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Review Article

Transfer RNA-derived small RNAs in cardiovascular diseases: Progress and perspectives

Xinru Wen [a], Simin Wang [b], Hongyan Chen [b], Huihui Zhang [a], Yuqiang Ji [b,*]

[a] The College of Life Sciences, Northwest University, Xi'an 710127, China
[b] The First Affiliated Hospital of Northwest University, Xi'an 710002, Shaanxi, China

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ABSTRACT

tRNA-derived small RNAs (tsRNAs) are a class of noncoding RNAs (ncRNAs) generated via the site-specific enzymatic cleavage of mature or precursor tRNAs. They are ubiquitously expressed across diverse species and are detectable in numerous cell lineages and extracellular fluids like blood and serum. They regulate gene expression at multiple levels and are functionally implicated in pivotal biological processes, including cell cycle regulation and immune response modulation. Accumulating evidence has implicated tsRNAs in both the initiation and development of cardiovascular diseases (CVDs). This article provides an overview of the classification and biological functions of tsRNAs before delving into their specific roles and mechanisms in cardiovascular pathophysiology. It aims to offer perspectives on novel therapeutic strategies, as well as the early diagnosis and prognosis assessment of CVDs.

1. Introduction

tRNAs are highly conserved and abundant noncoding RNAs (ncRNAs), constituting 10–15% of total cellular RNAs [1]. Their function as molecular adaptors is central to protein synthesis, decoding mRNA codons and transporting the correct amino acids to the ribosomal machinery [2]. Most tRNAs are 70–90nt molecules that adopt the conserved cloverleaf secondary structure [3], which consists of the dihydrouracil (D) arm, the anticodon loop, the pseudouridine (TψC) arm, and variable regions. This secondary structure then folds into a reversed "L"-shaped tertiary structure of tRNAs.

tRNA-derived small RNAs (tsRNAs) are defined as 18–40 nucleotide (nt) regulatory molecules, produced by the enzymatic cleavage of mature or precursor tRNAs [4]. Sharing a similar size range with microRNAs (miRNAs), tsRNAs were originally viewed as a specialized form of miRNAs. Current research has revealed that tsRNAs differ from miRNAs in biogenesis, with tsRNAs exhibiting more versatile functions. They regulate gene expression at the transcriptional, post-transcriptional, and translational levels and participate in key cellular processes such as regulation of cell cycle progression and modulation of immune response [5].

Cardiovascular diseases (CVDs) are the leading global cause of death; their growing prevalence imposes a substantial and increasing healthcare burden worldwide. Thus, there is an urgent need to pioneer innovative preventive and therapeutic approaches against CVDs. Emerging evidence increasingly points to tsRNAs holding significant promise as innovative targets for early diagnosis, improved prognosis, and therapy in a range of diseases. Regarding CVDs, tsRNAs are deeply implicated in the pathological mechanisms underlying conditions such as atherosclerosis (AS), ischemic myocardial injury, heart failure (HF), and cardiomyopathy. This review commences with the biogenesis and classification of tsRNAs, proceeds to outline their principal biological functions, and culminates in an exploration of their roles and a mechanistic dissection of their involvement in CVDs.

2. Generation and classification

The production of tsRNAs involves the precise cleavage of either precursor (pre-tRNAs) or mature tRNAs, which defines the two major subtypes of tRNA-derived RNA fragments (tRFs). This classification hinges on two key parameters: the position of cleavage and the size of the fragment [6]. The first group comprises approximately 14- to

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* Corresponding author.
E-mail addresses: 1549656983@qq.com (X. Wen), 502894001@qq.com (S. Wang), 784406235@qq.com (H. Chen), 15036473601@163.com (H. Zhang), jyqshandong@hotmail.com (Y. Ji).

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30-nt-long fragments originating from pre-tRNAs or tRFs [7,8]. The second group includes tRNA halves (tiRNAs), which are approximately 31- to 40-nt-long tRNA fragments [9].

2.1. tRFs

tRF-1 (16–48 nt) is probably generated during tRNA maturation through cleavage by RNase Z and Elac2 [10]. Characterized by the presence of an anticodon loop, tRF-2 is a novel class of fragments processed from tRNAGlu, tRNAAsp, tRNAGly, and tRNATyr, and was first reported in breast cancer cells. However, the enzyme(s) responsible for its biogenesis remain unclear [11]. tRF-3 encompasses the tRNA segment spanning from the T-loop periphery to the 3'-end. These fragments typically measure 18 or 22 nucleotides (nt) in length and consist of two primary subtypes: tRF-3a and tRF-3b. tRF-3 typically contains a CCA-terminal sequence and is generated by cleavage within the T-loop by Dicer, angiogenin, or other members of the RNase A superfamily [12]. tRF-5 is derived from the 5′-end of mature tRNA, originating from the D-loop or the region between the D-loop and the anticodon loop; most of tRF-5 is generated through cleavage by Dicer [13]. tRF-5 falls into three classes based on length and structural features: tRF-5a (14–16 nt) is defined by its predominantly single-stranded nature and pre-D-loop cleavage. tRF-5b (22–24 nt) is partially double-stranded and results from post-D-loop cleavage. tRF-5c (28–30 nt) adopts a double-stranded conformation and is generated by cleavage preceding the anticodon loop. [14]. A new tRNA fragment family, coined i-tRF for its internal position within mature tRNAs, lacks the standard 5′ or 3′ ends. These fragments are located internally, spanning a region that starts after the 5′ end and ends before the first "C" in the 3′ CCA sequence [13]. i-tRFs are categorized based on their cleavage site: those cleaved in the anticodon loop are termed A-tRF, those in the variable region are V-tRF, and those in the D-loop are D-tRF. This nomenclature directly reflects their respective biogenesis locations [15].

2.2. tiRNA

tiRNA, also known as tRNA half, is induced under a range of physicochemical and biological stresses, including hypoxia, heat shock, oxidative stress, UV radiation, viral infection, and phosphate deficiency [16,17]. The biogenesis of tiRNA fragments involves a precise cleavage event occurring within the anticodon loop of mature tRNAs, resulting in 30- to 40-nt-long 3′- and 5′-terminal fragments. Although initially reported as stress-induced RNAs, subsequent studies revealed tiRNA generation under nonstress conditions [18]. Based on their terminal composition, tiRNAs are classified as 3′-tiRNAs or 5′-tiRNAs [19,20]. 5′-tiRNAs and 3′-tiRNAs differ in their terminal modifications, with the former bearing phosphate groups and the latter hydroxyl groups at both ends [21]. Unlike the processing mechanisms of miRNAs and siRNAs, tiRNAs are produced via the specific enzymatic processing by angiogenin [14,15].

3. Biological functions

Emerging data reveal the evolutionary conservation of tsRNAs, displaying a wide distribution spanning bacteria, fungi, plants, and animals [22]. As mentioned earlier, they regulate gene expression and participate in several biological processes. These functional capacities allow tsRNAs to participate in the regulation of key pathological processes underlying cancers, metabolic disorders, neurological diseases, and CVDs [23]. This section describes the main functions of tsRNAs, including gene regulation at multiple levels and the modulation of cell cycle progression and immune response (see Fig. 1).

3.1. Key regulatory mechanisms of tsRNA-Mediated gene expression

3.1.1. Transcriptional regulation

A key function of tsRNAs is the transcription-independent regulation of nuclear genes. This is achieved, in part, through a unique nuclear silencing mechanism reliant on Dicer, which operates differently from both post-transcriptional mRNA targeting and epigenetic transcriptional repression. These tsRNAs bind to the nuclear protein AGO2 (Argonaute 2) and target the intronic sequences of nascent mRNAs transcribed from specific genes through sequence complementarity, thereby inducing nascent RNA silencing of the target genes [24]. Zhang et al. [25] comparing tissue samples from individuals with gastric lesions to healthy controls revealed a progressive decrease in tRF-33 expression as pathology advanced. Mechanistically, tRF-33 was shown to inhibit tumor cell viability by recruiting AGO2 to repress STAT3 mRNA (Fig. 2A).

Additionally, certain tsRNAs, such as 5′-tsRNA-Glu, can regulate transcription through a mechanism shared with PIWI-interacting RNAs (piRNAs). This finding suggests that this class of small RNAs may converge on similar regulatory circuits. For example, the tRNA-Glu-derived piRNA (td-piR(Glu)) can bind to PIWIL4 to form a complex, subsequently recruiting SETDB1, SUV39H1, and heterochromatin protein 1β to the promoter region of CD1A. This facilitates H3K9 methylation and culminates in robust transcriptional suppression of the CD1A gene [26] (Fig. 2B).

3.1.2. Post-transcriptional regulation

Some tsRNAs can bind to mRNAs and regulate mRNA stability in the same manner as miRNAs, thereby influencing post-transcriptional gene regulation and affecting disease development [27–29]. By binding AGO, these tsRNAs serve as the guiding molecules for the assembly of the RNA-induced silencing complex (RISC). Subsequently, through sequence complementarity, they bind to the 3′-untranslated region (3′-UTR) of target genes, leading to the degradation of the target mRNAs. This binding mechanism is consistent with the transcriptional regulation process described above, except for a key difference: the final fate of the mRNA [30]. For example, mature human B cell-derived tRNA fragments (3′-CCA tsRNAs) bind to AGO and sequence-specifically target RNAs to inhibit translation, illustrating their capacity to employ miRNA-mimetic mechanisms for gene regulation [31]. Certain 5′-tsRNAs can modulate mRNA stability by competitively binding to RNA-binding proteins (RBPs), thereby interfering with mRNA-RBP interactions. For instance, tRFGlu can compete for binding to YBX1 (Y-box-binding protein 1), preventing YBX1 from interacting with its target mRNAs and leading to mRNA destabilization and degradation, ultimately affecting gene expression [32] (Fig. 3A). Similarly, specific 5′ tRF-Cys can preferentially interact with the RBP IGF2BP1, modulating transcript stability and ultimately upregulating c-Myc protein levels [33]. (Fig. 3B). Additionally, in chondrocytes, tRF-3003a mediates post-transcriptional regulation of JAK3 via assembly into AGO/RISC complexes [34].

3.1.3. Translational regulation

tsRNAs function by repressing core translational machinery—such as ribosomal proteins and initiation/elongation factors—thereby exerting control over general mRNA translation [35].

(1) Regulation of Specific Proteins

Under normal conditions, the RNA chaperone La/SSB binds to stem-loop IV of the hepatitis C virus (HCV) internal ribosome entry site (IRES) to promote the viral protein synthesis driven by this RNA element [22]. In Huh7 cells, tRF_U3_1 (derived from a pre-tRNA 3′ trailer) binds La/SSB, thereby disrupting its interaction with the HCV IRES and suppressing viral translation. Through this competition for a limited host protein pool, such tRFs ultimately confer resistance to multiple La/SSB-dependent RNA viruses [36] (Fig. 4A).

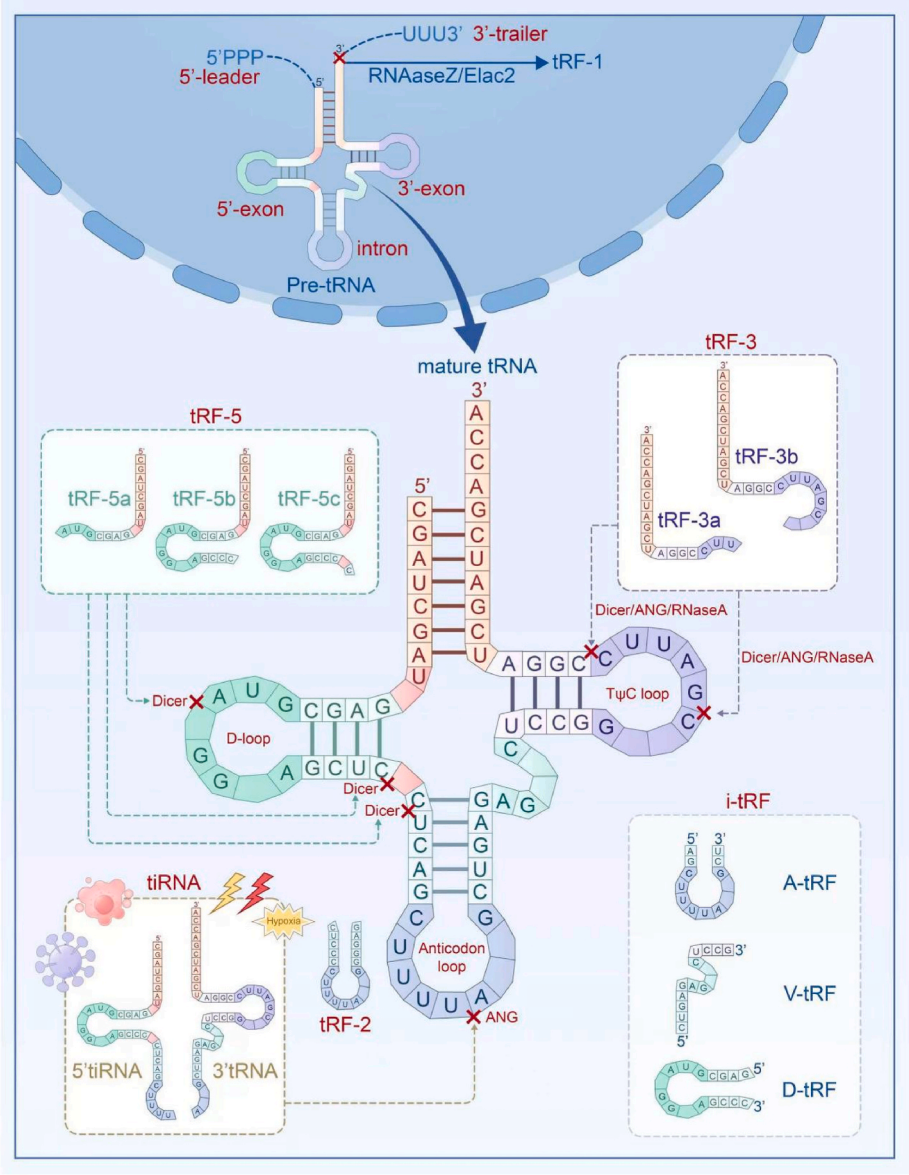

Fig. 1. Schematic overview of tsRNA biogenesis and classification. This figure depicts the generation of tRNAs and their subsequent processing into tsRNAs, detailing the five main subclasses (tRF-1, tRF-2, tRF-3, tRF-5, and i-tRF) and their respective cleavage positions on the precursor tRNA. tRF-1 is generated from pre-tRNA. The other four tsRNA subtypes originate from the different regions of mature tRNAs. tiRNA has two subtypes: 5'-tiRNA and 3'-tiRNA.

In 2018, a study reported the regulatory mechanism of tsRNAs on target genes and their critical role in stress responses of *Drosophila*. tsRNAs specifically recognize and inhibit the translation of target gene mRNAs through their conserved sequences. This process involves the binding of AGO2 to tRNA-derived tsRNAs, which then specifically bind through partial complementarity to the target mRNAs and inhibit their translation. The global translation activity is consequently inhibited as tsRNAs target and repress the synthesis of essential translational components, such as ribosomal proteins (RPs) and initiation/elongation factors (IEFs) [35] (Fig. 4B).

(2) Regulation of Ribosome Function

The analysis of small noncoding (sncRNAs) associated with ribosomes in *Trypanosoma brucei* revealed significant induction of 3′-tiRNAThr under starvation conditions. Moreover, during recovery from starvation stress, this tiRNA binds to the 60S subunit of ribosomes and polysomes and to monomeric 80S ribosomes, where it enhances translation by promoting mRNA loading [37] (Fig. 4C).

(3) Regulation of Translation Initiation

5′ tiRNA-Ala, bearing a terminal oligo-guanine (TOG) sequence, can form RNA G-quadruplexes (RG4) and interact with the HEAT1 repeat of eIF4G. This binding thereby destabilizes the eIF4F complex on the m7GTP cap, leading to its displacement. Consequently, the impaired assembly of eIF4F at the cap structure ultimately blocks 48S ribosomal scanning [38] (Fig. 4D). Further research revealed that the highly expressed pseudouridine synthase PUS7 can bind to TOG-containing, converting uridine (U) at position 8 to pseudouridine (Ψ). PUS7-mediated pseudouridylation (Ψ) plays a selective role in translation during early embryonic development. Additional studies have shown that PUS7-mediated Ψ guides tsRNAs to inhibit translation. The Ψ-containing TOG tRF-5 (18 nt) binds to PABPC1 and recruits eIF4G. This recruitment ultimately displaces the eIF4A/G complex from mRNAs, leading to a suppression of overall translation [39] (Fig. 4E).

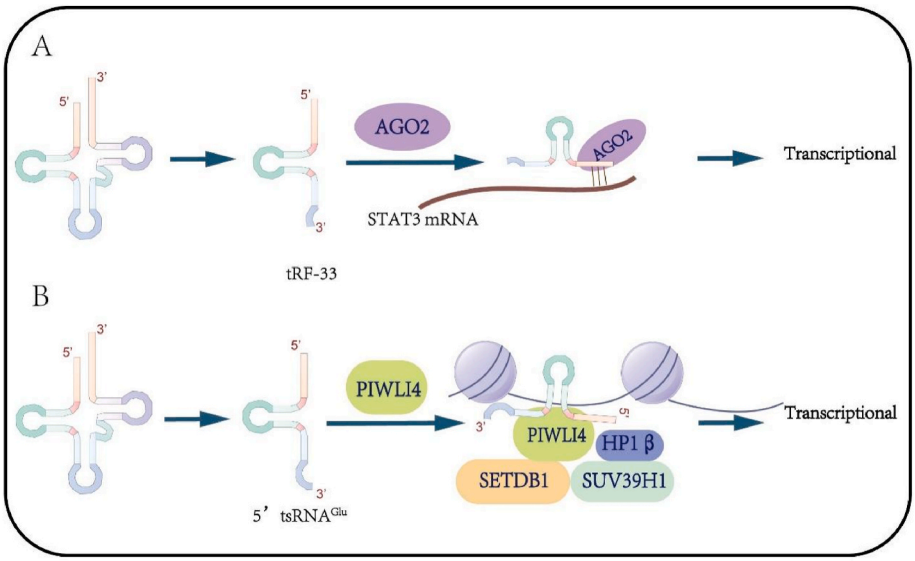

Fig. 2. **A** tRF-33 binds to AGO2 and silences STAT3 mRNA, leading to nascent RNA silencing of the target gene, thus regulating the transcriptional process. **B** The binding of td-piR(Glu) to PIWIL4 initiates complex formation, leading to the recruitment of SETDB1, SUV39H1, and heterochromatin protein 1β to the CD1A promoter. This recruitment facilitates H3K9 methylation and consequently induces strong transcriptional suppression of CD1A.

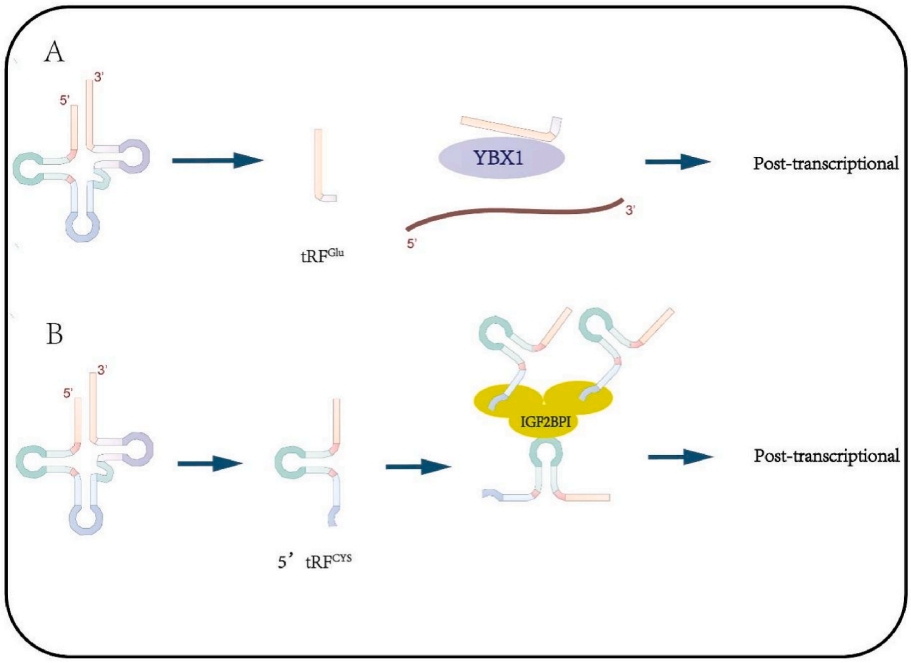

Fig. 3. **A** tRFGlu influences the post-transcriptional process by competitively binding to Y-box-binding protein 1 (YBX1), thereby inhibiting mRNA-YBX1 interaction and subsequently leading to mRNA destabilization and degradation. **B** 5′-tRFCYS preferentially interacts with the RNA-binding protein IGF2BP1, modulating transcript stability and regulating the post-transcriptional process.

3.2. Regulation of epigenetic inheritance

Epigenetic inheritance is the transmission of changes in chromatin state in the absence of alterations to the DNA sequence itself [40]. It can be regulated through key mechanisms such as DNA methylation, histone modification, chromatin remodeling, and ncRNAs interaction [41].

3.2.1. tsRNAs and DNA methylation

DNA methylation is an epigenetic process characterized by the covalent attachment of methyl groups to DNA. Using a paternal HFD mouse model, small RNA sequencing of spermatozoa identified a marked increase in the expression of tRF-5 family members; moreover, these tsRNAs were delivered to the embryo to regulate the promoter methylation of Peg3 through fertilization. This finding is the first demonstration that sperm tsRNAs mediate the intergenerational inheritance of metabolic disorders in father by modulating the methylation of embryonic genes [42].

3.2.2. tsRNAs and histone modification

Histone modification involves structural changes in histone proteins in response to relevant enzymes. In immune cells, IL-4-mediated downregulation of the td-piR(Glu) precursor prevents the formation of a td-piR(Glu)/PIWIL4 complex that would otherwise recruit H3K9 methyltransferase and heterochromatin protein 1β to silence CD1a via

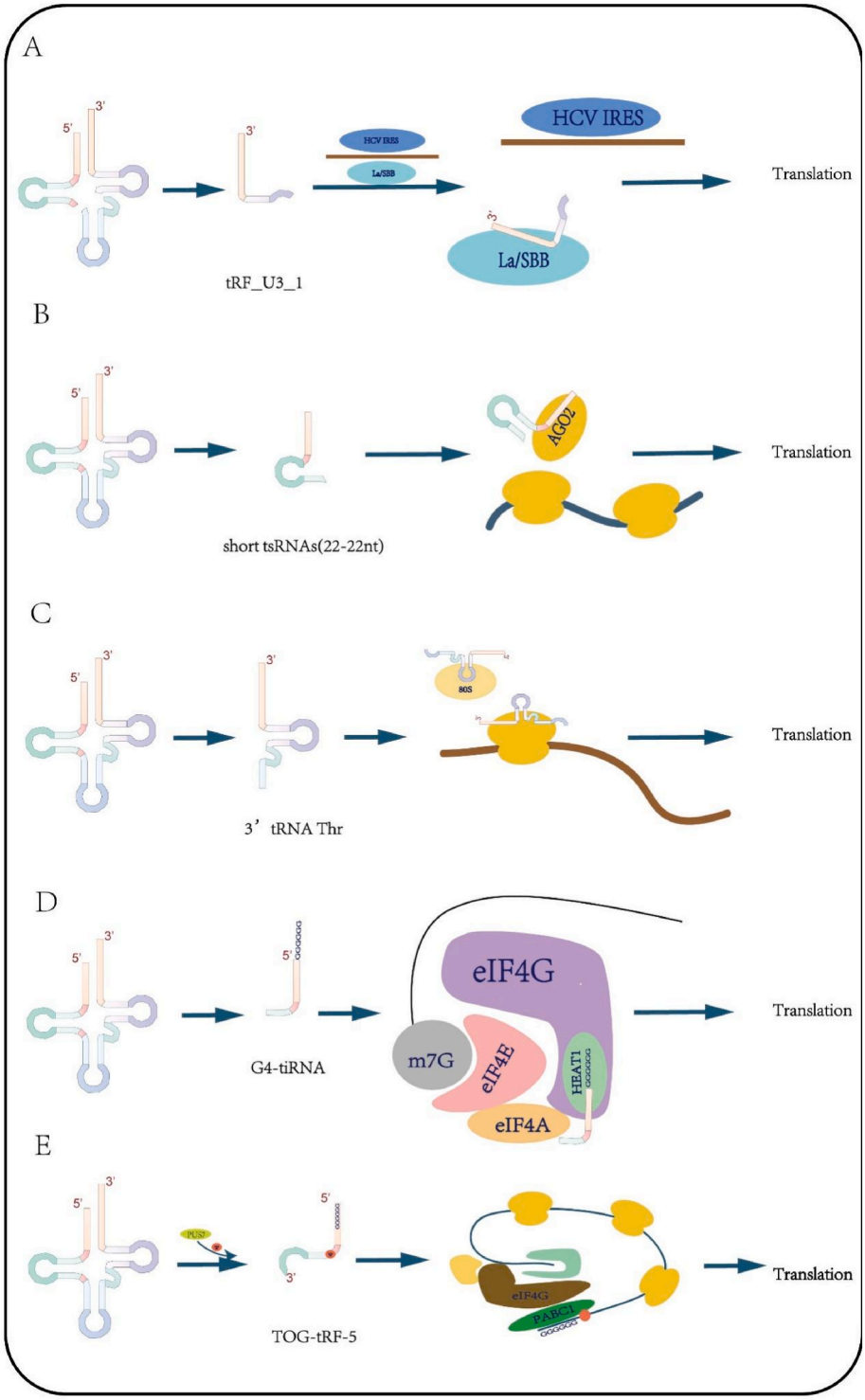

Fig. 4. **A** tRF_U3_1 directly binds to La/SSB and inhibits La/SSB–HCV IRES interaction, thereby significantly suppressing HCV IRES-mediated translation. **B** Short tsRNAs (20–22 nt) bind to AGO2 through partial complementarity and specifically inhibit translation, resulting in the suppression of translation of certain RPs and IEFs, which further downregulates the global translation activity. **C** 3′-tiRNAThr binds to the 60S subunit of ribosomes and polysomes and to monomeric 80S ribosomes, promoting mRNA loading to enhance the translation process. **D** The terminal oligo-guanine (TOG) sequence of 5′ tiRNA-Ala allows it to form RG4 structures, which interact with eIF4G's HEAT1 repeat. This interaction destabilizes the eIF4F initiation complex on the m7GTP cap, leading to its displacement. The consequent failure to assemble eIF4F at the cap thus specifically inhibits 48S scanning and translation regulation. **E** Ψ-containing TOG-tRF-5 (18 nt) binds to PABPC1 and subsequently interacts with eIF4G, displacing the eIF4A/G complex from mRNAs. This leads to overall suppression of translation, thus modulating the translation process.

promoter methylation. This process reflects tsRNA-mediated gene control through histone modification [43].

3.2.3. tsRNAs and chromatin remodeling

tsRNAs play a significant role in chromatin remodeling, which involves dynamic changes in chromatin packaging, histone organization, and DNA conformation during key cellular processes. They function by directly interacting with remodeling complexes or indirectly regulating relevant RNA-protein dynamics. 5'-tRF-Gly-GCC (tRF-GG) functions to suppress endogenous retrotransposon MERVL and its associated genes by regulating their chromatin formation, a process involving heterochromatin-mediated encapsulation and repression of MERVL. tRF-GG regulates U7 snRNA to modulate histone supply, thereby facilitating heterochromatin formation and transcriptional repression of MERVL elements. This leads to the downregulation of associated genes and a reduction in chromatin accessibility within these silenced regions [44].

3.2.4. Interaction of tsRNAs with ncRNAs

Pekarsky et al. [45] characterized ts-4521 and ts-3676 as piRNAs that interact with overexpressed PIWIL2 to mediate transposon silencing in both chronic lymphocytic leukemia and lung cancer. Yeung et al. [46], for the first time, discovered the gene silencing function mediated by tsRNAs in HIV. tRF-3 (tRF-3LysUUUU) derived from tRNALys was aberrantly expressed in HIV-infected MT4 T cells, and its binding to HIV's primer binding site (PBS) and AGO2 significantly reduced HIV-1 RNA replication. This finding suggests that this tsRNA can inhibit HIV-1 replication through the RNAi mechanism and could serve as a new molecule to control HIV replication.

3.2.5. tsRNAs and transposons

Transposon elements (TEs) are genomically mobile sequences whose transposition is epigenetically regulated, primarily through DNA methylation and histone modifications [47] Schorn et al. [48] linked tsRNAs to transposon regulation, demonstrating in mice that tRF-3-LysUUUU (18 nt) competitively binds to the tRNA PBS sequence. This competition with mature tRNAs inhibits retroviral cDNA synthesis, thereby suppressing endogenous retroviral retrotranscription. The authors also found tRF-3 (18-22 nt) accumulation on the methyltransferase Setdb1 in mouse embryonic stem cells, further suggesting that tRF-3 promotes histone H3K9 methylation to inhibit retrotransposon activity. Another study showed high accumulation of tRFs in pollen-containing male gametes of unstressed wild-type flowering plants and in similar reproductive structures of nonflowering plants. Further experiments revealed that tRFs are processed by Dicer-like 1 and subsequently loaded into AGO1, forming complexes analogous to those of tiny RNAs. Building on the mechanistic principle that plant small/-medium RNAs mediate direct transcript cleavage, the tRF-AGO1 complex similarly targets and cleaves the mRNA products of transcriptionally active transposons [49]. This study demonstrated that tRFs are certainly small RNAs with regulatory functions similar to tiny RNAs and can regulate genome stability by targeting TE transcripts.

3.3. Regulation of cell cycle

tsRNAs play a dual role in cell fate: under normal conditions, they can function as endogenous apoptotic signals to promote cell death; however, under cellular stress, upregulated tsRNA levels suppress this apoptotic function, thereby promoting cell proliferation and cycle progression, ultimately favoring malignancy [50]. tRF-1001 is derived from the 3′-end of the transcriptional precursor of Ser-TGA tRNA, and its knockdown impairs normal cell proliferation, leading to a substantial accumulation of cells in the cell cycle G2 phase [6]. Zhu et al. [51] reported that tRFLys-CTT-010 enhances triple-negative breast cancer proliferation via glucose-6-phosphatase-mediated metabolic reprogramming, while hyperosmotic stress conversely induces apoptosis in wild-type MEFs by triggering mitochondrial cytochrome *c* release and subsequent apoptotic body formation [52]. Saikia et al. [53] proposed that ANG treatment protects MEFs and primary neurons from hyperosmotic stress-induced apoptosis by generating 5′- and 3′-tiRNAs. These tiRNAs sequester cytoplasmic Cyt *c* into ribonucleoprotein complexes, thereby inhibiting apoptosome formation and activity.

3.4. Regulation of immune responses

As central regulators, tsRNAs coordinate immune cell function, immune-related gene expression, and signaling pathway activation via integrated mechanisms to sustain immune homeostasis.

In 2019, Chiou et al. [54] (2019) found that T cells, in a signal-dependent manner, induce the release of specific 5′- and internal 3′-derived tRFs (from non-variable loop tRNAs) via extracellular vesicles (EVs) by engaging multivesicular bodies (MVBs). Disrupting EV generation traps these tRF-loaded EVs within MVBs. Subsequently, differential serum tRNA expression was identified in patients with systemic lupus erythematosus (SLE) and lupus nephritis (LN) [55]; This finding offers novel clinical insights for autoimmune disease management. Specifically, the serum level of tRF-His-GTG-1 is significantly elevated in SLE patients. Its combination with anti-dsDNA antibodies shows promise as a noninvasive diagnostic biomarker for SLE. Moreover, its expression profile may further aid in the precautionary diagnosis of lupus nephritis (LN) in these patients [56]. This further confirms the clinical relevance of tRF-His-GTG-1 in SLE.

4. tsRNAs and CVDs

4.1. tsRNAs and AS

AS is a chronic inflammatory disease primarily involving lipid deposition, plaque formation, and endothelial inflammation. Plaque proliferation can predispose patients to complications like acute myocardial infarction and ischemic cardiomyopathy [57]. Wang et al. [58] performed RNA sequencing on carotid endothelia from AS patients and healthy controls, identifying tRF-Gly-GCC-009 as substantially upregulated in AS. Functional annotation via Gene Ontology (GO) analysis further suggested that this tRF primarily regulates cell adhesion processes involving plasma membrane adhesion molecules. RNA sequencing identified significant upregulation of tRF-Gly-GCC in the carotid intima of AS patients. Bioinformatics analyses (KEGG and others) suggested its involvement in key pathways such as Apelin, Notch, and calcium signaling, along with cell adhesion processes associated with AS. Subsequent gain-of-function experiments validated that tRF-Gly-GCC enhances cell proliferation and migration by negatively regulating MHC protein expression [59]. Using the comprehensive PANDORA-Seq method, sncRNAs associated with atherosclerosis (AS) were profiled in LDLR−/− mice. This identified upregulated tsRNAs-Arg-CCG in the AS intima. Subsequent overexpression in HMEC-1 cells further elevated key pro-atherogenic factors (IL-6, IL-1α, ICAM-1, VCAM-1, MCP-1), suggesting a conserved role in promoting endothelial inflammation and AS progression [60]. A recent study identified a cholesterol-sensitive hepatic tsRNA, namely tsRNA-Glu-CTC, in C57BL/6 mouse livers. tsRNA-Glu-CTC overexpression induces hypercholesterolemia and hepatic steatosis, in contrast, its genetic ablation protects against diet-induced hypercholesterolemia and AS in mice. The underlying mechanism involves tsRNA-Glu-CTC–SREBP2 interaction through an E-box motif to regulate tsRNA transcription, ultimately influencing disease onset [61].

4.2. tRNAs and ischemic myocardial injury

Ischemic myocardial injury may result in necrotic tissue damage, which can be partially counteracted by post-ischemic angiogenesis to restore blood supply and tissue function [62]. Using deep sequencing

and bioinformatics, researchers in China compared ischemic and contralateral brain tissues from rodents. This identified upregulated tRNAVal (CAC) and tRNAGly (GCC) in ischemic rat brains, a result further confirmed in mouse ischemia and cellular hypoxia models. In functional studies, transfection assays showed that the upregulation of these tRNAs significantly impaired key vascular endothelial cell (EC) functions, including proliferation, migration, and tube formation [63]. To investigate caloric restriction (CR) in alleviating ischemic injury, three experimental groups were established: normal control (NORM), isoproterenol (ISO)-induced myocardial ischemia (MI), and CR-pretreated ISO-induced MI (CR + MI). High-throughput sequencing of tsRNA expression profiles revealed differential patterns: two tsRNAs (tRF-Gly-TCC-018 and tiRNA-His-GTG-004) were downregulated in the MI group but restored in the CR + MI group, while three others (tRF-Cys-GCA-022, tRF-Lys-CTT-026, tRF-Met-CAT-008) showed the opposite trend. Bioinformatics analysis further suggested that these tsRNAs might mediate therapeutic effects by regulating macromolecular metabolism [64]. n male SD rat cardiomyocytes subjected to ischemia/reperfusion (I/R) injury, hypoxia-induced HIF-1α enhanced ANG transcription, thereby elevating cytoplasmic levels of tiRNA-Met-CAT-002. This tiRNA suppressed the translation of Bnip3, consequently enhanced cellular survival, and ultimately reduced autophagy levels. These findings suggest that tiRNA-Met-CAT-002 may protect against I/R injury by modulating autophagy pathways [65]. A hypoxia-responsive tiRNA (tiRNA-HAR) is significantly upregulated under ischemic/hypoxic conditions. Its mechanism involves direct binding to HuR, which stabilizes p53 by enhancing their interaction. Thus, by targeting the HuR/p53 signaling axis after myocardial infarction, tiRNA-HAR serves as a key regulator of cardiomyocyte apoptosis and cardiac injury, presenting itself as a novel therapeutic target for ischemic heart disease [66].

4.3. tRNAs and pulmonary arterial hypertension (PAH)

PAH is characterized as a heterogeneous disorder of abnormally increased pulmonary arterial pressure. Hypoxia and oxidative stress constitute major pathogenic factors in the initiation and progression of PAH [67]. Compared to healthy individuals, PAH patients exhibited abnormal expression of 816 tRNAs, among which eight were further validated to be differentially expressed. These included four upregulated (tRF3a-AspGTC-9, 5'-tiRNA-31-GluCTC-16, i-tRF-31:54-Val-CAC-1, tRF3b-TyrGTA-4) and four downregulated species (5'-tiRNA-33-LysTTT-4, i-tRF-8:32-Val-AAC-2, i-tRF-2:30-His-GTG-1, i-tRF-15:31-Lys-CTT-1). Their predicted target genes were enriched in pathways governing cellular metabolism, proliferation, differentiation, and apoptosis [68]. Zhang et al. discovered that, compared to healthy subjects, patients with PAH exhibited significant upregulation of 8-oxoguanine-modified tRF-1-AspGTC in pulmonary tissues and serum. Furthermore, 5o8G tRF-4 retargeted and suppressed the expression of WNT5A (Wingless-type MMTV integration site family, member 5A) and CASP3, ultimately counteracting hypoxia-induced proliferation and apoptosis resistance in pulmonary arterial smooth muscle cells [69]. A significantly reduced plasma concentration of i-tRF-15:31-Lys-CTT-1 was exhibited in PAH patients relative to healthy controls [70]. An association was found between lower plasma i-tRF-15:31-Lys-CTT-1 levels and reduced survival in PAH, suggesting its potential as a prognostic biomarker [41]. tRF-1:32-Glu-TTC-2-M2, downregulated in PAH ventricles, exerts antifibrotic and functional benefits upon overexpression. This is achieved through its direct interaction with P4HA2, resulting in the inhibition of P4HA2 expression and activity, which dampens collagen synthesis and fibroblast activation. The specificity of this mechanism is supported by the partial reversal of effects upon P4HA2 reconstitution [71].

4.4. tsRNAs and atrial fibrillation (AF)

AF represents a clinically prevalent condition of cardiac arrhythmia. Epicardial adipose tissue (EAT) is a potential arrhythmogenic niche capable of releasing diverse bioactive molecules, including exosomes containing tsRNAs [72]. To investigate AF-related tsRNA regulatory mechanisms in epicardial adipose tissue (EAT), researchers performed RNA sequencing on EAT samples from AF patients and sinus rhythm controls. Analysis revealed significant upregulation of tRF-SeC-TCA-001 and tiRNA-Gly-CCC-003 in AF, conversely, tRF-Gly-GCC-002 and tRF-Tyr-GTA-007 were downregulated. Bioinformatics analysis further suggested that the target genes of these tsRNAs likely promote AF pathogenesis by modulating multiple signaling pathways [73]. Xie et al. [74] performed small RNA sequencing on atrial myocardial tissues from an AF mouse model and found upregulated tsRNAs-5008a levels. *In vitro* knockdown of tsRNAs-5008a coupled with RNA immunoprecipitation revealed that, following tsRNAs-5008a knockdown, the amount of tsRNAs-5008a and SLC7A11 mRNA enriched by AGO2 antibodies was significantly reduced. This finding indicates that tsRNAs-5008a is involved in AF pathogenesis by binding to SLC7A11 through AGO2, which further suppresses SLC7A11 expression and ultimately promotes ferroptosis. Sequencing of atrial appendage tissues from AF patients showed significantly elevated levels of tsRNAs-5006c-LysCTT in AF. Bioinformatics analysis also demonstrated a close association of these tsRNAs with calcium signaling pathways and adrenergic signaling pathways in cardiomyocytes [75].

4.5. tRNAs and aortic dissection (AD)

AD is a CVD with a relatively low incidence rate but a high mortality rate; it is characterized by rupture of the aortic intima, hematoma formation within the aortic wall, and subsequent dissection of the aortic wall layers [76,77]. RNA sequencing analysis comparing aortic dissection (AD) tissues with normal aortic tissues identified significant upregulation of tRF-1:30-chrM.Met-CAT. Bioinformatics and functional experiments subsequently validated that this upregulated tRF enhances the proliferation, migration, and phenotypic transformation of vascular smooth muscle cells (VSMCs) [78]. 5′-tiRNA-Cys-GCA expression was markedly downregulated in aortic tissues from AD patients, ox-LDL-treated VSMCs, and AD model mice. Functional studies confirmed its regulatory role in VSMC proliferation, migration, and phenotypic transformation. Mechanistically, bioinformatics and experimental evidence indicate it directly binds to and modulates STAT4, thus regulating these cellular processes [79]. In previous research, tRF-Gly-CCC levels were reduced in the vascular samples of patients, while tRF-Gly-CCC directly suppressed Ccnd1 expression, which is crucial for maintaining VSMC functioning and regulation of inflammatory cell response [80].

4.6. tsRNAs and heart failure (HF)

HF, an epidemic of modern lifestyle, is a clinical syndrome with multiple etiologies, leading to cardiac structural abnormalities and functional impairment [81]. To elucidate how epicardial adipose tissue (EAT) tsRNAs regulate heart failure (HF), RNA sequencing was performed on HF patient EAT. This identified significant downregulation of tRF-Tyr-GTA-010 and tRF-Tyr-GTA-011. Bioinformatics and functional analyses further indicated that their target genes converge on pathways regulating calcium transport, sphingolipid signaling, and adrenergic signaling, suggesting a protective role [82].

4.7. tsRNAs and endothelial hyperplasia

Endothelial hyperplasia refers to pathological vascular remodeling characterized by abnormal VSMC proliferation and migration following endothelial injury [83]. Jiang et al. used a rat common carotid artery balloon injury model to induce endothelial hyperplasia and conducted small RNA sequencing and tsRNA library screening to identify differentially expressed tsRNAs in hyperplastic arteries. tRF-Glu-CTC was

significantly upregulated in carotid arteries exhibiting endothelial hyperplasia. Bioinformatics analysis and miRanda/TargetScan target gene predictions showed that tRF-Glu-CTC binds to fibromodulin (FMOD) mRNA. Transfection experiments further demonstrated that tRF-Glu-CTC overexpression negatively regulates FMOD levels while enhancing VSMC proliferation and migration [84]. Recently, using high-throughput sequencing, Zhang et al. [85] analyzed PS-NP-treated VSMCs and discovered upregulated tRF-1:30-chrM.Met-CAT. Further experiments confirmed its role in promoting VSMC proliferation, migration, and phenotypic conversion. In contrast, tiRNA-Glu-CTC induced phenotypic conversion through a different mechanism involving Cacna1f downregulation.

4.8. tsRNAs and cardiomyopathy

Cardiomyopathy encompasses a group of myocardial disorders marked by structural and functional damage, including various subtypes broadly categorized as acquired or hereditary, with hypertrophic cardiomyopathy being the most common [86]. Zhao et al. [87] performed RNA sequencing on high glucose (HG)-stimulated primary cardiomyocytes to determine tRF expression. This revealed significant upregulation of tRF-5014a under HG-induced injury. Functional analyses showed that knocking down tRF-5014a in this model further reduced cell viability, increased cell death, and elevated IL-1β and IL-18 levels, indicating its pivotal role in cardiomyocyte injury associated with dilated cardiomyopathy. Pathological cardiac hypertrophy (PCH) is a physiological adaptive response in which the heart maintains cardiac function in response to physiological or pathological cardiac overload; it is characterized by upd cardiomyocyte volume and cardiac weight [88]. Persistent pathological stress can induce PCH, characterized by cardiomyocyte enlargement, myocardial fibrosis, and cardiomyocyte death [89]. Xu et al. [90] identified via comparative small RNA sequencing that plasma tRF-21-NB8PLML3E as downregulated in PCH patients. To explore its function, simulation transfection was performed in Ang II-stimulated H9c2 cells. Integrated bioinformatics analysis indicated that the target genes of this tRF are mainly enriched in metabolic processes and participate in ribosomal regulation. Wang et al. [91] analyzed plasma tsRNAs from PCH patients and healthy controls, and identified significant downregulation of tRF-16-R29P4PE, a finding consistent with that in Ang II-stimulated H9c2 cardiomyocytes. In Ang II-induced rats, administration of a tRF-16-R29P4PE analog improved cardiac function, reduced fibrosis and hypertrophy, and ameliorated metabolic and mitochondrial dysfunction. Mechanistically, this tRF modulates HIF-1α-mediated PPARα signaling by engaging PACE4, which directly interacts with HIF-1α, thereby restoring glucose and lipid metabolism. In a parallel study on cardiac hypertrophy, transcriptome analysis identified tRF-Glu-CTC-013, whose overexpression attenuated hypertrophy, inflammation, and fibrosis. This effect was mediated through its binding to the TAS1R3 3'-UTR, suppressing TAS1R3 expression and enhancing autophagy in cardiomyocytes [92]. A mouse sepsis model established through cecal puncture showed elevated 5'-tiRNA-33-CysACA-1 expression in septicemic cardiomyopathy (SCM). Validation experiments revealed that 5'-tiRNA-33-CysACA-1 targets the mRNA stability of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α), a key molecule in mitochondrial biogenesis. This impedes mitochondrial biogenesis, leading to impaired mitochondrial function in cardiomyocytes and promoting SCM development [93].

4.9. tsRNAs and other cardiac-related and vascular disorders

4.9.1. Varicose veins (VV)

VV constitute a predominant clinical manifestation of chronic venous insufficiency [94]. Current research indicates significantly elevated tRF-36 expression in patients with VV, which modulates the expression of Notch receptors (1, 2, and 3) while concurrently upregulating smooth muscle cell markers SMA-α and SM22α [95]. Using small RNA sequencing, Yu et al. compared tRF expression between VV patient venous tissues and adjacent normal tissues. They found two tsRNAs significantly upregulated and one downregulated in patients. Functional enrichment analysis (GO/KEGG) further showed that their target genes are predominantly enriched in Wnt, MAPK, and calcium signaling pathways, underscoring their importance in VV development [96].

4.9.2. Rheumatic heart disease (RHD)

RHD is characterized as a chronic autoimmune valvular disorder following an immune response to Group A streptococcal infection [97, 98]. Transcriptomic profiling identified reduced AS-tDR-001363 levels in RHD patients who had developed AF, relative to RHD patients without AF. Bioinformatics analysis revealed that the target gene of AS-tDR-001363 is C-C chemotactic ligand 5 (CCL5), which has diverse functions in transcription, DNA binding, and intracellular transcriptional regulation. Subsequent validation experiments confirmed the role of CCL5 as a target gene for AF. These results advance our understanding of AF pathogenesis in RHD patients, paving the way for a novel target with therapeutic and diagnostic potential [99].

4.9.3. Fulminant myocarditis (FM)

In a study on tsRNAs in familial myocardiopathy (FM), Wang et al. reported that plasma tiRNA-Gln-TTG-001 levels were significantly elevated in pediatric patients during the acute phase versus controls. In vitro experiments confirmed its upregulated production and release. Bioinformatics analysis (GO/KEGG) suggested its target genes are involved in myotube differentiation and metabolism, while pathways including Ras, MAPK, and PI3K-Akt were implicated in FM pathogenesis [100]. Recent studies indicate that 5'-tiRNA-Gln-TTG-001 is upregulated in acute myocarditis patients' plasma and correlates positively with cardiac injury markers. This tiRNA exerts pro-inflammatory effects on AC16 cells, exacerbating inflammatory damage. Mechanistically, it binds to the 3'-UTR of CLIC4, activating and promoting its expression, which ultimately aggravates cardiomyocyte inflammatory injury [101]. The key tsRNAs involved in various cardiovascular diseases and their biological functions are summarized in Table 1.

5. Research limitations and future directions

5.1. Limitations of current research

Despite the promising research prospects of tsRNAs in the field of CVDs, this area remains in its early stages and faces several challenges:

5.1.1. Insufficient depth of mechanistic research and unclear causal relationships

Most studies are still observational, primarily reporting the differential expression of specific tsRNAs in particular CVDs. However, the precise molecular mechanisms of these tsRNAs (e.g., upstream and downstream regulatory networks) in disease pathogenesis and progression remain unclear. The same tsRNA may exert opposite effects at different disease stages or in different cell types, posing a major challenge for defining its functions. Moreover, the interactive networks between tsRNAs and other ncRNAs (e.g., miRNAs and lncRNAs) require urgent investigations.

5.1.2. Bottlenecks in technology and methodology

(1) Challenges in Detection and Quantification: The short sequences and abundant nucleotide modifications of tsRNAs make it difficult to accurately capture and quantify using traditional high-throughput sequencing technologies, leading to poor comparability and reproducibility of data across different platforms.

Table 1
The role of tsRNA in cardivovascular disease.

diseases	tsRNA	up/down	Models/Samples	function	references
Atherosclerosis	tRF-Gly-GCC-009	up	Carotid intima of AS patient	Cell adhesion processes associated with plasma membrane adhesion molecules	[58a]
	tRF-Gly-GCC	up	Arterial samples with atherosclerosis	Regulate the expression of pro-atherosclerotic genes in human endothelial cells	[59]
	tsRNA-Arg-CCG	up	The atherosclerotic (AS) intima of low-density lipoprotein (LDL) receptor-deficient (LDLR−/−) mice	Regulate the Expression of Pro-Atherosclerotic Genes in Human Endothelial Cells	[60]
	tsRNA-Glu-CTC	up	C57BL/6 mouse liver	Regulate hypercholesterolaemia and hepatic steatosis	[61]
ischemic injury	tRNAVal and tRNAGly	up	Rat ischemic right brain/uninjured left brain tissue	Cell proliferation, migration, and angiogenesis	[63]
	tRF-Gly-TCC-018、tiRNA-His-GTG-004	up	Myocardial ischemic tissues induced by isoprenaline (ISO)	Regulate the metabolism of macromolecules	[64]
	tiRNA-Met-CAT-002	up	Cardiomyocytes of myocardial ischemia/reperfusion (I/R) injury in male SD rats	regulate the autophagic process	[65]
	tiRNA-HAR	up	hypoxic mouse cardiomyocytes	regulate cardiomyocyte apoptosis and myocardial injury	[66]
pulmonary hypertension (PH)	5o8GtRF-1-AspGTC	up	The lung tissues and serum of patients with PH	Regulation of hypoxia-induced proliferation and apoptosis resistance in pulmonary artery smooth muscle cells	[69]
	tRF-1:32-Glu-TTC-2-M2	up	PAH patients and RV tissues from monocrotaline (MCT) rats	Alleviated left ventricular fibrosis and improved left ventricular function.	[71]
Atrial Fibrillation (AF)	tsRNA-5008a	up	Atrial myocardial tissues of male C57BL/6J mice	Regulation of Ferroptosis and myocardial fibrosis	[74]
	tsRNA 5006c-LysCTT	up	Atrial appendage tissue from patients with atrial fibrillation	Regulate the calcium signaling pathway and adrenergic signaling pathway in cardiomyocytes	[75]
Aortic Dissection (AD)	tRF-1:30-chrM.Met-CAT	up	Aortic tissues of patients with AD	Regulate the proliferation, migration and phenotypic transformation of vascular smooth muscle cells (VSMCs)	[78]
	5′-tiRNA-Cys-GCA	down	Human aortic tissues	Proliferation and migration of VSMCs	[79]
	tRF-Gly-CCC	down	Vascular samples from AD patients	Regulate vascular smooth muscle cell function and inflammatory cell response	[80]
Heart Failure(HF)	tRF-Tyr-GTA-010 and tRF-Tyr-GTA-011	down	Epicardial adipose tissue (EAT) samples of patients with HF	calcium ion transport	[82]
vascular smooth muscle cells (VSMC) Endothelial Hyperplasia	tRF-Glu-CTC	up	The model of intimal hyperplasia induced by the balloon injury model of the common carotid artery in male SD rats	Regulates Fiber Modulating Protein (FMOD) levels and ups vascular smooth muscle cell proliferation and migration.	[84]
	tRF-1:30-chrM.Met-CAT	up	Vascular smooth muscle cells of 6-week-old male C57BL/6 mice exposed to polystyrene nanoplastics (PS-NP)	proliferation, migration and phenotypic transformation of vascular smooth muscle cells (VSMCs)	[85]
Cardiomyopathy/ Pathological Cardiac Hypertrophy (PCH)	tRF-5014a	up	Primary cardiomyocytes are extracted from neonatal mice (3–5 days old) and treated with high glucose.	Regulate cell viability and the release of pro-inflammatory cytokines in cells under HG conditions.	[87]
	21-NB8PLML3E	down	H9c2 cells stimulated by Angiotensin II (Ang II)	Participate in the regulation of ribosomes	[90]
	tRF-16-R29P4PE	down	H9c2 cardiomyocytes stimulated by Angiotensin II (Ang II)	Regulate abnormal cellular glucose and lipid metabolism	[91]
	tRF-Glu-CTC-013	up	Angiotensin II (Ang II)-induced mouse cardiac hypertrophy model	Regulate inflammation and fibrosis	[92]
	5′tiRNA-33-CysACA-1	up	Sepsis model in mice established by cecal ligation and puncture	Regulate mitochondrial function in cardiomyocytes	[93]
Varicose Veins (VV)	tRF-36	up	Varicose veins and adjacent normal vascular tissue	Regulate Notch 1, 2, and 3 expression, and SMC markers (SMA-α and SM22α) compared with control HVSMCs.	[95]
	tRF-36-F900BY4D84KRIME、tRF-23-87R8WP9IY	up	Venous tissues of patients with VV	Regulate myotube differentiation and metabolism	[96]
Rheumatic heart disease (RHD)	AS-tDR-001363	down	The cardiac muscle of patients with RHD	Transcription, DNA binding, and intracellular transcriptional regulation.	[99]
Fulminant Myocarditis (FM)	5′tiRNA-Gln-TTG-001	up	human ventricular tissue	proinflammatory effects in AC16 cells	[100]
	5′tiRNA-Gln-TTG-001	up	Plasma samples from patients with acute myocarditis	Regulate cardiomyocyte inflammatory injury	[101]

(2) Inconsistency in tsRNA Nomenclature and Annotation: The current lack of a unified international naming standard, with inconsistent naming conventions (e.g., based on location and parental tRNA), severely hinders data integration, sharing, and cross-study comparisons.
(3) Lack of Models for *In Vivo* Functional Validation: Most studies rely on cell models, and there is a lack of genetic animal models with the capability to display specific knockdown or overexpression of endogenous tsRNAs. This limits the *in vivo* validation of causal relationships.

5.1.3. Core hurdles to clinical translation

(1) Extreme Scarcity of Clinical Validation

Currently, there are no registered clinical trials targeting tsRNAs.

The sensitivity, specificity, and prognostic value of tsRNAs as diagnostic biomarkers are mostly based on small-sample exploratory cohorts and lack validation in large-scale, multicenter prospective studies. Standardization of sample processing and detection methods is also a prerequisite before clinical application.

(2) Challenges related to *In Vivo* Delivery and Targeting

A major challenge in the application of tsRNAs for drug development is designing the approach to efficiently, specifically, and safely deliver tsRNA-based therapeutic molecules (mimics or antisense oligonucleotides) to target cardiovascular cells/tissues.

5.2. Future research strategies and prospects

To overcome these limitations and advance the field of tsRNAs from basic research to clinical application, future efforts should focus on the following strategic directions:

5.2.1. Strengthen mechanistic and functional studies

(1) Systematically elucidate the upstream/downstream regulatory axes and causal roles of specific tsRNAs in CVDs by comprehensively integrating multi-omics analyses (e.g., epitranscriptomics and proteomics), gene editing technologies, and novel animal models.
(2) Investigate the dynamic changes in tsRNA expression and function in specific cells (e.g., cardiomyocytes, endothelial cells, and smooth muscle cells) and disease stages.

5.2.2. Promote technological innovation and standardization

(1) Develop Novel Detection Technologies: Foster next-generation sequencing and highly sensitive detection platforms for accurately identifying modified tsRNAs and integrate these platforms with artificial intelligence to enhance data analysis depth.
(2) Establish and Promote Global Standards: Unify naming conventions, improve and promote tsRNA databases (e.g., tsRBase, MINTbase, and tRFdb), and enable data standardization and sharing.
(3) Develop Novel *In Vivo* Tools: Utilize technologies such as nanoparticle delivery and adeno-associated virus vectors to conduct gain-of-function/loss-of-function studies of tsRNAs in animal models, laying the foundation for preclinical efficacy evaluation.

5.2.3. Accelerate clinical translation and precision medicine applications

(1) Develop Liquid Biopsy Biomarker Panels: Leverage the high stability of tsRNAs in exosomes/EVs to validate the value of multi-tsRNA panels for early CVDs diagnosis, risk stratification, prognosis assessment, and treatment response monitoring through large-scale cohort studies.
(2) Innovate RNA-Targeted Therapeutic Strategies:Mimic Replacement Therapy: Develop chemically modified synthetic mimics of cardio-protective tsRNAs (e.g., certain tiRNAs) for therapeutic intervention.

Antisense Oligonucleotide (ASO) Inhibition Therapy: Design specific ASOs to silence pathogenic tsRNAs. Preclinical studies have already demonstrated the remarkable potency of these ASOs.

(3) Tackle Delivery Challenges: Focus on developing heart/vascular-targeted nanodelivery systems to improve treatment specificity and safety.
(4) Initiate Rigorous Clinical Trials: Progress stepwise from retrospective analyses to prospective interventional clinical trials to validate the efficacy of tsRNA-based diagnostic kits and the safety and preliminary efficacy of tsRNA-based therapies.

5.2.4. Integrating tsRNAs into the broader ncRNAs regulatory network

CVDs involves a complex regulatory network of ncRNAs. miRNAs play critical roles in post-transcriptional gene regulation and are deeply implicated in processes such as cardiac remodeling, myocardial hypertrophy, fibrosis, heart failure, and atherosclerosis. circRNAs primarily function as miRNA sponges but also engage in protein binding and translational regulation, critically influencing pathologies such as myocardial ischemia, arrhythmias, and atherosclerosis. Notably, recent studies have demonstrated that mitochondria-encoded circRNAs (mecciRNAs) modulate mitochondrial permeability and reactive oxygen species (ROS) homeostasis, thereby affecting the progression of heart failure and highlighting their therapeutic potential [102]. lncRNAs contribute to cardiac development and remodeling through diverse mechanisms including chromatin remodeling and transcriptional interference. tsRNAs, generated through tRNA cleavage via distinct biogenetic pathways, exhibit remarkable structural stability and efficient packaging into extracellular vesicles, supporting their roles in intercellular communication.

Emerging evidence suggests that tsRNAs may integrate into the broader ncRNAs regulatory network through at least four principal mechanisms: competitive binding with miRNAs for shared targets, regulatory cascades that influence tsRNA biogenesis, functional synergy or antagonism within shared signaling pathways, and structural interactions with circRNAs or lncRNAs [103,104].

Nevertheless, the precise molecular mechanisms underlying the interactions between tsRNAs and other ncRNAs remain largely unexplored. A systematic elucidation of how tsRNAs integrate into and modulate existing ncRNAs networks will be essential for a comprehensive understanding of transcriptional dysregulation in CVDs and mayl provide a theoretical foundation for the development of novel multi-target RNA-based therapeutic strategies.

5.3. Conclusion and outlook

As novel key regulators in the cardiovascular regulatory network, tsRNAs offer a fresh perspective to understand the pathological mechanisms of CVDs and develop novel diagnostic and therapeutic strategies. Their unique biological properties (e.g., high stability and disease specificity) confer them immense potential in the fields of liquid biopsy and RNA-targeted therapy. Although current research has major limitations regarding mechanistic depth, technical standards, and clinical validation, these challenges clearly delineate the path for future breakthroughs. Through interdisciplinary collaboration and integration of cutting-edge omics technologies, bioengineering, and clinical medicine, tsRNAs are poised to transition from “promising biomolecules” to “practical clinical tools” within the next decade. This progress will ultimately propel cardiovascular medicine into a new era characterized by more precise diagnosis, prevention, and treatment of CVDs.

CRediT authorship contribution statement

Xinru Wen: Writing – review & editing, Writing – original draft, Investigation. **Simin Wang:** Supervision, Funding acquisition. **Hongyan Chen:** Supervision, Funding acquisition. **Huihui Zhang:** Writing – review & editing, Visualization. **Yuqiang Ji:** Writing – review & editing, Conceptualization.

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Declaration of competing interest

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

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