cells, Nat. Cell Biol. vol. 16 (2) (2014) 191–198.
[77] D.P. Patil, et al., M6 A RNA methylation promotes XIST-mediated transcriptional repression, Nature vol. 537 (7620) (2016) 369–373.
[78] P. Knuckles, et al., Zc3h13/Flacc is required for adenosine methylation by bridging the mRNA-binding factor RbM15/spenito to the m6 a machinery component Wtap/Fl(2)d, Genes Dev. vol. 32 (5–6) (2018) 415–429.
[79] D. Dominissini, et al., Topology of the human and mouse m6A RNA methylomes revealed by m6A-seq, Nature vol. 485 (7397) (2012) 201–206.
[80] K.D. Meyer, Y. Saletore, P. Zumbo, O. Elemento, C.E. Mason, S.R. Jaffrey, Comprehensive analysis of mRNA methylation reveals enrichment in 3′ UTRs and near stop codons, Cell vol. 149 (7) (2012) 1635–1646.
[81] G. Zheng, et al., ALKBH5 Is a Mammalian RNA Demethylase that Impacts RNA Metabolism and Mouse Fertility, Mol. Cell vol. 49 (1) (2013) 18–29.
[82] A.S. Warda, et al., Human METTL16 is a N 6 –methyladenosine (m 6 A) methyltransferase that targets pre-mRNAs and various non-coding RNAs, EMBO Rep. vol. 18 (11) (2017) 2004–2014.
[83] H. Shima, et al., S-adenosylmethionine synthesis is regulated by selective N6-adenosine methylation and mRNA degradation involving METTL16 and YTHDC1, Cell Rep. vol. 21 (12) (2017) 3354–3363.
[84] G. Jia, et al., N6-Methyladenosine in nuclear RNA is a major substrate of the obesity-associated FTO, Nat. Chem. Biol. vol. 7 (12) (2011) 885–887.
[85] Y. Ueda, et al., AlkB homolog 3-mediated tRNA demethylation promotes protein synthesis in cancer cells, Sci. Rep. vol. 7 (2017) 1–10.
[86] D.P. Patil, B.F. Pickering, S.R. Jaffrey, Reading m6A in the transcriptome: m6A-binding proteins, Trends Cell Biol. vol. 28 (2) (2018) 113–127.
[87] X. Wang, et al., N6-methyladenosine modulates messenger RNA translation efficiency, Cell vol. 161 (6) (2015) 1388–1399.
[88] K.D. Meyer, et al., 5′ UTR m6A promotes cap-independent translation, Cell vol. 163 (4) (2015) 999–1010.
[89] J. Zhou, J. Wan, X. Gao, X. Zhang, S.R. Jaffrey, S.B. Qian, Dynamic m6 A mRNA methylation directs translational control of heat shock response, Nature vol. 526 (7574) (2015) 591–594.
[90] C.R. Alarcón, H. Goodarzi, H. Lee, X. Liu, S. Tavazoie, S.F. Tavazoie, HNRNPA2B1 is a mediator of m6A-dependent nuclear RNA processing events, Cell vol. 162 (6) (2015) 1299–1308.
[91] R.W. Yao, Y. Wang, L.L. Chen, Cellular functions of long noncoding RNAs, Nat. Cell Biol. vol. 21 (5) (2019) 542–551.
[92] K.C. Wang, H.Y. Chang, Molecular mechanisms of long noncoding RNAs, Mol. Cell vol. 43 (6) (2011) 904–914.
[93] A.A. Mansour, et al., Toward differentiation, Sci. (80-.). vol. 347 (6225) (2015) 1002–1006.
[94] J.M. Fustin, et al., XRNA-methylation-dependent RNA processing controls the speed of the circadian clock, Cell vol. 155 (4) (2013) 793.
[95] S. Ke, et al., A majority of m6A residues are in the last exons, allowing the potential for 3′ UTR regulation, Genes Dev. vol. 29 (19) (2015) 2037–2053.
[96] S. Müller, et al., IGF2BP1 promotes SRF-dependent transcription in cancer in a m 6 A- and miRNA-dependent manner, Nucleic Acids Res. vol. 47 (1) (2019) 375–390.
[97] N. Liu, Q. Dai, G. Zheng, C. He, M. Parisien, T. Pan, N6 -methyladenosine-dependent RNA structural switches regulate RNA-protein interactions, Nature vol. 518 (7540) (2015) 560–564.
[98] N. Liu, K.I. Zhou, M. Parisien, Q. Dai, L. Diatchenko, T. Pan, N6-methyladenosine alters RNA structure to regulate binding of a low-complexity protein, Nucleic Acids Res. vol. 45 (10) (2017) 6051–6063.
[99] K.I. Zhou, et al., Regulation of co-transcriptional Pre-mRNA Splicing by m6A through the Low-Complexity Protein hnRNPG, Mol. Cell vol. 76 (1) (2019) 70–81. e9.
[100] B. Wu, et al., Molecular basis for the specific and multivariant recognitions of RNA substrates by human hnRNP A2/B1, Nat. Commun. vol. 9 (1) (2018).
[101] A.E. Arguello, A.N. Deliberto, R.E. Kleiner, RNA chemical proteomics reveals the N6-methyladenosine (m6a)-regulated protein-RNA interactome, J. Am. Chem. Soc. vol. 139 (48) (2017) 17249–17252.
[102] R.R. Edupuganti, et al., N6-methyladenosine (m6A) recruits and repels proteins to regulate mRNA homeostasis, Nat. Struct. Mol. Biol. vol. 24 (10) (2017) 870–878.
[103] M. Holcik, N. Sonenberg, Translational control in stress and apoptosis, Nat. Rev. Mol. Cell Biol. vol. 6 (4) (2005) 318–327.
[104] B. Walters, S.R. Thompson, Cap-independent translational control of carcinogenesis, Front. Oncol. vol. 6 (MAY) (2016) 1–8.
[105] A.M. El-Naggar, P.H. Sorensen, Translational control of aberrant stress responses as a hallmark of cancer, J. Pathol. vol. 244 (5) (2018) 650–666.
[106] P. Anderson, N. Kedersha, P. Ivanov, Stress granules, P-bodies and cancer, Biochim. Biophys. Acta - Gene Regul. Mech. vol. 1849 (7) (2015) 861–870.
[107] J.R. Buchan, R. Parker, Eukaryotic stress granules: the ins and outs of translation, Mol. Cell vol. 36 (6) (2009) 932–941.
[108] A.M. Bogorad, K.Y. Lin, A. Marintchev, Novel mechanisms of eIF2B action and regulation by eIF2 phosphorylation, Nucleic Acids Res. vol. 45 (20) (2017) 11962–11979.
[109] N. Stöhr, et al., ZBP1 Regul. mRNA Stab. Cell. Stress vol. 175 (4) (2006) 527–534.
[110] A.M. El-Naggar, et al., Translational activation of HIF1α by YB-1 promotes sarcoma metastasis, Cancer Cell vol. 27 (5) (2015) 682–697.
[111] M. Averna, et al., Fragile X Protein Binds mRNAs, Involv. Cancer Progress. Modul. Metastas Form (2013) 1523–1536.
[113] S.P. Somasekharan, et al., YB-1 regulates stress granule formation and tumor progression by translationally activating G3BP1, J Cell Biol. vol. 208 (7) (2015) 913–929.
[114] C. Zhang, D. Samanta, H. Lu, J.W. Bullen, H. Zhang, I. Chen, Hypoxia induces Breast Cancer stem Cell phenotype HIF-Depend. ALKBH5-Mediat. M. 6 A-demethylation NANOG mRNA (2016) 2047–2056.
[115] J. Zhou, et al., N6-methyladenosine guides mRNA alternative translation during integrated stress response, Mol. Cell vol. 69 (4) (2018) 636–647.e7.
[116] N. Bley, et al., Stress granules are dispensable for mRNA stabilization during cellular stress, Nucleic Acids Res. vol. 43 (4) (2015).
[117] J.R.M. Sophie Mokas, et al., Uncoupling stress granule assembly and translation initiation inhibition, Mol. Biol. Cell vol. 20 (2009) 2673–2683.
[118] S. Hofmann, V. Cherkasova, P. Bankhead, B. Bukau, G. Stoecklin, Translation suppression promotes stress granule formation and cell survival in response to cold shock, Mol. Biol. Cell vol. 23 (19) (2012) 3786–3800.
[119] L. Zhang, et al., IGF2BP1 overexpression stabilizes PEG10 mRNA in an m6A-dependent manner and promotes endometrial cancer progression, Theranostics vol. 11 (3) (2021) 1100–1114.
[120] Y. Zhang, et al., M6A modification-mediated CBX8 induction regulates stemness and chemosensitivity of colon cancer via upregulation of LGR5, Mol. Cancer vol. 18 (1) (2019) 1–16.
[121] S. Zhu, et al., An oncopeptide regulates m6A recognition by the m6A reader IGF2BP1 and tumorigenesis, Nat. Commun. vol. 11 (1) (2020) 1–14.
[122] S. Müller, et al., The oncofetal RNA-binding protein IGF2BP1 is a druggable, post-transcriptional super-enhancer of E2F-driven gene expression in cancer, Nucleic Acids Res. vol. 48 (15) (2020) 8576–8590.
[123] Z. Yang, T. Wang, D. Wu, Z. Min, J. Tan, B. Yu, RNA N6-methyladenosine reader IGF2BP3 regulates cell cycle and angiogenesis in colon cancer, J. Exp. Clin. Cancer Res. vol. 39 (1) (2020) 1–15.
[124] Q. Wang, et al., METTL3-mediated m 6 A modification of HDGF mRNA promotes gastric cancer progression and has prognostic significance, Gut vol. 69 (7) (2020) 1193–1205.
[125] R.W. Yao, Y. Wang, L.L. Chen, Cellular functions of long noncoding RNAs, Nat. Cell Biol. vol. 21 (5) (2019) 542–551.
[126] S.J. Liu, H.X. Dang, D.A. Lim, F.Y. Feng, C.A. Maher, Long noncoding RNAs in cancer metastasis, Nat. Rev. Cancer vol. 21 (7) (2021) 446–460.
[127] M. Cheng, et al., High-throughput profiling of alpha interferon- and interleukin-28B-regulated microRNAs and identification of let-7s with anti-hepatitis C virus activity by targeting IGF2BP1, J. Virol. vol. 87 (17) (2013) 9707–9718.

[128] X. Zhou, et al., MiR-625 suppresses tumour migration and invasion by targeting IGF2BP1 in hepatocellular carcinoma, Oncogene vol. 34 (8) (2015) 965–977.
[129] F.Y. Liu, et al., MiR-216b is involved in pathogenesis and progression of hepatocellular carcinoma through HBx-miR-216b-IGF2BP2 signaling pathway, Cell Death Dis. vol. 6 (3) (2015) 1–12.
[130] I.O. Fawzy, M.T. Hamza, K.A. Hosny, G. Esmat, H.M. El Tayebi, A.I. Abdelaziz, MiR-1275: a single microRNA that targets the three IGF2-mRNA-binding proteins hindering tumor growth in hepatocellular carcinoma, FEBS Lett. vol. 589 (17) (2015) 2257–2265.
[131] H. Huang, L. Li, K. Wen, Interactions between long non-coding RNAs and RNA-binding proteins in cancer (Review), Oncol. Rep. vol. 46 (6) (2021).
[132] C. Oliveira-Mateos, et al., The transcribed pseudogene RPSAP52 enhances the oncofetal HMGA2-IGF2BP2-RAS axis through LIN28B-dependent and independent let-7 inhibition, Nat. Commun. vol. 10 (1) (2019).
[133] Y. Hosono, et al., Oncogenic role of THOR, a conserved cancer/testis long non-coding RNA, Cell vol. 171 (7) (2017) 1559–1572.e20.
[134] F. Yang, et al., Long non-coding RNA GHET1 promotes gastric carcinoma cell proliferation by increasing c-Myc mRNA stability, FEBS J. vol. 281 (3) (2014) 802–813.
[135] Y. Xu, Y. Zheng, H. Liu, T. Li, Modulation of IGF2BP1 by long non-coding RNA HCG11 suppresses apoptosis of hepatocellular carcinoma cells via MAPK signaling transduction, Int. J. Oncol. vol. 51 (3) (2017) 791–800.
[136] C. Wang, et al., A cancer-testis non-coding RNA LIN28B-AS1 activates driver gene LIN28B by interacting with IGF2BP1 in lung adenocarcinoma, Oncogene vol. 38 (10) (2019) 1611–1624.
[137] H. Wu, et al., LINC01021 maintains tumorigenicity by enhancing N6-methyladenosine reader IMP2 dependent stabilization of MSX1 and JARID2: implication in colorectal cancer, Oncogene vol. 41 (13) (2022) 1959–1973.
[138] F. Ma, et al., Long non-coding RNA FGF13-AS1 inhibits glycolysis and stemness properties of breast cancer cells through FGF13-AS1/IGF2BPs/Myc feedback loop, Cancer Lett. vol. 450 (January) (2019) 63–75.
[139] J. He, et al., A novel, liver-specific long noncoding RNA LINC01093 suppresses HCC progression by interaction with IGF2BP1 to facilitate decay of GLI1 mRNA, Cancer Lett. vol. 450 (2019) 98–109.
[140] T. Gao, X. Liu, B. He, Y. Pan, S. Wang, Long non-coding RNA 91H regulates IGF2 expression by interacting with IGF2BP2 and promotes tumorigenesis in colorectal cancer, Artif. Cells, Nanomed. Biotechnol. vol. 48 (1) (2020) 664–671.
[141] Y. Wang, et al., LncRNA LINRIS stabilizes IGF2BP2 and promotes the aerobic glycolysis in colorectal cancer, Mol. Cancer vol. 18 (1) (2019) 1–18.
[142] M. Ye, S. Dong, H. Hou, T. Zhang, M. Shen, Oncogenic role of long noncoding RNAMALAT1 in thyroid cancer progression through regulation of the miR-204/IGF2BP2/m6A-MYC signaling, Mol. Ther. Nucleic Acids vol. 23 (88) (2021) 1–12.
[143] M. Hämmerle, et al., Posttranscriptional destabilization of the liver-specific long noncoding RNA HULC by the IGF2 mRNA-binding protein 1 (IGF2BP1), Hepatology vol. 58 (5) (2013) 1703–1712.
[144] S. Boudoukha, S. Cuvellier, A. Polesskaya, Role of the RNA-binding protein IMP-2 in muscle cell motility, Mol. Cell. Biol. vol. 30 (24) (2010) 5710–5725.
[145] S. Lu, et al., N6-methyladenosine reader IMP2 stabilizes the ZFAS1/OLA1 axis and activates the Warburg effect: implication in colorectal cancer, J. Hematol. Oncol. vol. 14 (1) (2021) 1–23.
[146] X. Li, L. Yang, L.L. Chen, The biogenesis, functions, and challenges of circular RNAs, Mol. Cell vol. 71 (3) (2018) 428–442.
[147] L.S. Kristensen, M.S. Andersen, L.V.W. Stagsted, K.K. Ebbesen, T.B. Hansen, J. Kjems, The biogenesis, biology and characterization of circular RNAs, Nat. Rev. Genet. vol. 20 (11) (2019) 675–691.
[148] C. Zhou, et al., Genome-Wide Maps of m6A circRNAs identify widespread and cell-type-specific methylation patterns that are distinct from mRNAs, Cell Rep. vol. 20 (9) (2017) 2262–2276.
[149] X.O. Zhang, H. Bin Wang, Y. Zhang, X. Lu, L.L. Chen, L. Yang, Complementary sequence-mediated exon circularization, Cell vol. 159 (1) (2014) 134–147.
[150] C. Tang, et al., m6A-dependent biogenesis of circular RNAs in male germ cells, Cell Res. vol. 30 (3) (2020) 211–228.
[151] R.X. Chen, et al., N 6-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis, Nat. Commun. vol. 10 (1) (2019) 1–15.
[152] O.H. Park, et al., Endoribonucleolytic cleavage of m6A-containing RNAs by RNase P/MRP complex, Mol. Cell vol. 74 (3) (2019) 494–507.e8.
[153] I. Legnini, et al., Circ-ZNF609 is a circular RNA that can be translated and functions in myogenesis, Mol. Cell vol. 66 (1) (2017) 22–37.e9.
[154] N.R. Pamudurti, et al., Translation of CircRNAs, Mol. Cell vol. 66 (1) (2017) 9–21.e7.
[155] M. Zhang, et al., A novel protein encoded by the circular form of the SHPRH gene suppresses glioma tumorigenesis, Oncogene vol. 37 (13) (2018) 1805–1814.
[156] W.C. Liang, et al., Translation of the circular RNA circβ-catenin promotes liver cancer cell growth through activation of the Wnt pathway, Genome Biol. vol. 20 (1) (2019) 1–12.
[157] Y. Yang, et al., Extensive translation of circular RNAs driven by N 6 -methyladenosine, Cell Res. vol. 27 (5) (2017) 626–641.
[158] J.U. Guo, V. Agarwal, H. Guo, D.P. Bartel, Expanded identification and characterization of mammalian circular RNAs, Genome Biol. (2014).
[159] J. Zhao, et al., Transforming activity of an oncoprotein-encoding circular RNA from human papillomavirus, Nat. Commun. vol. 10 (1) (2019).
[160] G. Di Timoteo, et al., Modulation of circRNA metabolism by m6A modification, Cell Rep. vol. 31 (6) (2020).
[161] B. Li, et al., circNDUFB2 inhibits non-small cell lung cancer progression via destabilizing IGF2BPs and activating anti-tumor immunity, Nat. Commun. vol. 12 (1) (2021) 1–15.
[162] F. Xie, et al., CircPTPRA blocks the recognition of RNA N6-methyladenosine through interacting with IGF2BP1 to suppress bladder cancer progression, Mol. Cancer vol. 20 (1) (2021) 1–17.
[163] D. Hanniford, et al., Epigenetic silencing of CDR1as drives IGF2BP3-mediated melanoma, Invasion Metastas vol. 37 (1) (2020).
[164] R.X. Chen, et al., N 6-methyladenosine modification of circNSUN2 facilitates cytoplasmic export and stabilizes HMGA2 to promote colorectal liver metastasis, Nat. Commun. vol. 10 (1) (2019) 1–15.
[165] A. Chellamuthu, S.G. Gray, The RNA methyltransferase NSUN2 and its potential roles in cancer, Cells vol. 9 (8) (2020) 1–22.
[166] L. Mahapatra, C. Mao, N. Andruska, C. Zhang, D.J. Shapiro, High-throughput fluorescence anisotropy screen for inhibitors of the oncogenic mrna binding protein, IMP-1, J. Biomol. Screen. vol. 19 (3) (2014) 427–436.
[167] L. Mahapatra, N. Andruska, C. Mao, J. Le, D.J. Shapiro, A Novel IMP1 Inhibitor, BTYNB, targets c-Myc and inhibits melanoma and ovarian cancer cell proliferation, Transl. Oncol. vol. 10 (5) (2017) 818–827.
[168] N. Wallis, et al., Small molecule inhibitor of Igf2bp1 represses Kras and a pro-oncogenic phenotype in cancer cells, RNA Biol. vol. 19 (1) (2022) 26–43.
[169] C. Dahlem, et al., First small-molecule inhibitors targeting the RNA-binding protein IGF2BP2/IMP2 for cancer therapy, ACS Chem. Biol. vol. 17 (2) (2022) 361–375.
[170] K.E. Elagib, et al., Neonatal expression of RNA-binding protein IGF2BP3 regulates the human fetal-adult megakaryocyte transition, J. Clin. Invest vol. 127 (6) (2017) 2365–2377.
[171] T. Rivera Vargas, et al., Post-transcriptional regulation of cyclins D1, D3 and G1 and proliferation of human cancer cells depend on IMP-3 nuclear localization, Oncogene vol. 33 (22) (2014) 2866–2875.
[172] M. Köhn, M. Lederer, K. Wächter, S. Hüttelmaier, Near-infrared (NIR) dye-labeled RNAs identify binding of ZBP1 to the noncoding Y3-RNA, Rna vol. 16 (7) (2010) 1420–1428.
[173] S. Sim, J. Yao, D.E. Weinberg, S. Niessen, J.R. Yates, S.L. Wolin, The zipcode-binding protein ZBP1 influences the subcellular location of the Ro 60-kDa autoantigen and the noncoding Y3 RNA, RNA vol. 18 (1) (2012) 100–110.
[174] C. Oliveira-Mateos, et al., The transcribed pseudogene RPSAP52 enhances the oncofetal HMGA2-IGF2BP2-RAS axis through LIN28B-dependent and independent let-7 inhibition, Nat. Commun. vol. 10 (1) (2019).
[175] A. Padrón, S. Iwasaki, N.T. Ingolia, Proximity RNA labeling by APEX-seq reveals the organization of translation initiation complexes and repressive RNA granules, Mol. Cell vol. 75 (4) (2019) 875–887.e5.
[176] L. Statello, C.J. Guo, L.L. Chen, M. Huarte, Gene regulation by long non-coding RNAs and its biological functions, Nat. Rev. Mol. Cell Biol. vol. 22 (2) (2021) 96–118.
[177] F.M. Fazal, et al., Atlas of subcellular RNA localization revealed by APEX-Seq, Cell vol. 178 (2) (2019) 473–490.e26.
[178] R.J. Ries, et al., m6A enhances the phase separation potential of mRNA, Nature vol. 571 (7765) (2019) 424–428.
[179] J.H. Lee, et al., Enhancer RNA m6A methylation facilitates transcriptional condensate formation and gene activation, Mol. Cell vol. 81 (16) (2021) 3368–3385.e9.
[180] M. Anders, et al., Dynamic m6a methylation facilitates mRNA triaging to stress granules, Life Sci. Alliance vol. 1 (4) (2018) 1–12.
[181] L. Jiang, et al., Interaction of tau with HNRNPA2B1 and N6-methyladenosine RNA mediates the progression of tauopathy, Mol. Cell vol. 81 (20) (2021) 4209–4227.e12.
[182] B. Boyerinas, et al., Let-7 modulates acquired resistance of ovarian cancer to Taxanes via IMP-1-mediated stabilization of multidrug resistance 1, Int. J. Cancer vol. 130 (8) (2012) 1787–1797.
[183] P.S. Mongroo, et al., IMP-1 displays cross-talk with K-Ras and modulates colon cancer cell survival through the novel proapoptotic protein CYFIP2, Cancer Res. vol. 71 (6) (2011) 2172–2182.
[184] S. Weinlich, S. Hüttelmaier, A. Schierhorn, S.E. Behrens, A. Ostareck-Lederer, D. H. Ostareck, IGF2BP1 enhances HCV IRES-mediated translation initiation via the 3′UTR, RNA vol. 15 (8) (2009) 1528–1542.
[185] J. Yao, Y. Sasaki, Z. Wen, G.J. Bassell, J.Q. Zheng, An essential role for β-actin mRNA localization and translation in Ca2+-dependent growth cone guidance, Nat. Neurosci. vol. 9 (10) (2006) 1265–1273.
[186] T. Eom, L.N. Antar, R.H. Singer, G.J. Bassell, Localization of a B-Actin messenger ribonucleoprotein complex with zipcode-binding protein modulates the density of dendritic filopodia and filopodial synapses, J. Neurosci. vol. 23 (32) (2003) 10433–10444.
[187] J. Zhang, et al., Comprehensive profiling of novel microRNA-9 targets and a tumor suppressor role of microRNA-9 via targeting IGF2BP1 in hepatocellular carcinoma, Oncotarget vol. 6 (39) (2015) 42040–42052.
[188] W. Gu, A.L. Wells, F. Pan, R.H. Singer, Feedback regulation between zipcode binding protein 1 and β-catenin mRNAs in breast cancer cells, Mol. Cell. Biol. vol. 28 (16) (2008) 4963–4974.
[189] B. Liao, Y. Hu, G. Brewer, RNA-binding protein insulin-like growth factor mRNA-binding protein 3 (IMP-3) promotes cell survival via insulin-like growth factor II signaling after ionizing radiation, J. Biol. Chem. vol. 286 (36) (2011) 31145–31152.
[190] R. Suvasini, et al., Insulin growth factor-2 binding protein 3 (IGF2BP3) is a glioblastoma-specific marker that activates phosphatidylinositol 3-kinase/

mitogen-activated protein kinase (PI3K/MAPK) pathways by modulating IGF-2, J. Biol. Chem. vol. 286 (29) (2011) 25882–25890.
[191] B. Liao, Y. Hu, D.J. Herrick, G. Brewer, The RNA-binding protein IMP-3 is a translational activator of insulin-like growth factor II leader-3 mRNA during proliferation of human K562 leukemia cells, J. Biol. Chem. vol. 280 (18) (2005) 18517–18524.
[192] C. Shen, et al., M6A-dependent glycolysis enhances colorectal cancer progression, Mol. Cancer vol. 19 (1) (2020) 1–19.
[193] Y. Hosono, et al., Oncogenic role of THOR, a conserved cancer/testis long non-coding RNA, Cell vol. 171 (7) (2017) 1559–1572.e20.
[194] C. Wang, et al., A cancer-testis non-coding RNA LIN28B-AS1 activates driver gene LIN28B by interacting with IGF2BP1 in lung adenocarcinoma, Oncogene vol. 38 (10) (2019) 1611–1624.
[195] J.A. Chao, Y. Patskovsky, V. Patel, M. Levy, S.C. Almo, R.H. Singer, ZBP1 recognition of β-actin zipcode induces RNA looping, Genes Dev. vol. 24 (2) (2010) 148–158.