Non-coding RNA Research 10 (2025) 63–69

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.keaipublishing.com/en/journals/non-coding-rna-research

Review Article

Research progress on the tsRNA biogenesis, function, and application in lung cancer

Yu Chen [a,b], Zhuowei Shao [a,b], Shibo Wu [a,*]

[a] Department of Respiratory Medicine, The Affiliated Lihuili Hospital of Ningbo University, Ningbo, China
[b] Health Science Center, Ningbo University, Ningbo, Zhejiang, China

ARTICLE INFO

Keywords:
tRNA
tsRNA
tRF
tiRNA
Biogenesis
Function
Lung cancer
Biomarker

ABSTRACT

In recent years, there has been a mounting occurrence of lung cancer, which stands as one of the most prevalent malignancies globally. This rise in incidence poses a significant hazard to human health, making lung cancer a matter of grave concern. It has been shown that tRNA-derived small non-coding RNA (tsRNA) is involved in the development of tumors, especially lung cancer, through mechanisms such as regulating mRNA stability, influencing protein translation, and acting as epigenetic regulators. Recent studies have shown that tsRNA is abnormally expressed in the plasma and tissues of lung cancer patients, and its expression level is closely related to the malignancy degree and postoperative recurrence of lung cancer. Therefore, for lung cancer patients, tsRNA represents a promising non-invasive biomarker, exhibiting significant potential for facilitating early diagnosis and prognostic evaluation, and for achieving precision treatment of lung cancer by regulating its expression. This article focuses on the biogenesis of tsRNA and its ability to promote lung cancer cell proliferation and invasion. In addition, the specific clinical significance of tsRNA in lung cancer was discussed. Finally, we discuss the need for further improvement of small RNA sequencing technology, and the future research directions and strategies of tsRNA in lung cancer and tumor diseases were summarized.

1. Introduction

Lung cancer, the leading cause of cancer-related deaths worldwide, poses a significant threat to global public health, according to the GLOBOCAN 2020 estimates from the IARC [1]. In China, lung cancer is the leading cause of cancer-induced morbidity and mortality, and its incidence has been rising in recent decades [2]. With the advancements in modern medicine, targeted therapy and immunotherapy have achieved significant success in the treatment of lung cancer patients, but the overall five-year survival rate still remains low at 16.8 % [3,4].

Transfer RNA (tRNA) is a key molecule in translation. This molecule delivers amino acids to the ribosome in a mRNA-guided manner [5]. Under the action of ribonuclease, tRNA can be fragmented to yield a class of small RNAs known as tRNA-derived small RNAs (tsRNAs), which participate in numerous cellular processes [6]. Accumulating evidence suggests that tsRNAs occupy a pivotal position in diverse biological processes pertinent to the pathogenesis of various diseases, especially cancer [7–10]. Abnormally expressed tsRNA promotes tumorigenesis and development through various mechanisms. Moreover, tsRNAs hold potential to become diagnostic biomarkers and therapeutic targets for cancer [11–13]. High-throughput RNA sequencing has demonstrated significant differences between tsRNA expression in lung cancer tissues and neighboring tissues, highlighting their clinical value as biomarkers. This article will present the categorization and the underlying biological processes of tsRNA, summarize the role of tsRNAs in lung carcinogenesis and progression, their applications in lung cancer diagnosis and prognosis and therapeutic strategies, and further discuss the challenges and future perspectives of tsRNA research in the field of lung cancer.

2. The biogenesis and function of tsRNAs

2.1. The biogenesis of tsRNAs

TsRNAs are a class of non-coding small RNAs originated from either precursor tRNA or mature tRNA [14]. These tsRNAs are categorized into two major groups: tiRNA (tRNA-derived stress-induced RNA) and tRF (tRNA-derived RNA fragment). Depending on the cleavage site of tRNA, tRFs are categorized into i-tRF, tRF-5, and tRF-1, tRF-2, tRF-3. Moreover, based on whether they contain 5′ or 3′ sequences, tiRNAs can also be distinguished as 5′-tiRNAs or 3′-tiRNAs [15].

* Corresponding author.
E-mail address: woshibo2015@yeah.net (S. Wu).

https://doi.org/10.1016/j.ncrna.2024.09.004
Received 25 June 2024; Received in revised form 18 August 2024; Accepted 1 September 2024
Available online 4 September 2024

Stress-induced tiRNA is a small RNA of approximately 30–50 nucleotides in length generated by the specific cleavage of the anticodon loop of mature tRNA by angiogenin (ANG) in the cytoplasm [16,17]. 5′-tiRNA starts at the 5′ end and includes the D-loop, terminating at the anticodon, while 3′-tiRNA starts at the anticodon and includes the TψC-loop, terminating at the 3′ end.

As shown in Fig. 1, tRFs, which originate from mature or precursor tRNA, are small RNAs with an approximate length of 14–30 nucleotides, and are subdivided into i-tRF, tRF-5, and tRF-1, tRF-2, tRF-3. Mature tRNAs can form tRF-5 through Dicer-mediated cleavage of the region between anticodon loop and D-loop. By cutting D-loop, anticodon, and D loop stem, the tRF-5 comprises of three subtypes: tRF-5a, tRF-5b, and tRF-5c, characterized by distinct length ranges of 14–16, 22–24, and 28–30 nucleotides, respectively [18]. Angiopoietin, Dicer, or exonucleases cleave mature tRNA to form tRF-3 containing a 3′ end, which is further divided into two subtypes: tRF-3a and tRF-3b, with lengths of 18 nt and 22 nt, respectively [8]; The anticodon loop produces tRF-2 under anoxic conditions. tRF-2 does not include the 5 ′end and 3′ end regions, but contains the anticodon loop and part of the anticodon stem [19]; Precursor tRNA, an initial product of tRNA gene transcription, is cleaved by RNase Z to form tRF-1, which comprises the 3 ′tail of the multi-U sequence, with a length of 16–48 nt [4]; I-tRF is an internal tRF produced by mature tRNA containing D loop and T loop sequences, excluding the 5 ′and 3′ terminal regions [20].

2.2. The functions of tsRNAs

2.2.1. RNA silencing

Originally, scholars discovered that tsRNA participates in RNA silencing through associations with different AGOs [21]. Later, a research team found that HisGTG3'tsRNA and 18-nt-LeuCAG3'tsRNA are linked to Ago2-mediated cleavage [22]. The Dutta team discovered that tRF-5s and tRF-3s bind to Ago in a manner similar to that of miRNAs, and their association with Ago1, 3, and 4 is more robust than their association with Ago2 [8]. Specific types I or types II tsRNA bind to mRNAs, inducing Ago2-mediated cleavage or mRNA degradation, which can lead to gene silencing [23]. Inside the nucleus, in distinction to the PTGS and TGS mechanisms that promote gene silencing, a Dicer-dependent tsRNA blocks translation of newly transcribed RNA into protein through Ago2, forming nuclear gene silencing [24]. Another study found that tRF-3 forms a hybrid with Ago1 in a Dicer-independent manner, inhibiting post-transcriptional expression of the YBX1 transcript [25]. The tRF-Ago1 complex specifically targets and cleaves endogenous mRNA produced by transcriptionally active TEs in plants [26]. In fruit flies, the number of tsRNA increases with age, and RNA-seq results indicate that the differential expression genes-related signaling pathways are mainly concentrated in the immune system and cancer [27]. However, some specific tRFs competitively replace YBX1 transcripts from YBX1 by sequence specificity, inhibiting YBX1 expression post-transcriptionally and thus suppressing the occurrence and progression of cancer [20].

2.2.2. Translational regulation

Previous studies have shown that endogenous tRFs do not regulate gene expression in the same way that miRNAs do, and that a conserved sequence at the 5′ end of 5′-tRFs - the "GG" dinucleotide - is required for 5′-tRFs to repress translation [28]. 5'-tiRNA^{Ala} can replace part of eIF4G/eIF4A from uncapped and capped mRNA and inhibit protein translation by inhibiting the initial stage of translation [29]. Pavel Ivanov's team's research shows that 5'-tiRNA^{Ala} inhibits translation by forming RG4. When it cannot form RG4, 5'-tiRNA^{Ala} cannot replace eIF4F complex component eIF4E or eIF4G from mRNA m7GTP cap [30]. Research has found that in the archaeal species called Haloferax volcanii, Val-tRF primarily binds to small ribosomal subunits and inhibits mRNA binding to small ribosomes, thus impeding peptide bond formation and protein production [31,32]. The Kay team has discovered that a LeuCAG3'tsRNA can interact with the CDS and 3′UTR sequences of RPS28 mRNA through base pairing in both mice and human cells, thereby enhancing translation of the mRNA [33,34].

2.2.3. RNA reverse transcription regulation

TsRNAs are also participating in the regulation of RNA reverse transcription. It has been found that tRF5-GlyCCC and tRF5-LysCTT promote respiratory syncytial virus replication [35]. However, the mechanism of tsRNA's role in virus replication has not been fully elucidated. In the same year, another study found that 3′CCA tRFs do not change the levels of RNA or protein, but they specifically inhibit the reverse transcription of LTR-RTs before RNaseH product formation [36]. Ruggero et al. confirmed that tRF-3019 can serve as a primer for the reverse transcriptase of HTLV-1, thereby directing its reverse transcription activity [37]. Their research also found that one end of tRF-3019 is complementary to the primer binding site of HTLV-1 and that in vitro reverse transcription experiments using tRF-3019 RNA produced the expected PCR product. An overview of critical tsRNA that

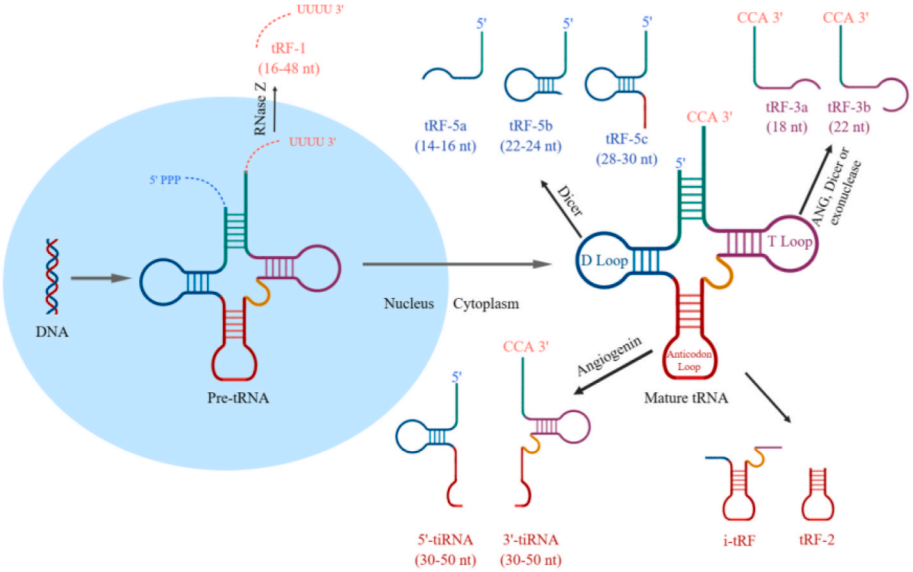

Fig. 1. Overview of the biogenesis of tsRNA.

paticipate in hallmarks of cancer is displayed in Fig. 2.

3. tsRNA in lung cancer

tsRNAs are playing an influential role in the genesis and progression of many tumors. With the fast development of RNA sequencing technology, the expression profiles and potential functions of tRNAs in cancer cells could be further explored. There is an increasing body of research showing that tsRNA is abnormally expressed in many cancers [38–41]. Significant changes in tsRNA expression profiles in lung cancer tissues compared to normal lung tissues [39,42,43]. These dysregulated tsRNA play an essential role in the biological functions of cancer, and we focus on its ability to promote lung cancer cell proliferation and invasion. Fig. 3 provides a general overview of tsRNA and related pathways.

3.1. Sustaining proliferative signaling

Continuous cell proliferation and uninhibited cell growth are considered to be one of the basic characteristics of cancer. This process involves multiple genes and proteins, particularly some kinases and kinase receptors [44,45]. Currently, the epidermal growth factor receptor (EGFR) signaling pathway is most well-known in lung cancer. The overexpression of EGFR is observed in a substantial proportion, ranging from 40 to 80 percent, of NSCLC as well as numerous other epithelial malignancies [46]. Studies have shown that 3′-tRFs can promote the occurrence of most (13/15) tumors by activating Ras/MAPK, TSC/mTOR, and RTK signaling [47]. Additionally, in animal experiments, the inhibition of 5′-IleAAT-8-1-L20 (cancer-driving tRF) can inhibit the progression of lung cancer cells. It has shown that some tRF-1s are downregulated in lung cancer cells, and that these tRF-1s may induce the occurrence of lung cancer through the MARK signaling pathway [43]. In addition, Shao et al. demonstrated that NSCLC cell proliferation and cell cycle progression can be regulated by tRF-Leu-CAG [48]. When tRF-Leu-CAG was knocked down, the expression of AURKA was inhibited.

In addition, there have been many reports linking tsRNA to lung cancer cell proliferation, but the associated signaling pathways remain unclear. For example, AS-tDR-007333 is noticeably upregulated in NSCLC tissues, plasma, and cells, and its overexpression enhances the proliferation of NSCLC cells [42]. Inhibition of tRF-Leu-CAG, which is less abundant in normal tissues than in NSCLC tumor tissues, inhibits cell proliferation and impedes cell cycle [49]. Inhibition of tRF-20-S998LO9D (a tRF-5) reduces the proliferation of lung squamous cell carcinoma (SK-MES-1) cells [49]. Ts-46 and Ts-47 have been shown to affect the growth of lung cancer cell lines [39,41]. The expression of tsRNA-5001a is notably elevated in lung adenocarcinoma tissues, and its overabundance significantly enhances cell proliferation [50].

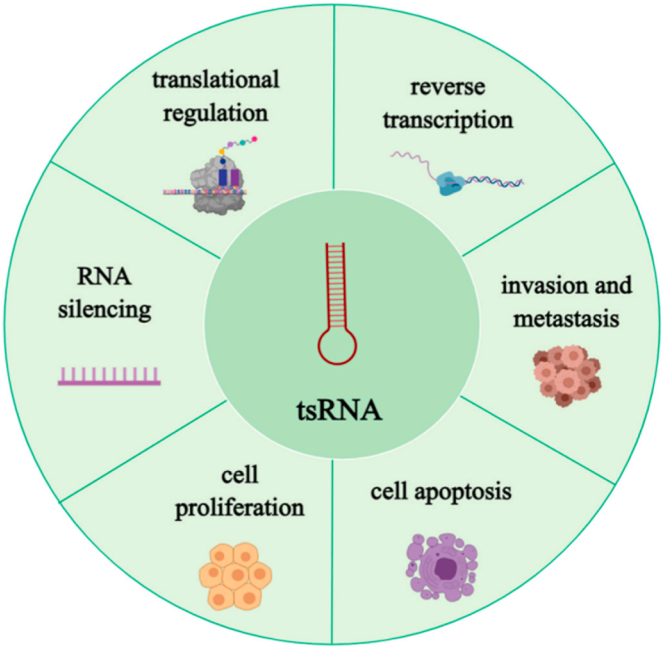

Fig. 2. Overview of critical tsRNAs that paticipate in hallmarks of cancer.

We know that tsRNA can affect gene expression by interacting with mRNA or other RNA molecules [51]. In lung cancer cells, tsRNA may regulate the expression of these genes by interacting with oncogenes, thereby affecting the proliferation and apoptosis of lung cancer cells. It is known that there are a large number of single nucleotide variations (SNVs) in UTRs regions in NSCLC [52], which can change the secondary structure of RNA and miRNA target sites. This change may lead to changes in the expression level of some oncogenes, because miRNAs usually inhibit their translation or promote their degradation by binding to specific mRNA sequences. If tsRNA can interact with these mRNAs targeted by miRNAs, they may indirectly affect the stability and expression of these oncogenes. For example, if the mRNA of an oncogene is stabilized due to the action of miRNAs, but subsequently interacted with by tsRNA, this may affect the final expression level of the gene. tsRNA may achieve this by changing the stability of mRNA, promoting its translation or inhibiting its degradation. In addition, tsRNA may further regulate the expression of oncogenes by affecting mRNA splicing, translation efficiency or other epigenetic modifications.

3.2. Activating metastasis and invasion

Invasion and metastasis cascades are unique features of cancer, including a multi-step process: initial local invasion, subsequent intravasation, transformation, extravasation, and ultimately colonization. Lung cancer metastasis and invasion are important factors affecting patient prognosis, and tsRNA plays a role in this process. For example, AS-tDR-007333 [42], tRF-21-RK9P4P9L0 [53], ts-46 [39], and ts-47 [39] have been studied, but the mechanisms by which these tsRNA are involved in lung cancer metastasis and invasion have not been thoroughly explored. In research on other cancers and tsRNA, the tRF-19-PNR8YPJZ exosome was found to specifically target AXIN2 in pancreatic cancer cells. This targeted modulation results in a diminished expression of AXIN2, which activates the Wnt signaling pathway, causing cancer cell proliferation and metastasis [54]. In a study of breast cancer lung metastasis, it was found that the oligomerization of Nucleolin with Mthfd1l and Pafah1b1 was enhanced by 5′-tRFCys, which became a higher-ranking transcript-stabilizing ribonucleoprotein complex, thereby promoting breast cancer metastasis [55]. Notably, in another breast cancer study, it was found that breast cancer metastasis could be suppressed by the binding of tRFs to the oncogenic RNA-binding protein YBX1 [56]. Therefore, in lung cancer, it is necessary to further study how tsRNA participates in the metastasis and invasion.

4. Clinical significance of tsRNA in lung cancer

Currently, clinical diagnosis of lung cancer mainly relies on imaging studies and pathological biopsy, which have certain trauma and are not conducive to early diagnosis and prognostic evaluation. Exosomes, which are membrane-bound carriers with a diameter of 30–100 nm secreted by most cell types, are present in various types of body fluids. Exosomes are composed of proteins and complex RNA. Among them, there have been numerous reports on microRNA (miRNA), circular RNA, and long noncoding RNA as biomarkers, while research on tsRNA is still limited. In terms of regulatory mechanisms, tsRNA exhibits a resemblance to miRNAs, but its high stability and expression level make it an ideal biomarker for cancer actionable clinical diagnostic, prognostic, and therapeutic strategies, along with various other pathologies [11–13,

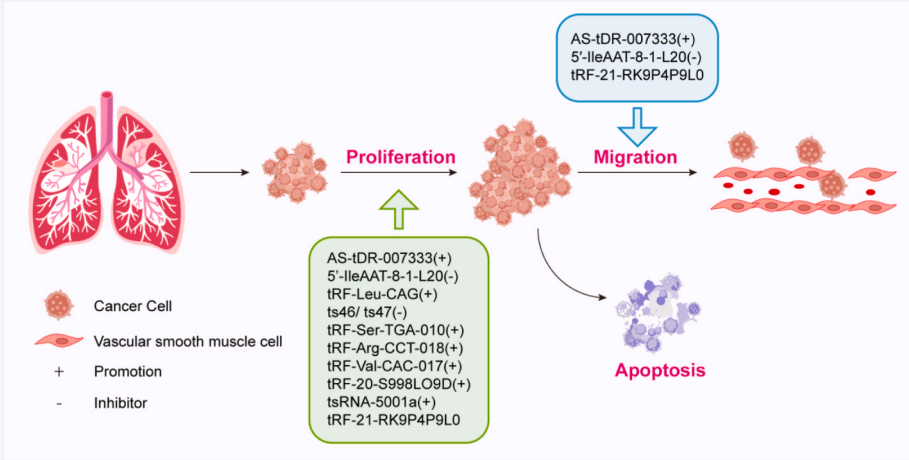

Fig. 3. The functions of tsRNAs in lung cancer.

57,58].

4.1. Application of tsRNA in actionable clinical diagnostic

Compared with healthy individuals, it was found that the expression levels of a class of exosomal tRFs were notably decreased in early lung cancer patients. Among them, exosomal tRF-Ala-AGC-036 is also related to tumor stage [59]. In addition, Pekarsky et al. found down-regulated ts-4521 and ts-3676, with potential antitumor functions in lung cancer and chronic lymphocytic leukemia [10]. The involvement of both tsRNAs in the processes of apoptosis and chromatin structure has been reported, thereby indicating their plausible function in modulating the proliferation of tumor cells and the survival of lung cancer cells [39]. Upregulation of TRF-Leu-CAG has been observed in NSCLC, particularly during the advanced stages of the disease. This upregulation is implicated in the regulation of cell cycle progression, specifically through its targeting of aurka [60]. Additionally, studies have found that healthy individuals, patients with lung cancer, and patients with tuberculosis can be distinguished from each other by a molecular signature consisting of small noncoding RNAs in the blood with an AUC of up to 0.93 [60]. In a cohort study for pulmonary nodules, five elevated tsRNA in lung cancer patients' blood were integrated with CT information to form a risk assessment model that effectively distinguished between benign and malignant pulmonary nodules (The respective AUC values recorded for tiRNA-Gln-TTG-001, tRF-Ser-TGA-003, tRF-Val-CAC-005, tRF-Ala-AGC-060, and tRF-Val-CAC-024 were 0.686, 0.873, 0.767, 0.887, and 0.682), and it provides a reliable diagnosis for some patients with pulmonary nodules who are not suitable for traumatic examination [61]. Overall, these results imply a significant contribution of tsRNAs to the advancement of tumorous conditions, the association between tsRNA dysregulation and lung cancer progression suggests their potential role in early detection and disease surveillance. In addition, CTCs and ctDNAs are highly regarded for their non-invasive capabilities in early cancer detection and survival prognosis, and when comparing them to the widely studied CTCs and ctDNAs, tsRNAs not only exhibit higher abundance, but also simpler approach to technical detection. This comparative advantage underscores the potential of tsRNAs as a promising avenue for enhancing the accuracy and efficiency of cancer diagnostics [62].

4.2. Application of tsRNA in prognostic

In addition to diagnosis, tsRNA is also associated with the prognosis of various tumors such as esophageal squamous cell carcinoma, colorectal cancer, pancreatic cancer, liver cancer, etc. [12,63–65]. The level of tsRNA is also related to the recurrence and survival prognosis [66]. In lung cancer, the expression levels of some tRFs are significantly related to lymph node metastasis stage and carcinoembryonic antigen expression level [67]. Serum tRF-31-79MP9P9NH57SD levels are also related to tumor size and the malignancy of lymph nodes. Tumor patients have higher levels of this tRF, while after surgery, its expression is significantly decreased [68]. A study of LUAD revealed an inverse correlation between tRF-21-RK9P4P9L0 expression and patient prognosis. Suppression of this tRF in A549 and H1299 cell lines significantly diminished their proliferative, migratory, and invasive capacities [53]. Another study found that the upregulation of tsRNA-5001a increased the risk of recurrence after surgery in LUAD patients and was linked to poor prognosis The mechanism may be that tsRNA-5001a binds to the anti-tumor gene GADD45G, reduces its stability, inhibits its anti-tumor function, further accelerates tumor proliferation, and thus worsens the prognosis of lung adenocarcinoma [50]. Studies on mouse tumor models have found that lung cancer can induce heart dysfunction through tRFs and thereby affect its prognosis [69].

The molecular prognosis of lung cancer is a hot research field, and its research heat has gone beyond the TNM stage, and entered the personalized genetic tumor analysis with immunohistochemistry, microarray and mutation spectrum. However, despite a large number of studies, no molecular prognostic markers have been clinically adopted because most have failed in subsequent cross validation. Develop a new prognostic tool and analysis method based on tsRNA, and play a certain role in tumor curative effect and prognosis judgment by monitoring the specific tsRNA level of peripheral blood after lung cancer treatment.

4.3. Application of tsRNA in therapeutic strategies

At present, with the in-depth study of targeted tumor therapy, more and more studies now begin to pay attention to the performance of tsRNA in disease treatment. tsRNA also shows therapeutic potential in a variety of diseases, such as malignant tumors [70,71], neurodegenerative diseases [72], cardiovascular diseases [73] and metabolic diseases [74]. In contrast to the normal physiological state, the abundance of tsRNAs is significantly altered in the pathological state, indicating that tsRNA may promote or inhibit the occurrence and development of disease by regulating cell stimulating factors. First, disease progression consists of intricate signaling cascades. By binding to specific targets within these pathways, tsRNA can either activate or silence these targets, thereby initiating or terminating signal transduction, ultimately contributing to therapeutic effects. For example, a study of breast cancer revealed that 5′-tiRNAVal exerts a suppressive effect on the Wnt/β-catenin signaling cascade through its targeting of FZD3 [75]. Similarly, Huang et al. reported that tRF/miR-1280 exhibits an inhibitory effect on CRC metastasis by directly engaging the 3′ UTR of the Notch ligand

JAG2, consequently inhibiting the activity of Notch signaling pathways [38]. At present, the research of tsRNA in the treatment of lung cancer is still in its infancy. Studies have shown that vitamin D induces mitochondrial dysfunction and inhibits the progression of NSCLC through the tsRNA −07804/CRKL axis [71]. In addition, studies have found that epigallocatechin-3-gallate (EGCG) regulates the iron death pathway by downregulating tsRNA-13502 and changing the expression of key regulators of iron death (GPX4/SLC7A11 and ACSL4), thereby promoting the accumulation of iron, MDA and ROS, and ultimately inducing iron death in NSCLC cells [76]. These results revealed that tsRNA may be able to develop therapeutic strategies with good efficacy and less side effects for lung cancer.

5. Challenges and future perspectives

Despite the considerable promise of applying tsRNA to early diagnosis, prognostic evaluation, and therapeutic targets in lung cancer, there remain numerous challenges that require further resolution.

Although tsRNA is enriched in exosomes, it contains various unique RNA modifications, posing challenges for deep sequencing detection and quantification [77,78]. PANDORA-seq overcomes these problems through T4PNK or AlkB treatment, thus improving the cDNA library construction process and achieving more accurate sequencing results, especially for modified tsRNAs and rsRNAs [79]. Another small RNA sequencing method, called CPA-seq, is applied to detect small RNAs with multiplexed ends or methylation modifications by Cap-Clip, T4PNK and AlkB/AlkB treatment [80], The recent development of these novel small RNA sequencing technologies and the analysis software of small RNAs such as iSRAP [81], iSmaRT [82], and SPORTS1.0 [83], make the detection of tsRNA in clinical settings more convenient and accurate.

The establishment of the tsRNA database also provides better data support for the study of tsRNA.tRFdb is the first tsRNA database covering small RNA-seq data for 8 different species, but the data have not been updated in recent years [84]. PtRFdb is a database of tRFs on plants, including 10 different plant species [85]. tRex is the first tsRNA database for the model plant *Arabidopsis thaliana*, including small RNA sequencing results from different tissues, ecotypes, genotypes or stress conditions [86]. Databases on human tsRNAs are also constantly being updated. For example, MINTbase 2.0 provides a dataset of tsRNAs from the Cancer Genome Atlas (TCGA) database, but does not include tRF-1 [87]. tRF2Cancer can identify tRFs in 32 cancers and analyses their expression [88]. tRFexplorer [89] and OncotRF [90] not only provide expression profiles of tsRNAs, but also correlation analysis functions, survival analysis, and so on, but tRFexplorer excludes tRNA and tRF-i. In order to study the expression patterns of tsRNAs in different genetic backgrounds or conditions, tsRBase integrates small RNA-seq data from 20 different species, including animals, plants, fungi and bacteria [91]. Another database, called tsRFun, provides more in-depth functional analyses, such as prognostic value analysis functions, and also establishes networks of interactions between tsRNAs, miRNAs and mRNAs [92]. Based on the tRFtarget 1.0 database, tRFtarget 2.0 integrates OncotRF, MINTbase v2.0, tRFexplorer, tRBase, tsRFun and tatDB data sources, adds rRNA, LncRNA and protein-coding genes with a length of >50 kb, and provides powerful functional analysis of tsRNAs [93]. The ongoing enhancement of the tsRNA database provides strong support for exhaustive investigations into the diverse biological roles of tsRNAs in different contexts. TsRNA has demonstrated enormous potential for molecular diagnosis in clinical cancer, neurodegenerative diseases, and other diseases, and may also become a next hotspot in lung cancer research.

In the future, to further understand the function of tsRNA and its role in lung cancer and tumor disease, there is still much work to be carried out: first, to develop more accurate detection technology and quantitative methods; The second is to deeply analyze the specific mechanism of tsRNA in tumorigenesis and development. tsRNA affects cell proliferation and differentiation through a variety of mechanisms, including interference with translation, regulation of gene expression, participation in reverse transcription and so on. It is urgent to further study and reveal the specific details of these mechanisms and the differences in their roles in different types of tumors; The third is to explore the application potential of tsRNA as a biomarker and therapeutic target. In the future, we can focus on how to use tsRNA to regulate relevant signaling pathways to develop new anticancer therapies; Fourth, interdisciplinary cooperation promotes the all-round development of tsrna research. tsRNA research is not limited to the fields of biology and medicine, but also involves many disciplines such as chemistry and physics. For example, the development of high-throughput liquid chromatography tandem mass spectrometry. These studies will help to improve the early diagnosis rate and treatment effect of lung cancer and other tumors, and ultimately improve the prognosis and quality of life of patients.

6. Conclusion

tsRNA plays an influential role in lung cancer progression. As a non-invasive biomarker, it has shown great potential in cancer diagnostics and prognostic evaluation and therapeutic strategies. However, to realize the clinical potential of tsRNA, further improvements in small RNA sequencing technology and research into the regulatory mechanism of tsRNA are required.

Funding

This work was supported by Hubei Chen-Xiaoping Science Foundation (No.CXPJJH122011- 008).

Availability of data and materials

Not applicable as no datasets were generated or analyzed.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent for publication was obtained from both participants.

CRediT authorship contribution statement

Yu Chen: Writing – original draft. **Zhuowei Shao:** Writing – review & editing. **Shibo Wu:** Conceptualization.

Declaration of Competing interest

The authors declare that there is no conflict of interest in this work.

Acknowledgements

Not applicable.

Abbreviations

tRNA	Transfer RNA
tsRNA	tRNA-derived small RNA
tRF	tRNA-derived RNA fragment
tiRNA	tRNA-derived stress-induced RNA
LTR-RT	long terminal repeat-retrotransposons
RG4	RNA G-quadruplex

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