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The Roles of tRNA-Derived Fragments in Cancers: Updates and Perspectives

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Abstract: The non-coding RNAs (ncRNAs) have been reported in numerous studies, and their significant roles in several diseases have been verified subsequently. tRNA-derived fragments (tRFs) are a newly discovered class of small ncRNAs which are produced by mature or precursor tRNAs. In light of the development of RNA sequencing, the evidences have shown that tRFs are widely involved in the generation and progression of diseases by series mechanisms including RNA silencing, translational regulation, epigenetic regulation, reverse-transcriptional regulation, cellular apoptosis. Several researches have identified tRFs participate varied aspects in several cancers. Furthermore, these novel tRFs may hold significant potential as both diagnostic biomarkers and therapeutic targets in clinical applications. In this review, we discuss the biogenesis and classification of tRFs, illustrate the fundamental functions of tRFs, and summarize the most recent discoveries of tRFs in cancers.

Keywords: non-coding RNA; tRNA-derived fragments; biomarker; cancer

1. Introduction

Non-coding RNAs (ncRNAs) have been the focus of many studies over the last few decades, including long non-coding RNAs (lncRNAs) and small non-coding RNAs (sncRNAs), in various biological processes [1]. There is increasing evidence that sncRNAs play critical roles in multiple regulatory processes, including transcription, post-transcription, and translation. The involvement of sncRNAs in complex mechanisms is vital to the development and progression of cancers and their potential value as biomarkers and/or therapeutic targets has gaining heightened focus [2,3].

With the development of high-throughput sequencing technology and improvements in bioinformatics analysis, in addition to endogenous siRNAs (endosiRNAs), microRNAs (miRNAs), and Piwi-interacting RNAs (piRNAs) [4], researchers have uncovered the existence of a new type of sncRNAs derived from tRNAs, called tRNA-derived fragments (tRFs). tRFs, 14 to 32 nt long single-stranded RNA, are generated from mature tRNAs or precursor tRNAs at different sites under the control of a set of highly conservative and precise site-specific cutting mechanisms [1,5,6]. Emerging evidence indicates that tRFs may participate in cell proliferation, priming of viral reverse transcriptases, regulation of gene expression, RNA processing, modulation of the DNA damage response, tumor suppression, and neurodegeneration [7]. Moreover, tRFs have emerged as key contributors to the development and progression of multiple human pathologies, including cancer [8,9], inflammation [10], metabolic disorder [11], infection [12–14], and neurodegenerative disease [15,16]. Here, we will review the biogenesis and classification of tRFs and demonstrate parts of the major biological functions of tRFs as well as recent reports on the roles of tRFs in different types of cancer.

2. Biogenesis and Classification

tRNAs experience comprehensive processing and a series of chemical modifications throughout their lifecycle. In eukaryocyte, pre-tRNAs undergo ribonuclease P and ribonuclease Z cleavage of the 5' leader and 3' tail sequences respectively [17,18]. And the addition of the CCA tail is catalyzed by CCA-adding enzyme (tRNA nucleotidyltransferase) [19]. This is accompanied by further modifications, ultimately leading to the formation of mature tRNA. The structure of mature tRNA is highly conserved and characterized by a distinctive configuration comprising four arms (stem and loop): the D-arm, anticodon arm, TΨC arm, acceptor arm, and variable arm at the connection of the anticodon arm and the TΨC arm [20,21]. Mature tRNAs or pre-tRNAs can be cleaved at specific positions by corresponding ribonucleases, thereby generating a diverse array of tRFs [22–24]. As classified, tRNAs can generate 5 subtypes of tRFs: tRF-5 (5'-tRF), tRF-3(3'-tRF), i-tRF, tRNA halves and tRF-1. The former four types of tRFs are derived from mature tRNAs, and tRF-1s come from pre-tRNA.

tRF-5s are produced by cleavage of the 5' end in D-arm and tRF-3s are produced through cleavage of the 3' end in TΨC arm, respectively [25,26]. tRF-5s can be classified into three specific subtypes for diverse length: i) type a (14–16 nt), ii) type b (22–24 nt), and iii) type c (28–30 nt), and the cleavage sites for type a, b, and c locates in the D loop, D stem, and the 5' half of the anticodon stem [5,27]. The tRF-3s can be cleaved into two subcategories: tRF-3a and tRF-3b. The diversity between these two subtypes is that the members of tRF-3b family are ~4 nt longer than the tRF-3a family, which the length of tRF-3a is 18 nt and tRF-3b is 22 nt long approximately [5,28]. Generally, tRF-5s and tRF-3s are generated from Dicer-dependent fashion [14,28]; however, now evidences from subsequent investigations have revealed that angiogenin (ANG) and other members of the ribonuclease A superfamily are actively involved in the biogenesis of these tRFs [28,29].

i-tRFs are a new type of tRF that originate from the internal zone of mature tRNAs. Different starting positions of cleavage define the different i-tRF subtypes. Based on the location of the 5'terminus along the mature tRNA, one research divided i-tRFs into six subtypes [30]. In addition, there are other classification methodologies. The generation of i-tRFs may be associated with some specific conditions such as hypoxia [31]. The biogenesis and generation of i-tRFs are demonstrated incompletely and still require further research.

tRNA halves, also defined as tRNA-derived stress-induced RNAs (tiRNAs), are generated through the cleavage of mature tRNAs at the anticodon arm by ANG, divided into 5'-half and 3'-half [32]. 5'-halves have 30–35 nts ranging from the 5' end to the anticodon loop, while 3'- halves have 40–50 nts from the anticodon loop to the 3' end [6,26]. As a stress-inducible ribonuclease, the biological function of ANG exhibits a strong correlation with the cellular status. Under various stress conditions including heat shock, ultraviolet irradiation, hypoxia, arsenite exposure, lack of amino acids, and viral infection, the specific cleavage of tRNAs by ANG is typically induced, leading to the generation of tRNA halves [26,33–35]. One study found that ANG is not the only RNase that produces tRNA halves, as other RNases may also be involved in this procession [36]. Whereas, tRNA halves are often produced disproportionately, leading to a much more amount of 5'-halves than 3'-halves [37].

Distinct from other tRFs, tRF-1s are produced from tRNA maturation, which is originated from the 3' trailer fragment of tRNA before the addition of CCA tail trimmed by the endonuclease Z (RNaseZ/ELAC2) [23,38]. With 16–48 nt in length, tRF-1s begin the downstream of the 3' end in the pre-tRNA and end with a polyuridine sequence (UUUUU, UUCUU, AUCUU, or GUCUU) [23,39]. However, tRF-1s are almost cytoplasmic, which is considered to undergo translocation following their biogenesis in the nucleus [40].
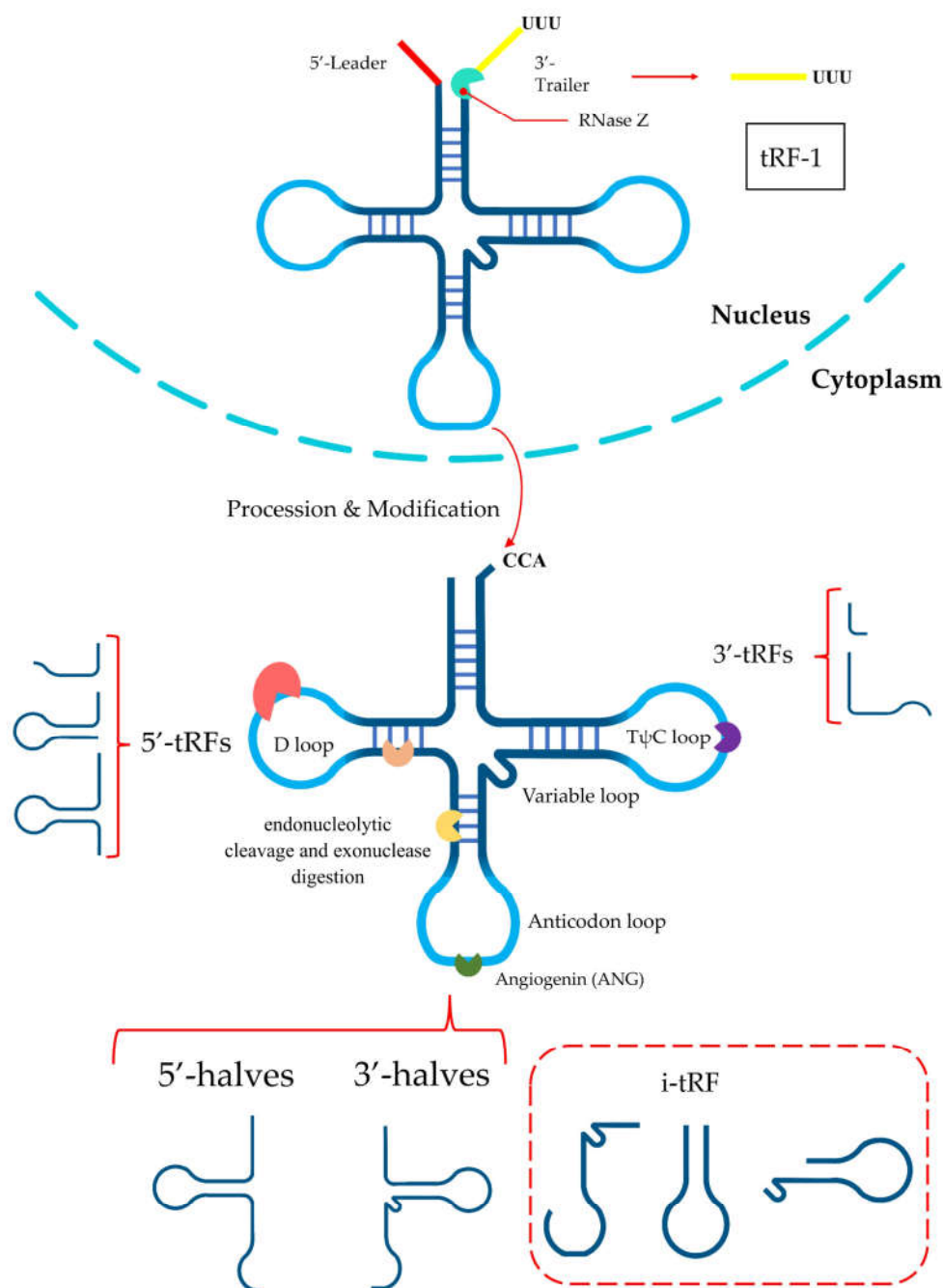
Figure 1. Different types of tRNA-derived RNA fragments. tRF-5s are produced by cleavage of the 5' end in D-arm and tRF-3s are produced through cleavage of the 3' end in TψC arm. tRNA halves are generated through the cleavage of mature tRNAs at the anticodon arm by ANG. i-tRFs are a new type of tRF that originate from the internal zone of mature tRNAs. tRF-1s are produced from tRNA maturation.

3. Biological Functions of tRFs

Increasing depth of RNA sequencing has enabled the discovery of the Biogenesis and the clarification of Categories of tRFs, which gives us an opportunity to Explore the fundamental functions of tRFs. Although the biological functions of tRFs are complicated and necessitate additional investigation, our current knowledge of their function has been summarized into five categories as follows, including RNA silencing, translational regulation, epigenetic regulation, reverse-transcriptional regulation, cellular apoptosis.

3.1. RNA Silencing

Recent researches cast more light on tRFs' important roles in RNA interference (RNAi)-mediated silencing. Several studies have indicated that disparate tRFs show distinct affinities with various AGO subtypes. Meta-analysis of PAR-CLIP data reveals that tRF-5s and tRF-3s are associated with AGO1, 3 and 4 rather than AGO2, and analysis of positional T to C mutational frequency indicates the pattern of the association between tRFs and Argonautes is similar to that of miRNAs [5]. For example, Green's group illustrated that a specific tRF namely tRF-3003a，produced by the cleavage of tRNA-CysGCA confers gene silencing of Janus Kinase 3 (JAK3) via AGO/RISC formation in osteoarthritis chondrocytes [41]. In contrast to microRNAs, tRFs exhibit a distinct subcellular localization predominantly within the cytoplasmic compartment and demonstrate selective binding to Argonautes, while notably lacking association with the MOV10. Moreover, tRF-3s exhibits canonical microRNA-/siRNA-like trans-silencing capacity, while tRF-1 does not exhibit apparent trans-silencing activity [38]. Further study shows that Dicer-dependent tRFs promote gene silencing through a mechanism distinct from PTGS and TGS which can lead to downregulation of target genes by targeting introns via nascent RNA silencing (NRS) in nuclei [42]. In addition to AGO-dependent mechanism for gene silencing by tRFs, AGO-independent mechanisms have been confirmed to exist, including competitive binding of target proteins with mRNAs. Hee et al. demonstrated RF-U3-1 inhibits HCV IRES-mediated translation by sequestering the limiting amounts of La/SSB available in the cytoplasm via La/SSB knockout Huh7 cell lines [43]. Hence, tRFs might be involved in multiple pathways to regulate RNA silencing which is urgingly needed to be discovered.

3.2. Translational Regulation

tRFs can modulate translational processes through the regulation of translation initiation, elongation, and ribosome biogenesis, thereby exerting an influence on the overall synthesis of proteins. The involvement of tRFs in the regulation of translation was initially discovered in stress-related conditions [32]. It has identified that transfection of natural 5'-halves, but not 3'-halves, results in the suppression of global translation in U2OS cells [32]. As previously mentioned, cellular stress leads to the production of tRNA halves by ANG. These specific 5'-tiRNAs such as 5'-tiRNAAla and 5'-tiRNACys can possess the ability to displace the mRNA cap-binding protein eIF4E [44]. Further research found this restraint is achieved by the aggregation of 5'-tiRNAs into tetrameric G-quadruplexes (G4) mediated through the 5' terminal oligoguanine (5' TOG) motif [45,46]. G4-tiRNAs, confirmed to be necessary for tRFs in the regulation of mRNA translation, can directly binding to the HEAT1 domain of eIF4G [45,47]. And this displacement can induce the phospho-eIF2α independent assembly of stress granules (SGs) and leading to the failure of the translation initiation scanning process, consequently suppressing the global translation [48].

Besides tRNA halves, the tRF-5s can also affect translation. A study demonstrated in embryonic stem cells, the Ψ modification at U8 mediated by PUS7 can motivate TOG -containing tRF-5s to bind to polyadenylate-binding protein 1 (PABPC1), a protein in charge of eIF4G/A interaction and initiation of cap-dependent translation. The mTOG-PABPC1 complex can intercept PABPC1 recruitment to eIF4F, thus blocking translation [49]. And a general conserved "GG" dinucleotide in tRF-5s is also revealed to engage the process of protein translation [50].

A considerable fact in the production of tsRNAs is the 5-methylcytosine (m5C) modification. NSun2 is a specific cytosine-5 RNA methyltransferase of proteins that methylates the cytidine residues of most tRNAs. When in abstraction of NSun2, the loss of cytosine-5 RNA methylation increases the cleavage of tRNA resulting an accumulation of 5'tRFs. These abnormal processes reduce protein translation rates eventually [37].

Besides, tRFs can also promote protein generation through strengthening translation-induced ribosome biogenesis. Binding at least two ribosomal protein (RPS28 and RPS15) mRNAs, a kind of 3'-tRF from -tRNALeu (CAG) can enhance translation [51].

3.3. Epigenetic Regulation

The regulation of genetic expression is mediated through an integrated interplay between genomic DNA sequences and epigenetic regulatory mechanisms. Epigenetics regulate gene expression mainly through DNA methylation, histone modification, nucleosome remodeling, and ncRNA regulation [52]. Previous studies have highlighted the evidence suggesting that Epigenetic mis-regulation can culminate in human diseases, such as cancer [53]. Here we will summarize potential epigenetic mechanisms of tRFs into two basic parts: PIWI-independent epigenetic regulation and PIWI-dependent epigenetic regulation.

Transposons are genetic sequences that can translocate their sites within a genome [54], which together with their repetitive sequences contribute to the formation and function of chromosomes, and induce epigenetic regulation of specific genes. Because of the high mobility and mutation of transposons, eukaryotic cells have evolved retiform epigenetic mechanisms in order to preserve the genetic integrity [55]. Furthermore, Substantial evidence has shown that various cancers are significantly correlated with the transcriptional activity of transposons which is concordant with above statement. Recently, Andrea et al. discovered that tRF-3s (18 and 22 nt in length) containing the 3'-terminal CCA sequence of mature tRNAs could inhibit long terminal repeat (LTR)-retrotransposons (also known as endogenous retroviruses; ERVs) by different mechanisms involving sequence complementarity with the PBS sequence [56]. Besides, Sharma et al. identified that 5' tRF-Gly-GCC (tRF-GG) affects chromatin accessibility in MERVL elements and throughout heterochromatin in embryonic stem (ES) cells and preimplantation embryos [57]. Sharma's discovery suggests that the underlying mechanisms of interactions between tRFs and chromatin remain to be elucidated, thereby offering novel insights for future investigations.

Next, we will briefly introduce PIWI-dependent epigenetic regulation of tRFs. Couvillion et al. revealed the potential connection between tRF-3s, 18–22 nt length tsRNA with the predominant 5' end in the TΨC loop and the 3' end at the mature tRNA 3' terminus, and the Tetrahymena thermophila Ago/Piwi protein Twi12 and their essential roles in epigenetic regulation [58]. They discovered that tRF-3 is implicated in nuclear translocation of Twi12, while Twi12 plays essential roles in ribosomal RNA processing by assembling with Xrn2 and Tan1 proteins [58]. Another research elucidated that IL-4 potently decreases the biogenesis of a PIWI-interacting RNAs (piRNAs), tRNA-Glu–derived piRNAs [td-piR(Glu)]. Further, Xue Zhang et al. revealed that the td-piR(Glu)/PIWIL4 complex recruits SETDB1, SUV39H1, and heterochromatin protein 1b to the CD1A promoter region and facilitates H3K9 methylation, leading to the significant inhibition of transcription of CD1A [59]. These results suggest that td-piR(Glu) participates in chromatin remodeling in immune cells.

3.4. Reverse-Transcriptional Regulation

A part of roles of tRFs in reverse transcription have also been demonstrated by some studies including gene expression and oncology [60]. A study conducted in mice has identified that 3'-tRFs are crucial regulators of the retrotransposons in the cell [61]. Transposable elements (TEs) actuate transcription, and in mice, the most active transposons are long terminal repeat (LTR)-retrotransposons, also called as endogenous retroviruses (ERVs). There is a large amount of 3'-tRFs attacking ERVs in mouse stem cell lines. The 18 nt 3'-tRFs specifically restrain ERVs' activity by competing with tRNAs for the highly conserved primer binding site (PBS) of ERVs, resulting the blockade of reverse transcription. Meanwhile, it is noteworthy that the 22 nt 3'-tRFs can also bind to the PBS sequence, which affect transposon expression by post-transcriptionally silencing of ERV mRNA [61]. Both of these two 3'-tRFs inhibit ERVs activity by different mechanisms but both depending on base complementarity with PBS sequence.

And in viral, especially in retrovirus infection, tRFs can affect the reverse transcription. Human T cell lymphotroic virus Type I (HTLV-1) is a human retrovirus first discovered [62]. In infected CD4 cells, tRF-3s are considerably more abundant than other tRFs [63]. Among the tRF-3s, tRF-3019 corresponds to the 3' end of tRNA-Pro, the tRNA considered to be the primer for HTLV-1 reverse transcriptase [64]. The portion of tRNA-Pro corresponding to tRF-3019 is complementary to the

HTLV-1 PBS, which may reveal that the tRF would be fully sufficient as a primer for reverse transcription. As a reverse transcription primer, this special kind of tRF-3 can induce HTLV-1 to initiate reverse transcription and accumulate the replication of virus [60,63].

3.5. Cellular Apoptosis

Recent studies have indicated the potential role of tRFs in regulating cell apoptosis. Previous reports demonstrated that apoptosome formation in vitro was inhibited by the addition of in vitro-synthesized full-length tRNAs [65–67]. Subsequent research has disclosed that angiogenin-induced accumulation of tRNA halves (or tiRNAs) is associated with increased survival in hyper-osmotically stressed mouse embryonic fibroblasts by inhibiting cell apoptosis. The underlying mechanism is that Cyt c released from the mitochondria during hyperosmotic stress forms RNPs with tRNAs, which disturb the formation of the apoptosome by interfering the interaction of apoptotic protease activating factor-1 (APAF1) and Cyt c. Saikia et al. revealed a novel signaling pathway that interferes with Cyt c-mediated caspase activation, a novel function of tiRNAs as inhibitors of apoptosome formation and function, and a novel antiapoptotic mechanism involving ANG-mediated tRNA cleavage. However, how cytochrome c recognizes specific tRNA targets needs further research [68].

Another study discovered a novel tRFs, tRF-3022b, which shows an increasing trend in CRC tissues compared to adjacent normal tissues, utilizing whole-transcriptome sequencing technology. tRF-3022b plays a vital role in apoptosis inhibition and CRC progression through the regulatory pathway by binding to galectin 1 (LGALS1) and macrophage migration inhibitory factor (MIF) in CRC cells [69]. But tRFs are not always play the bad guy in cancer. Ling Pan et al. identified an inflammatory cytokine – regulated transfer RNA – derived (tRNA-derived) fragment, tRF-21-VBY9PYKHD (tRF-21), which suppresses the progression of pancreatic ductal adenocarcinoma (PDAC) by enhancing apoptosis. Further research revealed that tRF-21 knockdown promotes the phosphorylation of heterogeneous nuclear ribonucleoprotein L (hnRNP L) and the formation of hnRNP L and dead-box helicase 17 (DDX17) complexes. These complexes play crucial roles in splicing Caspase 9 into Caspase 9b (with anti-apoptotic specificity) and mH2A1.2 (with pro-invasive specificity), while upregulation of tRF-21 exerts the opposite effect [70].

4. tRFs in Cancer

Through deep sequencing and microarrays, more tRFs have been detected and promoted the development of several tRF-related databases [51,71]. Thus, the function of tRFs in specific disease is clear gradually. The occurrence and progression of cancers are closely associated with abnormal gene expression. More empirical data substantiates the involvement of tRFs in a multitude of biological mechanisms that are intricately linked to the oncogenesis and advancement of malignancies. One possible explanation is rapid proliferation in tumor cells often results in deficiency of blood supply leading to hypoxic stress and other tumor microenvironment (TME). To adapt the stressful environments, tumors adopt several unique mechanisms which may promote the production of tRFs for responses to stress. Given the distinct spatiotemporal characteristics of various cancer cell types, the interactions between different cancer cells and their respective internal tRFs exhibit significant heterogeneity.
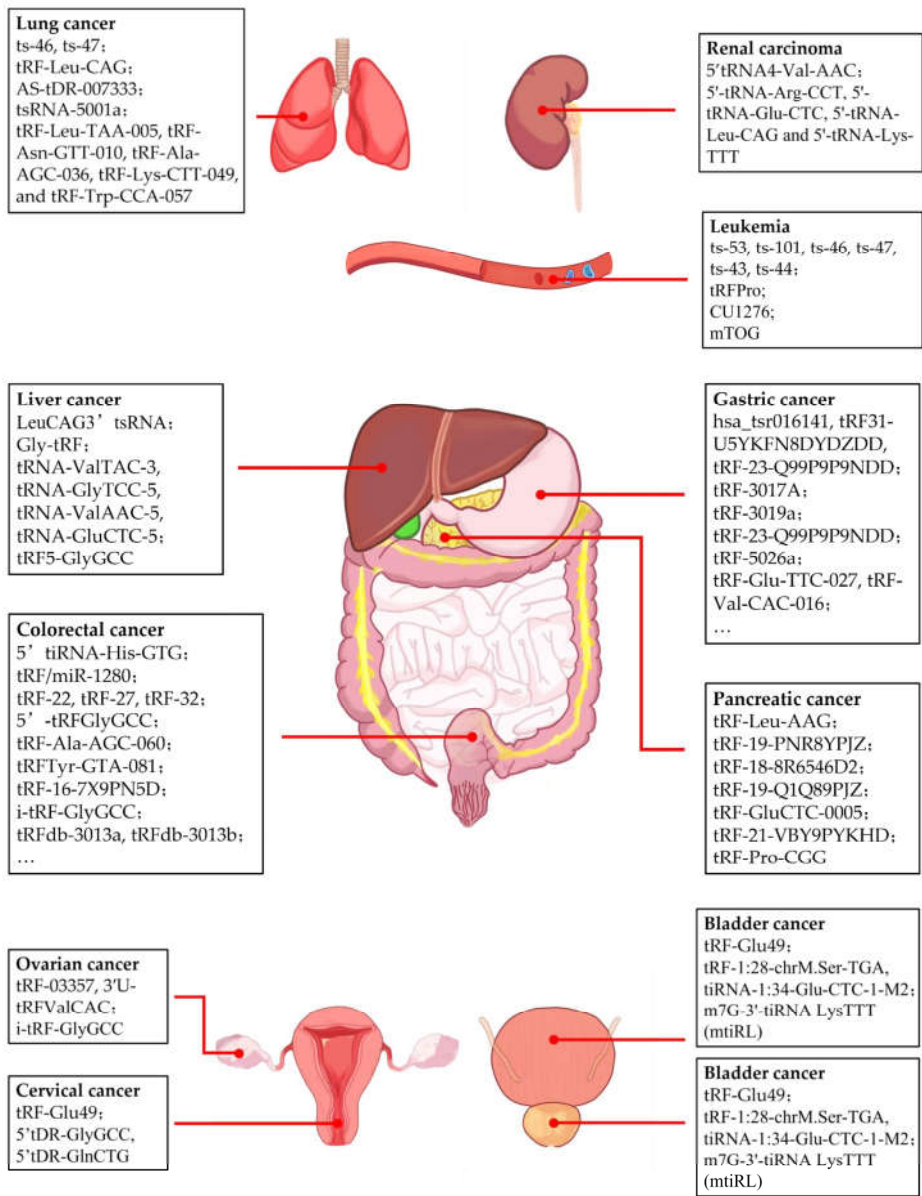
Figure 2. Fuctions of tRFs in different kinds of cancer. tRFs are associated with many types of cancer including breast cancer, prostate cancer, pancreatic cancer, liver cancer, gastric cancer, colorectal cancer, leukemia, lung cancer, and other cancers. These tRFs play differing roles in different types of cancer by various mechanisms.

4.1. Breast Cancer

Breast cancers (BC) is the most common cancer in tRFs studies. The role of tRFs in BC has received increasing attention over the past few years. tRFs is serving as promising candidates for BC diagnostic and prognostic biomarkers and targets of possible therapy. A few tRFs have been identified as differentially expressed in BC [72]. High-throughput sequencing is applied to identifying differentially expressed tsRNAs in plasma samples of patients with BC, and a study has found some specific tsRNAs in plasma could play a role as diagnostic and prognostic biomarkers [73]. The circulating tRF-ArgCCT-017, tRF-Gly-CCC-001 and tiRNA-Phe-GAA-003 are upregulated in plasma samples of BC patients, indicating their potential as biomarkers [73]. By using custom tsRNA microarray chip, it has found a signature of 34 tsRNAs able to distinguish the normal cells

with BC cells in comparation [72]. And the expression of the same tRFs also varies in two cell lines from different stages of BC, suggesting that tRF may play a regulatory role during tumor development.

Different kinds of tRFs have various functions in BC tumorigenesis and progression. A few tRFs have been found to act as enhancing factors in BC. Through regulation of ribosomal protein, tRF-19-W4PU732S from the mature tRNA-Ser-AGA can affect the cancer [74]. Targeting inhibition of RPL27A (ribosomal protein-L27A), tRF-19-W4PU732S promotes BC cell proliferation, malignant activity, invasion, EMT and CSC phenotypes, and the suppression of apoptosis. Sex hormone-dependent tRNA-derived RNAs (SHOT-RNAs) are specifically expressed in ER-positive BC cell lines, and 5'-SHOT-RNA can also accelerate cell proliferation in BC cells similarly [75]. Farina et al. demonstrated ts-112 as an oncogenic tRF which was selectively inhibited by tumor suppressor RUNX1 to prevent overactive expression in breast epithelial cells [76]. Recently it was discovered that tRF-33 from mature tRNA-LysTTT, was significantly upregulated in human epidermal receptor 2 (HER2)-negative BC cells and tissue [77]. By directly interacting with the 3'-UTR of IGF1, tRF-33 was identified to lead to the downregulation of IGF1 mRNA expression and protein synthesis, eventually disrupting mitochondrial homeostasis and contributing to the progression of BC pathogenesis.

Some tRFs that act as tumor suppressors have also been identified. Under hypoxic stress, a new class of tRFs is produced from tRNAGlu, tRNAAsp, tRNAGly, and tRNATyr [31]. This class of tRFs has a same motif that corresponds to the YBX1 implicated in cancer progression and shown to promote cancer metastasis [78,79]. These tRFs can inhibit the development of BC metastasis by binding YBX1 and displacing multiple oncogenic transcripts such as EIF4EBP1 and AKT1. There is a first study to show that 5'-tiRNAVal as a new tumor-suppressor can directly target the 3'-UTR sequence in frizzled class receptor 3 (FZD3), inhibit the FZD3-mediated Wnt/β-Catenin signaling pathway in BC cells [80]. And its downregulation in serum was positively related to BC pathological stage and lymph node metastasis. Coming from the 3'-end of the mature tRNAGluTTC, tRF3E is specifically expressed in healthy mammary glands but not in BC. This tRF specifically interacts with nucleolin (NCL), and causes the release of p53 mRNA promoting its translation by competing for NCL. Through NCL-mediated mechanism, tRF3E proposes inhibition of BC cell proliferation [81].

Triple-negative breast cancer (TNBC) is the most aggressive and malignant type of BC with restricted treatment options, chemoresistance and poor prognosis. By analysis of the expression profiles of tRFs in cancer stem cells (CSCs) isolated from TNBC and non-TNBC cell lines, research found the tDR-000620 acted as a novel candidate biomarker for the early detection of recurrence in TNBC patients independently, with the continuously lower expression level in TNBC CSCs and serum samples [82]. tRFLys-CTT-010 is significantly increased in TNBC and promotes TNBC proliferation and migration. tRFLys-CTT-010 interacted with glucose6-phosphatase catalytic subunit (G6PC) to regulate lactate production and glycogen consumption, leading to cell survival and proliferation [83]. It reminds us that the adjustment of glucose metabolism and tRFLys-CTT-010/G6PC axis may provide innovative therapeutic targets for TNBC treatment.

In treatment of BC, the modulation of the above tRFs may represent a promising approach to suppress tumor growth and progression. Several studies have demonstrated that these novel targets could lead to improved therapeutic efficacy. However, it should be noted that the drug resistance during treatment may also be associated with tRFs. tDR-0009 and tDR-7336 from hypoxia were found involved in maintenance of stem cell population and cellular response to IL-6, thereby facilitating the doxorubicin resistance in TNBC [84]. Besides, in HER2-positive BC patients, a specific monoclonal antibody trastuzumab has immensely prolonged the survival of these patients [85]. Overexpression of tRF-27 competitively binding to Ras GTPase-activating protein-binding proteins 1 and 2 (G3BPs) and activated mechanistic target of rapamycin complex 1(MTORC1) to enhance cell proliferation and entice the resistance of HER2-positive BC against trastuzumab [86]. Meanwhile, the potential of tRFs to alleviate chemoradiotherapy resistance is still noteworthy. It has discovered that the silencing of 3'tRF-AlaAGC enhanced the sensitivity of BC cells to Adriamycin through the NF-κb signaling pathway [87].

4.2. Prostate Cancer

Prostate cancer is the third leading cause of cancer-related death among men worldwide [88]. Previous study reported the discovery and differential expression of tRFs in clinical samples of PCa [89]. Michael et al. analyzed the expression of tRFs in fresh frozen patient samples derived from normal adjacent prostate and different stages of PCa by RNA-sequencing and found that the tRF-5s comprise the most abundant class of tRFs in general and represent the major class among upregulated tRFs. To the contrary, the tRF-3s types are dominant among downregulated tRFs in PCa [90]. Analysis of tRFs profiles from the Prostate Cancer (PRAD) datasets of The Cancer Genome Atlas (TCGA) found that tRFs have extensive correlations with messenger RNAs (mRNAs). These correlations are disrupted in PRAD, which suggests disruptions of the regulatory network in the disease state [91]. Researches above indicate that tRFs might play an important role in the pathogenesis of cancer.

Yong Sun Lee et al. discovered a specific tRF-1 called tRF-1001, generated in the cytoplasm by a prostate cancer susceptibility gene tRNA 39-endonuclease ELAC2, is necessary for cell proliferation in PCa [23]. In addition, the expression of 5′-SHOT-RNA also has significant functional involvement in cell proliferation. Sex HOrmone-dependent TRNA-derived RNAs (SHOT-RNAs) are specifically and abundantly expressed in androgen receptor (AR)-positive prostate cancer cell lines, which produced from amino-acylated mature tRNAs by angiogenin-mediated anticodon cleavage, promoted by sex hormones and their receptors [75].

As for the treatment, cisplatin is a standard treatment for prostate cancer. Changwon Yang et al. confirmed that tRF-315 derived from tRNALys prevents cisplatin-induced apoptosis and alleviated cisplatin-induced mitochondrial dysfunction in prostate cancer cells (LNCaP and DU145) by targeting the tumor suppressor gene GADD45A. Thus, tRF-315 diminishes therapeutic effect of cisplatin in prostate cancer [92].

Moreover, newly growing evidence highlights that METTL1 depletion causes the loss of m7G tRNA methylation and promotes the biogenesis of 5′ terminal oligoguanine-containing tRNA fragments (5′TOGs), which enhances the synthesis of key regulators of tumor growth suppression, interferon pathway, and immune effectors, providing novel insights into prostate cancer therapeutic strategies [93].

4.3. Pancreatic Cancer

Extensive research has gradually revealed the pivotal role and clinical potential of tRFs in pancreatic cancer. The expression of tRF-Leu-AAG is observably upregulated in pancreatic cancer (PC) cells as compared to adjacent normal tissues detected by high-throughput second-generation sequencing techniques, positively correlated with cell proliferation, migration, and invasion. Studies have shown that UPF1, a downstream target gene of tRF-Leu-AAG, promotes the development of pancreatic cancer when downregulated [94]. Similarly, tRF-19-PNR8YPJZ promotes pancreatic cancer migration and invasion by acting through the AXIN2 axis [95]. Moreover, tRF-18-8R6546D2, a novel oncogenic factor, promotes PC malignancy partly by directly silencing ASCL2 and further regulating its downstream genes such as MYC and CASP3 [96]. To the contrary, the downregulation of tRF-19-Q1Q89PJZ in pancreatic cancer promotes cell proliferation and metastasis by inhibiting HK1 expression [97]. As for pancreatic ductal adenocarcinoma (PDAC), the upregulation of tRF-GluCTC-0005 enhances the mRNA stability of WDR1, thereby promoting cancer cell proliferation, migration, and invasion [98], and also plays a crucial role in PDAC liver metastasis [99]. On the other hand, tRF-21-VBY9PYKHD (tRF-21), a tumor suppressor in PDAC, promotes cancer cell proliferation, migration, and invasion when downregulated. The downregulation provokes hnRNP L-DDX17 activity in order to form the Caspase 9b and mH2A1.2, thereby promoting PDAC cell malignant phenotypes [70]. Study also highlights the role of tRFs as potential biomarkers for PDAC prognosis and therapy. Jun Li et al. revealed that the significant downregulation of tRF-Pro-CGG is associated with an advanced TNM stage (P=0.000) and the N stage (P=0.000) of patients. More importantly, low tRF-Pro-CGG expression predicts poor survival in PDAC patients (P=0.003) [100].

4.4. Liver Cancer

At present, research on the role of tRFs in liver cancer is still lacking, especially related to their molecular mechanisms. A specific tRF-3 derived from the Leu-CAG tRNA (LeuCAG3'tsRNA) was reported in 2017. Inhibition of LeuCAG3'tsRNA induced apoptosis in HeLa and HCT-116 cells in vitro and in a patient-derived orthotopic hepatocellular carcinoma model in mice. Behind molecular mechanism is that LeuCAG3'tsRNA interacts with RPS28 and RPS15, two ribosomal protein mRNAs, to enhance their translation and increase tumor cell viability [51]. Recent research reported that glycine tRNA-derived fragment (Gly-tRF), generated from the 5'-arm of glycine tRNA, was highly expressed in HCC cell lines and tumor tissues. Gly-tRF increased the liver cancer stem cell (LCSC) subpopulation proportion and LCSC-like cell properties, and promoted Epithelial-mesenchymal transition (EMT). Mechanistically, Gly-tRF decreased the level of Nedd4 family interacting protein 2 (NDFIP2) mRNA by binding to the NDFIP2 mRNA 3' UTR and also activate the AKT signaling pathway [101]. Another research confirmed that Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) is direct target of Gly-tRF. Overexpression of Gly-tRF enhances growth and migration of HCC cells in vivo [102]. These findings suggests that Gly-tRF could act as a tumor promoter and provide new targets for the prognostic evaluation and treatment of HCC. Accumulating evidence demonstrates that tRFs could also have potential clinical values, no matter in diagnosis, prognosis or treatment of HCC. Yi Zuo et al. built a random forests (RF) diagnostic model based on tsRNA profiling of paired tumor and adjacent normal samples. This model can be reliably utilized in the diagnosis of liver cancer and high- low risk classification of patients based upon tsRNA characterization [103]. Lei Zhu et al. compared exosomal tsRNA levels between liver cancer patients and healthy donors, revealed that levels of four tsRNAs (tRNA-ValTAC-3, tRNA-GlyTCC-5, tRNA-ValAAC-5 and tRNA-GluCTC-5) are significantly higher in liver cancer patients [104]. This finding demonstrates that plasma exosomal tsRNA could serve as a novel diagnostic biomarker for HCC. A growing number of studies have revealed that radiotherapy can not only killing tumor cells directly, but also enhance NK cell cytotoxicity in tumor cells by upregulating NKG2D ligands [105,106]. However, radiotherapy also suppresses the antitumor immunity of NK cells, which limits therapeutic efficacy [107,108]. Yihang Gong et al. revealed that glycocholic acid (GCA)/tRNA-derived fragment 5 (tRF5)-GlyGCC signaling axis is activated in mouse HCC model after radiotherapy. tRF5-GlyGCC epigenetically upregulates Runx2 by interacting with KDM6B and then transcriptionally activates ITGBL1 and S100A9 expression in HCC cells, which further reduces NK cell cytotoxicity directly and attracts myeloid-derived suppressor cell (MDSC) to inhibit NK cell function indirectly, respectively [109]. This research highlights the possibility that radiotherapy combined with tRF5-GlyGCC inhibitor in order to potentiate NK cell antitumor immunity and prevent HCC recurrence postresection.

4.5. Gastric Cancer

Increasing numbers of tRFs involved in Gastric cancer (GC) have been revealed. In GC tissues and serum, several researches have been demonstrated respectively that the overexpression of hsa_tsr016141, tRF31-U5YKFN8DYDZDD and tRF-23-Q99P9P9NDD were closely related to tumor grade, lymph node metastasis and invasion [110–112]. Derived from tRNA-Val-TAC, tRF-3017A regulated the invasion and migration of GC cells through forming the RNA-induced silencing complex (RISC) with Ago2 to target silencing tumor suppressor gene NELL2 [9]. Besides targeting the gene, another study showed tRF-3019a, a kind of 3'-tRF, bound with mRNA 3'UTR of tumor suppressor gene F-box protein 47 (FBXO47), leading to GC cell proliferation, migration and invasion [113]. Concurrently, certain upregulated tRFs can modulate metabolic processes within tumor cells. The overexpressed tRF-23-Q99P9P9NDD could bind to the 3'UTR site of acyl-coenzyme A dehydrogenase short/branched chain (ACADSB) thereby affecting GC lipid metabolism and ferroptosis and promote progression of tumor [114].

Additionally, a significant number of downregulated tRFs have been identified in GC. Some special tRFs, including tRF-33-P4R8YP9LON4VDP and tRF-193L7L73JD, disrupt the cell cycle of GC cells at G0/G1 phases, thereby suppressing their growth and proliferation [115,116]. Certain tRFs exert impacts on GC through their regulatory effects on signal transduction pathways. tRF-5026a inhibited the occurrence and development of GC through PI3K/AKT signaling pathway, however, it was observed in a low expression in GC tissues and cells [117]. And it also found that tRF-5026a can change cell cycle progression in GC. The MAPK signaling pathway is also discovered to be involved in the regulatory network orchestrated by GC-associated tRFs. tRF-Glu-TTC-027 showed the capacity in regulation of MAPK pathway probably targeting the sites of 3' UTR in transforming growth factor beta 2 (TGFB2) [118]. Similarly, tRF-Val-CAC-016 directly targeted the Calcium Voltage-Gated Channel Subunit Alpha1 D (CACNA1d) to regulate MAPK signaling pathway in GC progression [119]. Meanwhile, tRF-Tyr bound directly to the hnRNPD protein and competitively displaced the binding of hnRNPD to the c-Myc 3'UTR, regulating the c-Myc/Bcl2/Bax pathway and ultimately inhibiting the progression of GC [120].

Now the utilization of these tRFs in GC detection is currently under exploration. A kind of 3'tRF tRF-Val directly bound to the EEF1A1, mediated its transport into the nucleus and promoted its interaction with MDM2, a specific p53 E3 ubiquitin ligase, thus promoting proliferation and invasion, and inhibited apoptosis in GC cells [121]. This finding may provide a new potential therapeutic target for GC and a new explanation for the occurrence of GC. And effective therapies may be achieved through modulation of the tRFs above which functions within the signal transduction pathway.

4.6. Colorectal Cancer

Colorectal cancer (CRC) has been the third most commonly diagnosed cancer worldwide and is the second leading cause of cancer death [122]. The mechanisms of tRFs in CRC remain under investigation. Some of tRFs can affect signaling pathways to act carcinogenic or anti-carcinogenic effects. A specific 5'-half, 5'tiRNA-His-GTG can induce cell apoptosis under the regulation of HIF1α/angiogenin (ANG) axis. It reduces the expression of LATS2, a core kinase within the Hippo signal pathway, and subsequently promotes CRC cells multiplication and tumor growth by inhibition of the Hippo pathway [35]. Research has found that tRF/miR-1280 targeted a notch ligand JAG2 to activate the Notch signal pathway and enhances CRC tumor stem cell activity, promoting proliferation and metastasis of CRC [123]. tRFs can also affect the progression of CRC by regulating transcription process. Specifically targeting to the SPIB, 5'tiRNA-Gly-GCC regulates the promoter region of STAT6 and stimulates STAT6 transcription, and positively modulates the cJAK1/STAT6 signaling pathway to contribute to the advancement of CRC collectively [124]. Influenced by tumor-associated mesenchymal cells within the TME, Tumor cells should undergo epithelial-mesenchymal transition (EMT) to gain the ability of metastasis, and the elevated expression of Claudin will accelerate EMT formation [125]. The anti-CRC mechanism of tRF-20M0NK5Y93 is to suppress Claudin-1 and attenuate the invasion, migration and metastasis of CRC [123].

Given the differential expression of tRFs in CRC patients, a growing body of research has been dedicated to investigating their potential biomarkers utility and developing new diagnostic methods. One study chose tRF-22/27/32 as plasma markers for CRC diagnose. By analyzing the RNA results of plasma from CRC patients and healthy individuals, these tRFs showed higher diagnostic values than traditional tumor markers [126]. And the combination of tRFs and traditional markers may get a more effective diagnostic result. When combined with CEA and CA199, the sensitivity and specificity of 5'-tRFGlyGCC in distinguishing CRC patients are 86% and 84% respectively, revealing clinical application potential [127]. Through the upregulated tRF-Ala-AGC-060 and downregulated tRFTyr-GTA-081 and combining with CEA, the diagnostic efficacy for CRC screening is better compared to individual diagnostic methods [128].

In therapy, radiotherapy and chemotherapy always serve as critical strategies in CRC treatment. Substantial downregulation of tRF-16-7X9PN5D was found in radioresistant CRC cells. It presents a link between tRNA and cancer radiation resistance that tRF-16-7X9PN5D could target MKNK1 and

enhance the phosphorylation of eIF4E, contributing to the radio resistance in CRC cells eventually [129]. As a natural compounds, quercetin is recognized for its anti-cancer ability against CRC [130]. It found that quercetin changed the sensitivity of CRC to conventional chemotherapeutic agent 5-FU through tRFs and enhanced the effect of 5-FU in CRC cells. Moreover, quercetin could regulate the expression of specific tRFs and elevate the apoptotic effect of quercetin in tumor cells [131]. And one notable thing is the significant association between intestinal microbiota including Escherichia coli and CRC [132]. Coming from non-pathogenic Escherichia coli, 5′-tRF-Leu (CAA) showed the ability of suppressing CRC cells [133].

The functions of tRFs also reflect in the prediction of prognosis in CRC patients. The level of i-tRF-GlyGCC in CRC tissues was significantly lower than normal tissues, and patients with relatively higher i-tRF-GlyGCC have shorter disease-free survival (DFS) and overall survival (OS) periods, and an increased risk of recurrence [134]. It also identified this influence to adverse prognosis was evident among patients at the TNM stage II. A recent study has found that the tRFdb-3013a and tRFdb-3013b were significantly decreased in colon and rectum adenocarcinomas, especially in patients with lymphatic or vascular invasion present. This reduction of the two tRFs are significantly associated with a worse clinical survival rate and a shortened OS period in CRC patients, showing the potential as novel biomarkers for prognosis in CRC [135].

4.7. Leukemia

Studies have also begun to uncover tRF signatures in leukemia. Previously Veronica Balatti et al. demonstrated that dysregulation of the T-cell leukemia/lymphoma 1 (TCL1) oncogene is a critical contributing event in the pathogenesis of B-cell chronic lymphocytic leukemia (CLL). Furthermore, they found that ts-53 targets the 3′UTR of TCL1, a key oncogene in the development of aggressive CLL and that its down-regulation in leukemic cells is inversely correlated with TCL1 expression, contributing to CLL progression [136]. Together with ts-53, ts-101, ts-46, and ts-47 are also downregulated in CLL [72]. Similarly, another report elucidated that compared with normal B cells, both ts-43 and ts-44 derived from distinct transcripts of pre-tRNAHis, as well as tRF-5 from tRNAHis, are downregulated in CLL [137]. Researches above indicate that dysregulations of tRFs are ubiquitous in CLL and related to tumorigenesis.

Apart from CLL, tRFs also play a vital role in other types of leukemia. Human T-cell leukemia virus type 1 (HTLV-1) is the causative agent of adult T-cell leukemia/lymphoma (ATLL). Reverse transcription (RT) is considered as a key event in the retroviral life cycle. A recent study determined that a 3′18 nt tRNAPro-derived fragment (tRFPro), packaged into HTLV-1 particles, serves as an RT primer in vitro [138]. These findings indicate tRFPro could represent a novel target for therapies aimed at controlling HTLV-1 infection [63]. Roy L. Maute et al. discovered a novel tRFs, CU1276 is abundant in normal germinal center B cells but absent in germinal center-derived lymphomas, suggesting a role in the pathogenesis of this disease. Furthermore, CU1276 suppresses proliferation and modulates the molecular response to DNA damage due to repression of endogenous RPA1, an essential gene involved in many aspects of DNA dynamics [139]. Researchers also found that pseudouridylation (Ψ) of a stem cell-enriched tRF subtype, mini tRFs containing a 5′ terminal oligoguanine (mTOG), selectively inhibits aberrant protein synthesis programs, through disturbing the recruitment of translational co-activator PABPC1-interacting protein 1 (PAIP1), thereby strongly repressing the translation. Dysregulation of mTOG is clinically associated with leukemic transformation and reduced patient survival. These findings define a critical role for tRFs and Ψ in difficult-to-treat subsets of myelodysplastic syndrome (MDS) characterized by high risk of progression to acute myeloid leukemia (AML) [140].

4.8. Lung Cancer

Lung cancer was the most frequently diagnosed cancer in 2022, responsible for almost 2.5 million new cases, or one in eight cancers worldwide (12.4% of all cancers globally) [122]. However, further research is needed on the role of tRFs in lung cancer, especially their underlying molecular

mechanisms. Previous study indicated that ts-53, ts-101, ts-46, and ts-47 are not only downregulated in CLL, but also in lung cancer. Overexpression of ts-46 and ts-47 in H1299 and A549 lung cancer cell lines leads to a strong inhibition of colony formation compared with untreated cells, confirming that tsRNAs affect cell growth and survival in lung cancer [136]. Yang Shao et al. reported a novel type of tRNA halves, tRF-Leu-CAG, which is upregulated in NSCLC tumor tissues and NSCLC cell lines, and serum concentration of tRF-Leu-CAG is significantly associated with NSCLC stage progression. They also found that inhibition of tRF-Leu-CAG suppressed cell proliferation and impeded cell cycle in H1299 cells. All these findings reveal the potential therapeutic value of tRF-Leu-CAG [141]. Another tRF, a 28 nt long tRF-5 cleaved at site 1 to 28 on the 5′ end of tRNA-Gly-GCC, AS-tDR-007333 were identified in pre- and post-operation plasma from patients with NSCLC. AS-tDR-007333 is significantly upregulated in NSCLC tissues, plasma, and cells and clinically associated with poorer prognosis. Further study demonstrated that overexpression of AS-tDR-007333 enhanced proliferation and migration of NSCLC cells by activating MED29 through two different pathways. Firstly, interacting with HSPB1, AS-tDR-007333 enhances H3K4me1 and H3K27ac in MED29 promoter, thereby activating MED29 expression. Secondly, AS-tDR-007333 increases the transcription of MED29 promoter by stimulating the expression of transcription factor ELK4 [142]. Fang Hu et al. illustrated that tsRNA-5001a is significantly upregulated in lung adenocarcinoma tissues and positively correlated to the risk of postoperative recurrences and poor prognosis in patients [143]. Recent studies have cast light on diagnostic and therapeutic potential of tRFs in lung cancer. Gu et al. developed a TRY-RNA signature composed of tRFs, rRNA-derived small RNAs, and YRNA-derived small RNAs from human peripheral blood mononuclear cells, which precisely discriminates between healthy control, lung cancer and pulmonary tuberculosis [144]. Baibing Zheng et al. discovered that the expression levels of exosomal tRF-Leu-TAA-005, tRF-Asn-GTT-010, tRF-Ala-AGC-036, tRF-Lys-CTT-049, and tRF-Trp-CCA-057 were significantly downregulated in NSCLC patients. This significant difference suggests that these five exosomal tRFs may be promising diagnostic biomarkers for NSCLC [145].

4.9. Other Cancers

In addition, tRFs have also been reported in other cancers including ovarian cancer, cervical cancer, bladder cancer, and renal cancer.

For ovarian cancer, differentially expressed tRFs were verified in high-grade serous ovarian cancer (HGSOC), involved in the functions of protein phosphorylation, transcription and cell migration and the pathway of cancer, and the MAPK and Wnt signaling pathways. Importantly, tRF-03357 promoted SK-OV-3 cell proliferation, migration and invasion by targeting and downregulating HMBOX1 [146]. Similarly, 3′U-tRFValCAC, derived from pre-tRNAValCAC, also promotes SK-OV-3 cell growth and migration [147]. Another research focused on clinical benefit of tRFs in ovarian cancer and highlighted the significant association of i-tRF-GlyGCC with advanced FIGO stages, suboptimal debulking and most importantly, with early progression and poor overall survival of EOC patients [148].

For cervical cancer, Yang Wang et al. identified a potential tumor suppressor gene tRF-Glu49 in cervical carcinoma, inhibiting cervical cell proliferation, migration and invasion processes by directly regulating the oncogene, fibrinogen-like protein-1 (FGL1) [149]. On the contrary, two 5'-tRFs, 5'tDR-GlyGCC and 5′tDR-GlnCTG, were revealed to enhance tumor progression of cervical cancer by promoting ribosome assembly and preventing cell apoptosis [150]. Further research is needed to reveal the underlying mechanism of tRFs in pathogenesis and progression of cervical cancer.

For bladder cancer, diagnosis of bladder cancer is primarily by invasive tests now, however, more researches are devoting to the exploration of tRFs as screening and diagnostic biomarkers for bladder cancer. A 5′-tRF, 5′-tRF-LysCTT, was associated with aggressive tumor phenotype, early progression and poor survival, and the integration of 5′-tRF-LysCTT with the clinically available markers could achieve superior specificity and improve prediction of disease progression for bladder cancer [151]. The circulating tRF-1:28-chrM.Ser-TGA and tiRNA-1:34-Glu-CTC-1-M2 were

specifically expressed by bladder cancer cells and were positively associated with the degree of malignancy, which are not only applied as new biomarkers but also expected to provide novel targets in the therapy of bladder cancer [152]. tRFs have also demonstrated potential in treatment of bladder cancer. A novel m7G-modified tRF, m7G-3'-tiRNA LysTTT (mtiRL), has been defined as a critical molecule to promote bladder cancer malignancy in vitro and in vivo and provided an efficient way to treat bladder cancer by targeting this tRF [153].

To date, studies investigating the role of tRFs in renal carcinoma remains relatively limited, but certain tRFs have been implicated in modulating the tumorigenesis and progression of renal carcer. In clear cell renal cell carcinoma (ccRCC), a study has identified the 5'tRNA4-Val-AAC expression had an inverse correlation with the stage and grade of tumor [154]. And another research found four kinds of 5'-halves were downregulated in the serum and tissue of ccRCC. Their lower expression not only indicated a potential role as tumor suppressors, but alco suggesting the potential of these 5'-halves as novel ccRCC biomarkers [155].

Table 1. Functional tRFs in different types of cancer.

Cancer type	tRF name	Role	Function	Ref
Breast cancer (BC)	tRF-ArgCCT-017, tRF-Gly-CCC-001, tiRNA-Phe-GAA-003	upregulate in BC plasma samples	potential biomarker of BC	[73]
	tRF-19-W4PU732S	oncogenic factor	promote proliferation and malignance of BC and suppress apoptosis by inhibiting RPL27A	[74]
	5'-SHOT-RNA	oncogenic factor	promote proliferation of BC	[75]
	ts-112	oncogenic factor	promote proliferation of BC	[76]
	tRF-33	oncogenic factor	disrupt mitochondrial homeostasis and promote progression of BC by interacting with IGF1	[77]
	tRFGlu, tRFAsp, tRFGly, tRFTyr	tumor suppressor	inhibit metastasis of BC via YBX1 displacement	[78,79]
	5'-tiRNAVal	tumor suppressor	inhibit the FZD3-mediated Wnt/β-Catenin signaling pathway in BC	[80]
	tRF3E	tumor suppressor	inhibit proliferation of BC through NCL-mediated mechanism	[81]
	tDR-000620	downregulate in TNBC CSCs and serum sample	potential biomarker of TNBC	[82]
	tRFLys-CTT-010	oncogenic factor	promote proliferation of TNBC by regulating glucose metabolism	[83]

			via tRFLys-CTT-010/G6PC axis	
	tDR-0009 and tDR-7336	drug-resistance driver	facilitate doxorubicin resistance in TNBC	[84]
	tRF-27	oncogenic factor drug-resistance driver	facilitate trastuzumab resistance and promote cell proliferation in BC	[86]
	3'tRF-AlaAGC	drug-resistance driver	enhance the Adriamycin sensitivity in BC via NF-κb signaling pathway by silencing 3'tRF-AlaAGC	[87]
Prostate cancer (PCa)	tRF-1001	oncogenic factor	promote proliferation of PCa	[23]
	5'-SHOT-RNA	oncogenic factor	promote proliferation of PCa	[75]
	tRF-315	drug-resistance driver	facilitate cisplatin resistance in PCa	[92]
	5'TOGs	tumor suppressor	inhibit proliferation of PCa	[93]
Pancreatic cancer (PC)	tRF-Leu-AAG	oncogenic factor	promote proliferation, migration, and invasion of PC by downregulating UPF1	[94]
	tRF-19-PNR8YPJZ	oncogenic factor	promote migration and invasion of PC via AXIN2 axis	[95]
	tRF-18-8R6546D2	oncogenic factor	promote malignancy of PC by silencing ASCL2 and regulating MYC and CASP3	[96]
	tRF-19-Q1Q89PJZ	tumor suppressor	inhibit proliferation and metastasis of PC by suppressing HK1 expression	[97] [97]
	tRF-GluCTC-0005	oncogenic factor	promote proliferation, migration and invasion of PDAC and liver metastasis	[98,99]
	tRF-21-VBY9PYKHD	tumor suppressor	promote proliferation, migration, and invasion of PDCA when downregulated	[70]
	tRF-Pro-CGG	downregulate in advanced PC	potential biomarker of PC	[100]
Liver cancer	LeuCAG3'tsRNA	oncogenic factor	increase viability of HCT-116 cell by interacting with RPS28 and RPS15	[51]
	Gly-tRF	oncogenic factor	increase LCSC subpopulation	[101,102]

			proportion and promote EMT in liver cancer	
	tRNA-ValTAC-3, tRNA-GlyTCC-5, tRNA-ValAAC-5, tRNA-GluCTC-5	upregulate in liver cancer	potential biomarker of liver cancer	[104]
	tRF5-GlyGCC	radiotherapy inhibitor	reduce NK cell cytotoxicity and limit radiotherapeutic efficacy	[109]
Gastric cancer (GC)	hsa_tsr016141, tRF31-U5YKFN8DYDZDD, tRF-23-Q99P9P9NDD	oncogenic factor	upregulation is associated with tumor grade, lymph node metastasis and invasion	[110,111.112]
	tRF-3017A	oncogenic factor	promote migration and invasion of GC by targeting NELL2	[9]
	tRF-3019a	oncogenic factor	promote proliferation, migration and invasion of GC	[113]
	tRF-23-Q99P9P9NDD	oncogenic factor	promote progression of GC by affecting lipid metabolism and ferroptosis via targeting ACADSB	[114]
	tRF-33-P4R8YP9LON4VDP, tRF-193L7L73JD	tumor suppressor	inhibit proliferation of GC by disrupting cell cycle	[115,116]
	tRF-5026a	tumor suppressor	inhibit progression of GC via PI3K/AKT signaling pathway and regulate cell cycle	[117]
	tRF-Glu-TTC-027, tRF-Val-CAC-016	tumor suppressor	inhibit malignance of GC via MAPK pathway	[118,119]
	tRF-Tyr	tumor suppressor	inhibit progression of GC via c-Myc/Bcl2/Bax pathway	[120]
	tRF-Val	oncogenic factor	promote proliferation and invasion and inhibit cell apoptosis of GC	[121]
Colorectal cancer (CRC)	5'tiRNA-His-GTG	oncogenic factor	promote proliferation and inhibit cell apoptosis of CRC	[122]
	tRF/miR-1280	oncogenic factor	promoting proliferation and	[123]

			metastasis of CRC via Notch signal pathway	[123]
	5'tiRNA-Gly-GCC	drug-resistance driver	facilitate 5-FU resistance in CRC	[124]
	tRF-20M0NK5Y93	tumor suppressor	inhibit metastasis of CRC by suppressing Claudin-1	[125]
	tRF-22, tRF-27, tRF-32	upregulate in CRC tissue and plasma samples	potential biomarker of CRC	[126]
	5'-tRFGlyGCC	upregulate in CRC plasma samples	potential biomarker of CRC	[127]
	tRF-Ala-AGC-060	upregulate in CRC tissue samples	potential biomarker of CRC	[128]
	tRFTyr-GTA-081	downregulate in CRC tissue samples	potential biomarker of CRC	[128]
	tRF-16-7X9PN5D	radiosensitizer	promote proliferation, migration, invasion and radio resistance when downregulated	[129]
	5'-tRF-Leu (CAA)	tumor suppressor	inhibit progression of CRC	[133]
	i-tRF-GlyGCC	downregulate in CRC tissue samples	potential biomarker of CRC	[134]
	tRFdb-3013a, tRFdb-3013b	downregulate in colon and rectum adenocarcinomas	potential biomarker of CRC	[135]
Leukemia	ts-53, ts-101, ts-46, and ts-47, ts-43, ts-44	tumor suppressor	promote progression of CLL	[72,136,137]
	tRFPro	RT primer of HTLV-1	potential target for preventing ATLL	[138]
	CU1276	tumor suppressor	inhibit proliferation and molecularly modulate DNA damage repair	[139]
	mTOG	dysregulation associated with leukemic transformation	potential biomarker for MDS transformation to AML	[140]
Lung cancer	ts-46, ts-47	tumor suppressor	inhibit proliferation of lung cancer cell lines when upregulated	[136]
	tRF-Leu-CAG	oncogenic factor upregulated in NSCLC tissues and cell lines	inhibit proliferation and impede cell cycle of NSCLC potential biomarker of NSCLC	[141]
	AS-tDR-007333	oncogenic factor upregulated in NSCLC tissues and plasma	promote proliferation and migration of NSCLC	[142]

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			potential biomarker of NSCLC	
	tsRNA-5001a	upregulated in lung adenocarcinoma tissues	potential biomarker for poor prognosis	[143]
	tRF-Leu-TAA-005, tRF-Asn-GTT-010, tRF-Ala-AGC-036, tRF-Lys-CTT-049, and tRF-Trp-CCA-057	downregulated in NSCLC tissues	potential biomarker of NSCLC	[145]
ovarian cancer	tRF-03357, 3'U-tRFValCAC	oncogenic factor	promote proliferation, migration and invasion of SK-OV-3 cell	[146,147]
	i-tRF-GlyGCC	upregulation is associated with advanced FIGO stages	potential biomarker of ovarian cancer	[148]
cervical cancer	tRF-Glu49	tumor suppressor	inhibit proliferation of cervical carcinoma by regulating FGL1	[149]
	5'tDR-GlyGCC, 5'tDR-GlnCTG	oncogenic factor	promote progression of cervical cancer	[150]
bladder cancer	5'-tRF-LysCTT	upregulation is associated with poor prognosis	potential biomarker of bladder cancer	[151]
	tRF-1:28-chrM.Ser-TGA, tiRNA-1:34-Glu-CTC-1-M2	oncogenic factor	promote malignancy of bladder cancer	[152]
	m7G-3'-tiRNA LysTTT (mtiRL)	oncogenic factor	promote malignancy of bladder cancer	[153]
renal carcinoma	5'tRNA4-Val-AAC	downregulation is associated with advanced stage	potential biomarker of ccRCC	[154]
	5'-tRNA-Arg-CCT, 5'-tRNA-Glu-CTC, 5'-tRNA-Leu-CAG and 5'-tRNA-Lys-TTT	downregulated in tumor tissues and serum samples	potential biomarker of ccRCC	[155]

5. Conclusions and Perspective

With the application of novel technologies such as high-throughput transcriptome sequencing, the researches of tRFs are growing tremendously, while their diversity and functional roles have also been progressively elucidated. Numerous tRFs have been collated and collected into several databases, facilitating further discovery and functional researches. Related to the situation of cells, the production of tRFs may be influenced by the stress conditions. The tRFs can be primarily divided into tRNA halves and tRFs, and other special fragments such as i-tRFs, tRF-1s. Meanwhile, various modifications of tRNAs regulate tRF biogenesis, and influence the stability and function of tRFs. We

review the key roles of tRFs including nascent RNA silencing, translation regulation, epigenetic gene silencing, and reverse transcription inhibition.

Increasing evidence has manifested that tRFs are associated with many aspects of various kinds of cancer, which are involved in the generation, procession and migration of tumors. Here, we summarized the related tRFs relevant with several cancer types such as breast cancer, gastric cancer, liver cancer, colorectal cancer and pancreatic cancer, prostatic cancer and so on. Whereas, the underlying mechanisms of how tRFs regulate tumors are still understood incompletely. Meanwhile, the biological function of the same tRFs seem different in diverse types of cancer. Furthermore, the characteristics of distinct types of cancers, including growth patterns, metastatic behaviors and tumor microenvironment heterogeneity, drive the production of different tRFs that exert varied functional roles [156]. For example, the hypoxia-induced tRFs play important roles in BC [31]. And according to the different expression levels in related cancer, some specific tRFs can be applied as as novel non-invasive biomarkers for the diagnosis and detection of cancer, and therapeutic targets for clinical application.

There are still some limitations in the research of tRF. The nomenclature of tRF is debated, leading to the inconsistency in publications and confusion of readers. Some tRFs are named by the order of discovery, and this difference may hinder the searching and publication [72,157]. And although several tRFs dysregulated in cancer have been characterized, their underlying mechanisms of action require further investigation to verify, particularly the determination of causal relationships. There is a long process to utilize tRF in clinic as biomarkers for cancer. Although some researches emphasized the potential of tRF for cancer diagnosis, the detection of tRFs mainly relies on high throughput sequencing and other innovative methods, which are relative expensive or complicated for large scale detection clinically. So more attempts are compulsory for developing appropriate tRF testing methods.

tRFs and their functional roles are being progressively elucidated. Accumulating evidence from series studies has demonstrated significant associations between tRF dysregulation and cancer progression. Further investigations remain imperative to comprehensively identify the mechanistic contributions of tRFs in oncogenesis and to utilize as clinically actionable biomarkers and innovative therapeutic targets for cancer diagnosis and prognosis.

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