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tRN-A-RS Acts As Biomarker for Cancer and Other Diseases

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Abstract

Background: tRNA and ARS, tRN-A-RS, pivot the translational machinery. How their aberrances correlate to diseases, neurological conditions, metabolic disorders, and cancer is the purpose of this study.

Methods: Information was retrieved from the literature and from databases, such as OMIM and MITOMAP, related to disease and cancer. Changes of expressions of ARSs were assessed from analyzing NGS data available from TCGA, ENCODE and lately from roadmap epigenomics.

Results: A total of 647 tRNAs and 37 ARSs reside in the genomic pool of human, aberrant expressions of some of the nuclear tRNAs and cytoplasmic ARSs correlate predominately to cancer, while anomalous pathways in mitochondria relate more to other diseases. tRNA fragments juggle between tumor suppressor and oncogenic pathways. Brain cancer and neurological disorders seem to gain impetus from translation machinery components. However, investigation of the causes of the diseases particularly cancer due to the aberrations continues to be hamstrung by the lack of deep sequencing reads of tRNAs in different cell lines, and this needs to be addressed.

Conclusions: Increased cell proliferation requires elevated protein synthesis levels and makes the correlation between tumour cells and deregulated tRN-A-RS components in translation plausible. We draw the network of tRN-A-RS with cancer and other diseases, and present and expand on some of the hypotheses on the underlying molecular mechanisms, opening up new avenues for research.

Keywords: tRNA; Nuclear; Cytoplasmic; Mitochondrial; ARS/ARS2; Disease; Cancer; Neurological disorder

Introduction

In our recent work on eukaryotic tRNAs, the abundant presence of tRNA structures with dissimilarities to the standard cloverleaf was discussed [1,2]. These observations have received support recently [3]. In human, many of the tRNA isoacceptors have mismatched stem structure. Modifications are observed in acceptor stem (Acc-Stem), D-stem, D-loop, anticodon stem (Ac-stem), Ac-loop, T-stem and TΨC loop (T-loop). For instance, from hg19 human genome data, the frequency of mismatched base pair G:A in D-Stem is maximum, followed by A:A in 3D base pairings, A:C in T-Stem; G:A, C:C and T:T in Ac-stem and finally A:C and C:A in Acc-stem. In $tRNA^{Val}$ these mismatches reach the maximum of 72.77%, followed closely by 67.74% in $tRNA^{Gln}$. Figure 1A summarizes the deviations from the classical tRNA cloverleaf and L-shaped 3D structure. This called for intensive investigation on the functionalities, the expression levels and their fluctuations in the various cell types. The concept of tRNA isodecoders clearly originated from similar notions [4] all sorts of deviations needed careful analysis, they might lead potentially to new paradigm. Use of RNA-seq data from varied cell types has confirmed the differences in expression of tRNA genes between normal and cancer cell lines. The differences in cell-specific histone modifications amongst tRNAs have come to the attention. All of these adduce that during the transformation from normal to cancer/diseased cell, tRNA undergoes significant changes to their expressions. In this paper nuclear tRNA is denoted (n)tRNA; mitochondrial tRNA is (mt)tRNA. There are 625 (n) tRNAs and 22 (mt)ctRNAs.

In addition to tRNA, aminoacyl tRNA synthetase, ARS, an important component of translation, also shows altered levels in cancer. ARS attaches the correct amino acid onto its tRNA by catalyzing the esterification of a specific cognate amino acid or its antecedent to one of all its attuned cognate tRNAs to form anaminoacyl-tRNA. An amino acid ester of tRNA is called an aminoacyl-tRNA or sometimes a charged tRNA. This process called “charging” or “loading” is followed by transfer of amino acid from tRNA to growing peptide via ribosome, thus playing an imperative role in DNA translation, i.e. the expression of genes to create proteins [5]. The cytoplasmic aminoacyl tRNA synthetase genes are designated with single letter amino acid code followed by RS; the mitochondrial counterpart has a ‘2’ suffix. In human, the number of ARS/ARS2 genes is 37, distinguished into two distinct sets based on protein localization; 18 cytoplasmic ARS (including the bifunctional glutamyl-prolyl-tRNA synthetase, EPRS, in charge for aminoacylation of Glu and Pro, FARS needs two separate genes A and B); 17 mitochondrial ARS2 (QARS2 does not exist) and 2 dual-localized ARSs, GARS and KARS, in both cytoplasm and mitochondria [6-8]. The mitochondrial translation machinery is a combination of products of nuclear and mtDNA-encoded genes. The genes necessary for mitochondrial translation which are encoded in the nucleus have to be transported from the nucleus and imported into the mitochondrion [9,10].

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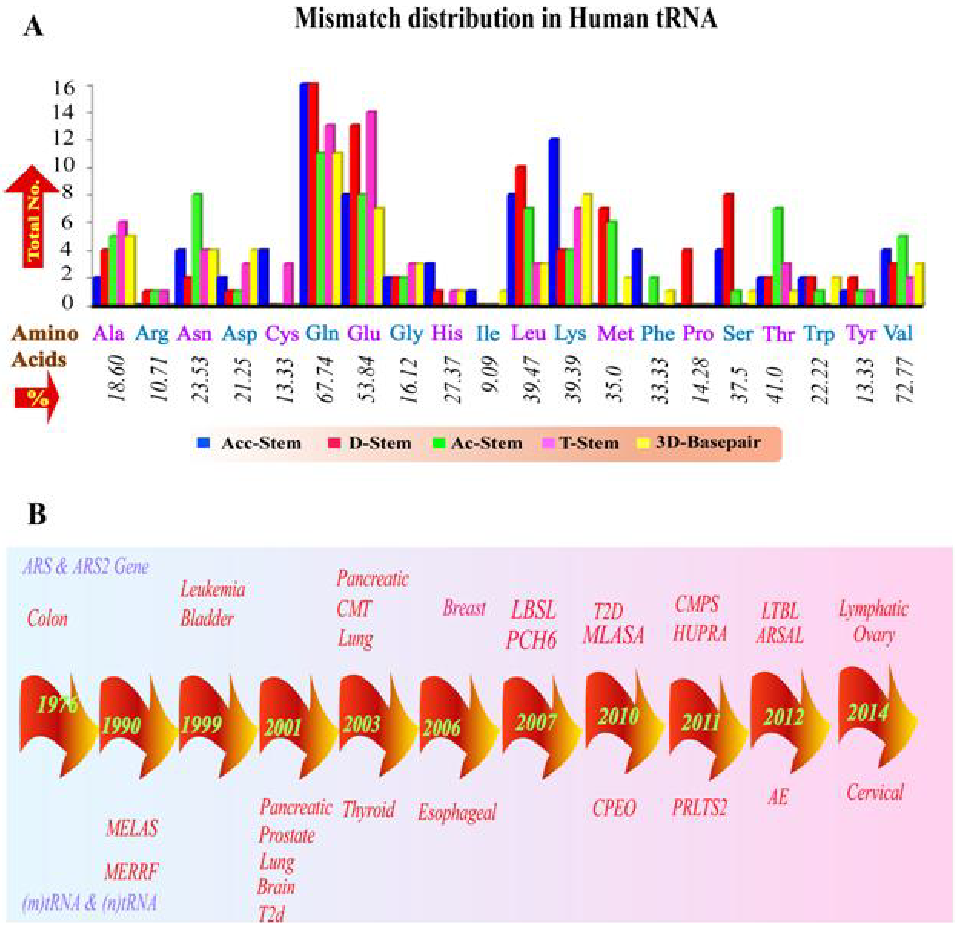

Figure 1: (A) The mismatch distribution in human tRNA (hg19 human genome data), Below the X axis, the overall mismatch % per amino acid is presented (B) Chronology of discovery of the link of ARS, ARS2, (n) tRNA and (mt) tRNA to diseases and cancer.

Translation produces proteins and controls growth and size of cells, suggesting that their alterations relate to anomalous development and progression. Effective and accurate translation requires some definite features, maintaining overall shapes and structures, proper recognition between tRNA-ARS to decode mRNA. While conserving their indispensable role in translation, tRN-A-RS have acquired unique functions during evolution [11, 12]. Recent efforts have revealed that beyond their canonical functions, they are active in cell signaling, cell survival, metabolism of amino acids, stress response programs, regulation of enzyme synthesis and apoptosis. Deviations of tRNAs and ARSs genes, therefore, are part of etiology and progression of cancer and diseases. The data on these are now just beginning to develop from individual studies. Although possessing microscopic structure, tRNAs have high stability and tolerance to nucleases [13,14]. High stability of tRNA is imparted by posttranscriptional modification of tRNA. Structural stabilization and/or folding of tRNA that is resultant of nucleotide modification increases thermal stability and protect tRNA against catalytic degradation by nucleases. A link between tRNA structural stability and modification has become apparent, particularly in mitochondrial tRNA, perhaps because these are less well structured and less extensively modified than their cytosolic counterparts. Off late, in yeast it is established that tRNA stability *in vivo* depends not only on the tRNA sequence itself but also on its modification silhouette [15,16]. However, not all modifications have same effect on all tRNAs. Degradation is the biological consequences for tRNAs lacking structural stabilization, which in turn is due to lack of proper modification or tRNA hypomodification [17]. A substantial body of evidence has emerged on lack of correct modification or mutations of (n) and (mt)tRNAs associated with diseases and cancer, sparking widespread interest [18]. Along with tRNAs, ARSs are also associated with neuronal diseases, cancer and autoimmune disorders [19, 20]. ARSs being housekeeping genes, over a long period their connection to diseases and cancer remained unsuspected. Expressions of ARS vary dynamically from cell to cell, and under stress conditions. Not just in diseases, ARS alterations are reported in cancer as well [21]. Apart from ARS, ARS2 are linked to several disorders. Thus, an extensive catalogue of diseases link with the pool of (n)tRNA, (mt)tRNA, ARS and ARS2 genes. The process of analyzing tRNA expression by deep sequencing is a recent favorite [22]. Emergence of deep sequencing to assess the genome-wide tissue-specific tRNA expression level has revealed that the (n) tRNAs and (mt) tRNAs exhibit distinct expression patterns, indicating that tRNAs might potentially be used as biomarkers for cancer. This NGS expedition of tRNA needs lot more sequencing of cancer cell lines to reveal the extent tRNAs are part of the cancer puzzle. Figure 1B gives a snapshot of how the subject has evolved over the past decades. We discuss here in details the link of tRNA and ARS to diseases, particularly neural disorders and with special focus on cancer.

tRNA deviates from normal course

Although the role of tRNA is supposedly known, but the changes in their expression levels have been associated with cancer, other disorders, suggesting crucial correlations of tRNAs in cellular processes. Alteration of tRNA modification, aminoacylation and composition affect translation and change other related processes. Reports have appeared clearly linking defects in tRNA modifications to diseases such as cancer, type 2 diabetes mellitus, T2DM, neurological disorders, and mitochondria-associated disorders. Modifications in all stem and loop, except Ac-loop, are crucial for tRNA structure and stability; modifications in the Ac-loop affect the accuracy of translation. Several reports propose direct link between tRNA modifications and cancer of skin, breast, bladder, and colorectal.

Diseases associated with (mt) tRNA and (n) tRNA

Diseases, including diabetes, cardiomyopathies, encephalopathies and others have been linked to point mutations in (mt)tRNA genes [23]. Muscular and nervous systems that consume relatively large energies are affected by mitochondrial defects. Chronic Progressive External Ophtalmoplegia, CPEO, is mainly caused by anomalies in mitochondrial genome. Sequence analysis of CPEO patients identified potential pathogenic mutation in (mt)tRNA$^{\text{Val}}$ and (mt)tRNA$^{\text{Gly}}$, namely T1658C and A10006G, changing the T-loop and D-loop structures respectively [24]. In a report, T4272C mutations in (mt) tRNA$^{\text{Ile}}$, detected in CPEO, is linked to ragged-red and cytochrome c oxidase, COX, negative fibers in skeletal muscle [25]. Besides, a novel heteroplasmic mutation in the (mt)tRNA$^{\text{Asn}}$ due to a single base substitution, A5692G, is suspected in CPEO [26]. (mt)tRNA$^{\text{Ala}}$ and (mt)tRNA$^{\text{Leu}}$ are also associated with CPEO [27]. Thus, multiple (mt) tRNA mutations underlie CPEO. Mitochondrial encephalomyopathy lactic acidose stroke-like episodes (MELAS), mitochondrial myopathy (MM), myoclonic epilepsy with ragged-red fibers (MERRF) are some of the important mitochondrial diseases that are caused due to alterations in (mt)tRNAs. Being mitochondrial disorder, MELAS and MERRF are inherited from female genomes. MELAS is associated with mutations observed in Ac-stem and D-loop of (mt)tRNA$^{\text{Leu}}$, and in Ac-stem of (mt) tRNA$^{\text{Lys}}$. MELAS patients lack 5-taurinomethyluridine (tm5U) on (mt) tRNA$^{\text{Leu(UAA)}}$, whereas lack of 5-taurinomethyl-2- thiouridine (tm5s2U) on (mt)tRNA$^{\text{Lys(UUU)}}$ is seen in MERRF patients [28]. A3242G transition in D-loop of tRNA$^{\text{Leu(UUR)}}$ is particularly linked to MELAS affliction, along with T3271C mutation (U40 in the anticodon stem of tRNA) in tRNA$^{\text{Leu(UUR)}}$ [29-31]. In the MELAS syndrome, A3243G mutation (A14 in the D-loop of tRNA) is reported to reduce (mt)tRNA$^{\text{Leu(UUR)}}$ aminoacylation and hypomodification of its anticodon wobble position, affecting recognition of UUG codons [32,33]. This leads to a decrease of steady-state levels of respiratory chain complexes and affect respiration rate [34]. Intriguingly, mutation at the same location may also be associated with other diseases. A3243G mutation is directly linked with MELAS, A3243T is correlated with encephalomyopathy [35]. A3243G mutations in the D-loop of (mt)tRNA$^{\text{Leu}}$ and A8296G mutation in the accepter stem of (mt)tRNA$^{\text{Lys}}$ are associated with Diabetes Mellitus, DeaFness, DMDF [36]. Mostly the variations in (mt)tRNA$^{\text{Leu}}$ are linked to MELAS, in an odd case G4332A transition in (mt)tRNA$^{\text{Gln}}$ is reported [37]. On the other hand, MERRF has been associated with an A→G transition in the T-loop of the (mt)tRNA$^{\text{Lys}}$ gene [38,39]. In addition, A8296G and G8363A mutations in Acc-stem and T8356C, A8344G point mutations in T-stem of (mt)tRNA$^{\text{Lys}}$ are linked to MERRF [40]. Four mutations, namely, T3250C in D-loop, C3254G in D-stem, A3302G and C3303T at Acc-stem of (mt)tRNA$^{\text{Leu(UUR)}}$ are correlated to MM [36]. Recently it has been reported that an A→G transition at nucleotide position 7526 in (mt)tRNA$^{\text{Asp}}$ is correlated to MM [41]. In a patient suffering from MM and abnormal mitochondrial proliferation in the muscle (ragged-red fibres), the G36 nucleotide within the (mt) tRNA$^{\text{Pro(UGG)}}$ anticodon was substituted to UGA encoding Ser [42]. Other (mt)tRNA related diseases like Lethal Infantile Mitochondrial Myopathy, LIMM, T2DM, Maternally Inherited Diabetes and Deafness, MIDD, are associated with (mt)tRNA$^{\text{Thr}}$, (mt)tRNA$^{\text{Ser}}$, and (mt)tRNA$^{\text{Glu}}$ respectively [36]. It is noteworthy that (mt)tRNA$^{\text{Leu}}$ alterations correlate with 27 different diseases. To date, only two pathogenic mutations have been recognized in tRNA$^{\text{Ser(AGY)}}$. C12246A point mutation in the highly conserved T-stem is associated with chronic intestinal pseudo-obstruction with myopathy and ophthalmoplegia, and heteroplasmic C12258A point mutation in the highly conserved Acc-stem is found in diabetes mellitus and deafness [43]. Recent findings suggest that the novel mutation 12207G>A in tRNA$^{\text{Ser(AGY)}}$ affect the processing of the precursor tRNA and influence the stability, the amino acid charging efficiency and the overall efficiency of translation of the tRNA [44]. Mitochondrial neuro gastrointestinal encephalomyopathy, MNGIE, is caused by the G8313A mutation in the D-Loop of (mt)tRNA$^{\text{Lys}}$ [36]. Recent report suggests a novel mutation, the heteroplasmic 1630A>G in (mt)tRNA$^{\text{Val}}$, is linked with MNGIE [45]. A recent study reveals a higher frequency of mitochondrial DNA (mtDNA) variations in women with repeated pregnancy loss, RPL. Point mutations A15907G in the D-stem, A15924G and G15928A in the Ac-stem, G15930A in the V-loop of tRNA$^{\text{Thr}}$ are correlated with RPL; one point mutation T15972C in D-loop of tRNA$^{\text{Pro}}$ is linked to RPL [46]. tRNA$^{\text{Ile(GAU)}}$ mutation is linked to hypertension. Probably the lower level of tRNA$^{\text{Ile(GAU)}}$ reduce the amount of respiratory complexes I, III and IV. Consequently, the overall respiratory capacity is reduced, which in turn increases the level of ROS and leads to hypertension [47]. Additionally, a homoplasmic mutation A4435G (A37 in the anticodon loop of tRNA) considerably decreases the level of the (mt)tRNA$^{\text{Met(CAU)}}$ and reduces translation in mitochondria, and is considered to be an inherent risk factor for hypertension [48]. (mt)tRNA mutations are catalogued in variety of databases, such as MITOMAP, and Online Mendelian Inheritance in Man, OMIM [49,50].

In contrast to the (mt)tRNA, diseases are less linked to (n)tRNA. Neurodegenerative disease is sometimes accompanied by (n)tRNA depletion or accumulation of unspliced pre-tRNA [13]. Problem of tRNA maturation is generally linked to defective cleavage and polyadenylation factor I subunit 1, CLP1 [51,52]. An R140H mutation in human CLP1 disrupts interactions of the tRNA with the tRNA splicing endonuclease complex (TSEN) and diminishes pre-tRNA processing in fibroblasts and neurons [53,54]. Individuals affected show signs of brain malformations, microcephaly, developmental delays and intellectual disabilities with symptoms alike pontocerebellar hypoplasia [54].

Variations in anomalous tRNA methylation are linked to diseases [55]. Mutation in cytosine-5 RNA methyltransferase, NSUN2, fails to methylate (n)tRNA$^{\text{Asp}}$ at C47 and C48, leading to Dubowitz syndrome (DS), a mental disorder [56]. Additionally, mutation in the NSUN2, leads to site-specific loss of m5C modification in tRNAs. Lack of these modifications at positions 48-50 increases the angiogenin-mediated endonucleolytic cleavage in the Ac-loop of tRNAs and reduces protein translation [55]. Dysregulation of translation may alter local protein synthesis which is crucial for synapse development. This may explain the higher susceptibility of neuronal cells to damage [57]. Depletion of (n)tRNA$^{\text{Gln(CUG)}}$ increases frame shifting frequencies linked to Huntington Disease, HD [58].

Overall, (mt)tRNAs experience higher rate of mutation compared to (n)tRNA [59,60]. This may be because there are multiple (n)tRNA genes in the human genome, whereas only one of most (mt)tRNAs. All the diseases related to altered (mt)tRNAs are in Table 1.

Sl. No.	Diseases	tRNA (Single letter aa code)
1.	AD	R
2.	ADPD	Q, E, P, T
3.	AISA	L
4.	AMDF	V
5.	AX	E, Y
6.	CAD	K
7.	CM	H, I, L
8.	Cardiomyopathy Familial Hypertrophic	L
9.	Cataracts	L
10.	CHD	T
11.	CIPO	G, S
12.	COPD	R
13.	COX Deficiency	Q, Y, W
14.	CPEO	A, N,I,L
15.	DEAF	S
16.	Deafness Related Disorder	S
17.	DEMCHO	Y
18.	Dilated Cardio Myopathy	L
19.	DMDF	L
20.	Dysarthria, Neurosensorial Deafness	P
21.	Early-Onset Cataracts	E
22.	EM	C, Q, E, G, I, K
23.	Encephalo Cardio Myopathy	I
24.	Exercise Intolerance	L, W
25.	Exercise-Induced Muscle "burning"	G
26.	Fatigue, and Hyper CKemia	G
27.	FICP	I
28.	Hearing loss	E, L, K, S
29.	Hemiplegia	V
30.	Hypertension	M
31.	Infantile Myopathy	S
32.	Infantile Respiratory Enzyme Deficiency	T
33.	Kearns-Sayre Syndrome	L
34.	Lactic Acidose	L
35.	Leigh Syndrome	I, K
36.	LHON	L
37.	Limb Weakness	W
38.	LIMM	T
39.	ME	K
40.	MELAS	C, H, I, L, K, F, V
41.	MERRF	H, I, L, K
42.	MHCM	G
43.	MICM	K
44.	MIDD	E, K
45.	MILS	Y
46.	Mitochondrial Abnormality in Bipolar Disorder	Y
47.	Mitochondrial Myopathy	N, Q, E, I, L, F, P, S, T, Y
48.	MMC	L
49.	MND	C
50.	MNGIE	K
51.	MS	D, K,
52.	Multiple Sclerosis	I
53.	Myoglobinuria	F
54.	Neurological Disease	F
55.	Neurosensory Disease	H
56.	NSHL	L
57.	Nystagmus and Leukoencephalopathy	P
58.	Ophthalmoplegia	A, I, L
59.	PEO	N,C, I, K
60.	Progressive Paraparesis	E
61.	Progressive Encephalo Myopathy	L, S, Y
62.	Pure Myopathy	T, S
63.	Renal Disease in Childhood	F
64.	RP	P, L
65.	RRF	S
66.	SM	K
67.	SNHL	S
68.	Spastic Paraparesis	L
69.	Stroke	L
70.	T2D	S, Q, E, K, Y
71.	TLE	C
72.	WS	L
(Abbreviation details given in Glossary)		

Table 1: Mitochondrial tRNAs associated with disease.

Cancer linked to (mt)tRNA-(n)tRNA

Hallmark of cancer is alteration in the gene regulation by point mutations or deletions, duplication, admixtures (heteroplasmy), epimutations etc. Non-coding RNAs are involved in carcinogenesis [61]. (mt)tRNA modification is reported many times in cancer cell lines, thus (mt)tRNA mutation pattern can endorse cancer diagnosis and tumor growth prediction [62]. For example, G4450A transition in (mt) tRNA^{Met} gene is linked to splenic lymphoma with villous lymphocytes. This mutation leads to mitochondrial morphological alterations. Again, D-loop mutations of (mt)tDNA have been reported in several carcinomas of breast, gastric, hepatocellular, head and neck and many more [62]. In breast cancer cell lines and in breast tumors, overexpression of both (n) and (mt)tRNAs have been reported. Aberrant abundance of (n)tRNA^{iMet}, not (n)tRNA^{eMet}, is thought to be key element in breast oncogenic transformation, followed by overexpression of others, such as (n)tRNA^{Ser}, (n)tRNA^{Tyr} and (n)tRNA^{Thr}. Compared to (n), (mt)tRNAs overexpress in breast cancer cell lines [63]. Interestingly, it is noted that elevated level of (n)tRNA^{iMet} shoots up the global expression profile of tRNA, escalating cell metabolic activity and cell proliferation [64]. Increased translation in multiple myeloma is due to overexpression of (n)tRNA, particularly of (n)tRNA^{Arg} and (n)tRNA^{Leu}; occasionally of (n)tRNA^{Ile}. It is noteworthy that (n)tRNA^{iMet} fails to dictate the fate of multiple myeloma, thus, curiously, (n)tRNA^{iMet} is not a mandate for oncogenic transformation in all tissues.

Discovery of RNA interference, RNAi, and microRNA, miRNA, mediated gene regulation have gained attention. However, in the last few years, small RNAs derived from tRNAs have come into lime light [65]. Such tRNAs have been called by various names like tRNA halves, tRNA-derived RNA fragments (tRFs), retrenched tRNA (rtRNA), stress-induced small RNAs (tiRNAs), tRNA-derived small RNAs (tsRNAs) or urinary bladder carcinoma RNAs (ubcRNAs) [14,65-67]. tRNA fragments occur in almost all walks of life, their functions in the body are being investigated. Decreasing level of oxygen and cellular stress generates and multiplies the tRNA fragments. It is suggested that some modifications may be responsible for tRNA cleavage [18]. Remarkably, it was shown that tRNAs are processed to shorter forms in cancer [68]. RNases, particularly, Dicer, RNase Z, and angiogenin that are potential biomarkers for predicting cancer risk have a role in the generation of tRNA fragments in cancer cells. A targeted therapeutic approach for cancer treatment, named tRNase ZL-utilizing efficacious (TRUE) gene silencing, is developed based on ability of RNase Z to recognize and cleave any pre-tRNA-like complex. Similarly, angiogenin, a member of the RNase A superfamily, also known as RNase 5, cleaves mature tRNAs in response to specific stimuli, such as nutritional deficiency, hypoxia,

No.	Name of tRNA	Cancer Name	PMID
		Mitochondrial tRNA	
1.	tRNA^{Arg}	Lung and Multiple Myeloma	18834532 19450555
2.	tRNA^{Asp}	Cervical Cancer	22357541
3.	tRNA^{Cys}	Lung Cancer	18834532
4.	tRNA^{His}	Colon and Kidney Cancer	18834532, 22238681
5.	tRNA^{Ile}	Multiple myeloma and Breast Cancer	19450555, 7606938
6.	tRNA^{Leu}	Oral, Endometrial, Lung, Kidney, Multiple Myeloma and Cervical Cancer	18834532, 23851045, 17886251.16884381 11145497, 19450555
7.	tRNA^{Lys}	Cervical	22357541
8.	tRNA^{Met}	Multiple Myeloma	19450555
9.	tRNA^{Phe}	Gastric Cancer	12970877
10.	tRNA^{Pro}	Nasopharyngeal Carcinoma	18376149
11.	tRNA^{Ser}	Bladder Cancer	12418552
12.	tRNA^{Thr}	Breast Cancer	7606938
13.	tRNA^{Tyr}	Hodgkin's Tumors, T-cell Lymphoma	6921079, 18347422
14.	tRNA^{Val}	Hepatocellular Carcinoma	20006738
		Nuclear tRNA	
1.	tRNA^{Arg}	Multiple Myeloma, Breast, Ovarian Cancer	19450555, 19783824, 11058163
2.	tRNA^{Asn}	Colorectal Cancer, Hodgkin's Tumors	24852749, 6921079
3.	tRNA^{Asp}	Hodgkin's Tumors	6921079
4.	tRNA^{His}		
5.	tRNA^{Ile}	Multiple Myeloma	19450555
6.	tRNA^{Leu}	Breast Cancer, Multiple Myeloma	25447904, 19450555
7.	tRNA^{Met}	Multiple Myeloma, Hodgkin's Tumors	9450555, 6921079
8.	tRNA^{iMet}	Breast, Gastric and Colorectal Cancer	23431330, 9442927
9.	tRNA^{Phe}	Pulmonary Carcinogenesis, Hodgkin's Tumors	15994936, 6921079
10.	tRNA^{Ser}	Breast Cancer	19783824
11.	tRNA^{Thr}	Breast Cancer	19783824
12.	tRNA^{Tyr}	Breast, Ovarian Cancer	19783824, 11058163
13.	Pre-tRNA^{Leu}	Osteosarcoma, Breast and Embryonic Kidney Cancer	20233713
14.	Pre-tRNA^{Tyr}	Hepatoma	15498584

Table 2: tRNAs Associated with cancer.

heat shock, and oxidative stress, which are common for cancerous cell [66]. The varied form of stress results in different forms of tRFs [69]. Lui et al. presented the results of deep sequencing method, and characterized the small RNA profile for human cervical carcinoma cell lines, and also established that in human prostate cancer, the most abundant group of small RNA, just after miRNAs, is tRFs. Knocking down the specific tRF, a dramatic loss in cell proliferation and their viability was observed. Using sequencing, computational analysis and northern blot assays, it has been observed that, in human cells, the tRFs may act as miRNA-like molecules, serving as a post transcriptional regulator [68]. Recent research reveals that tRNA fragments could be present in high amounts in metastatic samples. Using Illumina/Solexa deep sequencing method, evidence of the presence of tRNA derived fragments in prostate cancer cells has emerged. Not the whole tRNAs, but 3´-tRNA fragments of pre-tRNA^{Ser}, tRF-1001, dictate prostate cancer cell proliferation, but the precise mechanism of oncogenic transformation by tRNA fragments is yet to be discovered [8]. Recently it has been observed that small RNAs derived from tRNAs, namely, 5′ tRNA-halves, 5′tRHs, ~30-35 nts in length, are abundant in liver; increase significantly during chronic viral infection, and alter in abundance in liver cancer associated with these infections. Chronic Hepatitis B infection appeared to increase the level of 5´tRNA fragments in hepatocellular carcinoma both in humans and in chimpanzee. These 5′tRHs are derived from either tRNA^{Gly} or tRNA^{Val}. Real time PCR has confirmed that 5′tRH abundance increases in HBV and HCV infected liver compared to the uninfected tissues. Interestingly, tRNAs from which 5′tRH^{Gly} and 5′tRH^{Val} are potentially derived, share a unique sequence motif in the Ac-stem-loop region not found in other tRNAs [69]. Tumor suppressive role of tRF has been recorded in breast cancer, owing to their capacity of reducing the stability of multiple oncogenic transcripts by displacing oncogenic RNA-binding protein YBX1 from their 3´-UTR. These tRFs are derived from tRNA^{Glu}, tRNA^{Asp}, tRNA^{Gly} and tRNA^{Tyr} [70]. tRNA fragments, either oncogenic or tumor suppressive in role, reveal novel pathways of directing gene expression.

Along with these reports, there is long list of tRNAs involved in disease and cancer. The alterations catalogue in Table 2, of tRNAs (n) and (mt), has the details.

Aminoacyl tRNA synthetase genes association to disease and cancer

The patho-physiological mechanism and role of ARS genes in disease and cancer require knowing the secondary functions of ARS genes.

ARS/ARS2 gene mutation causing diseases

Mistranslation due to ARS and ARS2 recognition perplexity can be one source of disease [71,72]. Both ARS and ARS2 genes are mutated causing several diseases. Generally, these kinds of mutations and structural distortions sprout in domains other than those utilized in translation for ARS [73,74]. In case of ARS2, mutation is observed

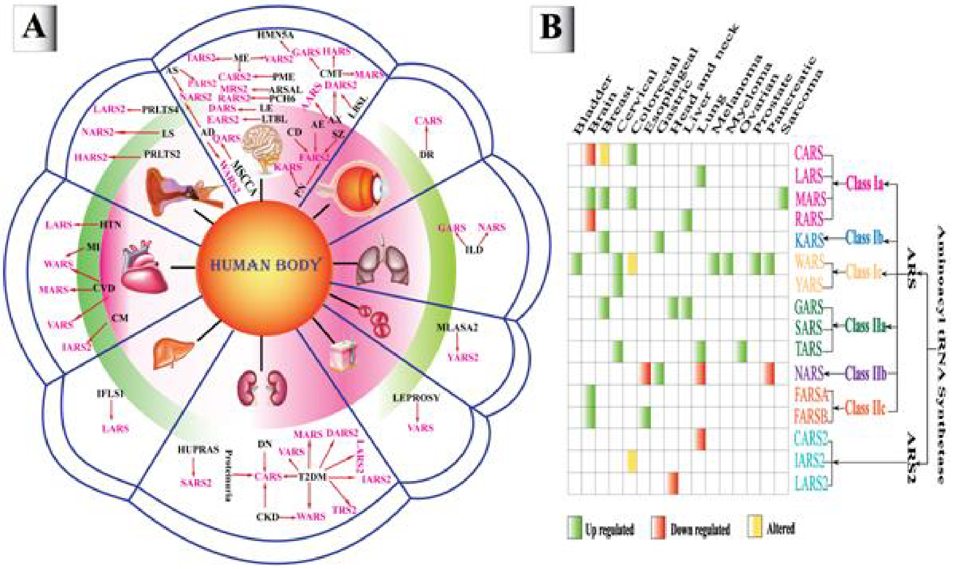

Figure 2: ARS/ARS2 gene perturbation in disease and cancer. (A)Link of ARS and ARS2 to disease in corresponding organs are depicted in this figure (B) Heatmap represents the expression status of ARS/ARS2 genes in cancer.

in editing domain along with aminoacylation domain and catalytic domain [7].

A defect in mitochondrial protein synthesis is attributed to mutations in ARS2 genes, leading to several mitochondrial disorders [7]. Leukoencephalopathy with brain stem and spinal cord involvement and lactate elevation, LBSL, an autosomal recessive disease, manifest the mutation of aspartyl tRNA synthetase, DARS2. LBSL is associated with spasticity, cerebellar ataxia and variable degree of cognitive impairment [75]. Following the initial report, several studies confirm the association of DARS2 with LBSL [76,77]; approximately nine diversified DARS2 missense mutations are implicated in LBSL. Of these mutations, some may directly affect catalytic activity of enzymes; others impair protein expression and dimerization [77]. It is noteworthy that DARS2 intron 2 mutation, affecting the splicing of 3rd exon, is seen in almost all LBSL patients [76]. NGS determined that DARS2 is also mutated in ataxia and spasticity [78]. Genome scan has shown that DARS2 is associated with T2DM [79]. T2DM has association with many other ARS2 genes. Leucyl tRNA synthetase, LARS2, and threonyl tRNA synthetase, TARS2 are susceptibility genes of T2DM. H324Q variant of LARS2 is thought to enhance T2DM [78, 79]. Premature ovarian failures accompanied by hearing loss symptoms compose Perrault Syndrome. Several mutations in LARS2 along with mutations in histidine tRNA synthetase, HARS2, are associated with Perrault syndrome [80,81].

Similar to DARS2, DARS paves the way to brain disorder. DARS is also mutated in patients affected with leukoencephalopathy [82]. Resembling LBSL, there is another variety of leukoencephalopathy characterized by hypomyelination with brain stem and spinal cord involvement and leg spasticity, HBSL. It is reported that for HBSL patient, DARS2 have both homozygous and heterozygous mutation, causing non-synonymous changes to seven highly conserved amino acids [83]. On the other hand, LARS is not linked to T2DM like LARS2. Instead, LARS endorses homozygous missense mutation in infantile hepatopathy, a life-threatening liver-disorder [84]. That apart, Charcot–Marie–Tooth, CMT, disease has a widespread association to many ARS mutations. CMT is a group of clinically and genetically heterogeneous peripheral neuropathies characterized by distal muscle weakness and impaired sensation in the extremities. CMT is fairly common, occurring in 1 out of 2,500 individuals. Glycyl tRNA synthetase, GARS, is mutated in CMT type 2D, CMT2D. GARS was the first synthetase gene discovered to be mutated in human disease [85,86]. p.R329H variant of alanyl tRNA synthetase, AARS, has reduced enzymatic activity and is found to segregate from patient suffering from CMT type 2N, CMT2N [87,88]. In tyrosyl tRNA synthetase, YARS, a portion of amino acid chain, i.e. VKQV from position 153-156 is deleted in CMT neuropathy, CMT dominant intermediate type C caused by demyenilation or axonal degradation or both. Flaws in YARS gene lead to partial loss of aminoacylation activity [89]. Along with these three ARS genes, lysyl-tRNA synthetase, KARS, mutation is also identified in CMT intermediate recessive type B [87]. P.L133H and p.Y173SfsX7 mutations sternly influence the KARS activity in CMT [90]. The last few years witnessed a number of ARS mutations as being the cause of CMT. In addition to the 4 ARS genes, methionyl tRNA synthetase, MARS, and histidyl tRNA synthetase, HARS, are also implicated in CMT. It is reported that HARS acts through a different pathogenic mechanism than GARS or YARS [91].

A particular ARS/ARS2 may be mutated leading to a multiple of diseases, and a single disease can be due to multiple ARS/ARS2 mutations. Along with the disease, we map the organs that are affected most. To improve our understanding of the genetic and functional mechanisms by which ARS mutations lead to disease, we sought to: (1) identify and characterize ARS gene mutations in several diseases and disease-causing mutation; (2) retrieve the genetic locus; (3) denote the root organ(s) from where the disease originates and (4) finally tabulate them with supporting evidence in Figure 2A, to get an overview of all possible ARS and ARS2 genes related to the diseases. Remarkably, Figure 2A makes it evident that neural disorders have the highest links to multiple ARS/ARS2 mutations.

ARS/ARS2 in oncogenic pathway

Along with catalytic activity domains, ARS also contains other regions to interact with diverse regulatory factors. During evolution, new domains are appended to ARS. This structural convolution may be linked to a functional flexibility with assorted uses, including oncogenic pathways. The oncogenic pathways embraced by ARS/ARS2 genes vary from apoptosis to angiogenesis, cell growth to cell proliferation and signal transduction. The alterations of ARS/ARS2 genes in cancer cell pose the question: are they altered to meet the increasing protein need of cancer cells, or are they the drivers of oncogenesis? A database of cancer causing ARS is available, supporting the involvement of ARS in cancer [92].

Unlike in other diseases, just three ARS2 genes are reported to be altered in cancer. LARS2 is genetically and epigenetically deregulated in nasopharyngeal carcinoma, NPC, mainly due to the chromosome 3p deletion. Chromosome 3p21.3 harboring LARS2 frequently is rearranged within 3p. It is reported that LARS2 acts as a haploinsufficient tumor suppressor gene in NPC [93,94]. Upstream alteration of mitochondrial isoleucyl tRNA synthetase gene, IARS2 is reported to be associated with hereditary non-polyposis colorectal cancer, HNPCC, the exact mechanism and function of IARS2 is still to be discovered [95]. CARS2 is detected to slack its manifestation in lung cancer [96].

In contrast to mitochondrial ARS2, 12 cytoplasmic ARS are linked to cancer. Brain cancer has the maximum number of ARS genes with modified expression compared to normal. MARS is upregulated in glioblastoma, a type of brain cancer, favoring tumor progression. Amplification of chromosome 12q13 is thought to be the reason behind MARS overexpression [21]. Phenylalanyl tRNA synthetase, FARS2, is upregulated in glioblastoma multiforme, GBM, whereas cysteinyl-tRNA synthetase, CARS is downregulated in GBM. Arginyl tRNA synthetase, RARS, is downregulated in case of brain cancer, but the same gene is upregulated in liver cancer. Following brain cancer, colorectal cancer and cervical cancer have significant correlations with ARS genes. Promoter hypomethylation of serine tRNA synthetase, SARS, makes it a candidate tumor suppressor gene in prostate cancer [97]. GARS, ubiquitous in nature, a homodimer, is reported to be upregulated in papillary thyroid carcinoma [98], hepatocellular carcinoma, due to low oxygen response in association with erythropoietin gene expression, [99] and many more depicted in Figure 2B. A complete overview of all ARS/ARS2 related to cancer, available to date, appears in Figure 2B.

Hypotheses on mechanisms of tRN-A-RS link to diseases and cancer

Translation machinery components have multifaceted relationship with diseases and cancer; failure of translation fidelity, mutation and structural distortions lead to errors. To comprehend the overall picture, all the players, their network with neural disorders, diseases and cancer is in Figure 3.

tRNA over-expression is a general consequence in all tumors, (n)tRNAs and (mt)tRNAs are potential biomarkers of malignancy. Differential expression status of tRNA isoacceptors may augment

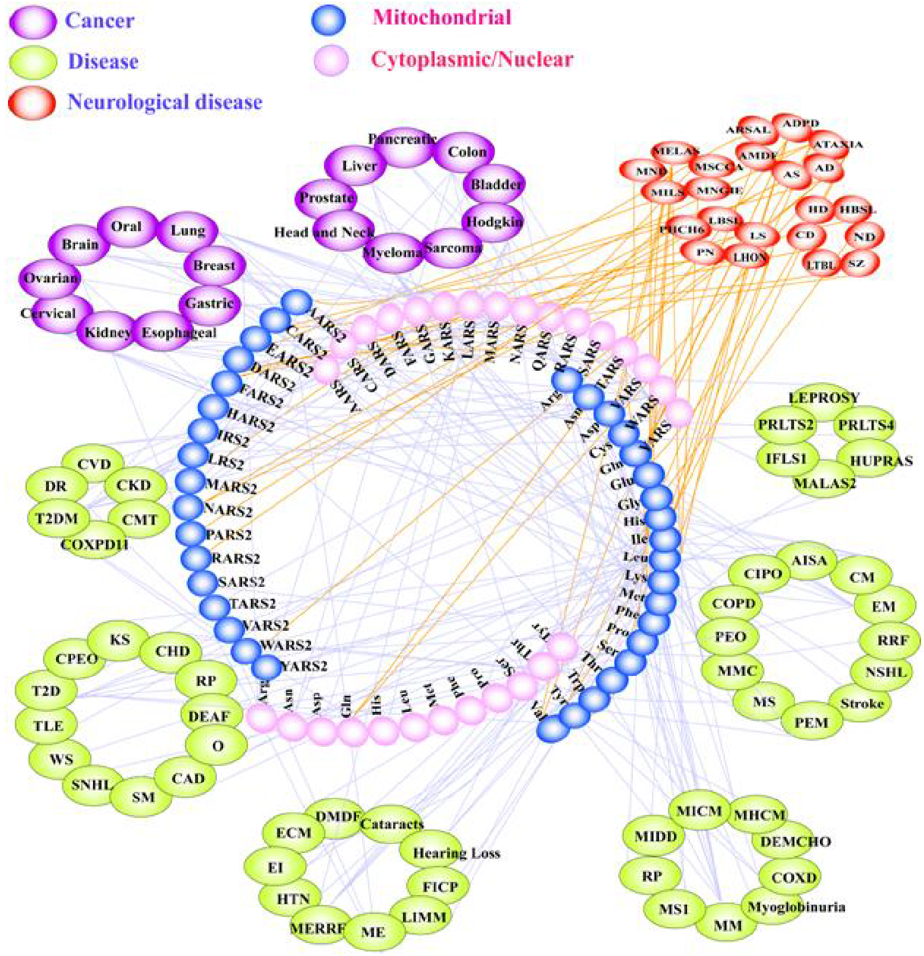

Figure 3: Network of [(n) and (mt)] tRNAs and ARS/ARS2 linked to diseases and cancer. This network highlights the neurological disorders, as they are frequent compared to other diseases. (Abbreviation details given in Glossary).

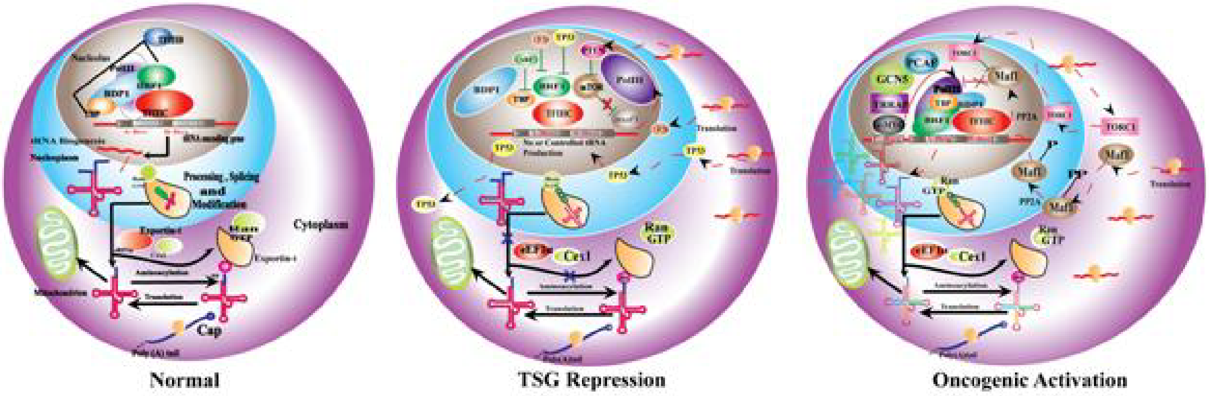

Figure 4: tRNA regulation mechanism. The change of expression based on tumor suppressor gene and oncogenic control on Pol III complex is represented.

translation of specific cancer related genes via their codon usages, imposing additional level of regulation. A quantitative and qualitative change in protein expression is observed in cancer cells, with favored translation of growth factors, cell-cycle promoters, and proto-oncogenes, such as VEGF, cyclin D1, and c-Myc.

For potential post-translational regulation of proteins involved in signal transduction, tRNAs have to be a part of the critical mechanism, Figure 4. tRNA synthesis can be regulated by oncogene and tumor suppressor genes, TSGs. To regulate tRNA biogenesis, all these interact with RNA Pol III components. TSGs such as TP53 and Rb (retinoblastoma protein) control tRNA synthesis during cell cycle progression. TP53 directly binds to TFIIIB complex, particularly TBP, averting its contact with TFIIIC, thus avoiding Pol III recruitment to target genes, including tRNA genes. This mechanism is useful during cellular stress, regressing tRNA productions to minimize mRNA translation. Similarly, Rb directly binds to the TFIIIB complex, especially Brf1 and TBP to regulate tRNA biogenesis. ADP-Ribosylation Factor, ARF, a TSG, also follows the same pathway. The turning point is when TSG are repressed during malignancy. In more than 50% of cancer, TP53 is mutated or inactivated. Rb is also deleted or idled in a large number of tumors [100]. PTEN (Phosphatase and tensin homolog), another TSG, inactivates mTOR (mammalian Target-of-Rapamycin) and thereby enable Maf1 to inhibit RNA Pol III activity. This mechanism disrupts the link of TBP and Brf1. If PTEN is turned on for a long stretch, serine phosphorylation of Bdp1 increases. All these interactions ultimately control the transcription capacity of RNA Pol III [101]. Their inactivation leads to the release of TFIIIB from their bond, as a result rejuvenating RNA Pol III function. In addition, during malignancy different oncogenes are produced which enhance RNA Pol III activity. Target-of-Rapamycin, TOR, a conserved serine/threonine kinase, is a vital regulator of cell growth and proliferation and exists in two distinct protein complexes, TORC1 and TORC2. TORC1 regulates metabolism and growth, while TORC2 maintains the actin cytoskeleton. TORC1 regulates RNA Pol III by interacting with RNA Pol III repressor Maf1 and inhibiting it through phosphorylation of conserved serine residues on Maf1 [102,103]. Thus, TORC1 via RNA Pol III drives tissue and body growth during development. Another oncogene, Myc, directly localizes at tRNA genes by associating with the Brf component of the TFIIIB complex and recruits the histone modifying enzymes-GCN5 and TRRAP-to promote transcription [104]. The conserved Ras family of G-proteins, H-Ras, K-Ras and N-Ras, function as molecular switches that control cell growth, proliferation, survival, differentiation including stimulation of protein synthesis. Activation of Ras/ERK pathway can crosstalk with other signaling pathways, such as TORC1 and Myc, and upregulate their protein levels [105]. Highly transcribed mRNA in tumors raise codon concentration for a subset of tRNAs. As a result, imbalance in tRNA pool is seen due to skewed codon usage, ultimately escalating translational error. These reflect how different oncogenes and tumour suppressor pathways can congregate on RNA Pol III to control tRNA production. Mei and coworkers in 2010 showed that tRNAs bind to the cytochrome c and, therefore, inhibit the activation of caspase 9, thus preventing cancerous cells from apoptosis. Along with the above mentioned pathways, there is report of tRNA being hypermethylated in cancer cells. Not only internal change, external factors can also influence the level of tRNA expression. Alcohol intake related to estrogen receptor positive, ER+, breast cancer patients increase the transcription capacity of RNA Pol III genes, amplifying the level of pre-(n)tRNA^{Leu} genes. However, overexpression of BRCA1 decreases the induction of tRNA^{Leu} genes by alcohol. On the other hand, reduction of BRCA1 by targeting siRNA to it slightly increases the transcription of the RNA Pol III genes [106]. Thus, changing tRNA concentrations have pleiotrophic effects. However, measuring the tRNA level is a challenge. Firstly, because, large numbers of tRNA modifications make it difficult to map the reads of deep sequencing and secondly folded structure of tRNA prevents its hybridization on tRNA chips.

While increased expression level of tRNA is linked to cancer, their modifications are linked to diseases. tRNAs undergo wide-ranging chemical modifications, from simple methylation of the base or ribose ring to extensive "hypermodification" of the canonical bases, that are being correlated to the efficiency, conformity and specificity of translation [107]. In eukaryotes, more than 100 chemically diverse modifications have been identified so far, many of which are conserved among organisms (see MODOMICS database) and between tRNAs encoded in the nuclear or organelle genomes. Generally, positions 9, 26, 32, 34, 37, 38, 48, 49, 50 of tRNA are affected most by different modifications that ultimately lead to diseases [108]. Conserved modifications across all domains of life underscore their biological importance. In spite of exhaustive biochemical characterization, the physiological roles of most tRNA modifications are unidentified. It is noteworthy that modifications within and around the anticodon are anticipated to have a direct role in increasing translational efficiency, while modifications external to the anticodon region help to preserve the structural integrity of the tRNA. Disruption of these modifications alters the structure of tRNA, causing different genetic diseases. If Ac-loop is mutated, then there is translational error due to failure of codon-anticodon recognition. Interestingly, it is observed

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that anticodon specificity plays a role in tRNA alteration [109]. On the other hand, mutations in other regions distort the structure. As a result, we hypothesize that aminoacylation or attachment to ribosome is hindered, leading to mistranslation. Alterations in the translation factors that facilitate mRNA translation generate many diseases. These variations either can increase or decrease translation, along with the formation of misfolded proteins, changing protein dynamics. These modifications are encountered in (n)tRNA and (mt)tRNA. As the tRNA level shoots up in cancer, there is some doubt whether all these undergo homogeneous modification. Supply of tRNA-modifying enzyme must be high in order to combat the tRNA-number growth in cancer cells. This raises the question, is the pool of required enzymes sufficiently maintained during malignancy. If not, there will be disruption to tRNA modification. While (mt)tRNAs are frequently related to numerous diseases, only a few (n)tRNAs have this link. Since both (n)tRNA and (mt)tRNA undergo modifications, then why just (mt)tRNA is linked to disease, is it because control of modification is weaker in mitochondria compared to nucleus? It has been suggested that mutation load of (mt) tRNA is higher compared to (n)tRNA [59,60]. This exemplifies the differences between mitochondrial and nuclear mutations and the role of heteroplasmy in the subsequent phenotype. This may be due to faster evolutionary rate of mitochondria than that of the nuclear. Mitochondrion has less effective DNA damage repair mechanism than nucleus and hence mitochondrial gene regulation becomes easily aberrant [110,111]. Curiously, identical modifications in tRNA link to more than one disease. This raises the possibility that not a single mutation, but a combination of mutations correlate to diseases. We expect technological innovations will elucidate translational missense error frequencies and solve unreciprocated glitches.

Along with tRNA, ARS is also an important factor of translation. Venturing the reason behind the link of ARS to cancer, we mined that YARS, WARS, EPRS and SARS are associated to angiogenesis and vascular development, whose imbalances contribute in oncogenic pathway. While N-terminal fragments of YARS and WARS act as angiogenic factors for endothelial cells, C-terminal of SARS harbor unique domain that has role in vascular development. In contrast, EPRS imposes translational silencing of VEGF-A via IFN-γ, thus acting as anti-angiogenic factor [112,113]. Impairment of vascular development may not only be related to cancer but to several cardiovascular diseases [114]. Finding the link of KARS to metastasis, one major cause of death in cancer, remains a challenge. A laminin signal translocates KRS to plasma membrane and KARS interacts and stabilizes a 67-KDa laminin receptor, 67LR. 67LR on the other hand interacts with cell migrating component MAPK, and leads to metastatic transformation of cancer cell. Thus, KARS can form an anti-metastatic target [114]. The C-terminal domains of YARS and KARS act as inflammatory cytokines, which cause chronic inflammations in many cancers, particularly solid tumors. Immune cells inflict tumor initiation, growth and progression intervened by proinflammatory cytokines. IARS, HARS and AARS are efficiently cleaved by granzyme B, a serine protease released by cytoplasmic granules within cytotoxic T cells and natural killer, NK, cells and involved in the induction of programmed cell death in the target cell, thus eliminating cells that have become cancerous, to generate autoantigenic fragments with chemokine activity [115]. QARS, known to be an apoptosis suppressor, inhibits the pro-apoptotic signaling pathway through glutamine-dependent interaction with apoptosis signal-regulating kinase 1, ASK1, induced by heat shock, irradiation, and c-Myc overexpression. Antiapoptotic function of QARS is induced by ASK1, but is weakened by the deprivation of cellular concentration of Gln. Fas ligation dissociates the interaction of QARS and ASK1, thus mediating apoptosis [116]. YARS and RARS secreted from apoptotic tumor cells arrest translation and mediate the production of required cytokines inducing apoptosis [85]. Interestingly, cell proliferation mitogenic signal dissociates MARS from multi-ARS complex and translocates it to nucleoli enhancing rRNA synthetase. Thus, MARS switches its role, synchronizing rRNA synthesis in the nucleolus in proliferative condition and protein synthesis in cytoplasm in normal condition [85]. It is interesting to note that only three ARS2 are linked to cancer. The reason remains elusive.

Alterations in the ARS as well as ARS2 that facilitate mRNA translation, generate many diseases. Due to their vital role in the course of translation, mutations that affect strategic components of the translation machinery or translation factors might be expected to have similar phenotypic effects in a broad range of tissues. As mentioned before, various changes are encountered by ARS and ARS2, ranging from transition, transversion, deletion, point mutation, homozygous and heterozygous missense mutation. These mutations occur in exon or intron, but mostly in exon at nucleotide sequence level. It is interesting to note that many genetic mutations of ARS do not affect its role in translation, yet are related to the cause of several diseases. During evolution, a side catalytic domain, and other regulatory domains, is added to ARS/ARS2. Mutations also occur in these domains at protein level. It is striking that while many ARS2 are linked to diseases, there are hardly any associations to cancer. Impaired mitochondrial translation, resulting from mutations in mitochondrial tRNA synthetase and tRNA modifying genes, causes familiar human genetic diseases [72].

Discussion

The above survey shows that the mutations are prolific, and results in diverging phenotypes. All the supporting data reveals that both ARS and ARS2 mutation is highly associated with diseases, whereas the number of ARS mutation in case of cancer is much more compared to ARS2. Further structural and function analysis of ARS genes provide evidence that they have an impact on human life and contribute to the regulation and coordination processes in the mitochondria and nuclear genes simultaneously. Besides playing the major canonical role, their non-canonical pathways have a widespread impact; indeed, many researchers consider them as the hotspot of the regulation system [7-13,21,22]. Different factors are found to be associated with these gene mutations, like abnormal synthesis of enzyme, oxidative stress condition and other intrinsic and extrinsic causes. Approximately 15 organs are affected by ARS/ARS2 mutation causing several diseases. It has been found that neurodegenerative, cardiovascular and T2DMs are highly correlated with ARS2 genes. Interestingly, Alzheimer disease is found associated with NRS2 and WRS2 genes, the same disease also associated with (mt)tRNA^{Arg}, (mt)tRNA^{Gln}, (mt)tRNA^{Glu}, (mt) tRNA^{Pro} and (mt)tRNA^{Thr}. It has been noted earlier that early onset mitochondrial disorders have connection to protein-coding gene (mainly in complex-I) mutation, whereas tRNA mutation sprouts in late onset mitochondrial diseases. This means that tRNA mutation is better tolerated compared to mutation in protein coding genes [117].

About 12 ARS genes and 2 ARS2 genes are associated with 12 types of cancer. WARS gene is correlated to 6 types of cancer. On the other hand, brain cancer is linked to five different ARS genes, Figure 2B. It is noteworthy that while ARS2 genes are consistently linked to neurological disorders, ARS genes are greatly altered in brain cancer. It is observed that brain is affected significantly by deformations in ARS/ARS2, however, only three ARS are allied to neurological diseases, and none of the ARS2 is yet connected to brain cancer. tRNAs remain unlinked to brain cancer, nevertheless, (mt)tRNAs are part of the neurological disease etiology. The correlation of translation machinery complex with brain is being increasingly addressed.

tRNAs are linked to breast, liver, prostrate, lung, ovarian, lymphoid, esophageal, leukemia, bladder, kidney and other cancer. The expression levels of (mt)tRNAs are found to be high in brain as compared to other tissue like thymus, lymph node, ovary, liver, testis etc [118]. In total at least 15 (mt)tRNAs and 11 (n)tRNAs are now linked to cancer. It is found that at least 15 types of cancer have association to both types of tRNAs. $tRNA^{Ala}$, $tRNA^{Gln}$, $tRNA^{Glu}$, $tRNA^{Gly}$ and $tRNA^{Trp}$, nuclear and mitochondrial, are so far not linked to cancer. At least 72 diseases are linked to (mt)tRNAs; in contrast (n)tRNAs rarely correlate to diseases. Hence, some of the mutations may be valuable biomarkers for tumor aggressiveness and may play an impending role in tumorigenesis.

Many distortions are seen in tRNA in hg19 human genome data, Figure 1A. We observed that compared to normal counterparts, tRNAs have varying histone modifications, but could not assess their effects. From all the reports and analysis of hg19 tRNAs, we estimate that distortion of tRNA in this reference genome does not truly reflect on cancer or diseases. Support of this inference comes from Figure 1A, 67.74% $tRNA^{Gln}$ and 53.84% of $tRNA^{Glu}$ have mismatched base pairs, none of them are connected to cancer as yet. We observed subtle changes in tRNA internal promoters when bases are mismatched, suggesting variations in expressions, but no such link was found for the transcription terminator sequences. The variations in tRNA promoters in cancer cell lines and their effects remain an open issue.

tRNAs are enzymatically cleaved, yielding distinct classes of tRNA-derived fragments, tRFs. These tRFs derived from $tRNA^{Asp}$, $tRNA^{Glu}$, $tRNA^{Gly}$, $tRNA^{Ser}$, $tRNA^{Tyr}$ and $tRNA^{Val}$, are either oncogenic or tumor suppressive in nature. Just six tRFs are related to cancer now. Clearly, new tRNA related NGS data on cancer cell lines is required to solve the unsettled mysteries. As the search continues for novel therapeutic tools for cancer, further analysis of non-canonical roles of translation machinery components becomes even more important.

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