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Review

The role of tRNA-derived fragments in prostate cancer: a review

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Abstract

Prostate Cancer (PCa) is a leading malignancy in men in developed countries. The lack of reliable prognostic markers in PCa hinders effective treatment, leading to potential patient misclassification and overtreatment with associated side effects. Recent advances in high-throughput sequencing have enabled the identification of tRNA-derived fragments (tRFs), small non-coding RNAs derived from tRNA cleavage. tRFs regulate crucial cellular processes like viability, differentiation, and homeostasis, implicating them in disease development, particularly cancer. Their potential as biomarkers for early diagnosis and prognosis, as well as targets for precision therapies, is increasingly recognized. This review focuses on the key biological functions of tRFs, including RNA silencing, translation regulation, and epigenetic regulation. It summarizes recent findings on tRFs in PCa, exploring their potential as clinical biomarkers and therapeutic targets.

Keywords: Prostate cancer; tRNA-derived fragments (tRFs); SHOT-RNAs; Non-coding RNA; Biomarker.

1. Introduction

Prostate cancer (PCa) is a leading cause of cancer and the second most common cause of cancer-related mortality in men [1]. This heterogeneous disease is influenced by genetic, environmental, and social factors, contributing to variable survival rates and epidemiology across different populations [2]. Affecting primarily men aged 45-60, PCa treatment is hindered by a lack of reliable biomarkers to predict disease outcomes [3]. This deficiency leads to potential overtreatment and associated side effects from surgery and radiation. While prostate-specific antigen (PSA) testing is used for diagnosis and prognosis, its limited specificity makes routine screening controversial, as it cannot effectively differentiate between benign conditions and aggressive tumors. This highlights the need for improved diagnostic and prognostic tools [4]. Understanding the molecular mechanisms underlying PCa is crucial for identifying effective biomarkers and therapeutic strategies. Recent advances in high-throughput sequencing have revealed a new class of small noncoding RNAs: tRNA-derived fragments (tRFs) [5-7]. These 14-50 nucleotide fragments originate from precursor or mature tRNAs and participate in gene silencing, RNA processing, and protein translation, influencing cell stress response, growth, and differentiation [8, 9]. tRFs also play significant roles in various human diseases, including cancer [10]. tRFs have been classified into six categories according to their cleavage sites in the parental tRNA: 5′-tRFs, 3′-tRFs, 5′-tRNA

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halves, 3′-tRNA halves, i-tRFs, and 3′U-tRFs, also referred to as tsRNAs or 1-tRFs [11, 12]. tRFs are found widely across life. Initially considered tRNA degradation byproducts, their prevalence and consistent expression now suggest an important biological function [13-15]. This review explores the biogenesis, classification, and roles of tRFs, summarizing their presence and impact on prostate cancer as described in the current literature.

2. Classification and biogenesis of tRFs

tRNA-derived fragments (tRFs) are classified based on their origin within pre-tRNAs or mature tRNAs. Four main classes exist: 1-tRFs, generated by RNase Z (ELAC2) cleavage during pre-tRNA processing; [16, 17] 5′-tRFs, derived from the 5′ end near the D-loop of mature tRNAs; 3′-tRFs, derived from the 3′ end near the TψC loop; and i-tRFs, originating from internal tRNA sites[18]. tRNA halves, including 5′- and 3′-halves, are produced via angiogenin (ANG) cleavage at the anticodon loop and are also known as tRNA-derived stress-induced RNAs [19,20] (Figure 1). Aberrant tRF expression is implicated in cancer development and progression, affecting cell proliferation, metastasis, and overall malignancy [21]. Consequently, tRFs are promising biomarkers for cancer diagnosis, prognosis, and sub-typing.

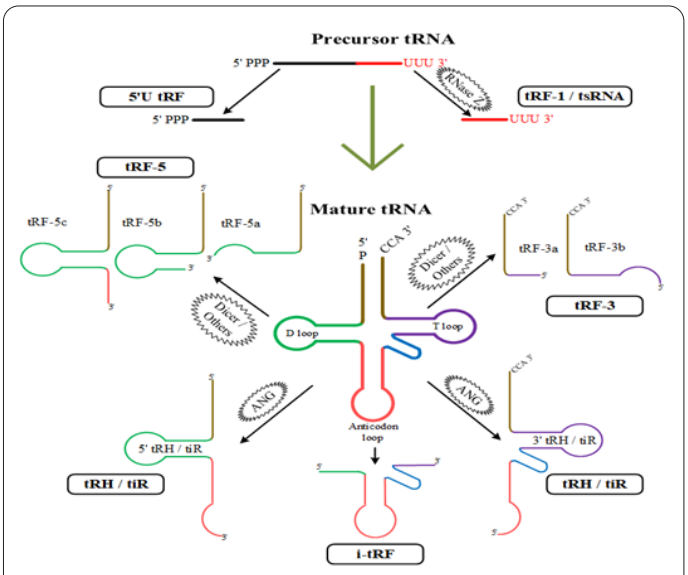

Fig. 1. Classification and biogenesis of tRF [22]

3. tRF function

3. 1. Regulation of transcription

Transcription is regulated by tRNA-derived small RNAs (tsRNAs). For example, Zhang *et al*. (2016) found that a tRNA-Glu-derived piRNA (td-piR(Glu)) interacts with PIWIL4 to recruit SETDB1, SUV39H1, and HP1β to the CD1A promoter, promoting H3K9 methylation and suppressing CD1A transcription in human monocytes [23]. Similarly, sperm tRFs preferentially associate with promoter regions, potentially influencing metabolic trait inheritance and embryonic development [12]. tRFs, both Dicer-dependent and -independent, dynamically regulate processes during the transition from youth to adulthood. They interact with Argonaut proteins (AGOs) to form RNA-induced silencing complexes (RISCs), which bind to partially complementary regions, primarily within the 3' UTR of target mRNAs, resulting in translational repression and mRNA degradation [7, 24]. In Tetrahymena, 3'-tRF, along with 5'-tRF, associates with the PIWI protein Twi12 to activate the exonucleases Xrn2 and Tan1 for rRNA processing [25]. In Tetrahymena, 3'-tRF, along with 5'-tRF, associates with the PIWI protein Twi12 to activate the exonucleases Xrn2 and Tan1 for rRNA processing [26]. Furthermore, a set of i-tRFs originating from tRNAs like tRNAGlu, tRNAAsp, tRNAGly, and tRNATyr disrupt YBX1 binding to the 3′UTRs of oncogenic transcripts in breast cancer cells, counteracting YBX1's stabilizing effect [27]. Finally, tsGlnCTG interacts with IGF2BP1, an RNA-binding protein that stabilizes c-Myc mRNA, leading to decreased transcript stability and enhanced differentiation of mouse embryonic stem cells [28].

3. 2. Regulation of translation

tRFs regulate global translation, acting as both positive and negative modulators. For example, ANG-induced 5′-tiRNAs, such as 5′-tiRNAAla and 5′-tiRNACys, inhibit translation initiation by displacing the eIF4G/A/F complex from capped mRNA with the help of YB-1, promoting stress granule formation [19]. Conversely, the Leu-CAG 3′-tRF enhances ribosome biogenesis by interacting with RPS28 and RPS15 mRNAs, increasing their translation and tumor cell viability [29]. Furthermore, the 5′-tRF Gln19 promotes translation elongation in HeLa cells by associating with the multi-syntetase complex (MSC); however, 5′-tRFs with a conserved GG-dinucleotide motif at their 3′ ends can destabilize the MSC and inhibit ribosome maturation [30, 31].

3. 3. In apoptosis

Beyond gene silencing and translation regulation, tRFs influence apoptosis. Hyperosmotic stress induces apoptosis in wild-type mouse embryonic fibroblasts by releasing cytochrome c from mitochondria and forming apoptosomes [32]. ANG treatment protects mouse embryonic fibroblasts (MEFs) and primary neurons from hypertonicity-induced apoptosis by generating 5′- and 3′-tiRNAs. These tiRNAs sequester cytosolic cytochrome c (Cyt c) into a ribonucleoprotein complex, limiting apoptosome formation and subsequent apoptosis [33].

3. 4. Regulation of reverse transcription

Transposable elements (TEs) are mobile DNA segments whose transposition can disrupt genomic stability, leading to potentially harmful heterochromatin [34]. Consequently, TE transcription is often epigenetically regulated via DNA methylation and histone modifications. However, recent evidence suggests that tRNA-derived fragments (tRFs) also play a role in TE regulation. Specifically, 3'-tRFs inhibit mouse LTR-retrotransposons (ERVs) by competing with intact tRNAs for the primer binding site (PBS), thereby blocking reverse transcription. Conversely, tRF-3019 acts as a primer for the reverse transcriptase of human T cell leukemia virus type 1 (HTLV-1), enhancing viral infection [35, 36]. The 18-nucleotide 3′-tRNA fragments (3′-tRFs) specifically inhibit the activity of mouse LTR-retrotransposons, also known as endogenous retroviruses (ERVs), by competing with intact tRNAs for the highly conserved primer binding site (PBS) of these retrotransposons. This competition effectively blocks the reverse transcription process of the ERVs [36]. Another study indicates that tRF-3019 functions as a primer for the reverse transcriptase of human T cell leukemia virus type

1 (HTLV-1) by binding to the primer binding site (PBS), which subsequently enhances the viral infection process [37].

4. Role and clinical value of tRFs in cancers

MINTbase v2. 0, published in 2018, compiles 26, 531 unique human tRFs from TCGA data (as of October 2017) and serves as a resource for cancer-related tRF studies [38]. Correlation network analyses have revealed race and ethnicity-dependent associations between tRFs and mRNA in prostate adenocarcinoma and triple-negative breast cancer [39], highlighting the role of tRFs in posttranscriptional regulation in cancer. Aberrant tRF expression and function are observed across various cancers, including breast, gastric, and colorectal cancers, and correlate with clinical characteristics and survival outcomes [40, 41]. This analysis highlights the significant role of tRFs in posttranscriptional regulation related to cancer. It emphasizes that abnormal expression and function of specific tRFs are observed in various cancers, including breast, gastric, and colorectal cancers. Additionally, it points to a correlation between the dysregulation of tRFs and clinical characteristics as well as survival outcomes in cancer patients [42-44]. Overall, tRFs play a significant role in cancer development and progression, influencing key processes such as tumor cell proliferation, metastasis, apoptosis, and resistance to chemotherapy [21, 45, 46].

5. Type of tRFs in prostate cancer

5. 1. tRF-1001

In 2009, Lee et al. identified tRF-1001, a tRF-1 derived from a Ser-TGA tRNA precursor, in a prostate cancer cell line using high-throughput RNA sequencing [7]. tRF-1001, a representative tRF-1 molecule, initiates immediately after the mature tRNA's 3′ end, prior to CCA addition. The 3′ ends of tRF-1 molecules are characterized by 5-6 consecutive thymines, indicative of RNA polymerase III termination sites [47]. These 3′-trailer sequences are generated during tRNA maturation by the tRNA endonuclease ELAC2[48]. ELAC2 knockdown reduces tRF-1001 levels while increasing pre-tRNA levels, confirming that tRF-1001 biogenesis occurs in the cytoplasm, where both molecules are exclusively localized [7]. tRF-1001 plays a significant role in cancer, especially in cell proliferation, and exhibits elevated expression in various cancer cell lines, correlating with cell growth. As a functional RNA fragment, tRF-1001 influences colon cancer cell proliferation by inducing G2 phase arrest. Given its cytoplasmic generation by ELAC2, a gene linked to prostate cancer susceptibility, tRFs like tRF-1001 are considered a distinct class of short RNAs with precise sequences and specific expression patterns, suggesting their potential as therapeutic targets or biomarkers for cancer diagnosis and prognosis [7, 49]. Studies indicate that tRF-1001 expression is dysregulated in prostate cancer tissues compared to normal tissues and correlates with clinical parameters like Gleason scores and progression-free survival [50, 51]. Elevated tRF-1001 levels in prostate cancer patients are associated with poorer prognoses, highlighting their potential as independent prognostic biomarkers for disease progression [46, 52]. The sequence of tRF-1001 is 5′-AAATAAGAGCACCCGCTTC-3′.

5. 2. tRF-Glu-TTC-2

tRF-Glu-TTC-2, a tRF-5c subtype generated from glutamic acid tRNA via cleavage by Dicer and angiogenin, is frequently detected in prostate cancer (PCa) tissues by RNA in situ hybridization. Quantitative RT-PCR analysis confirmed that tRF-Glu-TTC-2 expression is significantly elevated in PCa tissues compared to normal adjacent tissues, indicating its potential oncogenic role in PCa initiation and progression. High expression levels of tRF-Glu-TTC-2 correlate closely with tumor size and Gleason score, and functional studies demonstrate that its overexpression promotes PCa cell proliferation, while knockdown suppresses tumor growth both in vitro and in vivo. These findings suggest that tRF-Glu-TTC-2 acts as a novel oncogene driving PCa growth and may serve as a promising molecular marker for diagnosis and a potential therapeutic target in prostate cancer management. Its association with increased tumor cell proliferation indicates that tRF-Glu-TTC-2 may be a cancer-promoting gene linked to PCa progression and prognosis. Targeting tRF-Glu-TTC-2 (sequence: 5-TCGACTCCCGGTATGGGAACCA-3) [53]. Represents a potential therapeutic strategy to slow tumor growth and improve PCa treatment effectiveness, warranting further investigation of its mechanisms and therapeutic potential.

5. 3. tRF -315, tRF -544

tRF-315 and tRF-544, two tRNA-derived fragments (tRFs), exhibit contrasting expression patterns in prostate cancer and are implicated in cancer biology. tRF-315, derived from tRNA(Lys)-CTT (5-CCCGGCTAGCTCAGTCGGTAGAGCATGG -3) and typically 18-22 nucleotides long, is often upregulated in cancer tissues. Conversely, tRF-544, derived from tRNA(Phe)-GAA (5-TCCCTGG TTCGATCCCGGGTTTCGGCA-3) and typically 14-30 nucleotides long, is usually downregulated [55, 56]. The tRF-315/tRF-544 ratio shows promise as a biomarker for prostate cancer progression; a higher ratio correlates with poorer progression-free survival and shorter time to relapse, suggesting that monitoring these levels could inform patient outcomes [55, 57].

Both tRFs influence cellular processes, including gene regulation and stress response. tRF-315 interacts with oncogenic proteins, potentially impacting tumor growth and metastasis [55, 58], and prevents apoptosis in prostate cancer cells, particularly in response to cisplatin, by targeting genes like GADD45A. Differential expression suggests their regulatory roles in tumor biology, modulating gene expression and oncogenic transcript stability, crucial for cancer development [59, 60]. Research has shown that tRF-544 is downregulated in prostate cancer tissues compared to healthy tissues. The ratio of tRF-544 has been identified as a potential biomarker for prostate cancer progression. A higher ratio correlates suggesting that monitoring this ratio could aid in assessing tumor aggressiveness and guiding treatment strategies [18, 54]. Knockdown experiments show that reducing tRF-315 inhibits prostate cancer cell proliferation, indicating its oncogenic role. Given its involvement in tumor progression and treatment response, tRF-315 is being explored as a potential therapeutic target to improve cancer treatment [54, 57, 61].

5. 4. tRF-562

Prostate cancer RNA sequencing reveals significant

deregulation of tRNA-derived fragments (tRFs), including tRF 562 (5-TCGATTCCCGGCCAACGC-3), compared to normal tissue. This differential expression, with both up- and downregulation, suggests a role for tRFs in tumor biology [50].

5. 5. SHOT-RNAs

Sex hormone-dependent TRNA-derived RNAs (SHOT-RNAs), a newly discovered class of tRNA-derived small RNAs, are produced through angiogenin (ANG)-mediated cleavage of aminoacylated mature tRNAs at the anticodon loop [62]. Similar to tRNA-derived stress-induced RNAs (tiRNAs), which also result from ANG-mediated cleavage under stress conditions [62, 63].

SHOT-RNAs are particularly expressed in sex hormone-dependent cancers. In these cancers, where sex hormones and their receptors are crucial for development and progression, SHOT-RNAs influence sex hormone signaling, stimulating ANG-mediated tRNA cleavage and generating two types: 5′-SHOT-RNAs (5′-phosphate, 3′-cyclic phosphate) and 3′-SHOT-RNAs (5′-hydroxyl, 3′-amino acid). Notably, 5′-SHOT-RNAs promote cell proliferation [64]. SHOT-RNAs are significantly expressed in estrogen receptor-positive breast cancer and androgen receptor-positive prostate cancer but not in other cancer types or receptor-negative counterparts [54, 64] suggesting specific regulation by sex hormones. Their distinct expression pattern makes SHOT-RNAs potential biomarkers for diagnosing and monitoring hormone-dependent cancers, reflecting potential tumor behavior and patient prognosis.

6. Methods

This review was conducted through a systematic literature search using databases such as PubMed, Google Scholar, Web of Science, and ScienceDirect, focusing on peer-reviewed articles (2010–2024) related to tRNA-derived fragments (tRFs) and their role in prostate cancer (PCa). Key search terms included "tRNA-derived fragments, " "tRFs, " "prostate cancer, " "SHOT-RNAs, " and "non-coding RNA biomarkers. " Relevant studies were selected based on their focus on tRF biogenesis, classification, molecular functions, and clinical implications in PCa, while non-English and irrelevant publications were excluded. Data extraction centered on the mechanisms of tRF action, including their roles in transcription, translation, apoptosis, and retrotransposon regulation, with particular emphasis on well-characterized tRFs such as tRF-1001, tRF-Glu-TTC-2, tRF-315, tRF-544, tRF-562, and SHOT-RNAs. Bioinformatics resources, including MINTbase v2. 0 and TCGA datasets, were utilized to analyze tRF expression profiles in PCa. Additionally, experimental evidence from knockdown studies, qRT-PCR, and RNA-seq was evaluated to assess tRF interactions with key proteins (e. g. , YBX1, IGF2BP1, angiogenin) and their impact on cancer progression. Clinical correlations, such as associations with Gleason scores, progression-free survival, and therapeutic resistance, were also examined to explore the diagnostic, prognostic, and therapeutic potential of tRFs in PCa. This comprehensive approach ensured a thorough synthesis of current knowledge on tRFs in prostate cancer.

7. Conclusion and suggestion

The study identifies a new class of small non-coding RNAs, known as tRNA- derived fragments (tRFs), as potential clinical biomarkers for diagnosing, prognosing, and classifying tumors in prostate cancer (PCa) patients. This article suggests that tRFs can offer important diagnostic and prognostic insights that are independent of the Gleason score, potentially aiding clinicians in developing improved treatment strategies. Further investigation into these dysregulated tRFs is expected to uncover new mechanisms related to the development and progression

Table1. Summarize various tRNA-derived fragments (tRFs) in prostate cancer.

Name	Sequence	Origin	Role / Implication in cancer
tRF-1001	5′-AAATAAGAGCACCCGCTTC-3′	Derived from Ser-TGA tRNA precursor	Elevated in cancer; induces G2 arrest; associated with prognosis
tRF-Glu-TTC-2	5-TCGACTCCCGGTATGGGAACCA-3′	Derived from glutamic acid tRNA	Elevated in prostate cancer; promotes proliferation; potential therapeutic target
tRF-315	(5-CCCGGCTAGCTCAGTCGGTAGAGCATGG -3)	Derived from tRNA(Lys)-CTT	Upregulated in cancer tissues, tRF-315 promotes tumor growth; inhibits apoptosis; knockdown reduces proliferation
tRF-544	(5-TCCCTGGTTCGATCCCGGGTTTCGGCA-3)	Derived from tRNA(Phe)-GAA	Downregulated in prostate cancer tissues, Higher tRF-315/tRF-544 ratio linked to poor prognosis
tRF-562	5-TCGATTCCCGGCCAACGC-3′	Derived from tRN -GLy	Deregulated in prostate cancer tissue, may play role in tumor biology; both up/down regulated
SHOT-RNAs	Derived via angiogenin cleavage; 5'-SHOT and 3'-SHOT	From mature tRNAs at anticodon loop, hormone-dependent expression	Promote cell proliferation; potential biomarkers in hormone-dependent cancers

of PCa. Although tRFs show great promise as diagnostic, prognostic, and therapeutic targets in cancer, several limitations must be addressed for their clinical application. A key limitation is the intra- and inter-heterogeneity of tRF expression, which complicates the identification of universal tRF biomarkers for cancer diagnosis and prognosis. Additionally, the unclear molecular mechanisms underlying the dysregulation of tRF expression in cancer further hinder their clinical use. The advancement of tRF-based therapies also encounters challenges, including the effective delivery of therapeutic tRFs to targeted cells and tissues and the risk of off-target effects that could impact normal cellular functions. There is a need for more research to establish safe and effective delivery methods for therapeutic tRFs and to assess their potential toxicity and side effects. Furthermore, the limited understanding of the range of tRF functions and regulatory mechanisms in biological processes impedes the development of targeted tRF-based therapies. The intricate nature of tRF-mediated regulatory networks and their interactions with other regulatory molecules and pathways necessitates further exploration to fully realize the potential of tRFs in cancer diagnosis and treatment.

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