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Emerging roles of tRNA in cancer

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ABSTRACT

Transfer RNAs (tRNAs) play pivotal roles in the transmission of genetic information, and abnormality of tRNAs directly leads to translation disorders and causes diseases, including cancer. The complex modifications enable tRNA to execute its delicate biological function. Alteration of appropriate modifications may affect the stability of tRNA, impair its ability to carry amino acids, and disrupt the pairing between anticodons and codons. Studies confirmed that dysregulation of tRNA modifications plays an important role in carcinogenesis. Furthermore, when the stability of tRNA is impaired, tRNAs are cleaved into small tRNA fragments (tRFs) by specific RNases. Though tRFs have been found to play vital regulatory roles in tumorigenesis, its formation process is far from clear. Understanding improper tRNA modifications and abnormal formation of tRFs in cancer is conducive to uncovering the role of metabolic process of tRNA under pathological conditions, which may open up new avenues for cancer prevention and treatment.

1. Introduction

Composed of 70–90 nucleotides, tRNA is a class of small non-coding ribonucleic acid folded into "clover" secondary conformation and L-shaped tertiary structure with the basic function of carrying and transporting amino acids. As a connecting molecule between mRNA and protein, tRNA plays a central role in translation, delivering amino acids onto the ribosome and translating nucleotide sequences into corresponding polypeptide chains in the manner of codon-anticodon pairing [1,2]. tRNA accounts for about 4–10% of all cellular RNA [3].

The sequences of tRNA in mammalian genomes are highly conserved. Many tRNA genes, with the same anticodon, are distributed in different places in the genome but share the same sequence. The reference human genome of hg19 contains 446 tRNA genes distributed in 280 sequences, and the gene number/gene sequence ratio is 1.59 [4]. Using hg38 reference annotation, 429 highly confident tRNA genes were obtained [5]. Chip-seq studies of RNA polymerase III (Pol III) subunits and transcription factors show that most tRNA isocode genes are transcribed in different cell types [6]. However, there is a great diversity of tRNA and tRNA may obtain gene diversity by increasing the misacylation tendency of non-homologous tRNA synthetase. The diversity of tRNAs has also been suggested as a possible explanation for their fine-tuning of translation in a cell type or cell state-dependent manner. For example, sequence changes in tRNA bodies can regulate aminoacylation status, or efficiency of ribosome loading [7,8].

On the other hand, the unprecedented complexity of tRNA biosynthesis, modification pattern, regulation, and function play an important role in the occurrence and development of many diseases including cancer. The latest research of tRNA in tumors brings up many new ideas for the prevention and treatment of cancers. Till now, more than 100 modifications have been identified in all human tRNA isoforms. After specific modifications, usually under some stress conditions, tRNA will break up and generate small tRNA fragments (tRFs). With the richness of its modification and the diversity of its derived tRFs, tRNAs play a broad range of roles in tumorigenesis [9]. This review summarizes the most

Abbreviations: tRNA, transfer RNA; tRFs, tRNA fragments.

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Abbreviations

tRFs	tRNA fragments
Pol III	RNA polymerase III
m7G	7-methylguansine
Q	queuosine
mcm5s2U	methoxycarbonylmethyl-2-thiouridine
Ψ	pseudouridine
m5C	5-methylcytosine
TGT	tRNA-guanine transglycosylase
ICC	intrahepatic cholangiocarcinoma
NPC	nasopharyngeal carcinoma
EMT	epithelial-mesenchymal transition
ESCC	esophageal squamous cell carcinoma
IRES	intrinsic ribosomal entry site
MAPK	mitogen-activated protein kinase
IRES	intrinsic ribosomal entry site
PUS	pseudouridine synthase
5-FU	5-fluorouracil
TMZ	temozolomide
Pol II	RNA polymerase II
CESC	cervical squamous cell carcinoma and endocervical adenocarcinoma
COAD	colon adenocarcinoma
GBM	glioblastoma
LC	lung cancer
BC	breast cancer
HNSC	head and neck squamous cell carcinoma
T-ALL	acute lymphoblastic leukemia
ANG	angiopoietin
TNBC	triple-negative breast cancer
PRAD	prostatic carcinoma
B-ALL	acute B lymphocytic leukemia
CRC	colorectal cancer
U34	uridine 34
SG	stress granules

recent research progress of tRNA-centered cancer development process, focusing on tRNA modification, stability, and the consequences of structural breakage in cancer.

2. Abnormal tRNA modifications and cancer

The initial product of Pol III is the tRNA precursor which undergoes a complex series of biological processes to be converted into the mature tRNA [10], including removal of the 5′ precursor conductor by RNase P, RNase E, and RNase PH, cleavage of the 3′ tail by RNase T, adding CCA to the 3′ end by CCA adding enzyme, and multiple modifications of tRNA bases [11].

Various tRNA modifications have been found in tRNA anticodons, which are essential for tRNA to carry out its biological functions. The sequence of tRNA is more conserved than that of mRNA, and many modifications on tRNA have been confirmed to occur at several fixed positions. During the transfer of amino acids from the 3′ terminus of tRNA to the growing peptide chain, anticodons at positions 34, 35, and 36 of tRNA recognize specific codons on mRNA through hydrogen bonding at the A site of the ribosome. There is an important "wobbling pairing" in codon-anticodon interactions, where base pairing between the third position of the codon and the first position of the anticodon (position 34 of the tRNA) does not always follow Watson-Crick rule but adapts to various irregular pairings. The presence of a variety of modified nucleotides at position 34 (wobble modification) is an important regulator of wobbling pairing. In addition to wobble modification, position 37 is another hot spot for tRNA modification. This position is adjacent to the anticodon and plays a regulatory role in maintaining reading and pairing. There are also many modifications present on tRNA bodies, including on the D-arm, T-arm, and variable loop, which are involved in maintaining the structural stability of tRNA. Recent studies have shown that tRNA modifications can be dynamically regulated based on the levels of cellular metabolites and environmental cues. The anomaly of tRNA modification at any position may lead to diseases including the occurrence of cancer [12]. Studies show that some positions have relatively fixed modifications, while some modifications occur on multiple positions. The diversity of tRNA modifications has attracted increasing attention in cancer research. During the past two decades, at least 16 new tRNA modifications have been identified across various organisms. This review focuses on roles of several major tRNA modifications in tumorigenesis, including 7-Methylguansine (m^7G), queuosine (Q), Methoxycarbonylmethyl-2-thiouridine (mcm^5s^2U), pseudouridine (Ψ) and 5-methylcytosine (m^5C) (Fig. 1). Some latest techniques for detecting tRNA modifications are summarized in Table 1 [13–22].

2.1. 7-methylguanosine (m^7G) modification

The modification of tRNA by 7-methylguanosine (m^7G) is widely found in bacteria and eukaryotes, usually at position 46. Through hydrogen bonding with bases G22 and C13, m^7G modification makes this position positively charged and enhances the stability of tRNA [23–26]. In 2019, methyltransferase *METTL1* was identified as the writer of m^7G [27], regulating m^7G modification of tRNA. In 2021, Orellana et al. demonstrated that *METTL1/WDR4* promoted m^7G modification of tRNA, which reduced ribosomal pause and improved translation efficacy [28]. In tumors, m^7G-tRNA modification selectively enhances the translation of oncogenic transcripts and plays a cancer-promoting role. For example, m^7G modification plays a key tumorigenic function in intrahepatic cholangiocarcinoma (ICC) by up-regulating genes of cell cycle and epidermal growth factor receptor (*EGFR*) pathway [29]. When *METTL1/WDR4* is depleted, reduced m^7G modification results in decreased translation of tumor-relevant mRNAs, and impaired cell proliferation, colony formation, cell invasion, and tumorigenicity [30]. In breast cancer, the expression of *METTL1* is clearly negatively correlated with patient prognosis. Silencing *METTL1* inhibited the proliferation, migration, and invasion of breast cancer cells mediated by *EGFR/EFEMP1* up-regulation [31]. In nasopharyngeal carcinoma (NPC), high expression of *METTL1/WDR4* promotes the growth and metastasis of NPC cells in vitro and in vivo. *ARNT*, the upstream transcription factor of *METTL1*, promoted the expression of *METTL1*, affected m^7G modification of tRNA, up-regulated the WNT/β-catenin signaling pathway, and finally enhanced the epithelial-mesenchymal transition (EMT) and chemotherapy resistance of NPC cells [32]. In esophageal squamous cell carcinoma (ESCC), *METTL1/WDR4* is significantly up-regulated. Knockdown of *METTL1* or *WDR4* results in reduced m^7G-tRNA modification and reduced translation of oncogenic transcripts enriched in the *RPTOR/ULK1*/autophagy pathway [33].

2.2. Queuosine (Q) modification

Queuine is a nucleoside analogue of guanosine through base exchange. It is present at the first position of the anticodon loop of tRNA for histidine, aspartic acid, asparagine, and tyrosine. The reaction is catalyzed by tRNA-guanine transglycosylase (*TGT*), which was identified in 1982 [34]. In 2014, Remi Zallot et al. reported that the eukaryotic *TGT* consists of catalytic subunit (*QTRT1*) and homologous accessory

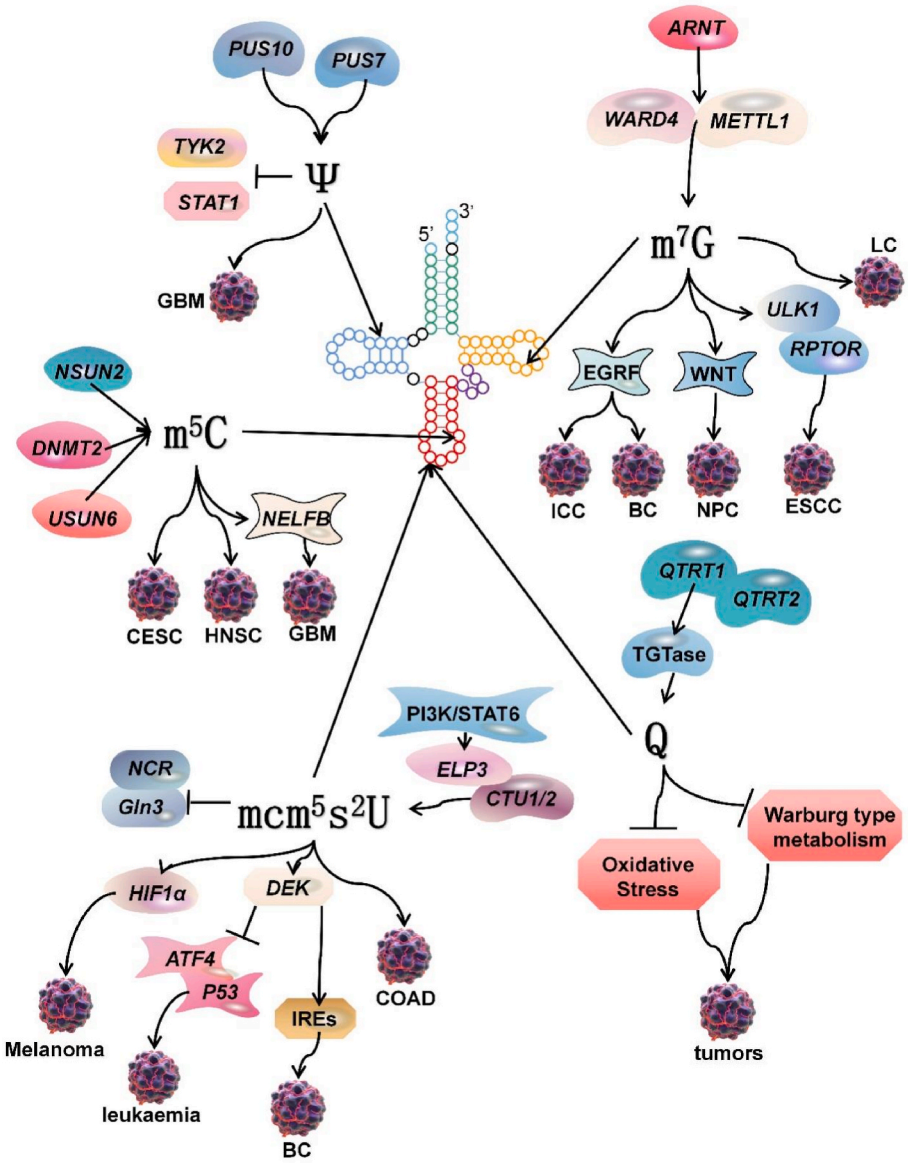

Fig. 1. tRNA modifications and cancer. Common sites and enzymes for Q, mcm5s2U, ψ, m7G, and m5C modifications on tRNA. Alterations of modifying enzymes lead to excessive or absent of modifications, change of the expression of tumor-related genes, and activating or inhibiting of certain cancer-related signaling pathways. Increased ψ modification and m5C lead to the proliferation of glioblastoma, HNSC, and CESC. U34 mcm5s2-tRNA modification promotes the development of breast cancer, melanoma, COAD, and leukemia. Deficiency of Q modification promotes tumor cell proliferation. m7G-tRNA modification selectively enhances the translation of oncogenic mRNA and plays a pivotal carcinogenic role. (HNSC: head and neck squamous cell carcinoma; CESC: cervical squamous cell carcinoma and endocervical adenocarcinoma; BC: breast cancer; COAD: colon adenocarcinoma; GBM: glioblastoma; LC: lung cancer; ESCC: esophageal squamous cell carcinoma; NPC: nasopharyngeal carcinoma; ICC: intrahepatic cholangiocarcinoma).

subunit (*QTRTD1*) [35]. As early as the 1980s, it was found that cytoplasmic or mitochondrial tRNA lacked Q modification in a variety of tumors [36]. In 1992, this modification was found to be associated the occurrence and development of human colon adenocarcinoma [37]. Recent studies have confirmed that low Q-tRNA is closely linked to uncontrolled cell proliferation and malignant tumors. Low Q-modification of tRNA is caused by the decrease of tRNA guanine transglycosylase activity, which may be a potential therapeutic target [38,39]. Loss of *QTRT1* in human breast cancer cells changes the function of regulatory genes and affects the proliferation and migration of tumor cells [40]. A study shows that queuine promotes antioxidant defense system by increasing antioxidant enzyme activities and inhibits oxidative stress and tumorigenesis, which may be one of the reason why loss of Q-tRNA is associated with tumor [41]. In addition, loss of Q modification can promote Warburg type metabolism, which is beneficial to the energy metabolism of tumors [42].

2.3. U34 mcm^5s^2-tRNA modification

Post-transcriptional modifications of tRNA on the wobble uridine 34 (U34) base are highly conserved and contribute to translational fidelity. Modification of the wobble site by mcm^5s^2U is known to enable wobble pairing and optimizing the codon translation rate to improve the translation fidelity and ensure the extension of the translated peptide [43–48]. The absence of this modification may cause ribosome stalling [49]. Researchers found that *ELP3* and *CTU1/2*, as partner enzymes in U34 mcm^5s^2-tRNA modification, up-regulated the expression of *DEK* oncogene through mcm^5s^2-tRNA modification, which further up-regulated the expression of intrinsic ribosomal entry site (IRES) invasive transfer factor and promoted the invasion and metastasis of breast cancer [50]. The modification of U34 position also plays an important role in melanoma development and drug resistance. Research found that the survival of melanoma cells expressing BRAFV600E oncogene depends on tRNA modifications at U34, and simultaneously inhibition of MAPK signaling and *ELP3/CTU1/2* kills melanoma cells and overcomes resistance to MAPK-targeted therapy alone. Specifically, *ELP3/CTU1/2* enhances the translation of *HIF1α* mRNA by modifying U34 to maintain a high level of *HIF1α* protein content to promote glycolysis in melanoma cells and promote cancer progression [51]. Furthermore, studies have shown that *ELP3/CTU1/2* knockdown sensitizes drug-resistant melanoma to targeted therapy [52]. In addition, loss of U34 modification enhances nuclear import of *Gln3* and activates

Table 1
Techniques for identifying tRNA modifications.

Modification	Technique	Detection mechanism
Queuosine (Q)	APB and Northern blot	The method is based on the copolymerization of boric acid (N-acryloyl-3-aminobenylboric acid (APB)) in a polyacrylamide gel and the interaction between this derivative and the free *cis*-diol group of tRNA. During electrophoresis, the *cis*-diol group slows the Q-modified tRNA, which can then be separated from the unmodified tRNA and quantified using Northern blot analysis [13].
Queuosine (Q)	PAQS-seq	Periodate treatment oxidizes the Q base, resulting in specific missing tags in RNA-seq data. Single-base resolution of Q modification in tRNA can then be obtained from biological RNA samples by Nextgen sequencing [14].
3-Methylcytidine (m^3C)	HAC-seq	Specific cleavage of tRNA chains at m^3C is induced by aniline treatment following hydrazine treatment [15].
5-Methoxycarbonylmethyl-2-thiouridine (mcm^5s^2U)	Gamma-toxin endonuclease	The gamma-toxin endonuclease is used to cut tRNA containing the mcm5s2U modification. This technique, combined with Northern blotting, enables rapid and sensitive detection of changes in the modification status of mcm^5s^2U [16].
4-Thiourdine (s^4U)	MTSEA biotin-XX s^4U detection system	MTSEA biotin-XX reacts only with s^4U and not with other sulfur-modified nucleosides in tRNA, such as s^2U derivatives, and could specifically label s^4U [17].
Pseudouridine (Ψ)	Nanopore sequencing	Most RNA modifications result in systematic base-calling errors, and the signature of these base-calling "errors" can be used to identify the types of underlying RNA modifications [18].
7-Methylguansine (m^7G)	TRAC-Seq	m^7G TRAC-seq involves processing size selection of RNA to remove the major tRNA modification followed by sodium borohydride (NaBH4) to reduce the m7G site and subsequent aniline-mediated cleavage of the RNA strand at the resulting nonbasic site. The cleaved sites are subsequently ligated with adapters to construct libraries for high-throughput sequencing [19].
7-Methylguansine (m7G)	m7G-MaP-seq	The m7G-modified position is converted to a non-basic site by sodium borohydride reduction, recorded directly as a cDNA mutation by reverse transcription and sequenced [20].
5-Formylcytidine (f^5C)	Photo-facilitated detection and sequencing	f^5C is visualized using a semistable ylide label and could be distinguished from a similar 5-formyluridine [21].
5-Formylcytidine (f^5C)	Protonation-dependent sequencing	The combination of protonation with electron-withdrawing substituents can change the molecular orbital energy of the modified cytidine nucleosides and enhance the reactivity and sensitivity of detecting 5 fC in tRNA [22].

NCR (nitrogen catabolite repression) gene, affects TOR signaling pathway, inhibits cell division and growth, and reverses the resistance of cancer cells to rapamycin, which may be another mechanism of U34 modification on the occurrence and development of tumors [53]. Recent studies have shown that tumor-associated M2 macrophages up-regulate the expression of *ELP3* by activating *PI3K* and *STAT6* signaling pathways, and *ElP3* further activates *mTOR* complex 2 (mTORC2) to drive the progression of intestinal tumors. On the contrary, classical M1 macrophages downregulate the expression of *ELP3*. The modification of U34 is differently regulated among different subtypes of macrophages, and its imbalance plays an important role in tumorigenesis [54]. For example, the modification at U34 exhibited anti-tumor effect in leukemia and lymphoma. Deletion of *ELP3* induces a *p53*-dependent checkpoint, activates *ATF4*, upregulates protein synthesis, affects hematopoietic stem cell differentiation, and promotes the development of leukemia and lymphoma with *p53* mutation [55]. In addition, *ELP3* deletion blocks the T Cell cycle and impairs T follicular helper cell response by activating *ATF4* [56].

2.4. Pseudouridine (Ψ) modification

Pseudouridine modification is the most abundant modification in RNA [57]. Pseudouridine synthase (PUSs) writes pseudouridine modification into RNA. There are 13 types of pseudouridine modifications identified in human, which play different roles [58]. In glioblastoma, *PUS7* modified tRNA which reduced *TYK2* translation, inhibited *STAT1* pathway, and resulted in tumor proliferation. *PUS7* can be specifically targeted by small molecule inhibitors, which may be a new target for cancer treatment [59]. *PUS10* modification of tRNA promotes cell growth and may play a role in tumor proliferation [60]. Recent studies have shown that abundance of tRNA-derived fragments carrying Ψ modification in stem cells hinders the recruitment of translation coactivator *PABPC1* interacting protein 1 (*PAIP1*) and inhibits the translation of mRNA, promoting the transplantation and differentiation of hematopoietic stem cells and progenitor cells (HSPCs) in patients with myelodysplastic syndrome (MDS) [61]. In general, although Ψ modification has been recognized for a long time, its biological function remains to be thoroughly investigated.

2.5. 5-methylcytosine (m^5C) modification

5-methylcytosine (m^5C) is present on mRNA, rRNA, and tRNA in multiple species. As a reversible epigenetic modification, m^5C modification affects the fate of RNA molecules and plays important roles in a variety of biological processes [62]. Modification with m^5C may occur at multiple tRNA positions and play different roles. For example, m^5C at the junction of the variable loop and the T-stalk increases the stability of the tRNA by increasing the hydrophobicity of the base pair and promoting base stacking [63]. Modification with m^5C at position 38 plays a role in protecting tRNA from stress-induced endonuclease mediated fragmentation [64]. *DNMT2*, a member of the DNA methyltransferase

superfamily, catalyzes the formation of m^5C at position 38 in the tRNA anticodon loop. This modification by *DNMT2* is highly conserved in mammals, and its alteration is closely associated with the occurrence and development of cancer [65]. Loss of *DNMT2* reduces the stability of tRNA and negatively affects the integrity of genome [66], which may contribute to the occurrence of tumors. NOL1/NOP2/SUN domain family member 2 (*NSUN2*), another m^5C writer, also plays a carcinogenic role in a variety of cancers [67]. Studies have shown that knockdown of *NSUN2* and m^7G modifying enzyme *METTL1* in HeLa cells significantly enhances the sensitivity of cells to 5-fluorouracil (5-FU) chemotherapy, suggesting that targeting *NSUN2* and *METTL1* may be a treatment strategy for cervical cancer [67]. Enrichment of *NSUN2* modified tRNA has also been found in ovarian cancer, which is associated with increased tumor heterogeneity [68]. High expression of *NSUN2* is also associated with poor prognosis of head and neck squamous cell carcinoma [69]. *NSUN6*, another member of the 5-NOL1/-NOP2/SUN domain family, mediates m^5C modification to halt *NELFB* transcription in glioblastoma, thereby overcoming temozolomide (TMZ) resistance in glioblastoma [70]. The expression of *NSUN6* is down-regulated in prostate cancer, which may be an index for the prognosis of prostate cancer [71]. The role of m^5C modification in mRNA has been extensively studied, whereas its role in tRNA remains to be fully explored.

3. Production and fragmentation of tRNA in cancer

In addition to a variety of modifications, the production and fragmentation of tRNA are also important biological processes, which are regulated by many factors. During these processes, gene mutations, deletions, or over-activation under stress conditions will lead to abnormal synthesis or fragmentation of tRNA, resulting in pathological consequences (Figs. 2 and 3). Recently, the involvement of these processes in cancer have caught much attention of researchers, which provides a new research direction for exploring the mechanism of carcinogenesis.

3.1. Abnormal tRNA synthesis in cancer

The synthesis of tRNA requires the involvement of multiple enzymes. Pol III is a polymerase that transcribe tRNA in eukaryotes and is essential for tRNA production [72]. Estrogen receptor α (*ERα*) is highly expressed in breast cancer and targets Pol III-transcribed genes, including *RMRP*, a positive regulator of cell cycle progression, and *RN7SL1*, a tumor-inducing inflammatory response gene, to promote the progression of breast cancer [73]. In glioblastoma, the Pol II-dependent transcription factor *SOX4* was found to block the recruitment of TATA box binding protein and Pol III, thereby hindering tRNA synthesis. Inhibition of *tRNAiMet* synthesis by this mechanism blocked the proliferation of glioblastoma cells [74]. In breast and colorectal cancer, chemotherapy reduced the DNA binding activity of Pol III, leading to decreased tRNA transcription and cell cycle arrest, which contributed to cancer chemotherapy resistance [75]. Telomerase reverse transcriptase (*TERT*) enhances chromatin recruitment of Pol III regulatory subunit *RPC32*, leading to increased tRNA production and promoting cancer cell proliferation. Knocking out *TERT* in mouse model of breast cancer reduces tRNA level, inhibits tumor proliferation, and improves the survival rate

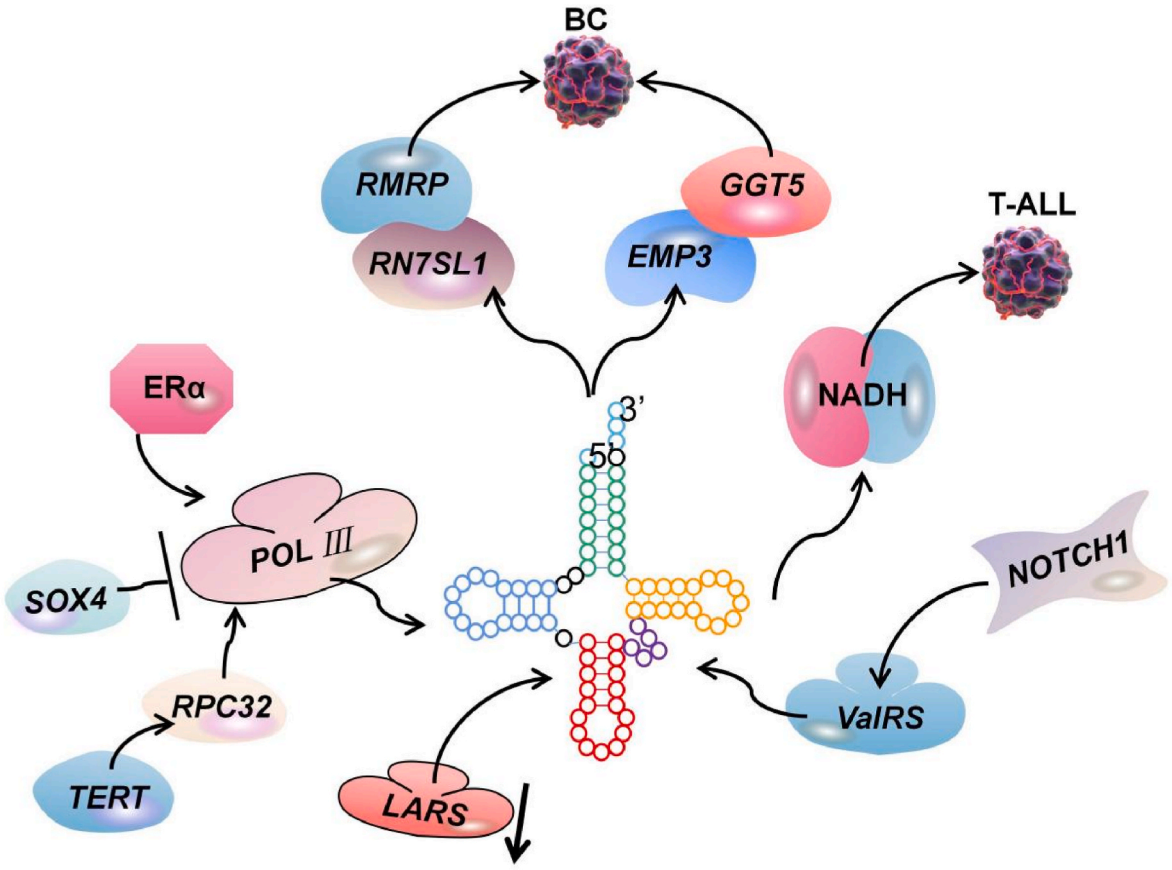

Fig. 2. Abnormal tRNA synthesis in cancer. The production of tRNA is a complex biological process, including initial synthesis, modifications, and maturation. RNA Pol III is an key tRNA synthetase in huma. Studies have found that a variety of factors affect the expression of RNA Pol III, thereby changing the synthesis of tRNA and leading to tumorigenesis. Aminoacyl-synthetase plays an important role in determining the amino acid carrying capacity of tRNA. Deficiency of *LARS* leads to the proliferation of breast cancer cells, and increase of *ValRS* promotes the progression of T-ALL. (T-ALL: acute lymphoblastic leukemia; BC: breast cancer; *LARS*: leucyl-tRNA synthetase; *ValRS*: valyl-tRNA synthetase).

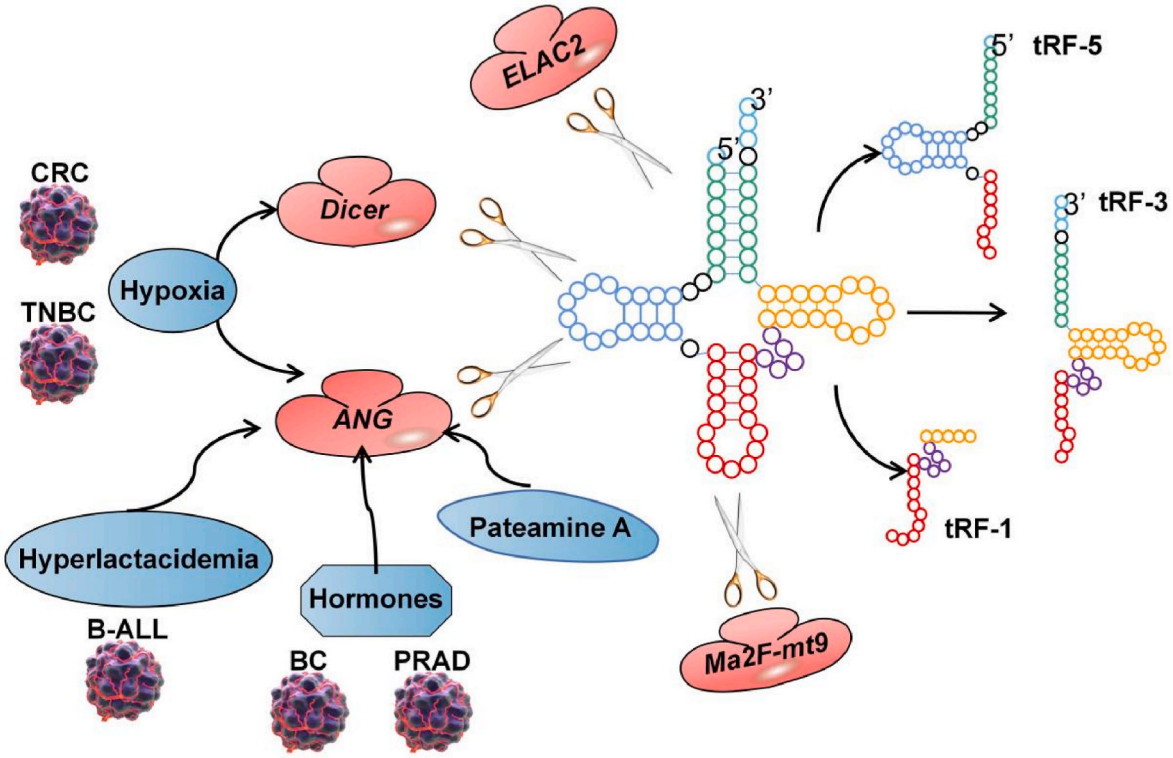

Fig. 3. tRNA fragmentation in cancer. In cells, tRNAs are cleaved into tRFs by various enzymes, including *ANG, Dicer, Ma2F-mt9, and ELAC2.* The syntheses of tRNA modification enzymes increase under certain stress conditions including chemotherapy, hypoxia, high lactate, and abnormal hormone levels, resulting in drug resistance and tumor development. (CRC: colorectal cancer; TNBC: triple-negative breast cancer; PRAD: prostatic carcinoma; BC: breast cancer; B-ALL: acute B lymphocytic leukemia).

[76]. These results suggest that *TERT* may not only affect the activity of telomerase, but also act as an upstream regulator of Pol III, affecting the synthesis of tRNA and participating in the occurrence and development of cancers. Sarah E. Dremel et al. found that herpes simplex virus-1 (HSV-1) altered transcription of host Pol III and promoted expression of tRNA is conducive to viral infection [77]. This work sheds new light on the mechanism of occurrence and development of viral infection-related tumors.

Besides Pol III, other factors were found to participate in tRNA synthesis and maturity. leucyl-tRNA synthetase (*LARS*) is lost in breast cancer, leading to the disorder of leucine-tRNA synthesis and the inhibition of the translation of leucine-rich codons of mRNA. As a result, the expression of some growth suppressor genes including epithelial membrane protein 3 (*EMP3*) and gamma-glutamyltransferase 5 (*GGT5*) is disrupted, which promotes the proliferation of breast cancer [78]. In acute lymphoblastic leukemia (T-ALL), *NOTCH1* upregulates the expression of valine aminoacyl-tRNA synthetase and promotes the progression of T-ALL. Restriction of dietary valine intake can reduce the translation rate of mRNA encoding mitochondrial complex I subunits, resulting in defective assembly and impaired oxidative phosphorylation of complex I, cutting off the energy supply of T-ALL cells through the mitochondrial pathway, and limiting the occurrence and development of T-ALL [79].

In addition to the tRNA encoded by nuclear genes, mitochondrial tRNA mutations are also involved in a variety of cancers. By sequencing the genomes and transcriptomes of 527 tumors and 14 cancers, James B Stewart and colleagues observed a large number of mutations and accumulation of immature tRNA precursors in mitochondria. Mutations in tRNAs not only affects their own synthesis, but also impairs the translation of relevant gene transcripts [80]. Recent studies have shown that abnormal methylation of mitochondrial DNA affects the expression of related tRNAs and drives the process of tumorigenesis. In endometrial cancer, *tRNA-Arg-TCT-4-1* hypermethylation promotes cell proliferation, while demethylation arrests cells in G0/G1 phase and inhibits tumor proliferation and migration [81].

3.2. tRNA fragmentation in cancer

Initially, tRNA-derived fragments were considered to be useless metabolites of cells, but gradually they were found to have certain biological functions. Recently, the biological function of tRNA fragmentation has become a research hot spot, and the abnormal formation of tRFs in cancers has also attracted lots of attention. Various mechanisms lead to tRNA lack of modification, reduced stability, and tRFs formation. Among them, stress response is a widely studied mechanism. Research found that angiopoietin (*ANG*) mediated tRNA cleavage to produce tRFs under stress. The resulting tRFs interacted with *YB-1* and participated in the formation of stress granules (SG) [82]. Furthermore, tRFs formed during stress were found to form a unique stable four-molecule aggregate RNA G-quadruplex (RG4) which played a key role in regulating mRNA translation [83].

In colorectal cancer cells, hypoxia up-regulates *Dicer1* expression, leading to tRNA degradation and the production of *tRF-20-MEJB5Y13*, and promoting the invasion and migration of CRC cells [84]. Another study found that *ANG* was up-regulated in colorectal cancer and produced a large number of tRFs, which promoted colorectal cancer invasion [85]. Hypoxia-induced tRFs formation was also found in triple-negative breast cancer (TNBC) cell lines. Fragments *tDR-0009* (derived from *tRNA-Gly-GCC-1-2*) and *tDR-7336* (derived from *tRNA--Gly-GCC-1-2*) are mainly involved in the maintenance of cell stemness and cell response to interleukin 6 (*IL-6*), which may be the reason for the resistance of TNBC to adriamycin [86]. Drugs for cancer treatment such arsenite and pateamine A can also promote *ANG* to cleave tRNA into tRFs which participate in the assembly of stress particles [87]. All these

evidence suggest a role of tRFs in cancer drug resistance. High plasma lactate environment is a key factor in the development of human malignant tumors. In mouse model, researchers found that high lactate induced *ANG*, enhanced the expression of 5′tRFs, and promoted the development of B-cell lymphoma [88]. In breast cancer and prostate cancer, abnormal sex hormones are a major hallmark, and the over-expression of sex hormones promotes *ANG* to cleave tRNA into 5′tRFs and 3′tRFs, which stimulates the proliferation of tumor cells [89]. Studies also found that sex hormone-induced tRFs are heterogeneous in breast cancer [90]. This suggests a more profound regulatory mechanism for tRFs formation. In this connection, it has been confirmed that *ANG* overexpression selectively clears specific tRNAs, including *tRNAGlu*, *tRNAGly*, *tRNALys*, *tRNAVal*, *tRNAHis*, *tRNAAsp*, and *tRNASeC*. Moreover, enzymes other than *ANG* also play roles in cutting and producing shorter tRFs [91]. For instance, *MazF-mt9* was found to cleave tRNA at a single site within the D-loop or anticodon with high specificity. Unlike *ANG*, *MazF-mt9* cleans tRNA and forms tRFs to inhibit stress response [92]. Eun-Jin Choi et al. discovered a new enzyme *ELAC2* that cleaves tRNA during respiratory syncytial virus (RSV) infection to promote viral infection and may play a role in the progression of clear cell renal cell carcinoma (ccRCC) [93].

4. Conclusion

tRNA plays a key role in protein synthesis. Any abnormal changes in tRNA may lead to abnormal protein synthesis and consequentially lead to pathological conditions such as cancer.

There are a lot of modifications on tRNA to ensure the proper biological function of tRNA. With the progress of sequencing technology, more and more new modifications have been discovered, and abnormal tRNA modifications have been found closely associated with the occurrence of cancers [13,15,94–96]. But in general, the regulatory mechanism of tRNA modification and its role in cancer are far from clear. Furthermore, some modifications such as m1A are widely spread in mRNA, whereas its alteration in tRNA and the role in tumorigenesis are still largely unknown. In this regard, more efforts are still needed to characterize tRNA-specific modifications, which affect some pivotal functions of tRNA such as the ability of tRNA to recognize codons and carry amino acids, as it directly changes the expression of proteins at the translational level. In addition, these tRNA modifying enzymes are highly likely to serve as the target for tumor therapy. It should be pointed out that a specific kind of modification may appear in different positions of tRNA and play different roles, corresponding to different catalytic enzymes. However, there are still a lot of gaps in this question, and lots of modification enzymes of many sites have not been characterized. Their functions need to be further studied, which may be a challenge but also bring us new hope.

In addition, it is important to point out that the cleavage of tRNA under certain conditions has not attracted much attention of researchers till recently. Specific tRFs were found to be significantly differentially expressed in a variety of cancers and were closely associated with the prognosis of cancer patients [97–100]. tRFs may serve as early diagnostic biomarkers. Their production may also be a major reason of drug resistance. However, research in this field is still very limited, and the enzymes involved in tRNA cleavage and their mechanisms of action warrant further exploration. Moreover, targeting these processes may reverse drug resistance and is promising to improve the efficacy of current cancer treatment strategies. Importantly, further studies are warranted for identifying the tRNA-cleaving enzymes and unveiling their mechanisms of action including the motifs they recognize during cleavage, factors affecting the cleavage in tumor microenvironment, and so on. Although the fragments of tRNA, tRFs, have been found to have similar functions as microRNA, some studies have shown that tRFs possess more diverse functions associated with its modifications such as stabilizing mRNA. A clearer understanding of the generation and function of tRFs will help us decipher the role of tRNA in the molecular network of tumorigenesis at post-transcriptional, translational, and post-translational levels. In summary, there are still many unanswered questions about tRNA, a widely known non-coding RNA, and further studies on its generation, modification, and fragmentation are expected to lead to new breakthroughs in cancer therapy.

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One sentence summary

Complex modifications occur on tRNAs and abnormal modifications may lead to functional abnormalities or breakage and formation of tRF_S, which plays a role in the occurrence and development of tumors.

Author contribution

DR, YM, MY, DW, YW, QY and CG collected the related literature and drafted the manuscript. WX, FW and ZZ participated in the design of the review and drafted the manuscript. All authors have read and approved the final manuscript.

Declaration of competing interest

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

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References

[1] R. Giege, Toward a more complete view of tRNA biology, Nat. Struct. Mol. Biol. 15 (10) (2008) 1007–1014.
[2] M.V. Rodnina, W. Wintermeyer, The ribosome as a molecular machine: the mechanism of tRNA-mRNA movement in translocation, Biochem. Soc. Trans. 39 (2) (2011) 658–662.
[3] S. Kirchner, Z. Ignatova, Emerging roles of tRNA in adaptive translation, signalling dynamics and disease, Nat. Rev. Genet. 16 (2) (2015) 98–112.
[4] M. Parisien, X. Wang, T. Pan, Diversity of human tRNA genes from the 1000-genomes project, RNA Biol. 10 (12) (2013) 1853–1867.

[5] F. Juhling, M. Morl, R.K. Hartmann, M. Sprinzl, P.F. Stadler, J. Putz, tRNAdb 2009: compilation of tRNA sequences and tRNA genes, Nucleic Acids Res. 37 (Database issue) (2009) D159–D162.
[6] C. Kutter, G.D. Brown, A. Goncalves, M.D. Wilson, S. Watt, A. Brazma, et al., Pol III binding in six mammals shows conservation among amino acid isotypes despite divergence among tRNA genes, Nat. Genet. 43 (10) (2011) 948–955.
[7] R. Giege, M. Sissler, C. Florentz, Universal rules and idiosyncratic features in tRNA identity, Nucleic Acids Res. 26 (22) (1998) 5017–5035.
[8] T. Dale, O.C. Uhlenbeck, Amino acid specificity in translation, Trends Biochem. Sci. 30 (12) (2005) 659–665.
[9] M. Yang, Y. Mo, D. Ren, S. Liu, Z. Zeng, W. Xiong, Transfer RNA-derived small RNAs in tumor microenvironment, Mol. Cancer 22 (1) (2023) 32.
[10] A. Vannini, P. Cramer, Conservation between the RNA polymerase I, II, and III transcription initiation machineries, Mol. Cell 45 (4) (2012) 439–446.
[11] E.M. Phizicky, A.K. Hopper, tRNA biology charges to the front, Genes Dev. 24 (17) (2010) 1832–1860.
[12] T. Suzuki, The expanding world of tRNA modifications and their disease relevance, Nat. Rev. Mol. Cell Biol. 22 (6) (2021) 375–392.
[13] C. Cirzi, F. Tuorto, Analysis of queuosine tRNA modification using APB Northern Blot Assay, Methods Mol. Biol. 2298 (2021) 217–230.
[14] C.D. Katanski, C.P. Watkins, W. Zhang, M. Reyer, S. Miller, T. Pan, Analysis of queuosine and 2-thio tRNA modifications by high throughput sequencing, Nucleic Acids Res. 50 (17) (2022) e99.
[15] J. Cui, Q. Liu, E. Sendinc, Y. Shi, R.I. Gregory, Nucleotide resolution profiling of m3C RNA modification by HAC-seq, Nucleic Acids Res. 49 (5) (2021) e27.
[16] J.M. Lentini, D. Fu, Monitoring the 5-methoxycarbonylmethyl-2-thiouridine (mcm5s2U) modification utilizing the gamma-toxin endonuclease, Methods Mol. Biol. 2298 (2021) 197–216.
[17] Y. Sugio, R. Yamagami, N. Shigi, H. Hori, A selective and sensitive detection system for 4-thiouridine modification in RNA, RNA 29 (2) (2023) 241–251.
[18] O. Begik, M.C. Lucas, L.P. Pryszcz, J.M. Ramirez, R. Medina, I. Milenkovic, et al., Quantitative profiling of pseudouridylation dynamics in native RNAs with nanopore sequencing, Nat. Biotechnol. 39 (10) (2021) 1278–1291.
[19] S. Lin, Q. Liu, Y.Z. Jiang, R.I. Gregory, Nucleotide resolution profiling of m(7)G tRNA modification by TRAC-Seq, Nat. Protoc. 14 (11) (2019) 3220–3242.
[20] C. Enroth, L.D. Poulsen, S. Iversen, F. Kirpekar, A. Albrechtsen, J. Vinther, Detection of internal N7-methylguanosine (m7G) RNA modifications by mutational profiling sequencing, Nucleic Acids Res. 47 (20) (2019) e126.
[21] X.Y. Jin, Z.R. Huang, L.J. Xie, L. Liu, D.L. Han, L. Cheng, Photo-facilitated detection and sequencing of 5-Formylcytidine RNA, Angew Chem. Int. Ed. Engl. 61 (49) (2022), e202210652.
[22] C.N. Link, S. Thalalla Gamage, D. Gallimore, R. Kopajtich, C. Evans, S. Nance, et al., Protonation-dependent sequencing of 5-Formylcytidine in RNA, Biochemistry 61 (7) (2022) 535–544.
[23] C. Tomikawa, 7-Methylguanosine modifications in transfer RNA (tRNA), Int. J. Mol. Sci. 19 (12) (2018).
[24] A. Alexandrov, M.R. Martzen, E.M. Phizicky, Two proteins that form a complex are required for 7-methylguanosine modification of yeast tRNA, RNA 8 (10) (2002) 1253–1266.
[25] V.S. Zueva, A.S. Mankin, A.A. Bogdanov, L.A. Baratova, Specific fragmentation of tRNA and rRNA at a 7-methylguanine residue in the presence of methylated carrier RNA, Eur. J. Biochem. 146 (3) (1985) 679–687.
[26] V. Marchand, L. Ayadi, F.G.M. Ernst, J. Hertler, V. Bourguignon-Igel, A. Galvanin, et al., AlkAniline-seq: profiling of m(7) G and m(3) C RNA modifications at single nucleotide resolution, Angew Chem. Int. Ed. Engl. 57 (51) (2018) 16785–16790.
[27] L.S. Zhang, C. Liu, H. Ma, Q. Dai, H.L. Sun, G. Luo, et al., Transcriptome-wide mapping of internal N(7)-methylguanosine methylome in mammalian mRNA, Mol. Cell 74 (6) (2019) 1304–13016 e8.
[28] O. Katsara, R.J. Schneider, m(7)G tRNA modification reveals new secrets in the translational regulation of cancer development, Mol. Cell 81 (16) (2021) 3243–3245.
[29] Z. Dai, H. Liu, J. Liao, C. Huang, X. Ren, W. Zhu, et al., N(7)-Methylguanosine tRNA modification enhances oncogenic mRNA translation and promotes intrahepatic cholangiocarcinoma progression, Mol. Cell 81 (16) (2021) 3339–33355 e8.
[30] J. Ma, H. Han, Y. Huang, C. Yang, S. Zheng, T. Cai, et al., METTL1/WDR4-mediated m(7)G tRNA modifications and m(7)G codon usage promote mRNA translation and lung cancer progression, Mol. Ther. 29 (12) (2021) 3422–3435.
[31] X. Ying, B. Liu, Z. Yuan, Y. Huang, C. Chen, X. Jiang, et al., METTL1-m(7) G-EGFR/EFEMP1 axis promotes the bladder cancer development, Clin. Transl. Med. 11 (12) (2021) e675.
[32] B. Chen, W. Jiang, Y. Huang, J. Zhang, P. Yu, L. Wu, et al., N(7)-methylguanosine tRNA modification promotes tumorigenesis and chemoresistance through WNT/beta-catenin pathway in nasopharyngeal carcinoma, Oncogene 41 (15) (2022) 2239–2253.
[33] H. Han, C. Yang, J. Ma, S. Zhang, S. Zheng, R. Ling, et al., N(7)-methylguanosine tRNA modification promotes esophageal squamous cell carcinoma tumorigenesis via the RPTOR/ULK1/autophagy axis, Nat. Commun. 13 (1) (2022) 1478.
[34] S. Noguchi, Y. Nishimura, Y. Hirota, S. Nishimura, Isolation and characterization of an Escherichia coli mutant lacking tRNA-guanine transglycosylase. Function and biosynthesis of queuosine in tRNA, J. Biol. Chem. 257 (11) (1982) 6544–6550.
[35] R. Zallot, C. Brochier-Armanet, K.W. Gaston, F. Forouhar, P.A. Limbach, J. F. Hunt, et al., Plant, animal, and fungal micronutrient queuosine is salvaged by members of the DUF2419 protein family, ACS Chem. Biol. 9 (8) (2014) 1812–1825.
[36] E. Randerath, H.P. Agrawal, K. Randerath, Specific lack of the hypermodified nucleoside, queuosine, in hepatoma mitochondrial aspartate transfer RNA and its possible biological significance, Cancer Res. 44 (3) (1984) 1167–1171.
[37] U. Gunduz, M.S. Elliott, P.H. Seubert, J.A. Houghton, P.J. Houghton, R. W. Trewyn, et al., Absence of tRNA-guanine transglycosylase in a human colon adenocarcinoma cell line, Biochim. Biophys. Acta 1139 (3) (1992) 229–238.
[38] C. Pathak, Y.K. Jaiswal, M. Vinayak, Hypomodification of transfer RNA in cancer with respect to queuosine, RNA Biol. 2 (4) (2005) 143–148.
[39] M. Vinayak, C. Pathak, Queuosine modification of tRNA: its divergent role in cellular machinery, Biosci. Rep. 30 (2) (2009) 135–148.
[40] J. Zhang, R. Lu, Y. Zhang, Z. Matuszek, W. Zhang, Y. Xia, et al., tRNA queuosine modification enzyme modulates the growth and microbiome recruitment to breast tumors, Cancers 12 (3) (2020).
[41] C. Pathak, Y.K. Jaiswal, M. Vinayak, Queuine promotes antioxidant defence system by activating cellular antioxidant enzyme activities in cancer, Biosci. Rep. 28 (2) (2008) 73–81.
[42] P. Hayes, C. Fergus, M. Ghanim, C. Cirzi, L. Burtnyak, C.J. McGrenaghan, et al., Queuine micronutrient deficiency promotes Warburg metabolism and reversal of the mitochondrial ATP synthase in Hela cells, Nutrients 12 (3) (2020).
[43] A. Esberg, B. Huang, M.J. Johansson, A.S. Bystrom, Elevated levels of two tRNA species bypass the requirement for elongator complex in transcription and exocytosis, Mol. Cell 24 (1) (2006) 139–148.
[44] D.D. Nedialkova, S.A. Leidel, Optimization of codon translation rates via tRNA modifications maintains proteome integrity, Cell 161 (7) (2015) 1606–1618.
[45] H. Tukenmez, H. Xu, A. Esberg, A.S. Bystrom, The role of wobble uridine modifications in +1 translational frameshifting in eukaryotes, Nucleic Acids Res. 43 (19) (2015) 9489–9499.
[46] R. Klassen, A. Bruch, R. Schaffrath, Independent suppression of ribosomal +1 frameshifts by different tRNA anticodon loop modifications, RNA Biol. 14 (9) (2017) 1252–1259.
[47] K. Joshi, M.J. Bhatt, P.J. Farabaugh, Codon-specific effects of tRNA anticodon loop modifications on translational misreading errors in the yeast Saccharomyces cerevisiae, Nucleic Acids Res. 46 (19) (2018) 10331–10339.
[48] R. Klassen, R. Schaffrath, Collaboration of tRNA modifications and elongation factor eEF1A in decoding and nonsense suppression, Sci. Rep. 8 (1) (2018), 12749.
[49] N. Ranjan, M.V. Rodnina, Thio-modification of tRNA at the wobble position as regulator of the kinetics of decoding and translocation on the ribosome, J. Am. Chem. Soc. 139 (16) (2017) 5857–5864.
[50] S. Delaunay, F. Rapino, L. Tharun, Z. Zhou, L. Heukamp, M. Termathe, et al., Elp3 links tRNA modification to IRES-dependent translation of LEF1 to sustain metastasis in breast cancer, J. Exp. Med. 213 (11) (2016) 2503–2523.
[51] F. Rapino, S. Delaunay, F. Rambow, Z. Zhou, L. Tharun, P. De Tullio, et al., Codon-specific translation reprogramming promotes resistance to targeted therapy, Nature 558 (7711) (2018) 605–609.
[52] F. Rapino, P. Close, Wobble uridine tRNA modification: a new vulnerability of refractory melanoma, Mol Cell Oncol 5 (6) (2018), e1513725.
[53] V. Scheidt, A. Judes, C. Bar, R. Klassen, R. Schaffrath, Loss of wobble uridine modification in tRNA anticodons interferes with TOR pathway signaling, Microb. Cell 1 (12) (2014) 416–424.
[54] D. Chen, I. Nemazanyy, O. Peulen, K. Shostak, X. Xu, S.C. Tang, et al., Elp3-mediated codon-dependent translation promotes mTORC2 activation and regulates macrophage polarization, EMBO J. 41 (18) (2022), e109353.
[55] A. Rosu, N. El Hachem, F. Rapino, K. Rouault-Pierre, J. Jorssen, J. Somja, et al., Loss of tRNA-modifying enzyme Elp3 activates a p53-dependent antitumor checkpoint in hematopoiesis, J. Exp. Med. 218 (3) (2021).
[56] P. Lemaitre, Q. Bai, C. Legrand, A. Chariot, P. Close, F. Bureau, et al., Loss of the transfer RNA wobble uridine-modifying enzyme Elp3 delays T cell cycle entry and impairs T follicular helper cell responses through deregulation of Atf4, J. Immunol. 206 (5) (2021) 1077–1087.
[57] J. Ge, Y.T. Yu, RNA pseudouridylation: new insights into an old modification, Trends Biochem. Sci. 38 (4) (2013) 210–218.
[58] N.S. Heiss, S.W. Knight, T.J. Vulliamy, S.M. Klauck, S. Wiemann, P.J. Mason, et al., X-linked dyskeratosis congenita is caused by mutations in a highly conserved gene with putative nucleolar functions, Nat. Genet. 19 (1) (1998) 32–38.
[59] D.Y. Zhang, G.L. Ming, H. Song, PUS7: a targetable epitranscriptomic regulator of glioblastoma growth, Trends Pharmacol. Sci. 42 (12) (2021) 976–978.
[60] J. Song, Y. Zhuang, C. Zhu, H. Meng, B. Lu, B. Xie, et al., Differential roles of human PUS10 in miRNA processing and tRNA pseudouridylation, Nat. Chem. Biol. 16 (2) (2020) 160–169.
[61] N. Guzzi, S. Muthukumar, M. Ciesla, G. Todisco, P.C.T. Ngoc, M. Madej, et al., Pseudouridine-modified tRNA fragments repress aberrant protein synthesis and predict leukaemic progression in myelodysplastic syndrome, Nat. Cell Biol. 24 (3) (2022) 299–306.
[62] H. Song, J. Zhang, B. Liu, J. Xu, B. Cai, H. Yang, et al., Biological roles of RNA m (5)C modification and its implications in Cancer immunotherapy, Biomarkers Res. 10 (1) (2022) 15.
[63] V.Y. Vare, E.R. Eruysal, A. Narendran, K.L. Sarachan, P.F. Agris, Chemical and conformational diversity of modified nucleosides affects tRNA structure and function, Biomolecules 7 (1) (2017).
[64] F. Tuorto, R. Liebers, T. Musch, M. Schaefer, S. Hofmann, S. Kellner, et al., RNA cytosine methylation by Dnmt2 and NSun2 promotes tRNA stability and protein synthesis, Nat. Struct. Mol. Biol. 19 (9) (2012) 900–905.
[65] Z.X. Huang, J. Li, Q.P. Xiong, H. Li, E.D. Wang, R.J. Liu, Position 34 of tRNA is a discriminative element for m5C38 modification by human DNMT2, Nucleic Acids Res. 49 (22) (2021) 13045–13061.

[66] B. Genenncher, Z. Durdevic, K. Hanna, D. Zinkl, M.B. Mobin, N. Senturk, et al., Mutations in cytosine-5 tRNA methyltransferases impact mobile element expression and genome stability at specific DNA repeats, Cell Rep. 22 (7) (2018) 1861–1874.
[67] M. Okamoto, M. Fujiwara, M. Hori, K. Okada, F. Yazama, H. Konishi, et al., tRNA modifying enzymes, NSUN2 and METTL1, determine sensitivity to 5-fluorouracil in HeLa cells, PLoS Genet. 10 (9) (2014), e1004639.
[68] J.C. Yang, E. Risch, M. Zhang, C. Huang, H. Huang, L. Lu, Association of tRNA methyltransferase NSUN2/IGF-II molecular signature with ovarian cancer survival, Future Oncol. 13 (22) (2017) 1981–1990.
[69] L. Lu, G. Zhu, H. Zeng, Q. Xu, K. Holzmann, High tRNA transferase NSUN2 gene expression is associated with poor prognosis in head and neck squamous carcinoma, Cancer Invest. 36 (4) (2018) 246–253.
[70] C.U. Awah, J. Winter, C.M. Mazdoom, O.O. Ogunwobi, NSUN6, an RNA methyltransferase of 5-mC controls glioblastoma response to temozolomide (TMZ) via NELFB and RPS6KB2 interaction, Cancer Biol. Ther. 22 (10–12) (2021) 587–597.
[71] R. Yang, X. Liang, H. Wang, M. Guo, H. Shen, Y. Shi, et al., The RNA methyltransferase NSUN6 suppresses pancreatic cancer development by regulating cell proliferation, EBioMedicine 63 (2021), 103195.
[72] E. Lesniewska, M. Boguta, Novel layers of RNA polymerase III control affecting tRNA gene transcription in eukaryotes, Open Biol. 7 (2) (2017).
[73] J.R. Malcolm, N.K. Leese, P.I. Lamond-Warner, W.J. Brackenbury, R.J. White, Widespread association of ERalpha with RMRP and tRNA genes in MCF-7 cells and breast cancers, Gene 821 (2022), 146280.
[74] J. Yang, D.K. Smith, H. Ni, K. Wu, D. Huang, S. Pan, et al., SOX4-mediated repression of specific tRNAs inhibits proliferation of human glioblastoma cells, Proc. Natl. Acad. Sci. U. S. A. 117 (11) (2020) 5782–5790.
[75] J. Guillon, H. Coquelet, G. Leman, B. Toutain, C. Petit, C. Henry, et al., tRNA biogenesis and specific aminoacyl-tRNA synthetases regulate senescence stability under the control of mTOR, PLoS Genet. 17 (12) (2021), e1009953.
[76] E. Khattar, P. Kumar, C.Y. Liu, S.C. Akincilar, A. Raju, M. Lakshmanan, et al., Telomerase reverse transcriptase promotes cancer cell proliferation by augmenting tRNA expression, J. Clin. Invest. 126 (10) (2016) 4045–4060.
[77] S.E. Dremel, F.L. Sivrich, J.M. Tucker, B.A. Glaunsinger, N.A. DeLuca, Manipulation of RNA polymerase III by herpes simplex virus-1, Nat. Commun. 13 (1) (2022) 623.
[78] M.C. Passarelli, A.M. Pinzaru, H. Asgharian, M.V. Liberti, S. Heissel, H. Molina, et al., Leucyl-tRNA synthetase is a tumour suppressor in breast cancer and regulates codon-dependent translation dynamics, Nat. Cell Biol. 24 (3) (2022) 307–315.
[79] P. Thandapani, A. Kloetgen, M.T. Witkowski, C. Glytsou, A.K. Lee, E. Wang, et al., Valine tRNA levels and availability regulate complex I assembly in leukaemia, Nature 601 (7893) (2022) 428–433.
[80] J.B. Stewart, B. Alaei-Mahabadi, R. Sabarinathan, T. Samuelsson, J. Gorodkin, C. M. Gustafsson, et al., Simultaneous DNA and RNA mapping of somatic mitochondrial mutations across diverse human cancers, PLoS Genet. 11 (6) (2015), e1005333.
[81] M. Rossello-Tortella, A. Bueno-Costa, L. Martinez-Verbo, L. Villanueva, M. Esteller, DNA methylation-associated dysregulation of transfer RNA expression in human cancer, Mol. Cancer 21 (1) (2022) 48.
[82] S.M. Lyons, C. Achorn, N.L. Kedersha, P.J. Anderson, P. Ivanov, YB-1 regulates tiRNA-induced Stress Granule formation but not translational repression, Nucleic Acids Res. 44 (14) (2016) 6949–6960.
[83] S.M. Lyons, D. Gudanis, S.M. Coyne, Z. Gdaniec, P. Ivanov, Identification of functional tetramolecular RNA G-quadruplexes derived from transfer RNAs, Nat. Commun. 8 (1) (2017) 1127.
[84] N. Luan, Y. Mu, J. Mu, Y. Chen, X. Ye, Q. Zhou, et al., Dicer1 promotes colon cancer cell invasion and migration through modulation of tRF-20-MEJB5Y13 expression under hypoxia, Front. Genet. 12 (2021), 638244.
[85] S. Li, X. Shi, M. Chen, N. Xu, D. Sun, R. Bai, et al., Angiogenin promotes colorectal cancer metastasis via tiRNA production, Int. J. Cancer 145 (5) (2019) 1395–1407.
[86] Y. Cui, Y. Huang, X. Wu, M. Zheng, Y. Xia, Z. Fu, et al., Hypoxia-induced tRNA-derived fragments, novel regulatory factor for doxorubicin resistance in triple-negative breast cancer, J. Cell. Physiol. 234 (6) (2019) 8740–8751.
[87] M.M. Emara, P. Ivanov, T. Hickman, N. Dawra, S. Tisdale, N. Kedersha, et al., Angiogenin-induced tRNA-derived stress-induced RNAs promote stress-induced stress granule assembly, J. Biol. Chem. 285 (14) (2010) 10959–10968.
[88] X. Mo, S. Du, X. Chen, Y. Wang, X. Liu, C. Zhang, et al., Lactate induces production of the tRNA(his) half to promote B-lymphoblastic cell proliferation, Mol. Ther. 28 (11) (2020) 2442–2457.
[89] S. Honda, P. Loher, M. Shigematsu, J.P. Palazzo, R. Suzuki, I. Imoto, et al., Sex hormone-dependent tRNA halves enhance cell proliferation in breast and prostate cancers, Proc. Natl. Acad. Sci. U. S. A. 112 (29) (2015) E3816–E3825.
[90] M. Shigematsu, Y. Kirino, 5'-Terminal nucleotide variations in human cytoplasmic tRNAHisGUG and its 5'-halves, RNA 23 (2) (2017) 161–168.
[91] Z. Su, C. Kuscu, A. Malik, E. Shibata, A. Dutta, Angiogenin generates specific stress-induced tRNA halves and is not involved in tRF-3-mediated gene silencing, J. Biol. Chem. 294 (45) (2019) 16930–16941.
[92] J.M. Schifano, J.W. Cruz, I.O. Vvedenskaya, R. Edifor, M. Ouyang, R.N. Husson, et al., tRNA is a new target for cleavage by a MazF toxin, Nucleic Acids Res. 44 (3) (2016) 1256–1270.
[93] E.J. Choi, W. Wu, K. Zhang, I. Lee, I.H. Kim, Y.S. Lee, et al., ELAC2, an enzyme for tRNA maturation, plays a role in the cleavage of a mature tRNA to produce a tRNA-derived RNA fragment during respiratory syncytial virus infection, Front. Mol. Biosci. 7 (2020), 609732.
[94] Y.L. Pang, R. Abo, S.S. Levine, P.C. Dedon, Diverse cell stresses induce unique patterns of tRNA up- and down-regulation: tRNA-seq for quantifying changes in tRNA copy number, Nucleic Acids Res. 42 (22) (2014), e170.
[95] J.F. Hu, D. Yim, D. Ma, S.M. Huber, N. Davis, J.M. Bacusmo, et al., Quantitative mapping of the cellular small RNA landscape with AQRNA-seq, Nat. Biotechnol. 39 (8) (2021) 978–988.
[96] L. Dou, W. Zhou, L. Zhang, L. Xu, K. Han, Accurate identification of RNA D modification using multiple features, RNA Biol. 18 (12) (2021) 2236–2246.
[97] Y. Wu, X. Yang, G. Jiang, H. Zhang, L. Ge, F. Chen, et al., 5'-tRF-GlyGCC: a tRNA-derived small RNA as a novel biomarker for colorectal cancer diagnosis, Genome Med. 13 (1) (2021) 20.
[98] Y. Zhang, Z. Bi, X. Dong, M. Yu, K. Wang, X. Song, et al., tRNA-derived fragments: tRF-Gly-CCC-046, tRF-Tyr-GTA-010 and tRF-Pro-TGG-001 as novel diagnostic biomarkers for breast cancer, Thorac. Canc. 12 (17) (2021) 2314–2323.
[99] Y. Shen, X. Yu, Y. Ruan, Z. Li, Y. Xie, Z. Yan, et al., Global profile of tRNA-derived small RNAs in gastric cancer patient plasma and identification of tRF-33-P4R8YP9LON4VDP as a new tumor suppressor, Int. J. Med. Sci. 18 (7) (2021) 1570–1579.
[100] Y. Huang, H. Zhang, X. Gu, S. Qin, M. Zheng, X. Shi, et al., Elucidating the role of serum tRF-31-U5YKFN8DYDZDD as a novel diagnostic biomarker in gastric cancer (GC), Front. Oncol. 11 (2021), 723753.