T RNA-derived fragments: Emerging biomarkers and targets in precision oncology

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Abstract: Transfer RNA-derived fragments (t RFs) are a novel class of non-coding RNAs generated from tRNA processing. They participate in various biological processes, including the regulation of mRNA stability, translation, and epigenetic modifications. In recent years, with the advancement of high-throughput sequencing and bioinformatics, studies have revealed that t RFs are aberrantly expressed in multiple malignancies, such as gastric, colorectal, lung, and ovarian cancers. Furthermore, their dysregulation is closely associated with tumorigenesis, invasion, metastasis, and drug resistance, suggesting that t RFs hold great potential as novel diagnostic markers and prognostic indicators. This review systematically elaborates on the biogenesis, classification, and latest research progress of t RFs in cancer diagnosis and treatment. It also discusses the current challenges and future directions in this field, aiming to provide references for the clinical translation of t RFs in precision oncology.

Keywords: transfer RNA, derived fragments, cancer, diagnosis, treatment, biomarker, liquid biopsy, non-coding RNA

1. Introduction

1.1. Biological characteristics of ncRNA and t RFs

Cancer represents a major public health challenge that severely threatens human health. Its pathogenesis is complex, characterized by difficulties in early diagnosis and a high propensity for recurrence and metastasis. A significant challenge in current oncology research lies in discovering novel biomarkers that meet the rigorous requirements for both high sensitivity and specificity. Consequently, the scientific community has focused its attention on non-coding RNAs (ncRNAs)—molecules that play critical regulatory roles in the initiation and progression of malignant tumors. Based on nucleotide length, ncRNAs are primarily categorized into long non-coding RNAs (lnc RNAs) and short non-coding RNAs. Among short ncRNAs, microRNAs and other small ncRNAs play vital regulatory roles in fundamental life processes such as cell proliferation and differentiation. Abnormalities in their expression or function have been confirmed to be associated with the development of various complex pathological conditions, including malignant tumors, neurological disorders, and immune system diseases [1-2].

Transfer RNA-derived fragments (t RFs), also known as tRNA-derived small RNAs, are a class of ncRNAs that have garnered significant attention in recent years. Regarded as an ancient class of small ncRNAs, they may have emerged earlier than more specialized small ncRNAs and participate in intracellular and intercellular functional regulation and communication [3]. Initially considered byproducts of random degradation, t RFs are now recognized, through in-depth research, as an important group of functional novel small ncRNAs. More importantly, t RFs are stably present in various cancers and exert crucial regulatory functions, making them a cutting-edge hotspot in current tumor research.

Transfer RNA (tRNA) is a class of ncRNA composed of 76 to 90 nucleotides and plays a key role in protein synthesis. Its function is to recognize mRNA codons and transport the corresponding amino acids to the ribosome, thereby participating in polypeptide chain synthesis [4]. However, recent studies have updated this traditional understanding. Research indicates that tRNAs can undergo precise, site-specific cleavage to generate a series of biologically functional small tRNA-derived fragments. Depending on the

https://doi.org/10.62852/csa/2026/246

cleavage sites on the precursor tRNA, these can form tRNA-derived stress-induced RNAs (ti RNAs) or other t RF subtypes [5]. T RFs are widely expressed across various tissues and organs; their generation is not a result of random degradation but is precisely regulated by highly conserved cleavage mechanisms [6].

Accumulating evidence shows that t RFs can bind to RNA or proteins and play significant roles in the development of various complex diseases—such as malignant tumors, infectious diseases, and neurodegenerative lesions—by participating in key pathways including translational regulation, DNA damage response, epigenetic regulation, RNA metabolism, and cell cycle control [7]. Furthermore, with the development of high-throughput sequencing and analysis technologies, researchers are now able to establish corresponding t RF databases by aligning t RFs to known tRNA genes, thereby supporting in-depth research on t RFs in different cancers [8].

1.2. Specificity of t RFs in tumor research and the purpose of this review

Although the occurrence of malignant tumors is influenced by various environmental and endogenous factors, fundamentally, it is a disease driven by genetic abnormalities. Existing studies have fully confirmed that t RFs are universally dysregulated in common malignant tumors such as breast cancer, lung cancer, and colorectal cancer. They exert important biological functions during key stages including early tumor screening, initiation and progression, metastasis, and therapeutic response [9-11]. With the continuous discovery of novel endogenous t RFs, research consistently indicates that the functions of t RFs exhibit distinct tumor-type specificity. Moreover, even within different developmental stages of the same cancer, the roles of t RFs can be diametrically opposed. This has further stimulated researchers' interest in exploring their potential value in cancer diagnosis and treatment [12].

2. Biogenesis and types of t RFs

Since HOAGLAND et al. [13] discovered the involvement of tRNA in protein synthesis over 60 years ago, it has remained a focal point in biomedical research. The biosynthesis of tRNA begins with the transcription of its gene by RNA polymerase III, generating a precursor tRNA (pre-tRNA) that contains 5′ leader and 3′ trailer sequences. After being transported to the cytoplasm, the excess sequences at the 5′ and 3′ ends are removed by endonucleases P and Z, respectively. Subsequently, a CCA sequence is added to the 3′ end by a nucleotidyltransferase to complete the maturation process. Following this, the pre-tRNA must undergo various chemical modifications, including aminoacylation, and fold into a characteristic cloverleaf secondary structure, ultimately becoming a mature tRNA to ensure its structural stability and biological function [14]. Mature tRNA molecules exhibit a highly conserved spatial conformation, and their functional units systematically comprise the following core components: the dihydrouridine (DHU) arm (containing loop and stem structures), the anticodon arm (containing loop and stem), the variable loop, the T ψ C arm (containing the pseudouridine loop and stem), and the acceptor stem responsible for amino acid recognition [15].

Under specific positions and conditions, various nucleases—such as Dicer, RNase Z, RNase P, and angiogenin—can cleave precursor or mature tRNAs. This process generates small tRNA-derived fragments that differ in sequence origin and length, primarily including ti RNAs and t RFs [16]. Based on the cleavage sites of endonucleases on the tRNA molecule, tRNA-derived fragments can be classified into the following major subtypes: tRF-1, tRF-2, tRF-3, tRF-5, and i-t RF [3, 17]. Furthermore, different t RF subtypes exhibit distinct intracellular localizations: tRF-1 is primarily located in the cytoplasm, and its generation depends on the cleavage of the 3′ end of pre-tRNA by RNase Z/ELAC2 [18]; tRF-3 is derived from the 3′ end of mature tRNA and is similarly localized in the cytoplasm, generated by cleavage from angiogenin, Dicer, or exonucleases acting on the T ψ C loop [19]; tRF-5 is mainly enriched in the nucleus, with an abundance typically higher than that of tRF-1 and tRF-3, and is generated by Dicer cleavage of the D-loop region at the 5′ end of mature tRNA [16]; tRF-2/i-t RF originates from the middle region of mature tRNA and was initially identified in tumor cells. These are mainly derived from tRNA Asp, tRNA Glu, tRNA Tyr, and tRNA Gly, although their specific cleavage enzymes and related mechanisms remain not fully elucidated [20]. According to the nomenclature rules of t RF databases, for example, each tRF-1 can be sequentially named tRF-1001, tRF-1003, tRF-1004, etc., based on the order of discovery. Additionally, based on

https://doi.org/10.62852/csa/2026/246

fragment length and cleavage position on the tRNA, tRF-3 can be further divided into tRF-3a and tRF-3b, while tRF-5 can be categorized into tRF-5a, tRF-5b, and tRF-5c [18] (Figure 1).

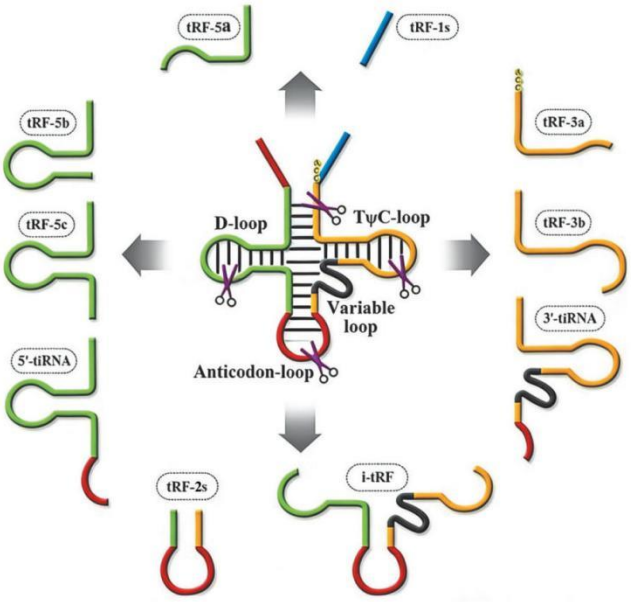

Figure 1. Generation and structure of ts RNAs [16].

3. The role of t RFs in cancer early diagnosis, progression, and prognosis prediction

Given the specific expression profiles of t RFs in various malignant tumor tissues and body fluids, research into their use as diagnostic markers has expanded widely. This provides new directions for the early screening, prognostic evaluation, and discovery of therapeutic targets for malignant tumors.

3.1. Diagnostic and prognostic role of t RFs in lung cancer

Existing studies indicate that the expression patterns of t RFs are significantly associated with the pathogenesis, disease progression, and clinical prognosis of lung adenocarcinoma. YU et al. [21] analyzed t RF expression profiles across 12 tumor types in the TCGA database and identified 11 t RFs that were significantly upregulated in most tumors. Among them, the 3′-terminal cancer-associated tRF-1 (CAT1) derived from tRNA-Ala-AGC-1-1 was highly expressed in various tumor tissues and promoted cell cycle progression, proliferation, migration, and invasion of lung cancer cells by maintaining NOTCH2 protein stability. The study also found that plasma CAT1 expression levels in patients with lung adenocarcinoma were significantly higher than those in healthy controls, suggesting that CAT1 holds important clinical application prospects for the non-invasive diagnosis and targeted therapy of lung adenocarcinoma, and is expected to become a next-generation biomarker for the clinical management of this disease. Another study identified a novel t RF, AS-tDR-007333, which is upregulated in the plasma and cancer cells of patients with non-small cell lung cancer (NSCLC). It promotes lung cancer progression through a dual mechanism: activating HSPB1-mediated histone methylation and ELK4-mediated transcriptional regulation. Further plasma-based t RF sequencing analysis highlighted the potential of t RFs in the early diagnosis of lung cancer. Meanwhile, other studies have confirmed that t RF-Leu-CAG may accelerate the cell cycle by activating Aurora Kinase A and driving cancer cells across the G0/G1 checkpoint; thus, t RF-Leu-CAG is expected to serve as a novel diagnostic marker and therapeutic target for NSCLC [22].

3.2. tRFs in breast cancer: from diagnosis to drug resistance

In the early diagnosis of breast cancer, HUANG et al. [23] screened a serum tRF profile comprising tDR-7816, tDR-5334, and tDR-4733, which showed promising application prospects for the early

https://doi.org/10.62852/csa/2026/246

identification of non-triple-negative breast cancer. Similarly, SUN et al. [24] discovered through high-throughput sequencing data that the expression levels of tRF-30-JZOYJE22RR33 and tRF-27-ZDXPHO53KSN were significantly elevated in serum samples from breast cancer patients with trastuzumab resistance, suggesting that these two may serve as novel markers for assessing drug resistance in breast cancer. Regarding breast cancer progression, researchers also found that a hypoxia-induced t RF-Glu can delay breast cancer progression by directly binding to and inhibiting the activity of YBX1 [10]. Furthermore, another study revealed that tRF-27 can induce trastuzumab resistance in HER2-positive breast cancer cells by binding to lysosome-associated membrane protein 1 to compete for the NTF2 domain, thereby activating the mTORC1 signaling pathway [25]. In summary, studies have revealed that different t RFs play complex and even opposing regulatory roles in cancer progression, highlighting their importance in precision medicine. Based on this, t RFs possess dual value in breast cancer as both non-invasive diagnostic markers and novel therapeutic targets, providing new ideas for the development of precision medical strategies [26].

3.3. Expression differences and drug resistance prediction of t RFs in colorectal cancer

In recent studies on colorectal cancer (CRC), XU et al. [27] identified that ts RNA-Gly GCC is significantly upregulated in CRC tissues and confirmed that its expression level is associated with 5-fluorouracil (5-FU) resistance. Studies in 5-FU resistant cell lines further suggested that ts RNA-Gly GCC can serve not only as a diagnostic marker for CRC but also to predict sensitivity to chemotherapy. In addition, 5'iRNA-His-GTG has also been proven to be highly expressed in CRC tissues and promotes the development of diabetic retinopathy in patients with malignant tumors by inducing HIF-1α accumulation [28]. However, another t RF, tRF3008A, shows significantly decreased expression in the plasma and tumor tissues of cancer patients and is significantly associated with advanced stages and metastasis of CRC [29].

3.4. tRFs in gastric and liver cancer: progression and prognosis

In gastric cancer research, the expression of t RF-Tyr was found to be significantly reduced. It inhibits gastric cancer progression by competitively binding to c-Myc by targeting hn RNPD. This indicator is positively correlated with the overall survival of patients, while showing negative correlations with adverse clinicopathological features such as tumor aggressiveness, lymph node metastasis, TNM stage progression, and increased tumor volume [30]. Conversely, tRF-3017A is highly expressed during lymph node metastasis in gastric cancer. It drives tumor cell metastasis to lymph nodes by binding to the AGO2 protein to form the RISC complex, thereby inhibiting the expression of the tumor suppressor gene NELL2 [31]. ZHANG et al. [32] found that tRF-33 binds to the AGO2 protein in gastric cancer tissues to negatively regulate the STAT3 pathway. This regulatory mechanism effectively delays the disease progression of gastric cancer, confirming that tRF-33 possesses important translational medical value in the early warning and clinical diagnosis of gastric cancer. In the field of hepatocellular carcinoma (HCC), RUI et al. [33] discovered a novel t RF, HCETSR, which is significantly downregulated in HCC. It negatively regulates HCC progression by inhibiting the oncogenes CCND1 and MMP7, indicating its potential as a prognostic marker. Gly-tRNA-derived fragments induce the migration behavior of HCC by activating the phosphorylation process of the AKT signaling pathway, promoting the transition of epithelial cells to a mesenchymal phenotype [34].

3.5. The role of t RFs in other malignant tumors and future perspectives

Furthermore, t RFs play key roles in the progression, metastasis, treatment, and prognosis of other malignancies, such as prostate cancer, ovarian cancer, cervical cancer, and pancreatic cancer. For instance, tRF-315 derived from tRNA-Lys is highly expressed in prostate cancer and can mitigate cisplatin-induced mitochondrial-dependent apoptosis [35]. Elevated levels of 3'U-tRF (Val CAC) in ovarian cancer are significantly associated with an increased risk of early progression and poorer survival rates following first-line platinum-based chemotherapy [36]. In pancreatic cancer, JIN et al. [37] found that ti RNAs such as AS-tDR-00064, AS-tDR-00069, AS-tDR-00102, and AS-tDR-01391 are upregulated in cancer cells, but their direct relationship with tumor progression and prognosis requires further systematic validation. Although current research on t RFs in the aforementioned cancers is still in its preliminary stages, existing

https://doi.org/10.62852/csa/2026/246

achievements have preliminarily revealed their important roles in key biological processes such as tumorigenesis and metastasis, foreshadowing broad prospects for exploration. In conclusion, as more novel t RFs are identified, and their roles and potential mechanisms in cancer early diagnosis, development, and prognosis are continuously elucidated, an in-depth analysis of t RF mechanisms and detection methods is expected to provide entirely new diagnostic markers and therapeutic targets for the clinical diagnosis and treatment of malignant tumors.

4. Advances in diagnostic detection technologies for t RFs

T RFs are characterized by their short length and high sequence specificity, making accurate detection a key factor for their clinical application. Due to its simplicity and cost-effectiveness, q RT-PCR remains the most commonly used method for t RF detection, though it has certain limitations. Therefore, to improve the detection efficiency of q RT-PCR for t RFs, specific strategies have been adopted. For instance, when detecting the content of HCETSR in liver cancer tissues and cells, a stem-loop reverse transcription primer is typically used to reverse transcribe small RNAs, followed by Sanger sequencing of the purified amplification products to enhance the specific recognition of t RFs [33]. Furthermore, YU et al. [21] utilized Db-PCR (differential base PCR), a TaqMan qPCR-based technology, which provides a highly sensitive and specific method for the quantitative detection of t RFs by precisely distinguishing single-nucleotide differences at the t RF termini. This technique was used to detect and validate the expression levels of CAT1 in lung cancer tissues and plasma, laying a technical foundation for the clinical detection of t RFs.

Leveraging its technical advantages of high throughput and high sensitivity, high-throughput sequencing has become a core tool for the systematic screening and identification of t RFs, providing a new dimension for comprehensively analyzing their profiles. Through small RNA sequencing, researchers can detect the expression profiles of thousands of t RFs in a single experiment, thereby screening for differentially expressed candidate markers. HUANG et al. [23] used high-throughput sequencing technology to identify 4,021 differentially expressed t RFs in control groups and breast cancer cells, further screening out several candidate markers including tDR-7816, tDR-5334, and tDR-4733, which showed promising applications in non-triple-negative breast cancer. Similarly, SUN et al. [24] also employed high-throughput t RF & ti RNA sequencing to detect 6,309 differentially expressed t RFs/ ti RNAs in control groups and breast cancer cell lines. Subsequent validation using quantitative PCR showed that the expression levels of tRF-30-JZOYJE22RR33 and tRF-27-ZDXPHO53KSN were significantly associated with poor clinical outcomes in breast cancer, suggesting that they could serve as independent molecular indicators for assessing disease prognosis. This "sequencing screening + qPCR validation" strategy has become the standardized workflow for t RF biomarker research.

5. Application potential of t RFs in liquid biopsy

The excellent stability and high abundance of t RFs in body fluid samples allow them to overcome many limitations of traditional biomarkers in liquid biopsy, making them highly regarded as ideal biomarkers in this field. Studies have shown that t RFs are highly stable in biological fluids such as plasma, serum, and cerebrospinal fluid, with the abundance of some t RFs even surpassing that of traditional miRNA biomarkers. This provides a significant advantage for non-invasive diagnosis, particularly for early cancer screening and treatment monitoring.

Taking lung cancer as an example, the expression level of CAT1 in the plasma of lung adenocarcinoma patients is significantly higher than that in healthy controls, and its expression is closely related to tumor progression [21]. Similarly, the high expression of AS-tDR-007333 in the plasma of patients with non-small cell lung cancer has also been validated in clinical samples, providing a new direction for minimally invasive diagnosis of lung cancer [11]. In serum samples from breast cancer patients with trastuzumab resistance, significantly elevated expression levels of tRF-30-JZOYJE22RR33 and tRF-27-ZDXPHO53KSN were observed. Correlation analysis suggests their potential involvement in the drug resistance process, indicating that they can be used not only for diagnosis but also for predicting treatment response [24]. In liquid biopsy studies of colorectal cancer, serum levels of ts RNA-Gly GCC are associated with tumor burden and chemotherapy resistance, suggesting that this biomarker holds important

https://doi.org/10.62852/csa/2026/246

clinical application potential for disease progression monitoring and treatment strategy formulation [27]. It is worth noting that the strategy of combining multiple t RF biomarkers is expected to be promoted in cancer diagnosis to improve the accuracy and specificity of detection.

6. Cancer therapeutic strategies targeting t RFs

Based on the molecular pathways through which t RFs participate in tumorigenesis, researchers have designed various targeted intervention strategies, including antisense oligonucleotides (ASOs), small interfering RNA (siRNA), and nanodrug delivery systems. In terms of clinical translation, the main challenges faced by t RF-based therapies include delivery efficiency and specificity issues. Specifically, the in vivo delivery of ASOs and siRNA requires highly efficient carrier systems to protect nucleic acid drugs from degradation and precisely target tumor tissues. It has been reported that inhibiting the expression of 5′-tRHGly(GCC) using ASOs successfully induced tumor regression in xenograft mouse models, demonstrating the therapeutic feasibility of targeting t RFs and providing direct evidence for t RFs as therapeutic targets [38]. Furthermore, ASO therapy targeting CAT1 has also shown tumor growth inhibition effects in lung cancer models, further validating the therapeutic value of targeting oncogenic t RFs [21]. In a constructed mouse model of colorectal cancer, experiments validated the significant efficacy of a delivery system using poly(β-aminoester) (PAE) material. By combining 5-FU with a ts RNA-Gly GCC inhibitor to form a PAE@5-FU/ts inhibitor complex, this delivery system was able to significantly suppress tumor progression and improve the chemosensitivity of colorectal cancer cells to 5-FU, with no obvious toxic reactions observed. This strategy of combining t RF inhibitors with traditional chemotherapeutic drugs provides a new approach to overcoming chemotherapy resistance and opens up new therapeutic avenues [27]. Meanwhile, in the treatment of liver cancer, the tumor-suppressive effect of HCETSR suggests the potential of alternative therapies; introducing HCETSR mimics can significantly inhibit hepatocellular carcinoma progression, providing a direction for the clinical application of tumor-suppressive t RFs.

In conclusion, numerous t RF-related clinical trials have been initiated or are about to be launched, which are expected to provide key data on the safety and efficacy of t RF-based therapies.

7. Current research challenges and limitations

Despite the broad application prospects of t RFs in tumor diagnosis and treatment, there are still several critical issues in this field that urgently need to be addressed. First, there is the issue of a chaotic nomenclature system for t RFs. The lack of a unified standard for naming similar t RFs across different studies—such as the interchangeable use of terms like "t RF," "sRNA," and "t RH"—may reduce the comparability of research findings. Second, it is well known that tRNAs contain numerous modified nucleotides, and these fragments are primarily located in critical tRNA regions that possess both structural and functional importance. The impact of tRNA modified bases (such as m7G, pseudouridine, etc.) on the biogenesis and function of t RFs remains unclear. These modifications may alter the stability, target-binding capacity, and intracellular localization of t RFs, but their specific roles have yet to be elucidated [39].

Synthesizing existing research, regarding mechanisms, most studies have only focused on the interaction between t RFs and single targets, while the understanding of their global regulatory roles within complex signaling networks remains insufficient. Furthermore, it is important to note that t RFs exhibit significant functional heterogeneity across different cancers. Elucidating the molecular mechanisms driving this heterogeneity is a particularly crucial step in understanding their precise regulatory functions. At the level of clinical translation, the development of delivery systems for t RF-based therapies remains a bottleneck. Although carriers such as PAE have shown some efficacy, specific delivery systems for different tissues and organs still require optimization. Meanwhile, standardized detection protocols for t RFs as diagnostic biomarkers have not yet been established, and the lack of comparability in detection results among different laboratories hinders their clinical application and promotion.

8. Future research directions and development trends

Future research on t RFs needs to deeply analyze the relationship between tRNA modifications and t RF functions. It is necessary to utilize single-cell sequencing and mass spectrometry technologies to map t RF

https://doi.org/10.62852/csa/2026/246

modification landscapes and reveal the regulatory mechanisms of modifications on their functions. In terms of diagnostic applications, focus should be placed on developing intelligent diagnostic models combining multiple t RFs. By integrating the expression data of multiple t RFs and constructing machine learning models, the accuracy and specificity of malignant tumor identification can be improved. Simultaneously, exploring the combined application of t RFs with other biomarkers (such as exosomal proteins) to build a multi-dimensional cancer diagnostic system is highly recommended. In clinical research, efforts should focus on the development of highly efficient delivery systems and the optimization of combination treatment strategies. For instance, utilizing new technologies such as lipid nanoparticles and viral vectors can improve the targeting and bioavailability of t RF therapies. Furthermore, based on the immunomodulatory functions of t RFs, exploring their combined application with immunotherapies such as PD-1/PD-L1 inhibitors may become the key to breaking through existing therapeutic bottlenecks.

Current research still lacks a systematic exploration of the regulatory mechanisms of t RFs within the tumor microenvironment. For example, whether t RFs produced by stromal cells such as tumor-associated macrophages and fibroblasts participate in tumor-stroma interactions, and how t RFs affect immune cell function, are both areas that urgently need to be explored. These studies will lay a new theoretical foundation for the application of t RFs in tumor immunotherapy.

9. Conclusion

As an emerging class of ncRNAs, t RFs demonstrate significant scientific value and clinical potential in cancer diagnosis and treatment. In terms of diagnosis, the stability and specificity of t RFs in body fluids make them promising candidates for the next generation of non-invasive diagnostic biomarkers. Regarding treatment, strategies such as ASO therapy and nanomedicine targeting t RFs have achieved remarkable results in animal models, opening up new avenues for precision cancer therapy.

Currently, research on t RFs is still in its infancy, with numerous critical scientific questions awaiting elucidation, and significant technical bottlenecks hindering their clinical translation. In the future, multidisciplinary collaboration is essential to deeply dissect the biological functions and mechanisms of t RFs, develop standardized detection methods and highly efficient therapeutic strategies, and accelerate the translation of t RF research findings into clinical practice. This will hopefully provide innovative solutions for the early screening and precision treatment of malignant tumors.

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https://doi.org/10.62852/csa/2026/246