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The m6A Epitranscriptome as an Architect of Metastatic Organotropism in Gastrointestinal Cancers: Shaping the Hepatic and Peritoneal Pre-metastatic Niche

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Abstract. Metastasis, not the primary tumor, accounts for most deaths from gastrointestinal (GI) cancers, and GI metastases display striking organ tropism: colorectal, pancreatic, and gastric cancers preferentially colonize the liver, gastric cancer the peritoneum, esophageal squamous cell carcinoma the lymph nodes. Yet the molecular logic instructing disseminating cells where to land remains poorly understood. N6-methyladenosine (m6A), the most abundant internal mRNA modification, is dynamically installed, removed, and interpreted by dedicated Writers, Erasers, and Readers. Emerging evidence positions m6A as an architect of organotropism acting at three levels. At the seed level, m6A programs metastatic competence — epithelial–mesenchymal transition, stemness, and anoikis resistance. On the route level, m6A regulates chemokine gradients (CXCL1/CXCR2) and adhesion programs involved in portal, lymphatic, and transcoelomic spread of cancer cells. On the soil level, tumor-derived exosomes containing m6A-modified RNAs or RNAs sorted by m6A readers can remotely shape the pre-metastatic niche (PMN) in liver and abdomen through myeloid-derived suppressor cell recruitment, macrophage polarization, and stromal activation before actual arrival of tumor cells. Since PMN establishment is upstream of the onset of metastasis, the therapeutic window has been established within which m6A-targeting drugs such as METTL3 inhibitors, FTO inhibitors, and siRNAs loaded on nanoparticles may be used as adjuvant antitumoral therapy. In this review, we reframe the GI m6A field with the concept of seed-route-soil, describe organ tropism signatures, and speculate on how epitranscriptome modulation could turn the problem of organotropism into its potential solution.

Keywords: N6-methyladenosine, gastrointestinal cancer, metastatic organotropism, pre-metastatic niche, liver metastasis

1. Introduction

Cancers arising from the gastrointestinal tract (GI) – specifically the esophagus, stomach, liver, pancreas, and colon – together make up about 25 percent of all cancer diagnoses worldwide and cause nearly one-third of deaths attributable to cancer [1]. GI cancers have high mortality rates, which are primarily due to the metastatic nature of the disease, and the metastatic patterns of GI

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tumors are highly reproducible: colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), and gastric cancer (GC) metastasize through the portal venous system to the liver, GC also metastasizes to the peritoneal cavity, while esophageal squamous cell carcinoma (ESCC) often involves early metastasis to regional lymph nodes. In CRC, liver metastases occur in about 25–30 percent of patients and are the primary reason for mortality in CRC [2]. Peritoneal metastases are the hallmark of recurrence of GC with median survival of 3–6 months and with almost no five-year survivors [3] (Figure 1).

The seed and soil theory of Paget [4] further elaborated through the concept of pre-metastatic niche (PMN) [5, 6] suggests that primary tumors, before the dissemination of circulating tumor cells (CTCs), proactively prime their target organs using their secretome and extracellular vesicles [7-9]. This theory addresses the issue of organ tropism. Exosome-based integrins play a role in organotropic fusion (e.g., αvβ5 for liver tropism) [9], and exosomal macrophage migration inhibitory factor (MIF) of PDAC acts on Kupffer cells in the liver to create the fibrotic niche [10]. However, the upstream code of these niche education cues is not fully understood yet.

N6-methyladenosine (m6A) is the most prevalent internal modification of eukaryotic mRNA, dynamically installed by a methyltransferase complex (Writers: METTL3, METTL14, WTAP, METTL16), erased by demethylases (Erasers: FTO, ALKBH5), and decoded by binding proteins (Readers: YTHDF1/2/3, IGF2BP1/2/3) that respectively destabilize, translate, or stabilize modified transcripts [11-13]. Numerous studies have summarized m6A functions in GI cancer cell proliferation, immune evasion, and therapeutic resistance [14-16]. However, it is yet lacking a summary connecting m6A directly to GI tumor metastasis. In this study, we hypothesize the m6A transcriptome to be the architect of GI tumor metastatic organotropism, controlling both seed (metastatic ability of tumor cells), pathway (routes and chemokines in guiding tumor cells), and soil (preconditioned remote niche) of metastasis. In this way, we connect a list of molecular mechanisms to a navigation system that m6A acts as a "navigation system" for the tumor cells.

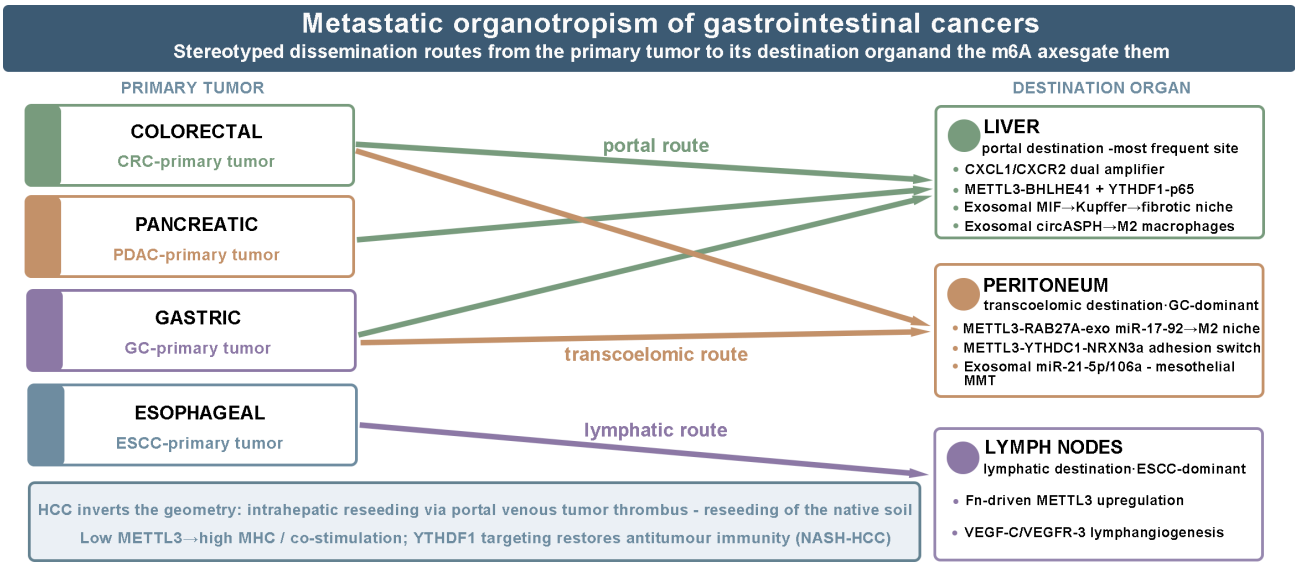

Figure 1. Metastatic organotropism of gastrointestinal cancers and the m6A-regulated guidance axes

GI primary cancers use predefined routes to reach their target sites: CRC, PDAC, and GC use the portal route to colonize the liver, GC and CRC use the transcoelomic route to metastasize to the peritoneal cavity, ESCC uses the lymphatic route to metastasize to lymph nodes, and hepatocellular carcinoma (HCC) uses the portal venous tumor thrombus route to metastasize back to its native

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hepatic tissue. Notable examples of the regulation of each of these routes by m6A-methylation include the dual amplifier CXCL1/CXCR2 (METTL3–BHLHE41 and YTHDF1–p65) and exosomal MIF in promoting the hepatic tropism, the METTL3–RAB27A-exosomal miR-17-92 and METTL3–YTHDC1–NRXN3α in promoting the peritoneal tropism, and the Fusobacterium nucleatum-driven METTL3 upreg

2. The m6A machinery: a metastasis-oriented primer

The m6A writer complex catalyzes methylation of adenosine residues present in the DRACH sequence (D = A/G/U, R = A/G, H = A/C/U), with the preference for m6A modifications near stop codons and in 3′ untranslated regions (3′ UTRs) [11, 12]. The fate of the corresponding transcript mediated by a particular m6A modification depends on its reader proteins: YTHDF2 mediates the interaction between the m6A-modified transcripts and CCR4–NOT deadenylase complex which accelerates the transcript decay, YTH N6-methyladenosine RNA-binding protein 1 (YTHDF1) stimulates the efficiency of translation, while IGF2BP1/2/3 stabilize their targets [11-13]. This reader-dependant dual nature of the effect, in which the same methyl mark can induce either degradation or stabilization, explains the frequent occurrence of the fact that the phenotype generated by a certain regulator in different cells varies, which is the fundamental idea for metastasis studies. Thus, METTL14 restricts the metastasis potential of CRC by accelerating the decay of the oncogenic long non-coding RNA (lncRNA) XIST and ARRDC4 by YTHDF2-dependent mechanisms [17, 18], while METTL3 promotes metastasis through stabilization of oncogenic mRNAs by IGF2BP1/2/3 [19].

3. The seed: m6A programming of metastatic competence

3.1. Epithelial–mesenchymal transition (EMT), stemness, and the "writer civil war"

EMT and cancer cell-induced stemness are responsible for motility and enhanced self-renewal ability to allow for the spread of tumors. METTL3 controls EMT in GI tumors by stabilizing mRNAs of EMT transcription factors and oncogenes via IGF2BP "readers" [16, 19]. In GC, TGF-β-mediated EMT and metastasis rely on the regulation of METTL3-dependent m6A mRNA modifications of Snail family proteins [20], whereas METTL3 facilitates GC progression and poor prognosis by stabilizing HDGF mRNA [21]. In CRCs, METTL3 contributes to tumor progression by inhibiting SOCS2 expression and activation of the JAK1/STAT3 signaling pathway [22, 23]. It is noteworthy that m6A machinery features endogenous antagonism, referred to as "writer civil war": while METTL3 promotes dissemination, its essential co-activator METTL14 decreases dissemination by degradation of XIST and ARRDC4 via the m6A/YTHDF2 pathway [17, 18]. Additionally, METTL3 may serve as a disseminator inhibitor in some contexts of CRCs via the p38/ERK signaling pathway [24].

3.2. Anoikis resistance and survival in circulation

The development of anoikis is a result of dissociation from the extracellular matrix, and a few disseminated cells are able to survive. The post-transcriptional regulation of m6A modification, which promotes stability of integrin signaling and antioxidants mRNAs via IGF2BP RNA-binding proteins, contributes to improved survival of circulating tumor cells in blood flow [16]. Since CTCs

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are characterized by an extremely short life span (ranging from minutes to several hours), small survival advantages lead to significant increases in the number of seeds that reach the liver.

3.3. Metabolic pre-adaptation to the destination organ

Colonization requires metabolic adaptations to the microenvironment, where the nutrient- and lipids-rich liver provides a different environment than the hypoxic, adipocyte-associated peritoneal milieu. In organ-specific manner, the m6A machinery is responsible for altering tumor metabolism: METTL14 decreases glycolysis in p53 wild-type CRC [25], on the other hand, METTL3-induced glycolysis metabolism, represented by METTL3-HDGF axis in gastric cancer [21], is more suitable for the Warburg phenomenon observed in tumors formed in hypoxic environment. Lactate derived from the tumor, apart from fueling the primary tumor growth, increases METTL3 levels in myeloid cells through lactylation of histone H3K18 [26] (Section 5).

4. The route: m6A gating of dissemination pathways

4.1. The portal–chemokine axis and hepatotropism

The CXCL1 axis is a key player in the process of guidance involved in gastrointestinal and liver metastasis. The chemo-attractant CXCL1 attracts CXCR2-expressing myeloid-derived suppressor cells (MDSCs), which in turn form a pre-metastatic niche and enable the development of metastasis in the liver [27]. m6A RNA modification regulates the CXCL1/CXCR2 axis at two amplification points. Increased activity of METTL3 in CRC cells leads to an increase in the translation of BHLHE41 transcription factor, which stimulates the transcription of CXCL1, depletion of METTL3 inhibits the attraction of MDSCs by 60%, and suppresses tumor progression [28]. At the same time, YTHDF1 increases the translation of NF-κB p65, which activates CXCL1 [29]. The binding of the writer (METTL3) with the reader (YTHDF1) produces a double amplification in the same pathway, leading to the steepest gradients of CXCL1 along the portal-hepatic axis [27].

4.2. The lymphatic route and ESCC nodal tropism

ESCC spreads early through a high density of submucosal lymphatics. Infection by intracellular Fusobacterium nucleatum (Fn) leads to the increase in m6A methylation due to METTL3 in ESCC, resulting in metastasis. Thus, a microbial pathway modifier is linked with the lymphotropic dissemination route. Lymphangiogenic signaling pathways regulated by m6A methylation, particularly vascular endothelial growth factor C (VEGF-C) and VEGF receptor-3 (VEGFR-3), remain unexplored.

4.3. The transcoelomic route and peritoneal tropism

The dissemination of GC cells to the peritoneal cavity requires their ability to adhere to the mesothelium and form colonies in the omental milky spots. The adhesive mechanisms, which are controlled by m6A modification, along with mesothelial–mesenchymal transition (MMT), and additionally influenced by mesothelial education via exosomes (as described in Section 5), favor peritoneal dissemination over hematogenous dissemination of GC cells. The new concept suggests that m6A modification does not simply enhance the process of metastasis but regulates the specific gradients of chemokines and adhesion programs, which can be recognized by the tumor cells.

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5. The soil: m6A shaping of the pre-metastatic niche

5.1. Exosomal m6A-modified RNAs as remote educators

The best studied remote niche education vectors are tumor-derived exosomes, where m6A controls both their production and cargo. The most detailed data are available for peritoneal metastasis of gastric cancer: Overexpression of METTL3 in GC cells introduces the m6A modification in the A502 position of RAB27A mRNA, which is then recognized by YTHDF1 protein to promote RAB27A translation and increase exosome secretion, METTL3 increases the enrichment of miR-17-92 cluster in the secreted vesicles. Exosomes enter the peritoneal macrophages, where miR-17/20a silences the SRC inhibitor SRCIN1 and activates SRC signaling and M2 macrophage polarization (increase in IL-10/TGF-β and decrease in IL-1/IL-6) promoting CD8+ T cell proliferation inhibition and cytotoxicity, thus generating an immunosuppressive pre-metastatic niche in the peritoneum before arrival of the tumor cells. In immunocompetent mice, GC exosomes produced by cells with high METTL3 levels are enough to generate peritoneal niches and accelerate metastasis, and macrophage depletion largely abolishes this process. This work identifies the first full causal chain —from m6A writer through exosome biogenesis to remote immune niche and organ-specific metastasis—which represents the soil side of this review. In addition to this exemplary model, cargo of exosomes is modified by m6A in general case [30, 31]: Exosomal RNA from colorectal cancer is modified by m6A, and its transfer causes M2 polarization of macrophages by delivery of STING [32], FTO/ALKBH5 activity of receiving cells influences exosome action even further. Thus, m6A participates in exosome-mediated remote niche education on both sides of the communication—the loading of cargo and recipient cell response.

5.2. Immune pre-conditioning of the niche

Before the presence of CTCs, PMNs become immunologically permissive. In the liver, recruitment of MDSCs through CXCL1 forms the core of suppressiveness [27, 28], while hepatic macrophages are simultaneously reeducated with exosomal miR-934 delivered from CRC cells. Exosomal packaging of miR-934 is dependent on the m6A reader protein hnRNPA2B1, leading to PTEN silencing, PI3K/AKT signaling pathway activation, and formation of CXCL13/CXCR5/NF-κB positive feedback loops for sustaining the immunosuppressive hepatic microenvironment [33]. In MDSCs, ALKBH5 promotes Arg-1 expression through mRNA stabilization and increases suppressive capacity [34]. Inhibiting ALKBH5 leads to changes in the microenvironment that enhance the effect of anti-programmed death-1 (PD-1) therapy [35]. Histone H3 lysine 18 (H3K18) lactylation induced by lactate upregulates METTL3 in myeloid cells, resulting in JAK1/STAT3-driven IL-10 and Arg-1 production [26]. Macrophage polarization is also associated with m6A methylation, as loss of METTL14 in $CD1q^+$ TAMs causes increased expression of EBI3 and inhibits $CD8^+$ T cell responses [36], while METTL3-induced maturation of miR-146b maintains M1 phenotype [37, 38]. In addition, METTL3 enhances natural killer (NK) cell–mediated antitumor response, so lack of METTL3 decreases immune surveillance of incoming CTCs [39].

5.3. Stromal and vascular remodeling

Exosomes from pancreatic ductal adenocarcinoma activate Kupffer cells to release TGF-β, which interacts with hepatic stellate cells to deposit fibronectin, thus generating a fibrotic matrix that not only arrests but sustains the invading tumor cells [10]. Further analysis of the stromal pathway at the

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cargo-RNA level has revealed that exosomal tRNA-derived fragment (tRF) tRF-GluCTC-0005 released by pancreatic ductal adenocarcinoma activates WDR1 mRNA translation within hepatic stellate cells to promote YAP-mediated cytokine secretion, myeloid-derived suppressor cell infiltration, and generation of a fibrotic microenvironment in KPC mice (KrasG12D/+, Trp53R172H/+, Pdx1-Cre). Furthermore, serum tRF-GluCTC-0005 exosome is a biomarker for liver metastases in patients [40]. However, whether and how m6A modification controls the regulation of the stromal axis, either in tRNA processing, exosomal cargo loading, or even stabilization, remains completely unknown and represents an immediate experimental goal (Section 8). A characteristic feature of the soil pathway is its temporal order: the stromal niche maturation precedes metastasis formation, resulting in a therapeutic time window (Section 7, Figure 2).

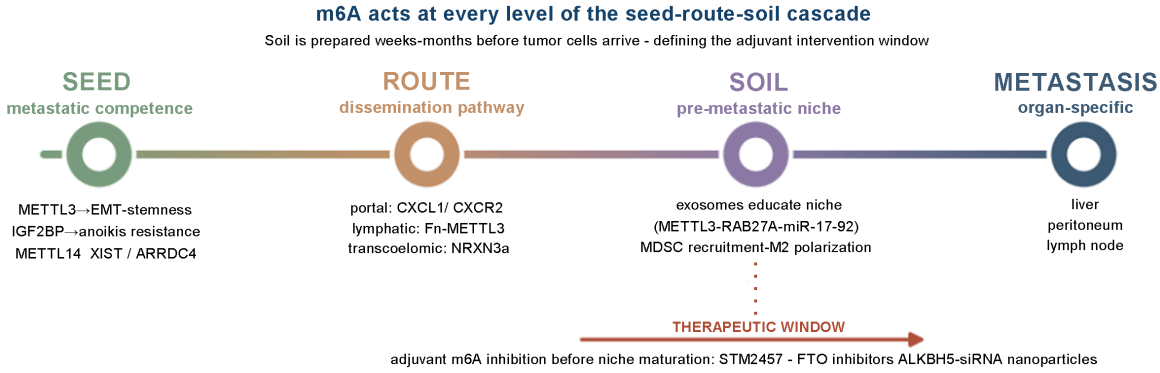

Figure 2. The seed–route–soil framework of m6A-driven metastatic organotropism

The m6A epitranscriptome influences the entire metastatic cascade. During the seeding phase, METTL3-associated EMT, stemness, and anoikis resistance through IGF2BP contribute to enhanced metastatic competence. In this process, the destruction of pro-metastatic transcripts by METTL14 serves as the opposing force. In the route phase, m6A controls the three dissemination routes (portal, CXCL1/CXCR2, lymphatic, Fusobacterium nucleatum-METTL3, transcoelomic, NRXN3α, and exosomal miRNAs). In the soil phase, exosomal education (METTL3-RAB27A-miR-17-92), immune preconditioning (myeloid-derived suppressor cell recruitment, macrophage polarization, lactate-METTL3-JAK1/STAT3 signaling), and stromal remodeling prepare the hepatic and peritoneal niches weeks to months before their colonization. The time precedence thus defines an adjuvant therapeutic window for targeting m6A before the arrival of circulating tumor cells.

6. Organ-specific tropism patterns

CRC → liver (and peritoneum). The most mechanistically thorough description of the GI tropism is given here. Portal drainage brings the CTCs to the liver with an environment conditioned by CXCL1 [27], METTL3, BHLHE41, and CXCL1 [28], alongside with YTHDF1 and NF-κB p65 [29], increase the migration gradient to colonize the liver. Fusobacterium nucleatum, which inhibits METTL3 expression to allow KIF26B-induced metastasis [41] and stabilizes programmed death-ligand 1 (PD-L1) via IFIT1 [42], migrates with the CRC cells and is present in the liver metastasis, serving as the microbial "co-pilot" for the liver colonization. Tumor-cell YTHDF2 loss changes the migration pattern through CX3CL1 release and macrophage recruitment [43]. Moreover, the peritoneum seeding in CRC occurs in about 7% of patients: in addition to the portal axis, METTL3 is upregulated in CRC peritoneal metastasis compared with the primary tumors and promotes the

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peritoneal dissemination through NRXN3α mRNA stabilization with YTHDC1-mediated m6A modification [44].

GC → peritoneum. Strongest organ-specific dataset on m6A tropism beyond colon cancer. Seed level: METTL3 plays a key role in the TGF-β induced epithelial–mesenchymal transition and promotes metastasis in gastric cancers and stabilizes HDGF mRNA to enhance invasive behavior, soil level: the METTL3-RAB27A-exosomal miR-17-92 axis converts peritoneal macrophages into immunosuppressive soil, leading to the creation of a full causal link from m6A modifications to organ-specific pre-metastatic niches. This pathway is also "contact-guided," in that gastric cancer cells that have been shed must survive anoikis in ascitic fluid and overcome the mesothelial barrier, during which time gastric cancer cells secreted exosomal miRs (miR-21-5p, miR-106a) mediate their degradation through mesothelial–mesenchymal transition via TGF-β/Smads [45, 46]. Clinically, METTL3 in primary tumors can be used to stratify peritoneal metastases, and METTL3-based nano-delivery systems engineered to regulate m6A modification have shown potential to enhance immunotherapy in gastric cancer [47].

PDAC → liver. PDAC is the cancer type that is characterized by the earliest development of metastases amongst gastroenteric malignancies, and the hepatic PMN paradigm was first formulated in PDAC models [10], desmoplastic primary tumors release exosome cargo conditioned with m6A modifications into the liver well in advance of detectable disease. As far as the seed is concerned, PDAC is characterized by the most prominent pro-metastatic m6A signature: METTL3 increases the stability of ID2 mRNA to maintain NANOG/SOX2-induced stemness [48] and increases the stability of E2F5 mRNA to promote growth and metastasis [49], pharmacological inhibition of METTL3 with STM2457 decreases PDAC invasion and metastasis through downregulation of the BRAF-regulated long non-coding RNA BANCR [50]. It should be mentioned that PDAC is an exceptional cancer type concerning METTL14: while METTL14 blocks the dissemination of CRC, it is increased in PDAC and methylates PERP mRNA, promoting growth and metastasis [51] – a strong sign of the organ level context dependency of the process.

ESCC → lymph nodes. METTL3 overexpression in response to Fn and subsequent lymphangiogenic programming predispose tumors to prefer nodal over hematogenous metastatic behavior. The causality of the above associations has been established through genetic evidence in that mice models with epithelium-specific Mettl3 conditional knockout and knockin reveal that m6A generated from METTL3 enzymatic activity promotes stability of NOTCH1 mRNA and activation of the Notch pathway leading to the development and progression of ESCC [52]. Additionally, clinicopathologic evidence connects the activity of the methyltransferase to nodal affinity such that 207 cases of resected ESCC tissues exhibit significant correlation between METTL3 protein levels and lymph node metastasis and advanced TNM stage as well as predict survival outcome [53].

HCC. Hepatocellular carcinoma disrupts the classical paradigm of tissue tropism and metastasis by primarily spreading inside the liver in the form of portal venous tumor thrombus, thereby "reseeding the native soil." Low levels of METTL3 are linked with MHC expression along with co-stimulation [15]. In addition to this, small interfering RNA (siRNA)-mediated knockdown of YTHDF1 in non-alcoholic steatohepatitis (NASH)-HCC models re-establishes antitumor immunity through the EZH2-IL-6 pathway [54], which suggests that the same reader, which controls the soil for CRC, regulates the surveillance of intrahepatic satellite tumors (Table 1).

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Table 1. Evidence-strength map of m6A regulation across the seed–route–soil cascade in gastrointestinal cancers

Cancer	Dominant destination	Seed	Route	Soil	Key m6A axes
CRC	Liver, peritoneum (~7%)	●●●	●●●	●●	METTL3–BHLHE41–CXCL1 [28], METTL3–NRXN3α [44], exosomal miR-934–M2 [33]
GC	Peritoneum, liver	●●●	●●	●●●	METTL3–Snail (TGF-β–EMT) [20], METTL3–HDGF [21], METTL3–RAB27A–exo-miR-17-92 [55]
PDAC	Liver	●●●	●	●	METTL3–ID2/E2F5 [48, 49], METTL14–PERP [51], exosomal tRF-GluCTC–WDR1/YAP (m6A-unmapped) [40]
ESCC	Lymph nodes	●●●	●●	○	Fn–METTL3 [56], METTL3–NOTCH1 [52]
HCC	Intrahepatic (native soil)	●●	●	●●	Low-METTL3–MHC axis [15], YTHDF1-dependent immune evasion in NASH-HCC [54]

●●●, causal in vivo evidence (genetic models or interventional studies), ●●, mechanistic evidence plus clinical correlation, ●, preliminary or single-study evidence, ○, not yet mapped. EMT, epithelial–mesenchymal transition, NASH, non-alcoholic steatohepatitis.

7. Clinical translation

7.1. Biomarkers of niche formation and organ-specific risk

Expression patterns of m6A regulators characterize GI tumors according to their immune and metastatic phenotype, and m6A-related scores can help predict prognosis and response to immunotherapy [57]. The most future-oriented application of this approach is the liquid biopsy of the PMN itself. This is no longer science fiction: in GC, primary-tumor METTL3 expression predicts peritoneal metastasis, while exosomal miR-17-92 — the METTL3-dependent PMN-inducing cargo — is measurable in the ascitic fluid and the bloodstream of GC patients as a potential predictor of peritoneal PMN development [55]. Sequential testing during the follow-up period after surgery may indicate the presence of an emerging "niche signal" many months prior to imaging detection of liver or peritoneal lesions, ctDNA tests have an average of 8.7 months lead time on imaging-detected disease recurrence in CRC patients [58]. Combinatorial signatures of organs specific to metastases (exosomal integrins [9] plus m6A-cargo profiles) may predict not just relapse but its location, allowing targeted organ-specific surveillance (hepatic MRI vs peritoneal cytology) based on predictions.

7.2. Targeting m6A as adjuvant anti-metastatic therapy

Targeting m6A modifications pharmacologically is happening at breakneck speed. An m6A-selective METTL3 inhibitor STM2457 is very promising preclinically [59], and it potentiates antitumor T-cell immune response [60], its orally available analog STC-15 has become the first m6A-selective inhibitor to be tested in first-in-human phase I trials in advanced solid tumors (ClinicalTrials.gov:

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NCT05584111). Moreover, FTO inhibitors (FB23-2, Dac51) have proven to be efficacious preclinically [61]. Nanoparticle-based ALKBH5 siRNA administration restores the gastrointestinal tumor microenvironment and potentiates anti-PD-1 treatment, and YTHDF1 knockout increases anti-PD-1 activity in preclinical colorectal cancer models. The organotropism paradigm suggests a different strategy for the use of m6A inhibitors: because the niche is already created before tumor seeding, m6A inhibitors should be used in an adjuvant setting after primary surgery and before niche maturation.

7.3. Site-directed combinations

For the peritoneal dissemination of gastric cancer, blocking m6A in combination with hyperthermal intraperitoneal chemotherapy (HIPEC) can tackle disseminated tumor cells as well as the mesothelial surface of the peritoneum, in the case of liver metastasis of colorectal cancer, m6A blockers may be considered in addition to hepatic-artery infusion or immunotherapy, where a METTL3/14-low and STAT1-high signature predicts responsiveness to immune checkpoint inhibition [62], for ESCC, exploration of m6A regulation should go hand-in-hand with chemoradiotherapy. The major problem is, however, cell type specificity: while YTHDF2 itself impedes tumor proliferation, it retains CD8+ T cell polyfunctionality [43, 63], which is of particular concern because the systematic inhibition of RNA binders would adversely affect the effector cells necessary for eliminating metastasis.

8. Conclusion

In the seed-route-soil paradigm, m6A is not an extra driver for GI cancer progression but a designer of metastatic organotropism since it controls seed competency, tunes cues that govern metastatic routes, and directs the education of soil via exosomes and immunomodulation. Since niche construction is a prerequisite for colonizing the niche, this perspective identifies a therapeutic opportunity to intervene in the process of metastasis not by treating it but by preventing it. This opportunity can be realized through single-cell profiling of niche epitranscriptome and specific targeting of m6A regulators within the pre-metastatic window.

There are three gaps in the research agenda. First, niche epitranscriptomic characterization: even though the role of METTL3–RAB27A–exosome axis in demonstrating that m6A can create a peritoneal PMN has been established, the current knowledge is based almost entirely on bulk m6A RNA immunoprecipitation sequencing (meRIP-seq). Its low resolution of approximately 200 nucleotides and inability to identify individual cells make it impossible to map the sites of epitranscription within a specific niche. Single-cell m6A characterization of hepatic and peritoneal PMNs as compared with their naive counterparts does not yet exist and will enable researchers to understand which soil cells become epitranscriptomically reprogrammed, if the GC paradigm is applicable for the hepatic niche of CRC and PDAC, and, specifically, if the role of m6A in creating the niche is mediated by the tRFs in exosomes in PDAC. Second, reversibility: if PMN creation relies on m6A, is the mature niche reversible by inhibition of m6A writers/erasers and at what time scale? Third, the microbial angle: Fn downregulates m6A differently in ESCC as compared with CRC and moves along with the metastatic cells, if microbiome modulation therapy affects the metastatic route through the epitranscriptome is unknown.

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