Metabolism Clinical and Experimental 94 (2019) 9–17

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Review

The tRNA-associated dysregulation in diabetes mellitus

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ARTICLE INFO

Article history:
Received 20 November 2018
Accepted 30 January 2019

Keywords:
Diabetes mellitus
tRNA mutation
tRNA modification
tRNA aminoacylation
tRNA derivative

ABSTRACT

Diabetes mellitus (DM) is a complex endocrine and metabolic disorder for human health and well-being. Deregulated glucose and lipid metabolism are the primary underlying manifestations associated with this disease. Transfer RNAs (tRNAs) are considered to mainly participate in protein translation and may contribute to complex human pathologies. Although the molecular mechanisms remain, for the most part, unknown, accumulating evidence indicates that tRNAs play a vital role in the pathogenesis of DM. This paper reviews different aspects of tRNA-associated dysregulation in DM, such as tRNA mutations, tRNA modifications, tRNA aminoacylation and tRNA derivatives, aiming at a better understanding of the pathogenesis of DM and providing new ideas for the personalized treatment of this metabolism-associated disease.

Contents

Abbreviations: T2DM, type 2 diabetes mellitus; tRNAs, transfer RNAs; aaRSs, aminoacyl-tRNA synthetases; Pol III, polymerase III; pre-tRNA, precursor tRNA; RNase P, ribonuclease P; RNase E, ribonuclease E; mRNA, messenger RNA; mt-tRNA, mitochondrial-encoded tRNA; mtDNA, mitochondrial DNA; MIDD, maternally inherited diabetes and deafness; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes; MERRF, myoclonic epilepsy with ragged red fibers; PCOS, polycystic ovary syndrome; DM, diabetes mellitus; ATP, adenosine triphosphate; AMPK, AMP-activated protein kinase; OCR, oxygen consumption rate; MMP, mitochondrial membrane potential; ROS, reactive oxygen species; IR, insulin resistance; MetS, metabolic syndrome; CDKAL1, Cdk5 regulatory associated protein 1-like 1; TRMT10A, tRNA methyltransferase 10 homologue A; GWASs, genome-wide association studies; ms^2t^6A, 2-methylthio-N6-threonyl carbamoyl adenosine; SNPs, single nucleotide polymorphisms; CIR, corrected insulin response; CpG, cytosine-phosphate-guanine; ER, endoplasmic reticulum; m^1G^9, methylate guanine at position 9; MTO1, mitochondrial optimization 1; GTPBP3, GTP-binding protein 3; τm^5U, 5-taurinemethyluridine; ATF4, activating transcription factor 4; EPRS, bifunctional aminoacyl-tRNA synthetase; GSIS, glucosestimulated insulin secretion; LARS2, leucyl-tRNA synthetase; DARS2, aspartyl-tRNA synthetase 2; TARS2, threonyl-tRNA synthetase 2; IARS2, isoleucyl-tRNA synthetase 2; BAT, brown adipose tissue; WARS2, tryptophanyl-tRNA synthetase 2; GSTA4, glutathione S-transferase A4; tsRNAs, tRNA-derived small RNAs; HFD, high-fat-diet; DNMT2, DNA methyltransferase-2; sncRNA, small non-coding RNA-mediated; tgCNV, tRNA gene copy number variation; Trsp, selenocysteine-tRNA; Nrf2, NF-E2-related factor 2; MT1E, metallothionein 1E; miRNA, microRNA; apoA-I, apolipoprotein A-I; rRNAs, ribosomal RNAs; hESCs, human ESCs; SOX4, sex-determining region Y-related high-mobility group box 4; STXBP6, syntaxin binding protein 6.

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https://doi.org/10.1016/j.metabol.2019.01.017
0026-0495/

1. Introduction

Diabetes mellitus (DM), a chronic metabolic noncommunicable disease, has attained epidemic proportions worldwide. It tends to result in multifarious complications such as cardiovascular and peripheral vascular disease, diabetic retinopathy, neuropathy and nephropathy [1]. Seriously, DM has become more prevalent across the world, which affected more than 425 million individuals in 2017 globally, and this number is projected to be almost 629 million by 2045 [2]. More than 90% of people with diagnosed DM have type 2 diabetes mellitus (T2DM) [3]. It is well documented that both genetic variations and environmental factors contributed to the risk of developing T2DM, and tremendous progress has been made in the understanding of its pathology over the past few decades [4]. Nevertheless, elaborate molecular mechanisms for the pathology of DM remain far from clear.

Transfer RNA (tRNA) is considered as a housekeeping product with its typical function as an adaptor molecule in protein translation machinery. Previously, it was a generally accepted fact that tRNA had little additional function. However, there was increasing evidence that the tRNA-associated dysregulation was related to many complex human diseases recently [5,6]. In some cases, mutations of mitochondrial-encoded tRNA (mt-tRNA) could cause severe respiratory chain defects and mitochondrial dysfunction, contributing to the development of DM [7]. Furthermore, the lack of vital tRNA modifications had pervasive and profound effects on protein synthesis, leading to diverse human disorders, including T2DM, cancer and neurological disorders [8]. It has been confirmed that tRNA post-transcriptional modification plays an important role in insulin secretion [9]. Notably, the aminoacyl-tRNA synthetases (aaRSs) might be involved not only in the aminoacylation of tRNAs, but also in various diseases [10]. This paper focuses on the different types of tRNA-associated dysregulation, such as tRNA mutations, tRNA modifications, tRNA aminoacylation, as well as tRNA derivatives, in the occurrence and development of DM (Fig. 1).

2. Biogenesis and structure of tRNAs

tRNAs, traditionally considered to participate in protein translation with fundamental function of carrying and transporting amino acids, are key for efficient and accurate protein synthesis. Actually, tRNAs belong to the most abundant small non-coding ribonucleic acids, constituting approximately 4–10% of all cellular RNAs [11]. The mature form of tRNAs has a length of 70–90 nucleotides and folds into a "clover" secondary structure and an L-shaped tertiary structure. Initial transcription product of RNA polymerase III (Pol III) is a typical precursor tRNA (pre-tRNA), containing 5′ leader and 3′ trailer extensions, which necessarily experiences a series of intricate biological steps to be converted to mature tRNA. For instance, the 5′ leader sequence can be removed by ribonuclease P (RNase P), the 3′ trailer can be cleaved by endonucleases and exonucleases such as ribonuclease E (RNase E), and the introns located between position 37 and 38 are removed through splicing reactions [12,13]. Furthermore, the sequence CCA, representing the site of aminoacylation in many organisms, is required to be added post-transcriptionally to the 3′ end with the help of enzymatic means after cleavage of the 3′ trailer [12]. Meanwhile, there are more than 90 multiple site-specific modifications in tRNAs [14], concentrating in two hotspots—the anticodon loop and the tRNA core region [15], which have an important role in biogenesis, correct structural folding and function. After maturation, each tRNA is charged with its cognate amino acid and pairs specifically with the messenger RNA (mRNA) by the interaction of codon-anticodon [16]. In addition, emerging evidence showed that under various stress conditions, pre-tRNAs or mature tRNAs were cleaved to produce tRNA derivatives that were involved in many specific physiological and pathological processes [17,18].

3. tRNA-associated dysregulation in DM

3.1. tRNA mutations in DM

It is widely known that virtually all eukaryotic cells contain mitochondria, whose own genome encodes 2 ribosomal RNAs (rRNAs), 22 tRNAs and 13 subunits of oxidative phosphorylation complexes [19]. Unlike chromosomal DNA, mitochondrial DNA (mtDNA) is inherited solely from the mother, which suggests that mitochondria carrying the pathogenic mutated mtDNA can accumulate during the course of organismal development. Notably, most of the pathogenic mutations of tRNA occurred in mt-tRNAs in the identified cases, and the reasonable explanation was the lack of efficient DNA repair systems in mtDNA [11]. Another explanation was likely that the gene encoding each cytoplasmic tRNA had multiple paralogs, while the mt-tRNA did not [20]. The cytoplasmic tRNA for each anticodon, except for a single gene for

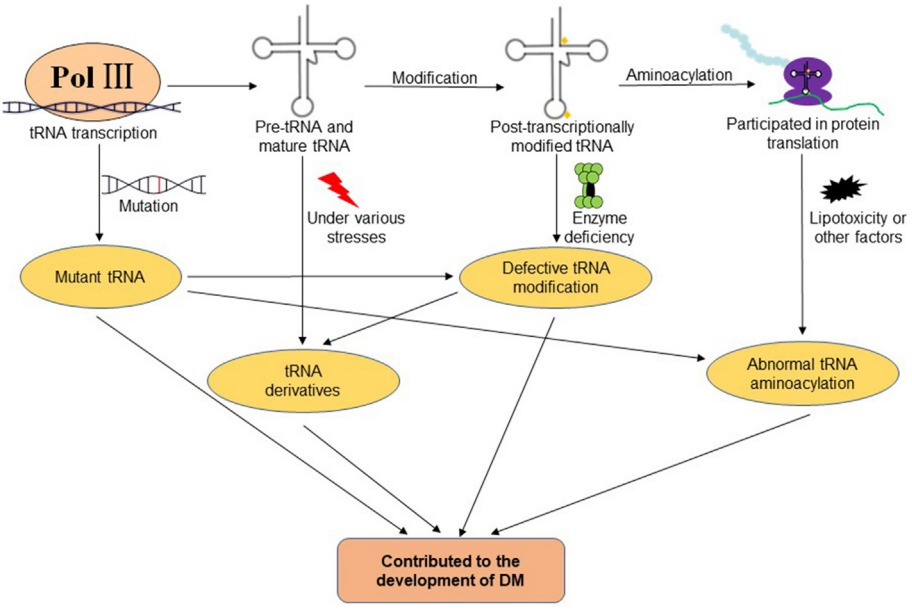

Fig. 1. Different types of tRNA-associated dysregulation in DM. The dysregulation including tRNA mutations, tRNA modifications, tRNA aminoacylation and tRNA derivatives all contributed to the development of DM. Abbreviations: tRNA, transfer RNA; DM, diabetes mellitus; Pol III, polymerase III; pre-tRNA, precursor tRNA.

$tRNA^{Tyr(ATA)}$, was encoded by up to 32 paralogous genes [21]. In this case, the relationships between genotypes and phenotypes were complex, owing to mitochondria-specific features such as mitotic segregation of maternally inherited mitochondria and heteroplasmy (wild-type and mutant mtDNA coexisted in the same mitochondrion or cell) [7]. Meanwhile, the expression of disease phenotype also depended on the threshold of mutation-affected mitochondria, which usually needed to exceed 85–90% in different tissues [11], implying the cell-specific aspects modulating the disease penetrance of mt-tRNA-based pathologies. To date, many tRNA mutations have been found to be closely related to the pathogenesis of DM. Since these mutations were also present in mtDNA, patients would exhibit syndromic forms of diabetes, such as maternally inherited diabetes and deafness (MIDD), mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged red fibers (MERRF) as well as polycystic ovary syndrome (PCOS) with DM.

Traditionally, both MIDD and MELAS are the most frequent maternally inherited mitochondrial disorders. Although their main clinical symptoms are different, they always have some same manifestations, such as stroke, dementia, epilepsy, myopathy, hearing impairment, DM, and short stature [22,23]. A common mt-$tRNA^{Leu(UUR)}$ A3243G mutation was first found in MELAS, and then this pathological mutation was identified as a pathogenetic factor for a family with maternally inherited T2DM and deafness [24,25]. A subsequent study demonstrated that MIDD, a distinct subtype of diabetes, was also associated with the mt-$tRNA^{Leu(UUR)}$ mutation [26]. Intriguingly, patients with this syndrome had no ketoacidosis and islet cell antibodies. Accumulated data revealed that the A3243G mutation could cause various impacts during the tRNA life cycle, such as the deficiency of aminoacylation of mutant tRNA [27] and hypomodification of its anticodon wobble position affecting recognition of UUG codon [28]. Recently, Lin et al. observed that the A3243G mutation caused deficiency of mitochondrial respiratory chain complexes I and IV, impaired cellular biogenesis under glucose deprivation, and decreased adenosine triphosphate (ATP) production [29]. The authors also found that the aberrant secondary cellular responses mediated by AMP-activated protein kinase (AMPK) signaling pathway might contribute to the development of the clinical phenotype. Novel evidence provided by Toompuu et al. suggested that dysfunctional tRNA caused by A3243G mutation could affect tRNA polyadenylation, which was associated with the PNPase/SUV3-mediated degradation [30].

In addition, there were many other mt-tRNA mutations that had an important role in DM. Crispim et al. supported that a T14709C mutation in mt-$tRNA^{Glu}$ could also cause syndromic forms of DM [31], which simultaneously reduced the activities of respiratory chain complexes I, III and IV [32]. Interestingly, McFarland et al. found that the homoplasmic T14709C mutation exhibited different phenotypes between individuals [33], suggesting that environmental or nuclear genetic factors made a crucial contribution to variation in phenotype. Recently, studies found that an mt-$tRNA^{Gly}$ T10003C mutation not only reduced the steady-state level of mt-$tRNA^{Gly}$, but also affected its secondary structure, leading to decreased oxygen consumption rate (OCR) and mitochondrial membrane potential (MMP), and increased production of reactive oxygen species (ROS) [34,35]. Strikingly, Ding et al. detected an mt-$tRNA^{Leu(UUR)}$ A3302G mutation in a Han Chinese family where the first and second generations exhibited T2DM, while the third generation manifested PCOS with insulin resistance (IR) [36]. They demonstrated that this mutation affected highly conserved base pairing and ultimately led to failure of tRNA metabolism., mt-$tRNA^{Leu(UUR)}$ C3275T, mt-$tRNA^{Gln}$ T4363C and mt-$tRNA^{Lys}$ A8343G, in a family with metabolic syndrome (MetS) and PCOS, where the second generation showed T2DM and MetS, Whereas one patient from the third generation manifested PCOS. [37]. These mutations caused a decrease in MMP, ATP production and mtDNA copy number, while a significant increase in ROS, which might explain the molecular mechanisms of the clinical phenotypes. In addition, lots of literature supported that other mutations, such as COI/mt-$tRNA^{Ser(UCN)}$ G7444A, mt-$tRNA^{Glu}$ A14692G, mt-$tRNA^{Leu(CUN)}$ T12317C, mt-$tRNA^{Lys}$ A8344G and mt-$tRNA^{Ser(UCN)}$ C7492T, were pathogenic and highly likely to be involved in the pathophysiology of DM [38–42]. In all, these mutations to some extent affected the synthesis of mitochondrial protein, causing severe respiratory chain defects and mitochondrial dysfunction, which finally contributed to the development of DM (Fig. 2).

3.2. tRNA modifications in DM

tRNA modifications and the enzymes catalyzing such modifications are involved in the pathogenesis of DM. In fact, various studies indicated that tRNA modifications could affect the stability, function as well as translation accuracy and efficiency of tRNA. It would be expected that defects in such modifications could have profound and generalized effects on protein synthesis and result in DM. Up to now, the tRNA modification defects associated with DM have been mainly related to Cdk5 regulatory associated protein 1-like 1 (CDKAL1), tRNA methyltransferase 10 homologue A (TRMT10A) and taurine-containing tRNA modifications (Fig. 3).

3.2.1. tRNA modifications catalyzed by CDKAL1

Accumulated genome-wide association studies (GWASs) have shown that CDKAL1 is one of the susceptibility genes for T2DM. It catalyzes the methylthiolation of N^6-threonyl carbamoyl adenosine (t^6A) at position 37 in $tRNA^{Lys(UUU)}$ to form 2-methylthio-N^6-threonyl carbamoyl adenosine (ms^2t^6A), which is necessary for the accurate translation of the only two Lys codons, AAA and AAG [43]. Meaningfully, different single nucleotide polymorphisms (SNPs) located within the CDKAL1 gene confer risk of T2DM to varying degrees. Previously, Steinthorsdottir et al. discovered the rs7756992 of CDKAL1 in individuals of European ancestry and Asian populations [44]. They believed that homozygous carriers of this risk allele had an estimated 20% lower corrected insulin response (CIR) than heterozygotes or non-carriers, suggesting that this variant could increase the risk of T2DM by reducing insulin secretion. Interestingly, the rs7756992 had a protective effect against retinopathy [45] and nephropathy [46] but increased cancer risk in patients with DM [47]. Another study by Groenewoud et al. supported that rs7754840 of CDKAL1 reduced the first phase of glucose-stimulated insulin secretion but had no effect on the second phase, and this variant was not associated with the insulin sensitivity [48]. Likewise, The CDKAL1 rs10946398 showed a significant association with decreased insulin secretion, but not with IR [49]. Moreover, other variants of CDKAL1, such as rs9465871, rs7766070, rs1012635, rs9460546, etc., were also confirmed to be related to T2DM [50–53]. Using 1000 Genomes Project data, we found that the variants in CDKAL1 were in differential linkage disequilibrium. Thus, these variants were not independent and had the same effect, which conferred risk of T2DM through reduced insulin secretion rather than IR (Table 1). Significantly, Zhou et al. found that the level of CDKAL1-v1, a specific splicing variant of CDKAL1, was reduced in individuals carrying T2DM-associated SNPs (rs10946398 and rs7756992) in CDKAL1 [54]. Meanwhile, CDKAL1-v1 was a short variant and a non-coding transcript, which regulated the CDKAL1 level by competitive binding to a CDKAL1-targeting microRNA (miRNA). Thus, the authors believed that the risk SNPs in CDKAL1 could reduce CDKAL1-v1 level, which in turn increased miRNA-mediated suppression of CDKAL1. However, taking into account a moderately linked SNP of rs9366357 in multiple regression models, Locke et al. demonstrated that the relation between rs7756992 and CDKAL1-v1 was abolished or substantially reduced [55]. Furthermore, by introduction or removal of a cytosine-phosphate-guanine (CpG) site, certain T2DM-associated SNPs, including rs7754840 in CDKAL1, could influence gene function through differential DNA methylation [56]. To some extent, these studies explained the pathogenesis of T2DM in individuals with risk CDKAL1 SNPs and provided ideas for studying the relationship between CDKAL1 SNPs and CDKAL1 enzyme.

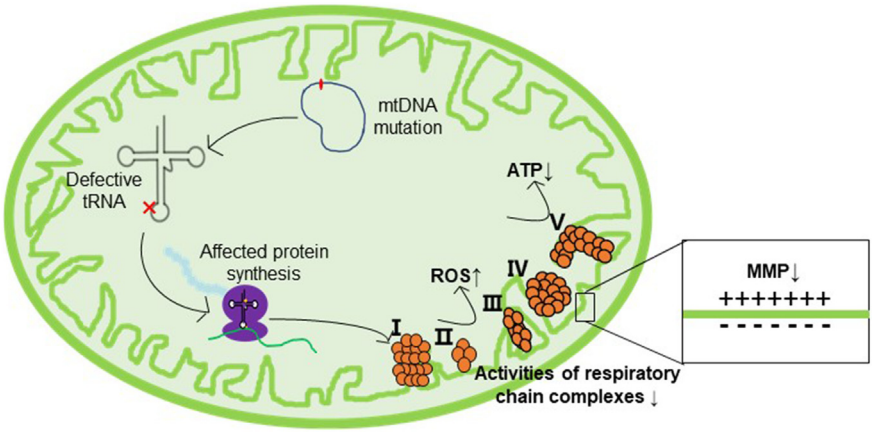

Fig. 2. Molecular mechanisms of DM caused by mt-tRNA mutations. Defective tRNA affected protein synthesis, which ultimately resulted in severe respiratory chain deficiency and mitochondrial dysfunction. Abbreviations: mt-tRNA, mitochondrial-encoded tRNA; mtDNA, mitochondrial DNA; MMP, mitochondrial membrane potential; ROS, reactive oxygen species; ATP, adenosine triphosphate.

Indeed, increasing evidence showed the relationship between T2DM and molecular function of CDKAL1, providing new conceptual frameworks that improved our mechanistic understanding of this disease. A systematic study by Wei et al. discovered that in mice with pancreatic beta cell-specific knockdown of CDKAL1, the pancreatic islet was hypertrophied, and glucose-stimulated insulin secretion was reduced, resulting in glucose intolerance [43]. Meanwhile, the authors observed that CDKAL1 deficiency might affect proinsulin translation, causing the impairment of the processing of proinsulin, which in turn led to endoplasmic reticulum (ER) stress followed by beta cell dysfunction. Based on their findings, the lysine content of proinsulin in mutant cells was lower than wild-type cells, and the levels of C-peptide (a by-product of proinsulin processing) were lower in the islets and serum in the mutant mice. Since one of the two lysines in human proinsulin was located at the cleavage site between the C-peptide and the A chain, the authors believed that the misreading of this Lys codon in proinsulin would affect the cleavage, thus disturbing the processing of proinsulin. Xie et al. established a method to directly measure the level of ms^2-modification in $tRNA^{Lys(UUU)}$ in human peripheral blood samples, as an indicator of CDKAL1 enzyme activity [57]. Through this method, they demonstrated that the level of ms^2-modification was decreased in individuals with risk allele of CDKAL1 (rs7754840). Additionally, Brambillasca et al. observed that the expression of secretory granule proteins, in addition to proinsulin and insulin, were reduced in CDKAL1-silenced cells, which might affect glucose-stimulated insulin secretion [58]. Another study found that mitochondrial function in adipose tissue was affected in adipose-specific CDKAL1 KO mice [59]. Although glucose tolerance and insulin sensitivity were unchanged in the mice, it remains to be tested whether this mechanism is present in pancreatic islets or in other metabolically relevant tissues.

3.2.2. tRNA modifications catalyzed by TRMT10A

TRMT10A is a mammalian ortholog of yeast TRM10 that has tRNA methyltransferase activity, which enables S-adenosylmethionine to specifically methylate guanine at position 9 (m^1G^9) in several tRNAs [60]. Recently, studies found that TRMT10A was associated with a syndrome of microcephaly, intellectual disability, short stature and young onset diabetes. Moreover, TRMT10A was found in the nucleus, and it was ubiquitously present but more abundant in human brain and pancreatic islets [61], which was consistent with the main clinical

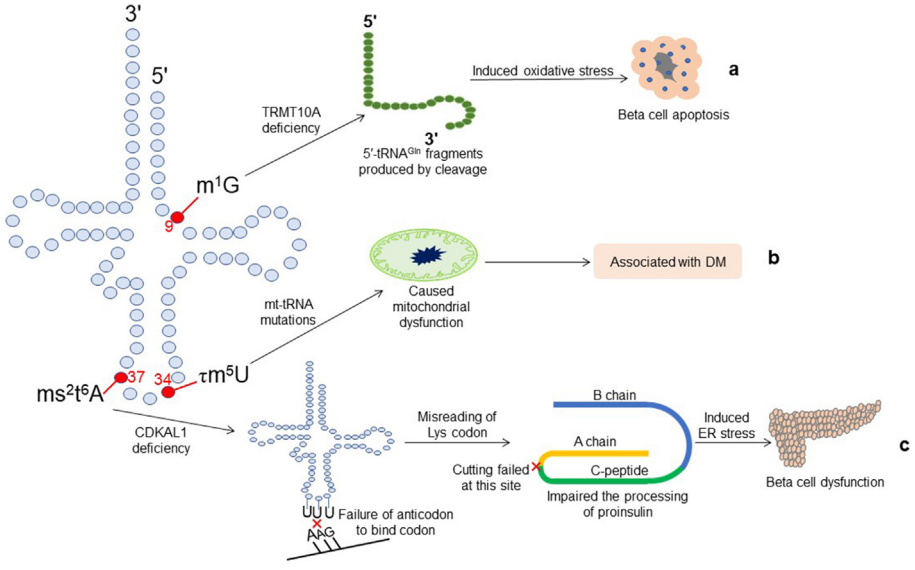

Fig. 3. Molecular mechanisms of DM caused by tRNA modification defects. a TRMT10A deficiency affected m^1-modification at position 9 and mediated the oxidative stress and beta cell apoptosis. b mt-tRNA mutations affected τm^5-modification at position 34, causing mitochondrial dysfunction. c CDKAL1 deficiency affected ms^2-modification at position 37, and then led to the misreading of Lys codon in proinsulin, which induced ER stress and beta cell dysfunction. Abbreviations: tRNA, transfer RNA; DM, diabetes mellitus; TRMT10A, tRNA methyltransferase 10 homologue A; CDKAL1, Cdk5 regulatory associated protein 1-like 1; ER, endoplasmic reticulum.

Table 1
T2DM associated variants within CDKAL1 gene.

SNP	Subject population	Position	SNP location	Effect	References
rs7756992	European ancestry and Hong Kong of Han Chinese ancestry	20679478	Intron	Conferred risk of T2DM through reduced insulin secretion rather than insulin resistance	[44]
rs7754840	Netherlands and Germany	20661019	Intron		[48]
rs10946398	Xuzhou, China	20660803	Intron		[49]
rs9465871	Korea	20717024	Intron		[50]
rs7766070	Lebanon	20686342	Intron		[51]
rs1012635	European descent	20675064	Intron		[52]
rs9460546	Korea	20663401	Intron		[53]
rs9366357	North European descent	20599397	Intron		[55]

symptoms of patients. The new findings of TRMT10A indicated a broader association of tRNA methyltransferases in the pathogenesis of DM.

Igoillo-Esteve et al. discovered a causal nonsense mutation in TRMT10A, which changed an arginine codon into a stop at position 127 [61]. In this case, TRMT10A mRNA and protein were absent in lymphoblasts from the mutation individuals; meanwhile, TRMT10A silencing had no effect on insulin secretion, that is, it did not impair beta cell function, but resulted in stress-induced apoptosis. This apoptosis indicated that TRMT10A might be involved in protective stress responses. Analogously, no mRNA and protein of TRMT10A was detected in a 17-year-old female with a homozygous contiguous gene deletion involving TRMT10A [62]. The patient had several characteristics typical to type 1 diabetes mellitus, such as ketoacidosis and islet cell autoantibodies. However, she had a good glycemic control 22 months after onset of diabetes and maintained relatively normal glucose levels over 3 days without insulin treatment. In particular, Gillis et al. found that patients with a homozygous p.Gly206Arg mutation in TRMT10A were initially presented with ketotic and non-ketotic hypoglycaemic events, and subsequently converted to DM during puberty [63]. Further study showed that wild-type and variant enzymes had the same affinity for $tRNA^{Gly}_{(GCC)}$, thus the authors believed that the decrease in methyltransferase activity of the mutant enzyme might be due to the loss of binding ability to S-adenosylmethionine. Moreover, a homozygous nonsense p.Glu27Stop mutation in TRMT10A also played a key role in the pathological process of the syndrome [64]. Narayanan et al. found that two pediatric patients (a 12-year-old girl and a 10-year-old boy) with compound heterozygotes nonsense mutations, p.Arg93Stop and p.Arg133Stop in TRMT10A, had no phenotype of DM [65]. We suspect that the stress-induced apoptosis of beta cells will become increasingly serious with age, eventually leading to serious consequences of DM. Usually, tRNAs were stable in vivo, but defects in tRNA modifications might lead to their degradation or fragmentation by endonucleases [66]. Cosentino et al. demonstrated that TRMT10A deficiency, including p.Arg127Stop and p.Glu27Stop mutations, caused tRNA guanosine 9 hypomethylation, which in turn led to $tRNA^{Gln}$ fragmentation [67]. Interestingly, 5- but not 3-tRNA fragments accumulated during the process, suggesting that m^1G^9 prevented $tRNA^{Gln}$ cleavage. The authors also found that the 5′-$tRNA^{Gln}$ fragments mediated TRMT10A deficiency-induced oxidative stress and beta cell apoptosis, revealing a hitherto unknown mechanism of pancreatic cell death. Altogether, the pathogenic mutations in TRMT10A gene produced a syndrome associated with DM, but it was required to unequivocally ascertain the full repertoire of tRNA modifications catalyzed by TRMT10A.

3.2.3. Taurine-containing tRNA modifications

Beyond that, studies indicated that taurine, a sulfur-containing amino acid, made a significant contribution to the developing of DM. Merino et al. identified the nitrogen metabolism pathway and its components, such as taurine, glycine and phenylalanine, which were correlated to increased risk for T2DM among normoglycaemic individuals [68]. From another perspective, taurine had a good therapeutic potential for DM and its related complications [69]. Earlier study by Suzuki et al. observed that there were two novel taurine-containing modified uridines in mt-tRNAs, indicating that taurine was involved in the mt-tRNA modifications [70]. Recently, Fakruddin et al. suggested that the deficiency of mitochondrial optimization 1 (MTO1), an enzyme that catalyzed taurine-containing modification of mt-tRNA, severely impaired mitochondrial translation and respiratory activity, resulting in abnormal mitochondrial morphology [71]. They also revealed that the intrinsic protein homeostasis network between the mitochondria and cytosol played a vital role in the treatment of mitochondrial diseases. Furthermore, GTP-binding protein 3 (GTPBP3) was another enzyme that catalyzed taurine-containing modification, and the GTPBP3 knockout cells also showed mitochondrial dysfunction [72]. Strikingly, the authors found that 5-taurinemethyluridine (τm^5U) was down-regulated and the taurine moiety of τm^5U was replaced with glycine in taurine-depleted cells. Studies have confirmed that mt-tRNA mutations associated with DM, such as A3243G, could lead to a lack of taurine wobble base-modification at position 34 in the mutant tRNAs [73]. Therefore, we suggest that the defects of taurine-containing modification lead to mitochondrial dysfunction, which may result in both impaired insulin secretion and IR, but more clinical and experimental evidence is urgently needed.

3.3. tRNA aminoacylation in DM

tRNA aminoacylation, the linkage of a single amino acid to its homologous tRNA isoacceptor by aaRS, is the first step in genetic translation [74]. Many literatures suggested that aaRSs had a direct functional importance, as well as possess biomarker potential, for T2DM. Krokowski et al. demonstrated that activating transcription factor 4 (ATF4) could coordinately induce the expression of amino acid transporter and aaRS genes in beta cells during ER stress, suggesting that the increased levels of amino acid transporters could serve as the early diagnostic biomarkers for the development of DM [75]. Similarly, Zhang et al. found that certain metabolic pathways, such as aminoacyl-tRNA biosynthesis and taurine and hypotaurine metabolism, were involved in the development of early T2DM. [76]. Chu et al. found that the level of bifunctional aminoacyl-tRNA synthetase (EPRS) was down-regulated in patients with T2DM, which might indicate that low expression of EPRS was detrimental to the protection against the inflammatory response and aggravated IR and beta cell dysfunction [77]. Moreover, under lipotoxicity, changes in histone modifications, mRNA levels, and metabolite profiles in clonal INS-1 832/13 beta cells, such as a decrease in the aminoacyl-tRNA synthesis pathway, might affect glucose responsiveness and insulin secretion [78]. Meaningfully, by studying the chronological sequence between different cell events in human islets exposed to fatty acid palmitate, Sargsyan et al. clearly illustrated the early biological changes in T2DM [79]. They believed that at early time points, protective events, including up-regulation of metallothioneins, aaRSs and fatty acid-metabolising proteins, dominated over deleterious events, which contributed to enhanced glucosestimulated insulin secretion (GSIS). After prolonged exposure to palmitate, deleterious events, including inhibition of fatty acid detoxification enzymes, had a greater impact, leading to impaired GSIS.

Furthermore, leucyl-tRNA synthetase (LARS2) was shown to be a potentially susceptible gene for T2DM [80]. Reiling et al. analyzed 58 tagging SNPs in 13 genes involved in mitochondrial function for association with T2DM susceptibility [81]. Although the authors ruled out the major effects of common variants in selected genes, including three aaRS genes such as aspartyl-tRNA synthetase 2 (DARS2), threonyl-tRNA synthetase 2 (TARS2) and isoleucyl-tRNA synthetase 2 (IARS2), deep sequencing and analysis of rare variants were needed to gain a deeper understanding of the role of these genes in the pathogenesis of T2DM. Activation of brown adipose tissue (BAT) could correct hyperlipidemia and improve deleterious effects of IR, suggesting that BAT played an important role in obesity and elevated blood lipids [82]. New evidence showed that tryptophanyl-tRNA synthetase 2 (WARS2) could regulate BAT function, thereby improving lipid and glucose metabolism [83]. In adipose tissue, the effects of protein carbonylation were associated with increased oxidative stress and involved in the pathophysiology of IR and its progression towards T2DM [84,85]. The silence of glutathione S-transferase A4 (GSTA4) increased carbonylation of several mitochondrial proteins, including the phosphate carrier protein, NADH dehydrogenase 1α subcomplexes 2 and 3, translocase of inner mitochondrial membrane 50, and valyl-tRNA synthetase, which was associated with cytokine-dependent mitochondrial dysfunction and IR in adipocyte [86]. Apolipoprotein A-I (apoA-I), a major component of high-density lipoprotein, could increase insulin secretion and production in pancreatic beta cells [87]. A metabolomics research demonstrated that aminoacyl-tRNA biosynthesis was dysregulated in apoA-I knockout mice, which might be helpful for further understanding the role of high-density lipoprotein in T2DM [88]. It was noteworthy that Qijian mixture, a new traditional Chinese medicine, was mainly used to treat T2DM [89]. The study found that this drug could affect the aminoacyl-tRNA biosynthesis metabolism, which might be one of the mechanisms to effectively alleviate T2DM.

3.4. tRNA derivatives and other tRNA dysregulation in DM

tRNA derivatives were generated by cleavage of the pre-tRNAs or mature tRNAs under various environmental stresses. It has been mentioned above that the 5'-tRNA^{Gln} fragments could mediate TRMT10A deficiency-induced oxidative stress and beta cell apoptosis [67]. Recently, studies found that sperm tRNA derivatives represented a type of paternal epigenetic factor, which might mediate intergenerational inheritance of diet-induced metabolic diseases [90,91]. In their experiments, sperm tRNA-derived small RNAs (tsRNAs), from a paternal high-fat-diet (HFD) mouse, might alter gene expression of metabolic pathways in early embryos and islets of F1 offspring, ultimately leading to the metabolic disorder. Of note, Zhang et al. found that the deletion of tRNA methyltransferase DNA methyltransferase-2 (DNMT2) could eliminate sperm small non-coding RNA-mediated (sncRNA-mediated) transmission of HFD-induced metabolic disorders [92]. The possible reason was that DNMT2 deletion prevented HFD-induced m^2G and m^5C RNA modifications and altered sperm sncRNA expression profile. These novel literatures motivated people to look for epigenetic factors behind metabolic diseases such as T2DM and obesity.

Through high-throughput quantitative approach, Yan et al. found that some modifications of small RNA in DM mouse liver were significantly changed, for example, the levels of Gm and m^5Cm in tRNA were decreased and increased, respectively, when compared with those in normal mouse liver, indicating that modifications of small RNA were associated with DM [93]. What's more, Iben et al. examined the tRNA gene copy number variation (tgCNV) in six individuals, suggesting that the difference might lead to phenotypic differences between individuals [94]. At the same time, combined with genetic diversity and previous GWAS, the authors concluded that the proportion of tRNA^{Lys} isoacceptors could contribute to the development of T2DM. Overexpression of an i^6A^- mutant selenocysteine-tRNA (Trsp) could reduce synthesis of these selenoproteins in mice, which promoted glucose intolerance and presented a T2DM-like phenotype [95]. Analogously, Yagishita et al. established two conditional Trsp-KO mouse lines, Trsp-^{RIP}KO mice and Trsp^{Ins1}KO mice, to study the relationship between hypothalamic function and DM [96]. They observed that the Trsp^{RIP}KO mice showed deletion of Trsp in both hypothalamic cells and pancreatic beta cells, leading to serious IR and leptin resistance, while the Trsp-^{Ins1}KO mice expressing Cre specifically in pancreatic beta cells, but not in the hypothalamus, did not display these symptoms. These results suggested that endogenously produced oxidative stress in the hypothalamus could lead to T2DM by triggering IR. Meanwhile, they revealed that enhancement of NF-E2-related factor 2 (Nrf2) could inhibit hypothalamic oxidative stress and improve insulin and leptin resistance, suggesting that Nrf2 regulation might be a therapeutic approach to T2DM.

4. Conclusion and future perspective

Indeed, a growing series of evidence has identified that tRNA-associated dysregulation, such as tRNA mutations, tRNA modifications, tRNA aminoacylation and tRNA derivatives, is of tremendous value and potential in DM progression (Table 2). Noteworthily, studies of tRNA derivative are relatively rare and may become a hot spot in the pathophysiology of DM in the future.

Meaningfully, studies found that urinary epithelial cells were the preferred non-invasive available tissue to test the A3243G mutation, and it provided a basis for the detection of DM with mt-tRNA mutations [97]. Karicheva et al. discovered that the mitochondrial targeting of recombinant tRNAs bearing the identity elements for human mitochondrial leucyl-tRNA synthetase could correct the consequences of A3243G mutation, thus extending the potential therapeutic strategy of mitochondrial disorders [98]. To assess the predictive power of a genetic risk score for T2DM incidence, researchers analyzed eleven susceptibility SNPs identified through GWASs and replicated in Japanese populations [99]. The results suggested that it was promising to add a genetic risk score to improve the prediction of T2DM. Zeng et al. created isogenic human ESCs (hESCs) with mutations of T2DM susceptibility genes and found that the CDKAL1 mutation caused impaired glucose secretion in pancreatic beta-like cells differentiated from these lines [100]. At the same time, the authors identified a candidate drug through high-content chemical screen and demonstrated that this drug could rescue CDKAL1-specific defects by inhibiting the FOS/JUN pathway, which provided a new idea for the precision treatment of DM. Studies have confirmed that the sex-determining region Y-related high-mobility group box 4 (SOX4) is associated with the increased T2DM risk linked to an intronic SNP in CDKAL1 [101,102]. The increased expression of SOX4 reduced insulin secretion and increased diabetes risk by upregulation of syntaxin binding protein 6 (STXBP6) that locked the fusion pore in a partially expanded state and thereby prevented the delivery of insulin into the extracellular space. These interesting findings suggested that interventions promoting fusion pore expansion might act as a new treatment method of DM. Lately, Takahashi et al. found that reactive sulfur species could regulate tRNA ms^2-modification and promote insulin secretion [103]. The forced expression of metallothionein 1E (MT1E) could save the glycolipotoxicity of CDKAL1 mutant cells and pancreatic beta cell dysfunction [104]. These are early days to think of reliable approaches to develop the diagnosis and treatment of DM, so more studies are required.

Still, several questions may be addressed through future studies. Up to now, we have described the physiological link between DM and certain tRNA modifications, but little is known about the molecular mechanisms that trigger hypomodified tRNAs and affect protein translation. It is known that tRNA modifications play an important role in the fidelity and efficiency of mRNA translation. In T2DM, due to defects in CDKAL1, the synthetic proinsulin lacks lysine, leading to misfolding of proinsulin and preventing proteolytic processing, but it is uncertain what amino acid (if any) replaces lysine. Hence, it is necessary to find direct evidence that protein misfolding affects insulin production.

Table 2
tRNA-associated dysregulation in DM.

Types of tRNA-associated dysregulation	Dysregulation status	Effects	Mechanisms	References
tRNA mutations	mt-tRNA$^{Leu(UUR)}$ A3243G mutation	The mutation caused MIDD, and the patient had no ketoacidosis and islet cell antibodies	Caused respiratory chain deficiency and mitochondrial dysfunction	[25–30]
	mt-tRNA^{Glu} T14709C mutation	Caused syndromic forms of DM, including MIDD, MELAS and MERRF	Caused respiratory chain deficiency and mitochondrial dysfunction	[31–33]
	mt-tRNA^{Gly} T10003C mutation	Caused MIDD	Caused respiratory chain deficiency and mitochondrial dysfunction	[34,35]
	mt-tRNA$^{Leu(UUR)}$ A3302G mutation	The mutation was related to PCOS with IR, and the first and second generations showed T2DM, while the third showed PCOS with IR	Caused disrupted base pairing and lower copy number	[36]
	mt-tRNA$^{Leu(UUR)}$ C3275T, mt-tRNA^{Gln} T4363C and mt-tRNA^{Lys} A8343G mutations	Caused MetS and T2DM in the second generation and PCOS in the third	Caused respiratory chain deficiency and mitochondrial dysfunction	[37]
	COI/mt-tRNA$^{Ser(UCN)}$ G7444A, mt-tRNA^{Glu} A14692G, mt-tRNA$^{Leu(CUN)}$ T12317C, mt-tRNA^{Lys} A8344G and mt-tRNA$^{Ser(UCN)}$ C7492T mutations	Caused syndromic forms of DM	Caused respiratory chain deficiency and mitochondrial dysfunction	[38–42]
	Mitochondrial targeting of recombinant tRNAs	Corrected the consequences of A3243G mutation	Rescued the respiration	[98]
tRNA modifications	Knockdown of CDKAL1	Caused hypertrophied pancreatic islet and reduced insulin secretion	Impaired the processing of proinsulin	[43]
	p.Arg127Stop mutation in TRMT10A	Caused a syndrome of young onset diabetes, short stature and microcephaly with intellectual disability	Induced oxidative stress and beta cell apoptosis	[61,67]
	Homozygous deletion of TRMT10A	Associated with a syndrome of growth failure, intellectual disability, delayed puberty, as well as DM, and exhibited ketoacidosis and islet cell autoantibodies	Unknown	[62]
	p.Gly206Arg mutation in TRMT10A	Associated with a syndrome of microcephaly, intellectual disability, short stature, delayed puberty and disturbed glucose metabolism	Decreased the methyltransferase activity of the mutant enzyme	[63]
	p.Glu27Stop mutation in TRMT10A	Caused young adult-onset diabetes with intellectual disability, microcephaly and epilepsy	Induced oxidative stress and beta cell apoptosis	[64,67]
	Lack of taurine-containing modification	Associated with syndromic forms of DM	Caused by mt-tRNA mutations	[28,73]
	Reactive sulfur species	Promoted insulin secretion	Regulated tRNA ms^2-modification	[103]
	Forced expression of MT1E	Saved the glycolipotoxicity of CDKAL1 mutant cells and beta cell dysfunction	Relieved ER stress	[104]
tRNA aminoacylation	Deficiency of aminoacylation	Associated with syndromic forms of DM	Caused by mt-tRNA$^{Leu(UUR)}$ A3243G mutation	[27]
	The levels of aaRSs	Served as biomarkers for T2DM	Unknown	[75–79]
	H324Q variant in LARS2	Served as susceptible gene for T2DM	Unknown	[80]
	Transgenic rescue of WARS2 variant	Improved lipid and glucose metabolism	Regulated BAT function	[83]
	Increased carbonylation of valyl-tRNA synthetase	Associated with mitochondrial dysfunction and IR in adipocyte	Silence of GSTA4	[86]
	Dysregulated aminoacyl-tRNA biosynthesis	Associated with the pathogenesis T2DM	apoA-I knockout	[88]
tRNA derivatives	5′-tRNA^{Gln} fragments	Caused oxidative stress and beta cell apoptosis	Caused by TRMT10A deficiency	[67]
	Sperm tsRNA from a paternal HFD mouse	Caused metabolic disorder of F1 offspring	Altered gene expression of metabolic pathways in islets	[90,91]
	Deletion of tRNA methyltransferase DNMT2	Eliminated sperm sncRNA-mediated metabolic disorders	Prevented RNA modifications and altered sperm sncRNA expression profile	[92]
Other tRNA dysregulation	Changes in small tRNA modification levels	Showed the correlation of small RNA modifications with DM	Unknown	[93]
	The proportion of tRNA^{Lys} isoacceptors	Contributed to the development of T2DM	Unknown	[94]
	The overexpression of an i^6A^- mutant Trsp	Promoted glucose intolerance and T2DM-like phenotype	Reduced synthesis of selenoproteins	[95]
	The knockout of Trsp	Caused T2DM by triggering IR	Caused oxidative stress in the hypothalamus	[96]

Moreover, the molecular mechanisms linking genotype and phenotype remain unclear. For DM, heterogeneity is more prevalent because all known pathogenic tRNA mutations are present in mtDNA. Mutations in different gene loci may have the same phenotypic effect and, conversely, the same pathogenic variant may cause different clinical phenotypes. This complex relationship makes mitochondrial disease a particularly challenging area of medicine. Nonetheless, it is important to decipher the biochemical and molecular mechanisms linking any tRNA mutation to the corresponding pathological status. At the same time, in-depth research on nuclear genes as well as the cross-talk between mtDNA and nuclear genes can also provide more information on the genetic basis of DM.

In summary, tRNA-associated dysregulation provides new ideas for the pathogenesis and treatment of DM. Taking the role of tRNA-associated dysregulation in DM into account may broaden the spectra of novel therapy for metabolic disease in the future.

Authors' contributions

ZZ, BS and DSY contributed towards the concept and manuscript writing; WRJ and SQH revised and supervised overall project. All authors read and approved the final version of manuscript.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgements

The authors wish to acknowledge Xiaochuan Zhang from the First Affiliated Hospital of Zhengzhou University, China for editing of English grammar and syntax of the manuscript.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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