RELATIONSHIP OF TRANSFER RNAs WITH EPIGENETIC FACTORS AND RETROELEMENTS

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Abstract. A hypothesis is proposed about the role of evolutionary relationship of retroelements with transfer RNAs (tRNAs) on their processing to form small non-coding RNAs. This is evidenced by the use of tRNA as primers for reverse transcriptase, origin of SINE2 from tRNA, use of LINE1 enzymes by tRNA for pseudogenes formation. Under the influence of RISC enzymes, tRFs are formed from tRNA, that control gene expression at the epigenetic level. Non-coding RNAs formed from transcripts of retroelements are characterized by similar properties. An assumption has been made about the functioning of a species-specific epigenetic network between such non-coding RNAs formed from retroelements and tRNAs. Decoding such a network may open up the possibility of creating new epigenetic agents for the treatment of human diseases, and will also allow us to determine mechanisms of genetic code emergence in evolution. One of the bases for this network formation may be the distribution and composition of tRNAs and retroelements in the genome. I have provided data on this network mechanisms formation, describing the similar functional properties of tRNAs and retroelements, their influence on the same targets and pathways in the human organism. I suppose that the relationship between tRNAs and retroelements arose as an integral property of living things when life arose in RNA world, where tRNAs were originally used to perform many regulatory catalytic functions, one of which was later transformed into the transfer of amino acids for protein synthesis.

Keywords: evolution, non-coding RNA, processing, retroelements, reverse transcriptase, RNA interference, tRNA, transposable elements, tsRNA.

List of Abbreviations

HERV – human endogenous retrovirus
lncRNA – long noncoding RNA
LTR – long terminal repeat
MIRs – mammalian-wide interspersed repeats
MN – malignant neoplasm
ncRNA – noncoding RNA
RE – retroelement
RT – reverse transcriptase
TE – transposable element
tRF – tRNA fragment
tRNA – transfer RNA
tsRNA – tRNA derived small RNA

Introduction

Transposable elements (TEs) are specific structures in eukaryotic, archaeal and bacterial genomes that move to new loci in the same genome. They occupy about 2/3 of the human genome (de Koning *et al.*, 2011), which is explained by their important regulatory functions (Johnson & Guigo, 2014). There are 2 classes of TEs: class I - retroelements (REs), which transpose by copying RNA into DNA using reverse transcriptase (RT) and inserting it back into the genome at a new locus; class II - DNA transposons that move by cutting and pasting. REs include containing long terminal repeats (LTR-REs) and not containing them (non-LTR REs). Their transposition mechanisms differ: non-LTR REs cleave DNA targets and use the 3' end to trigger reverse transcription. Most LTR-REs in all living organisms use the 3' end of tRNA for reverse transcription priming (Schorn & Martienssen, 2018).

Autonomous REs that use self-encoded enzymes for transpositions in the human genome include non-LTRs REs LINEs (long interspersed nuclear elements) and LTR-RE HERVs (human endogenous retroviruses). Non-autonomous REs use autonomic RE enzymes for their transpositions: these are non-LTR REs SINE (short interspersed nuclear elements) and SVA (SINE-VNTR-Alu). SINEs occupy at least 13% of the entire human genome (Zhang *et al.*, 2021) and are divided into 3 types: SINE1/7SL, SINE2/tRNA, SINE3/5S (Kojima, 2018). SINE3/5S include Alu elements, there are 1.3 million of them in the human genome (10% of

all DNA sequences) (Conti *et al.*, 2015). SINE2 evolved through the integration of reverse transcribed tRNAs. Another name for these REs are MIRs (mammalian-wide interspersed repeats). They consist of 260 base pairs and are found in all mammals genomes, characterized by high divergence and presence in orthologous sites of various species. After Alus, MIRs are the most common in primate genomes (Smit & Riggs, 1995), amounting to about 600,000 copies and occupying up to 3% of human DNA (Zhang *et al.*, 2021).

TEs are the most important evolutionary sources of non-coding RNAs (ncRNAs), such as microRNAs (Mustafin & Khusnutdinova, 2023) and long ncRNAs (lncRNAs) (specific functional RNA molecules longer than 200 nucleotides) (Johnson & Guigo, 2014; Hadjiargyrou & Delihas, 2013). The most famous ncRNAs are transfer RNAs (tRNAs), their function is to transfer amino acids into a polymerizing chain of proteins or peptides on ribosomes. However, in addition to this function, an unexpected discovery turned out that under the influence of specific ribonucleases, tRNAs form even smaller molecules that are involved in the epigenetic regulation of gene expression and were called tRFs (tRNA fragments) and tRNA halves. The common name for such molecules is tsRNA - an abbreviation for small RNAs derived from tRNAs. In addition to lncRNAs, microRNAs and tRNAs, many small ncRNAs are also known, among which functional fragments from ribosomal RNAs (sRFs), small interfering RNAs (siRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snRNAs) and piwi interacting RNAs (piRNAs) (Cao *et al.*, 2020).

It should be noted that 83% of human lncRNAs genes contain at least one RE fragment, and 41% of lncRNA exons are proven to originate from REs (Johnson & Guigo, 2014). Moreover, transcripts processing of LTR-RE (Lu *et al.*, 2014) and LINE1 (Honson & Macfarlan, 2018) genes directly leads to the formation of lncRNAs that perform various regulatory functions (Fig. 1). LncRNAs are epigenetic factors because they do not change DNA sequences, but influence gene expression in ontogenesis through interactions with the enzyme RNA polymerase, with complexes that modify histones and with DNA-binding proteins. In most cases, they function in complex with proteins, forming ribonucleoproteins. However, lncRNAs can exhibit independent catalytic functions as ribozymes (Long *et al.*, 2017).

Despite their name "non-coding", lncRNAs are able to bind to ribosomes and be translated into functional peptides (Nelson *et al.*, 2016; Zhang *et al.*, 2013). This reflects the role of REs as sources of protein-coding genes in evolution (Feschotte, 2008). REs are also rich sources of miRNAs that are involved in gene expression regulation. Since RES are also key sources of lncRNAs (Johnson & Guigo, 2014; Hadjiargyrou & Delihas, 2013) and microRNAs (Mustafin & Khusnutdinova, 2023) involved in the regulation of gene expression and transposons themselves, this indicates a global regulatory role of TEs in regulating the functioning of genomes (Fig. 2). It can be assumed that tRNAs and their processing products are also mediators of such mechanisms, as evidenced by data on their mutual regulation.

Mature tRNAs, in addition to transporting amino acids, have additional functions. They affect the polyadenylation of Alu elements (Rudinger-Thirion *et al.*, 2011), regulate premRNA splicing by pairing with the start codon (Kamhi *et al.*, 2010), function as insulators (Raab *et al.*, 2012). It should be noted that, compared to mitochondria and bacteria, eukaroite genomes are characterized by a significantly larger number of both TEs and tRNA genes, as well as the multifunctionality of their transcripts, which may indirectly indicate their evolutionary relationship. Specifically, humans have a total of 22 mitochondrial tRNA genes and more than 610 nuclear tRNA genes according to the human genomic tRNA database (gtRNAdb, hg19). About half of these 610 tRNA genes are expressed. Processing of their transcripts leads to maturation of many types of tRNA, complementary to 61 codons for the translation process (Chan & Lowe, 2016). Preservation of such tRNA genes diversity in evolution is most likely due to the role of REs in their expansion and their involvement in ep-

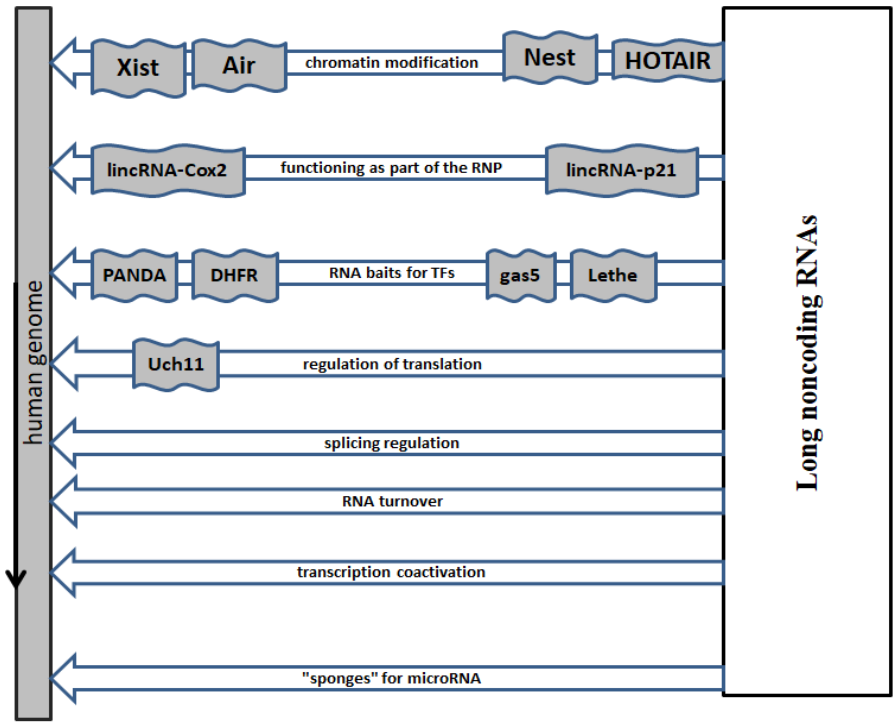

Fig. 1. Functions of lncRNAs

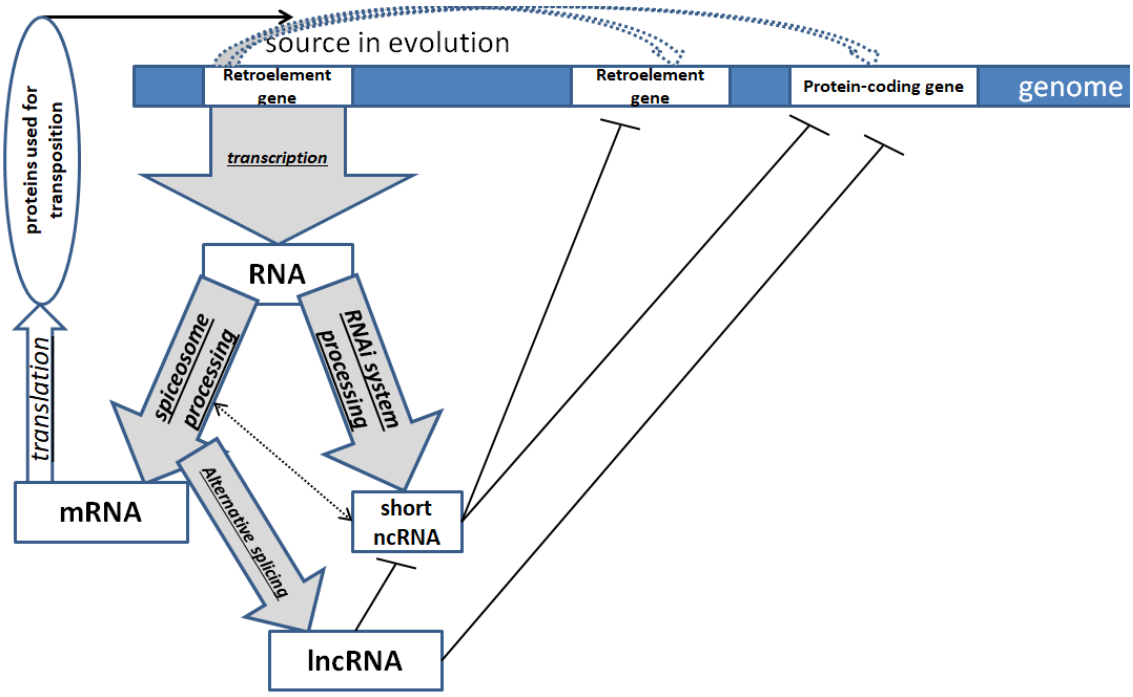

Fig. 2. Multifunctionality of retroelements transcripts

igenetic regulation of genome functioning, in addition to their direct role in translation. Indeed, the distribution of tRNA genes in the human genome is characterized by the formation of 277 clusters with an average size of 2.2 tRNA genes per 1 cluster (maximum 29 tRNA genes). These clusters form 256 physically contacting domains at the DNA level, containing 1 or more tRNA genes. On average, there are 2.3 tRNA genes per domain, with a maximum size of 33 tRNA genes per domain (Borte *et al.*, 2017).

Multifunctionality of tRNA is also evidenced by studies of SINEs (since SINE2 originated from tRNA), which act as tissue-specific gene enhancers (Zhang et la., 2019), insulators (forming a functional complex for the formation of chromatin loops to regulate gene expression) (Wang *et al.*, 2015), promoter sources (25% of all human promoters contain RE sequences, most of which originate from SINE) (Jordan *et al.*, 2003), regulators of reverse splicing for circular RNAs formation (Chen *et al.*, 2020), perform post-transcriptional regulation mRNA through complementary nucleotide pairing (Maquat, 2020). In addition, 61.5% of all SINE2 are located in the introns of protein-coding genes, which indicates their regulatory significance (Zhang *et al.*, 2021). Like LINE1s (Honson & Macfarlan, 2018) and HERVs (Lu *et al.*, 2014), SINEs are sources for the formation of tissue-specific lncRNAs. MIRs are sources for specific to brain, cerebral cortex, ovary, prostate and testis lncRNAs (Chishima *et al.*, 2018). Since REs play an important role in epigenetic system functioning (Mustafin & Khusnutdinova, 2017), it is important to determine the functions of tsRNAs and their relationship with epigenetic factors in order to assess the pathways of the relationship between tRNAs and REs.

Relationship of tsRNAs with epigenetic factors

Epigenetic factors include methylation of specific DNA loci (for example, CpG islands), histone modifications (methylation, acetylation), RNA interference under ncRNA influence (Park *et al.*, 2020), pseudouridylation of RNAs by pseudouridine synthase (Guzzi *et al.*, 2018). tRNA and tsRNAs are closely associated with all epigenetic factors, both as their targets and tools for regulation. For example, both mature tRNAs and their tsRNAs undergo pseudouridylation, which is necessary for them to perform specific functions (Guzzi *et al.*, 2018). At the same time, tRNAs themselves are actively involved in epigenetic regulation, since tRNAs are processed into 4 types of tRF: 3'-terminal tRF-3, 5'-terminal tRF-5, tRF-1 (3'-tRNA precursor fragment) (Kumar *et al.*, 2014; Park *et al.*, 2020) and internal tRF (tRF-2 – arises from the anticodon loop) (Su *et al.*, 2020). Like microRNA molecules, tRNA processing products, such as tRF-3s and tRF-5s, participate in RNA interference, tissue-specifically regulating the expression of specific genes (Kumar *et al.*, 2014).

It is interesting that tRFs, formed by the action of ribonucleases on tRNA, are found not only in humans and all eukaryotes, but even in bacteria, which indicates the ancient origin of the functionality of these molecules and a possible evolutionary relationship with REs (Kuscu *et al.*, 2018). Formation of 18-26 nucleotides in length tRF, associated with non-random asymmetric tRNA processing, is significantly increased in virus-infected or stressed cells. In plants, they accumulate in large numbers in wild-type male gametes that are not subject to stress. In Arabidopsis, tRFs, like miRNAs, are processed by Dicer-like1, binding to AGO1. The resulting tRF-AGO1 complex acts on specific targets and cleaves mRNA of transcriptionally active REs (Martinez *et al.*, 2017). However, in humans and other animals, tRF-3 is used to regulate mRNA translation in a Dicer-independent pathway through AGO. tRF-3s are also interact with TNRC6 and GW182 proteins, which are involved in RNAi as part of RISC (Kuscu *et al.*, 2018). Different length tRFs perform different functions. For example, 18-nucleotides long tRF-3s block reverse transcription, while 22-nucleotides long tRF-3s cause post-transcriptional silencing of specific genes (Schorn *et al.*, 2017).

Participation of tsRNAs in a wide variety of physiological processes (response to stress, immune modulation, sperm maturation, neovascularization, and others) and pathological processes (cancer, metabolic diseases, autoimmune and neurological diseases) has been described (Park *et al.*, 2020). tRNA halves, 30–35 nucleotides long, are formed by ribonuclease cleavage of tRNA within the anticodon loop. They are found in the bloodstream of humans, monkeys, rats, and mice. They are also found in biological fluids and human semen. The tRNA halves have been proposed to be potential systemic signaling molecules of the immune sys-

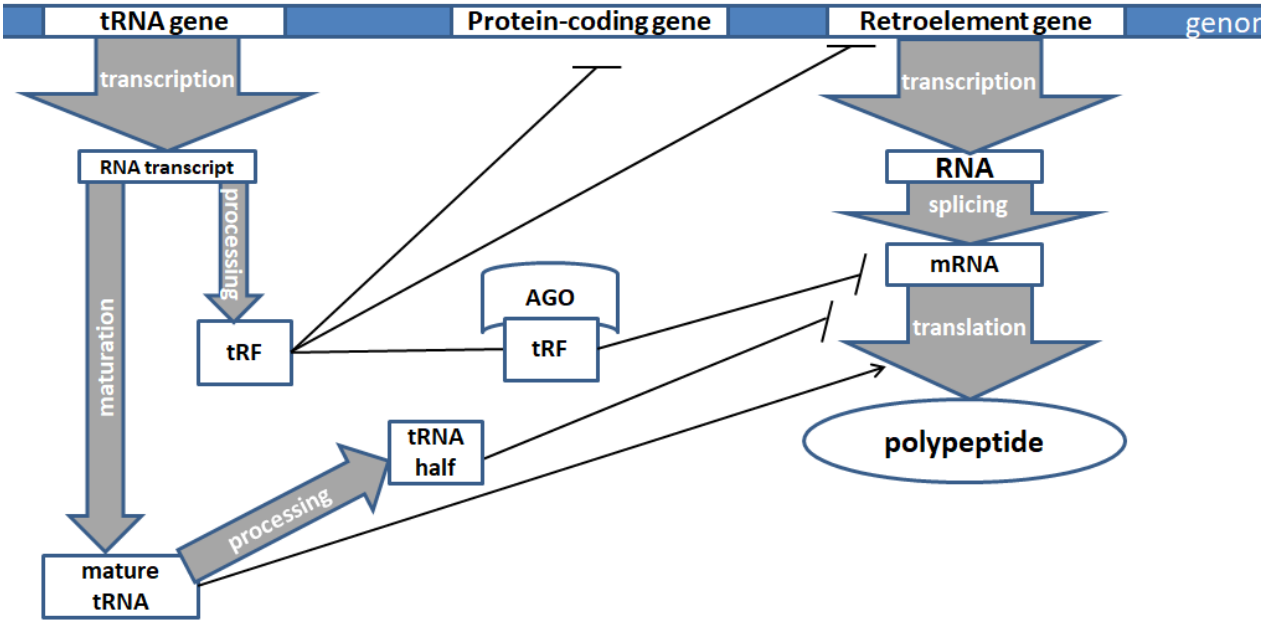

Fig. 3. Multifunctionality of tRNA transcripts

tem (Dhhbi *et al.*, 2015). REs also play an important role in the functioning of the immune system, as evidenced by their role in the development of autoimmune pathology (Mustafin, 2022b). The formation of 5'tRNA halves is not a product of random degradation of tRNA, but is catalyzed by a specific enzyme, Angiogenin (ANG) endonuclease, with functional molecules formation (Wang *et al.*, 2013), which, in particular, inhibit the initiation of translation due to interaction with ribosomes during stress (Ivanov *et al.*, 2011). Expression of tRNA-halves is induced by stress, viral infections, ultraviolet radiation, heat shock, hypoxia, and nutritional deficiency (Cao *et al.*, 2020). Activation of REs expression of also occurs in response to stress, viral infections, external and internal influences, due to which they control the epigenetic regulation of genome functioning in ontogenesis (Mustafin & Khusnutdinova, 2017; Mustafin, 2022a). tRNA halves are normally determined in blood plasma, fetal liver and placenta, extracellular vesicles, urine, cerebrospinal fluid, semen (Su *et al.*, 2020). Thus, due to transcript processing, tRNAs perform different functions of controlling the expression of REs and protein-coding genes (Fig. 3), which is similar to REs functions (compare Fig. 2).

According to The Cancer Genome Atlas analysis, 322 individual specific tsRNAs have been annotated in humans, the number of which is increasing every year (La Ferlita *et al.*, 2019). Comparison of tRNA expression in the human brain and cell culture showed a difference between tRNA genes within the same set of isocoders (having the same sequence of tRNA anticodons), which may be associated with non-canonical functions of tRNA. As a result, the amount of tRF changes tissue-specifically in the heart, skeletal muscles, ovaries and brain (Torres *et al.*, 2019). Tissue-specific tRNA expression has also been identified in more primitive animals such as Caenorhabditis elegans (Sagi *et al.*, 2016). In experiments on mice, tissue-specific expression of tRNA halves (formed under the influence of angiogenin ribonuclease) in the liver and heart was determined (Fu *et al.*, 2009). These properties of tsRNAs are similar to REs, which are also characterized by pronounced tissue-specific features of transcription, which is reflected in the regulatory effect on gene expression and cell differentiation (Lee *et al.*, 2015; Pavlicev *et al.*, 2015; Gerdes *et al.*, 2016; Ito *et al.*, 2017). Therefore, it is necessary to dwell in more detail on the disclosure of the general functional properties of tRNAs and REs. Since tRNAs are the oldest of

all RNAs in the living world and are inherent in all living organisms, since they are necessary for protein synthesis, it can be assumed that at the origin of life on Earth in the RNA world, these molecules originally functioned as REs tools. As confirmation of this hypothesis, I present data on the relationship between REs and tRNAs not only due to direct and epigenetically mediated interactions, but also due to the presence of common targets and pathways for their processing.

Relationship of transfer RNAs with retroelements

Like tRNA molecules, transcripts of retroelements can form several functional variants: participate in the regulation of molecular reactions in the cell nucleus as ncRNAs (Lu *et al.*, 2014, Honson & Macfarlan, 2018), and also undergo processing to form smaller ncRNAs (Mustafin, Khusnutdinova, 2023). The resulting ncRNAs have a vast spectrum of regulatory functions, many of which overlap with the functions of tsRNA. At the same time, one of the most important functions, indicating a close evolutionary relationship between REs and tRNAs, is the protection of the genome from REs (since ncRNAs formed from REs transcripts cause silencing not only of protein-coding genes, but also of their own REs, other TEs and exogenous viruses). This may be due to the evolutionary relationship between tRNAs and retroviruses (Martinez, 2018), since tRNAs serve as primers for their RT (Kramerov & Vassetzky, 2011). Although LTR-REs use the 3' end of tRNAs for reverse transcription as primers, tRFs within the RNA interference system block RE reverse transcription by binding to a highly conserved tRNA primer binding site (Schorn & Martienssen, 2018). In experiments on mice, it was shown the relationship between ncRNAs formed from tRNA in the regulation of ontogenesis. Specific 5'-fragments of tRNA-Gly-GCC were found to be negative regulators of genes expressed in embryonic development and interacting with MERVL. However, protein restriction in males reduces let-7 levels and increases tRNA-Gly-GCC (Sharma *et al.*, 2016).

The role of processed tRNA transcripts in REs silencing may indicate their evolutionary relationship, as indicated by the complementarity of the nucleotide sequences required for their interaction (Kumar *et al.*, 2014; Martinez *et al.*, 2017). In addition, tRNAs in eukaryotic genomes are used as the basis for the formation of the most common non-autonomous REs (Gogolevsky *et al.*, 2009). That is, tRNA genes themselves are sources of genes for non-autonomous REs, such as SINE. Chimeric SINE elements, called HaSE3, have been identified in insects. They are made up of tRNA and 5S rRNA (Wang *et al.*, 2012a). This indicates a close evolutionary relationship between REs and tRNAs, which develops in different taxa during phylogenesis, playing a role in the formation of different species. For example, it was revealed that in amoebae and yeast, which belong to different kingdoms, there was a convergent evolution of the choice of the site of integration upstream of tRNA genes by retroelements, which indicates an ancient evolutionary relationship between REs and tRNA during the origin of life on Earth (Kling *et al.*, 2018). In the human genome, tRF-3s are highly complementary to LTR-REs. tRNAs undergo stress-induced processing with the formation of stable RNA molecules, which is typical for all eukaryotes. In this case, various functional ncRNA molecules, derivatives of tRNA, 30–50 nucleotides long are formed under the influence of ribonuclease-Z (Li *et al.*, 2012).

An important proof of the evolutionary relationship between REs and tRNAs is the identified ability of ncRNA molecules formed from tRNAs to suppress the expression of REs, which implies the presence of identical nucleotide sequences between them (Li *et al.*, 2012). Since tRNAs are the oldest functional RNAs in evolution, these data indicate a possible common origin of tRNAs and REs at the emergence of life on Earth (Mustafin & Khusnutdinova, 2019). In yeast, it was revealed that the Ty3 retroelement integrase interacts with RNA polymerase-3, which transcribes tRNA genes. In this way, Ty3 retroelements regulate tRNA expression. In the slime mold Dictyostelium discoideum, ribonuclease encoded in the retroele-

ment DGLT-A interacts with the TFIIIC subunit of POLIII (Kling *et al.*, 2018). Bioinformatics analysis has shown that at least 1300 Alus in the human genome transcribed by Pol III (Conti *et al.*, 2015). Many mammalian SINE species contain a transcription terminator for POLIII as well as AATAAA on their A-rich tail (Class T(+) SINE) (Borodulina *et al.*, 2016).

A common property of tRNA and REs is also the formation of microRNA molecules during the processing of their transcripts. Numerous human miRNAs are described that are formed during the processing of EC transcripts or evolved from REs in evolution (Mustafin & Khusnutdinova, 2023). Non-coding RNA CU1276 is 22 nucleotides long and is produced in humans by post-transcriptional modification of five annotated tRNAs. This ncRNA has all the structural and functional properties of miRNA (Maute *et al.*, 2013). Previously annotated microRNA miR-4454 turned out to be a product of tRNAHis processing (Reinsborough *et al.*, 2019). miR-1260a, miR-1260b, miR-3182, miR-4521, miR-7977 microRNAs are tRF molecules (Venkatesh *et al.*, 2016).

A specific ncRNA formed during tRNA processing and designated tRF-5 Gly-GCC (tRF-GG) was involved in the silencing of genes interacting with the endogenous retrovirus MERVL. In addition, tRF-GG was involved in the regulation of histone modification in the regions where MERVL is located in the genome, promoting the formation of heterochromatin in these loci and suppressing the expression of this endogenous retrovirus (Boskovic *et al.*, 2020). The relationship between REs and tsRNAs is also determined in relation to interferon. It is known that REs are inducers of interferon synthesis. This explains the role of REs activation in the development of aseptic inflammation as a factor of aging (De Cecco *et al.*, 2019) and is used in the method of viral mimicry to stimulate the immune response against tumors (Chen *et al.*, 2021). At the same time, interferon-stimulated genes encode proteins that cleave tRNA: ribonuclease S13 cleaves tRNA, ribonuclease S11 cleaves tRNAThr, tRNASer, ribonuclease L forms tRNA halves from tRNAGln, tRNAHis, tRNAPro (Su *et al.*, 2020).

Since a large cluster of human tRNA genes is colocalized in the region of the genome where the genes of the major histocompatibility complex (MHC) and the genes for the inflammatory response and stress response are located, which may also be due to the role of tRNA in immune responses (Dhhbi *et al.*, 2015), tRNAs can have a regulatory effect on the expression of genes of the immune system and used as insulators. This is evidenced by structural analysis data published in 2023, which showed that the yeast Ty1 RE integrase induces a PolIII configuration that facilitates the retention of this integrase on chromatin, increasing the likelihood of this RE integration. This may explain the locus-specific Ty1 insertions near the tRNA genes (Nguyen *et al.*, 2023). RE Ty3 integrates highly specifically in a narrow window upstream of the genes transcribed by POLIII. This is due to the interaction of the Ty3 integrase chromodomain with the transcription factor TFIIIB and the tRNA genes, which determines the extreme accuracy of the position of the fusion site (Abascal-Palacios *et al.*, 2021). Thousands of tRNA-derived SINE2s (MIRs) function as insulators for CD4+ T lymphocytes. They are located near the T-cell receptor genes, in the T-cell-specific boundaries between active and repressive chromatin (Wang *et al.*, 2015). Therefore, the study of the relationship between tRNAs and REs can become the basis for the possible regulation of the immune response in autoimmune pathology, in which both REs (Mustafin, 2022b) and tRNAs play an important role (Zhu *et al.*, 2020).

The study of relationship between tRNAs and REs is promising in connection with the role of tsRNAs in the regulation of ontogenesis at the earliest stages. For example, if REs are shown to be necessary for cell division starting from stage 2 cells (Wang *et al.*, 2016; Honson & Macfarlan, 2018), small RNA sequencing at various stages of preimplantation development in mice showed a surge in tsRNA expression at cell stage 8. These tsRNAs are mainly tRF-5s (Yang *et al.*, 2016). In mice, totipotent embryonic 2-cell cells are identified by reactivation of MuERV-L REs with leucine tRNA as primer (Furuta & Nakamura, 2021). Thus, REs and tRNAs have a regulatory effect on similar targets and pathways (Table 1).

Table 1

Functional relationship of tRNAs derived small ncRNAs with retroelements

Object of influence	Roles of tRNA (References)	Roles of tRFs (References)	Role of tRNA halves (References)	Role of retroelements (References)
miRNA formation	source for miRNA (Maute *et al.*, 2013; Reinsborough *et al.*, 2019)	they may be miRNAs themselves (Venkatesh *et al.*, 2016)	–	source for miRNA (Mustafin & Khusnutdinova, 2023)
POLIII	genes interact with it for their own transcription (Kling *et al.*, 2018)	–	–	genes interact with it for their own and for tRNA transcription (Conti *et al.*, 2015; Borodulina *et al.*, 2016)
protein translation	transfer for amino acids	inhibit by affecting ribosome biogenesis (Kim *et al.*, 2017) and by complementary pairing of nucleotides with mRNA (Kusku *et al.*, 2018)	specifically inhibit (Krishna *et al.*, 2019)	inhibit due to the formation of lncRNAs (Lu *et al.*, 2014, Honson & Macfarlan, 2018) and miRNAs during their transcripts processing (Mustafin & Khusnutdinova, 2023)
immune response	interferon response gene targets (Su *et al.*, 2020), HLA gene insulators (Dhhbi *et al.*, 2015)	–	potential immune signaling molecules (Dhhbi *et al.*, 2015)	stimulate interferon response (De Cecco *et al.*, 2019; Chen *et al.*, 2021)
retroelements	affects Alu elements polyadenylation (Rudinger-Thirion *et al.*, 2011)	inhibit reverse transcription (Schorn *et al.*, 2017) and affect histone modifications (Boskovic *et al.*, 2020)	–	mutual regulation between different REs with the help of their transcription processed products (Mustafin, 2022a)
protein-coding genes	function as insulators (Raab *et al.*, 2012)	post-transcriptional silencing of specific genes (Schorn *et al.*, 2017; Kuscu *et al.*, 2018)	inhibit translation initiation by interacting with ribosomes under stress (Ivanov *et al.*, 2011); regulate pre-mRNA splicing by pairing with a start codon (Kamhi *et al.*, 2010)	regulate expression *in cis* and *in trans* (Mustafin 2022a); function as gene enhancers (Zhang et la., 2019), insulators (Wang *et al.*, 2015); promoter sources (Jordan *et al.*, 2003); reverse splicing regulators for circular RNAs formation (Chen *et al.*, 2020); post-transcriptional regulation of mRNA (Maquat, 2020)

End of table 1

Object of influence	**Roles of tRNA (References)**	**Roles of tRFs (References)**	**Role of tRNA halves (References)**	**Role of retroelements (References)**
embryonic development	–	regulate gene expression (Yang *et al.*, 2016) and RE transcription (Boskovic *et al.*, 2020)	stimulate cell differentiation (Krishna *et al.*, 2019)	necessary for exit from the 2-cell stage of the embryo (Wang *et al.*, 2016; Honson & Macfarlan, 2018)
carcinogenesis	–	tumor suppressors (Goodarzi *et al.*, 2015) and oncogenes (Zhang *et al.*, 2019a; Zhou *et al.*, 2019)	promote cell proliferation (Honda *et al.*, 2015)	stimulate tumor growth (Mustafin, 2022a) and antitumor immune response (Chen *et al.*, 2021).

Prospects for the study of transfer RNAs in the development of human diseases

The above data on the close functional relationship of REs with tRNAs and their processing products indicate prospects of research in this area for the search for new methods of human diseases treating, since tRNAs, tRFs, tRNA halves play an important role in the etiopathogenesis of various human pathologies. Research in this area may improve the possibilities of antiviral therapy. Moreover, data on the role of tRNAs in antiviral response is an additional confirmation of their evolutionary relationship with REs. Indeed, interaction of tRNA with p66/p66 of HIV leads to conformational asymmetry of the two subunits with the formation of a mature RT p66/p51 dimer. Thus, tRNAs contribute to the maturation of infectious HIV particles (Ilina *et al.*, 2018). In humans, tRNA(Lys)s are used as primers for virus transcription, as well as tRNA(Asn), are specifically packaged into HIV1 virions (Pavon-Eternod *et al.*, 2010). Moreover, tRNAs regulate the binding of Gag of the HIV virus to the host membrane (Todd *et al.*, 2017). Respiratory syncytial virus induces 5'tRNA halves formation of in human respiratory epithelial cells by cleaving the tRNA anticodon loop with Angiogenin enzyme. At the same time, 5' tRNA halves formed from tRNA-Glu-CTC promote respiratory syncytial virus replication (Wang *et al.*, 2013). Therefore, it is possible to use tRNA as a target for antiviral therapy as a new direction in medicine.

Inducers of tsRNA formation are aging, oxidative stress, and metabolic changes leading to myocardial hypertrophy. In this regard, tsRNAs are considered as potential targets for the diagnosis and treatment of cardiac pathology (Cao *et al.*, 2020). Human aortic smooth muscle cells study revealed an increase in the expression of 887 specific tsRNAs and a decrease in the expression of 951 tsRNAs in proliferating cells compared to resting ones. Their role in the development of vascular diseases caused by abnormal proliferation of smooth muscle cells is assumed (Zhao *et al.*, 2022). Role of tRNA halves in the development of neurodegenerative diseases (amyotrophic lateral sclerosis, Parkinson's disease) is assumed, since mutations in the Angiogenin gene play a role in their development, since Angiogenin is necessary for tRNA halves formation (Sheng & Xu, 2016)

The cellular enzyme tRNA nucleotide transferase can function as telomerase for RNA viruses genomes that adopt tRNA-like structures at their 3' ends (Ekland & Bartel, 1996). This indicates a close relationship between tRNA and retroelements, which may reflect their evolutionary relationship, since telomerase evolved from REs (Garavis *et al.*, 2013). At the same time, telomerase and REs play an important role in the development of malignant neoplasms (Mustafin, 2022a), which indicates the possible involvement of tRNA in this pathology. Indeed, telomerase RT stimulates cancer cell proliferation by upregulating tRNA expression (Khattar *et al.*, 2016). It was found that tRNA halves increase the proliferation of breast and prostate cancer cells under the influence of sex hormones (Honda *et al.*, 2015). In addition, the involvement of tRNA halves in the pathogenesis of breast cancer was shown by deep sequencing of blood samples in patients compared with healthy controls (Dhabi *et al.*, 2014). Like miRNAs (Mustafin & Khusnutdinova, 2023), tsRFs can have oncosuppressive (Goodarzi *et al.*, 2015) and oncogenic activity (Zhang *et al.*, 2019a; Zhou *et al.*, 2019) for various cancers. In this regard, there is also a relationship with REs, which play an important role both in cancer development (Mustafin, 2022a) and in antitumor immune response (Chen *et al.*, 2021).

Conclusion

I suggest that tRNAs are the most ancient ncRNAs formed during the processing of RE transcripts in the DNA-RNA world before the formation of the DNA-RNA-proteins world at the origin of life on Earth. Initially, they could perform other regulatory functions, but in the course of selection, molecules were retained that could specifically bind to amino acids, thus stabilizing and connecting to an anticodon on another RNA molecule. The ability of tRNA molecules to be processed into other functional molecules reflects the ancient universal property of REs. I suggest that in the distribution of

tRNA genes in genomes, REs played a role as sources of these genes and their integration with the formation of gene clusters. This is evidenced by the specific property of REs, i.e., the processing of transcripts with the formation of functional molecules, which is inherent in tRNA genes. A deeper study of the relationship between RE genes and tRNAs can become the basis for deciphering species-specific structural and functional coding, which is the driver of epigenetic regulation of genes during the individual development of an organism. It can be assumed that influencing this encoding can become the basis for targeted therapy for diseases of the cardiovascular and nervous system, as well as for prolonging life. In this case, REs can be objects of influence, and small ncRNAs can be tools. This is evidenced by recent studies, presented in the article, of tRF, tRNA halves, tRNA and REs multifunctionality.

The relationship between REs and tsRNA is determined in various ways of their functioning: 1. REs (LTR-containing) use tRNA as primers for reverse transcription (which is due to the identity and complementarity of their nucleotide sequences, probably due to a single origin during the emergence of life on Earth). 2. SINE2 (MIR), which belong to REs, are formed in evolution by reverse transcription of tRNAs. Their persistence in human genome indicates the functional role of tRNAs, which goes far beyond amino acid transfer. I assume that at the dawn of the origin of life in the world of RNA, tRNAs originally performed many catalytic functions, some of which have been preserved and coincide with the functions of RE. Therefore, not only tRNA pseudogenes, but also tRNAs themselves can be conditionally attributed to REs, as evidenced by the functions of their processed transcripts. 3. REs are characterized by the multifunctionality of their transcripts depending on their processing systems. One of the important ones is the performance of catalysis as lncRNAs and the use of RE-derived miRNAs in RISC. Transfer RNAs have similar properties, since the transcripts of their genes, like REs, can be processed by different systems, with the formation of tRF-1s, tRF-2s, tRF-3s, trF-5s, tRNA halves, which have specific functions. 3. REs are inducers of interferon, which stimulates genes whose protein products cleave tRNA into tsRNA. At the same time, tsRNAs inhibit the REs activity in different ways: due to RNAi in the RISC system and by inhibiting reverse transcription. 4. Like REs, tRNAs are sources of microRNA formation. Moreover, previously annotated microRNAs turned out to be tRFs. 5. Non-coding RNAs formed from transcripts of both REs and tRNA are important epigenetic regulators of genome functioning. 6. REs and tRNAs are key regulators of embryonic development and cell differentiation, starting from the two-cell stage of the embryo. 7. Changes in the expression of REs and tRNAs are determined in malignant neoplasms, cardiovascular diseases, and viral infections, which suggests the prospect of studying their relationship for use in medicine.

Funding: there is no funding for the work.

Conflicts of Interest: the author declares no conflict of interest.

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