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Review article

Effects of N6-methyladenosine modification on metabolic reprogramming in digestive tract tumors

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ABSTRACT

N6-methyladenosine (m6A), the most abundant RNA modification within cells, participates in various biological and pathological processes, including self-renewal, invasion and proliferation, drug resistance, and stem cell characteristics. The m6A methylation plays a crucial role in tumors by regulating multiple RNA processes such as transcription, processing, and translation. Three protein types are primarily involved in m6A methylation: methyltransferases (such as METTL3, METTL14, ZC3H13, and KIAA1429), demethylases (such as FTO, ALKBH5), and RNA-binding proteins (such as the family of YTHDF, YTHDC1, YTHDC2, and IGF2BPs). Various metabolic pathways are reprogrammed in digestive tumors to meet the heightened growth demands and sustain cellular functionality. Recent studies have highlighted the extensive impact of m6A on the regulation of digestive tract tumor metabolism, further modulating tumor initiation and progression. Our review aims to provide a comprehensive understanding of the expression patterns, functional roles, and regulatory mechanisms of m6A in digestive tract tumor metabolism-related molecules and pathways. The characterization of expression profiles of m6A regulatory factors and in-depth studies on m6A methylation in digestive system tumors may provide new directions for clinical prediction and innovative therapeutic interventions.

1. Introduction

RNA modifications constitute a significant facet of epigenetic modifications and are present in diverse RNA types, such as messenger RNAs (mRNAs), transfer RNAs (tRNAs), ribosomal RNAs (rRNAs), circular RNAs (circRNAs), micro RNAs (miRNA), and long non-coding RNAs (lncRNAs) [1–4]. Eukaryotes exhibit an abundance of over 170 RNA modifications, including 5-methylcytosine (m5C), N1-methyladenosine (m1A), N6-methyladenosine (m6A), pseudouridine (Ψ), and 5-methyluridine (m5U) [5,6]. Among these, m6A is the most studied modification, facilitated by pioneering approaches like high-throughput sequencing and specific

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antibodies-based methodologies [7,8]. Methylated RNA immunoprecipitation and sequencing (MeRIP-seq), a technology used to locate m6A sites at the transcriptome-wide scale, has revealed over 12,000 distinct m6A sites and regions with high m6A methylation [9]. Recognizing the limitations of MeRIP-seq (an average resolution of 100–200 nucleotides), efforts have led to the development of refined techniques with enhanced sensitivity and resolution. These encompass mapping methods based on the single-nucleotide-resolution including m6A individual-nucleotide-resolution Crosslinking and Immunoprecipitation (miCLIP), and Site-specific Cleavage And Radioactive-labeling followed by Ligation-assisted Extraction and Thin-layer chromatography (SCARLET) [10,11]. Given the limitation associated with the quantification of m6A stoichiometry, cross-reactivity, and antibodies for antibody-based technologies, innovative m6A detection methods have emerged, including m6A-sensitive RNA-Endoribonuclease-Facilitated sequencing (m6A-REF-seq) and Multiomic And Zero backup RNA-Sequencing (MAZTER-seq) [12,13], which operate in an antibody-independent manner. Moreover, sequencing methodologies based on single-base resolution, such as glyoxal and nitrite-mediated deamination of unmethylated adenosines (GLORI), are also being developed to apply for absolute quantification and precise mapping of m6A [14]. These methodologies have revealed multiple m6A characteristics, with a prominent distribution observed in near-stop codons and 3′untranslated regions (3′UTRs) [15,16]. Functionally, m6A influences all stages of RNA metabolism processing, impacting alternative splicing, folding, translation, and degradation [17–19]. Notably, m6A has been implicated in exerting a pivotal role in the regulation of diverse biological contexts and disease progression, including stem cell differentiation, immunoregulation, bacterial infection, and cancer development [20–23].

Digestive tract malignancies represent a class of diseases characterized by strong heterogeneity and rapid progression, often marked by inadequate treatment responses [24,25]. Despite considerable efforts, the current therapeutic strategies for the treatment of digestive tract tumors remain inadequate, resulting in unsatisfactory overall postoperative survival rates for patients [26,27]. These tumor types include liver cancer (especially hepatocellular carcinoma, HCC), gastric cancer (GC), colorectal cancer (CRC), pancreatic cancer (PC), and esophageal cancer (EC), collectively posing a significant challenge to global healthcare resources [28]. Therefore, investigating the molecular mechanisms underlying the pathogenesis of these digestive tract tumors holds immense importance. Recent evidence has demonstrated a close association between aberrantly expressed m6A modifications and human tumor metabolisms [29–31]. The development of digestive tract malignancies is a multi-step process involving complex interactions between m6A modification and reprogrammed metabolic pathways [32]. By gaining deeper insights into these mechanisms, we can better understand the developmental trajectories of these tumors and provide a basis for the development of more effective therapeutic strategies [33–36].

The “Warburg effect” or “aerobic glycolysis” is universally recognized as a hallmark of metabolic reprogramming in tumor cells, wherein tumor cells preferentially opt for cytoplasmic glycolysis to generate energy, even under aerobic or anoxic conditions [37,38]. This metabolic shift towards glycolysis is a common feature observed in many cancer types, including digestive tract tumors [39]. Additionally, tumor cells exhibit alterations in lipid metabolism [40], marked by a significant increase in lipid synthesis, uptake, and storage, primarily to mainly meet the heightened demand for cellular membrane components required for malignant behaviors [41]. These metabolic shifts are notably evident in digestive tract tumors and significantly contribute to their pathogenesis. In addition to changes in glucose and fatty acid metabolism, digestive tract tumors also demonstrate alterations in amino acid metabolism and mitochondrial activity, among other metabolic states [42–44]. These metabolic adaptations aid in supporting the growth and survival of tumor cells [45,46]. In recent years, a growing body of research has suggested that m6A modification plays a crucial role in the metabolic reprogramming of digestive tract tumors [47–49]. Therefore, investigating the effects and mechanisms underlying m6A methylation on key metabolic pathways within digestive tract tumors not only enhances our understanding of the intricate interplay between metabolism and digestive tract cancers but also offers new strategies for their diagnosis and treatment [48,50,51].

In this review, we focused on the effects of m6A methylation in regulating metabolic changes of digestive tract tumors based on our understanding of all the available relevant articles. We provide a comprehensive outline of the expression profiles, functional implications, detailed regulatory mechanisms of m6A methylation, and their potential clinical significance in digestive tract tumors. As for the literature search methods, we conducted an extensive literature search, including multiple databases such as PubMed, Web of Science, and EMBASE, using keywords such as “N6-methyladenosine,” “digestive tract tumors,” and “metabolic reprogramming.” Apart from online databases, we also reviewed recent conference abstracts and the latest articles published in relevant journals. For each high-impact article, we carefully read the abstracts and full texts to ensure their relevance to our research topic.

2. m6A methylation

The m6A methylation is a dynamic and reversible chemical modification process, mediated through the interactions of methyltransferases (m6A “writers”), demethylases (m6A “erasers”), and m6A “reader” proteins [52]. This section provides a comprehensive introduction to the major classifications and biological functions of m6A regulators in diverse biological processes.

2.1. m6A methyltransferase

m6A methyltransferases consist of several “writer” proteins, including well-established methyltransferase-like 3/5/14/16 (METTL3/5/14/16), WT1-associated protein (WTAP), zinc finger CCCH-type containing 13 (ZC3H13), vir-like m6A methyltransferase-associated (VIRMA, commonly known as KIAA1429), and RNA-binding motif protein 15 (RBM15) [53–56]. The potential presence of other lesser-explored m6A methyltransferases remains a plausible prospect. Usually, these m6A methyltransferases assemble into multicomponent methyltransferase complexes (MTC), which consist of a core heterodimer formed by METTL3 and METTL14, complemented by WTAP as the regulatory subunits for complex stabilization [57–60]. Most m6A

Table 1
Regulatory mechanisms of m6A methylation on metabolic reprogramming in digestive tract tumors.

Disease	Metabolism	Writer	Eraser	Reader	Related targets[a]	Underlying mechanism in tumor metabolism[b]	Refs.
liver cancer	glucose metabolism	METTL3	/	/	HIF-1α mRNA	HBXIP-mediated METTL3 overexpression increased HIF-1α level	[88]
	glucose metabolism	METTL14	/	/	USP48 mRNA	METTL14 maintained USP48 mRNA stability to inhibit SIRT6 degradation	[89]
	glucose metabolism	ZC3H13	/	/	PKM2 mRNA	ZC3H13-induced m6A-modified patterns abolished PKM2 mRNA stability	[90]
	lipid metabolism	METTL3, and METTL14	/	/	ACLY, and SCD1 mRNA	METTL14 and METTL3 directly increased the m6A modification of ACLY and SCD1 mRNA	[91]
	lipid metabolism	METTL5	/	/	18S rRNA	METTL5 mediated 18S rRNA m6A modification to upregulate the mRNA translation of ACSL4	[92]
	purine anabolism	METTL3	/	/	DTL mRNA	METTL3 upregulated the m6A modification of DTL	[93]
	glucose metabolism	/	ALKBH5	/	UBR7 mRNA	ALKBH5 stabilized and increased UBR7 expression and activated the Keap1/Nrf2/Bach1 axis to downregulate HK2 expression	[105]
	glucose metabolism	/	/	YTHDF3	PFKL mRNA	YTHDF3 suppressed the degradation of PFKL mRNA via m6A modification	[112]
	glucose metabolism	/	/	IGF2BP2	HK2, and GLUT1 mRNA	miR4458HG bound IGF2BP2 and facilitated IGF2BP2-mediated target mRNA stability of HK2 and GLUT1	[113]
colorectal cancer	glucose metabolism	METTL3	/	IGF2BP2, and IGF2BP3	HK2, and GLUT1 mRNA	METTL3 upregulated HK2 and GLUT1 expression and stabilities through an m6A-IGF2BP2/3- dependent mechanism	[94]
	glucose metabolism	METTL3	/	/	GLUT1 mRNA	METTL3 induced GLUT1 translation in an m6A-dependent manner and the activation of mTORC1 signaling	[95]
	glucose metabolism	METTL3	/	YTHDF1	LDHA mRNA	METTL3 and YTHDF1 enhanced the expression of LDHA.	[96]
	lipid metabolism	METTL3	/	YTHDF2	DEGS2 mRNA	Reduced METTL3 and YTHDF2 promoted DEGS2 expression	[98]
	iron metabolism	METTL4	/	IGF2BP2	TFRC mRNA	IGF2BP2 upregulated the expression of TFRC via METTL4	[99]
	glucose metabolism	METTL16	/	IGF2BP1	SOGA1 mRNA	METTL16 bound with IGF2BP1 and mediated SOGA1 mRNA to increase PDK4 expression	[97]
	glutamine metabolism	/	FTO	/	ATF4 mRNA	FTO enhanced ATF4 mRNA expression to upregulate DDIT4 and inactivate the mTOR pathway	[106]
	glucose metabolism	/	/	IGF2BP2	ZFAS1 mRNA	IGF2BP2 enhanced ZFAS1 expression to elevate OLA1 activity	[114]
	glutamine metabolism	/	/	YTHDF1	GLS1 mRNA	YTHDF1 promoted GLS1 expression	[115]
	mitochondrial metabolism	METTL3	/	HNRNPCL2	pri-mir-877	HNRNPCL2 recognized METTL3-modified pri-mir-877	[116]
	methionine metabolism	/	/	YTHDF1	PD-L1, and VISTA mRNA	YTHDF1 upregulated PD-L1 and VISTA expression in an m6A-dependent manner	[117]
colorectal cancer	glucose metabolism	METTL3	/	IGF2BP1	NDUFA4 mRNA	METTL3 increased NDUFA4 expression via IGF2BP1	[100]
	glucose metabolism	METTL14	/	/	LHPP mRNA	METTL14 upregulated LHPP expression to repress the phosphorylation of GSK-3β and the Wnt pathway	[101]
	lipid metabolism	METTL3	/	hnRNPA2B1	RPRD1B mRNA	METTL3 and hnRNPA2B1 induced RPRD1B overexpression with the assistance of lncRNA NEAT1 and then activated the c-Jun/c-Fos/AP1 axis	[102]
	mitochondrial oxidative phosphorylation (OXPHOS)	METTL3	/	/	AVEN, and DNAJB1 mRNA	METTL3 upregulated AVEN and DNAJB1 levels	[103]
	BH4 biosynthesis	METTL3	/	/	PBX1 mRNA	METTL3 combined with and stabilized PBX1 mRNA to increase GCH1 expression	[104]
	mitochondrial metabolism	/	FTO	/	caveolin-1 mRNA	FTO directly degraded caveolin-1 mRNA	[107]

(*continued on next page*)

Table 1 (*continued*)

Disease	Metabolism	Writer	Eraser	Reader	Related targets[a]	Underlying mechanism in tumor metabolism[b]	Refs.
	amino acid metabolism	/	ALKBH5	/	GLS2 mRNA	WZ35 downregulated the YAP-AXL-ALKBH5 axis and upregulated GLS2 mRNA	[108]
pancreatic cancer	glucose metabolism	/	ALKBH5	/	HDAC4 mRNA	ALKBH5 increased the expression of HDAC4 and HIF1α	[109]
	iron metabolism	/	ALKBH5	/	FBXL5 mRNA	ALKBH5 increased FBXL5 expression to downregulate IRP2 and SNAI1 proteins	[111]
	glucose metabolism	/	/	YTHDC1	miR-30d	YTHDC1 facilitated miR-30d biogenesis to inhibit GLUT1 and HK1 expression	[110]
esophageal cancer	lipid metabolism	/	FTO	YTHDF1	HSD17B11 mRNA	FTO upregulated HSD17B11 mRNA via YTHDF1	[118]

[a] HIF-1α (hypoxia-inducible factor-1α), USP48 (ubiquitin-specific protease 48), PKM2 (pyruvate kinase M2), ACLY (ATP citrate lyase), SCD1 (stearoyl-CoA desaturase1), DTL (a substrate receptor associated with the Cullin4-ring E3 ubiquitin ligase complex), UBR7 (ubiquitin protein ligase E3 component N-recognin 7), PFKL (phosphofructokinase), HK2 (hexokinase 2), GLUT1 (glucose transporter 1), LDHA (lactate dehydrogenase A), DEGS2 (Delta 4-desaturase sphingolipid 2), TFRC (transferrin receptor protein 1), SOGA1 (suppressor of glucose by autophagy), ATF4 (activating transcription factor 4), GLS1 (glutaminase 1), GLS2 (glutaminase 2), VISTA (V-domain Ig suppressor of T cell activation), NDUFA4 (NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4), LHPP (phospholysine phosphohistidine inorganic pyrophosphate phosphatase), RPRD1B (nuclear pre-mRNA domain-containing 1B), AVEN (apoptosis and caspase activation inhibitor), DNAJB1 (DnaJ heat shock protein family (Hsp40) member B1), PBX1 (pre-B-cell leukemia transcription factor 1), HDAC4 (histone deacetylase type 4), FBXL5 (F-box and leucine-rich repeat protein 5), HSD17B11 (recombinant 17-Beta-hydroxysteroid dehydrogenase Type 11).

[b] HBXIP (hepatitis B virus X-interacting protein), SIRT6 (sirtuins 6), ACSL4 (acyl-CoA synthetase long-chain family member 4), PDK4 (pyruvate dehydrogenase kinase 4), DDIT4 (DNA damage-inducible transcript 4), OLA1 (Obg-like ATPase 1), GSK-3β (glycogen synthase kinase-3 beta), GCH1 (GTP cyclohydrolase 1), WZ35 (curcumin analog), YAP (Yes1 Associated Transcriptional Regulator), AXL (receptor tyrosine kinase), IRP2 (iron regulatory protein 2), SNAI1 (snail homolog 1).

methyltransferases perform m6A deposition at the 6th nitrogen position of the adenosine base within RNA via their methyltransferase domain (MTD) to directly recognize the highly conserved RRACH sequences, which R means adenine or cytosine and H represents non-guanine [61–63]. The first identified methyltransferase, METTL3, is the primary catalytic core of the m6A MTC, which catalyzes m6A modification using S-adenosylmethionine (SAM) as the methyl donor [64]. Notably, the nuclear localization signal (NLS) and LH leading helix structure (LH) domains of METTL3 enable interactions with METTL4, forming an m6A heterodimeric complex [65,66]. METTL3 binds with the SAM methyl donor, while METTL14 provides an RNA-binding platform to facilitate METTL3 activity [67–69]. Subsequently, WTAP [17,70] recruits and localizes the METTL3/METTL14 complex into nuclear speckles. ZC3H13 enhances the anchoring of the complex within the nucleus [71]. Furthermore, KIAA1429 promotes the deposition specificity of the METTL3/-METTL14/WTAP complex within the 3' UTR and near-stop codon [56]. Collectively, these coordinated actions of diverse methyltransferases confer unique RNA-specific m6A modifications, thus manifesting distinct and concerted effects in the m6A methylation processes [72].

2.2. m6A demethylases

In addition to methyltransferases, the existence of m6A demethylases enables m6A methylation with its characteristic dynamic and reversible attributes [73]. Fat mass and obesity-associated protein (FTO) and Alk B homolog 5 (ALKBH5) are the primary mammalian RNA demethylases known to catalyze the removal of m6A modifications from RNA [74]. The discovery of the first m6A demethylase, FTO, initiated an increase in explorations into the functions of m6A methylation [75]. FTO is a member of the non-heme FeII/α-KG-dependent dioxygenase AlkB family, which demethylates the m6A methylation in nuclear RNA [76]. Studies have established that FTO can reverse m6A methylation in RNA to N6-hydroxymethyladeosine and N6-formyladenosine in a stepwise oxidative manner [77]. ALKBH5, another m6A demethylase, exhibits distinct m6A demethylation profiles, including RNA substrate preferences and tissue-specific distributions [78]. Notably, ALKBH5 is predominantly enriched in nuclear speckles and catalyzes m6A-to-A demethylation directly, without intermediates, characterized by unique structural attributes [20,79].

2.3. m6A-binding proteins

In addition to the dynamic regulation of m6A methyltransferases and demethylases, m6A binding proteins are required to specifically recognize m6A modification and influence subsequent biological functions [80]. These m6A binding proteins are functionally analogous to "readers" and primarily fall within three major categories. The YT521-B homology (YTH) domain-containing proteins represents the pioneering class of m6A readers. These proteins directly interact with m6A methylated RNA to mediate the functions of m6A [81,82]. The family of YTHDF (YTHDF1/2/3), YTHDC1, and YTHDC2 represent five discovered m6A readers with the highly conserved YTH RNA-binding domain in the mammalian cells [83]. Concurrently, the heterogeneous nuclear ribonucleoprotein (HNRNP) family (HNRNPA2B1, HNRNPC, and HNRNPG) are regarded as the indirect m6A readers. They bind to RNA-binding sites that undergo structural changes induced by m6A methylation instead of directly recognizing the m6A sites [84]. Additionally, the

insulin-like growth factor 2 mRNA binding proteins 1/2/3 (IGF2BP1/2/3) are the other m6A readers that participate in the stability of m6A-containing RNA [85].

Collectively, the interplay between m6A methyltransferases and demethylases in RNA governs the reversible regulation of m6A abundance and distribution. The m6A binding proteins further recognize and interact with m6A to mediate diverse biological functions, such as RNA processing, transport, and translation [86]. However, the presence and functional significance of m6A-related molecules remains largely unknown [87].

3. m6A regulates tumor metabolism in digestive tract tumors

Dysregulated m6A modifications play a pivotal role in the metabolic reprogramming of cancer cells, promoting the development of malignant tumors within the digestive system. Studies highlight the involvement of aberrant expression of m6A-related molecules, such as regulatory enzymes, binding proteins, and target RNAs, in the regulation of the metabolic dynamics of tumor cells [88–92]. Increasing lines of evidence have uncovered that m6A modifications regulate the expression and stability of key metabolism-related genes, thereby contributing to the metabolic reprogramming observed in digestive tract tumors [93–97] (**Table 1**). The following sections will focus on summarizing the mechanism underlying m6A's regulatory influence on tumor metabolism with respect to the three types of m6A effector molecules, including m6A methyltransferases, demethylases, and binding proteins (Fig. 1).

3.1. m6A methyltransferases and tumor metabolism

Increasing studies have reported that the abnormal expression of m6A writers in digestive system malignancies involves diverse modes of metabolic reprogramming (**Table 2**).

In HCC, hepatitis B virus X-interacting protein (HBXIP) was observed to upregulate METTL3 expression, consequently amplifying the m6A modification levels of hypoxia-inducible factor-1α (HIF-1α) mRNA. Enhanced levels of METTL3 and HIF-1α in human HCC tissues and cells (MHCC97 and HepG2) have been shown to exert carcinogenic effects through positively regulating glycolysis and cell aggressiveness. Notably, elevated METTL3 levels have been correlated with unfavorable overall survival in patients with HCC [88]. Conversely, METTL14 expression is reduced in human HCC liver tissues and cell lines (Huh-7 and HepG2), exhibiting a tumor-suppressive role in the progression of HCC. Furthermore, studies show that METTL14 could enhance the ubiquitin-specific protease 48 (USP48) level through the maintenance of USP48 mRNA stability. The elevated USP48 further repress the ubiquitination of sirtuins 6 (SIRT6), therefore mitigating aerobic glycolysis and hindering tumor metastasis in HCC [89]. Similarly, ZC3H13 is also downregulated in human HCC tissues and cell lines (HUH-7, Hep3B, HepG2, and SMMC-7721). Kaplan–Meier analysis showed that increased ZC3H13 levels are associated with more favorable survival conditions in patients with HCC. ZC3H13's anticancer properties have been attributed to its ability to inhibit pyruvate kinase M2 (PKM2) mRNA stability, thus attenuating glycolysis and cisplatin resistance [90]. Additionally, METTL3 and METTL14 have emerged as pivotal regulators of lipid metabolism in HCC progression. Overexpression of METTL3 and METTL14 in HCC LM3 cells induced increased m6A modification of stearoyl-CoA desaturase1

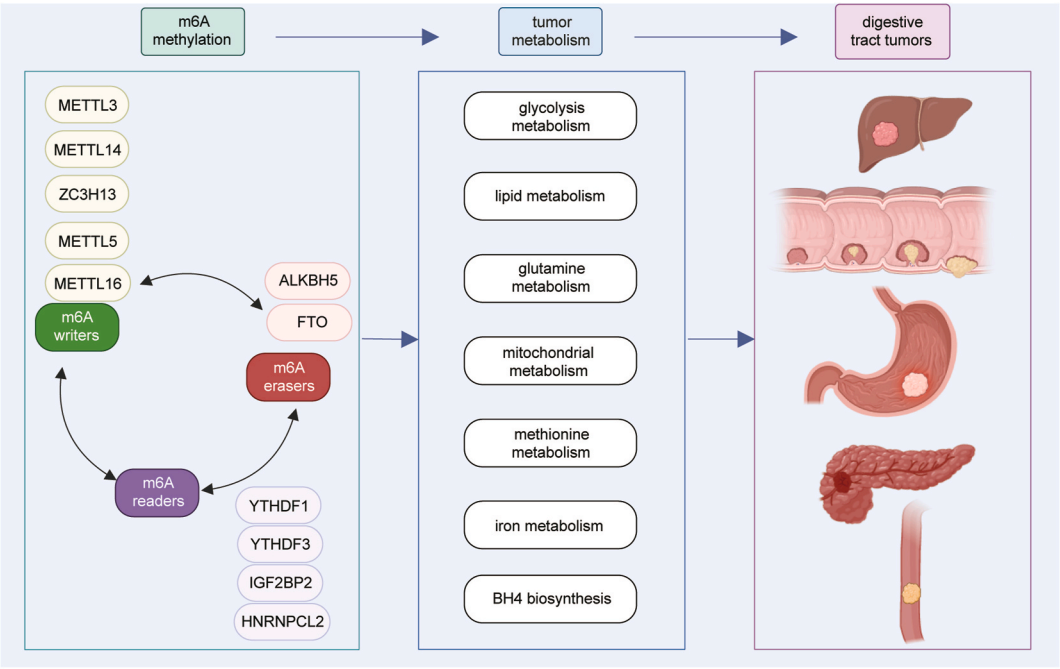

Fig. 1. Effects of m6A methylation on multiple tumor metabolisms in digestive tract tumors.

Table 2
Roles of m6A methylation in digestive tract tumors.

Disease[a]	m6A regulators	Metabolism	Role in diseases	Year	Refs.
HCC	METTL3	glucose metabolism	Carcinogenic effects	2021	[88]
	METTL14	glucose metabolism	Anti-cancer effects	2021	[89]
	ZC3H13	glucose metabolism	Anti-cancer effects	2021	[90]
	ALKBH5	glucose metabolism	Anti-cancer effects	2022	[105]
	YTHDF3	glucose metabolism	Carcinogenic effects	2022	[112]
	IGF2BP2	glucose metabolism	Carcinogenic effects	2023	[113]
	METTL3, and METTL14	lipid metabolism	Carcinogenic effects	2022	[91]
	METTL5	lipid metabolism	Carcinogenic effects	2022	[92]
	METTL3	purine anabolism	Carcinogenic effects	2023	[93]
CRC	METTL3, IGF2BP2, and IGF2BP3	glucose metabolism	Carcinogenic effects	2020	[94]
	METTL3	glucose metabolism	Carcinogenic effects	2021	[95]
	METTL3, and YTHDF1	glucose metabolism	Carcinogenic effects	2022	[96]
	METTL16, and IGF2BP1	glucose metabolism	Carcinogenic effects	2023	[97]
	IGF2BP2	glucose metabolism	Carcinogenic effects	2021	[114]
	METTL3, and YTHDF2	lipid metabolism	Anti-cancer effects	2021	[98]
	FTO	glutamine metabolism	Carcinogenic effects	2021	[106]
	YTHDF1	glutamine metabolism	Carcinogenic effects	2021	[115]
	YTHDF1	methionine metabolism	Carcinogenic effects	2023	[117]
	METTL3, and HNRNPCL2	mitochondrial metabolism	Carcinogenic effects	2020	[116]
	METTL4, and IGF2BP2	iron metabolism	Carcinogenic effects	2023	[99]
GC	METTL3	glucose metabolism	Carcinogenic effects	2022	[100]
	METTL14	glucose metabolism	Anti-cancer effects	2022	[101]
	METTL3	lipid metabolism	Carcinogenic effects	2022	[102]
	METTL3	mitochondrial oxidative phosphorylation	Carcinogenic effects	2022	[103]
	FTO	mitochondrial metabolism	Carcinogenic effects	2022	[107]
	ALKBH5	amino acid metabolism	Anti-cancer effects	2022	[108]
	METTL3	BH4 biosynthesis	Carcinogenic effects	2022	[104]
PC	ALKBH5	glucose metabolism	Carcinogenic effects	2023	[110]
	YTHDC1	glucose metabolism	Anti-cancer effects	2021	[118]
	ALKBH5	iron metabolism	Anti-cancer effects	2021	[111]
EC	FTO, and YTHDF1	lipid metabolism	Carcinogenic effects	2022	[109]

[a] HCC (hepatocellular carcinoma), CRC (colorectal cancer), GC (gastric cancer), PC (pancreatic cancer), EC (esophageal cancer).

(SCD1) and ATP citrate lyase (ACLY) mRNA, resulting in the upregulation of their expression and lipid accumulation [91]. Furthermore, METTL5 and its partner TRMT112 were demonstrated to promote lipid metabolism and accelerate HCC progression. High METTL5 levels, detected in human HCC tissues and cell lines (HepG2 and Huh-7), were associated with advanced pathological features and unfavorable overall survival in individuals with HCC. Further mechanistic exploration has revealed the role of METTL5 in upregulating the translation of acyl-CoA synthetase long-chain family member 4 (ACSL4) which is a crucial enzyme for lipid composition through the m6A modification of 18S rRNA [92]. Recent findings have highlighted the evident upregulation of m6A writer and reader genes in HCC with high purine anabolism. Furthermore, METTL3 was demonstrated to upregulate DTL (a substrate receptor associated with the Cullin4-ring E3 ubiquitin ligase complex), thereby facilitating purine anabolism and contributing to adverse clinical outcomes in HCC (Fig. 2) [93].

In CRC, studies have established the upregulation of METTL3 in CRC tissues and various CRC cell lines (such as Hep3B, BEL-7402, and SMMC-7721), positively correlating with unfavorable prognostic outcomes. METTL3 has been recognized as an oncogene capable of enhancing glucose metabolism and fueling CRC tumorigenesis. Mechanistically, studies have revealed that METTL3 upregulates hexokinase 2 (HK2) and glucose transporter 1 (GLUT1) stability and expression through its interaction with m6A reader, IGF2BP2/3 [94]. METTL3 further increases GLUT1 translation and activates mTORC1 signaling to promote glucose metabolism [95]. Additionally, METTL3 enhances the expression of lactate dehydrogenase A (LDHA), in conjunction with m6A reader YTHDF1, to boost glycolysis and confer 5-FU resistance in CRC cells (SW480 and HCT116) [96]. METTL16 was also reported to be bound with IGF2BP1 to positively mediate stability and expression of suppressor of glucose by autophagy (SOGA1) mRNA. This interaction increases pyruvate dehydrogenase kinase 4 (PDK4) expression, amplifying glycolytic metabolism and promoting CRC progression. Elevated METTL16 expression is considered an independent predictor of poor survival for patients with CRC [97]. However, METTL3 exerts an anticancer effect in CRC by mediating lipid metabolism pathways. The downregulation of METTL3 and YTHDF2 has been shown to elevate Delta 4-desaturase sphingolipid 2 (DEGS2) expression, further enhancing ceramide metabolism and promoting CRC carcinogenesis [98]. Additionally, METTL4 and m6A reader IGF2BP2 have been implicated in oncogenic roles, upregulating iron metabolism in CRC and being linked to unfavorable patient outcomes. Specifically, an increase in METTL4 and IGF2BP2 could recognize the methylation of transferrin receptor protein 1 (TFRC) mRNA, upregulating TFRC expression in CRC cells (HT-116 and SW480), therefore enhancing iron metabolism and CRC progression (Fig. 3) [99].

In GC, elevated expression of METTL3 has been associated with unfavorable patient outcomes. METTL3 increases NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 4 (NDUFA4) expression via IGF2BP1, subsequently enhancing cellular glycolysis and oxidative metabolism in GC cells, such as MKN45, AGS, and HGC27 [100]. On the other hand, METTL14 upregulates phospholysine phosphohistidine inorganic pyrophosphate phosphatase (LHPP) expression, dampening glycogen synthase kinase-3 beta (GSK-3β)

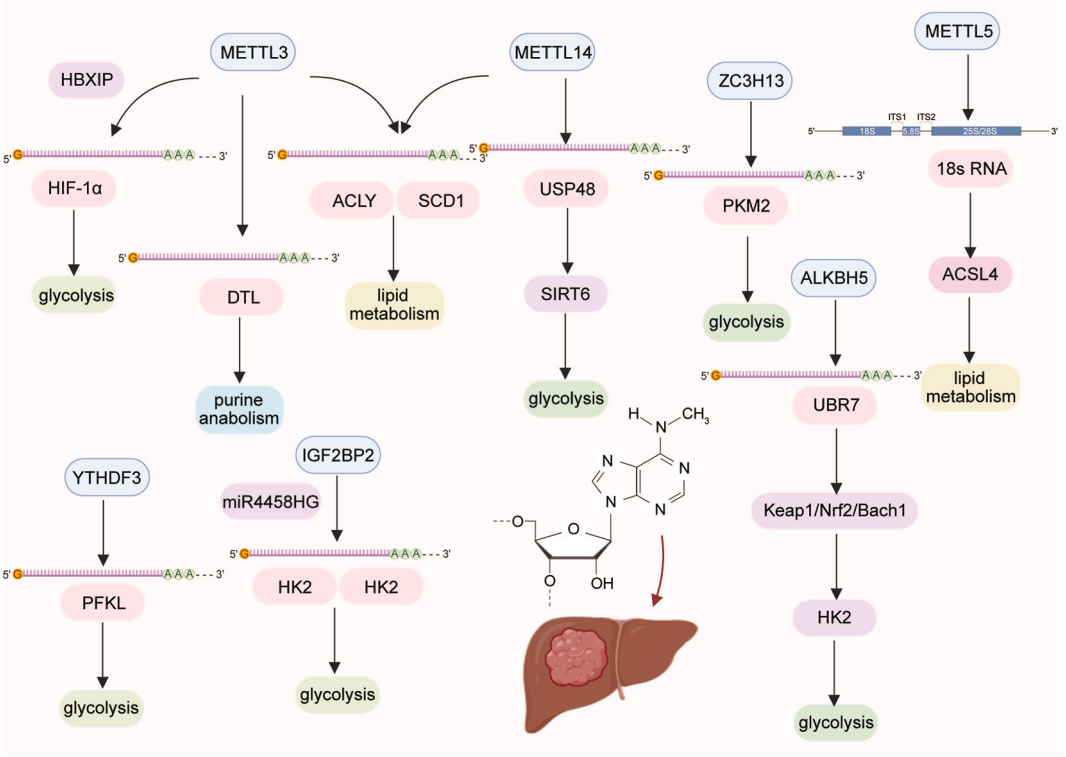

Fig. 2. Involvement of m6A methylation in the regulation of key metabolic enzymes in liver cancer. HIF-1α (hypoxia-inducible factor-1α), USP48 (ubiquitin-specific protease 48), PKM2 (pyruvate kinase M2), ACLY (ATP citrate lyase), SCD1 (stearoyl-CoA desaturase1), DTL (a substrate receptor associated with the Cullin4-ring E3 ubiquitin ligase complex), UBR7 (ubiquitin protein ligase E3 component N-recognin 7), PFKL (phosphofructokinase), HK2 (hexokinase 2), HBXIP (hepatitis B virus X-interacting protein), SIRT6 (sirtuins 6), ACSL4 (acyl-CoA synthetase long-chain family member 4).

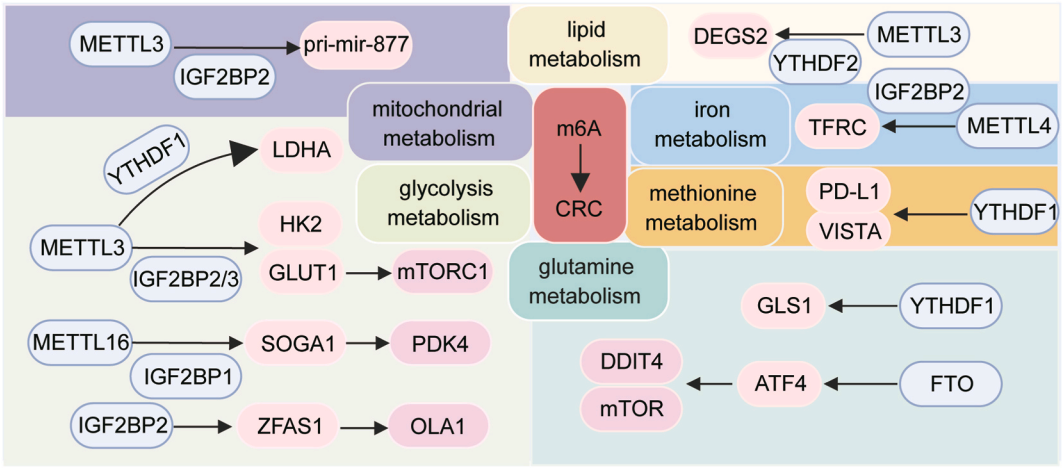

Fig. 3. Regulation of m6A methylation for key metabolic enzymes in multiple metabolic pathways of colorectal cancer. GLUT1 (glucose transporter 1), LDHA (lactate dehydrogenase A), DEGS2 (Delta 4-desaturase sphingolipid 2), TFRC (transferrin receptor protein 1), SOGA1 (suppressor of glucose by autophagy), ATF4 (activating transcription factor 4), GLS1 (glutaminase 1), VISTA (V-domain Ig suppressor of T cell activation), PDK4 (pyruvate dehydrogenase kinase 4), DDIT4 (DNA damage-inducible transcript 4), OLA1 (Obg-like ATPase 1).

phosphorylation and inhibiting the Wnt pathway. This suppresses glycolysis and underscores its tumor-suppressive role in GC cells, such as HGC27 and MGC-803 [101]. Furthermore, METTL3 has been found to regulate lipid metabolism and promote lymph node metastasis. In GC cells, AGS and HGC27, METTL3, along with the m6A reader HNRNPA2B1, induces the upregulation of nuclear pre-mRNA domain-containing 1B (RPRD1B) with the assistance of lncRNA NEAT1, thereby activating the c-Jun/c-Fos/AP1 pathway

and lipid metabolism [102]. Moreover, an integrative analysis combining proteomics and m6A microarray data has revealed that METTL3 could enhance apoptosis and caspase activation inhibitor (AVEN) and DnaJ heat shock protein family (Hsp40) member B1 (DNAJB1) levels to strengthen oxidative phosphorylation in GC BGC-823 cells [103]. METTL3 has also been identified as a key player in enhancing BH4 biosynthesis and advancing GC progression through its impact on elevating m6A modification of pre-B-cell leukemia transcription factor 1 (PBX1) mRNA, thereby enhancing GTP cyclohydrolase 1 (GCH1) expression [104].

3.2. m6A demethylases and tumor metabolism

Apart from m6A writers, m6A erasers also play pivotal roles in the metabolic reprogramming within digestive tract tumors. ALKBH5, notably downregulated in both human HCC tissues and Huh-7 cells, assumes a tumor-suppressive role through its active participation in the regulation of glycolysis and the inhibition of tumor growth. ALKBH5 stabilizes and increases ubiquitin protein ligase E3 component N-recognin 7 (UBR7) expression, thereby activating the Keap1/Nrf2/Bach1 axis to downregulate HK2 expression and restraining glycolysis and HCC tumorigenesis (Fig. 2) [105]. In CRC cells, SW480 and HCT116 upregulated FTO could decrease m6A modification of activating transcription factor 4 (ATF4) mRNA, subsequently enhancing ATF4 expression. Subsequently, increased ATF4 could elevate DNA damage-inducible transcript 4 (DDIT4) levels, effectively inactivating the mTOR pathway and promoting pro-survival autophagy during CRC glutaminolysis inhibition (Fig. 3) [106]. FTO has been shown to influence GC mitochondrial dynamics and carcinogenesis by regulating mitochondrial fission/fusion dynamics and metabolic pathways. The upregulated FTO in human GC tissues indicated a higher probability of metastasis in patients. Furthermore, FTO was observed to directly degrade caveolin-1 mRNA and inhibit mitochondrial fission in GC AGS and SGC-7901 cells. This subsequently enhanced mitochondrial respiration and ATP supplementation, facilitating GC tumor growth and metastasis [107]. In addition, studies have highlighted the involvement of ALKBH5 in the anti-cancer process of curcumin analog (WZ35)-mediated glutathione depletion through the reactive oxygen species (ROS)-Yes1 associated transcriptional regulator (YAP)- receptor tyrosine kinase (AXL)-glutaminase 2 axis [108].

In EC, elevated FTO expression within human EC tissues also signifies unfavorable patient outcomes. The overexpression of FTO could upregulate recombinant 17-Beta-hydroxysteroid dehydrogenase Type 11 (HSD17B11) levels through a YTHDF1-dependent mechanism, leading to increased lipid droplet formation and promoting the proliferation, migration, and stemness of EC cells such as KYSE510 and TE1 [109]. Under hypoxic conditions, a positive feedback loop of ALKBH5, histone deacetylase type 4 (HDAC4), and HIF-1α has been identified in PC cells such as PANC-1 and MIA PaCa-2. This feedback loop contributes to the promotion of glycolysis and metastasis in PC progression [110]. Another study has demonstrated the capabilities of ALKBH5 in exerting anti-cancer effects by regulating iron metabolism in PC. Multivariate Cox regression analyses of patients with PC suggested that ALKBH5 could be an independent prognostic indicator for patient prognosis. Mechanistically, ALKBH5 facilitates the upregulation of F-box and leucine-rich repeat protein 5 (FBXL5), subsequently decreasing the expression of iron regulatory protein 2 (IRP2) and modulator of epithelial-mesenchymal transition (EMT), snail homolog 1 (SNAI1). This orchestrated interplay effectively hinders intracellular iron overload and suppresses the EMT process within PC MIA PaCa-2 cells [111].

3.3. m6A-binding proteins and tumor metabolism

Increasing studies have established the indispensable regulatory roles of multiple m6A readers in the metabolic alterations of digestive tract tumors. Human HCC tissues show increased YTHDF3 expression, correlating with aggressive clinicopathological characteristics and unfavorable survival outcomes, such as larger tumor size, pathological stage, and vascular invasion. YTHDF3 also strengthens the expression of phosphofructokinase (PFKL) to promote glucose metabolism, therefore accelerating the proliferation, migration, and invasion of HCC cells, such as Huh7 and SNU449 [112]. Similarly, IGF2BP2 was also demonstrated to bind with miR4458HG and intensify HK2 and GLUT1 expression, consequently promoting glycolytic pathway, cell proliferation, and even the polarization of tumor-associated macrophage in HCC (Fig. 2) [113]. In CRC, elevated IGF2BP2 expression was observed across diverse CRC cell lines (especially HCT116, SW620, and HT29) and paired human cohorts. Moreover, IGF2BP2 expression is associated with the survival status of patients with CRC, including disease-free survival (DFS) and overall survival (OS). Functionally, IGF2BP2 enhances lncRNA ZFAS1 expression to elevate Obg-like ATPase 1 (OLA1) activity and ultimately accelerate glycolysis in CRC cells like HCT116 and SW620 [114]. The upregulated glutamine metabolism was also observed in CRC LoVo CDDP R cells. The evidence revealed that YTHDF1 promoted glutaminase (GLS) expression to facilitate glutamine metabolism and cisplatin resistance in CRC [115]. Furthermore, the upregulation of HNRNPCL2 in CRC was shown to be associated with mitochondrial metabolism and enhanced tumor aggressiveness. HNRNPCL2 recognizes METTL3-modified pri-mir-877 and suppresses the expression of electron transport chain (ETC) genes, leading to the reprogramming of mitochondrial metabolism in CRC [116]. Moreover, YTHDF1 enhances PD-L1 and V-domain Ig suppressor of T cell activation (VISTA) expression under a methionine-restricted diet (MRD) to induce tumor immune escape in CRC progression. Notably, YTHDF1 levels associate with an insensitive immunotherapy response and unfavorable prognosis of patients with CRC (Fig. 3) [117]. Meanwhile, YTHDF1 has been observed to amplify miR-30d biogenesis in PC through m6A-mediated stabilization, inhibiting pancreatic tumorigenesis. Mechanistically, miR-30d overexpression abolishes glycolysis, effectively inhibiting malignant behaviors of Panc-1 and MiaPaCa-2 cells through the suppression of glucose transporter 1 (GLUT1) and hexokinase 1 (HK1) expression [118].

4. Conclusion and perspectives

Numerous studies have increasingly substantiated the significance of m6A modification in reprogramming cancer metabolism.

Understanding the underlying mechanisms governing the impact of m6A modification on metabolic reprogramming is crucial for gaining novel insights into the development of malignant tumors within the digestive tract system. Extensive studies have confirmed the active contribution of the diverse m6A "writers," "erasers," and "readers" in the induction of major reprogrammed metabolic pathways, such as glucose metabolism, lipid metabolism, and amino acid metabolism of digestive tract tumors, by regulating the expression of pivotal genes involved in these pathways. With the recent advancement of sequencing technologies and the in-depth study of m6A modification, additional m6A regulators and m6A-modified RNAs could serve as potential targets for the clinical diagnosis, prognosis, and treatment of digestive tract tumors. However, the translation of m6A-targeted strategies into the clinical setting as potential therapeutic targets, sensitive diagnostic markers, or prognostic indicators for digestive tract tumors remains limited.

This review comprehensively summarizes the crucial role of m6A modification in regulating major metabolic pathways, particularly the glucose and fatty acid metabolic pathways within the digestive tract tumors. Through an in-depth investigation of the mechanisms governing m6A-mediated metabolic pathway reprogramming, we have not only deepened our understanding of the complexity of m6A regulation within digestive tract tumor metabolism but also paved the way for innovative diagnostic and therapeutic strategies. These metabolic pathways may interconnect and give rise to an intricate network of interconnected pathways. The inhibition of one pathway may trigger the activation of alternative pathways, thereby fulfilling the biosynthetic and survival prerequisites of cancer cells. Another potential reason is the intricate and coordinated nature of m6A modification, requiring the interplay of multiple factors involving methyltransferases, demethylases, and m6A binding proteins.

The dynamic and reversible nature of m6A modification, coupled with the interconnectedness of metabolic pathways, makes it challenging to design effective therapeutic strategies that can precisely target the intricacies of m6A-related mechanisms. These potential complexities compound the challenges in translating m6A-targeted strategies into clinical applications for regulating tumor metabolism. Additionally, the attention on m6A in digestive system tumors has only recently gained momentum. While most studies have focused on m6A in HCC, CRC, and GC, investigations within the context of EC remain relatively limited. Even within these studies, the emphasis has centered on major m6A "writers" such as METTL3, while the understanding of m6A "erasers" and "readers" has been relatively scarce. This highlights the need for further investigation of the specific roles and mechanisms of m6A modification within EC and other digestive system tumors, particularly focusing on the diverse array of m6A-associated proteins involved in the regulation of this modification.

The involvement of m6A RNA modification in regulating metabolic reprogramming processes within digestive tract tumors is becoming increasingly clear. M6A modification influences various aspects of tumor metabolism, including nutrient uptake, energy production, and biosynthesis. Given the substantial impact of metabolic alterations on the trajectory of cancer progression, there is a growing interest in exploring novel therapeutic strategies targeting m6A RNA modification. Future research should further elucidate the precise mechanisms through which m6A modification contributes to metabolic reprogramming in digestive tract tumors. Such exploration holds the potential to pave the way for the development of innovative therapeutic approaches aimed at targeting m6A RNA modification.

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CRediT authorship contribution statement

Liang Yu: Writing – original draft, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Yuan Gao:** Writing – original draft, Validation, Supervision, Methodology, Conceptualization. **Qiongling Bao:** Writing – original draft, Validation, Methodology. **Min Xu:** Writing – original draft, Methodology, Formal analysis, Data curation. **Juan Lu:** Writing – review & editing, Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization. **Weibo Du:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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