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Metabolism Meets Translation: Dietary and Metabolic Influences on tRNA Modifications and Codon Biased Translation

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ABSTRACT

Transfer RNA (tRNA) is not merely a passive carrier of amino acids, but an active regulator of mRNA translation controlling codon bias and optimality. The synthesis of various tRNA modifications is regulated by many "writer" enzymes, which utilize substrates from metabolic pathways or dietary sources. Metabolic and bioenergetic pathways, such as one-carbon (1C) metabolism and the tricarboxylic acid (TCA) cycle produce essential substrates for tRNA modifications synthesis, such as S-Adenosyl methionine (SAM), sulfur species, and α-ketoglutarate (α-KG). The activity of these metabolic pathways can directly impact codon decoding and translation via regulating tRNA modifications levels. In this review, we discuss the complex interactions between diet, metabolism, tRNA modifications, and mRNA translation. We discuss how nutrient availability, bioenergetics, and intermediates of metabolic pathways, modulate the tRNA modification landscape to fine-tune protein synthesis. Moreover, we highlight how dysregulation of these metabolic-tRNA interactions contributes to disease pathogenesis, including cancer, metabolic disorders, and neurodegenerative diseases. We also discuss the new emerging field of GlycoRNA biology drawing parallels from glycobiology and metabolic diseases to guide future directions in this area. Throughout our discussion, we highlight the links between specific modifications, their metabolic/dietary precursors, and various diseases, emphasizing the importance of a metabolism-centric tRNA view in understanding many pathologies. Future research should focus on uncovering the interplay between metabolism and tRNA in specific cellular and disease contexts. Addressing these gaps will guide new research into novel disease interventions.

1 | Introduction

Cells have evolved the capacity to respond to a wide variety of extrinsic and intrinsic stimuli to ensure their survival. Responding to nutrient availability, depletion, and metabolic cues is essential to ensure proper energy regulation. In recent years, our understanding of the intimate links between translation and metabolism has allowed for a new understanding of a variety of physiological and pathological phenomena (Biffo et al. 2024; Snieckute et al. 2022; Tang et al. 2024). Cancer cells,

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for example, possess a large array of metabolic adaptations that regulate translation to ensure survival in the stressful tumor microenvironment (TME) (Nakahara et al. 2023; Tang et al. 2024; Yang et al. 2024). mRNA translation is an energy-expensive process that is tightly controlled to ensure a balance between nutrient availability, cellular needs, and protein synthesis needs (Biffo et al. 2024; Warner et al. 2001). Thus, mRNA translation adapts dynamically to various stimuli and cues, including metabolic changes that are required to maintain cellular function (Biffo et al. 2024; Tang et al. 2024). mRNA translation shows remarkable plasticity in response to various stimuli, such as starvation and metabolic stress, that prioritizes the translation of stress-response-specific transcripts while conserving energy via globally downregulating protein production (Costa-Mattioli and Walter 2020; Rashad 2024; Tang et al. 2024). Thus, understanding this plasticity, and what regulates it, is vital in understanding an array of pathologies from metabolic diseases to cancer and aging.

Transfer RNA (tRNA) is understandably one of the major regulators of mRNA translation plasticity (Rashad 2024; Suzuki 2021). One of the interesting features when considering the diverse and dynamic roles of tRNA in mRNA translation is the mismatch between the codons to be decoded and the anticodons available for decoding (dos Reis et al. 2004). That is, 48 tRNA anticodons (in human cells) are available to decode 64 mRNA codons encoding for 20 amino acids (dos Reis et al. 2004; Suzuki 2021). This genetic code redundancy allows for translational plasticity and dynamic regulation in response to various stimuli (Dedon and Begley 2022; Huber et al. 2022; Nedialkova and Leidel 2015; Rashad 2024; Torrent et al. 2018). tRNA modifications at the wobble position (position 34 of the tRNA) are thus essential to expand the codon decoding capacity of certain anticodons and allow for non-cognate pairings (Dedon and Begley 2022; Rashad 2024; Suzuki 2021). This property allowed for the regulation of mRNA translation via codon biased translation (Camiolo et al. 2012; Dedon and Begley 2022; Nedialkova and Leidel 2015; Rashad 2024; Yarian et al. 2002). To date, more than 170 RNA modifications have been identified, spanning all life forms from prokaryotes to eukaryotes (Delaunay et al. 2024; Suzuki 2021). Most modifications are thought to affect tRNA stability and folding outside the anticodon loop and to optimize base-pairing for those in and around the anticodon. Nonetheless, the biological functions of many modifications are yet to be fully understood in cell, condition, and disease-specific contexts. This poses important challenges when considering the roles of tRNA modifications in any context. For example, the translational demands and metabolic adaptations unique to particular tissues or cells are likely to shape how specific modifications influence the translation process (Rashad 2024). Therefore, more work is needed, at many levels, to fully grasp the complexity of tRNA modifications and their roles in disease. Nonetheless, the links between tRNA modifications and metabolism and diet are one of the most interesting fields of research that has been gaining traction in recent years (Biffo et al. 2024; Rashad 2024; Tang et al. 2024). Certain tRNA modifications have been linked to diet and the microbiome, such as queuosine (Q) (de Crécy-Lagard et al. 2024; Rashad 2024). Others have been linked to one carbon (1-C) metabolism, such as mitochondrial taurine-methylation modifications (Morscher et al. 2018), glycation products, such as 3-(3-amino-3-carboxypropyl)uridine (acp^3U) (Xie et al. 2024), or amino acid intake, such as N6-threonylcarbamoyladenosine (t^6A) (Wu et al. 2024). In this review, we will revisit the intimate and complex links between tRNA modifications and diet and metabolism with a specific focus on eukaryotic systems. Due to significant differences between eukaryotic and archaeal or prokaryotic mechanisms, our discussion will be limited to eukaryotic systems. We will attempt to unravel this complex interaction while providing a blueprint for future research into tRNA-metabolism coupling and its diseases relevance.

2 | The Multilevel Regulation of mRNA Translation by tRNA

tRNA regulates and interacts with mRNA translation not only via wobble modifications, but through various phenomena that has been studied extensively in the literature. While in this review we focus mainly on tRNA modifications, the other aspects of tRNA biology should be kept in mind when one dissects its role in regulating translation and metabolism. In this section, we will provide an overview of the various processes by which tRNA can dynamically regulate mRNA translation.

2.1 | tRNA Transcript Expression

tRNAs are transcribed from tRNA genes via RNA polymerase III (Arimbasseri and Maraia 2016). tRNAs are transcribed as pre-tRNAs, some containing introns which need further processing to generate mature tRNAs (Hayne et al. 2022; Yuan et al. 2023) (Figure 1). The maturation events include the removal of the 5′ leader, 3′ trailer, intron splicing by the TSEN (tRNA splicing endonuclease) complex, and the addition of the 3′CCA end (Hayne et al. 2022; Kirchner and Ignatova 2015). Recent studies have shown that tRNA isoacceptors, and in turn the anticodons they express, are stably expressed across tissues and developmental stages (Ando et al. 2025; Gao et al. 2024; Pinkard et al. 2020). However, variations occur at the level of isodecoders, tRNA transcripts (here defined as mature tRNAs) that share the same anticodon sequence but vary elsewhere (Gao et al. 2024; Pinkard et al. 2020) (see Box 1). Nonetheless, in disease conditions, tRNA isoacceptors levels can change to drive specific translational programs. For example, it was shown that specific tRNAs can drive breast cancer metastasis by stabilizing and enhancing the translation of pro-metastatic mRNAs through interacting with their cognate codons (Goodarzi et al. 2016). Furthermore, during oxidative stress, tRNA isoacceptors levels change to drive stress response programs and antioxidant proteins translation via codon biased translation (Torrent et al. 2018) (Figure 2, see Box 2). Nonetheless, determining tRNA expression via sequencing is not an easy task, and library preparation methods entail various technical steps that made the study of tRNA expression somewhat restrictive (Goodarzi et al. 2016; Hu et al. 2021; Pinkard et al. 2020). For example, many reverse transcriptase enzymes are unable to resolve the many modifications and structural elements in the tRNAs, resulting in the inability to synthesize full-length tRNA cDNAs (Hu et al. 2021; Pinkard et al. 2020). New advances in tRNA sequencing, such as nanopore direct tRNA sequencing, could provide a breakthrough that allows more researchers to study tRNA expression dynamics in various conditions and diseases (Lucas et al. 2024).

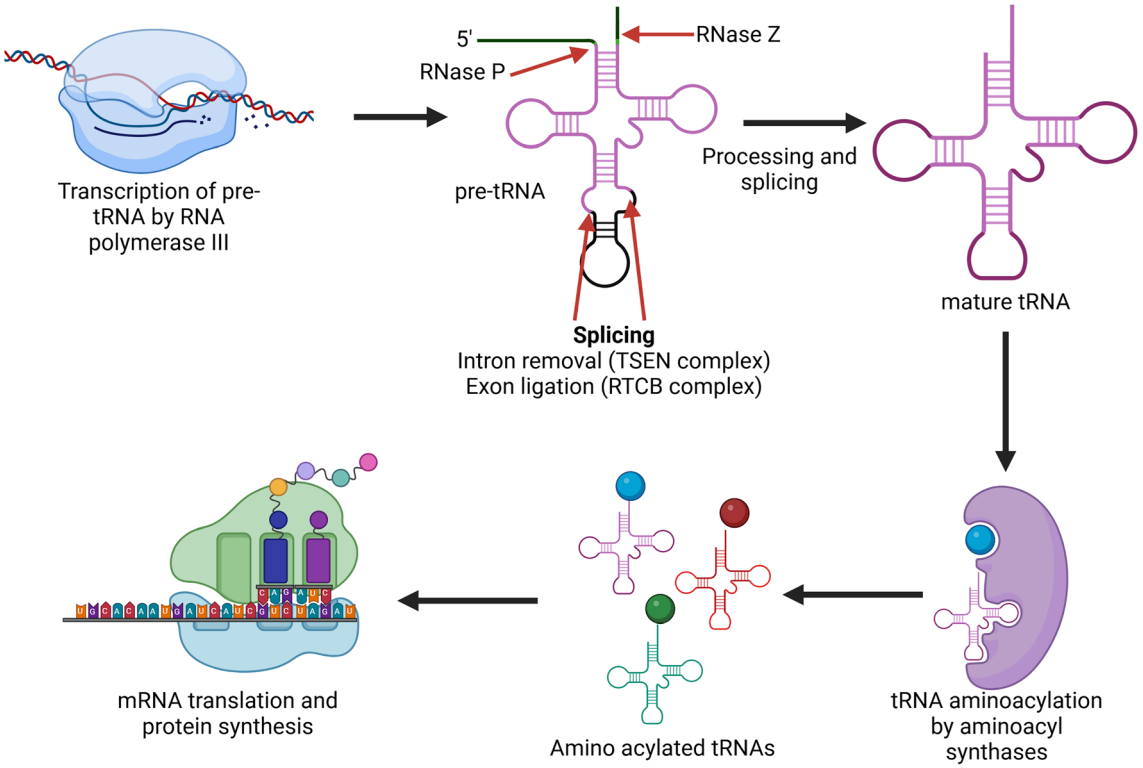


FIGURE 1 | tRNA transcription and processing: tRNAs are transcribed by RNA Pol III from the DNA as pre-tRNAs. Pre-tRNAs are then processed by the tRNA splicing endonuclease (TSEN) complex to mature tRNA. Mature tRNAs are then aminoacylated by aminoacyl tRNA synthetases (AARS), and the aminoacylated tRNAs are then used for mRNA translation and protein synthesis. Created in BioRender. https://BioRender.com/l90k470.

2.2 | tRNA Modifications

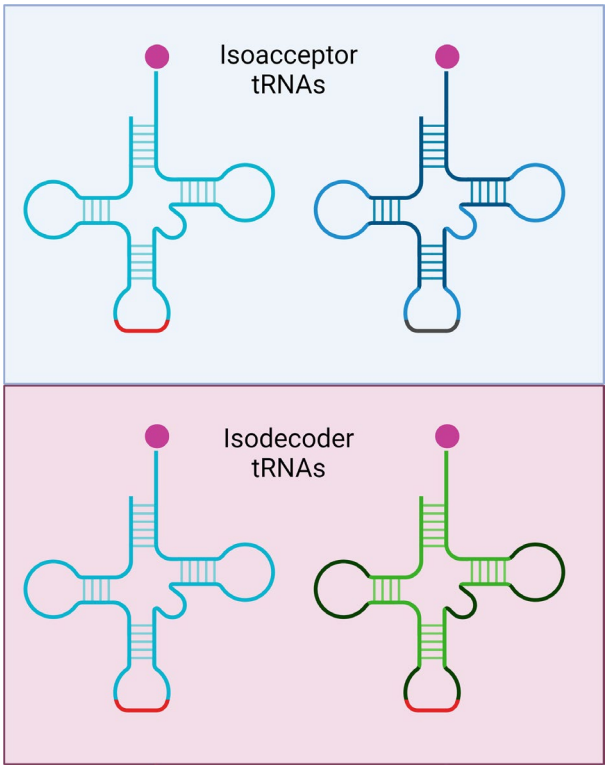
tRNAs are heavily decorated by chemical modifications, on average 13 per tRNA molecule or 1 per 3 nucleotides (Kirchner and Ignatova 2015; Rashad 2024; Suzuki 2021) (Figure 3A, Table 1). tRNA modifications contribute to the tRNA translational role through various mechanisms. tRNA modifications in the D (dihydrouridine) or T (TΨC; pseudouridine) loops contribute to tRNA structural stability and are essential for correct tRNA recognition by aminoacyl synthases (Giegé and Eriani 2023; Rashad, Han, et al. 2020; Schultz et al. 2024; Suzuki, Ueda, et al. 1997; Sylvers et al. 1993; Tuorto et al. 2012). Position 34, or the wobble position, is a hotbed for modifications, which allows for the expansion of the genetic code and non-cognate base-pairings (Suzuki 2021) (Figure 3B,C). Modifications at position 34 can be dynamically regulated via their stoichiometry or tRNA transcript expression to drive synonymous codon bias and translational shifts (Chionh et al. 2016; Dedon and Begley 2022; Giguère et al. 2024; Huber et al. 2022; Rashad 2024; Suzuki 2021). Modifications at the wobble position are also important for maintaining the ribosomal reading frame and avoiding frameshifting and the consequent dysfunctional protein production (Dixit et al. 2021). In addition, the loss of cytosolic or mitochondrial tRNA wobble modifications can lead to various genetic conditions, such as MELAS and MERRF syndromes that will be discussed later in this review (Bento-Abreu et al. 2018; Matsumura et al. 2023). Another hotbed for modifications is position 37. Which, while not being in the anticodon, is essential for codon decoding fidelity and efficiency and the maintenance of the reading frame (Akiyama et al. 2024; Rosselló-Tortella et al. 2020). In the following sections, we will discuss in more detail certain tRNA modifications in light of their connection to metabolic pathways and cues.

2.3 | tRNA Amino Acylation

tRNA aminoacylation is the essential step during which cognate amino acids are attached to the corresponding tRNAs to be further carried to the site of translation (Alberts et al. 2022; Kwon et al. 2019). tRNA aminoacylation is carried out by a group of enzymes called aminoacyl-tRNA synthetases (AARS), which are divided into two classes (I and II) based on the architecture of the active site of the enzyme (Kwon et al. 2019; Sung et al. 2022). AARS activate the cognate amino acid via ATP hydrolysis to form adenylated amino acid (amino acid bound to AMP), after which the amino acid is transferred to the 3′ end of the tRNA (containing a CCA sequence) and linked via an ester linkage to form the final aminoacyl-tRNA molecule that will be used for translation (Alberts et al. 2022; Kwon et al. 2019) (Figure 4A). Mis-acylation of tRNAs (i.e., charging tRNAs with incorrect amino acid) can lead to deleterious consequences on protein synthesis (Lee et al. 2006) (Figure 4B). Thus, AARS possess proofreading capabilities to ensure correct amino acid incorporation (Lee et al. 2006; Perona and Gruic-Sovulj 2014). Nonetheless, during stress, mis-acylation is observed, which was theorized to be a mechanism to protect proteins against ROS damage via mis-incorporating methionine into proteins (Netzer et al. 2009). AARS are associated with a variety of diseases such as cancer and a variety of genetic diseases (Kwon et al. 2019;

BOX 1 | Isodecoders versus isoacceptors tRNAs.

Isoacceptors refer to tRNAs encoding the same amino acids but having different anticodon sequences, thus decoding different codons for the same amino acid. Isodecoders refer to tRNAs encoding the same amino acid and having the same anticodon sequences but differ in the tRNA sequences elsewhere. Created in BioRender. https://BioRender.com/x11r437.



Sung et al. 2022). For example, Valine aminoacyl-tRNA synthetase (VARS) promotes melanoma therapy resistance via driving codon-biased translation towards valine-containing transcripts (El-Hachem et al. 2024). Mutations in several AARS genes are associated with Charcot–Marie–Tooth disease (CMT) (Wei et al. 2019; Zuko et al. 2021). There are important links between tRNA modifications and tRNA aminoacylation. Certain tRNA modifications were shown to be essential for correct aminoacylation of tRNAs (Giegé and Eriani 2023; Schultz et al. 2024). Several modifications in positions 34 (such as Q and I) and 37 (such as yW and t^6A) act as identity elements for tRNA recognition by AARS (Giegé and Eriani 2023; Zhang, Zhou, et al. 2024). Modifications in the T-arm can also impact aminoacylation (Schultz et al. 2024). We could speculate that hypomodification of any tRNA modification would ultimately impact aminoacylation, however, not all modifications are interrogated from this aspect in the available literature. The level of tRNA aminoacylation can be indeed impacted by dietary inputs and amino acid availability (Paley and Perry 2018). Amino acid starvation, for example, can modulate the levels of tRNA aminoacylation, and in turn, codon-biased translation (Dittmar et al. 2005; Ofverstedt et al. 1994). Thus, it becomes clear, though not thoroughly studied, that dietary and metabolic factors impacting amino acid levels can influence mRNA translation via tRNA aminoacylation, adding another layer of complexity to tRNA functions.

2.4 | tRNA Derived Small Non-Coding RNAs

tRNA has been recognized as a source of small non-coding RNAs called tRNA-derived fragments, or tDRs (although some articles refer to them as tsRNAs or tRFs) (Holmes et al. 2023; Rashad, Han, et al. 2020; Rashad, Niizuma, et al. 2020; Sanadgol et al. 2022). The first set of tDRs was tRNA halves, produced during stress by angiogenin-mediated cleavage of tRNAs into 5′ and 3′ halves (Emara et al. 2010; Ivanov et al. 2011; Yamasaki et al. 2009). However, other forms of tDRs are also produced from tRNA, such as 3′-tRFs, 5′-tRFs, and more (Chen et al. 2025; Muthukumar et al. 2024). tRNA cleavage was first thought to protect cells against stress via activating stress granules (SG) formation and translation repression (Emara et al. 2010; Ivanov et al. 2011; Yamasaki et al. 2009). However, recent findings suggest that tRNA halves do not induce SGs formation, and their expression is rather associated with cell death than a protective effect (Rashad, Han, et al. 2020; Rashad, Niizuma, et al. 2020; Sanadgol et al. 2022). tDRs were shown over the course of the last decade to function via various molecular mechanisms. tDRs were shown to interact with RNA binding proteins (RBPs), for example, by binding YBX1 to suppress its mRNA interaction (Goodarzi et al. 2015; Lyons et al. 2016). Certain tDRs were also shown to promote the translation of ribosomal proteins to maintain translation, and their suppression induces apoptosis by reducing the number of 40S ribosomal subunits (Kim, Fuchs, et al. 2017). tDRs are a hot topic in cancer biology, and many tDRs have been shown to play important roles in various cancers (Chen et al. 2025; Lee et al. 2023; Wang et al. 2024). tDRs have an important regulatory and signaling role in regulating metabolic cues. Hyperglycemia was shown to upregulate a certain tDR (termed tRF-3001a) which in turn can promote diabetes-associated neurovascular dysfunction (Zhu et al. 2023). Nonetheless, despite the wealth of literature on the potential roles of tDRs in diseases and their proposed modes of action, their biogenesis, processing, and actual function remain somewhat contentious. In addition, the role of modifications on tDRs remains poorly understood. An important question arises, whether the use of synthetic tDRs to study their function and interaction captures their true biological nature, or are the results skewed due to the absence of important naturally occurring tDRs modifications?

3 | Diet, Metabolism, and the Regulation of mRNA Translation

While in this review we focus on tRNA modifications, we take a detour in this section to quickly review the intricate links between diet, metabolism, and translation. These connections, which are becoming more apparent, reveal the intimate links and the complexity of metabolism-translational connections. Pathways such as the mTOR and the ribosome quality control (RQC) were shown, as discussed in the next section, to play important roles in regulating how our cells respond to changes in diet or energy intake and how their dysregulation

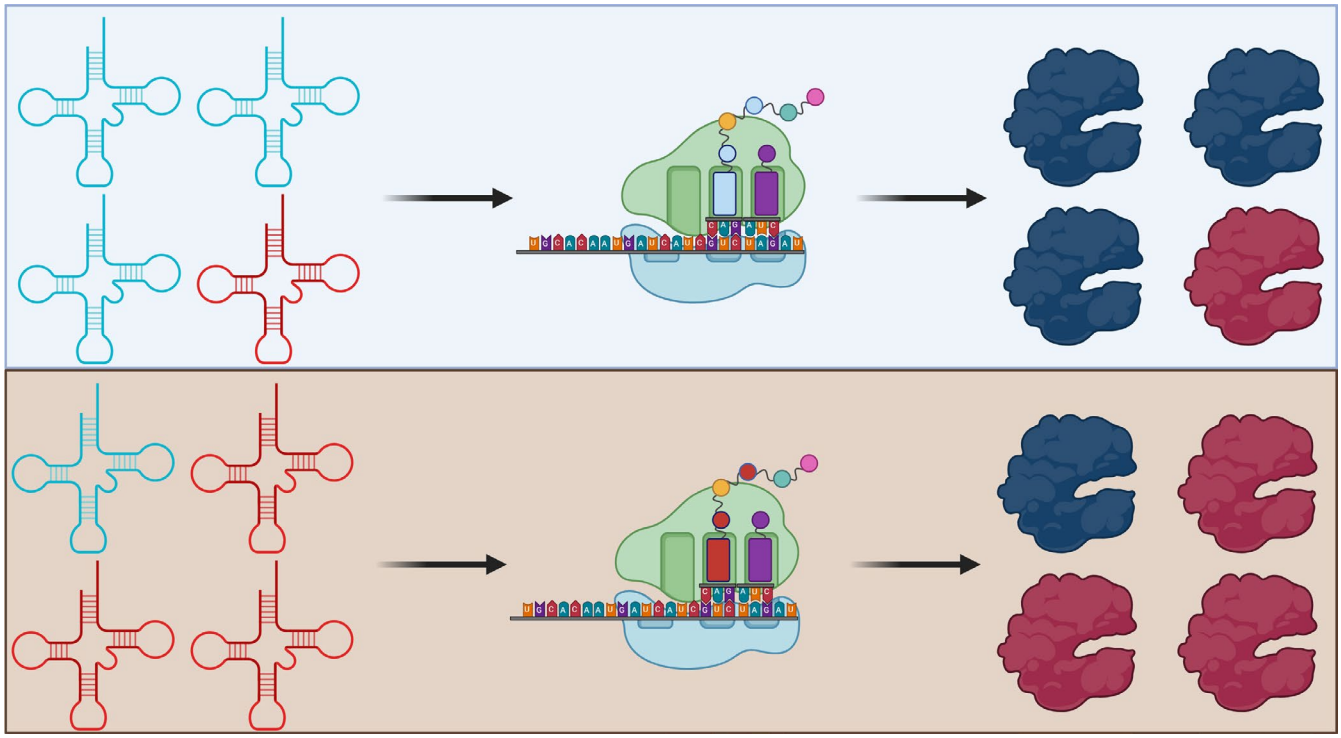


FIGURE 2 | The impact of tRNA expression on protein synthesis: Changes in tRNA transcription can drive codon-biased translation by dictating the available anticodon pool for decoding codons, thus leading to preferential translation of specific proteins enriched in specific codons/amino acids. Created in BioRender. https://BioRender.com/i28y771.

can contribute to metabolic diseases such as diabetes and more. These pathways are intimately connected to tRNA, therefore, examining these pathways is important in the context of this review.

3.1 | mTOR and Regulating of Translation

Mechanistic target of rapamycin or mTOR is a protein kinase that stands in the center of an intricate signaling network, orchestrating the balance between cellular growth and metabolic cues (Liu and Sabatini 2020). mTOR integrates diverse upstream signals ranging from nutrient availability and energy status to growth factors and stress cues to drive downstream pathways that regulate processes like protein synthesis, autophagy, and metabolism (Liu and Sabatini 2020) (Figure 5A). mTOR comprises a catalytic subunit along with multiple regulatory proteins and functions as the core of two distinct yet interconnected complexes, mTORC1 and mTORC2, each featuring its own unique set of regulatory components. mTORC1 assembly depends on its interaction with regulatory-associated protein of mTOR (RAPTOR) and mammalian lethal with SEC13 protein 8 (mLST8). In contrast, the formation of mTORC2 involves rapamycin-insensitive companion of mTOR (RICTOR), mLST8, and Sty1-interacting protein 1 (SIN1) (Figure 5A). Much of the work that has been done to understand mTOR function in metabolism and translation has been through dissecting the mTORC1 complex, the allosteric target of rapamycin (Dowling et al. 2010; Liu and Sabatini 2020). Emerging evidence reveals a complex interplay between mTOR signaling and tRNA dynamics, establishing an mTOR-tRNA axis influenced by tRNA synthesis, modifications, and aminoacylation, which plays a pivotal role in preserving translational homeostasis. To explore this, we will first briefly explain mTOR regulation and then examine the intricate interactions between mTOR and tRNA.

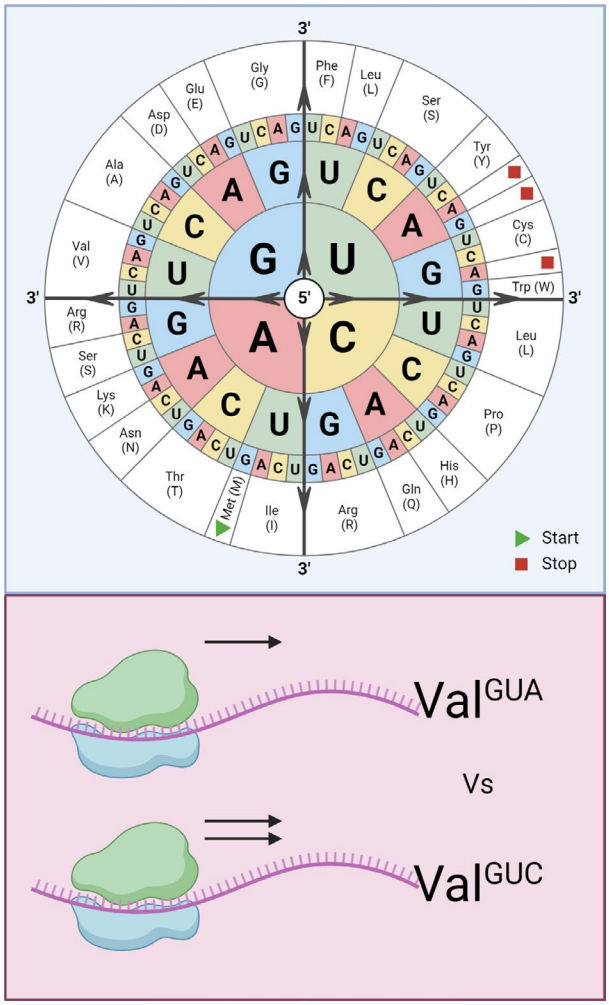
3.1.1 | Translation and Upstream Regulation of mTOR

The activity of mTORC1 is tightly regulated by dietary and metabolic cues (Figure 5B). Key inducers of mTOR activity include energy availability, amino acids, and growth signals such as insulin and insulin-like growth factors, which equip cells with the programming necessary for growth activation. The tuberous sclerosis complex (TSC), a critical negative regulator of mTORC1, serves as a central point where multiple signaling pathways converge to inhibit mTOR activity. TSC functions as a GTPase-activating protein (GAP) for the small GTPase Rheb, a direct activator of mTORC1.

When cellular energy levels drop, AMP-activated protein kinase (AMPK) is activated, leading to mTORC1 inhibition both directly via phosphorylation and indirectly through the activation of TSC. Additionally, low glucose levels can directly suppress mTORC1 by influencing RAG GTPases. Beyond energy signals, mTORC1 is directly regulated by amino acid sensing. Cytosolic amino acid levels are monitored by sensors such as castor1 and sestrin2, which inhibit the GATOR2-GATOR1-KICKSTOR complex, thereby suppressing mTORC1 when amino acid levels are low (Ban et al. 2004; González et al. 2012; Hara et al. 1998; Jewell et al. 2015; Kim et al. 2013; Meng et al. 2020; Wolfson and Sabatini 2017). Similarly, conditions such as DNA damage, hypoxia, and metabolic

BOX 2 | What is synonymous codon usage or codon bias?

Most amino acids are encoded in the DNA and RNA by multiple codons (Top, codon wheel), except for Met and Trp. This genetic codon redundancy allows for fine-tuning of translation via Synonymous codon usage, codon optimality, or codon bias. This refers to the relative decoding efficiency for different codons of the same amino acids. Thus, mRNAs enriched in one codon versus the other will be differentially translated (either more or less). This feature is one of the mechanisms by which cells respond to stress via alteration of tRNA expression and modifications, and it plays an important role in tRNA-mediated oncogenic programs. Created in BioRender. https://BioRender.com/f19x879.



stress—marked by nutrient or energy depletion—suppress mTOR activity, preventing growth under unfavorable circumstances. Furthermore, under anabolic conditions, mTOR promotes cell growth by shifting glucose metabolism away from oxidative phosphorylation toward glycolysis, supporting biomass synthesis. Additionally, mTOR directly regulates the synthesis of proteins, lipids, and nucleotides while inhibiting competing catabolic processes, such as autophagy and proteasomal or lysosomal degradation pathways.

3.1.2 | Translation and Downstream Effectors of mTOR

mTOR regulates translation by phosphorylating two key proteins: p70S6K1 (S6K1) and eIF4E-binding protein 1 (4EBP1), both of which are critical for initiating and maintaining mRNA translation (Figure 5B). S6K1 serves as a central hub for mTOR signaling. Upon activation by mTOR-mediated phosphorylation, S6K1 promotes ribosomal activation, initiates and elongates polypeptide synthesis, and supports pyrimidine synthesis, all of which are essential for protein production. In contrast, 4EBP1 acts as a negative regulator of translation. When active, 4EBP1 binds to eIF4E, a cap-binding protein essential for translation initiation, and prevents it from associating with eIF4G and eIF4A to form the heterotrimeric eIF4F complex. This inhibition blocks the recruitment of mRNAs to ribosomes, halting translation. eIF4E specifically recognizes and binds the 5′ cap structure (m^7G cap) of mRNA, making it a crucial player in the initiation of translation. mTOR's phosphorylation of 4EBP1 releases eIF4E, thereby enabling the assembly of the eIF4F complex and promoting ribosomal translation.

Acute and complete inhibition of mTOR in both complexes reduces the translation of all mRNAs to some degree and reduces global protein synthesis by ≈60%. Among the most affected are mRNAs containing 5′ terminal oligopyrimidine (TOP) motifs or TOP-like sequences, which are defined as mRNAs with a cytidine immediately after the 5′ cap, followed by an uninterrupted stretch of 4–14 pyrimidines. These mRNAs encode critical components of the translation machinery and proteins essential for cell growth. Their heightened sensitivity to mTOR inhibition arises from their reliance on mTORC1-mediated phosphorylation of 4E-BP. This phosphorylation event is crucial for the selective translation of TOP mRNAs, linking mTOR activity directly to the regulation of cellular growth and protein production (Thoreen et al. 2012).

3.1.3 | mTOR, tRNA, and Metabolic Regulation of Translation

mTORC1 plays a pivotal role in regulating tRNA gene expression by interacting with tRNA gene promoters (Kantidakis et al. 2010). Specifically, mTORC1 phosphorylates and inactivates MAF1, a key repressor of RNA polymerase III, which is responsible for tRNA transcription. This mechanism mirrors mTORC1's well-documented regulation of translation through 4E-BP inactivation (Kantidakis et al. 2010; Michels et al. 2010; Shor et al. 2010). Inhibition of mTORC1 reduces overall tRNA transcription, with specific tRNA pools being particularly sensitive. For example, tRNA-Leu^{CAA} and tRNA-Tyr^{GUA}, which are aminoacylated by leucyl-tRNA synthetase (LARS) and tyrosyl-tRNA synthetase (YARS), respectively, are upregulated via mTORC1 activation during processes like chemotherapy-induced senescence escape in cancer cells (Guillon et al. 2021). This underscores mTOR's role in selectively modulating tRNA pools, which in turn differentially shapes the proteome.

As mentioned, mTORC1 activity is regulated by nutrient availability, particularly amino acid levels, through the

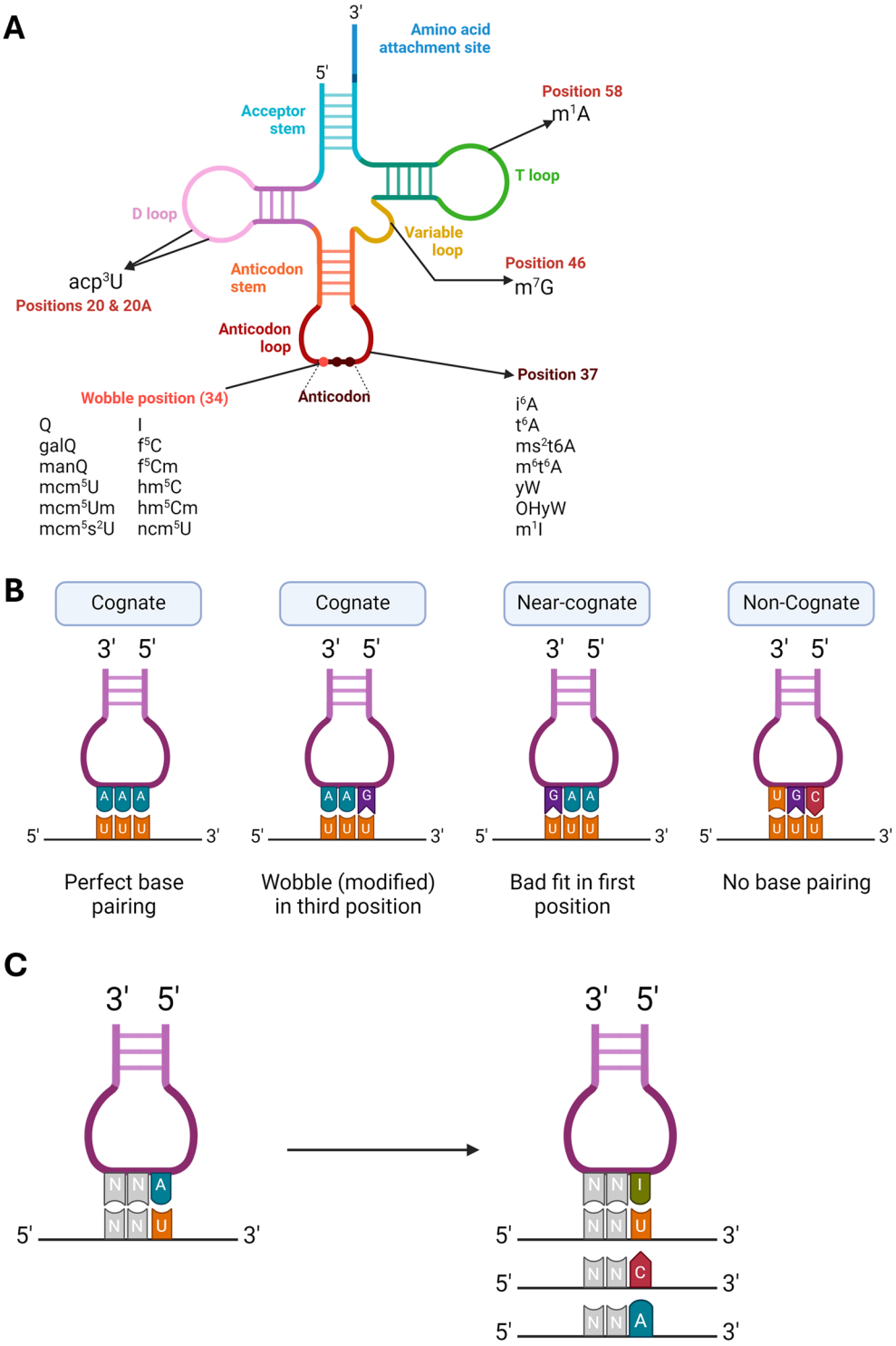


FIGURE 3 | tRNA modifications and codon decoding. (A) Examples of tRNA modifications at different positions. The full scientific names of the modifications are presented in Table 1. For a more detailed list of tRNA modifications, please see (Suzuki 2021). Created in BioRender. https://BioRender.com/c66f324. (B) Types of codon-anticodon pairing. Modifications at the wobble position allow for cognate base pairing between non-cognate nucleotides. In this example, G-U pairing. Created in BioRender. https://BioRender.com/i85q135. (C) Example of codon decoding expansion by Inosine modifications. Created in BioRender. https://BioRender.com/b75e540.

GATOR2-GATOR1-KICKSTOR complex. In addition to that, a novel tRNA-based mechanism has been uncovered that modulates mTORC1 activity. During amino acid depletion, uncharged tRNAs accumulate and activate general control non-depressible 2 kinase (GCN2). Activated GCN2 phosphorylates F-box only protein 22 (FBXO22), which then ubiquitinates mTORC1 at lysine 2066. This modification prevents substrate recruitment, effectively inhibiting mTORC1's kinase activity (Ge et al. 2023). Additionally, leucyl-tRNA synthetase (LARS), which catalyzes the aminoacylation of leucine to its cognate tRNA, also functions as a leucine sensor. It relays leucine availability to mTORC1 by activating RagD GTPase, thereby stimulating mTORC1 activity.

TABLE 1 | List of known and discussed tRNA modifications and their full scientific names.

Abbreviation	Full name
ac^4C	N4-acetylcytidine
acp^3U	3-(3-Amino-3-carboxypropyl)uridine
Am	2′-O-methyladenosine
Cm	2′-O-methylcytidine
cm^5U	5-Carboxymethyluridine
D	5-Carboxymethyluridine
f^5C	5-Formylcytidine
f^5Cm	5-Formyl-2′-O-methylcytidine
Gm	2′-O-methylguanosine
hm^5C	5-Hydroxymethylcytidine
hm^5Cm	2′-O-methyl-5-hydroxymethylcytidine
I	Inosine
i^6A	N6-isopentenyladenosine
m^1A	1-Methyladenosine
m^1G	1-Methylguanosine
m^1I	1-Methylinosine
m^1Y	1-Methylpseudouridine
$m^{2,2}7G$	N2,N2,7-trimethylguanosine
$m^{2,2}G$	N2,N2-dimethylguanosine
m^2G	N2-methylguanosine
m^3C	3-Methylcytidine
m^3U	3-Methyluridine
m^5C	5-Methylcytidine
m^5U	5-Methyluridine
m^5Um	5,2′-O-dimethyluridine
$m^{6,6}A$	N6,N6-dimethyladenosine
m^6A	N6-methyladenosine
m^6Am	N6,2′-O-dimethyladenosine
m^6t^6A	N6-methyl-N6-threonylcarbamoyladenosine
m^7G	7-Methylguanosine
manQ	Mannosyl-queuosine
galQ	Galactosyl-queuosine
$mchm^5U\_R$	5-(Carboxyhydroxymethyl) uridine methyl ester (R)
$mchm^5U\_S$	5-(Carboxyhydroxymethyl) uridine methyl ester (S)
mcm^5s^2U	5-Methoxycarbonylmethyl-2-thiouridine
mcm^5U	5-Methoxycarbonylmethyluridine
mcm^5Um	5-Methoxycarbonylmethyl-2′-O-methyluridine
ms^2i6A	2-Methylthio-N6-isopentenyladenosine
ms^2t6A	2-Methylthio-N6-threonylcarbamoyladenosine
ncm^5U	5-Carbamoylmethyluridine
ncm^5Um	5-Carbamoylmethyl-2′-O-methyluridine
oHyW	Hydroxywybutosine
Q	Queuosine
t^6A	N6-threonylcarbamoyladenosine
tm^5U	5-Taurinomethyluridine
tm^5S^2U	5-Taurinomethyl-2-thiouridine
Um	2′-O-methyluridine
Y	Pseudouridine
yW	Wybutosine

This pathway can be specifically inhibited by BC-LI-0186, a compound that blocks the leucine-sensing function of LARS in cancer (Han et al. 2012; Kim, Lee, et al. 2017). Beyond cancer and senescence, these findings suggest that targeting the tRNA/mTOR axis could influence cellular behavior in metabolic conditions such as obesity and diabetes, where mTOR activity is a central player in disease pathogenesis (Catania et al. 2011).

3.1.4 | tRNA Modifications and Regulation of mTOR Function

It has been reported that the tRNA modification m^1A at position 58, which is synthesized by TRMT6/TRMT61A, enhances TSC1 translation in hematopoietic stem cells (HSC), a key negative regulator of mTORC1 activity. Murine TRMT6-deficient HSC, experienced aberrant hyperactive mTORC1 signaling due to reduced translation elongation of *Tsc1* mRNA, leading to abnormal cell cycle progression, increased mitochondrial activity, and oxidative stress. Ultimately, this leads to exhausting the HSC pool, which could be saved partially by rapamycin, highlighting tRNA-m^1A-58 modification as a crucial translational checkpoint regulating mTORC1 activity (Zuo et al. 2024).

3.2 | Ribosome Quality Control and Metabolic Cues

Protein biosynthesis involves complex processes, and errors during translation can compromise protein quality (Spriggs et al. 2010). Ribosomes, the cellular machines responsible for protein synthesis, are abundant, with a typical cell containing approximately 10 million ribosomes. Each ribosome produces a new protein every 1–2 min, translating mRNA into the correct polypeptide sequence (Shi et al. 2017). During translation,

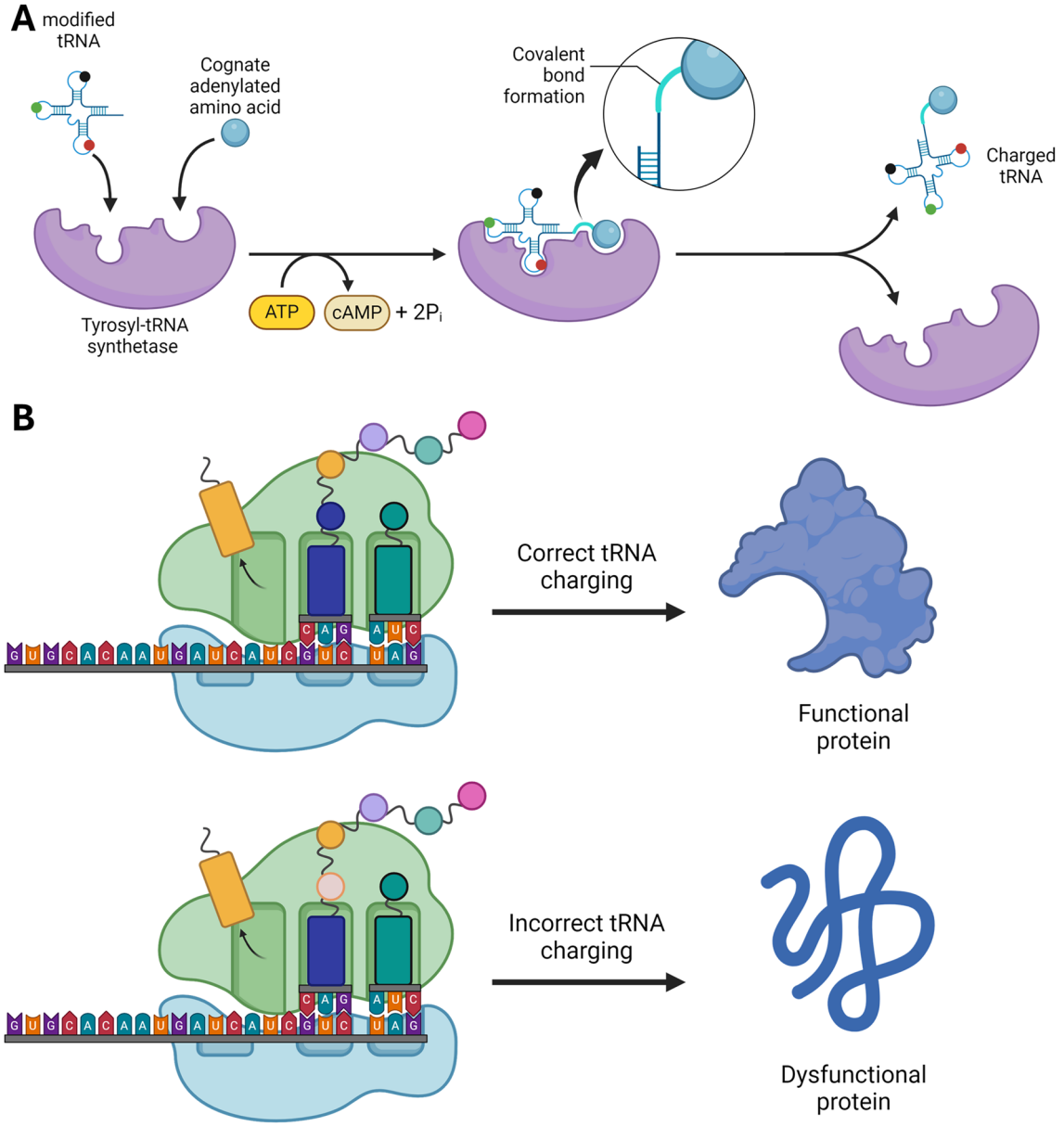


FIGURE 4 | tRNA aminoacylation and translation. (A) tRNA aminoacylation process. First, the tRNA and its cognate amino acid enter the active site of the specific synthetase. Next, Using ATP, the synthetase catalyzes the covalent bonding between the amino acid and the tRNA. The tRNA charged with the amino acid is released by the synthetase. Created in BioRender. https://BioRender.com/t47j685. (B) Mis-acylation can lead to the production of dysfunctional proteins by incorporating incorrect amino acids in the peptide sequence. Created in BioRender. https://BioRender.com/i59v250.

ribosomes assemble from two subunits, the 60S large subunit and the 40S small subunit, forming the 80S ribosome. The ribosome scans the mRNA starting at the 5′ end, locates the start codon, and begins translation through the open reading frame, elongating the nascent protein until reaching a stop codon. At this point, release factors free the newly synthesized protein for subsequent folding and processing based on its specific function (Schuller and Green 2018). However, translation faces challenges such as aberrant mRNAs containing damaged nucleotides, secondary structures, or missing termination codons. Shortages of specific amino acids, interactions between tRNAs and ribosomes, and certain codons can also hinder translation elongation (Schuller and Green 2018). These issues can cause ribosome stalling, trapping the ribosome with an incomplete polypeptide. If unresolved, such stalling can lead to translation arrest, protein aggregation, and proteotoxicity. While brief pauses during elongation are often resolved naturally, persistent stalling activates cellular stress responses and quality control mechanisms to rescue stalled ribosomes. There are three distinct pathways that resolve stalled ribosomes depending on the causing agent: the ribotoxic stress response (RSR) activated by Zakα (Vind, Snieckute, et al. 2020), ribosome associated quality control (RQC) activated by ZNF598, and integrated stress response (ISR) activated by GCN2 (Vind, Genzor, et al. 2020; Wu et al. 2020). Discussing all of them is beyond the scope of this work; however, they have been discussed thoroughly here (Filbeck et al. 2022; Joazeiro 2019; Pakos-Zebrucka et al. 2016; Vind, Genzor, et al. 2020). Quality control mechanisms link

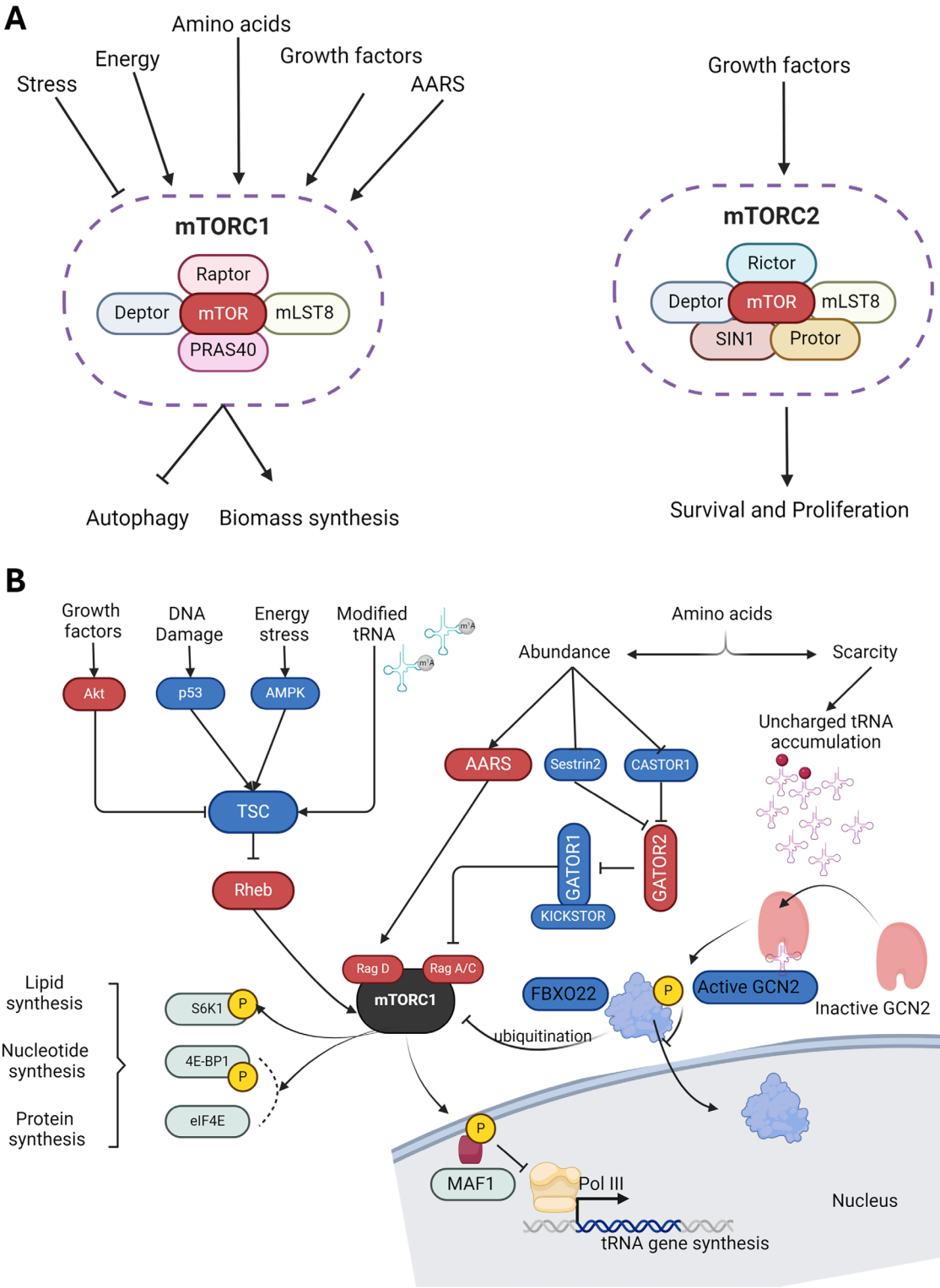


FIGURE 5 | An overview of the mTOR signaling network. (A) mTORC1 and 2 subunits and upstream regulators. Created in BioRender. https://BioRender.com/z24s972. (B) The signaling pathways upstream of mTORC1. Positive regulators of mTORC1 signaling are shown in red, and negative regulators are shown in blue. Downstream signaling effectors of mTORC1 are shown in green; SK6 and eIF4E support anabolism as a result of mTORC1 activation. mTORC1 and tRNA dynamics are linked through several pathways. Amino acid scarcity leads to the accumulation of uncharged tRNA activating GCN2 and FBXO22-mediated mTOR ubiquitination, while abundance leads to AARS-mediated mTORC1 activation. mTORC1 phosphorylates MAF1 and thereby relieving its inhibition of pol III transcription of tRNA genes. AARS, aminoacyl tRNA synthetase; FBXO22, F-box only protein 22; GCN2, general control nonderepressible 2; MAF1, MAF1 yeast homolog. Created in BioRender. https://BioRender.com/g77t784.

tRNA functionality and ribosome activity to translation fidelity. For example, in mammals, mutations in CNS-specific tRNA n-Tr20 impair translation and cause ribosome stalling at AGA codons (Ishimura et al. 2014). In bacteria, the loss of m^1G37 modification reduces tRNA aminoacylation efficiency, leading to codon-specific ribosome stalling and widespread changes in gene expression (Masuda et al. 2021). Amino acid depletion has been shown to activate both the RSR and ISR through their respective upstream activators. For instance, nutrient and amino acid starvation activate the RSR via ZAKα due to ribosomal stalling (Snieckute et al. 2022). As mentioned previously, amino acid depletion causes uncharged tRNAs to accumulate, activating GCN2. This activation inhibits mTORC1 substrate recruitment and suppresses global protein synthesis (Ge et al. 2023). GCN2 also moderates translational activity under amino acid scarcity by preventing excessive ribosome collisions. Notably, while amino acid starvation is essential for ribosome stalling and RSR activation, ribosomal collisions only occur in the absence of GCN2 activity, underscoring its critical role in moderating translation. These observations highlight GCN2 as a central integrator of nutrient status, linking amino acid availability to multiple pathways that regulate translation through sensing tRNA status, mTORC1 inhibition, and ribosome quality control.

4 | Dietary/Metabolic Regulation of tRNA Modifications

The regulation of tRNA modifications and their levels depends on multiple factors. tRNA expression, modifications' stoichiometry, and modifying enzyme levels are some of the important regulatory factors of tRNA modifications' levels in a given system (Dedon and Begley 2022; Pichot et al. 2023). An important factor regulating tRNA modifications levels is the supply of precursors and enzyme substrates for enzymatic tRNA modifications synthesis. In this section, we will review such relations between substrate/precursor availability, metabolic/dietary regulation of these substrates, tRNA modifications, and ultimately codon biased translation.

4.1 | tRNA Queuosine and the Link Between Gut Microbiome and Translation

Queosine (Q) is a wobble tRNA modification with a 7-deazaguanosine core structure and a bulky cyclopentene group-containing side chain (Suzuki et al. 2025). Q was recently thoroughly reviewed here (Suzuki et al. 2025) and here (Rashad 2024). However, it is important to highlight some interesting aspects of Q in terms of the regulation of cellular bioenergetics. In prokaryotes, Q can be synthesized de-novo from guanin triphosphate nucleoside (GTP) (de Crécy-Lagard et al. 2024). However, in eukaryotes, the synthesis of Q is dependent on the supply of its precursor, queuine (q), which is derived from gut microbiota or from diet (de Crécy-Lagard et al. 2024; Fergus et al. 2021; Rashad 2024). This nature of Q provides an interesting insight into how our gut bacteria, or our diet can directly influence mRNA translation. Q is present in four tRNAs: Asparagine (Asn), Aspartic acid (Asp), Histidine (His), and Tyrosine (Tyr) (Rashad 2024; Suzuki et al. 2025). Q is further glycosylated to galactosyl-queuosine (galQ) in Tyr and mannosyl-queuosine (manQ) in Asp tRNAs via the recently identified QTGAL and QTMAN enzymes, respectively (Zhao et al. 2023). Q allows the expansion of codon decoding from NAC codons to NAC/U codons (Ando et al. 2025; Fergus et al. 2021; Fergus et al. 2015). Without Q, NAU codons are prone to ribosome stalling and frameshifting, leading to improper decoding and mRNA translation (Dixit et al. 2021). Q is present in cytosolic and mitochondrial tRNAs and was shown to be essential for proper mitochondrial translation and function (Boland et al. 2009; Hayes et al. 2020; Kulkarni et al. 2021; Rashad 2024). Such links to mitochondrial function would, in theory, link Q levels to cellular bioenergetics and, consequently, to cellular metabolism. Nonetheless, QTRT1 KO mice are phenotypically normal apart from sex-dependent cognitive dysregulation due to hippocampal degeneration (Cirzi et al. 2023), in line with the relatively higher levels of Q in the brain compared to other organs (Ando et al. 2025). In fact, QTRT1 KO animals, apart from zebrafish, are viable and fertile (Cirzi et al. 2023; Zhao et al. 2023), which begets the question, whether Q is essential only during cellular stress, where cellular metabolism and bioenergetics need to be more tightly regulated to respond to the adverse environment (Rashad 2024). Despite several research groups working on Q modifications, its biological roles remain unclear. However, the potential links between Q and bioenergetics cannot be overlooked and should be investigated in future works.

4.2 | The Citric Acid Cycle and tRNA Modifications

A central process for generating energy in mitochondria-containing organisms is the tricarboxylic acid (TCA) cycle (Figure 6). The TCA cycle is essential for generation energy as well as metabolites for various biosynthetic and cellular processes (Arnold et al. 2022). The TCA cycle entails a series of steps starting from glucose breakdown to pyruvate followed by pyruvate breakdown to acetyl Co-A, whose oxidation as part of the TCA cycle accounts for $>60\%$ of oxygen consumption and energy production (Akram 2014) (Figure 6). Acetyl Co-A itself is a donor of the acetyl group in many reactions (Guertin and Wellen 2023). Indeed, the tRNA modification N4-acetylcitiidine (ac^4C) is synthesized by an acetyl transferase reaction catalyzed by the enzyme NAT10 (Arango et al. 2018; Schiffers and Oberdoerffer 2024). Another important TCA cycle byproduct for tRNA modifications synthesis is α-Ketoglutarate (or 2-oxoglutarate), which is essential for the synthesis of *5-hydroxymethylcytidine* (hm^5C) and *5-formylcytidine* (f^5C) tRNA modifications via ALKBH1 dioxygenase activity (Kawarada et al. 2017). The TCA cycle is impacted by dietary intake of micro and macronutrients as well as cellular metabolic needs (Arnold et al. 2022; Yoshii et al. 2019). Thus, the metabolic state of the cell can influence the status of tRNA and mRNA modifications through TCA cycle byproducts, and ultimately mRNA translation and protein synthesis. In this section, we will discuss these modifications and the links to the TCA cycle metabolites essential for their synthesis.

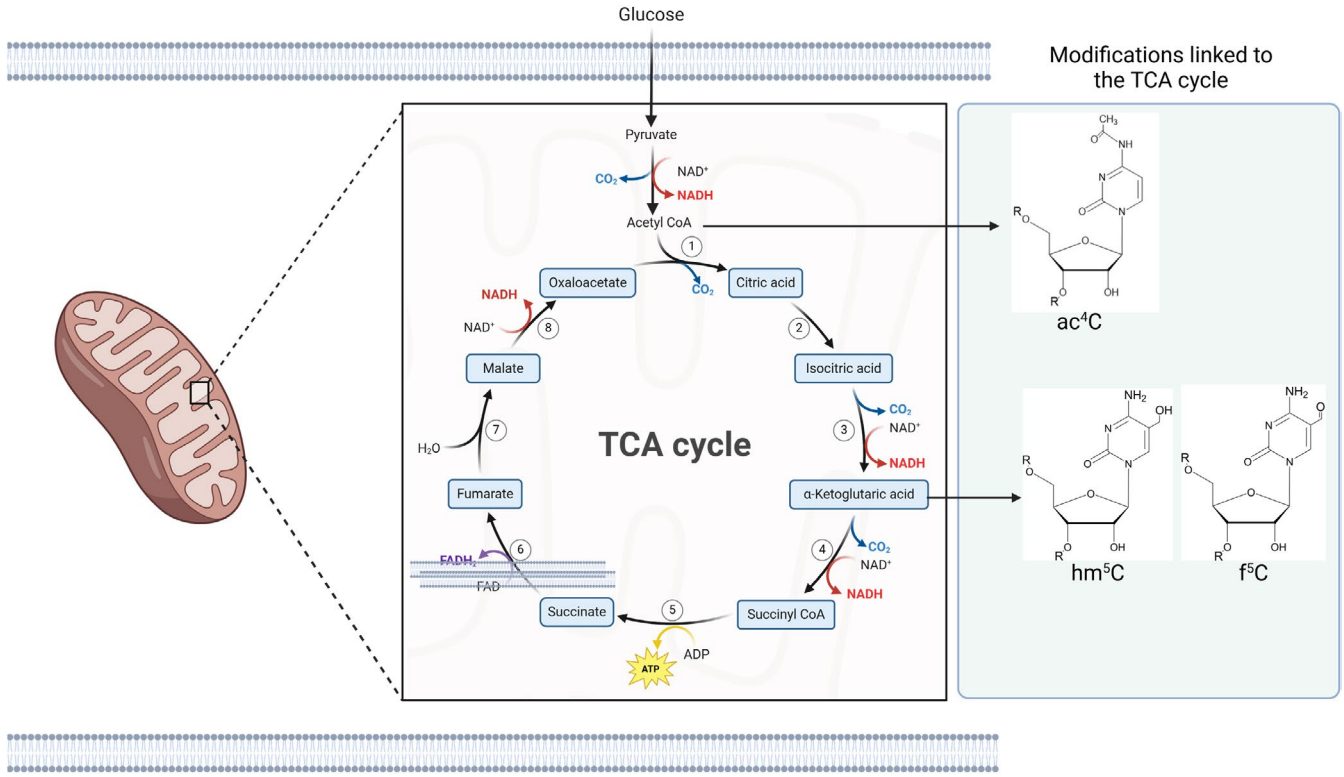


FIGURE 6 | The tricarboxylic acid (TCA) cycle and tRNA modifications linked to some of its products. Created in BioRender. https://BioRender.com/o04m704.

4.2.1 | ac^{4}C and Acetyl Co-A

Acetyl Co-A is an ancient molecule that is thought to predate ATP as an energy source (Martin 2020). Acetyl Co-A is produced by glucose, lipid, and amino acid catabolism, and is essential to power the TCA cycle (Arnold et al. 2022; Guertin and Wellen 2023). However, the roles of acetyl Co-A in cells are more diverse than just being an energy molecule. Acetyl Co-A is a substrate for lysine acetylation reactions, such as those regulating gene expression through histone acetylation (Shvedunova and Akhtar 2022). Acetyl Co-A is very well studied in cancer, and acetyl Co-A metabolic enzymes are often overexpressed in cancers (Guertin and Wellen 2023). In cancer, acetyl Co-A impacts oncogenesis via its role in the mevalonate pathway, de novo lipogenesis, and protein acetylation, as well as various cell-specific processes (reviewed extensively in Guertin and Wellen (2023)). However, the role of acetyl Co-A in promoting cancer through RNA acetylation remains relatively obscure in comparison. RNA acetylation is mediated by a non-redundant enzyme, N-acetyltransferase 10 (NAT10), in mammalian cells or its homolog in yeast and bacteria (Arango et al. 2018; Ikeuchi et al. 2008; Ito et al. 2014; Schiffers and Oberdoerffer 2024) (Figure 7A). ac^{4}C is present in mRNA, tRNA, and rRNA (Schiffers and Oberdoerffer 2024). Adaptor molecules guide the activity of NAT10 towards specific RNAs. THUMPD1 directs NAT10 to interact with 2 tRNAs: Ser^{CGA} and Leu^{UAG} (Broly et al. 2022; Yan et al. 2024). The box C/D small nucleolar RNA (snoRNA) SNORD13 directs NAT10 towards nucleotide 1842 of 18S rRNA via sequence complementation (Sharma et al. 2015; Sharma et al. 2017).

In tRNA, ac^{4}C is present at position 12 in the D-arm and is essential for maintaining tRNA tertiary structure as well as modifications present at the D and T-loops (Suzuki 2021) (Figure 7B). Initially, it was reported that ac^{4}C occurs in 2 tRNAs, Ser^{CGA} and Leu^{UAG} (Broly et al. 2022; Yan et al. 2024). However, ac^{4}C-RIP-seq identified an extended set of ac^{4}C-modified tRNAs (Wei et al. 2023). Nonetheless, targeted analysis for these tRNAs identified by ac^{4}C-RIP-seq using mass spectrometry is needed for confirmation. ac^{4}C does not occur in mitochondrial tRNAs and is restricted to cytosolic tRNAs (Suzuki 2021; Suzuki et al. 2020). The maintenance of tRNA structure is essential for various tRNA processes such as aminoacylation and proper codon decoding (Schultz et al. 2024; Suzuki 2021). Thus, loss of ac^{4}C from tRNA would impact codon decoding of the tRNAs depending on it for structure via structural instability and failure to properly aminoacylate the tRNAs. This is clear in the case of ac^{4}C hypomodification, where protein synthesis is globally impacted (Yan et al. 2024).

ac^{4}C in the mRNA is also associated with important translational effects that should be mentioned (Arango et al. 2018; Wei et al. 2023). However, the impact of ac^{4}C on mRNA is heavily dependent on its location within the transcript (Schiffers and Oberdoerffer 2024). ac^{4}C modifications within the 5′ untranslated region (5′UTR) can promote upstream translation initiation and suppress canonical start sites, while modifications in the coding sequence (CDS) can promote elongation (Arango et al. 2018, 2022; Schiffers and Oberdoerffer 2024). Alternatively, ac^{4}C within the Kozak sequence (CAUGG) represses initiation via interacting with initiator tRNA-Met (tRNA-iMet) t^{6}A modification (at position 37

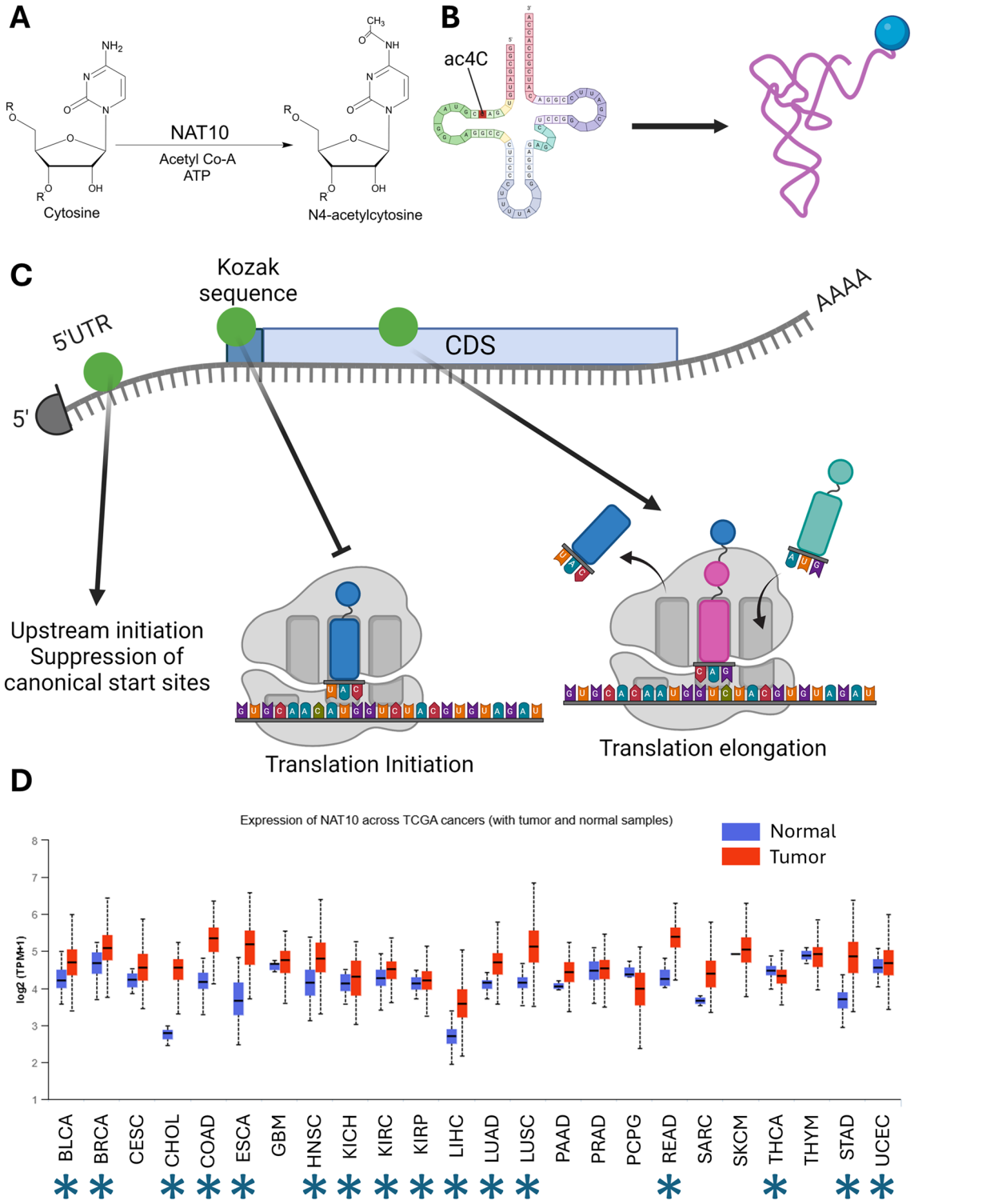


FIGURE 7 | (A) Synthesis of ac^{4}C by NAT10. (B) ac^{4}C is present at position 12 in the D-arm and is essential for maintaining tRNA tertiary structure. Created in BioRender. https://BioRender.com/r90s952. (C) ac^{4}C location in the mRNA sequence dictates its role in regulating translation. Created in BioRender. https://BioRender.com/j29l940. (D) Expression of NAT10 in multiple tumors. Data from the cancer genome atlas database. Hash indicates statistical significance. Data from ULCAN: https://ualcan.path.uab.edu/index.html.

of the tRNA) (Arango et al. 2022) (Figure 7C). The presence of ac^{4}C in mRNA is essential for mRNA translation as well as stability (Gong et al. 2024; Hu et al. 2024; Shuai et al. 2024). The impact on mRNA stability is linked to the translational efficiency conferred by ac^{4}C modifications present in the CDS (Arango et al. 2018).

The promiscuity of NAT10 activity on multiple RNA species, as well as its reported role in protein acetylation (Liu et al. 2020; Zheng et al. 2022), renders isolating its effect on a specific mRNA or process difficult when approaches such as gene knockdown or overexpression are employed (Schiffers and Oberdoerffer 2024). While targeting its adaptor molecules could

offer some degree of specificity, such as targeting THUMPD1 to study ac^4C in tRNA (Broly et al. 2022), this was not widely performed in the published literature (Wei et al. 2023; Yan et al. 2024). Thus, whether the observed effect is solely due to a specific mRNA/tRNA/rRNA effect or a combination of all is a difficult question to answer in each experimental setting. Nonetheless, NAT10 and ac^4C modification were implicated in many diseases and were shown to be important for a large array of processes (Achour and Oberdoerffer 2024). NAT10 was shown to play important roles in the regulation of the cell cycle, immunity, and development (Achour and Oberdoerffer 2024; Broly et al. 2022), conditions in which acetyl Co-A itself plays an important role (Guertin and Wellen 2023; Lee et al. 2014; Moussaieff et al. 2015), which signifies the intimate links between ac^4C and acetyl Co-A metabolism. NAT10, through ac^4C mRNA and tRNA modifications, was shown to play important roles in many cancers (Gong et al. 2024; Shuai et al. 2024; Wei et al. 2023; Yan et al. 2024). In fact, NAT10 expression is upregulated in multiple cancers (Figure 7D).

There are yet several limitations in studying ac^4C, mainly technical issues faced during attempts to map it via sequencing methods, whether chemical or antibody-based (Achour and Oberdoerffer 2024; Schiffers and Oberdoerffer 2024). While NAT10 is the canonical writer of ac^4C, there is yet an eraser to be identified. While ac^4C is static within tRNA and rRNA, this remains to be elucidated in mRNA (Achour and Oberdoerffer 2024). In addition, as mentioned above, isolating NAT10 function on a specific substrate remains a challenge. The links between acetyl Co-A metabolism and ac^4C levels are also an area that is understudied. Future works should attempt to highlight the dynamic relationship between acetyl Co-A metabolism and RNA acetylation, which would add an important and interesting layer to our understanding of the metabolic regulation of mRNA translation.

4.2.2 | α-Ketoglutarate (α-KG) and Anticodon Modifications

α-KG is an intermediate of the TCA cycle (Figure 6) and is linked to 2 tRNA modifications: hm^5C and f^5C, which occur in 2 tRNAs: mitochondrial tRNA-Methionine (mt-tRNA-Met^{CAU}) and cytosolic tRNA leucine (tRNA-Leu^{CAA}) (Kawarada et al. 2017) (Figure 8A). This modification pathway is a multistep pathway starting with N5-methylation of cytosine at position 34 by NSUN2 in the cytosol, or NSUN3 in the mitochondria. Next, ALKBH1, using α-KG and O_2 as substrates, oxygenates m^5C to hm^5C and further to f^5C. In the cytosol, these modifications are further 2′O-ribose methylated by FTSJ1 to hm^5Cm and f^5Cm respectively (Figure 8A). FTSJ1 does not localize in the mitochondria; thus, in the mitochondria, only f^5C exists. f^5Cm and f^5C promote the expansion of codon decoding by allowing the wobble cytosine to pair with adenosine (Figure 8B,C). This allows tRNA-Leu^{CAA} to decode both GUU and AUU leucine codons (Kawarada et al. 2017). In mammalian mitochondria, the AUA codon encodes for Met and not isoleucine (Ile) as in the cytosol (Haag et al. 2016; Kawarada et al. 2017). Thus, f^5C in mt-tRNA-Met^{CAU} allows for the proper amino acid incorporation into mitochondrial DNA-encoded proteins. This was shown to be important for mitochondrial function and cellular bioenergetics (Delaunay et al. 2022; Haag et al. 2016; Kawarada et al. 2017). Indeed, such regulation was implicated in cancer via mitochondrial translation regulation (Delaunay et al. 2022). The importance of f^5C for mitochondrial translation and function, and its dependence on α-KG, provides an interesting view into the bidirectional relationship between metabolic and bioenergetic output of the cells and how tRNA modifications interact and fine-tune it (Figure 8D). α-KG generated from the TCA cycle is essential for the synthesis of mitochondrial f^5C, which is in turn essential for respiratory complex functions and the TCA cycle, and so on (Delaunay et al. 2022; Haag et al. 2016; Kawarada et al. 2017) (Figure 8D). Such a feedback loop, while intriguing to consider, was not fully characterized in the literature. Again, such notions signify the importance of studying RNA modifications not only from the viewpoint of their enzyme function, but also from the viewpoint of the reaction substrates and how they connect to various metabolic and bioenergetic processes.

α-KG itself has many pleiotropic effects (Zdzisińska et al. 2017), it acts as a precursor for the endogenous biosynthesis of the amino acids; glutamate and glutamine, through cataplerotic reactions that prevent α-KG accumulation in the cells (Newsholme et al. 2003; Zdzisińska et al. 2017). Glutamate and glutamine further play important roles in many cells and organs (Newsholme et al. 2003). α-KG is also an important antioxidant that can suppress oxidative stress and protect against ROS-induced mitochondrial damage (Yamamoto and Mohanan 2003; Zdzisińska et al. 2017). While such antioxidant effects were attributed to the non-enzymatic oxidative decarboxylation scavenging activity of α-KG (Long and Halliwell 2011) or via interacting with cyanogens, such as cyanide, and forming intermediates that suppress their activity (Moore et al. 1986; Norris et al. 1990), there is another mechanism that could be at play. Previous works have shown that overexpressing ALKBH1 could alter how cells respond to oxidative stress (Rashad et al. 2021, 2022; Rashad, Han, et al. 2020). While these previous works have mainly focused on the potential demethylase activity of ALKBH1, the dioxygenase activity and the generation of hm^5C/f^5C could be a major factor that was overlooked. For example, overexpressing ALKBH1 protected cells from respiratory complex III inhibition-induced mitochondrial dysfunction and oxidative stress (Rashad et al. 2022). Whether α-KG supplementation could also modulate the level of anticodon modifications, thus driving mRNA translation toward a more antioxidant program, is an interesting thought that remains to be examined. α-KG also plays important roles in immune modulation, regulating bone structure and health, cardiovascular regeneration, aging and health span, and cancer (Minogue et al. 2023; Naeini et al. 2023; Wang et al. 2020; Xiang et al. 2024; Zdzisińska et al. 2017). While various processes have been attributed to these diverse effects of α-KG, such as histone methylation or metabolic rewiring, identifying whether anticodon modifications play a role is an unexplored mechanism given the wealth of literature on α-KG.

4.3 | L-Threonine and Translation Regulation

N6-threonylcarbamoyladenosine (t^6A), which is located at position 37 in cytosolic and mitochondrial tRNAs, is regulated by

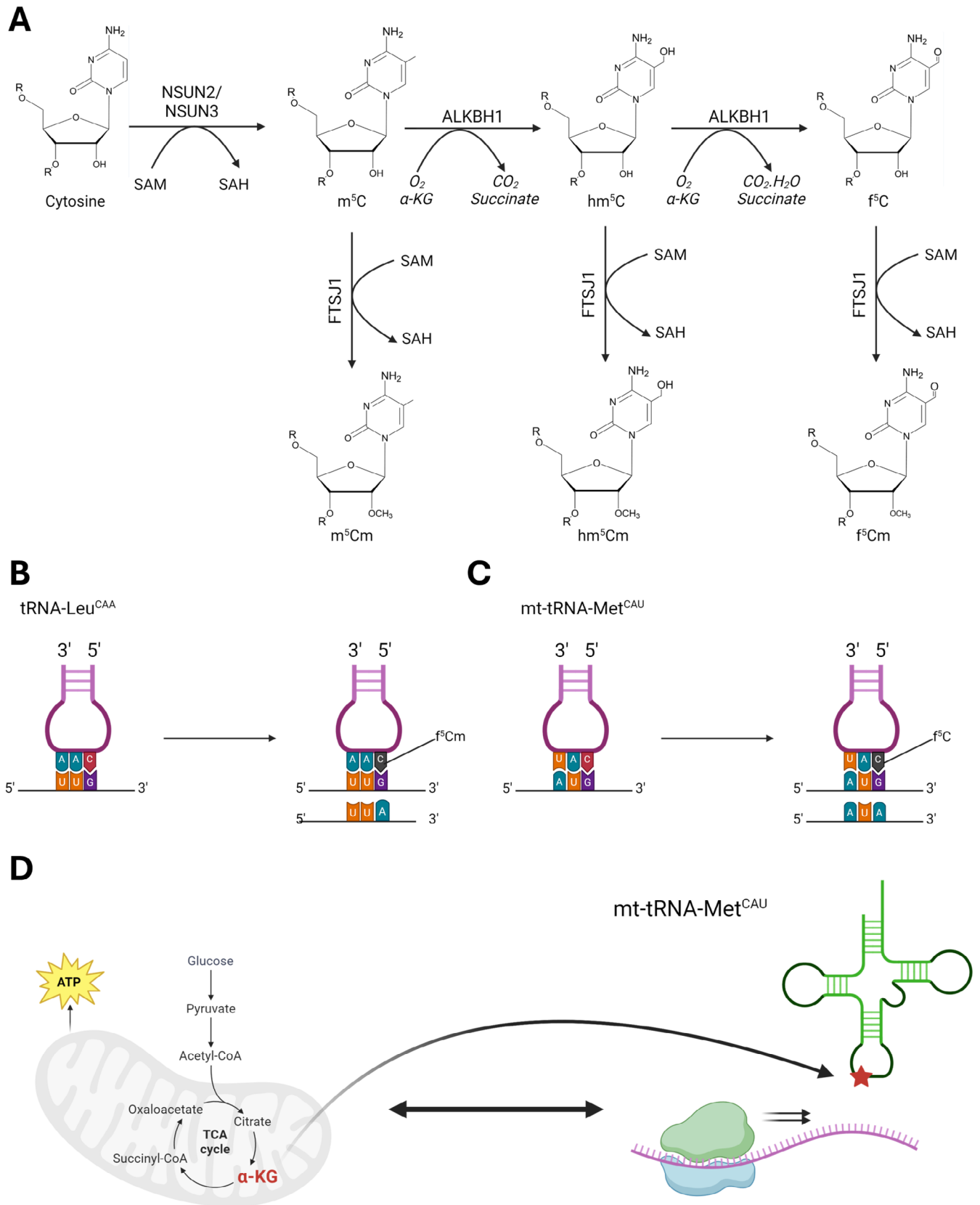


FIGURE 8 | α-KG and tRNA deoxygenation in the cytosol and mitochondria. (A) Modification synthesis pathway for hm^5C and f^5C using α-KG as a substrate. Created in BioRender. https://BioRender.com/l86i366. (B, C) Codon decoding by f^5Cm and f^5C in the cytosol and mitochondria, respectively. Created in BioRender. https://BioRender.com/r61n681. (D) Bidirectional relationship between α-KG and f^5C. Created in BioRender. https://BioRender.com/m94h274.

dietary inputs as well as mitochondrial respiration and TCA cycle activity (Lin et al. 2018; Suzuki 2021; Suzuki et al. 2020; Wu et al. 2024). The first step in t^6A biogenesis is the non-enzymatic reaction between L-Threonine and CO_2 or HCO_3^- to generate a carbamate intermediate. YRDC then uses ATP to convert this intermediate into threonylcarbamoyl-AMP (TC-AMP) which is then transferred to adenine at position 37 via the KEOPS complex in the cytosol or OSGEPL1 in the mitochondria (Lin et al. 2018; Srinivasan et al. 2011; Suzuki 2021; Suzuki et al. 2020; Zhou et al. 2020) (Figure 9A). t^6A can be further N6-methylated to m^6t^6A by TRMO (Kimura et al. 2014) or 2-methylthiolated into ms^2t^6A by CDKAL1 (Arragain et al. 2010; Santos et al. 2020; Wei et al. 2011). Thus, given this biosynthetic pathway, the rate-limiting steps for t^6A formation are mitochondrial activity and dietary availability of L-Threonine (Lin et al. 2018; Wu et al. 2024). t^6A is needed for proper decoding of ANN coding, which is achieved via codon stacking, leading to the stabilization of the codon-anticodon loop conformation and more efficient translation (Akiyama et al. 2024; Thiaville et al. 2016; Zhang, Zhou, et al. 2024). Loss of t^6A results in misincorporation of amino acids into the growing peptide chain as well as a reduction in tRNA aminoacylation, without impacting tRNA stability or abundance (Wu et al. 2024; Zhang, Zhou, et al. 2024).

In the mitochondria, t^6A is present in 5 tRNAs: mt-tRNA-Thr^{UGC}, mt-tRNA-Lys^{UUU}, mt-tRNA-Ser^{AGY}, mt-tRNA-Ile^{GAU}, and mt-tRNA-Asn^{GUU} (Lin et al. 2018; Zhang, Zhou, et al. 2024; Zhou et al. 2020). Mito-tRNA t^6A modifications are essential for proper mitochondrial mRNA translation and mitochondrial function (Lin et al. 2018; Zhang, Zhou, et al. 2024). Loss of mitochondrial t^6A via targeting OSGEPL1 leads to reduced mitochondrial respiration and ATP generation. This was due to downregulation of various mitochondrial as well as nuclear-encoded respiratory complex proteins, which mainly impacted respiratory complex I activity (Lin et al. 2018; Zhang, Zhou, et al. 2024). Indeed, loss of t^6A due to point mutation in mitochondrial tRNA was observed to occur in MERRF syndrome (Myoclonus epilepsy with ragged-red fibers) (Lin et al. 2018; Lott et al. 2013). In fact, multiple known point mutations in mitoDNA encoded tRNA genes were shown to abrogate or reduce t^6A levels (Lin et al. 2018). Another example is the m.15927G>A in mt-tRNA-Thr associated with Leber's hereditary optic neuropathy, also through mitochondrial dysfunction secondary to mitochondrial translation defects (Zhang, Li, et al. 2024). Nonetheless, loss of mitochondrial t^6A does not appear to interfere with normal mammalian embryogenesis and development (Zhang, Zhou, et al. 2024).

Cytosolic t^6A defects due to mutations in YRDC or KEOPS complex genes are also associated with several developmental disorders. The most famous example of which is Galloway-Mowat syndrome (GAMOS) (Arrondel et al. 2019; Braun et al. 2017; Treimer et al. 2022). GAMOS is characterized by early-onset steroid-resistant nephrotic syndrome and microcephaly (Arrondel et al. 2019). Mutations in YRDC, GON7, TPRKB, LAGE3, and TP53RK were found to occur in GAMOS patients (Arrondel et al. 2019; Braun et al. 2017; Treimer et al. 2022). Mutations in YRDC or KEOPS complex elements led to reduced t^6A levels, protein translational defects, reduced proliferation, and activation of the cellular stress response (Braun et al. 2017; Flores et al. 2017). Activation of DNA damage response (DDR) and apoptosis in neuronal progenitor cells was reported to be a consequence of these mutations leading to microcephaly (Braun et al. 2017). On the other hand, impaired podocyte migration could be attributed to the renal defects (Braun et al. 2017). It also appears that genetic defects of t^6A biosynthesis can lead to neural and renal phenotypes generally, not only in GAMOS (Edvardson et al. 2017; Schmidt et al. 2021). This could allude to specific translational programs needed in the brain and kidneys that render them highly sensitive to t^6A aberrations.

t^6A is also becoming a subject of interest in cancers. Studies have shown its role in hepatic, lung, and brain cancers (Guo et al. 2021; Shen et al. 2020; Wu et al. 2024). t^6A promotes a pro-oncogenic codon-biased translational program that promotes cell proliferation and self-renewal (Guo et al. 2021; Shen et al. 2020; Wu et al. 2024). Indeed, YRDC, the first enzyme is the biosynthetic pathway of t^6A and the subject of focus in the published literature, was upregulated at the mRNA level in multiple cancers except in kidney cancers and thyroid cancer, where it was downregulated (Figure 9B). This pattern of expression could signify a tissues-specific role of t^6A in regulating oncogenic mRNA translation that is far from being explored. In the work of (Wu et al. 2024), which explored the oncogenic role of t^6A and threonine thoroughly in glioblastoma (GB), t^6A was shown to be essential for maintaining glioma stem cells (GSCs) self-renewal capacity and translation via regulating ANN codon decoding. In addition, dietary L-Threonine restriction recapitulated the effects of t^6A loss and YRDC targeting and restricted tumor growth in vitro and in vivo, providing an interesting approach to target cancer via dietary manipulation of the epitranscriptome.

t^6A biosynthetic pathway is also linked to type 2 diabetes (T2D). t^6A methyl-thiolation to ms^2t^6A by CDKAL1 is essential for pancreatic β-cell function and insulin production (Arragain et al. 2010; Santos et al. 2020; Steinthorsdottir et al. 2007; Wei et al. 2011). ms^2t^6A is present in tRNA-Lys^{UUU} (Wei et al. 2011). ms^2t^6A is essential for the decoding of the Lys^{AAA} and Lys^{AAG} codons (Narendran et al. 2021; Santos et al. 2020). Lys is essential for the processing of pro-insulin to insulin via cleavage by PCSK1 (proprotein convertase subtilisin/kexin type 1) (Narendran et al. 2021; Santos et al. 2020). Thus, deficiency of ms^2t^6A leads to improper pro-insulin translation, its accumulation, and loss of glucose-stimulated insulin secretion and impaired glucose tolerance and disrupted energy metabolism, ultimately leading to T2D (Ohara-Imaizumi et al. 2010; Okamura et al. 2012; Santos et al. 2020; Steinthorsdottir et al. 2007; Wei et al. 2011).

Given this link between t^6A biosynthesis and ms^2t^6A levels and insulin secretion (Liu et al. 2024; Santos et al. 2020; Wei et al. 2011), one might consider whether L-Threonine supplementation could have a positive impact on T2D. On the contrary, multiple population studies highlighted that L-Threonine intake is a risk factor for lower insulin levels and increased glucose levels (Liu et al. 2023; Vangipurapu et al. 2019). Thus, the link to T2D appears to be strictly linked to ms^2t^6A and methylthiolation of tRNA (Arragain et al. 2010; Santos et al. 2020; Steinthorsdottir et al. 2007). Nonetheless, pleiotropic effects of L-Threonine unrelated to t^6A were reported. In mouse embryonic stem cells (mESCs) L-Threonine was shown to promote

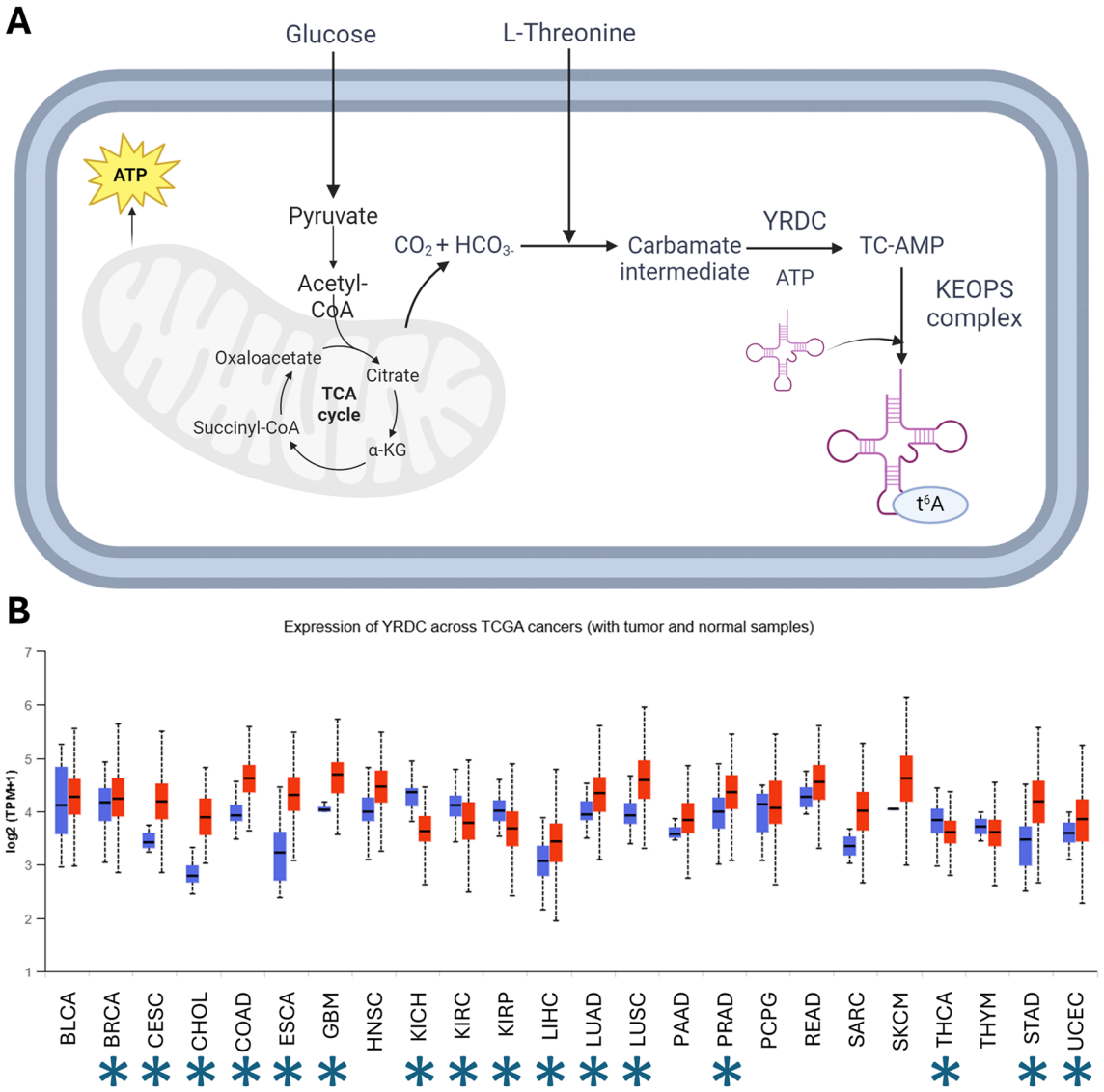


FIGURE 9 | L-Threonine and t^6A synthetic pathway. (A) Synthesis of t^6A modifications requires mitochondrial respiration generating CO_2 and L-Threonine supply. Created in BioRender. https://BioRender.com/q14z530. (B) Expression of YRDC in cancers. Data from the cancer genome atlas database. Hash indicates statistical significance. Data from ULCAN: https://ualcan.path.uab.edu/index.html.

S-adenosyl methionine (SAM) generation via the folate cycle, which was essential for histone methylation and maintenance of pluripotency (Shyh-Chang et al. 2013). However, this might not be the case in human cells, as the Threonine dehydrogenase gene, which is essential for linking L-Threonine to the folate cycle, is a pseudogene (Shyh-Chang et al. 2013; Wu et al. 2024). Threonine supplementation was also shown to extend lifespan in *Caenorhabditis elegans* via suppressing ferroptosis (Kim et al. 2022; Ravichandran et al. 2018). L-Threonine levels were shown to be reduced in aged rodent and human plasma (Darst et al. 2019; Wesley et al. 2019). Notably, the decline in mitochondrial function and respiration are hallmarks of aging (Guo et al. 2023; Tavallaie et al. 2020). Given that mitochondrial TCA cycle and CO_2 generation are rate limiting in the synthesis of t^6A, in addition to L-Threonine levels (Lin et al. 2018; Wu et al. 2024), the question of the potential role of t^6A and its downstream modifications, especially ms^2t^6A in aging, becomes more interesting.

4.4 | One-Carbon (1C) Metabolism and the Landscape of tRNA Modifications

One-carbon (1C) metabolism is a network of interconnected biochemical pathways that supply and utilize one-carbon units for critical cellular functions, linking transcription and translation by virtue of producing metabolites necessary for these steps to take place (Danchin et al. 2020) (Figure 10). 1C metabolism is essential for the biosynthesis of nucleic acids and amino acids, epigenetic and epitranscriptomic regulation, and maintenance of redox balance (Ducker and Rabinowitz 2017; Fox and Stover 2008). Folate plays a central role in 1C metabolism by serving as a carrier of one-carbon units essential for these processes (Zarou et al. 2021). One-carbon units are donated from amino acids, majorly serine, as well as glycine, and choline degradation products like dimethylglycine and methylglycine. Enzymes catalyze the transfer and utilization of these one-carbon units, with folate derivatives acting as the

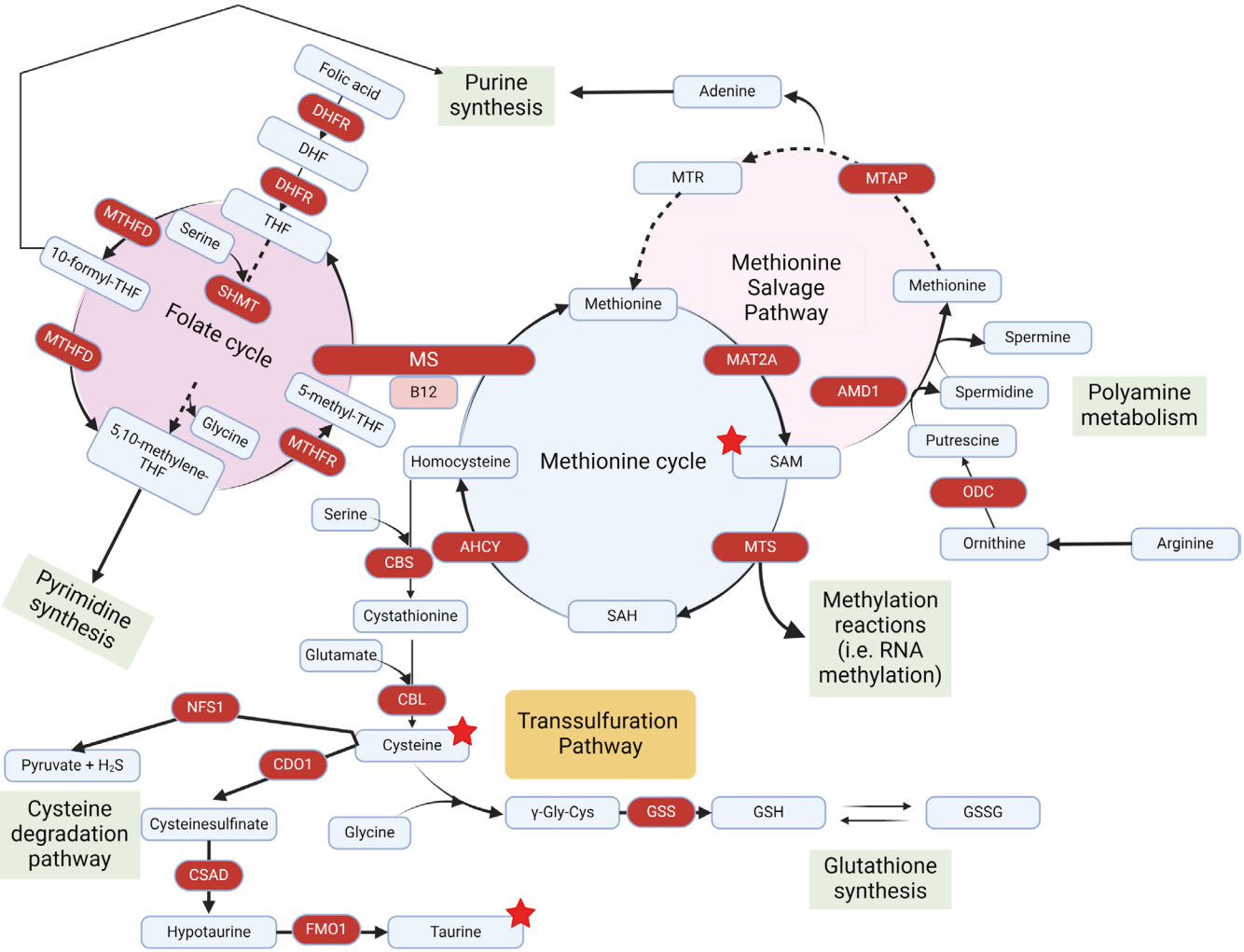


FIGURE 10 | One carbon (1C) metabolism. The diagram outlines the folate cycle, methionine cycle, and transsulfuration pathway. Folic acid is converted to THF, supporting purine and pyrimidine synthesis, while MTHFR facilitates methyl-THF production for methionine recycling, where SAM is synthesized, supporting the RNA methylation reaction. Homocysteine supports glutathione and redox balance, with cysteine and taurine synthesis supporting tRNA modifications. The pathway was constructed with information partially from Sanderson et al. (2019). Red star highlights metabolites discussed in the manuscript. Created in BioRender. https://BioRender.com/k51q339.

carriers. In animals, folate (vitamin B9) must be obtained from dietary sources. Dietary folate or its synthetic form, folic acid, undergoes conversion to tetrahydrofolate (THF) in two steps catalyzed by dihydrofolate reductase (DHFR), a process that requires NADPH as a cofactor.

THF is further converted to N5,N10-methylene THF by serine hydroxy methyltransferase (SHMT1 in the cytoplasm and SHMT2 in mitochondria), which transfers the hydroxymethyl group from serine to THF while converting serine to glycine in a reversible reaction (Garrow et al. 1993). The cellular localization of SHMT activity allows compartmentalized synthesis and catabolism of serine, depending on the supply and demand for 1C units. N5,N10-methylene THF is at the center of 1C metabolism, and it can be utilized for different outcomes and biosynthesis of multiple outputs depending on cell requirements. N5,N10-methylene THF is recycled back to THF by the enzyme thymidylate synthase, which in the process converts deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP). This is a very critical step because the synthesized dTMP is used for DNA synthesis.

Alternatively, N5,N10-methylene THF can be reduced to N5-methyl THF by methylene THF reductase (MTHFR). N5-methyl THF is involved in homocysteine re-methylation to methionine, a reaction catalyzed by methionine synthase (MS), which requires vitamin B12 as a cofactor. The synthesis of methionine from folate metabolism is intimately linked to translation, as methionine is the first amino acid residue in translation (Bhattacharyya and Varshney 2016). Methionine is subsequently converted to S-adenosylmethionine (SAM), an essential methyl donor for a myriad of molecules, including RNA and DNA methylation reactions that regulate epigenetics and epitranscriptomics (Chiang et al. 1996; Fischer et al. 2022).

N5,N10-methylene THF can also be oxidized to N5,N10-methenyl THF by methylene THF dehydrogenase (MTHFD) in a reversible reaction. Methenyl-THF is then converted to N10-formyl THF by Methenyl-THF cyclohydrolase (MTHFC). N10-formyl THF, the most oxidized form of folate, is indispensable for de novo purine synthesis, with one molecule of 10-formyl-THF required for each RNA or DNA base synthesized (Ducker

and Rabinowitz 2017; Pietzke et al. 2020). In mitochondria, 10-formyl-THF is used by the enzyme methionyl-tRNA formyltransferase (MTFMT) to formylate part of the mt-tRNA-Met pool. This formylated tRNA (N-formylmethionine-tRNA-Met) serves as the initiator for translation in mitochondria and thus is essential for proper mitochondrial function and respiration (Minton et al. 2018; Tucker et al. 2011). Since 10-formyl-THF cannot cross the mitochondrial membrane, it first gets hydrolyzed to formate by the MTHFD1-like enzyme (MTHFD1L) for transport.

The activated methyl cycle (methionine cycle) is completed through enzymatic steps that regenerate methionine from homocysteine and recycle N5-methyl THF back to THF. Homocysteine can be redirected out of the activated methyl cycle to form cystathionine by cystathionine beta-synthase, which requires the carbon backbone of serine and vitamin B6. Cystathionine then gets acted on by cystathionine gamma lyase to form α-Ketobutyrate and cysteine.

Cysteine can undergo further enzymatic transformations, contributing to taurine biosynthesis, glutathione production via the transsulfuration pathway, or pyruvate and hydrogen sulfide synthesis through cysteine desulfurase activity (Corona-Trejo et al. 2023). Taurine biosynthesis involves the oxygenation of cysteine-to-cysteine sulfinate by cysteine dioxygenase (iron-dependent), followed by decarboxylation to hypotaurine by cysteine sulfinic acid decarboxylase, and subsequent oxidation to taurine by hypotaurine dehydrogenase.

4.4.1 | SAM and tRNA Methylation

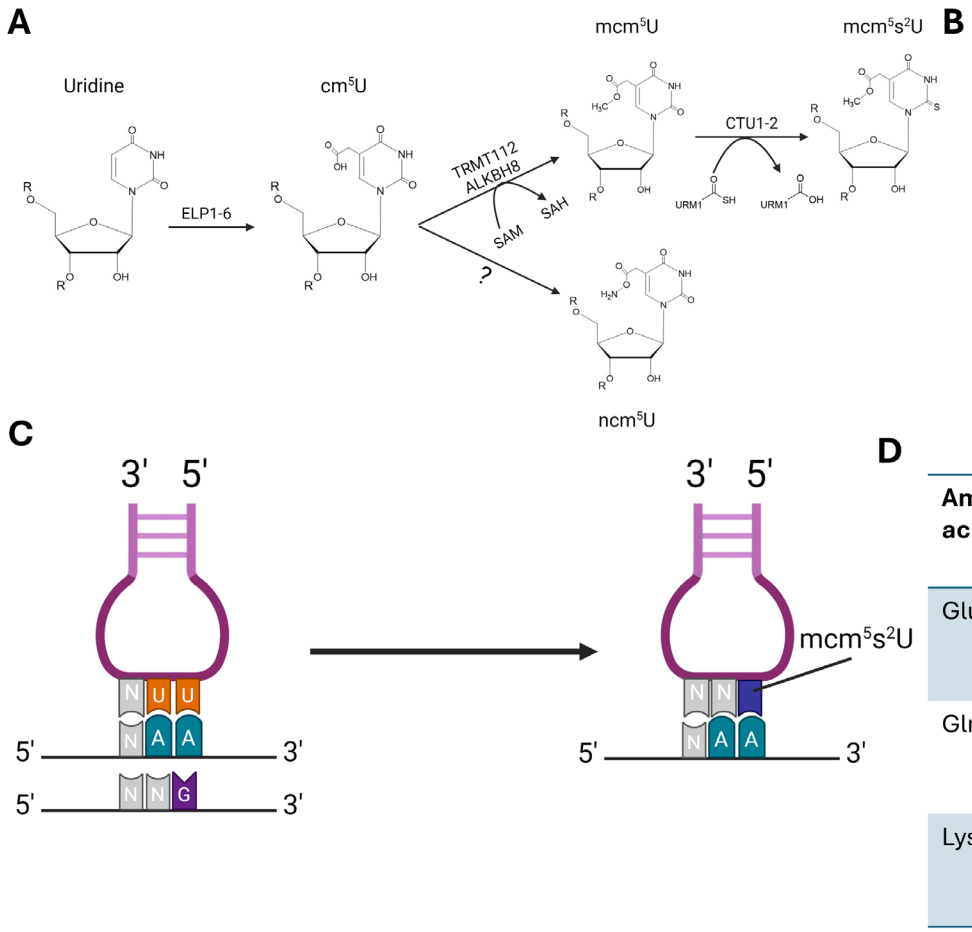
S-adenosylmethionine (SAM), a core product of 1C metabolism, is essential for methylation modifications of DNA, RNA, proteins, and other molecules, catalyzed by methyltransferase enzymes (MTases) (Fukumoto et al. 2022). In tRNA, methylation occurs in many positions, and they serve to stabilize tRNA structure and facilitate translation and codon decoding (Orellana et al. 2021; Rashad, Han, et al. 2020; Tuorto et al. 2012). SAM is produced from methionine in the methyl cycle (methionine cycle) (Figure 10). SAM is utilized for the methylation reaction leading to the production of s-adenosylhomocysteine (SAH). SAH is a competitive inhibitor of MTases; thus, the balance between SAM and SAH is essential in dictating the rate of methylation reactions (Fischer et al. 2022; Fukumoto et al. 2022). Studies have shown that SAM supplementation or targeting may serve as therapy for various conditions such as inflammation, cancer, and depression (Fischer et al. 2022; Li et al. 2017; Pascale et al. 2022; Peng et al. 2024; Yoon et al. 2016).

In RNA, SAM is essential for methyltransferase reactions in virtually all RNA species (Delaunay et al. 2024; Suzuki 2021; Xiong and Zhang 2023). In the tRNA, several of these modifications were shown to play important roles in various diseases and molecular processes. For example, m^7G at position 46 was shown to be a driver of oncogenesis via supporting codon-biased pro-oncogenic program in multiple cancers (Dedon and Begley 2022; Orellana et al. 2021; Zhang, Xu, et al. 2024). m^3C at position 32 was shown to regulate the cell cycle and DNA damage response via a serine codon-biased mRNA translation program (Cui et al. 2024). Loss of m^1G at position 9 due to genetic mutations in the TRMT10A gene leads to intellectual disability, microcephaly, diabetes, and short stature in humans and alters the mRNA translation via the destabilization of tRNA-iMet (initiator methionine) and tRNA-Gln^{CUG} (Tresky et al. 2024). m^1A at position 58 was shown to regulate stem cell self-renewal capacity and T-cell function (He, Wang, et al. 2024; Liu et al. 2022; Zuo et al. 2024). While it is important to know about all these modifications and their important roles in regulating translation and diseases, the purpose of this narration is to show how critical the supply of SAM via the 1C metabolism is to the maintenance of correct codon decoding and proteostasis via tRNA methylation.

4.4.2 | tRNA Thiolation and Sulfur Amino Acids

1C metabolism is an essential supplier of sulfur species, which are critical to tRNA thiolation reactions (Laxman et al. 2013; Pedrioli et al. 2008). Cysteine degradation by NFS1 leads to the release of sulfur species (Figure 10) which are transferred to tRNA in a multistep thiolation process that involves members of the ubiquitin-like protein family (Jüdes et al. 2016; Pedrioli et al. 2008). Sulfur released by NFS1 is transferred to MOCS3. MOCS3 transfers the sulfur to URM1 via adenylation followed by a subsequent thiocarboxylation. URM1 acts as the sulfur carrier in tRNA thiolation reactions (Chowdhury et al. 2012; Furukawa et al. 2000; Jüdes et al. 2016; Leidel et al. 2009; Pabis et al. 2020) which occur in cytosolic and mitochondrial tRNAs (Suzuki 2021). In this section, we will discuss the cytosolic thio-uridine modification mcm^5s^2U. Mitochondrial uridine thiolation modification will be discussed in the following Section 4.4.3.

mcm^5s^2U is synthesized in a multiple-step pathway that starts with the modification of U to cm^5U at the wobble position by the elongator complex proteins (ELP 1–6). This is followed by either methylation into mcm^5U by TRMT112 and ALKBH1 or alternatively modification into ncm^5U by a yet-to-be-identified enzyme. CTU1 and 2 further synthesize mcm^5s^2U by transferring a sulfur group from URM1 protein to mcm^5U (Figure 11A) (Schäck et al. 2020). mcm^5s^2U is present in 3 tRNAs: Glu^{UUC}, Lys^{UUU}, and Gln^{UUG} (Figure 11B). However, its upstream modification, mcm^5U, is present in another set of tRNAs, while the other arm of the pathway leading to the generating of ncm^5U occurs in a different set of tRNAs (Figure 11B). Thus, the synthesis of mcm^5s^2U is not a simple continuation in the elongator U34 modifications synthesis pathway, but rather highly regulated and sequence specific. The availability of sulfur amino acids, namely methionine and cysteine, tightly regulates the levels of mcm^5s^2U and its subsequent impact on codon decoding (Laxman et al. 2013). The 1C metabolism-sulfur availability-tRNA uridine thiolation pathway is thus intimately linked to provide metabolic cues to regulate or influence translation via substrate availability. Not only are mcm^5s^2U levels dependent on sulfur amino acids levels, but they also act as a sensor for amino acids availability. That is, cells deficient in mcm^5s^2U appear to be amino acid starved in the presence of abundant amino acids (Gupta et al. 2019).



Modification	tRNA
mcm^{5}U	Gly^{UCC} Arg^{UCU} Sec^{UCA}
mcm^{5}s^{2}U	Glu^{UUC} Lys^{UUU} Gln^{UUG}
ncm^{5}U	Ala^{UGC} Leu^{UAA} Pro^{UGG} Ser^{UGA} Thr^{UGU} Val^{UAC}

FIGURE 11 | tRNA thiolation and mcm^{5}s^{2}U modifications. (A) Synthetic pathway for mcm5s2u (Schäck et al. 2020). Created in BioRender. https://BioRender.com/j70a796. (B) tRNAs carrying modifications of this pathway at position 34. (C) Codon restriction by mcm5s2U. Created in BioRender. https://BioRender.com/x86z632. (D) Codon anticodon pairing of the 3 amino acids related to mcm^{5}s^{2}U. Note that for the synonymous codons (NAG), an anticodon is available for decoding. However, the wobble uridine can pair with the G in the third codon nucleotide (see Figure 3B). Thus, mcm^{5}s^{2}U restricts this pairing and restricts the codon decoding to NAA codons.

mcm^{5}s^{2}U, unlike other modifications discussed here, restricts codon decoding (Rapino et al. 2018, 2021). That is, mcm^{5}s^{2}U restricts the codon decoding of the UUN anticodons from NAA and NAG to NAA only (Figure 11C,D) (Rapino et al. 2018, 2021). mcm^{5}s^{2}U is essential for decoding NAA codons encoding for Glu, Gln, and Lys amino acids, and its loss, by editing elongator proteins or CTU1/2, leads to ribosome stalling at NAA codons, protein aggregation, and downregulation of proteins biased towards NAA codons via translational repression (Rapino et al. 2018, 2021). Evidence of the dispensability of mcm^{5}s^{2}U for NAG codons was shown in (Rapino et al. 2021), where mutating the coding sequence of KIFA4A, a gene enriched in NAA codons, to include NAG instead of NAA rescued its translational defects upon mcm^{5}s^{2}U depletion. mcm5s2U promotes the translation of proteins containing the hydrophilic amino acid motif [EKR]-[EKR]-[EKR]-R-[DEKR], and loss of mcm^{5}s^{2}U leads to aggregation of proteins enriched in this motif (Rapino et al. 2021). While the true nature of this link between mcm^{5}s^{2}U and hydrophilic amino acid motifs is not fully understood, it could be related to the dynamics of protein folding in the ribosome exit tunnel (Nilsson et al. 2015; Rapino et al. 2021). Glu (E), Gln (Q), and Lys (K) are all hydrophilic amino acids. Glu (E) and Lys (K) are clearly enriched in the [EKR]-[EKR]-[EKR]-R-[DEKR] motif. Thus, alterations in the decoding speed, or sudden enhanced translation of their NAG codons beyond the needed speed could, at least in theory, alter the dynamics of protein co-translational folding in the ribosome (Komar 2009; Nilsson et al. 2015; Wilson and Beckmann 2011). It is important to keep in mind that strategic pausing in translation is essential for proper protein folding, especially around difficult or complex structures in the protein (Komar 2009; Pechmann and Frydman 2013; Yu et al. 2015).

NAA codons, decoded by mcm^{5}s^{2}U, were shown to be enriched in specific genes and gene sets such as HIF1α, cell cycle-related genes, and specific protein families such as kinesins (Rapino et al. 2018, 2021). In addition, there is evidence of a sort of coupling between mTOR signaling and mcm^{5}s^{2}U presence in tRNA (Laxman et al. 2013; Leidel et al. 2009). Thus, mcm^{5}s^{2}U can act as a sensor for metabolic cues, and in tandem with other metabolic and growth pathways, to regulate cellular dynamics via fine-tuning mRNA translation. Dysregulation of mcm^{5}s^{2}U and the elongator-dependent tRNA modifications pathway was linked to various diseases. Apart from its established role in cancers such as melanoma (Rapino et al. 2018), mutations leading to loss of mcm^{5}s^{2}U were associated with bronchial asthma and neurodevelopmental and

neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) (Anderson et al. 2001; Bento-Abreu et al. 2018; Freeman et al. 2019; Hawer et al. 2018; Strug et al. 2009; Takeoka et al. 2001). Despite it being one of the most interesting tRNA modifications to study, our understanding of mcm^5s^2U remains incomplete, especially in the disease and tissue context as well as its links to metabolic diseases and sulfur metabolism disorders (Kožich and Stabler 2020).

4.4.3 | Mitochondrial tRNA Modifications and Taurine and Folate Metabolism

Taurine is a semi-essential amino acid characterized by an amine group and a sulfur group. It is vital for life, supporting multiple body systems, and has been identified as a key factor in aging and mitochondrial genetic disorders (Ohsawa et al. 2019; Singh et al. 2023; Sunada 2020; Yamori et al. 2010). Taurine is either dietary-derived or generated in the cells via the cysteine degradation pathway (Figure 10). Studies show that taurine levels in the blood decline with age, while supplementation has been demonstrated to extend both lifespan and health span in mice. Taurine has been found to reduce cellular senescence, protect against telomerase deficiency, suppress mitochondrial dysfunction, decrease DNA damage, and reduce inflammation (Singh et al. 2023). Experimental studies using genetic rat models highlight taurine's effectiveness in combating hypertension, stroke, and atherosclerosis. Additionally, higher urinary taurine levels are associated with lower cardiovascular disease (CVD) risk factors such as obesity, high blood pressure, and cholesterol. Taurine also helps mitigate fat deposition and liver damage in metabolic conditions (Yamori et al. 2010).

Taurine is essential for taurine methylation modifications of mitochondrial tRNAs (Asano et al. 2018; Sunada 2020). These modifications include tm^5U and tm^5s^2U, a thiolation-linked modification (Suzuki et al. 2020). tm^5U and tm^5s^2U are present at the wobble position of 5 mitochondrial tRNAs: Leu^{UUR}, Trp, Lys, Glu, and Gln (Matsumura et al. 2023; Suzuki et al. 2011b, 2020; Suzuki and Suzuki 2014). tm^5U is synthesized by the writers MTO and GTPBP3 using N5,N10-methylene THF and taurine as substrates for the reaction (Asano et al. 2018; Chen et al. 2016; Fakruddin et al. 2018; Kopajtich et al. 2014; Martinez-Zamora et al. 2015; Matsumura et al. 2023). tm^5U is further thiolated by MTU1 into tm^5s^2U using sulfur species generated by NFS1-mediated degradation of cysteine (Matsumura et al. 2023; Yan et al. 2006; Zhang et al. 2018) (Figure 12A).

This biosynthetic pathway shows the intimate link between taurine modifications and the mitochondrial folate cycle (Morscher et al. 2018). SHMT2, the mitochondrial analogue of SHMT, plays a crucial role in providing N5,N10-methylene THF via its catalytic activity (Morscher et al. 2018). N5,N10-methylene THF in turn provides the methyl donor needed for synthesizing tm^5U in the wobble position of mitochondrial tRNAs (Asano et al. 2018; Morscher et al. 2018). tm^5U and tm^5s^2U are essential for the accurate decoding of NNR codons (R = A or G, i.e., purines) and to prevent misreading of NNY codons (Y = U or C, i.e., pyrimidines) (Asano et al. 2018; Kirino et al. 2004; Suzuki et al. 2011b) (Figure 12B). tm^5U expands the codon decoding of mitochondrial anticodons via stabilizing the interaction between U and G by altering the classical U:G wobble geometry to that similar to Watson-Crick pairing, leading to better codon decoding (Kurata et al. 2008; Suzuki et al. 2011b). This codon expansion is essential for mitochondrial translation. In SHMT2-deficient human cells, for example, mitochondrial ribosome profiling reveals that the lack of this modification leads to disrupted translation, causing ribosome stalling at lysine (AAG) and leucine (UUG) codons (Morscher et al. 2018).

Folate itself is essential for mammalian development and proliferating tissues and its deficiency causes congenital heart defects, and impaired DNA synthesis and neural tube defects (NTDs), resulting in conditions ranging from anencephaly (incompatible with postnatal survival) to spina bifida, often associated with partial leg paralysis (Beaudin and Stover 2009; Copp et al. 2015; Hibbard 1964). Mitochondrial folate metabolism is essential for embryonic 1C unit metabolism, with deficiencies in enzymes like MTHFD1 causes embryonic lethality and severe NTDs (Momb et al. 2013; Narisawa et al. 2012). In children and adults, folate deficiency impacts hematopoiesis and immune function, leading to macrocytic anemia (Tandon et al. 2022). Folate deficiency might be contributing to these diseases via altering mitochondrial translation, not only via contributing to N-formylmethionine-tRNA-Met synthesis, but also via altering taurine modification levels (Asano et al. 2018; Minton et al. 2018; Morscher et al. 2018; Ormazabal et al. 2015).

Loss of taurine modifications leads to severe mitochondrial dysfunction and alteration of oxidative phosphorylation by interfering with the translation of mitochondrial DNA-encoded respiratory complex genes, leading to mistranslation, protein aggregation, and aberrant mitochondrial protein import (Asano et al. 2018; Chen et al. 2016; Fakruddin et al. 2018; Martinez-Zamora et al. 2015; Morscher et al. 2018). In zebrafish, loss of mitochondrial taurine modifications via enzymatic deletion leads to an array of aberrations, including defective embryonic development, hypertrophic cardiomyopathy, and hearing defects (Chen et al. 2016, 2019; Zhang et al. 2018).

In humans, mutations in mitochondrial tRNAs carrying taurine modifications or mutations in the writer enzymes can lead to an array of genetic diseases including MELAS syndrome (Mitochondrial encephalomyopathy lactic acidosis and stroke like episodes, mutations in mt-tRNA-Leu^{UUR} gene) (Homma et al. 2021; Kirino et al. 2004; Ohsawa et al. 2019; Sunada 2020), MERRF syndrome (myoclonic epilepsy with ragged red fibers, mutations in mt-tRNA-Lys genes) (Schaffer et al. 2014; Suzuki et al. 2011a), hypertrophic cardiomyopathy and lactic acidosis (mutations in MTO1 gene) (Baruffini et al. 2013), Hypertrophic cardiomyopathy and lactic acidosis and encephalopathy (mutations in GTPBP3 gene) (Kopajtich et al. 2014), and RILF (Reversible infantile liver failure, mutations in MTU1/TRMU gene) (Wu et al. 2016; Zeharia et al. 2009). These syndromes are all characterized by mitochondrial dysfunction due to translational defects leading to aberrant mitochondrial respiratory complex formation. Taurine deficiency itself can lead to symptoms resembling MELAS and MERRF due to mitochondrial dysfunction (Schaffer et al. 2014). In addition, taurine supplementation was shown to rescue the symptomatology of MELAS (Homma et al. 2021; Ohsawa et al. 2019; Schaffer et al. 2014;

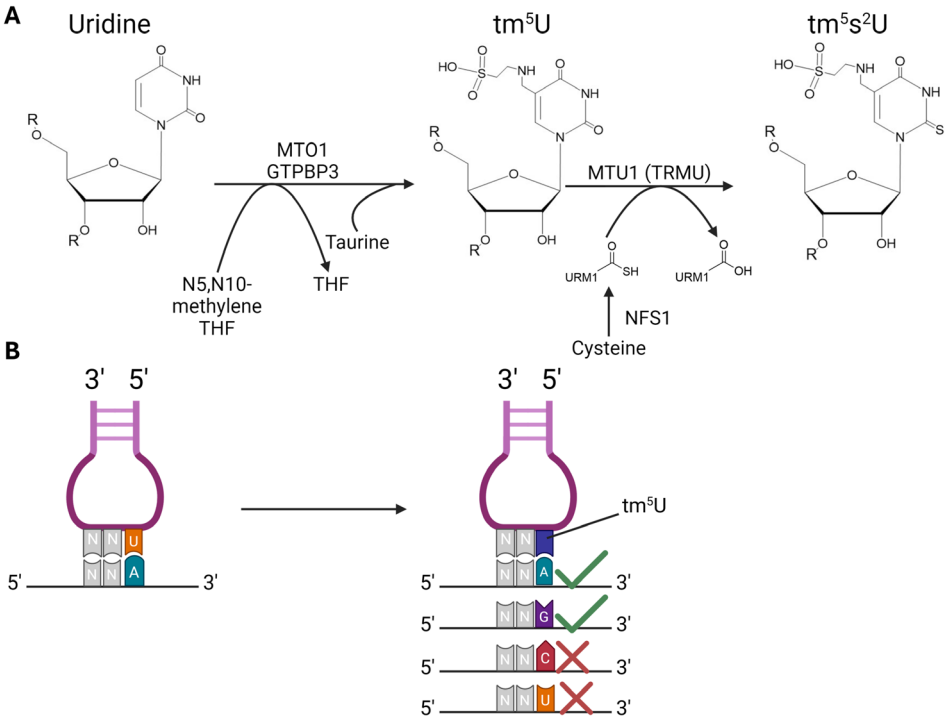


FIGURE 12 | Mitochondrial taurine-methylation modifications. (A) Biosynthetic pathway of mitochondrial taurine modifications. Created in BioRender. https://BioRender.com/z49j976. (B) tm^5U is essential for extending the codon decoding of UNN anticodons to NNA and NNG codons and restricts the pairing between UNN anticodons and NNC or NNU codons. Created in BioRender. https://BioRender.com/t33e443.

Sunada 2020), despite the core pathology being a mutation in the tRNA-Leu^{UUR} gene and not taurine deficiency.

Mutations in mt-tRNA-Leu^{UUR} genes that are attributed to MELAS have also been found to be associated with type 2 diabetes (T2D) (Kadowaki et al. 1994; Suzuki et al. 2003; Suzuki, Suzuki, et al. 1997). Mitochondrial dysfunction is one of the core pathophysiological processes in T2D, leading to high ROS generation and low ATP levels, and β-oxidation, and in turn, dysregulated bioenergetics homeostasis and insulin resistance (Kim et al. 2008; Lowell and Shulman 2005; Rovira-Llopis et al. 2017). Thus, dysfunctional mitochondrial translation could indeed lead to insulin resistance and T2D. Not surprisingly, taurine supplementation was shown to reduce glycaemic indices and improve insulin resistance as well as the risk for metabolic syndrome (Kim et al. 2012; Maleki et al. 2020; Moludi et al. 2022; Tao et al. 2022; Tzang et al. 2024). Folate was also shown to have benefits in T2D (Mokgalaboni et al. 2024; Zhao et al. 2018; Zhu et al. 2020). It is not unlikely that the effects of folate and taurine on T2D and metabolic syndrome could be linked to mitochondrial translation and function via tRNA taurine modifications. However, this is an area that is yet to be fully explored in taurine and folate biology and their links to T2D.

4.5 | N-Glycation and tRNA Modifications

A new addition to the ever-expanding repertoire of RNA modifications is the glycosylated tRNA modifications (Flynn et al. 2021; Suzuki et al. 2025; Xie et al. 2024; Zhao et al. 2023). We can divide this class into two subclasses, although this is mostly based on our current understanding and will likely change in the future. The first class is linked to Q modifications, discussed above, which includes manQ and galQ (Rashad 2024; Suzuki et al. 2025; Zhao et al. 2023). manQ and galQ are synthesized by QTMAN and QTGAL enzymes using UDP-mannose and UDP-galactose as sugar donors (Suzuki et al. 2025; Zhao et al. 2023). Both manQ (on tRNA-Asp) and galQ (on tRNA-Tyr) play roles in codon decoding and the expansion of their respective amino acids and in proteostasis. galQ is also essential to prevent stop codon readthrough (Zhao et al. 2023). manQ and galQ have been known to exist for years. However, their enzyme system has only been recently identified via seminal work by Zhao et al. (2023).

The second, and quite recently identified, class of glycosylated tRNA modifications refers to what is currently being called GlycoRNAs (Flynn et al. 2021). Seminal work from Flynn et al. reported the discovery of N-glycosylation of small RNAs and their representation on the cell surface (Flynn et al. 2021). Later work by Xie et al. (2024) identified the tRNA modifications, acp^3U, to be an attachment site for N-glycans. N-glycosylated small RNAs are represented on the cell surface and colocalize with lipid rafts (Flynn et al. 2021; Ma et al. 2024). GlycoRNAs are expected to play important roles, most importantly in cell–cell communication and immune modulation, akin to what is known about glycosylation in general (Reily et al. 2019). Indeed, GlycoRNAs were shown to suppress siglec receptors in vitro, which are important for natural killer (NK) cells' function (Flynn et al. 2021). They were also shown to regulate neutrophil recruitment and transmigration across endothelial cells (Zhang, Tang, et al. 2024).

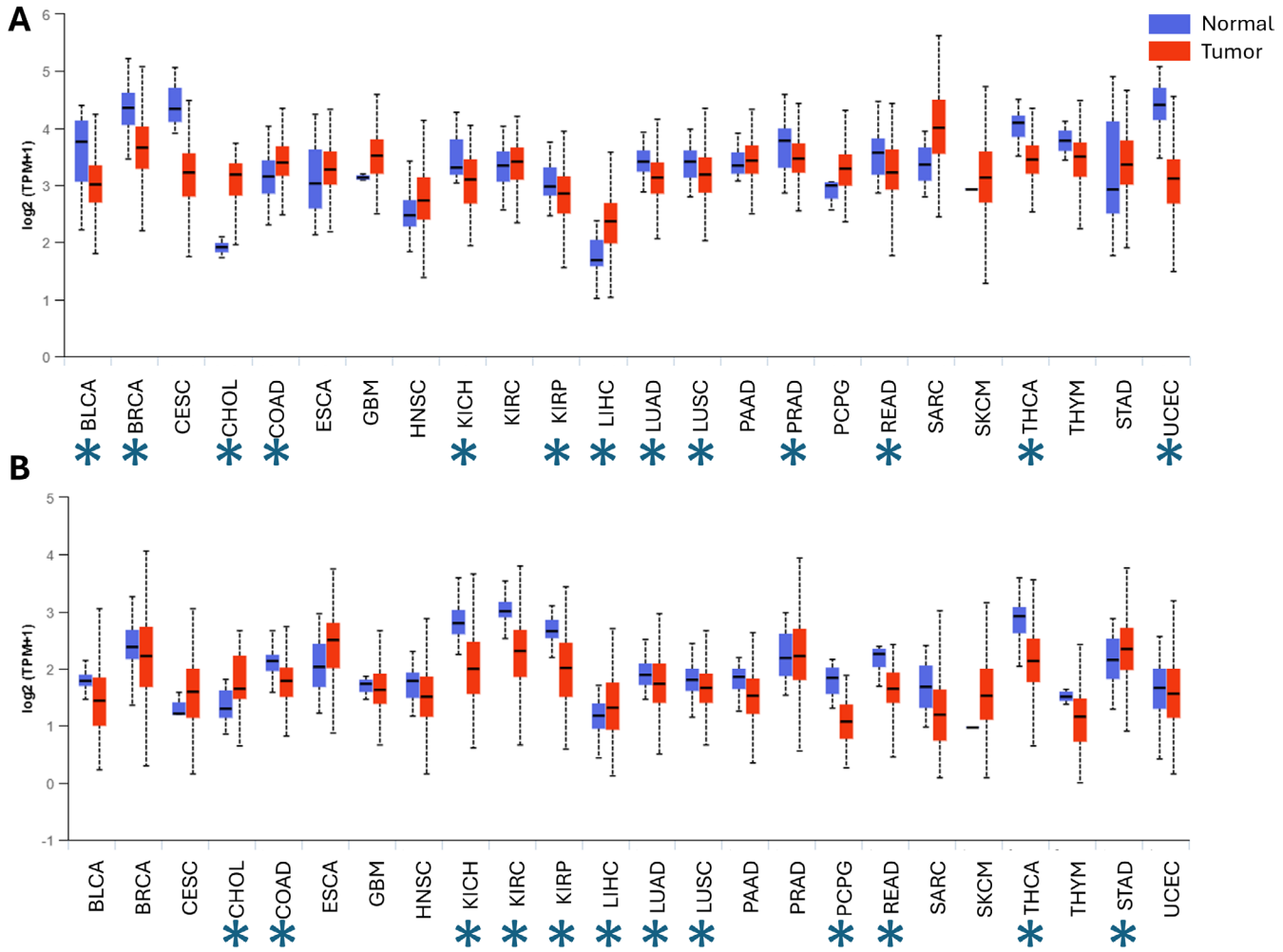


FIGURE 13 | Expression of DTWD1 (A) or DTWD2 (B) in cancers. Data from the cancer genome atlas database. Hash indicates statistical significance. Data from ULCAN: https://ualcan.path.uab.edu/index.html.

Nonetheless, the field of GlycoRNAs is still young, and the tools to study and detect GlycoRNAs are evolving (Kageler et al. 2024). In addition, acp^{3}U itself is one of the not-so-understood modifications at the molecular and disease relevance levels. Apart from its location in the D-arm of tRNA and its enzyme system (DTWD1 and DTWD2) (Takakura et al. 2019), it is not studied in diseases or in other conditions, beyond a few reports on the potential role of DTWD1 in cancer (Ma et al. 2015). acp^{3}U confers stability to tRNA and is essential for maintaining translation and cellular proliferation (Takakura et al. 2019). acp^{3}U is present in cytosolic but not mitochondrial tRNAs (Suzuki 2021; Suzuki et al. 2020; Takakura et al. 2019). One would expect that the links between GlycoRNAs and acp^{3}U would drive more research into its biological and disease relevance. Analysis of the cancer genome atlas data (TCGA) shows dysregulation of both DTWD1 and DTWD2 expression in multiple cancers (Figure 13). The expression, however, appears to be cancer and tissue specific. For example, the expression of DTWD1 and DTWD2 was lower in kidney cancer while it was higher in cholangiocarcinoma (Figure 13). This could allude to tissue, cell, or cancer-specific regulatory processes. Nonetheless, the gene expression of a given enzyme system does not equal changes in the corresponding tRNA modifications all the time, as the regulation of tRNA modifications is more complex and nuanced (Rashad 2024). Thus, studying the enzymes and the modification levels in cancers is important to fully elucidate their roles. In addition to these challenges, the enzymatic systems responsible for N-glycosylation of acp^{3}U modified RNAs remain to be discovered. Further, whether the N-glycosylation occurs on mature tRNAs first, then these tRNAs are further processed to tDRs, or whether the N-glycosylation occurs on tDRs carrying acp^{3}U remains to be elucidated. Such nuances are critical in understanding the biogenesis and functions of GlycoRNAs (Figure 14).

While there are still many unanswered questions regarding GlycoRNAs and acp^{3}U functions, the field of glycobiology could give us clues as to how we should direct the research in this area in the future (He, Zhou, et al. 2024; Reily et al. 2019). There are several types of glycosylated proteins and lipids in human cells, whose complex mechanisms of synthesis and regulation are beyond the scope of this review (Reily et al. 2019). The main types are N-glycosylated proteins, O-glycosylated proteins, glycosphingolipids (GSLs), proteoglycans, and glycosaminoglycans (Reily et al. 2019). Glycosylation regulates diverse processes such

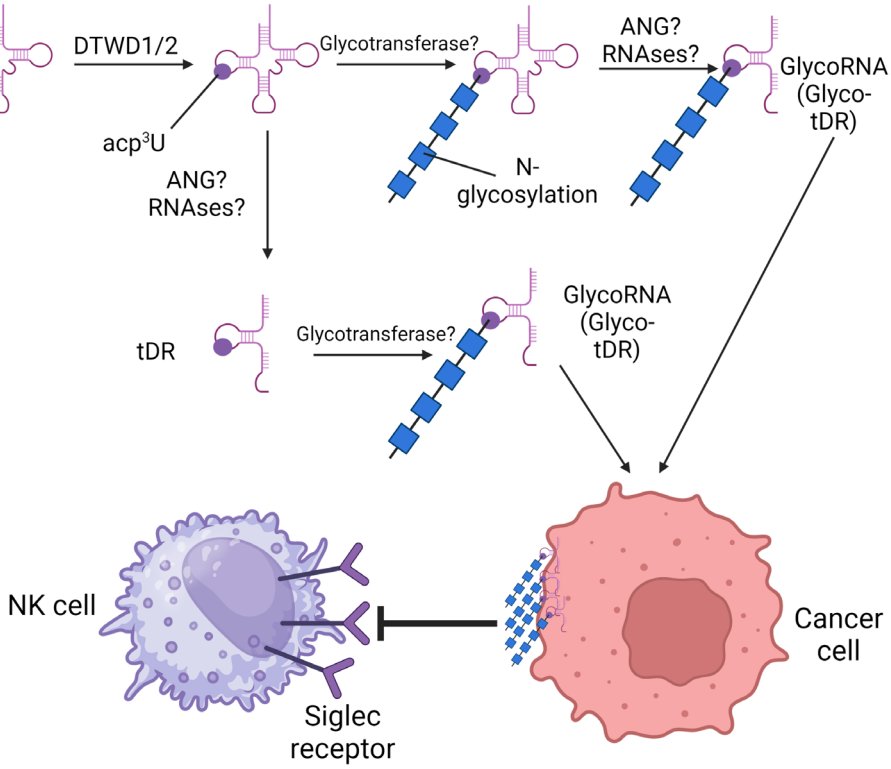


FIGURE 14 | A hypothesized model for GlycoRNAs biogenesis and function. DTWD1/2 synthesize acp^{3}U in the D-arm of mature tRNAs at position 20. Further N-glycosylation of acp^{3}U is mediated via a yet-to-be-identified glycotransferase enzyme system. Mature tRNAs are processed into N-glycated tDRs forming part (or all?) of the GlycoRNAs pool. Alternatively, mature tRNAs can be processed to tDRs, which are then glycosylated. GlycoRNAs are expressed on the cell surface of cancer cells and allow them to evade immune surveillance and targeting by suppressing siglec receptors on natural killer (NK) cells. Created in BioRender. Rashad (2024) Created in BioRender. https://BioRender.com/z88v875.

as regulating protein stability and folding, phase separation, regulation of cell adhesion, immune modulation, and signal transduction (He, Zhou, et al. 2024). Dysregulation of glycosylation is associated with many diseases, including congenital disorders of glycosylation, autoimmune diseases and chronic inflammation, diabetes, neurodegenerative diseases, and a wide variety of cancers (He, Zhou, et al. 2024; Reily et al. 2019). Indeed, changes in the diet, such as high-fat diet, can alter glycosylation patterns, and in turn impact cellular processes in many organs and cells (Mastrodonato et al. 2020; Paton et al. 2023). Thus, it is not unlikely that GlycoRNAs would also be sensitive to dietary changes and metabolic aberrations.

Given that dysregulation of the tRNA epitranscriptome is known to occur in many of these conditions, such as mutations of the CDKAL1 gene in diabetes leading to the loss of ms^{2}t^{6}A modification (Santos et al. 2020; Steinthorsdottir et al. 2007; Wei et al. 2011) or the dysregulation of tRNA modifications in many cancers (Dedon and Begley 2022), it seems likely that GlycoRNAs could also play roles in these glycation disorders. However, many challenges remain. Identifying the pathways and proteins responsible for GlycoRNAs synthesis, and whether they are RNA sequence specific or not, is an important problem to tackle. Characterizing the role of GlycoRNAs in the cells, and whether they play roles inside the cell in translation or only at the cell membrane, is another important one. These challenges, questions, and many more, are expected to be tackled in the coming years, along with efforts to understand the pathophysiologic roles of GlycoRNAs.

5 | Conclusion

The relation between tRNA and metabolism is complex and bidirectional. The tRNA epitranscriptome can influence metabolism by regulating mRNA translation. While metabolism can influence the tRNA epitranscriptome by providing substrates for the synthesis of tRNA modifications, or via mTOR-mediated tRNA transcription. In addition, both tRNA and metabolism are regulated by macro and micronutrient content of the diet. As highlighted in this review, there are several key areas that are understudied that require special attention to fully grasp the extent of this metabolic-tRNA-translation axis. How 1C metabolism influences tRNA modification levels, while studied, is not fully explored and requires more attention. GlycoRNA biology is an emerging and promising area that could link the tRNA epitranscriptome to a variety of non-canonical functions outside the scope of mRNA translation. Nonetheless, a huge amount of work is needed to fully resolve many of the questions around GlycoRNA biosynthesis and functions. It is also important to highlight that most studies on tRNA modifications were done in prokaryotes, yeast, or using cell lines. These models, while important from the standpoint of biochemical and molecular understanding of tRNA modifications and their role in codon decoding, are unable to recapitulate the complex 3D biology that occurs in the tissues. Cell lines commonly used are also not quite representative of primary cells, which is of concern when one studies physiology or pathology. Importantly, cellular metabolism in the context of a tissue is drastically different from when the same cell is cultured in a dish. Thus, more attention should

be given to studying various tRNA modifications in cell, tissue, and organ contexts. Understanding metabolic cues that impact cells in the complex environment of multicellular organisms is of utmost importance to fully comprehend the metabolism-tRNA-translation axis.

Author Contributions

Sherif Rashad: conceptualization (lead), data curation (lead), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (lead), project administration (lead), visualization (lead), writing – original draft (lead), writing – review and editing (equal). **Aseel Marahleh:** data curation (supporting), formal analysis (equal), funding acquisition (equal), investigation (equal), methodology (supporting), project administration (supporting), visualization (supporting), writing – original draft (supporting), writing – review and editing (equal).

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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References

Achour, C., and S. Oberdoerffer. 2024. "NAT10 and Cytidine Acetylation in mRNA: Intersecting Paths in Development and Disease." *Current Opinion in Genetics & Development* 87: 102207. https://doi.org/10.1016/j.gde.2024.102207.

Akiyama, N., K. Ishiguro, T. Yokoyama, et al. 2024. "Structural Insights Into the Decoding Capability of Isoleucine tRNAs With Lysidine and Agmatidine." *Nature Structural & Molecular Biology* 31, no. 5: 817–825. https://doi.org/10.1038/s41594-024-01238-1.

Akram, M. 2014. "Citric Acid Cycle and Role of Its Intermediates in Metabolism." *Cell Biochemistry and Biophysics* 68, no. 3: 475–478. https://doi.org/10.1007/s12013-013-9750-1.

Alberts, B., R. Heald, A. Johnson, et al. 2022. *Molecular Biology of the Cell*. 7th ed. W. W. Norton & Company.

Anderson, S. L., R. Coli, I. W. Daly, et al. 2001. "Familial Dysautonomia Is Caused by Mutations of the IKAP Gene." *American Journal of Human Genetics* 68, no. 3: 753–758. https://doi.org/10.1086/318808.

Ando, D., S. Rashad, T. J. Begley, et al. 2025. "Decoding Codon Bias: The Role of tRNA Modifications in Tissue-Specific Translation." *International Journal of Molecular Sciences* 26, no. 2: 706.

Arango, D., D. Sturgill, N. Alhusaini, et al. 2018. "Acetylation of Cytidine in mRNA Promotes Translation Efficiency." *Cell* 175, no. 7: 1872–1886.e1824. https://doi.org/10.1016/j.cell.2018.10.030.

Arango, D., D. Sturgill, R. Yang, et al. 2022. "Direct Epitranscriptomic Regulation of Mammalian Translation Initiation Through N4-Acetylcytidine." *Molecular Cell* 82, no. 15: 2797–2814. https://doi.org/10.1016/j.molcel.2022.05.016.

Arimbasseri, A. G., and R. J. Maraia. 2016. "RNA Polymerase III Advances: Structural and tRNA Functional Views." *Trends in Biochemical Sciences* 41, no. 6: 546–559. https://doi.org/10.1016/j.tibs.2016.03.003.

Arnold, P. K., B. T. Jackson, K. I. Paras, et al. 2022. "A Non-Canonical Tricarboxylic Acid Cycle Underlies Cellular Identity." *Nature* 603, no. 7901: 477–481. https://doi.org/10.1038/s41586-022-04475-w.

Arragain, S., S. K. Handelman, F. Forouhar, et al. 2010. "Identification of Eukaryotic and Prokaryotic Methylthiotransferase for Biosynthesis of 2-Methylthio-N6-Threonylcarbamoyladenosine in tRNA." *Journal of Biological Chemistry* 285, no. 37: 28425–28433. https://doi.org/10.1074/jbc.M110.106831.

Arrondel, C., S. Missoury, R. Snoek, et al. 2019. "Defects in t6A tRNA Modification due to GON7 and YRDC Mutations Lead to Galloway-Mowat Syndrome." *Nature Communications* 10, no. 1: 3967. https://doi.org/10.1038/s41467-019-11951-x.

Asano, K., T. Suzuki, A. Saito, et al. 2018. "Metabolic and Chemical Regulation of tRNA Modification Associated With Taurine Deficiency and Human Disease." *Nucleic Acids Research* 46, no. 4: 1565–1583. https://doi.org/10.1093/nar/gky068.

Ban, H., K. Shigemitsu, T. Yamatsuji, et al. 2004. "Arginine and Leucine Regulate p70 S6 Kinase and 4E-BP1 in Intestinal Epithelial Cells." *International Journal of Molecular Medicine* 13, no. 4: 537–543. https://doi.org/10.3892/ijmm.13.4.537.

Baruffini, E., C. Dallabona, F. Invernizzi, et al. 2013. "MTO1 Mutations Are Associated With Hypertrophic Cardiomyopathy and Lactic Acidosis and Cause Respiratory Chain Deficiency in Humans and Yeast." *Human Mutation* 34, no. 11: 1501–1509. https://doi.org/10.1002/humu.22393.

Beaudin, A. E., and P. J. Stover. 2009. "Insights Into Metabolic Mechanisms Underlying Folate-Responsive Neural Tube Defects: A Minireview." *Birth Defects Research. Part A, Clinical and Molecular Teratology* 85, no. 4: 274–284. https://doi.org/10.1002/bdra.20553.

Bento-Abreu, A., G. Jager, B. Swinnen, et al. 2018. "Elongator Subunit 3 (ELP3) Modifies ALS Through tRNA Modification." *Human Molecular Genetics* 27, no. 7: 1276–1289. https://doi.org/10.1093/hmg/ddy043.

Bhattacharyya, S., and U. Varshney. 2016. "Evolution of Initiator tRNAs and Selection of Methionine as the Initiating Amino Acid." *RNA Biology* 13, no. 9: 810–819. https://doi.org/10.1080/15476286.2016.1195943.

Biffo, S., D. Ruggero, and M. M. Santoro. 2024. "The Crosstalk Between Metabolism and Translation." *Cell Metabolism* 36, no. 9: 1945–1962. https://doi.org/10.1016/j.cmet.2024.07.022.

Boland, C., P. Hayes, I. Santa-Maria, S. Nishimura, and V. P. Kelly. 2009. "Queuosine Formation in Eukaryotic tRNA Occurs via a Mitochondria-Localized Heteromeric Transglycosylase." *Journal of Biological Chemistry* 284, no. 27: 18218–18227. https://doi.org/10.1074/jbc.M109.002477.

Braun, D. A., J. Rao, G. Mollet, et al. 2017. "Mutations in KEOPS-Complex Genes Cause Nephrotic Syndrome With Primary Microcephaly." *Nature Genetics* 49, no. 10: 1529–1538. https://doi.org/10.1038/ng.3933.

Broly, M., B. V. Polevoda, K. M. Awayda, et al. 2022. "THUMPD1 Bi-Allelic Variants Cause Loss of tRNA Acetylation and a Syndromic Neurodevelopmental Disorder." *American Journal of Human Genetics* 109, no. 4: 587–600. https://doi.org/10.1016/j.ajhg.2022.02.001.

Camiolo, S., L. Farina, and A. Porceddu. 2012. "The Relation of Codon Bias to Tissue-Specific Gene Expression in *Arabidopsis thaliana*." *Genetics* 192, no. 2: 641–649. https://doi.org/10.1534/genetics.112.143677.

Catania, C., E. Binder, and D. Cota. 2011. "mTORC1 Signaling in Energy Balance and Metabolic Disease." *International Journal of Obesity* 35, no. 6: 751–761. https://doi.org/10.1038/ijo.2010.208.

Chen, D., F. Li, Q. Yang, et al. 2016. "The Defective Expression of gtpbp3 Related to tRNA Modification Alters the Mitochondrial Function and Development of Zebrafish." *International Journal of Biochemistry & Cell Biology* 77, no. Pt A: 1–9. https://doi.org/10.1016/j.biocel.2016.05.012.

Chen, D., Z. Zhang, C. Chen, et al. 2019. "Deletion of Gtpbp3 in Zebrafish Revealed the Hypertrophic Cardiomyopathy Manifested by Aberrant Mitochondrial tRNA Metabolism." *Nucleic Acids Research* 47, no. 10: 5341–5355. https://doi.org/10.1093/nar/gkz218.

Chen, Y., Z. Shao, and S. Wu. 2025. "Research Progress on the tsRNA Biogenesis, Function, and Application in Lung Cancer." *Noncoding RNA Research* 10: 63–69. https://doi.org/10.1016/j.ncrna.2024.09.004.

Chiang, P. K., R. K. Gordon, J. Tal, et al. 1996. "S-Adenosylmethionine and Methylation." *FASEB Journal* 10, no. 4: 471–480.

Chionh, Y. H., M. McBee, I. R. Babu, et al. 2016. "tRNA-Mediated Codon-Biased Translation in Mycobacterial Hypoxic Persistence." *Nature Communications* 7, no. 1: 13302. https://doi.org/10.1038/ncomms13302.

Chowdhury, M. M., C. Dosche, H. G. Löhmannsröben, and S. Leimkühler. 2012. "Dual Role of the Molybdenum Cofactor Biosynthesis Protein MOCS3 in tRNA Thiolation and Molybdenum Cofactor Biosynthesis in Humans." *Journal of Biological Chemistry* 287, no. 21: 17297–17307. https://doi.org/10.1074/jbc.M112.351429.

Cirzi, C., J. Dyckow, C. Legrand, et al. 2023. "Queuosine-tRNA Promotes Sex-Dependent Learning and Memory Formation by Maintaining Codon-Biased Translation Elongation Speed." *EMBO Journal* 42, no. 19: e112507. https://doi.org/10.15252/embj.2022112507.

Copp, A. J., N. S. Adzick, L. S. Chitty, J. M. Fletcher, G. N. Holmbeck, and G. M. Shaw. 2015. "Spina Bifida." *Nature Reviews. Disease Primers* 1, no. 1: 15007. https://doi.org/10.1038/nrdp.2015.7.

Corona-Trejo, A., M. E. Gonsebatt, C. Trejo-Solis, et al. 2023. "Transsulfuration Pathway: A Targeting Neuromodulator in Parkinson's Disease." *Reviews in the Neurosciences* 34, no. 8: 915–932. https://doi.org/10.1515/revneuro-2023-0039.

Costa-Mattioli, M., and P. Walter. 2020. "The Integrated Stress Response: From Mechanism to Disease." *Science* 368, no. 6489: eaat5314. https://doi.org/10.1126/science.aat5314.

Cui, J., E. Sendinc, Q. Liu, S. Kim, J. Y. Fang, and R. I. Gregory. 2024. "M(3)C32 tRNA Modification Controls Serine Codon-Biased mRNA Translation, Cell Cycle, and DNA-Damage Response." *Nature Communications* 15, no. 1: 5775. https://doi.org/10.1038/s41467-024-50161-y.

Danchin, A., A. Sekowska, and C. You. 2020. "One-Carbon Metabolism, Folate, Zinc and Translation." *Microbial Biotechnology* 13, no. 4: 899–925. https://doi.org/10.1111/1751-7915.13550.

Darst, B. F., R. L. Koscik, K. J. Hogan, S. C. Johnson, and C. D. Engelman. 2019. "Longitudinal Plasma Metabolomics of Aging and Sex." *Aging (Albany NY)* 11, no. 4: 1262–1282. https://doi.org/10.18632/aging.101837.

de Crécy-Lagard, V., G. Hutinet, J. D. D. Cediel-Becerra, et al. 2024. "Biosynthesis and Function of 7-Deazaguanine Derivatives in Bacteria and Phages." *Microbiology and Molecular Biology Reviews* 88, no. 1: e0019923. https://doi.org/10.1128/mmbr.00199-23.

Dedon, P. C., and T. J. Begley. 2022. "Dysfunctional tRNA Reprogramming and Codon-Biased Translation in Cancer." *Trends in Molecular Medicine* 28, no. 11: 964–978. https://doi.org/10.1016/j.molmed.2022.09.007.

Delaunay, S., M. Helm, and M. Frye. 2024. "RNA Modifications in Physiology and Disease: Towards Clinical Applications." *Nature Reviews. Genetics* 25, no. 2: 104–122. https://doi.org/10.1038/s41576-023-00645-2.

Delaunay, S., G. Pascual, B. Feng, et al. 2022. "Mitochondrial RNA Modifications Shape Metabolic Plasticity in Metastasis." *Nature* 607, no. 7919: 593–603. https://doi.org/10.1038/s41586-022-04898-5.

Dittmar, K. A., M. A. Sørensen, J. Elf, M. Ehrenberg, and T. Pan. 2005. "Selective Charging of tRNA Isoacceptors Induced by Amino-Acid Starvation." *EMBO Reports* 6, no. 2: 151–157. https://doi.org/10.1038/sj.embor.7400341.

Dixit, S., A. C. Kessler, J. Henderson, et al. 2021. "Dynamic Queuosine Changes in tRNA Couple Nutrient Levels to Codon Choice in Trypanosoma Brucei." *Nucleic Acids Research* 49, no. 22: 12986–12999. https://doi.org/10.1093/nar/gkab1204.

dos Reis, M., R. Savva, and L. Wernisch. 2004. "Solving the Riddle of Codon Usage Preferences: A Test for Translational Selection." *Nucleic Acids Research* 32, no. 17: 5036–5044. https://doi.org/10.1093/nar/gkh834.

Dowling, R. J., I. Topisirovic, B. D. Fonseca, and N. Sonenberg. 2010. "Dissecting the Role of mTOR: Lessons From mTOR Inhibitors." *Biochimica et Biophysica Acta* 1804, no. 3: 433–439. https://doi.org/10.1016/j.bbapap.2009.12.001.

Ducker, G. S., and J. D. Rabinowitz. 2017. "One-Carbon Metabolism in Health and Disease." *Cell Metabolism* 25, no. 1: 27–42. https://doi.org/10.1016/j.cmet.2016.08.009.

Edvardson, S., L. Prunetti, A. Arraf, et al. 2017. "tRNA N6-Adenosine Threonylcarbamoyltransferase Defect due to KAE1/TCS3 (OSGEP) Mutation Manifest by Neurodegeneration and Renal Tubulopathy." *European Journal of Human Genetics* 25, no. 5: 545–551. https://doi.org/10.1038/ejhg.2017.30.

El-Hachem, N., M. Leclercq, M. Susaeta Ruiz, et al. 2024. "Valine Aminoacyl-tRNA Synthetase Promotes Therapy Resistance in Melanoma." *Nature Cell Biology* 26, no. 7: 1154–1164. https://doi.org/10.1038/s41556-024-01439-2.

Emara, M. M., P. Ivanov, T. Hickman, et al. 2010. "Angiogenin-Induced tRNA-Derived Stress-Induced RNAs Promote Stress-Induced Stress Granule Assembly." *Journal of Biological Chemistry* 285, no. 14: 10959–10968. https://doi.org/10.1074/jbc.M109.077560.

Fakruddin, M., F. Y. Wei, T. Suzuki, et al. 2018. "Defective Mitochondrial tRNA Taurine Modification Activates Global Proteostress and Leads to Mitochondrial Disease." *Cell Reports* 22, no. 2: 482–496. https://doi.org/10.1016/j.celrep.2017.12.051.

Fergus, C., M. Al-Qasem, M. Cotter, et al. 2021. "The Human tRNA-Guanine Transglycosylase Displays Promiscuous Nucleobase Preference but Strict tRNA Specificity." *Nucleic Acids Research* 49, no. 9: 4877–4890. https://doi.org/10.1093/nar/gkab289.

Fergus, C., D. Barnes, M. A. Alqasem, and V. P. Kelly. 2015. "The Queuine Micronutrient: Charting a Course From Microbe to Man." *Nutrients* 7, no. 4: 2897–2929. https://doi.org/10.3390/nu7042897.

Filbeck, S., F. Cerullo, S. Pfeffer, and C. A. P. Joazeiro. 2022. "Ribosome-Associated Quality-Control Mechanisms From Bacteria to Humans." *Molecular Cell* 82, no. 8: 1451–1466. https://doi.org/10.1016/j.molcel.2022.03.038.

Fischer, T. R., L. Meidner, M. Schwickert, et al. 2022. "Chemical Biology and Medicinal Chemistry of RNA Methyltransferases." *Nucleic Acids Research* 50, no. 8: 4216–4245. https://doi.org/10.1093/nar/gkac224.

Flores, J. V., L. Cordero-Espinoza, F. Oeztuerk-Winder, et al. 2017. "Cytosine-5 RNA Methylation Regulates Neural Stem Cell Differentiation and Motility." *Stem Cell Reports* 8, no. 1: 112–124. https://doi.org/10.1016/j.stemcr.2016.11.014.

Flynn, R. A., K. Pedram, S. A. Malaker, et al. 2021. "Small RNAs Are Modified With N-Glycans and Displayed on the Surface of Living Cells." *Cell* 184, no. 12: 3109–3124. https://doi.org/10.1016/j.cell.2021.04.023.

Fox, J., and P. Stover. 2008. "Chapter 1: Folate-Mediated One-Carbon Metabolism." In *Vitamins & Hormones*, vol. 79, 1–44. Academic Press.

Freeman, S., S. Mateo Sánchez, R. Pouyo, et al. 2019. "Proteostasis Is Essential During Cochlear Development for Neuron Survival and Hair

Cell Polarity." *EMBO Reports* 20, no. 9: e47097. https://doi.org/10.15252/embr.201847097.

Fukumoto, K., K. Ito, B. Saer, et al. 2022. "Excess S-Adenosylmethionine Inhibits Methylation via Catabolism to Adenine." *Communications Biology* 5, no. 1: 313. https://doi.org/10.1038/s42003-022-03280-5.

Furukawa, K., N. Mizushima, T. Noda, and Y. Ohsumi. 2000. "A Protein Conjugation System in Yeast With Homology to Biosynthetic Enzyme Reaction of Prokaryotes." *Journal of Biological Chemistry* 275, no. 11: 7462–7465. https://doi.org/10.1074/jbc.275.11.7462.

Gao, L., A. Behrens, G. Rodschinka, et al. 2024. "Selective Gene Expression Maintains Human tRNA Anticodon Pools During Differentiation." *Nature Cell Biology* 26, no. 1: 100–112. https://doi.org/10.1038/s41556-023-01317-3.

Garrow, T. A., A. A. Brenner, V. M. Whitehead, et al. 1993. "Cloning of Human cDNAs Encoding Mitochondrial and Cytosolic Serine Hydroxymethyltransferases and Chromosomal Localization." *Journal of Biological Chemistry* 268, no. 16: 11910–11916.

Ge, M. K., C. Zhang, N. Zhang, et al. 2023. "The tRNA-GCN2-FBXO22-Axis-Mediated mTOR Ubiquitination Senses Amino Acid Insufficiency." *Cell Metabolism* 35, no. 12: 2216–2230. https://doi.org/10.1016/j.cmet.2023.10.016.

Giegé, R., and G. Eriani. 2023. "The tRNA Identity Landscape for Aminoacylation and Beyond." *Nucleic Acids Research* 51, no. 4: 1528–1570. https://doi.org/10.1093/nar/gkad007.

Giguère, S., X. Wang, S. Huber, et al. 2024. "Antibody Production Relies on the tRNA Inosine Wobble Modification to Meet Biased Codon Demand." *Science* 383, no. 6679: 205–211. https://doi.org/10.1126/science.adi1763.

Gong, S., H. Qiao, J. Y. Wang, et al. 2024. "Ac4C Modification of lncRNA SIMALR Promotes Nasopharyngeal Carcinoma Progression Through Activating eEF1A2 to Facilitate ITGB4/ITGA6 Translation." *Oncogene* 43, no. 38: 2868–2884. https://doi.org/10.1038/s41388-024-03133-x.

González, I. M., P. M. Martin, C. Burdsal, et al. 2012. "Leucine and Arginine Regulate Trophoblast Motility Through mTOR-Dependent and Independent Pathways in the Preimplantation Mouse Embryo." *Developmental Biology* 361, no. 2: 286–300. https://doi.org/10.1016/j.ydbio.2011.10.021.

Goodarzi, H., X. Liu, H. C. Nguyen, S. Zhang, L. Fish, and S. F. Tavazoie. 2015. "Endogenous tRNA-Derived Fragments Suppress Breast Cancer Progression via YBX1 Displacement." *Cell* 161, no. 4: 790–802. https://doi.org/10.1016/j.cell.2015.02.053.

Goodarzi, H., H. C. B. Nguyen, S. Zhang, B. D. Dill, H. Molina, and S. F. Tavazoie. 2016. "Modulated Expression of Specific tRNAs Drives Gene Expression and Cancer Progression." *Cell* 165, no. 6: 1416–1427. https://doi.org/10.1016/j.cell.2016.05.046.

Guertin, D. A., and K. E. Wellen. 2023. "Acetyl-CoA Metabolism in Cancer." *Nature Reviews. Cancer* 23, no. 3: 156–172. https://doi.org/10.1038/s41568-022-00543-5.

Guillon, J., H. Coquelet, G. Leman, et al. 2021. "tRNA Biogenesis and Specific Aminoacyl-tRNA Synthetases Regulate Senescence Stability Under the Control of mTOR." *PLoS Genetics* 17, no. 12: e1009953. https://doi.org/10.1371/journal.pgen.1009953.

Guo, J., P. Zhu, Z. Ye, et al. 2021. "YRDC Mediates the Resistance of Lenvatinib in Hepatocarcinoma Cells via Modulating the Translation of KRAS." *Frontiers in Pharmacology* 12: 744578. https://doi.org/10.3389/fphar.2021.744578.

Guo, Y., T. Guan, K. Shafiq, et al. 2023. "Mitochondrial Dysfunction in Aging." *Ageing Research Reviews* 88: 101955. https://doi.org/10.1016/j.arr.2023.101955.

Gupta, R., A. S. Walvekar, S. Liang, Z. Rashida, P. Shah, and S. Laxman. 2019. "A tRNA Modification Balances Carbon and Nitrogen Metabolism by Regulating Phosphate Homeostasis." *eLife* 1, no. 8: e44795. https://doi.org/10.7554/eLife.44795.

Haag, S., K. E. Sloan, N. Ranjan, et al. 2016. "NSUN3 and ABH1 Modify the Wobble Position of Mt-tRNAMet to Expand Codon Recognition in Mitochondrial Translation." *EMBO Journal* 35, no. 19: 2104–2119. https://doi.org/10.15252/embj.201694885.

Han, J. M., S. J. Jeong, M. C. Park, et al. 2012. "Leucyl-tRNA Synthetase Is an Intracellular Leucine Sensor for the mTORC1-Signaling Pathway." *Cell* 149, no. 2: 410–424. https://doi.org/10.1016/j.cell.2012.02.044.

Hara, K., K. Yonezawa, Q. P. Weng, M. T. Kozlowski, C. Belham, and J. Avruch. 1998. "Amino Acid Sufficiency and mTOR Regulate p70 S6 Kinase and eIF-4E BP1 Through a Common Effector Mechanism." *Journal of Biological Chemistry* 273, no. 23: 14484–14494. https://doi.org/10.1074/jbc.273.23.14484.

Hawer, H., A. Hammermeister, K. E. Ravichandran, S. Glatt, R. Schaffrath, and R. Klassen. 2018. "Roles of Elongator Dependent tRNA Modification Pathways in Neurodegeneration and Cancer." *Genes* 10, no. 1: 19. https://doi.org/10.3390/genes10010019.

Hayes, P., C. Fergus, M. Ghanim, et al. 2020. "Queuine Micronutrient Deficiency Promotes Warburg Metabolism and Reversal of the Mitochondrial ATP Synthase in Hela Cells." *Nutrients* 12, no. 3: 871. https://doi.org/10.3390/nu12030871.

Hayne, C. K., T. A. Lewis, and R. E. Stanley. 2022. "Recent Insights Into the Structure, Function, and Regulation of the Eukaryotic Transfer RNA Splicing Endonuclease Complex." *Wiley Interdisciplinary Reviews: RNA* 13, no. 5: e1717. https://doi.org/10.1002/wrna.1717.

He, H., Y. Wang, X. Zhang, et al. 2024 "Age-Related Noncanonical TRMT6-TRMT61A Signaling Impairs Hematopoietic Stem Cells." *Nature Aging* 4, no. 2: 213–230. https://doi.org/10.1038/s43587-023-00556-1.

He, M., X. Zhou, and X. Wang. 2024. "Glycosylation: Mechanisms, Biological Functions and Clinical Implications." *Signal Transduction and Targeted Therapy* 9, no. 1: 194. https://doi.org/10.1038/s41392-024-01886-1.

Hibbard, B. M. 1964. "The Role of Folic Acid in Pregnancy; With Particular Reference to Anaemia, Abruption and Abortion." *Journal of Obstetrics and Gynaecology of the British Commonwealth* 71: 529–542. https://doi.org/10.1111/j.1471-0528.1964.tb04317.x.

Holmes, A. D., P. P. Chan, Q. Chen, et al. 2023. "A Standardized Ontology for Naming tRNA-Derived RNAs Based on Molecular Origin." *Nature Methods* 20, no. 5: 627–628. https://doi.org/10.1038/s41592-023-01813-2.

Homma, K., E. Toda, H. Osada, et al. 2021. "Taurine Rescues Mitochondria-Related Metabolic Impairments in the Patient-Derived Induced Pluripotent Stem Cells and Epithelial-Mesenchymal Transition in the Retinal Pigment Epithelium." *Redox Biology* 41: 101921. https://doi.org/10.1016/j.redox.2021.101921.

Hu, J. F., D. Yim, D. Ma, et al. 2021. "Quantitative Mapping of the Cellular Small RNA Landscape With AQRNA-Seq." *Nature Biotechnology* 39, no. 8: 978–988. https://doi.org/10.1038/s41587-021-00874-y.

Hu, Z., Y. Lu, J. Cao, et al. 2024. "N-Acetyltransferase NAT10 Controls Cell Fates via Connecting mRNA Cytidine Acetylation to Chromatin Signaling." *Science Advances* 10, no. 2: eadh9871. https://doi.org/10.1126/sciadv.adh9871.

Huber, S. M., U. Begley, A. Sarkar, et al. 2022. "Arsenite Toxicity Is Regulated by Queuine Availability and Oxidation-Induced Reprogramming of the Human tRNA Epitranscriptome." *Proceedings of the National Academy of Sciences of the United States of America* 119, no. 38: e2123529119. https://doi.org/10.1073/pnas.2123529119.

Ikeuchi, Y., K. Kitahara, and T. Suzuki. 2008. "The RNA Acetyltransferase Driven by ATP Hydrolysis Synthesizes N4-Acetylcytidine of tRNA Anticodon." *EMBO Journal* 27, no. 16: 2194–2203. https://doi.org/10.1038/emboj.2008.154.

Ishimura, R., G. Nagy, I. Dotu, et al. 2014. "RNA Function. Ribosome Stalling Induced by Mutation of a CNS-Specific tRNA Causes Neurodegeneration." *Science* 345, no. 6195: 455–459. https://doi.org/10.1126/science.1249749.

Ito, S., S. Horikawa, T. Suzuki, et al. 2014. "Human NAT10 Is an ATP-Dependent RNA Acetyltransferase Responsible for N4-Acetylcytidine Formation in 18 S Ribosomal RNA (rRNA)." *Journal of Biological Chemistry* 289, no. 52: 35724–35730. https://doi.org/10.1074/jbc.C114.602698.

Ivanov, P., M. M. Emara, J. Villen, S. P. Gygi, and P. Anderson. 2011. "Angiogenin-Induced tRNA Fragments Inhibit Translation Initiation." *Molecular Cell* 43, no. 4: 613–623. https://doi.org/10.1016/j.molcel.2011.06.022.

Jewell, J. L., Y. C. Kim, R. C. Russell, et al. 2015. "Metabolism. Differential Regulation of mTORC1 by Leucine and Glutamine." *Science* 347, no. 6218: 194–198. https://doi.org/10.1126/science.1259472.

Joazeiro, C. A. P. 2019. "Mechanisms and Functions of Ribosome-Associated Protein Quality Control." *Nature Reviews. Molecular Cell Biology* 20, no. 6: 368–383. https://doi.org/10.1038/s41580-019-0118-2.

Jüdes, A., A. Bruch, R. Klassen, M. Helm, and R. Schaffrath. 2016. "Sulfur Transfer and Activation by Ubiquitin-Like Modifier System Uba4•Urm1 Link Protein Urmylation and tRNA Thiolation in Yeast." *Microbial Cell* 3, no. 11: 554–564. https://doi.org/10.15698/mic2016.11.539.

Kadowaki, T., H. Kadowaki, Y. Mori, et al. 1994. "A Subtype of Diabetes Mellitus Associated With a Mutation of Mitochondrial DNA." *New England Journal of Medicine* 330, no. 14: 962–968. https://doi.org/10.1056/nejm199404073301403.

Kageler, L., J. Perr, and R. A. Flynn. 2024. "Tools to Investigate the Cell Surface: Proximity as a Central Concept in glycoRNA Biology." *Cell Chemical Biology* 31, no. 6: 1132–1144. https://doi.org/10.1016/j.chembiol.2024.04.015.

Kantidakis, T., B. A. Ramsbottom, J. L. Birch, S. N. Dowding, and R. J. White. 2010. "mTOR Associates With TFIIIC, Is Found at tRNA and 5S rRNA Genes, and Targets Their Repressor Maf1." *Proceedings of the National Academy of Sciences of the United States of America* 107, no. 26: 11823–11828. https://doi.org/10.1073/pnas.1005188107.

Kawarada, L., T. Suzuki, T. Ohira, S. Hirata, K. Miyauchi, and T. Suzuki. 2017. "ALKBH1 Is an RNA Dioxygenase Responsible for Cytoplasmic and Mitochondrial tRNA Modifications." *Nucleic Acids Research* 45, no. 12: 7401–7415. https://doi.org/10.1093/nar/gkx354.

Kim, H. K., G. Fuchs, S. Wang, et al. 2017. "A Transfer-RNA-Derived Small RNA Regulates Ribosome Biogenesis." *Nature* 552, no. 7683: 57–62. https://doi.org/10.1038/nature25005.

Kim, J., Y. Jo, D. Cho, and D. Ryu. 2022. "L-Threonine Promotes Healthspan by Expediting Ferritin-Dependent Ferroptosis Inhibition in *C. elegans*." *Nature Communications* 13, no. 1: 6554. https://doi.org/10.1038/s41467-022-34265-x.

Kim, J., G. Song, G. Wu, H. Gao, G. A. Johnson, and F. W. Bazer. 2013. "Arginine, Leucine, and Glutamine Stimulate Proliferation of Porcine Trophectoderm Cells Through the MTOR-RPS6K-RPS6-EIF4EBP1 Signal Transduction Pathway." *Biology of Reproduction* 88, no. 5: 113. https://doi.org/10.1095/biolreprod.112.105080.

Kim, J. A., Y. Wei, and J. R. Sowers. 2008. "Role of Mitochondrial Dysfunction in Insulin Resistance." *Circulation Research* 102, no. 4: 401–414. https://doi.org/10.1161/CIRCRESAHA.107.165472.

Kim, J. H., C. Lee, M. Lee, et al. 2017. "Control of Leucine-Dependent mTORC1 Pathway Through Chemical Intervention of Leucyl-tRNA Synthetase and RagD Interaction." *Nature Communications* 8, no. 1: 732. https://doi.org/10.1038/s41467-017-00785-0.

Kim, K. S., D. H. Oh, J. Y. Kim, et al. 2012. "Taurine Ameliorates Hyperglycemia and Dyslipidemia by Reducing Insulin Resistance and Leptin Level in Otsuka Long-Evans Tokushima Fatty (OLETF) Rats With Long-Term Diabetes." *Experimental & Molecular Medicine* 44, no. 11: 665–673. https://doi.org/10.3858/emm.2012.44.11.075.

Kimura, S., K. Miyauchi, Y. Ikeuchi, P. C. Thiaville, V. Crécy-Lagard, and T. Suzuki. 2014. "Discovery of the β-Barrel-Type RNA Methyltransferase Responsible for N6-Methylation of N6-Threonylcarbamoyladenosine in tRNAs." *Nucleic Acids Research* 42, no. 14: 9350–9365. https://doi.org/10.1093/nar/gku618.

Kirchner, S., and Z. Ignatova. 2015. "Emerging Roles of tRNA in Adaptive Translation, Signalling Dynamics and Disease." *Nature Reviews. Genetics* 16, no. 2: 98–112. https://doi.org/10.1038/nrg3861.

Kirino, Y., T. Yasukawa, S. Ohta, et al. 2004. "Codon-Specific Translational Defect Caused by a Wobble Modification Deficiency in Mutant tRNA From a Human Mitochondrial Disease." *Proceedings of the National Academy of Sciences of the United States of America* 101, no. 42: 15070–15075. https://doi.org/10.1073/pnas.0405173101.

Komar, A. A. 2009. "A Pause for Thought Along the Co-Translational Folding Pathway." *Trends in Biochemical Sciences* 34, no. 1: 16–24. https://doi.org/10.1016/j.tibs.2008.10.002.

Kopajtich, R., T. J. Nicholls, J. Rorbach, et al. 2014. "Mutations in GTPBP3 Cause a Mitochondrial Translation Defect Associated With Hypertrophic Cardiomyopathy, Lactic Acidosis, and Encephalopathy." *American Journal of Human Genetics* 95, no. 6: 708–720. https://doi.org/10.1016/j.ajhg.2014.10.017.

Kožich, V., and S. Stabler. 2020. "Lessons Learned From Inherited Metabolic Disorders of Sulfur-Containing Amino Acids Metabolism." *Journal of Nutrition* 150, no. Suppl 1: 2506s–2517s. https://doi.org/10.1093/jn/nxaa134.

Kulkarni, S., M. A. T. Rubio, E. Hegedűsová, et al. 2021. "Preferential Import of Queuosine-Modified tRNAs Into Trypanosoma Brucei Mitochondrion Is Critical for Organellar Protein Synthesis." *Nucleic Acids Research* 49, no. 14: 8247–8260. https://doi.org/10.1093/nar/gkab567.

Kurata, S., A. Weixlbaumer, T. Ohtsuki, et al. 2008. "Modified Uridines With C5-Methylene Substituents at the First Position of the tRNA Anticodon Stabilize U·G Wobble Pairing During Decoding." *Journal of Biological Chemistry* 283, no. 27: 18801–18811. https://doi.org/10.1074/jbc.M800233200.

Kwon, N. H., P. L. Fox, and S. Kim. 2019. "Aminoacyl-tRNA Synthetases as Therapeutic Targets." *Nature Reviews. Drug Discovery* 18, no. 8: 629–650. https://doi.org/10.1038/s41573-019-0026-3.

Laxman, S., B. M. Sutter, X. Wu, et al. 2013. "Sulfur Amino Acids Regulate Translational Capacity and Metabolic Homeostasis Through Modulation of tRNA Thiolation." *Cell* 154, no. 2: 416–429. https://doi.org/10.1016/j.cell.2013.06.043.

Lee, J. V., A. Carrer, S. Shah, et al. 2014. "Akt-Dependent Metabolic Reprogramming Regulates Tumor Cell Histone Acetylation." *Cell Metabolism* 20, no. 2: 306–319. https://doi.org/10.1016/j.cmet.2014.06.004.

Lee, J. W., K. Beebe, L. A. Nangle, et al. 2006. "Editing-Defective tRNA Synthetase Causes Protein Misfolding and Neurodegeneration." *Nature* 443, no. 7107: 50–55. https://doi.org/10.1038/nature05096.

Lee, S., J. Kim, P. N. Valdmanis, and H. K. Kim. 2023. "Emerging Roles of tRNA-Derived Small RNAs in Cancer Biology." *Experimental & Molecular Medicine* 55, no. 7: 1293–1304. https://doi.org/10.1038/s12276-023-01038-5.

Leidel, S., P. G. Pedrioli, T. Bucher, et al. 2009. "Ubiquitin-Related Modifier Urm1 Acts as a Sulphur Carrier in Thiolation of Eukaryotic Transfer RNA." *Nature* 458, no. 7235: 228–232. https://doi.org/10.1038/nature07643.

Li, Q., J. Cui, C. Fang, M. Liu, G. Min, and L. Li. 2017. "S-Adenosylmethionine Attenuates Oxidative Stress and Neuroinflammation Induced by Amyloid-β Through Modulation of Glutathione Metabolism." *Journal of Alzheimer's Disease* 58, no. 2: 549–558. https://doi.org/10.3233/jad-170177.

Lin, H., K. Miyauchi, T. Harada, et al. 2018. "CO_2-Sensitive tRNA Modification Associated With Human Mitochondrial Disease." *Nature Communications* 9, no. 1: 1875. https://doi.org/10.1038/s41467-018-04250-4.

Liu, G. Y., and D. M. Sabatini. 2020. "mTOR at the Nexus of Nutrition, Growth, Ageing and Disease." *Nature Reviews. Molecular Cell Biology* 21, no. 4: 183–203. https://doi.org/10.1038/s41580-019-0199-y.

Liu, H. Y., Y. Y. Liu, F. Yang, et al. 2020. "Acetylation of MORC2 by NAT10 Regulates Cell-Cycle Checkpoint Control and Resistance to DNA-Damaging Chemotherapy and Radiotherapy in Breast Cancer." *Nucleic Acids Research* 48, no. 7: 3638–3656. https://doi.org/10.1093/nar/gkaa130.

Liu, Y., H. Wang, Y. Liang, et al. 2023. "Dietary Intakes of Methionine, Threonine, Lysine, Arginine and Histidine Increased Risk of Type 2 Diabetes in Chinese Population: Does the Mediation Effect of Obesity Exist?" *BMC Public Health* 23, no. 1: 1551. https://doi.org/10.1186/s12889-023-16468-z.

Liu, Y., X. Yang, J. Zhou, et al. 2024. "OSGEP Regulates Islet β-Cell Function by Modulating Proinsulin Translation and Maintaining ER Stress Homeostasis in Mice." *Nature Communications* 15, no. 1: 10479. https://doi.org/10.1038/s41467-024-54905-8.

Liu, Y., J. Zhou, X. Li, et al. 2022. "tRNA-m1A Modification Promotes T Cell Expansion via Efficient MYC Protein Synthesis." *Nature Immunology* 23, no. 10: 1433–1444. https://doi.org/10.1038/s41590-022-01301-3.

Long, L. H., and B. Halliwell. 2011. "Artefacts in Cell Culture: α-Ketoglutarate Can Scavenge Hydrogen Peroxide Generated by Ascorbate and Epigallocatechin Gallate in Cell Culture Media." *Biochemical and Biophysical Research Communications* 406, no. 1: 20–24. https://doi.org/10.1016/j.bbrc.2011.01.091.

Lott, M. T., J. N. Leipzig, O. Derbeneva, et al. 2013. "mtDNA Variation and Analysis Using Mitomap and Mitomaster." *Current Protocols in Bioinformatics* 44, no. 1: 1–23. https://doi.org/10.1002/0471250953.bi0123s44.

Lowell, B. B., and G. I. Shulman. 2005. "Mitochondrial Dysfunction and Type 2 Diabetes." *Science* 307, no. 5708: 384–387. https://doi.org/10.1126/science.1104343.

Lucas, M. C., L. P. Pryszcz, R. Medina, et al. 2024. "Quantitative Analysis of tRNA Abundance and Modifications by Nanopore RNA Sequencing." *Nature Biotechnology* 42, no. 1: 72–86. https://doi.org/10.1038/s41587-023-01743-6.

Lyons, S. M., C. Achorn, N. L. Kedersha, P. J. Anderson, and P. Ivanov. 2016. "YB-1 Regulates tiRNA-Induced Stress Granule Formation but Not Translational Repression." *Nucleic Acids Research* 44, no. 14: 6949–6960. https://doi.org/10.1093/nar/gkw418.

Ma, Y., W. Guo, Q. Mou, et al. 2024. "Spatial Imaging of glycoRNA in Single Cells With ARPLA." *Nature Biotechnology* 42, no. 4: 608–616. https://doi.org/10.1038/s41587-023-01801-z.

Ma, Y., Y. Yue, M. Pan, et al. 2015. "Histone Deacetylase 3 Inhibits New Tumor Suppressor Gene DTWD1 in Gastric Cancer." *American Journal of Cancer Research* 5, no. 2: 663–673.

Maleki, V., M. Alizadeh, F. Esmaeili, and R. Mahdavi. 2020. "The Effects of Taurine Supplementation on Glycemic Control and Serum Lipid Profile in Patients With Type 2 Diabetes: A Randomized, Double-Blind, Placebo-Controlled Trial." *Amino Acids* 52, no. 6–7: 905–914. https://doi.org/10.1007/s00726-020-02859-8.

Martin, W. F. 2020. "Older Than Genes: The Acetyl CoA Pathway and Origins." *Frontiers in Microbiology* 11: 817. https://doi.org/10.3389/fmicb.2020.00817.

Martinez-Zamora, A., S. Meseguer, J. M. Esteve, et al. 2015. "Defective Expression of the Mitochondrial-tRNA Modifying Enzyme GTPBP3 Triggers AMPK-Mediated Adaptive Responses Involving Complex I Assembly Factors, Uncoupling Protein 2, and the Mitochondrial Pyruvate Carrier." *PLoS One* 10, no. 12: e0144273. https://doi.org/10.1371/journal.pone.0144273.

Mastrodonato, M., G. Calamita, D. Mentino, and G. Scillitani. 2020. "High-Fat Diet Alters the Glycosylation Patterns of Duodenal Mucins in a Murine Model." *Journal of Histochemistry and Cytochemistry* 68, no. 4: 279–294. https://doi.org/10.1369/0022155420911930.

Masuda, I., J. Y. Hwang, T. Christian, et al. 2021. "Loss of N(1)-Methylation of G37 in tRNA Induces Ribosome Stalling and Reprograms Gene Expression." *eLife* 12, no. 10: e70619. https://doi.org/10.7554/eLife.70619.

Matsumura, Y., F. Y. Wei, and J. Sakai. 2023. "Epitranscriptomics in Metabolic Disease." *Nature Metabolism* 5, no. 3: 370–384. https://doi.org/10.1038/s42255-023-00764-4.

Meng, D., Q. Yang, H. Wang, et al. 2020. "Glutamine and Asparagine Activate mTORC1 Independently of Rag GTPases." *Journal of Biological Chemistry* 295, no. 10: 2890–2899. https://doi.org/10.1074/jbc.AC119.011578.

Michels, A. A., A. M. Robitaille, D. Buczynski-Ruchonnet, et al. 2010. "mTORC1 Directly Phosphorylates and Regulates Human MAF1." *Molecular and Cellular Biology* 30, no. 15: 3749–3757. https://doi.org/10.1128/mcb.00319-10.

Minogue, E., P. P. Cunha, B. J. Wadsworth, et al. 2023. "Glutarate Regulates T Cell Metabolism and Anti-Tumour Immunity." *Nature Metabolism* 5, no. 10: 1747–1764. https://doi.org/10.1038/s42255-023-00855-2.

Minton, D. R., M. Nam, D. J. McLaughlin, et al. 2018. "Serine Catabolism by SHMT2 Is Required for Proper Mitochondrial Translation Initiation and Maintenance of Formylmethionyl-tRNAs." *Molecular Cell* 69, no. 4: 610–621.e5. https://doi.org/10.1016/j.molcel.2018.01.024.

Mokgalaboni, K., G. R. Mashaba, W. N. Phoswa, and S. L. Lebelo. 2024. "Folic Acid Supplementation on Inflammation and Homocysteine in Type 2 Diabetes Mellitus: Systematic Review and Meta-Analysis of Randomized Controlled Trials." *Nutrition & Diabetes* 14, no. 1: 22. https://doi.org/10.1038/s41387-024-00282-6.

Moludi, J., S. A. Qaisar, M. M. Kadhim, Y. Ahmadi, and M. Davari. 2022. "Protective and Therapeutic Effectiveness of Taurine Supplementation Plus Low Calorie Diet on Metabolic Parameters and Endothelial Markers in Patients With Diabetes Mellitus: A Randomized, Clinical Trial." *Nutrition & Metabolism (London)* 19, no. 1: 49. https://doi.org/10.1186/s12986-022-00684-2.

Momb, J., J. P. Lewandowski, J. D. Bryant, et al. 2013. "Deletion of Mthfd1l Causes Embryonic Lethality and Neural Tube and Craniofacial Defects in Mice." *Proceedings of the National Academy of Sciences of the United States of America* 110, no. 2: 549–554. https://doi.org/10.1073/pnas.1211199110.

Moore, S. J., J. C. Norris, I. K. Ho, and A. S. Hume. 1986. "The Efficacy of Alpha-Ketoglutaric Acid in the Antagonism of Cyanide Intoxication." *Toxicology and Applied Pharmacology* 82, no. 1: 40–44. https://doi.org/10.1016/0041-008x(86)90435-7.

Morscher, R. J., G. S. Ducker, S. H. Li, et al. 2018. "Mitochondrial Translation Requires Folate-Dependent tRNA Methylation." *Nature* 554, no. 7690: 128–132. https://doi.org/10.1038/nature25460.

Moussaieff, A., M. Rouleau, D. Kitsberg, et al. 2015. "Glycolysis-Mediated Changes in Acetyl-CoA and Histone Acetylation Control the Early Differentiation of Embryonic Stem Cells." *Cell Metabolism* 21, no. 3: 392–402. https://doi.org/10.1016/j.cmet.2015.02.002.

Muthukumar, S., C. T. Li, R. J. Liu, and C. Bellodi. 2024. "Roles and Regulation of tRNA-Derived Small RNAs in Animals." *Nature Reviews. Molecular Cell Biology* 25, no. 5: 359–378. https://doi.org/10.1038/s41580-023-00690-z.

Naeini, S. H., L. Mavaddatiyan, Z. R. Kalkhoran, S. Taherkhani, and M. Talkhabi. 2023. "Alpha-Ketoglutarate as a Potent Regulator for

Lifespan and Healthspan: Evidences and Perspectives." *Experimental Gerontology* 175: 112154. https://doi.org/10.1016/j.exger.2023.112154.

Nakahara, R., K. Maeda, S. Aki, and T. Osawa. 2023. "Metabolic Adaptations of Cancer in Extreme Tumor Microenvironments." *Cancer Science* 114, no. 4: 1200–1207. https://doi.org/10.1111/cas.15722.

Narendran, A., S. Vangaveti, S. V. Ranganathan, et al. 2021. "Silencing of the tRNA Modification Enzyme Cdkal1 Effects Functional Insulin Synthesis in NIT-1 Cells: tRNALys3 Lacking ms2- (ms2t6A37) is Unable to Establish Sufficient Anticodon:Codon Interactions to Decode the Wobble Codon AAG." *Frontiers in Molecular Biosciences* 7: 584228. https://doi.org/10.3389/fmolb.2020.584228.

Narisawa, A., S. Komatsuzaki, A. Kikuchi, et al. 2012. "Mutations in Genes Encoding the Glycine Cleavage System Predispose to Neural Tube Defects in Mice and Humans." *Human Molecular Genetics* 21, no. 7: 1496–1503. https://doi.org/10.1093/hmg/ddr585.

Nedialkova, D. D., and S. A. Leidel. 2015. "Optimization of Codon Translation Rates via tRNA Modifications Maintains Proteome Integrity." *Cell* 161, no. 7: 1606–1618. https://doi.org/10.1016/j.cell.2015.05.022.

Netzer, N., J. M. Goodenbour, A. David, et al. 2009. "Innate Immune and Chemically Triggered Oxidative Stress Modifies Translational Fidelity." *Nature* 462, no. 7272: 522–526. https://doi.org/10.1038/nature08576.

Newsholme, P., J. Procopio, M. M. Lima, T. C. Pithon-Curi, and R. Curi. 2003. "Glutamine and Glutamate—Their Central Role in Cell Metabolism and Function." *Cell Biochemistry and Function* 21, no. 1: 1–9. https://doi.org/10.1002/cbf.1003.

Nilsson, O. B., R. Hedman, J. Marino, et al. 2015. "Cotranslational Protein Folding Inside the Ribosome Exit Tunnel." *Cell Reports* 12, no. 10: 1533–1540. https://doi.org/10.1016/j.celrep.2015.07.065.

Norris, J. C., W. A. Utley, and A. S. Hume. 1990. "Mechanism of Antagonizing Cyanide-Induced Lethality by Alpha-Ketoglutaric Acid." *Toxicology* 62, no. 3: 275–283. https://doi.org/10.1016/0300-483x(90)90051-h.

Ofverstedt, L. G., K. Zhang, S. Tapio, U. Skoglund, and L. A. Isaksson. 1994. "Starvation In Vivo for Aminoacyl-tRNA Increases the Spatial Separation Between the Two Ribosomal Subunits." *Cell* 79, no. 4: 629–638. https://doi.org/10.1016/0092-8674(94)90548-7.

Ohara-Imaizumi, M., M. Yoshida, K. Aoyagi, et al. 2010. "Deletion of CDKAL1 Affects Mitochondrial ATP Generation and First-Phase Insulin Exocytosis." *PLoS One* 5, no. 12: e15553. https://doi.org/10.1371/journal.pone.0015553.

Ohsawa, Y., H. Hagiwara, S. I. Nishimatsu, et al. 2019. "Taurine Supplementation for Prevention of Stroke-Like Episodes in MELAS: A Multicentre, Open-Label, 52-Week Phase III Trial." *Journal of Neurology, Neurosurgery, and Psychiatry* 90, no. 5: 529–536. https://doi.org/10.1136/jnnp-2018-317964.

Okamura, T., R. Yanobu-Takanashi, F. Takeuchi, et al. 2012. "Deletion of CDKAL1 Affects High-Fat Diet-Induced Fat Accumulation and Glucose-Stimulated Insulin Secretion in Mice, Indicating Relevance to Diabetes." *PLoS One* 7, no. 11: e49055. https://doi.org/10.1371/journal.pone.0049055.

Orellana, E. A., Q. Liu, E. Yankova, et al. 2021. "METTL1-Mediated m7G Modification of Arg-TCT tRNA Drives Oncogenic Transformation." *Molecular Cell* 81, no. 16: 3323–3338. https://doi.org/10.1016/j.molcel.2021.06.031.

Ormazabal, A., M. Casado, M. Molero-Luis, et al. 2015. "Can Folic Acid Have a Role in Mitochondrial Disorders?" *Drug Discovery Today* 20, no. 11: 1349–1354. https://doi.org/10.1016/j.drudis.2015.07.002.

Pabis, M., M. Termathe, K. E. Ravichandran, et al. 2020. "Molecular Basis for the Bifunctional Uba4-Urm1 Sulfur-Relay System in tRNA Thiolation and Ubiquitin-Like Conjugation." *EMBO Journal* 39, no. 19: e105087. https://doi.org/10.15252/embj.2020105087.

Pakos-Zebrucka, K., I. Koryga, K. Mnich, M. Ljujic, A. Samali, and A. M. Gorman. 2016. "The Integrated Stress Response." *EMBO Reports* 17, no. 10: 1374–1395. https://doi.org/10.15252/embr.201642195.

Paley, E. L., and G. Perry. 2018. "Towards an Integrative Understanding of tRNA Aminoacylation-Diet-Host-Gut Microbiome Interactions in Neurodegeneration." *Nutrients* 10, no. 4: 410. https://doi.org/10.3390/nu10040410.

Pascale, R. M., M. M. Simile, D. F. Calvisi, C. F. Feo, and F. Feo. 2022. "S-Adenosylmethionine: From the Discovery of Its Inhibition of Tumorigenesis to Its Use as a Therapeutic Agent." *Cells* 11, no. 3: 409. https://doi.org/10.3390/cells11030409.

Paton, B., E. Foguet-Romero, M. Suarez, et al. 2023. "Brain N-Glycosylation and Lipidomic Profile Changes Induced by a High-Fat Diet in Dyslipidemic Hamsters." *International Journal of Molecular Sciences* 24, no. 3: 2883. https://doi.org/10.3390/ijms24032883.

Pechmann, S., and J. Frydman. 2013. "Evolutionary Conservation of Codon Optimality Reveals Hidden Signatures of Cotranslational Folding." *Nature Structural & Molecular Biology* 20, no. 2: 237–243. https://doi.org/10.1038/nsmb.2466.

Pedrioli, P. G., S. Leidel, and K. Hofmann. 2008. "Urm1 at the Crossroad of Modifications." *EMBO Reports* 9, no. 12: 1196–1202. https://doi.org/10.1038/embor.2008.209.

Peng, T. R., H. Y. Cheng, and T. W. Wu. 2024. "S-Adenosylmethionine (SAMe) as an Adjuvant Therapy for Patients With Depression: An Updated Systematic Review and Meta-Analysis." *General Hospital Psychiatry* 86: 118–126. https://doi.org/10.1016/j.genhosppsych.2024.01.001.

Perona, J. J., and I. Gruic-Sovulj. 2014. "Synthetic and Editing Mechanisms of Aminoacyl-tRNA Synthetases." *Topics in Current Chemistry* 344: 1–41. https://doi.org/10.1007/128_2013_456.

Pichot, F., M. C. Hogg, V. Marchand, et al. 2023. "Quantification of Substoichiometric Modification Reveals Global tsRNA Hypomodification, Preferences for Angiogenin-Mediated tRNA Cleavage, and Idiosyncratic Epitranscriptomes of Human Neuronal Cell-Lines." *Computational and Structural Biotechnology Journal* 21: 401–417. https://doi.org/10.1016/j.csbj.2022.12.020.

Pietzke, M., J. Meiser, and A. Vazquez. 2020. "Formate Metabolism in Health and Disease." *Molecular Metabolism* 33: 23–37. https://doi.org/10.1016/j.molmet.2019.05.012.

Pinkard, O., S. McFarland, T. Sweet, and J. Coller. 2020. "Quantitative tRNA-Sequencing Uncovers Metazoan Tissue-Specific tRNA Regulation." *Nature Communications* 11, no. 1: 4104. https://doi.org/10.1038/s41467-020-17879-x.

Rapino, F., S. Delaunay, F. Rambow, et al. 2018. "Codon-Specific Translation Reprogramming Promotes Resistance to Targeted Therapy." *Nature* 558, no. 7711: 605–609. https://doi.org/10.1038/s41586-018-0243-7.

Rapino, F., Z. Zhou, A. M. Roncero Sanchez, et al. 2021. "Wobble tRNA Modification and Hydrophilic Amino Acid Patterns Dictate Protein Fate." *Nature Communications* 12, no. 1: 2170. https://doi.org/10.1038/s41467-021-22254-5.

Rashad, S. 2024. "Queuosine tRNA Modification: Connecting the Microbiome to the Translatome." *BioEssays* 47, no. 2: e2400213. https://doi.org/10.1002/bies.202400213.

Rashad, S., S. R. Byrne, D. Saigusa, et al. 2022. "Codon Usage and mRNA Stability Are Translational Determinants of Cellular Response

to Canonical Ferroptosis Inducers." *Neuroscience* 501: 103–130. https://doi.org/10.1016/j.neuroscience.2022.08.009.

Rashad, S., X. Han, K. Sato, et al. 2020. "The Stress Specific Impact of ALKBH1 on tRNA Cleavage and tiRNA Generation." *RNA Biology* 17, no. 8: 1092–1103. https://doi.org/10.1080/15476286.2020.1779492.

Rashad, S., K. Niizuma, and T. Tominaga. 2020. "tRNA Cleavage: A New Insight." *Neural Regeneration Research* 15, no. 1: 47–52. https://doi.org/10.4103/1673-5374.264447.

Rashad, S., T. Tominaga, and K. Niizuma. 2021. "The Cell and Stress-Specific Canonical and Noncanonical tRNA Cleavage." *Journal of Cellular Physiology* 236, no. 5: 3710–3724. https://doi.org/10.1002/jcp.30107.

Ravichandran, M., S. Priebe, G. Grigolon, et al. 2018. "Impairing L-Threonine Catabolism Promotes Healthspan Through Methylglyoxal-Mediated Proteohormesis." *Cell Metabolism* 27, no. 4: 914–925. https://doi.org/10.1016/j.cmet.2018.02.004.

Reily, C., T. J. Stewart, M. B. Renfrow, and J. Novak. 2019. "Glycosylation in Health and Disease." *Nature Reviews. Nephrology* 15, no. 6: 346–366. https://doi.org/10.1038/s41581-019-0129-4.

Rosselló-Tortella, M., P. Llinàs-Arias, Y. Sakaguchi, et al. 2020. "Epigenetic Loss of the Transfer RNA-Modifying Enzyme TYW2 Induces Ribosome Frameshifts in Colon Cancer." *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 34: 20785–20793. https://doi.org/10.1073/pnas.2003358117.

Rovira-Llopis, S., C. Bañuls, N. Diaz-Morales, A. Hernandez-Mijares, M. Rocha, and V. M. Victor. 2017. "Mitochondrial Dynamics in Type 2 Diabetes: Pathophysiological Implications." *Redox Biology* 11: 637–645. https://doi.org/10.1016/j.redox.2017.01.013.

Sanadgol, N., L. König, A. Drino, M. Jovic, and M. R. Schaefer. 2022. "Experimental Paradigms Revisited: Oxidative Stress-Induced tRNA Fragmentation Does Not Correlate With Stress Granule Formation but Is Associated With Delayed Cell Death." *Nucleic Acids Research* 50, no. 12: 6919–6937. https://doi.org/10.1093/nar/gkac495.

Sanderson, S. M., X. Gao, Z. Dai, and J. W. Locasale. 2019. "Methionine Metabolism in Health and Cancer: A Nexus of Diet and Precision Medicine." *Nature Reviews. Cancer* 19, no. 11: 625–637. https://doi.org/10.1038/s41568-019-0187-8.

Santos, M., C. P. Anderson, S. Neschen, et al. 2020. "Irp2 Regulates Insulin Production Through Iron-Mediated Cdkal1-Catalyzed tRNA Modification." *Nature Communications* 11, no. 1: 296. https://doi.org/10.1038/s41467-019-14004-5.

Schäck, M. A., K. P. Jablonski, S. Gräf, et al. 2020. "Eukaryotic Life Without tQCUG: The Role of Elongator-Dependent tRNA Modifications in Dictyostelium Discoideum." *Nucleic Acids Research* 48, no. 14: 7899–7913. https://doi.org/10.1093/nar/gkaa560.

Schaffer, S. W., C. J. Jong, T. Ito, and J. Azuma. 2014. "Role of Taurine in the Pathologies of MELAS and MERRF." *Amino Acids* 46, no. 1: 47–56. https://doi.org/10.1007/s00726-012-1414-8.

Schiffers, S., and S. Oberdoerffer. 2024. "ac4C: A Fragile Modification With Stabilizing Functions in RNA Metabolism." *RNA* 30, no. 5: 583–594. https://doi.org/10.1261/rna.079948.124.

Schmidt, J., J. Goergens, T. Pochechueva, et al. 2021. "Biallelic Variants in YRDC Cause a Developmental Disorder With Progeroid Features." *Human Genetics* 140, no. 12: 1679–1693. https://doi.org/10.1007/s00439-021-02347-3.

Schuller, A. P., and R. Green. 2018. "Roadblocks and Resolutions in Eukaryotic Translation." *Nature Reviews. Molecular Cell Biology* 19, no. 8: 526–541. https://doi.org/10.1038/s41580-018-0011-4.

Schultz, S. K., C. D. Katanski, M. Halucha, et al. 2024. "Modifications in the T Arm of tRNA Globally Determine tRNA Maturation, Function, and Cellular Fitness." *Proceedings of the National Academy of Sciences of the United States of America* 121, no. 26: e2401154121. https://doi.org/10.1073/pnas.2401154121.

Sharma, S., J. L. Langhendries, P. Watzinger, P. Kötter, K. D. Entian, and D. L. Lafontaine. 2015. "Yeast Kre33 and Human NAT10 Are Conserved 18S rRNA Cytosine Acetyltransferases That Modify tRNAs Assisted by the Adaptor Tan1/THUMPD1." *Nucleic Acids Research* 43, no. 4: 2242–2258. https://doi.org/10.1093/nar/gkv075.

Sharma, S., J. Yang, R. van Nues, et al. 2017. "Specialized Box C/D snoRNPs Act as Antisense Guides to Target RNA Base Acetylation." *PLoS Genetics* 13, no. 5: e1006804. https://doi.org/10.1371/journal.pgen.1006804.

Shen, H., E. Zheng, Z. Yang, et al. 2020. "YRDC Is Upregulated in Non-Small Cell Lung Cancer and Promotes Cell Proliferation by Decreasing Cell Apoptosis." *Oncology Letters* 20, no. 1: 43–52. https://doi.org/10.3892/ol.2020.11560.

Shi, Z., K. Fujii, K. M. Kovary, et al. 2017. "Heterogeneous Ribosomes Preferentially Translate Distinct Subpools of mRNAs Genome-Wide." *Molecular Cell* 67, no. 1: 71–83. https://doi.org/10.1016/j.molcel.2017.05.021.

Shor, B., J. Wu, Q. Shakey, et al. 2010. "Requirement of the mTOR Kinase for the Regulation of Maf1 Phosphorylation and Control of RNA Polymerase III-Dependent Transcription in Cancer Cells." *Journal of Biological Chemistry* 285, no. 20: 15380–15392. https://doi.org/10.1074/jbc.M109.071639.

Shuai, Y., H. Zhang, C. Liu, et al. 2024. "CLIC3 Interacts With NAT10 to Inhibit N4-Acetylcytidine Modification of p21 mRNA and Promote Bladder Cancer Progression." *Cell Death & Disease* 15, no. 1: 9. https://doi.org/10.1038/s41419-023-06373-z.

Shvedunova, M., and A. Akhtar. 2022. "Modulation of Cellular Processes by Histone and Non-Histone Protein Acetylation." *Nature Reviews. Molecular Cell Biology* 23, no. 5: 329–349. https://doi.org/10.1038/s41580-021-00441-y.

Shyh-Chang, N., J. W. Locasale, C. A. Lyssiotis, et al. 2013. "Influence of Threonine Metabolism on S-Adenosylmethionine and Histone Methylation." *Science* 339, no. 6116: 222–226. https://doi.org/10.1126/science.1226603.

Singh, P., K. Gollapalli, S. Mangiola, et al. 2023. "Taurine Deficiency as a Driver of Aging." *Science* 380, no. 6649: eab9257. https://doi.org/10.1126/science.abn9257.

Snieckute, G., A. V. Genzor, A. C. Vind, et al. 2022. "Ribosome Stalling Is a Signal for Metabolic Regulation by the Ribotoxic Stress Response." *Cell Metabolism* 34, no. 12: 2036–2046. https://doi.org/10.1016/j.cmet.2022.10.011.

Spriggs, K. A., M. Bushell, and A. E. Willis. 2010. "Translational Regulation of Gene Expression During Conditions of Cell Stress." *Molecular Cell* 40, no. 2: 228–237. https://doi.org/10.1016/j.molcel.2010.09.028.

Srinivasan, M., P. Mehta, Y. Yu, et al. 2011. "The Highly Conserved KEOPS/EKC Complex Is Essential for a Universal tRNA Modification, t6A." *EMBO Journal* 30, no. 5: 873–881. https://doi.org/10.1038/emboj.2010.343.

Steinthorsdottir, V., G. Thorleifsson, I. Reynisdottir, et al. 2007. "A Variant in CDKAL1 Influences Insulin Response and Risk of Type 2 Diabetes." *Nature Genetics* 39, no. 6: 770–775. https://doi.org/10.1038/ng2043.

Strug, L. J., T. Clarke, T. Chiang, et al. 2009. "Centrotemporal Sharp Wave EEG Trait in Rolandic Epilepsy Maps to Elongator Protein Complex 4 (ELP4)." *European Journal of Human Genetics* 17, no. 9: 1171–1181. https://doi.org/10.1038/ejhg.2008.267.

Sunada, Y. 2020. "Taurine Therapy for MELAS, a Major Mitochondrial Disease." *Neurological Therapeutics* 37, no. 4: 661–663. https://doi.org/10.15082/jsnt.37.4_661.

Sung, Y., I. Yoon, J. M. Han, and S. Kim. 2022. "Functional and Pathologic Association of Aminoacyl-tRNA Synthetases With Cancer." *Experimental & Molecular Medicine* 54, no. 5: 553–566. https://doi.org/10.1038/s12276-022-00765-5.

Suzuki, S., Y. Oka, T. Kadowaki, et al. 2003. "Clinical Features of Diabetes Mellitus With the Mitochondrial DNA 3243 (A-G) Mutation in Japanese: Maternal Inheritance and Mitochondria-Related Complications." *Diabetes Research and Clinical Practice* 59, no. 3: 207–217. https://doi.org/10.1016/s0168-8227(02)00246-2.

Suzuki, T. 2021. "The Expanding World of tRNA Modifications and Their Disease Relevance." *Nature Reviews. Molecular Cell Biology* 22, no. 6: 375–392. https://doi.org/10.1038/s41580-021-00342-0.

Suzuki, T., A. Nagao, and T. Suzuki. 2011a. "Human Mitochondrial Diseases Caused by Lack of Taurine Modification in Mitochondrial tRNAs." *Wiley Interdisciplinary Reviews: RNA* 2, no. 3: 376–386. https://doi.org/10.1002/wrna.65.

Suzuki, T., A. Nagao, and T. Suzuki. 2011b. "Human Mitochondrial tRNAs: Biogenesis, Function, Structural Aspects, and Diseases." *Annual Review of Genetics* 45: 299–329. https://doi.org/10.1146/annurev-genet-110410-132531.

Suzuki, T., A. Ogizawa, K. Ishiguro, and A. Nagao. 2025. "Biogenesis and Roles of tRNA Queuosine Modification and Its Glycosylated Derivatives in Human Health and Diseases." *Cell Chemical Biology* 32, no. 2: 227–238. https://doi.org/10.1016/j.chembiol.2024.11.004.

Suzuki, T., and T. Suzuki. 2014. "A Complete Landscape of Post-Transcriptional Modifications in Mammalian Mitochondrial tRNAs." *Nucleic Acids Research* 42, no. 11: 7346–7357. https://doi.org/10.1093/nar/gku390.

Suzuki, T., T. Ueda, and K. Watanabe. 1997. "The 'Polysemous' Codon—A Codon With Multiple Amino Acid Assignment Caused by Dual Specificity of tRNA Identity." *EMBO Journal* 16, no. 5: 1122–1134. https://doi.org/10.1093/emboj/16.5.1122.

Suzuki, T., Y. Yashiro, I. Kikuchi, et al. 2020. "Complete Chemical Structures of Human Mitochondrial tRNAs." *Nature Communications* 11, no. 1: 4269. https://doi.org/10.1038/s41467-020-18068-6.

Suzuki, Y., S. Suzuki, Y. Hinokio, et al. 1997. "Diabetes Associated With a Novel 3264 Mitochondrial tRNALeu(UUR) Mutation." *Diabetes Care* 20, no. 7: 1138–1140. https://doi.org/10.2337/diacare.20.7.1138.

Sylvers, L. A., K. C. Rogers, M. Shimizu, E. Ohtsuka, and D. Söll. 1993. "A 2-Thiouridine Derivative in tRNAGlu Is a Positive Determinant for Aminoacylation by *Escherichia coli* Glutamyl-tRNA Synthetase." *Biochemistry* 32, no. 15: 3836–3841. https://doi.org/10.1021/bi00066a002.

Takakura, M., K. Ishiguro, S. Akichika, K. Miyauchi, and T. Suzuki. 2019. "Biogenesis and Functions of Aminocarboxypropyluridine in tRNA." *Nature Communications* 10, no. 1: 5542. https://doi.org/10.1038/s41467-019-13525-3.

Takeoka, S., M. Unoki, Y. Onouchi, et al. 2001. "Amino-Acid Substitutions in the IKAP Gene Product Significantly Increase Risk for Bronchial Asthma in Children." *Journal of Human Genetics* 46, no. 2: 57–63. https://doi.org/10.1007/s100380170109.

Tandon, R., J. Thacker, U. Pandya, M. Patel, and K. Tandon. 2022. "Parenteral vs Oral Vitamin B12 in Children With Nutritional Macrocytic Anemia: A Randomized Controlled Trial." *Indian Pediatrics* 59, no. 9: 683–687.

Tang, X., K. Li, Y. Wang, S. Rocchi, S. Shen, and M. Cerezo. 2024. "Metabolism and mRNA Translation: A Nexus of Cancer Plasticity." *Trends in Cell Biology* 27, no. 24: 00225–3. https://doi.org/10.1016/j.tcb.2024.10.009.

Tao, X., Z. Zhang, Z. Yang, and B. Rao. 2022. "The Effects of Taurine Supplementation on Diabetes Mellitus in Humans: A Systematic Review and Meta-Analysis." *Food Chemistry (Oxford)* 4: 100106. https://doi.org/10.1016/j.fochms.2022.100106.

Tavallaie, M., R. Voshtani, X. Deng, et al. 2020. "Moderation of Mitochondrial Respiration Mitigates Metabolic Syndrome of Aging." *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 18: 9840–9850. https://doi.org/10.1073/pnas.1917948117.

Thiaville, P. C., R. Legendre, D. Rojas-Benítez, et al. 2016. "Global Translational Impacts of the Loss of the tRNA Modification t6A in Yeast." *Microbial Cell* 3, no. 1: 29–45. https://doi.org/10.15698/mic2016.01.473.

Thoreen, C. C., L. Chantranupong, H. R. Keys, T. Wang, N. S. Gray, and D. M. Sabatini. 2012. "A Unifying Model for mTORC1-Mediated Regulation of mRNA Translation." *Nature* 485, no. 7396: 109–113. https://doi.org/10.1038/nature11083.

Torrent, M., G. Chalancon, N. S. de Groot, A. Wuster, and M. Madan Babu. 2018. "Cells Alter Their tRNA Abundance to Selectively Regulate Protein Synthesis During Stress Conditions." *Science Signaling* 11, no. 546: eaat6409. https://doi.org/10.1126/scisignal.aat6409.

Treimer, E., T. Kalayci, S. Schumann, et al. 2022. "Functional Characterization of a Novel TP53RK Mutation Identified in a Family With Galloway-Mowat Syndrome." *Human Mutation* 43, no. 12: 1866–1871. https://doi.org/10.1002/humu.24472.

Tresky, R., Y. Miyamoto, Y. Nagayoshi, et al. 2024. "TRMT10A Dysfunction Perturbs Codon Translation of Initiator Methionine and Glutamine and Impairs Brain Functions in Mice." *Nucleic Acids Research* 52, no. 15: 9230–9246. https://doi.org/10.1093/nar/gkae520.

Tucker, E. J., S. G. Hershman, C. Köhrer, et al. 2011. "Mutations in MTFMT Underlie a Human Disorder of Formylation Causing Impaired Mitochondrial Translation." *Cell Metabolism* 14, no. 3: 428–434. https://doi.org/10.1016/j.cmet.2011.07.010.

Tuorto, F., R. Liebers, T. Musch, et al. 2012. "RNA Cytosine Methylation by Dnmt2 and NSun2 Promotes tRNA Stability and Protein Synthesis." *Nature Structural & Molecular Biology* 19, no. 9: 900–905. https://doi.org/10.1038/nsmb.2357.

Tzang, C. C., L. Y. Chi, L. H. Lin, et al. 2024. "Taurine Reduces the Risk for Metabolic Syndrome: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *Nutrition & Diabetes* 14, no. 1: 29. https://doi.org/10.1038/s41387-024-00289-z.

Vangipurapu, J., A. Stancáková, U. Smith, J. Kuusisto, and M. Laakso. 2019. "Nine Amino Acids Are Associated With Decreased Insulin Secretion and Elevated Glucose Levels in a 7.4-Year Follow-Up Study of 5,181 Finnish Men." *Diabetes* 68, no. 6: 1353–1358. https://doi.org/10.2337/db18-1076.

Vind, A. C., A. V. Genzor, and S. Bekker-Jensen. 2020. "Ribosomal Stress-Surveillance: Three Pathways Is a Magic Number." *Nucleic Acids Research* 48, no. 19: 10648–10661. https://doi.org/10.1093/nar/gkaa757.

Vind, A. C., G. Snieckute, M. Blasius, et al. 2020. "ZAKα Recognizes Stalled Ribosomes Through Partially Redundant Sensor Domains." *Molecular Cell* 78, no. 4: 700–713.e707. https://doi.org/10.1016/j.molcel.2020.03.021.

Wang, Q., X. Song, Y. Zhang, et al. 2024. "A Pro-Metastatic tRNA Fragment Drives Aldolase A Oligomerization to Enhance Aerobic Glycolysis in Lung Adenocarcinoma." *Cell Reports* 43, no. 8: 114550. https://doi.org/10.1016/j.celrep.2024.114550.

Wang, Y., P. Deng, Y. Liu, et al. 2020. "Alpha-Ketoglutarate Ameliorates Age-Related Osteoporosis via Regulating Histone Methylations." *Nature Communications* 11, no. 1: 5596. https://doi.org/10.1038/s41467-020-19360-1.

Warner, J. R., J. Vilardell, and J. H. Sohn. 2001. "Economics of Ribosome Biosynthesis." *Cold Spring Harbor Symposia on Quantitative Biology* 66: 567–574. https://doi.org/10.1101/sqb.2001.66.567.

Wei, F. Y., T. Suzuki, S. Watanabe, et al. 2011. "Deficit of tRNALys Modification by Cdkal1 Causes the Development of Type 2 Diabetes in Mice." *Journal of Clinical Investigation* 121, no. 9: 3598–3608. https://doi.org/10.1172/jci58056.

Wei, N., Q. Zhang, and X. L. Yang. 2019. "Neurodegenerative Charcot-Marie-Tooth Disease as a Case Study to Decipher Novel Functions of Aminoacyl-tRNA Synthetases." *Journal of Biological Chemistry* 294, no. 14: 5321–5339. https://doi.org/10.1074/jbc.REV118.002955.

Wei, W., S. Zhang, H. Han, et al. 2023. "NAT10-Mediated ac4C tRNA Modification Promotes EGFR mRNA Translation and Gefitinib Resistance in Cancer." *Cell Reports* 42, no. 7: 112810. https://doi.org/10.1016/j.celrep.2023.112810.

Wesley, U. V., V. J. Bhute, J. F. Hatcher, S. P. Palecek, and R. J. Dempsey. 2019. "Local and Systemic Metabolic Alterations in Brain, Plasma, and Liver of Rats in Response to Aging and Ischemic Stroke, as Detected by Nuclear Magnetic Resonance (NMR) Spectroscopy." *Neurochemistry International* 127: 113–124. https://doi.org/10.1016/j.neuint.2019.01.025.

Wilson, D. N., and R. Beckmann. 2011. "The Ribosomal Tunnel as a Functional Environment for Nascent Polypeptide Folding and Translational Stalling." *Current Opinion in Structural Biology* 21, no. 2: 274–282. https://doi.org/10.1016/j.sbi.2011.01.007.

Wolfson, R. L., and D. M. Sabatini. 2017. "The Dawn of the Age of Amino Acid Sensors for the mTORC1 Pathway." *Cell Metabolism* 26, no. 2: 301–309. https://doi.org/10.1016/j.cmet.2017.07.001.

Wu, C. C., A. Peterson, B. Zinshteyn, S. Regot, and R. Green. 2020. "Ribosome Collisions Trigger General Stress Responses to Regulate Cell Fate." *Cell* 182, no. 2: 404–416. https://doi.org/10.1016/j.cell.2020.06.006.

Wu, X., H. Yuan, Q. Wu, et al. 2024. "Threonine Fuels Glioblastoma Through YRDC-Mediated Codon-Biased Translational Reprogramming." *Nature Cancer* 5, no. 7: 1024–1044. https://doi.org/10.1038/s43018-024-00748-7.

Wu, Y., F. Y. Wei, L. Kawarada, et al. 2016. "Mtu1-Mediated Thiouridine Formation of Mitochondrial tRNAs Is Required for Mitochondrial Translation and Is Involved in Reversible Infantile Liver Injury." *PLoS Genetics* 12, no. 9: e1006355. https://doi.org/10.1371/journal.pgen.1006355.

Xiang, K., M. Kunin, S. Larafa, et al. 2024. "α-Ketoglutarate Supplementation and NAD+ Modulation Enhance Metabolic Rewiring and Radiosensitization in SLC25A1 Inhibited Cancer Cells." *Cell Death Discovery* 10, no. 1: 27. https://doi.org/10.1038/s41420-024-01805-x.

Xie, Y., P. Chai, N. A. Till, et al. 2024. "The Modified RNA Base acp3U Is an Attachment Site for N-Glycans in glycoRNA." *Cell* 187, no. 19: 5228–5237. https://doi.org/10.1016/j.cell.2024.07.044.

Xiong, Q., and Y. Zhang. 2023. "Small RNA Modifications: Regulatory Molecules and Potential Applications." *Journal of Hematology & Oncology* 16, no. 1: 64. https://doi.org/10.1186/s13045-023-01466-w.

Yamamoto, H. A., and P. V. Mohanan. 2003. "Effect of Alpha-Ketoglutarate and Oxaloacetate on Brain Mitochondrial DNA Damage and Seizures Induced by Kainic Acid in Mice." *Toxicology Letters* 143, no. 2: 115–122. https://doi.org/10.1016/s0378-4274(03)00114-0.

Yamasaki, S., P. Ivanov, G. F. Hu, and P. Anderson. 2009. "Angiogenin Cleaves tRNA and Promotes Stress-Induced Translational Repression." *Journal of Cell Biology* 185, no. 1: 35–42. https://doi.org/10.1083/jcb.200811106.

Yamori, Y., T. Taguchi, A. Hamada, K. Kunimasa, H. Mori, and M. Mori. 2010. "Taurine in Health and Diseases: Consistent Evidence From Experimental and Epidemiological Studies." *Journal of Biomedical Science* 17, no. Suppl 1: S6. https://doi.org/10.1186/1423-0127-17-s1-s6.

Yan, Q., Y. Bykhovskaya, R. Li, et al. 2006. "Human TRMU Encoding the Mitochondrial 5-Methylaminomethyl-2-Thiouridylate-Methyltransferase Is a Putative Nuclear Modifier Gene for the Phenotypic Expression of the Deafness-Associated 12S rRNA Mutations." *Biochemical and Biophysical Research Communications* 342, no. 4: 1130–1136. https://doi.org/10.1016/j.bbrc.2006.02.078.

Yan, Q., J. Zhou, Y. Gu, et al. 2024. "Lactylation of NAT10 Promotes N4-Acetylcytidine Modification on tRNASer-CGA-1-1 to Boost Oncogenic DNA Virus KSHV Reactivation." *Cell Death and Differentiation* 31, no. 10: 1362–1374. https://doi.org/10.1038/s41418-024-01327-0.

Yang, H., V. A. Zingaro, J. Lincoff, et al. 2024. "Remodelling of the Translatome Controls Diet and Its Impact on Tumorigenesis." *Nature* 633, no. 8028: 189–197. https://doi.org/10.1038/s41586-024-07781-7.

Yarian, C., H. Townsend, W. Czestkowski, et al. 2002. "Accurate Translation of the Genetic Code Depends on tRNA Modified Nucleosides." *Journal of Biological Chemistry* 277, no. 19: 16391–16395. https://doi.org/10.1074/jbc.M200253200.

Yoon, S. Y., G. H. Hong, H. S. Kwon, et al. 2016. "S-Adenosylmethionine Reduces Airway Inflammation and Fibrosis in a Murine Model of Chronic Severe Asthma via Suppression of Oxidative Stress." *Experimental & Molecular Medicine* 48, no. 6: e236. https://doi.org/10.1038/emm.2016.35.

Yoshii, K., K. Hosomi, K. Sawane, and J. Kunisawa. 2019. "Metabolism of Dietary and Microbial Vitamin B Family in the Regulation of Host Immunity." *Frontiers in Nutrition* 6: 48. https://doi.org/10.3389/fnut.2019.00048.

Yu, C. H., Y. Dang, Z. Zhou, et al. 2015. "Codon Usage Influences the Local Rate of Translation Elongation to Regulate co-Translational Protein Folding." *Molecular Cell* 59, no. 5: 744–754. https://doi.org/10.1016/j.molcel.2015.07.018.

Yuan, L., Y. Han, J. Zhao, Y. Zhang, and Y. Sun. 2023. "Recognition and Cleavage Mechanism of Intron-Containing Pre-tRNA by Human TSEN Endonuclease Complex." *Nature Communications* 14, no. 1: 6071. https://doi.org/10.1038/s41467-023-41845-y.

Zarou, M. M., A. Vazquez, and G. Vignir Helgason. 2021. "Folate Metabolism: A Re-Emerging Therapeutic Target in Haematological Cancers." *Leukemia* 35, no. 6: 1539–1551. https://doi.org/10.1038/s41375-021-01189-2.

Zdzisińska, B., A. Żurek, and M. Kandefer-Szerszeń. 2017. "Alpha-Ketoglutarate as a Molecule With Pleiotropic Activity: Well-Known and Novel Possibilities of Therapeutic Use." *Archivum Immunologiae et Therapiae Experimentalis (Warsz)* 65, no. 1: 21–36. https://doi.org/10.1007/s00005-016-0406-x.

Zeharia, A., A. Shaag, O. Pappo, et al. 2009. "Acute Infantile Liver Failure due to Mutations in the TRMU Gene." *American Journal of Human Genetics* 85, no. 3: 401–407. https://doi.org/10.1016/j.ajhg.2009.08.004.

Zhang, J., W. Li, Z. Liu, et al. 2024. "Defective Post-Transcriptional Modification of tRNA Disrupts Mitochondrial Homeostasis in Leber's Hereditary Optic Neuropathy." *Journal of Biological Chemistry* 300, no. 9: 107728. https://doi.org/10.1016/j.jbc.2024.107728.

Zhang, N., W. Tang, L. Torres, et al. 2024. "Cell Surface RNAs Control Neutrophil Recruitment." *Cell* 187, no. 4: 846–860.e817. https://doi.org/10.1016/j.cell.2023.12.033.

Zhang, Q., L. Zhang, D. Chen, et al. 2018. "Deletion of Mtu1 (Trmu) in Zebrafish Revealed the Essential Role of tRNA Modification in Mitochondrial Biogenesis and Hearing Function." *Nucleic Acids Research* 46, no. 20: 10930–10945. https://doi.org/10.1093/nar/gky758.

Zhang, Y., W. Xu, C. Peng, S. Ren, S. Mustafe Hidig, and C. Zhang. 2024. "Exploring the Role of m7G Modification in Cancer: Mechanisms, Regulatory Proteins, and Biomarker Potential." *Cellular Signalling* 121: 111288. https://doi.org/10.1016/j.cellsig.2024.111288.

Zhang, Y., J. B. Zhou, Y. Yin, E. D. Wang, and X. L. Zhou. 2024. "Multifaceted Roles of t6A Biogenesis in Efficiency and Fidelity of

Mitochondrial Gene Expression." *Nucleic Acids Research* 52, no. 6: 3213–3233. https://doi.org/10.1093/nar/gkae013.

Zhao, J. V., C. M. Schooling, and J. X. Zhao. 2018. "The Effects of Folate Supplementation on Glucose Metabolism and Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials." *Annals of Epidemiology* 28, no. 4: 249–257.e1. https://doi.org/10.1016/j.annepidem.2018.02.001.

Zhao, X., D. Ma, K. Ishiguro, et al. 2023. "Glycosylated Queuosines in tRNAs Optimize Translational Rate and Post-Embryonic Growth." *Cell* 186, no. 25: 5517–5535. https://doi.org/10.1016/j.cell.2023.10.026.

Zheng, J., Y. Tan, X. Liu, et al. 2022. "NAT10 Regulates Mitotic Cell Fate by Acetylating Eg5 to Control Bipolar Spindle Assembly and Chromosome Segregation." *Cell Death and Differentiation* 29, no. 4: 846–860. https://doi.org/10.1038/s41418-021-00899-5.

Zhou, J. B., Y. Wang, Q. Y. Zeng, S. X. Meng, E. D. Wang, and X. L. Zhou. 2020. "Molecular Basis for t6A Modification in Human Mitochondria." *Nucleic Acids Research* 48, no. 6: 3181–3194. https://doi.org/10.1093/nar/gkaa093.

Zhu, J., C. Chen, L. Lu, K. Yang, J. Reis, and K. He. 2020. "Intakes of Folate, Vitamin B(6), and Vitamin B(12) in Relation to Diabetes Incidence Among American Young Adults: A 30-Year Follow-Up Study." *Diabetes Care* 43, no. 10: 2426–2434. https://doi.org/10.2337/dc20-0828.

Zhu, J. Y., W. Yao, X. S. Ni, et al. 2023. "Hyperglycemia-Regulated tRNA-Derived Fragment tRF-3001a Propels Neurovascular Dysfunction in Diabetic Mice." *Cell Reports Medicine* 4, no. 10: 101209. https://doi.org/10.1016/j.xcrm.2023.101209.

Zuko, A., M. Mallik, R. Thompson, et al. 2021. "tRNA Overexpression Rescues Peripheral Neuropathy Caused by Mutations in tRNA Synthetase." *Science* 373, no. 6559: 1161–1166. https://doi.org/10.1126/science.abb3356.

Zuo, H., A. Wu, M. Wang, L. Hong, and H. Wang. 2024. "tRNA m(1) A Modification Regulate HSC Maintenance and Self-Renewal via mTORC1 Signaling." *Nature Communications* 15, no. 1: 5706. https://doi.org/10.1038/s41467-024-50110-9.