

From RNA fate to cancer state transitions: m5C-driven metabolic and immune reprogramming (Review)

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Abstract. RNA 5-methylcytosine (m5C) regulates RNA stability, processing and translation, linking changes in nutrient supply and stress to cancer-cell behavior. Its consequences depend on the RNA substrate and the proteins that recognize or process the modification. This dependence helps explain why NOP2/Sun RNA methyltransferase 2 (NSUN2), NOP2 nucleolar protein, NSUN5, NSUN6 and tRNA aspartic acid methyltransferase 1 can affect proliferation, metabolism, immunity and treatment response differently. Across coding and noncoding RNAs, m5C regulation can sustain growth-related protein expression, alter DNA damage repair and support metabolic defenses against cell death. Metabolites also regulate writers and readers, creating feedback in specific tumor models that connects nutrient availability with RNA recognition. These relationships suggest several therapeutic approaches, including nucleoside analogues, writer or reader inhibition, substrate-RNA targeting and tumor-directed delivery. Experimental combinations can restore drug sensitivity, although simultaneous effects on immune cells or normal tissues may limit systemic treatment. Clinical translation requires relating treatment-induced RNA changes to drug exposure, tumor selectivity and immune-cell function, rather than relying on regulator expression alone.

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1. Introduction

RNA 5-methylcytosine (m5C) occurs in coding and noncoding (nc)RNAs whose stability, processing and translation influence protein production. The NOP2/Sun RNA methyltransferase (NSUN) family and transfer (t)RNA aspartic acid methyltransferase 1 (TRDMT1) differ in substrate recognition and localization, so similar changes in regulator expression need not produce the same RNA response (1,2). Oxygen or nutrient fluctuations, inflammation and repeated treatment can alter RNA processing and the availability of proteins needed for cancer-cell growth or survival. Expression-based studies have associated m5C regulators with prognosis and immune infiltration, but these associations do not identify the modified RNA responsible for the phenotype (3,4). The unresolved question is how a particular stress alters writer activity, reader binding and substrate selection, and how the resulting RNA changes affect cancer-cell behavior.

Metabolic signals can influence immune responses through substrate-specific RNA regulation. Glucose binding increases NSUN2 activity, which stabilizes three prime repair exonuclease 2 (TREX2) mRNA and limits cytosolic DNA accumulation and cyclic GMP-AMP synthase

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Abbreviations: m5C, RNA 5-methylcytosine; EV, extracellular vesicle

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(cGAS)/stimulator of interferon response cGAMP interactor 1 (STING) activation (5). Here, nutrient sensing affects immune signaling through a defined RNA target. Whether this relationship occurs in another tumor depends on the relevant RNA substrate and reader. Cancer cell-state transitions in response to stress involve changes in RNA fate, metabolic dependence, immune interactions and treatment tolerance. These stress-associated functional changes do not encompass all lineage plasticity or tumor evolution. Attributing these responses to RNA m5C requires site identification and writer perturbation, followed by RNA-fate measurements linked to phenotype rescue and reader-binding measurements where involved. Catalytic-mutant and RNA-specific rescue are particularly relevant because proteins such as NOP2 nucleolar protein (NOP2) retain functions that do not require methyltransferase activity (6).

Previous reviews have organized m5C findings by regulator and tumor type (7,8), RNA class (9,10) or biological function and therapeutic application (11,12). This review instead follows stress cues through writer-reader-substrate interactions and RNA fate to metabolic and immune responses, and then to therapeutic adaptation (Fig. 1). Comparing these processes across tumor models helps distinguish methylation-dependent effects from other regulator functions and tumor-cell adaptation from immune-cell responses. It also relates specific RNA changes to adaptive phenotypes, helping identify potentially targetable processes, such as the stabilization or translation of m5C-modified transcripts that support tumor-cell survival.

2. Molecular architecture and dynamic activation of the m5C regulatory system in cancer

Stress-responsive m5C regulation involves both the deposition of the modification and the subsequent processing of modified RNA. NSUN-family proteins and TRDMT1 act as writers, whereas Aly/REF export factor (ALYREF) and Y-box binding protein 1 (YBX1) function as readers or cooperate with other RNA-binding proteins. Hypoxia engages ALYREF-associated kinesin family member (KIF)20A/BUB1 mitotic checkpoint serine/threonine kinase regulation in cervical cancer, while lactylation enhances NSUN2-dependent regulation during pancreatic cancer perineural invasion (13,14). Inflammatory signaling and genomic alterations intersect with this machinery in different ways: circTMEM45A-associated RNA regulation promotes NLR family pyrin domain containing 3 activation, whereas alpha tocopherol transfer protein like amplification enhances NSUN2-dependent sterol regulatory element binding transcription factor 2 (SREBP2) mRNA modification in esophageal cancer (15,16). Renal cancer analyses also associate NSUN2 with glycolysis, histone lactylation and immune escape (17). Once engaged, NSUN2 can act on different transcripts, including SREBP2 in hepatocellular carcinoma and chaperonin containing TCP1 subunit 5 in lung adenocarcinoma (18,19). Their subsequent regulation depends on RNA-binding partners. YBX1 cooperates with eukaryotic translation initiation factor 4A1 to support closed-loop translation of linear ring finger protein 115 mRNA, while ALYREF-associated regulation supports colony stimulating factor 2 mRNA stability (20,21). ALYREF also participates in NSUN2-dependent leucine rich repeat containing

G protein-coupled receptor 4 regulation and platinum resistance in ovarian cancer (22). Changes in writer activity and RNA-binding partners can therefore alter which transcripts persist or are translated under stress (Fig. 2).

The separation between catalytic activity and RNA processing is particularly apparent for NOP2 nucleolar protein, also called NSUN1. Human NOP2 deposits m5C at C4447 of 28S ribosomal (r)RNA and associates with pre-rRNA and box C/D small nucleolar ribonucleoprotein complexes. Catalytically inactive NOP2 can nevertheless rescue aspects of pre-rRNA processing and complex assembly after NOP2 depletion (6). Ribosome assembly can therefore remain dependent on NOP2 even when it is independent of NOP2-mediated methylation. In hepatocellular carcinoma, NOP2-mediated modification of XPD mRNA is instead associated with transcript stability and tumor progression (23). These distinct RNA functions explain why loss of the whole protein cannot be treated as equivalent to inhibition of its catalytic activity.

NSUN5 acts on both rRNA and non-rRNA. Subsequent processing of the modified RNA can change the consequences of m5C deposition. NSUN5 deposits m5C on catenin beta 1 chromatin-associated RNA, after which tet methylcytosine dioxygenase 2 oxidizes m5C to RNA 5-hydroxymethylcytosine and RNA binding fox-1 homolog 2 (RBFOX2) recognizes the oxidized RNA and promotes its degradation. Reduced expression of β -catenin and CD47 enhances macrophage phagocytosis of glioma cells (24). In this setting, m5C deposition precedes RNA loss because oxidation creates the RNA species recognized by RBFOX2.

For NSUN6, substrate differences likewise accompany different effects on tumor growth. Its involvement in transfer RNA (tRNA)-Cys-derived fragments connects methylation with fragment activity and protein binding, whereas selected mRNA targets connect it to proliferation and migration (25). NSUN6 depletion increases pancreatic cancer cell proliferation and xenograft growth, and NSUN6-dependent NM23-H1 regulation restrains migration and epithelial-mesenchymal transition in lung cancer (26,27). By contrast, NSUN6-mediated modification of methyltransferase 3, N6-adenosine-methyltransferase complex catalytic subunit (METTL3) mRNA promotes colon adenocarcinoma progression (28). In the latter setting, regulation of an m6A-writing enzyme also allows an m5C-dependent RNA event to influence another modification system. These different substrates provide a basis for separating tumor-restraining from tumor-promoting NSUN6 activity.

TRDMT1 participates in both tRNA protection and damage-associated RNA regulation. It methylates C38 of tRNA-Asp and azacytidine inhibits methylation at this site. Its ubiquitination and removal at DNA lesions affect repair and treatment response (29,30). These functions can have different consequences for tumor survival. In anaplastic thyroid carcinoma, reduced TRDMT1 activity increases a tRNA-Gly-GCC-derived fragment that promotes growth (31). In hepatocellular carcinoma, TRDMT1 has instead been associated with resistance through ATP citrate lyase (ACLY)- or TNF superfamily member 10 (TNFSF10)-related regulation (32,33). The response to TRDMT1 inhibition therefore depends in part on whether loss of RNA protection, altered fragment production or impaired repair has the greater effect.

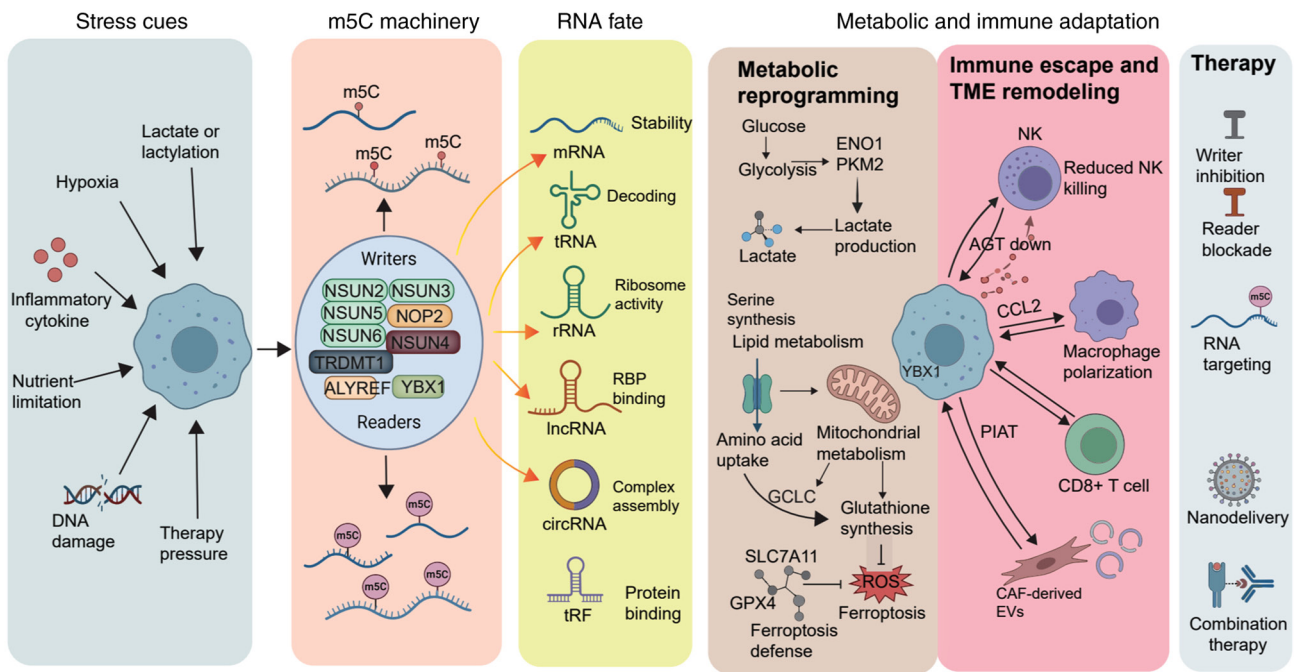


Figure 1. Stress-associated RNA regulation and cancer cell states. Hypoxia, nutrient availability, inflammation and treatment can alter m5C regulation. Writers deposit m5C on selected RNA substrates, while readers and associated RNA-binding proteins influence the fate of modified RNA. Changes in stability, export, splicing, translation and cleavage affect metabolic requirements, immune interactions and treatment tolerance. The relationships were studied in different tumor models and may vary with substrate expression and reader availability. NSUN2/3/4/5/6, NOP2/Sun RNA methyltransferases 2, 3, 4, 5 and 6; NOP2, NOP2 nucleolar protein; TRDMT1, tRNA aspartic acid methyltransferase 1; ALYREF, Aly/REF export factor; YBX1, Y-box binding protein 1; ENO1, enolase 1; PKM2, pyruvate kinase M2, an isoform encoded by PKM; GCLC, glutamate-cysteine ligase catalytic subunit; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione peroxidase 4; AGT, angiotensinogen; CCL2, C-C motif chemokine ligand 2; PIAT, perineural invasion-associated transcript; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; tRNA, transfer RNA; rRNA, ribosomal RNA; IncRNA, long noncoding RNA; circRNA, circular RNA; tRF, tRNA-derived fragment; RBP, RNA-binding protein; ROS, reactive oxygen species; TME, tumor microenvironment; EV, extracellular vesicle; NK, natural killer; CAF, cancer-associated fibroblast; CD8, cluster of differentiation 8.

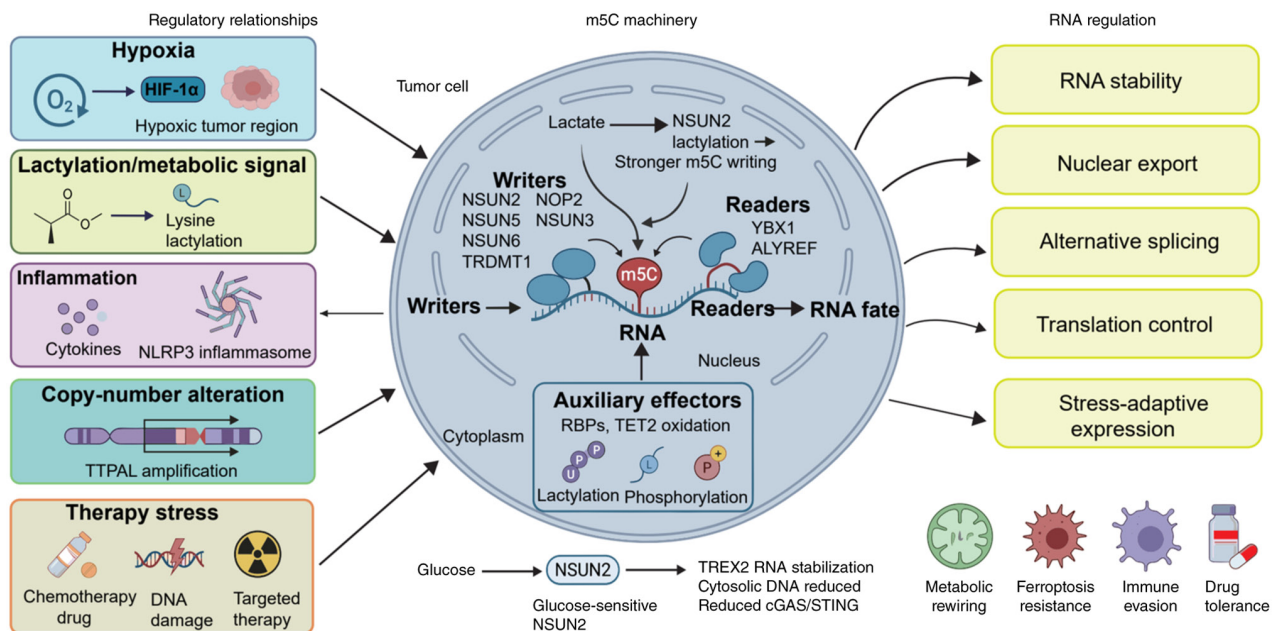


Figure 2. Regulation of m5C writers and readers by stress and metabolic signals. Hypoxia, lactylation, inflammation, copy-number changes and treatment alter the expression, localization or activity of m5C regulators. NSUN-family proteins and TRDMT1 deposit m5C, while YBX1 and ALYREF recognize modified RNA. TET2-mediated oxidation is distinct from m5C writing and reading. Glucose binding and protein modifications provide additional regulation of NSUN2, NSUN5 and YBX1. Changes in writer activity and reader binding affect subsequent RNA regulation. Substrate-specific RNA fates are shown in Fig. 3. NSUN2/3/5/6, NOP2/Sun RNA methyltransferases 2, 3, 5 and 6; NOP2, NOP2 nucleolar protein; TRDMT1, tRNA aspartic acid methyltransferase 1; YBX1, Y-box binding protein 1; ALYREF, Aly/REF export factor; HIF-1 α , hypoxia-inducible factor 1 subunit α (HIF1A); NLRP3, NLR family pyrin domain containing 3; TTPAL, α tocopherol transfer protein like; TREX2, three prime repair exonuclease 2; TET2, tet methylcytosine dioxygenase 2; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon response cGAMP interactor 1 (STING1); m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; RBP, RNA-binding protein.

3. RNA substrate spectrum and m5C-driven RNA fate

For mRNA, the most frequently reported consequence is altered transcript stability, but the direction and phenotype depend on the encoded protein. Increased stability supports cyclin L2 expression in ovarian cancer and AIF family member 2, ferroptosis suppressor-dependent ferroptosis defense in acute myeloid leukemia (34,35). NSUN2-dependent dihydroorotate dehydrogenase (quinone) regulation similarly connects mitochondrial ferroptosis defense with oxaliplatin resistance in colorectal cancer (36). In nasopharyngeal carcinoma, however, NSUN2-dependent regulation reduces TP53 mRNA stability (37). Both increased expression of a survival protein and reduced expression of a tumor suppressor can therefore favor tumor growth. Other targets connect the same RNA property to metabolism or dissemination. Apolipoprotein (APO)L1 and phosphoribosylformylglycin-amidine synthase regulation affects downstream PI3K-AKT activity and purine synthesis, respectively (38,39). KIF11 regulation promotes gastric cancer lymphatic metastasis, while LINC02167-associated kinase suppressor of ras 1 mRNA stabilization activates downstream ERK/MAPK signaling in colorectal cancer (40,41). Nuclear factor erythroid 2-related factor 2-related regulation and NSUN2/YBX1-dependent HGH1 cochaperone stabilization further connect RNA availability with redox defense and growth (42,43). Transcript abundance is not the only relevant change: NSUN2-dependent modification promotes ALYREF-mediated export of serine and arginine rich splicing factor 6 (SRSF6) mRNA. The resulting SRSF6 protein changes UDP-N-acetylglucosamine pyrophosphorylase 1 splicing, linking the RNA-export event to multidrug resistance in anaplastic thyroid cancer (44). Thus, the consequences of mRNA regulation reflect both the amount and the form of RNA available for protein production.

tRNA and rRNA affect that production more directly through the translational apparatus. NSUN2-dependent tRNA-Val-CAC regulation promotes codon-biased translation in triple-negative breast cancer, while stabilization of selected tRNAs supports oncogenic translation in anaplastic thyroid cancer (45,46). Protein synthesis can consequently change without a parallel increase in mRNA abundance. Cleavage introduces an additional outcome because tRNA-derived fragments may acquire functions distinct from those of the parent tRNA. A tumor-targeted tRNA-derived fragment strategy, for example, induces ovarian cancer ferroptosis by disrupting system Xc⁻-associated defense (47). At the ribosomal level, NSUN5 loss induces stress-adaptive translation in glioma, whereas other glioblastoma models associate NSUN5 with greater protein synthesis and growth (48,49). These glioma models show different relationships between NSUN5 activity, protein synthesis and stress adaptation. ncRNAs add control through protein recruitment: solute carrier family 16 member 1 (SLC16A1)-antisense 1 (AS1) associates with NSUN2 to stabilize heat shock protein family A (Hsp70) member 5 mRNA, and the NSUN5-circPPAP2A pathway affects immune suppression and anti-programmed cell death 1 sensitivity (50,51). Reader-dependent mRNA regulation provides a complementary route through STAT1/programmed cell death ligand 1 (PD-L1) in intrahepatic cholangiocarcinoma

and transmembrane 4 L six family member 1 in bladder cancer (52,53). ALYREF-associated ATP binding cassette subfamily G member 4 expression extends the consequences of RNA availability to drug efflux in castration-resistant prostate cancer (54). An HLA complex P5 (HCP5)-derived 132-amino-acid microprotein further regulates the reading step by enhancing YBX1-ELAV like RNA binding protein 1 (ELAVL1) interaction and preserving SLC7A11 and glucose-6-phosphate dehydrogenase mRNA stability (55). HCP5 affects these modified mRNAs through its micro-protein product, whereas SLC16A1-AS1 recruits NSUN2 as an RNA. These RNA classes therefore influence protein production through distinct combinations of stability, decoding, ribosome function and protein binding (Fig. 3).

4. m5C-driven tumor-cell-intrinsic malignant programs

RNA-fate changes support malignant behavior when they increase the availability of proteins required for cell division, survival or nutrient use. NSUN2-mediated phosphoglycerate kinase 1 (PGK1) mRNA stabilization promotes gastric cancer growth, invasion, stemness and glycolysis, while ALYREF-dependent isocitrate dehydrogenase [NADP(+)] 1 regulation supports intrahepatic cholangiocarcinoma progression (56,57). NSUN2-associated hexokinase domain containing 1 and phosphoglycerate dehydrogenase (PHGDH) regulation provides related metabolic support in retinoblastoma and colorectal cancer (58,59). Such metabolic effects complement the regulation of proteins acting more directly in division and survival. ALYREF stabilizes baculoviral IAP repeat containing 5 mRNA, linking transcript stability to survivin-associated mitotic control and apoptosis inhibition, whereas NOP2-mediated lamin B2 mRNA modification supports a protein involved in nuclear structure and cell division (60,61). Increased abundance of these proteins can support growth either by supplying metabolic intermediates or by sustaining cell division and survival.

Downstream signaling and metabolic demand then determine how those protein changes affect growth and dissemination. NSUN5-associated PI3K-AKT activity in prostate cancer and NSUN3-associated reactive oxygen species (ROS) accumulation in hepatocellular carcinoma accompany increased growth (62,63). NSUN5 and NSUN2 have also been associated with Wnt activity in gastric cancer and hepatocellular carcinoma, respectively (64,65). NSUN2-dependent Wnt/ β -catenin regulation promotes colon adenocarcinoma growth (66). NSUN2-dependent stabilization of TIAM Rac1 associated GEF 2 mRNA affects pancreatic cancer progression and downstream cytoskeletal regulation (67). Metabolic support operates alongside these signaling effects: NSUN2-dependent pyruvate kinase M2 (PKM2) regulation supports glucose use, while NSUN5-mediated glutaminase stabilization supports glutamine metabolism (68,69). Growth and motility still require survival after cells leave their normal attachment sites. In prostate cancer, NSUN2/ALYREF-dependent modification promotes autophagy-associated anoikis resistance, allowing cells to survive matrix detachment (70). Together, nutrient use, survival and motility support dissemination (Fig. 4). DNA damage and drug exposure impose additional requirements on repair and stress resistance.

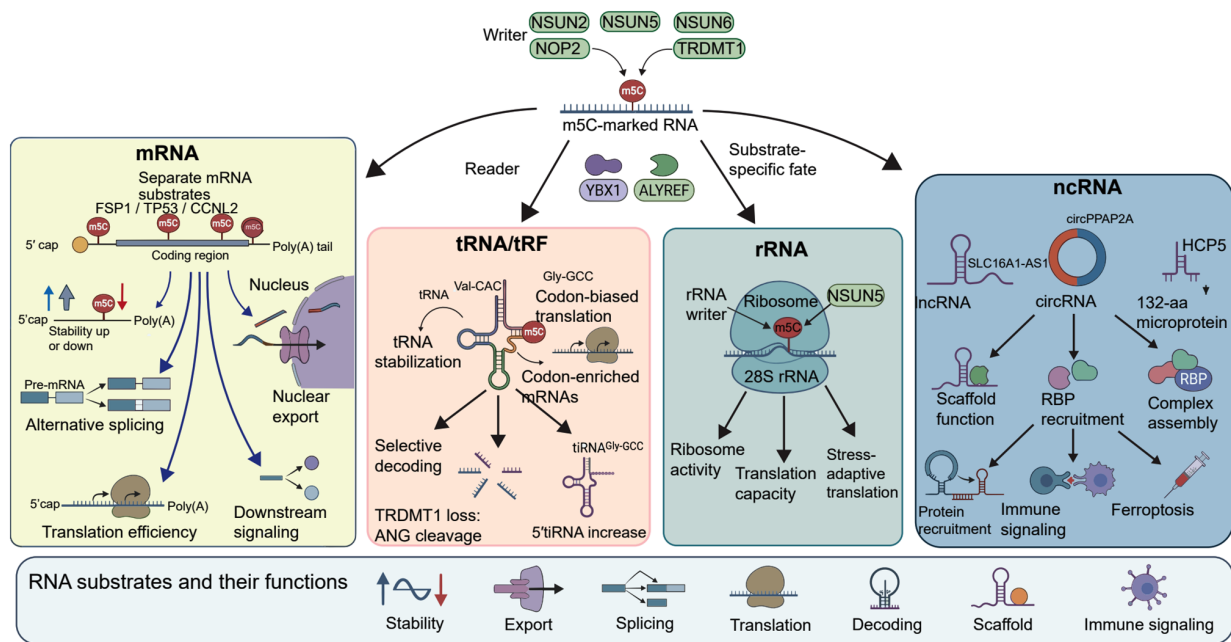


Figure 3. RNA substrates and m5C-associated RNA fates. mRNA modification can increase or decrease transcript stability and can affect export, splicing and translation. tRNA modification changes RNA stability and codon-dependent translation, while cleavage generates tRNA-derived fragments with additional functions. rRNA modification can alter ribosome activity and stress-adaptive translation in the models examined. lncRNAs and circRNAs can recruit proteins or organize RNA-protein complexes. The HCP5-derived 132-amino-acid microprotein illustrates how a noncanonical coding product can alter RNA-protein interactions. NSUN2/5/6, NOP2/Sun RNA methyltransferases 2, 5 and 6; NOP2, NOP2 nucleolar protein; TRDMT1, tRNA aspartic acid methyltransferase 1; YBX1, Y-box binding protein 1; ALYREF, Aly/REF export factor; FSP1, ferroptosis suppressor protein 1 (AIFM2); TP53, tumor protein p53; CCNL2, cyclin L2; SLC16A1-AS1, SLC16A1 antisense RNA 1; circPPAP2A, circular RNA derived from phospholipid phosphatase 1 (PLPPI, formerly PPAP2A); HCP5, HLA complex P5; ANG, angiogenin; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; tRNA, transfer RNA; rRNA, ribosomal RNA; lncRNA, long noncoding RNA; circRNA, circular RNA; ncRNA, noncoding RNA; tRF, tRNA-derived fragment; tRNA, tRNA-derived stress-induced RNA; 5'tiRNA-Gly-GCC, 5'tiRNA half derived from tRNA-Gly-GCC; tRNA-Val-CAC, valine tRNA with a CAC anticodon; tRNA-Gly-GCC, glycine tRNA with a GCC anticodon; RBP, RNA-binding protein; aa, amino acid; Poly(A), polyadenylate.

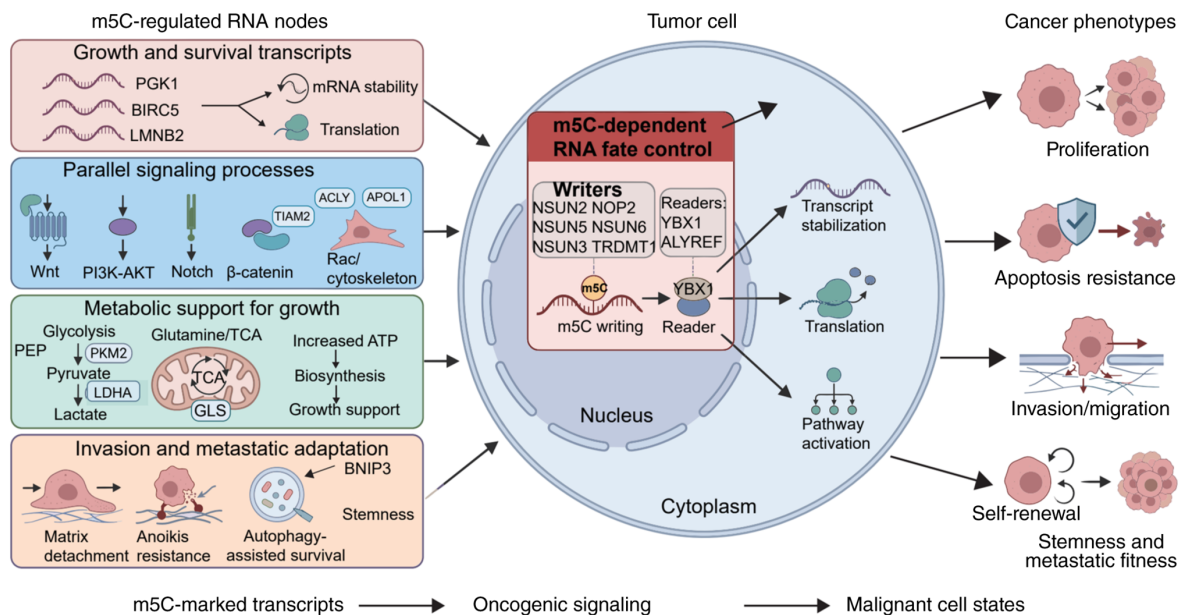


Figure 4. RNA regulation in cancer-cell growth and dissemination. m5C-associated regulation of PGK1, BIRC5 and LMNB2 affects transcript stability or protein expression and supports cell division or survival. Changes in signaling transcripts act upstream of the pathway activities shown. Metabolic proteins including PKM2, PGK1, IDH1 and GLS support nutrient use and biosynthesis. Autophagy-associated anoikis resistance contributes to survival after matrix detachment. Changes in RNA regulation precede the effects on proliferation, survival and invasion. NSUN2/3/5/6, NOP2/Sun RNA methyltransferases 2, 3, 5 and 6; NOP2, NOP2 nucleolar protein; TRDMT1, tRNA aspartic acid methyltransferase 1; YBX1, Y-box binding protein 1; ALYREF, Aly/REF export factor; PGK1, phosphoglycerate kinase 1; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5 (survivin); LMNB2, lamin B2; PKM2, pyruvate kinase M2, an isoform encoded by PKM; IDH1, isocitrate dehydrogenase [NADP(+)] 1; GLS, glutaminase; TIAM2, TIAM Rac1-associated guanine nucleotide exchange factor 2; ACLY, ATP citrate lyase; APOL1, apolipoprotein L1; LDHA, lactate dehydrogenase A; BNIP3, BCL2 interacting protein 3; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; Rac, Rac-family small GTPase; Wnt, Wnt-family signaling; Notch, Notch receptor signaling; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; PEP, phosphoenolpyruvate; ATP, adenosine triphosphate; TCA, tricarboxylic acid cycle; ECM, extracellular matrix.

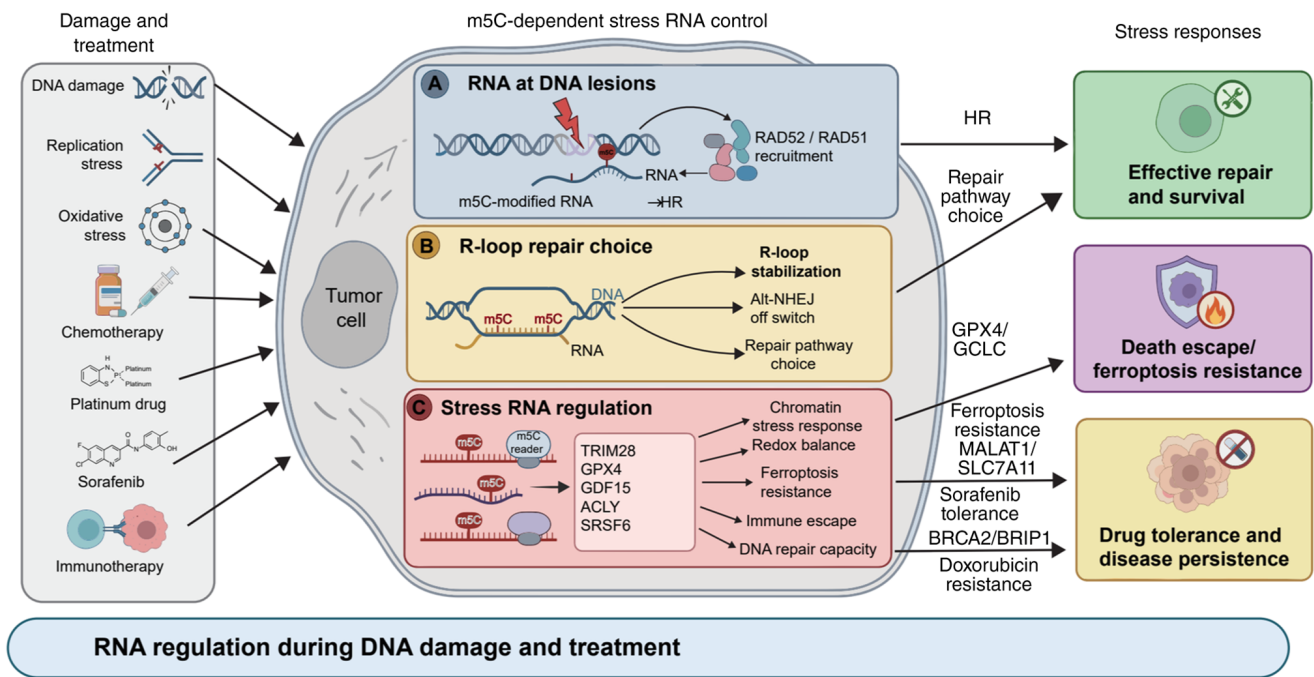


Figure 5. RNA regulation during DNA damage and therapeutic stress. (A) Local TRDMT1-dependent m5C modification of RNA at DNA lesions supports homologous recombination and recruitment of repair proteins. (B) Methylation of the RNA strand in R-loops affects RNA-DNA hybrids and can suppress Alt-NHEJ. (C) Regulation of stress- and treatment-associated RNAs affects chromatin responses, redox defense, ferroptosis susceptibility, repair capacity and immune escape. The panel includes modified RNA substrates and proteins whose abundance changes downstream of RNA regulation. Panels A and B concern DNA damage and genome maintenance, while panel C depicts treatment adaptation. TRDMT1, tRNA aspartic acid methyltransferase 1; RAD51, RAD51 recombinase; RAD52, RAD52 DNA repair protein; TRIM28, tripartite motif containing 28; GPX4, glutathione peroxidase 4; GDF15, growth differentiation factor 15; ACLY, ATP citrate lyase; SRSF6, serine and arginine rich splicing factor 6; GCLC, glutamate-cysteine ligase catalytic subunit; MALAT1, metastasis associated lung adenocarcinoma transcript 1; SLC7A11, solute carrier family 7 member 11; BRCA2, BRCA2 DNA repair associated; BRIP1, BRCA1 interacting DNA helicase 1; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; DNA, deoxyribonucleic acid; HR, homologous recombination; Alt-NHEJ, alternative non-homologous end joining.

5. m5C in DNA damage response and genome maintenance

At DNA lesions, RNA m5C can affect repair by changing the recruitment and residence of repair proteins. TRDMT1 loss reduces RAD51 and RAD52 recombinase recruitment, compromises homologous recombination and increases sensitivity to DNA double-strand breaks (2). RAD52 preferentially binds DNA-RNA hybrids containing m5C-modified RNA *in vitro*, providing a local explanation for the reduced repair-factor recruitment. R-loop methylation influences a different repair choice: TRDMT1-dependent m5C suppresses alternative non-homologous end joining (Alt-NHEJ) (71). In bladder cancer, NSUN2-dependent R-loop stabilization has also been associated with progression and cisplatin response (72). The relevant outcome therefore depends on the hybrid structure and repair pathway involved (Fig. 5A and B). Y RNA fragments offer a related RNA-binding mechanism by forming complexes with YBX1 that alter poly(ADP-ribose) polymerase 1 residence at DNA breaks (73). Whether this YBX1 complex requires m5C recognition remains unresolved.

Repair can also be affected by RNA regulation away from the immediate lesion. Forkhead box A1-dependent NSUN2 activity preserves tripartite motif containing 28 mRNA stability in prostate cancer, altering the abundance of a chromatin-associated protein rather than modifying RNA locally at a break (74). This creates a distinction between recruitment of repair machinery and the availability of proteins that influence chromatin responses. TRDMT1-dependent control of repeat

elements adds a further source of genome stress: Deficient osteosarcoma cells show impaired responses to exogenous RNA and increased retrotransposon activity during prolonged culture (75). These changes concern genome stress accumulated during prolonged culture rather than an acute chemotherapy response. RNA regulation can therefore affect genome maintenance at individual lesions or through longer-term changes in chromatin-associated proteins and repeat activity.

6. m5C-centered metabolic reprogramming

Survival under stress also depends on metabolic processes regulated by m5C. This regulation is bidirectional, as enzymes encoded by modified transcripts generate metabolites that can alter writer or reader activity. In colorectal cancer, NSUN2 and YBX1 stabilize enolase 1 mRNA and increase lactate production. Lactate then reinforces NSUN2 transcription and substrate interaction through H3K18 and NSUN2 K356 lactylation (76). A separate colorectal cancer study extends lactate sensitivity to the reading step, where YBX1 K92 lactylation enhances binding to modified RNA (77). Other glycolytic transcripts reach sustained expression through different regulatory combinations. NSUN5-dependent ENO3 stabilization increases glucose uptake and lactate production in clear cell renal cell carcinoma, while hypoxia-inducible factor (HIF)-1 α induction and ALYREF-dependent stability jointly support PKM2 expression in bladder cancer (78,79). THO complex subunit 3 and YBX1 maintain

6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4 mRNA export and stability in lung squamous cell carcinoma (80). NOP2-associated MYC regulation and NSUN5-mediated ephrin A3 (EFNA3) stabilization extend these effects to glycolytic transcription and upstream signaling in hepatocellular carcinoma (81,82). EFNA3 is a signaling ligand rather than a glycolytic enzyme, so its effect is indirect. Glucose binding increases NSUN2 activity and TREX2 mRNA stability, linking nutrient sensing to cGAS/STING suppression (5). A study on glioma also associated NSUN2 with glucose metabolism (83). The ENO1-lactate feedback was defined in colorectal cancer, while the other tumors involve different substrates, reader availability or initiating signals.

Beyond glycolysis, modified transcripts support the lipids, amino acids and energy needed for sustained growth. Cyclin-dependent kinase (CDK)13-dependent NSUN5 Ser327 phosphorylation promotes acetyl-CoA carboxylase mRNA modification, ALYREF-dependent export and fatty acid synthesis, whereas NSUN2-mediated sterol O-acyltransferase 2 regulation affects cholesterol metabolism and competition with T cells (84,85). Acyl-CoA synthetase long chain family member 3 (ACSL3) is associated with regulator patterns, but direct modification of a particular ACSL3 RNA site remains unestablished (86). Amino acid metabolism extends this RNA dependence to biosynthesis and methyl-donor supply. NSUN2 stabilizes PHGDH and serine hydroxymethyltransferase 2 mRNAs, supporting serine/glycine synthesis and one-carbon metabolism in acute myeloid leukemia (87). A study reported that methionine restriction or NOP2 depletion reduced the growth of MYC-driven liver tumors (88). Energy production can also be affected through mitochondrial RNA. NSUN3-dependent tRNA modification supports translation and oxidative phosphorylation in metastasis-initiating cells, while NSUN4-associated circERI3 modification affects mitochondrial energy metabolism (89,90). METTL17 provides a related mitochondrial-translation example involving ferroptosis and colorectal cancer growth, although its direct catalytic role in RNA m5C has not been established (91).

Metabolic support becomes relevant to cell-death resistance when it preserves antioxidant capacity or iron handling. In gastric cancer, N-alpha-acetyltransferase 10, NatA catalytic subunit-dependent NSUN2 K508 lactylation stabilizes glutamate-cysteine ligase catalytic subunit mRNA, increasing glutathione synthesis and resistance to doxorubicin-induced ferroptosis (92). NSUN5-dependent ferritin heavy chain 1 (FTH1) regulation suppresses ferroptosis in the same cancer type, while NSUN2-associated FTH1 regulation accompanies increased global protein synthesis in B-acute lymphoblastic leukemia (93,94). FTH1/ferritin light chain-associated protection against ferroptosis has also been described in mesenchymal stem cells (95). Glutathione peroxidase 4 (GPX4)-dependent redox defense involves both m6A and m5C regulation (96). SLC2A1 expression is also associated with prognosis and immune infiltration, although its direct regulation at an m5C site remains unresolved (97). Amino acid uptake can also affect the nutrients available to immune cells. ALYREF recognition of modified JunD proto-oncogene, AP-1 transcription factor subunit mRNA promotes SLC7A5, mTOR complex 1 activity and amino acid uptake in pancreatic ductal adenocarcinoma (98). This connects tumor nutrient uptake to

the amino acids available to CD8+ T cells. NSUN2-associated glucose reprogramming in hepatocellular carcinoma likewise involves tumor-immune nutrient competition (99). Tumor metabolic activity can therefore alter nutrient availability for immune responses (Fig. 6).

7. m5C-mediated immune escape and remodeling of the tumor microenvironment

Associations between m5C regulators and tumor immunity vary with the cells contributing to tissue-level expression. Regulator patterns in clear cell renal cell carcinoma and lung adenocarcinoma correlate with immune-cell composition and prognosis (3,4). Bulk and single-cell hepatocellular carcinoma analyses similarly associate DNA methyltransferase 1, NSUN5 and ALYREF with natural killer (NK)-cell infiltration or adverse clinical features (100,101). Reader- and long (l) ncRNA-based scores relate to macrophage infiltration and predicted drug response in bladder and colon cancer (102,103). Related scores in hepatocellular carcinoma and prostate cancer extend these associations to stromal and T-cell features (104,105). In glioblastoma, YBX1-positive tumor cells are associated with proliferation, whereas YBX1-positive myeloid cells show TNF- and APOE-related interactions (106). The RNA targets responsible for these cell-specific expression associations remain elusive.

Tumor-cell RNA regulation can affect immune function through secreted factors. In liver cancer cocultures, NSUN2 depletion increased angiotensinogen (AGT) expression and NK-cell killing. AGT neutralization reversed the increase, while exogenous AGT increased IFN- γ , TNF- α , perforin and the proportion of CD107a-positive NK cells (107). AGT therefore contributes to the NK-cell response following NSUN2 depletion (Fig. 7, part ①). A distinct secreted-factor mechanism operates after NSUN6 deficiency in pancreatic ductal adenocarcinoma. Reduced lysine demethylase 5A mRNA stability increases tumor-cell C-C motif chemokine ligand 2 (CCL2) transcription and secretion, which promotes immunosuppressive macrophage accumulation and weakens antitumor immunity. CCL2 blockade restores checkpoint-treatment sensitivity in the deficient mouse models (108). RNA regulation within myeloid cells can also change their activation state. In bladder cancer-associated macrophage models, NSUN2 lowers suppressor of cytokine signaling 3 (SOCS3) mRNA stability and export, relieving SOCS3 inhibition of JAK2/STAT3 and favoring M2 over M1 polarization (109). NSUN3 depletion in head and neck cancer also shifts macrophage proportions toward M1 (110). The effects of regulator depletion consequently depend on the RNA target and the participating immune cells.

Inflammatory signals can sustain RNA-dependent changes in cell behavior. In bladder cancer, KIF26B promotes NSUN2 ubiquitination and nuclear localization, increasing YBX1-associated IL-6 expression. IL-6 feeds back through STAT3, KIF26B transcription and NSUN2 acetylation (111). Cell death provides another means of altering the signals released by tumor cells. In pancreatic cancer, charged multivesicular body protein 4C (CHMP4C)/YBX1-associated caspase-8 (CASP8) mRNA regulation increases Casp8 protein and suppresses receptor interacting serine/threonine kinase 1 (RIPK1)/RIPK3/mixed lineage kinase domain like

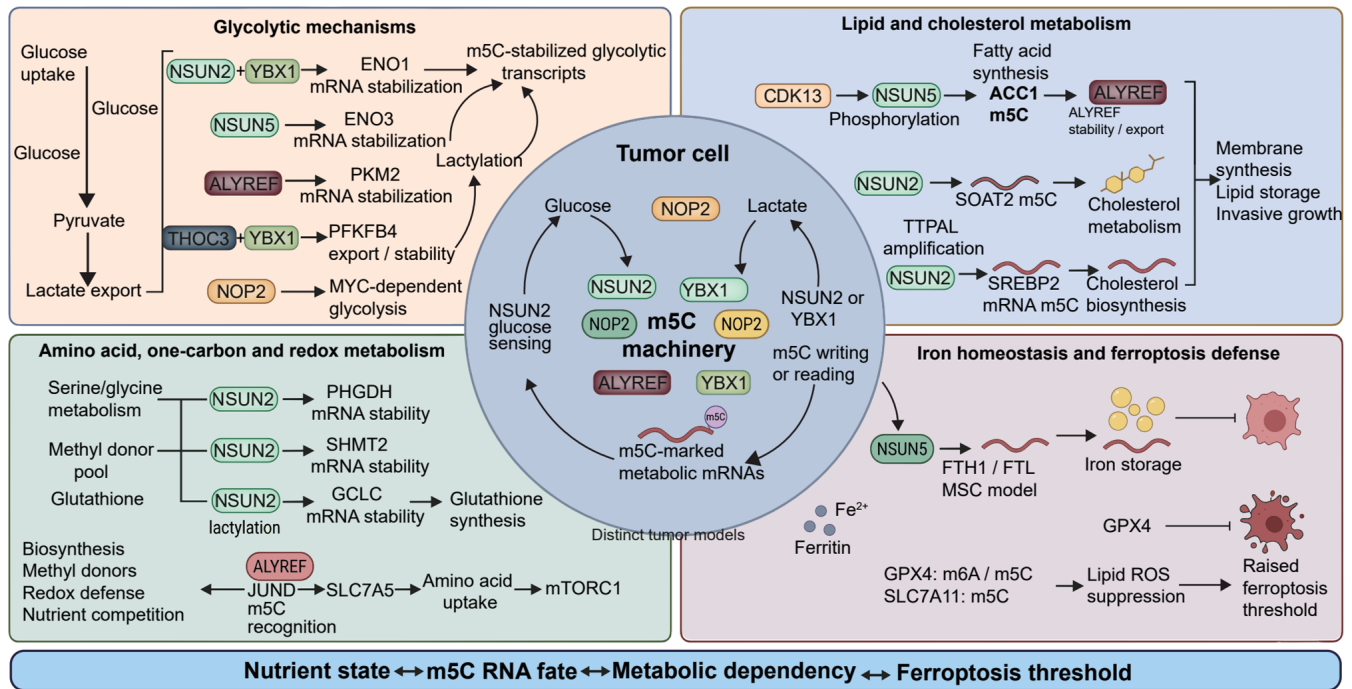


Figure 6. Metabolic processes associated with m5C regulation. Glycolytic examples include ENO1, ENO3, PKM2 and PFKFB4 RNA regulation and MYC-associated transcription. The ENO1-lactate feedback was defined in colorectal cancer and should not be extrapolated to all tumors. ACC1, SOAT2 and SREBP2 connect m5C-associated regulation to lipid or cholesterol metabolism. PHGDH, SHMT2, GCLC and JUND/SLC7A5 connect amino acid availability with biosynthesis, glutathione and nutrient competition. FTH1 and FTL regulate iron storage and protection against ferroptosis, including in a nonmalignant mesenchymal stromal-cell model. GPX4 regulation involves both m6A and m5C. NSUN2/5, NOP2/Sun RNA methyltransferases 2 and 5; NOP2, NOP2 nucleolar protein; YBX1, Y-box binding protein 1; ALYREF, Aly/REF export factor; THOC3, THO complex subunit 3; CDK13, cyclin dependent kinase 13; ENO1, enolase 1; ENO3, enolase 3; PKM2, pyruvate kinase M2, an isoform encoded by PKM; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 4; MYC, MYC proto-oncogene, basic helix-loop-helix transcription factor; ACC1, acetyl-CoA carboxylase 1 (ACACA); SOAT2, sterol O-acyltransferase 2; SREBP2, sterol regulatory element-binding protein 2 (SREBF2); TTPAL, alpha tocopherol transfer protein like; PHGDH, phosphoglycerate dehydrogenase; SHMT2, serine hydroxymethyltransferase 2; GCLC, glutamate-cysteine ligase catalytic subunit; JUND, JunD proto-oncogene, AP-1 transcription factor subunit; SLC7A5, solute carrier family 7 member 5; FTH1, ferritin heavy chain 1; FTL, ferritin light chain; GPX4, glutathione peroxidase 4; SLC7A11, solute carrier family 7 member 11; m5C, RNA 5-methylcytosine; m6A, N6-methyladenosine; RNA, ribonucleic acid; mRNA, messenger RNA; mTORC1, mechanistic target of rapamycin complex 1; MSC, mesenchymal stromal cell; ROS, reactive oxygen species; Fe²⁺, ferrous ion.

pseudokinase (MLKL)-dependent necroptosis. CHMP4C also promotes extracellular vesicle (EV)-associated phospho-MLKL export. Tumor-conditioned medium promotes mast-cell migration, while tumor-derived EV uptake increases mast-cell cytokine secretion (112). Stromal EVs can instead alter RNA recognition within recipient tumor cells. Cancer-associated fibroblast-derived EVs deliver the lncRNA PIAT, which limits NEDD4 like E3 ubiquitin protein ligase-dependent YBX1 degradation and increases binding to RNAs associated with perineural invasion (113). Stromal transfer can therefore alter YBX1 abundance and its interaction with modified RNAs in recipient tumor cells (Fig. 7).

8. m5C regulation in therapeutic stress and drug resistance adaptation

Drug exposure adds to these metabolic and immune pressures. Altered RNA regulation can preserve proteins that limit drug-induced cell death. Stabilization of SERPINB5 promotes cervical cancer chemotherapy resistance, while NSUN2-dependent SLC7A11 regulation supports redox defense in colorectal cancer (114,115). Non-SMC condensin I complex subunit G-associated NSUN2 regulation of GPX4 mRNA and ETS variant transcription factor 4/ALYREF-dependent PKM2 regulation similarly contribute to ferroptosis resistance

in hepatocellular carcinoma and intrahepatic cholangiocarcinoma, respectively (116,117). These metabolic defenses support survival, while other RNA targets affect responses to specific drugs. HIF1A promotes NSUN2-dependent growth differentiation factor 15 stabilization and reduces sorafenib sensitivity, whereas NSUN7 suppression restores 4-hydroxytamoxifen sensitivity in resistant breast cancer cells (118,119). NSUN5-dependent BRCA2 DNA repair associated and BRCA1 interacting DNA helicase 1 expression supports doxorubicin resistance through repair capacity (120). The DNMT2-m5C-ACLY pathway instead contributes to lenvatinib resistance through histone acetylation and downstream Notch signaling, while TRDMT1-associated TNFSF10 suppression has been linked to bortezomib resistance (32,33). The RNA target and the type of drug-induced injury influence which survival process is sustained (Fig. 5C).

Reader-dependent regulation can sustain resistance through several transcripts or through immune recognition. ALYREF regulation of TBL1X/Y related 1 and lysine methyltransferase 2E (inactive) increases APOC1 in oxaliplatin-resistant esophageal cancer, while NSUN2/ALYREF maintains PD-L1 expression in non-small cell lung cancer (121,122). Reducing RNA methylation can instead contribute to drug-induced cell death. A study reported that azacytidine reduced m5C on chromatin-associated RNA and contributed to leukemia cell

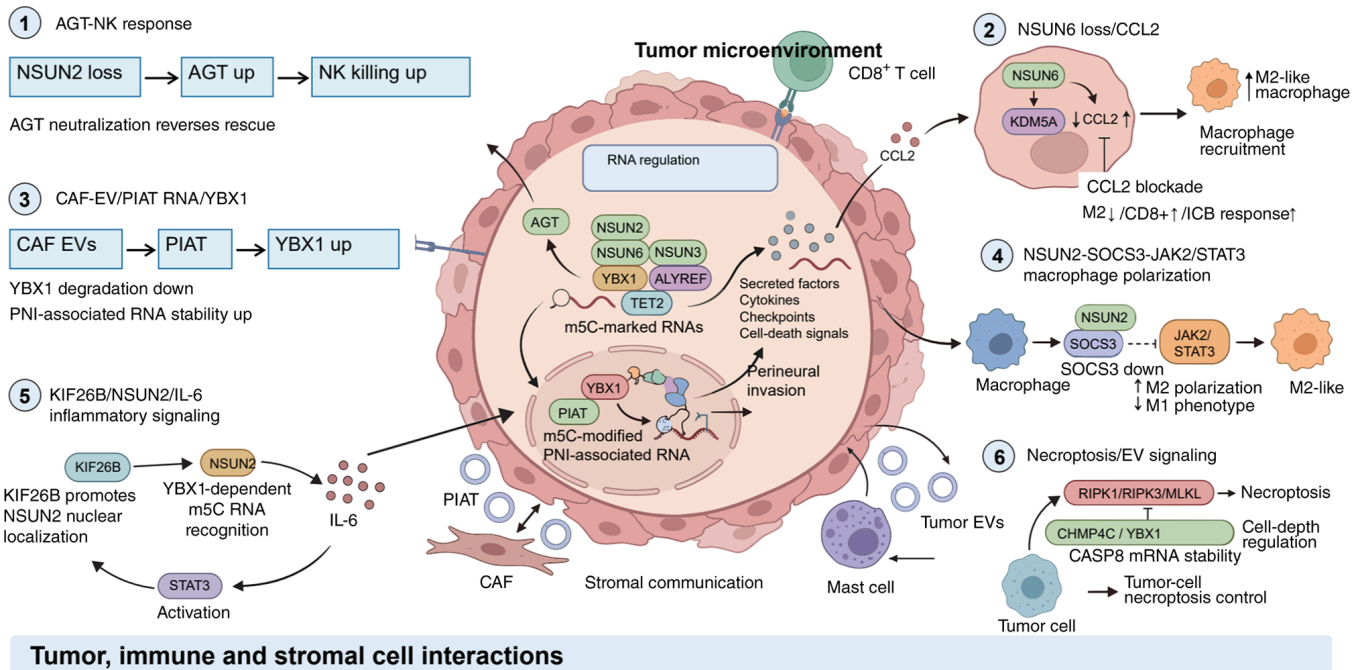


Figure 7. m5C-associated tumor, immune and stromal cell interactions. ① NSUN2 depletion increases AGT expression and NK-cell cytotoxicity in liver cancer cocultures. AGT neutralization reverses the increase in killing, while exogenous AGT enhances cytotoxic markers. ② Tumor-cell NSUN6 deficiency reduces KDM5A, increases CCL2 and promotes immunosuppressive macrophage accumulation. CCL2 blockade restores immune checkpoint blockade sensitivity in the deficient pancreatic cancer mouse models. ③ CAF-derived EVs deliver the lncRNA PIAT, reduce YBX1 degradation and promote binding to m5C-modified RNAs associated with perineural invasion. ④ Macrophage NSUN2-dependent SOCS3 regulation relieves inhibition of JAK2/STAT3 and favors M2 over M1 macrophage polarization. ⑤ KIF26B-associated NSUN2 regulation increases IL-6 and sustains STAT3-dependent inflammatory signaling. ⑥ CHMP4C/YBX1-associated CASP8 RNA regulation increases caspase-8 and suppresses RIPK1/RIPK3/MLKL-dependent necroptosis. CHMP4C also promotes EV-associated p-MLKL export from tumor cells. Tumor-conditioned medium supports mast-cell migration, while tumor-derived EVs increase mast-cell cytokine secretion. NSUN2/3/6, NOP2/Sun RNA methyltransferases 2, 3 and 6; ALYREF, Aly/REF export factor; YBX1, Y-box binding protein 1; TET2, tet methylcytosine dioxygenase 2; AGT, angiotensinogen; KDM5A, lysine demethylase 5A; CCL2, C-C motif chemokine ligand 2; SOCS3, suppressor of cytokine signaling 3; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; KIF26B, kinesin family member 26B; IL-6, interleukin 6; PIAT, perineural invasion-associated transcript; CASP8, caspase 8; CHMP4C, charged multivesicular body protein 4C; RIPK1, receptor interacting serine/threonine kinase 1; RIPK3, receptor interacting serine/threonine kinase 3; MLKL, mixed lineage kinase domain like pseudokinase; p-MLKL, phosphorylated MLKL; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; lncRNA, long noncoding RNA; NK, natural killer; CAF, cancer-associated fibroblast; EV, extracellular vesicle; ICB, immune checkpoint blockade; PNI, perineural invasion; CD8, cluster of differentiation 8; M1/M2, classically/alternatively activated macrophage phenotypes.

death (123). This RNA-related effect differs from the drug's DNA-hypomethylating activity. Its relevance to patient selection would depend on linking the RNA response to treatment outcome. m5C-related expression signatures in glioma and papillary thyroid cancer were found to be associated with prognosis or inferred treatment response (124,125). These scores describe expression patterns rather than directly measuring the RNA modification responsible for drug response.

9. Therapeutic implications: Targeting m5C-dependent regulation

Interventions against these RNA-dependent survival processes can target the chemical modification, writer or reader proteins, or substrate RNAs. Delivery systems determine which tissues are exposed to these interventions (Table I). Azacytidine inhibits DNMT2-dependent tRNA-Asp C38 methylation, whereas decitabine lacks the same RNA effect, but clinical use of either drug has not validated RNA m5C as a response marker (29). S-adenosylhomocysteine-based covalent DNMT2 compounds engage catalytic cysteine 79 (C79) in biochemical assays, whereas B19 binds NSUN3 and suppresses colorectal cancer growth in cell and animal

models (126,127). Erianin reduces NSUN2-associated ChaC glutathione specific gamma-glutamylcyclotransferase 1 regulation and vasculogenic mimicry in uveal melanoma models (128). In T-cell lymphoma models, including patient-derived xenografts, lanatoside C disrupts YBX1-MYC binding and also affects p300-dependent transcription (129). Inhibition of NSUN2/ALYREF/YBX1-associated control of Yes-associated transcriptional regulator also reduces tumor growth and metastasis in non-small cell lung cancer models (130). RNA-directed approaches narrow the intervention to a transcript or fragment, as illustrated by MALAT1-IN1, a small-molecule inhibitor of metastasis associated lung adenocarcinoma transcript 1 (MALAT1), and an inhibitor of 5'tiRNA-Gly-GCC, the 5'tRNA-derived stress-induced RNA (tiRNA half) generated from tRNA-Gly-GCC (31,131). For RNA interference, ROS-responsive ferrocene nanoparticles improve intravenous delivery of small interfering RNA targeting NSUN2 in gastric cancer models. Biodistribution and tumor uptake were measured, while longer-term exposure and toxicity remain unresolved (132). DNMT1-associated CDK1 regulation also links pyrimidine metabolism to drug response, although direct RNA methylation must be separated from the established DNA-methylation functions of DNMT1 (133).

Table I. m5C-directed interventions tested in experimental models.

Intervention	Experimental findings	Limitations for translation
Chemical modification: Azacytidine Protein: DNMT inhibitors	Reduces tRNA-Asp C38 methylation in cancer cell lines. Also reduces m5C on chromatin-associated RNA in leukemia cells (29,123). SAH-based compounds covalently engage catalytic C79 in biochemical assays (126).	Human use is established for the drug, but RNA-m5C-specific response markers are not validated. Cellular selectivity, exposure and animal efficacy remain unestablished for this compound series.
Protein: B19 and erianin	B19 binds NSUN3 in colorectal cancer models. Erianin targets NSUN2-associated CHAC1 regulation in uveal melanoma models (127,128).	Cell and animal results do not establish a safe therapeutic index in patients.
Protein: Reader-directed compounds	Lanatoside C disrupts YBX1-MYC binding in T-cell lymphoma models, including patient-derived xenografts. YB-B1 enhances cisplatin activity in ovarian cancer models (34,129).	Lanatoside C also acts on p300. Reader-specific contributions and systemic toxicity need separate testing.
RNA: MALAT1-IN1	Combined with sorafenib, interferes with MALAT1-associated ELAVL1/SLC7A11 regulation in hepatocellular carcinoma cell and animal models (131).	Intratumoral drug exposure, RNA-target specificity and patient-selection criteria remain unresolved.
RNA: tRNA fragment inhibition	A 5'tiRNA-Gly-GCC inhibitor combined with doxorubicin suppresses anaplastic thyroid carcinoma <i>in vivo</i> (31).	Effects of inhibiting one fragment must be separated from changes in its parent tRNA.
Delivery: siNSUN2 nanoparticles	ROS-responsive ferrocene carriers improve intravenous siNSUN2 delivery in gastric cancer models, with biodistribution and uptake measurements (132).	Longer-term biodistribution, release and toxicity require evaluation.
Combination with immune treatment	Glucose-NSUN2 disruption affects cGAS/STING. CCL2 blockade restores checkpoint sensitivity in NSUN6-deficient pancreatic cancer models (5,108).	The affected immune cells matter. Methionine restriction can impair CAR-T-cell function through reduced NKG7 RNA methylation (136).

RNA-m5C-directed efficacy has been evaluated in experimental models. The contribution of RNA m5C to clinical treatment response remains unresolved, including for drugs already used in patients. DNMT2, DNA methyltransferase 2, also termed TRDMT1; TRDMT1, tRNA aspartic acid methyltransferase 1; NSUN2/3/6, NOP2/Sun RNA methyltransferases 2, 3 and 6; CHAC1, ChaC glutathione specific gamma-glutamyl-cyclotransferase 1; YBX1, Y-box binding protein 1; MYC, MYC proto-oncogene, basic helix-loop-helix transcription factor; p300, EP300 lysine acetyltransferase; MALAT1, metastasis associated lung adenocarcinoma transcript 1; ELAVL1, ELAV like RNA binding protein 1; SLC7A11, solute carrier family 7 member 11; cGAS, cyclic GMP-AMP synthase; STING1, stimulator of interferon response cGAMP interactor 1; CCL2, C-C motif chemokine ligand 2; NKG7, natural killer cell granule protein 7; m5C, RNA 5-methylcytosine; RNA, ribonucleic acid; tRNA, transfer RNA; tRNA-Asp, aspartate tRNA; tiRNA, tRNA-derived stress-induced RNA; 5'tiRNA-Gly-GCC, 5'tRNA half derived from tRNA-Gly-GCC; SAH, S-adenosylhomocysteine; ROS, reactive oxygen species; CAR-T, chimeric antigen receptor T cell; siNSUN2, small interfering RNA targeting NSUN2; C38, cytosine at position 38 of tRNA; C79, cysteine residue 79 of DNMT2; B19, NSUN3-targeting bipyridine derivative; YB-B1, YBX1-targeting compound; MALAT1-IN1, small-molecule inhibitor of MALAT1.

The choice of a combination partner follows the resistance mechanism affected by the RNA intervention. MALAT1-IN1 with sorafenib addresses ELAVL1/SLC7A11-associated ferroptosis defense, whereas inhibition of 5'tiRNA-Gly-GCC with doxorubicin targets a fragment generated after TRDMT1 loss (31,131). In ovarian cancer, YB-B1 enhances cisplatin activity in cell and patient-derived xenograft models (34). Chemotherapy response also varies with the methyltransferase inhibited and the drug used. Combined NSUN2 and METTL1 depletion increases 5-fluorouracil sensitivity in HeLa cells, but TRDMT1 loss produces variable responses to doxorubicin and etoposide (134,135). Combining these interventions with immunotherapy may have opposing effects on tumor cells and immune effector cells. Disrupting glucose-NSUN2 regulation

increases cGAS/STING activity and CCL2 blockade restores checkpoint sensitivity after NSUN6 loss (5,108). However, methionine restriction reduces NK cell granule protein 7 (NKG7) mRNA methylation and weakens chimeric antigen receptor-T-cell killing in lung squamous cell carcinoma cocultures, with partial rescue after NKG7 restoration (136). Thus, an intervention that impairs tumor-cell adaptation may also impair the immune response intended to eliminate the tumor. Dose and schedule therefore need to balance tumor inhibition against injury to immune effector cells. The degree of additivity or synergy and the benefit to patients remain to be established.

Near-term clinical investigation is more feasible with existing nucleoside analogues than with newly developed writer inhibitors. Existing nucleoside analogues allow RNA

pharmacodynamic measurements during clinical treatment without first developing a new agent. Such measurements must still distinguish RNA effects from DNA hypomethylation and relate them to patient response. Among experimental candidates, reader-directed compounds evaluated in patient-derived tumors warrant further pharmacological comparison (34,129). Substrate-directed combinations also allow the RNA response to be tested alongside sensitivity to an existing drug, although neither approach is validated for patients selected by m5C status (131). *De novo* writer inhibitors face the additional problem of inhibiting tumor-dependent activity while retaining normal-tissue and immune-cell functions. A candidate RNA site and binding protein should therefore be linked to treatment sensitivity in the relevant tumor before being used for patient selection. In preclinical evaluations, measuring intratumoral concentrations of the therapeutic agent alongside target-RNA changes and immune-cell function would help determine whether a tolerated dose engages the intended mechanism.

10. Discussion

The contribution of m5C to stress adaptation depends on the modified RNA, its subsequent processing and the cell in which these changes occur. NSUN5 loss alters stress-adaptive translation in glioma, whereas NSUN6 can restrain pancreatic cancer growth (26,48). TRDMT1 loss in thyroid cancer instead increases tumor-promoting tRNA fragments (31). Functional differences can also arise independently of methylation. Catalytically inactive NOP2 can support ribosome assembly, so loss of the protein affects more than its methyltransferase activity (6). Metabolic and immune effects follow the same substrate dependence. ENO1-associated lactate production reinforces NSUN2 in colorectal cancer, while glucose-sensitive NSUN2 regulates TREX2 and cGAS/STING in separate systems (5,76). AGT neutralization and CCL2 blockade then reveal distinct immune responses after NSUN2 or NSUN6 depletion (107,108). Whether these processes coexist within one lesion remains unresolved.

The next experiments need to distinguish the RNA-specific effect from changes in other modifications, protein functions or cell populations. GPX4 regulation by m6A and m5C and NSUN6-dependent METTL3 modification raise the possibility that more than one RNA modification contributes to the same phenotype (28,96). In future studies, paired site perturbations and reader-binding measurements could separate additive, opposing and interdependent effects, provided sequence and expression controls account for the consequences of changing the cytosine itself. Site-resolved measurements are needed because conventional m5C-RNA immunoprecipitation sequencing does not directly identify the modified nucleotide or quantify its modification fraction (8,137). Combining these measurements with RNA stability or translation assays and phenotypic rescue can test functional consequences, as illustrated by NSUN6/KDM5A and MALAT1/SLC7A11 regulation (108,131). Cell-type-specific perturbation is then needed to determine where it occurs, as bulk measurements cannot resolve the different YBX1-associated patterns observed in glioblastoma tumor and myeloid populations (106). Building on patient-derived models used for reader-directed agents (34,129), future studies could compare the same drug combination in

m5C-dependent and independent tumors at matched exposures, alongside measurements of immune-cell killing. An RNA response that accompanies selective tumor inhibition could then be tested as a clinical pharmacodynamic marker. RNA m5C links stress exposure to changes in RNA stability, processing and translation, with effects that depend on the substrate and cell type. Therapeutic development therefore requires selective disruption of tumor-supporting RNA regulation while preserving normal-tissue and antitumor immune functions.

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YLZ and SSY conceived the review. SSY drafted the original manuscript. YLZ led the revision, critically revised the manuscript for important intellectual content and supervised the work. BLZ and XZT contributed to literature review and manuscript preparation. YLZ and SSY confirm the authenticity of all data and references cited in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During preparation and revision, the authors used ChatGPT (GPT-5.5; OpenAI; <https://chatgpt.com>) to assist with literature organization, manuscript restructuring, language editing and checks of consistency between text and schematic figures. The authors reviewed and edited the material and take full responsibility for the manuscript and figures.

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