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Review

Diabetes and diabetic associative diseases: An overview of epigenetic regulations of TUG1

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A R T I C L E I N F O

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A B S T R A C T

The epigenetic regulation of lncRNA TUG1 has garnered significant attention in the context of diabetes and its associated disorders. TUG1′s multifaceted roles in gene expression modulation, and cellular differentiation, and it plays a major role in the growth of diabetes and the issues that are related to it due to pathological processes. In diabetes, aberrant epigenetic modifications can lead to dysregulation of TUG1 expression, contributing to disrupted insulin signaling, impaired glucose metabolism, and beta-cell dysfunction. Moreover, it has been reported that TUG1 contributes to the development of problems linked to diabetes, such as nephropathy, retinopathy, and cardiovascular complications, through epigenetically mediated mechanisms. Understanding the epigenetic regulations of TUG1 offers novel insights into the primary molecular mechanisms of diabetes and provides a possible path for healing interventions. Targeting epigenetic modifications associated with TUG1 holds promise for restoring proper gene expression patterns, ameliorating insulin sensitivity, and mitigating the inception and development of diabetic associative diseases. This review highlights the intricate epigenetic landscape that governs TUG1 expression in diabetes, encompassing DNA methylation and alterations in histone structure, as well as microRNA interactions.

1. Introduction

In recent years, the investigation of epigenetic mechanisms has unveiled novel layers of complexity in the origin and advancement of diverse conditions, among them diabetes and its linked complications, mechanisms have a significant role (Abdelaleem et al., 2021). Diabetes mellitus, distinguished by persistent high blood sugar due to compromised insulin function or secretion, poses a worldwide health challenge with increasing occurrence (Chen et al., 2021, Bhat et al., 2023a, 2023b, 2023c). The complex interaction between genetic susceptibility and external elements contributes to the emergence of diabetes and its wide array of difficulties, spanning from cardiovascular ailments and kidney issues to retinal and nerve-related problems (Dieter et al., 2023a, 2023b). Among the emerging players in this multifaceted landscape, lncRNAs have garnered significant consideration for the roles they play in regulation within gene expression, particularly the lncRNA TUG1 (taurine-upregulated gene 1), and their potential as epigenetic modulators in diabetes and diabetic associative diseases. TUG1, initially recognized as a transcript increased by taurine treatment in retinal cells, has been implicated in diverse cellular processes through its involvement in epigenetic regulation (Duan et al., 2017, Dieter et al., 2023a, 2023b). Although initially linked to retinal development and function, subsequent studies have revealed its broader implications in various biological contexts, including cancer, neurodegeneration, and, more recently, diabetes (Bhat et al., 2022a, 2022b, 2022c, Esawy et al., 2022a, 2022b). The regulatory functions of TUG1 are mediated by its interactions with DNA, RNA, and proteins, suggesting its pivotal role in modulating gene expression networks. Epigenetic changes, such as those involved in the onset of diabetes and its sequelae (Fang et al., 2022). Regulations are critical determinants of Patterns of gene expression and cellular characteristics. In the context of diabetes, epigenetic alterations play a pivotal role in contributing to the underlying mechanisms of both type 1 and 2 diabetes, as well as their associated complications (Fisher, 2021). These modifications can affect the activation of essential genes implicated in insulin secretion, the metabolic processing of glucose, inflammation, and oxidative stress, thereby influencing disease progression (Fu et al., 2020a, 2020b). TUG1 emerges as a potential epigenetic player in the intricate molecular landscape of diabetes and its associative diseases. Recent studies have highlighted its dysregulation in pancreatic β-cells, liver, adipose, tissue, and cells that line the blood vessels, within the framework of diabetes (Kumariya et al., 2021, Heydari et al., 2023, Thapa et al., 2023a, 2023b, 2023c). TUG1′s

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involvement in key dietary processes, such as glucose homeostasis, insulin signaling, and lipid metabolism, suggests its broader implications in the development and management of diabetes (Lai et al., 2022). Additionally, the aberrant epigenetic modifications associated with TUG1 in diabetes may contribute to the onset, in the context of complications arising from diabetes, such as nephropathy, retinopathy, and cardiovascular diseases. Understanding the epigenetic regulations of TUG1 in diabetes and its associative diseases holds great promise for unveiling novel therapeutic avenues (Lei et al., 2022). The unique feature of epigenetic modifications being potentially reversible makes them attractive targets for therapeutic interventions (Lei et al., 2018). Strategies aimed at modulating TUG1 expression levels or its interacting partners could potentially restore normal gene expression patterns, ameliorate insulin resistance, enhance insulin secretion, and mitigate the development of diabetic complications (Li et al., 2023, Thapa et al., 2023a, 2023b, 2023c). However, significant challenges remain, including the need to decipher the intricate mechanisms underlying TUG1-mediated epigenetic regulations, identify specific target genes, and develop precise therapeutic interventions with minimal off-target effects (Li et al., 2021a, 2021b, 2021c). This review reveals the critical role of mechanisms like lncRNA TUG1 in the development of diabetes and its complications, emphasizing the complex interplay of genetic and environmental factors in disease emergence and progression. TUG1′s involvement in regulating gene expression and its potential as an epigenetic modulator opens new avenues for understanding diabetes pathogenesis and developing targeted therapies, despite challenges in unraveling its specific mechanisms and therapeutic applications (see Figs. 1–4).

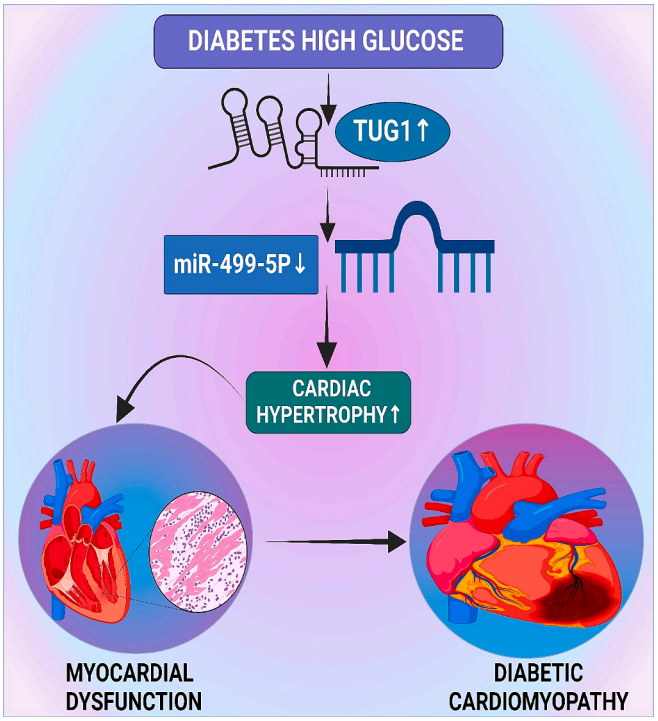

Fig. 2. Schematic diagram depicting the role of lncRNAs with dysregulated function in the aetiology of DCM.

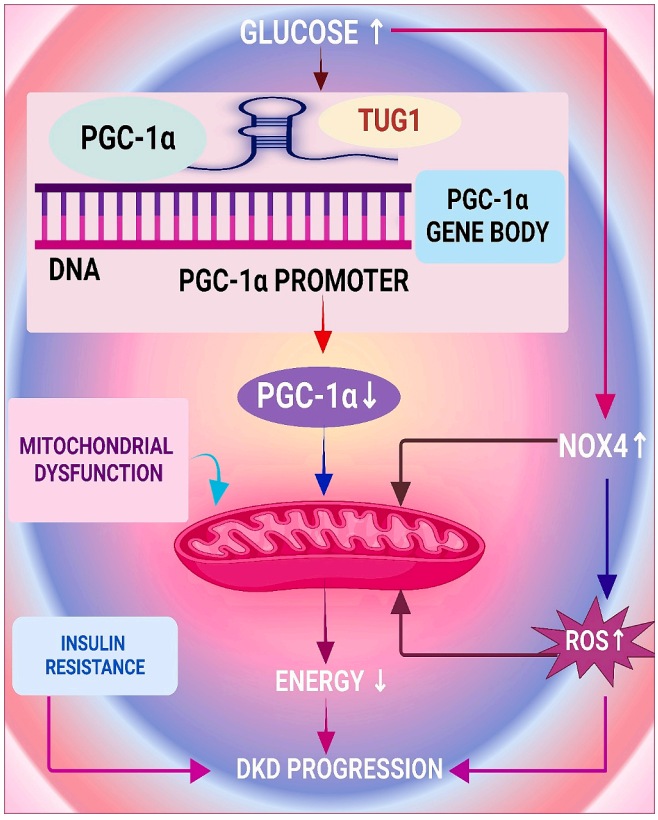

Fig. 1. Schematic representation shows that Podocytes affected by diabetes had lower levels of Tug1 expression. Epigenetic targeting by Tug1 controls PGC-1 expression. Alterations in mitochondrial structure and function occur when PGC-1 levels are lowered. The breakdown of mitochondrial activity leads to a lack of energy, a rise in reactive oxygen species (ROS), and, eventually, diabetic kidney disease. NOX4, NADPH oxidase 4; DKD, diabetic kidney disease.

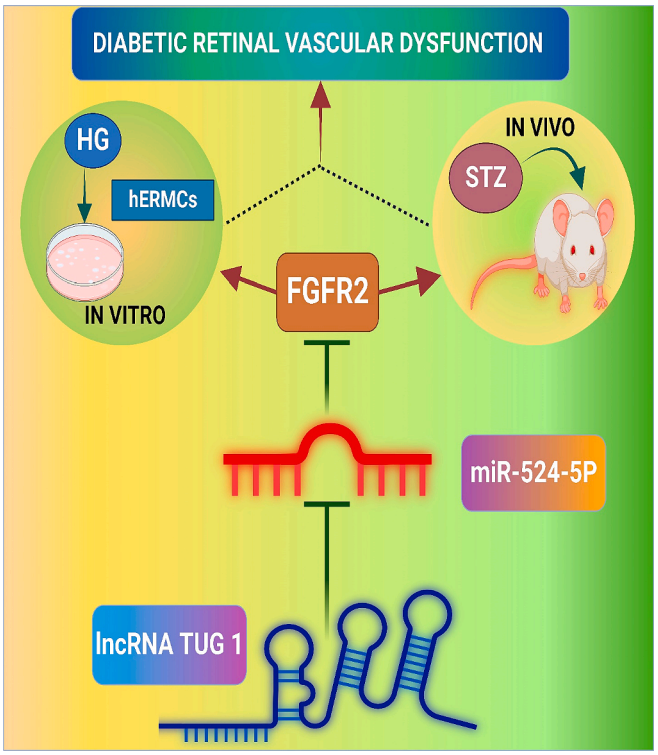

Fig. 3. Schematic representation shows, TUG1: A Sponge for miR-524-5p, Counteracting Hyperglycemia. miR-524-5p Targets FGFR2, Upregulated in High Glucose. TUG1 Suppression Enhances Diabetic Retinal Vascular Function.

2. TUG1 and diabetes

lncRNA TUG1 is linked to diabetes via influencing important biological functions such as insulin resistance, β-cell dysfunction, and

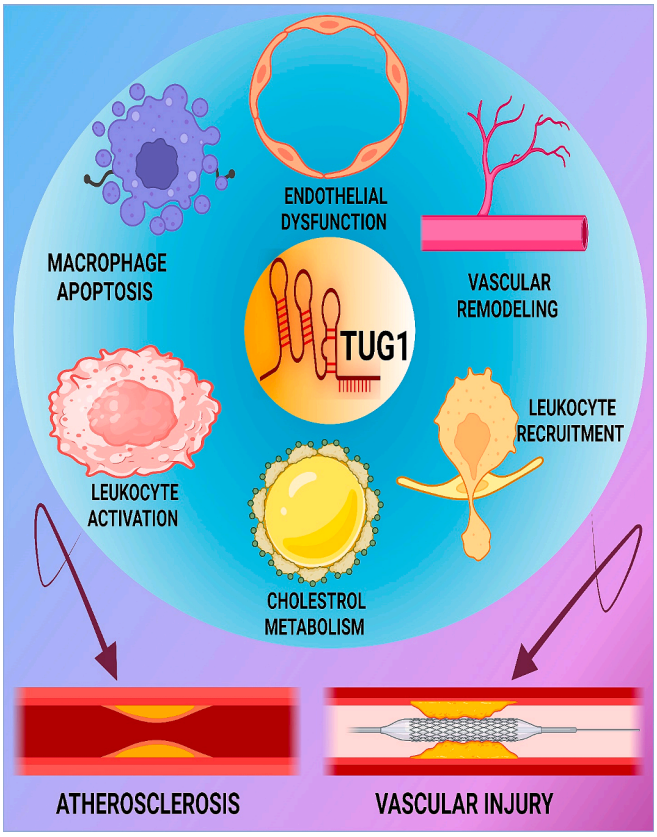

Fig. 4. Schematic representation shows the Role of lncRNAs in atherosclerosis.

inflammation (Li and Susztak, 2016). It can impact glucose homeostasis through its regulatory effects on gene expression and signaling pathways. TUG1′s involvement in diabetes highlights its capacity as a treatment focus for effectively controlling the disease's complex molecular mechanisms (Li et al., 2020a, 2020b, 2020c). Zhang et al. investigated TUG1′s role in T2DM onset and its mechanism. Animal models fed a high-fat diet and high-glucose cell cultures were used to measure TUG1 and SP1 levels. They were found to be downregulated and correlated. TUG1 was shown to bind SP1 promoters. TUG1 knockdown hindered cell proliferation and triggered programmed cell death in cells exposed to elevated glucose levels. The TUG1/FGF5/miR-188-3p axis was identified as a regulator of cell functions. Ultimately, SP1 downregulates TUG1 in T2DM cells, impacting islet cells through the interaction between miR-188-3p and FGF5, influencing proliferation and apoptosis (Zhang et al., 2021). Hsa-miR-607 is a specific miRNA that exhibits altered expression in T2DM patients compared to healthy controls. Its diagnostic potential is moderate, but when combined with other markers, it contributes to improved accuracy in diagnosing T2DM (Li et al., 2019). Hsa_circ_0071106 is a circular RNA molecule that has drawn concern for its possible function in various biological processes (Li et al., 2020a, 2020b, 2020c, Bhat et al., 2022a, 2022b, 2022c). Emerging research suggests its involvement in disease pathways, including its possible as a diagnostic or prognostic biomarker. Understanding the functions and mechanisms of hsa_circ_0071106 could provide valuable insights into its significance in well-being and illness contexts (Long et al., 2016). Su et al. investigated the latent ncRNAs as indicators for diagnosing T2DM. The research analyzes circRNAs, miRNAs, and lncRNAs in 101 T2DM patients and controls. Elevated expression of lncRNA, and MEG3 lncRNA, hsa-miR-29a-5p, hsa-miR-607, hsa-miR-3690, hsa_circ_0071271, hsa_circ_0000284, hsa_circ_0071106 TUG1 is observed in T2DM. The diagnostic potential of hsa-miR-607, hsa_circ_0071106, and lncRNA TUG1 individually yielded modest AUC values. However, combining these markers improved diagnostic accuracy, achieving an AUC of 0.798, 100.0 % precision and 75.2 % tolerance. Peripheral blood levels of these ncRNAs hold promise for clinical T2DM diagnosis (Gao et al., 2022, Su et al., 2022a, 2022b). MEG3 is a significant lncRNA implicated in diverse cellular processes. Its downregulation is connected to several illnesses, including cardiovascular conditions, cancer, and neurological disorders (Long et al., 2020). MEG3 acts as a vital control for the expression of genes and molecular pathways and can serve as a therapy or screening target due to its multifaceted roles in health and disease (López-Noriega and Rutter, 2020). Heydari et al. explored the roles of lncRNAs in type 2 diabetes and endoplasmic reticulum (ER) stress. Investigating TUG1, MALAT1, and MEG3, the research analyzes 57 diabetes patients and 32 healthy individuals. TUG1 and MEG3 expressions are elevated in diabetes, correlating with glycemic control markers and ER stress indicators. With links also expression MALAT1 ER stress 'with links also expression MALAT1′ markers. TUG1 and MEG3 might serve as markers for identifying ER stress associated with hyperglycemia in diabetes (Zhou et al., 2022a, 2022b, 2022c, Heydari et al., 2023). PDGF-BB/Wnt signaling, a vital pathway, plays a significant role in diabetes. Dysregulated in high glucose environments, it contributes to microvascular dysfunction and impaired angiogenesis, key factors in diabetic complications like diabetic foot (Mohammad et al., 2021, Meng et al., 2022a, 2022b). Understanding its intricate interactions with other factors could deliver data on relevant therapeutic interventions for addressing the vascular complications associated with diabetes (Petrica et al., 2021). Li et al. looked into the function of lncRNA. TUG1 in endothelial progenitor cells (EPCs) under high glucose conditions, is relevant to diabetic foot development. TUG1 enhances EPC invasion, migration, and tube formation impaired by high glucose. The mechanism involves TUG1′s alteration of the Wnt/PDGF-BB pathway via miR-29c-3p. In a diabetic mouse model, TUG1 overexpression stimulates angiogenesis in ischemic limbs. The study highlights TUG1 as a potential therapeutic target to restore EPC function and counter microvascular dysfunction in diabetes (Li et al., 2020a, 2020b, 2020c, Li et al., 2024). H19, an important long non-coding RNA, is implicated in diabetes. Its dysregulation is associated with various facets of the disease, including glycemic control and complications (Salazar-Torres et al., 2021). H19′s intricate regulatory functions make it a potential indicator and therapy target, holding the capacity for enhancing our understanding of diabetes and its management (Shen et al., 2019). Esawy et al. focused on IBS in diabetic patients and its association with lncRNAs H19 and TUG1. Assessing 42 healthy controls, 42 diabetic patients with IBS, and 42 diabetic patients, the research finds reduced expression of l TUG1 and lncRNA H19 in IBS-diabetic patients compared to healthy and diabetic-only individuals. TUG1 and H19 distinguish between patients who have diabetes alone and those who have both IBS and diabetes. TUG1 levels vary in different IBS types. Both lncRNAs predict disease severity and H19 acts as an independent predictor. This highlights the potential of H19 as a diagnostic marker and predictor for IBS severity in diabetes (Esawy et al., 2022a, 2022b, Zhao et al., 2023) (see Table 1).

SIRT1, a key regulator in cellular metabolism and stress response, is a crucial protein deacetylase implicated in various physiological processes. Its roles include DNA repair, inflammation modulation, and metabolic homeostasis through interactions with transcription factors and epigenetic modifiers (Spinetti et al., 2020, Shi et al., 2022). SIRT1′s involvement in these pathways positions it as a potential healing target for diverse conditions, like metabolic disorders, neurodegenerative diseases, and age-related ailments (Su et al., 2022a, 2022b). Zhang et al. investigated the TUG1/miR-204/SIRT1 axis's role in obesity-related diabetes. Diabetic mice were subjected to treatment with the TUG1 virus using a high-fat diet and streptozocin. Overexpressing TUG1 reduced body weight, glucose levels, and fat accumulation while increasing insulin tolerance. TUG1 upregulated SIRT1, AMPK, and ACC phosphorylation, and downregulated miR-204. miR-204 inhibition replicated these effects, and SIRT1 silencing attenuated them. Results suggest that TUG1 mitigates diabetes development by regulating the

Table 1
Summarize the role of TUG1 in Diabetes & Diabetic associative diseases.

Disease	Model	Mechanism	Biological activity	Reference
Diabetes	High-glucose cell model	Mir-188-3p/fgf5	Proliferation and apoptosis	(Zhang et al., 2021)
	Diabetic patients	Hsa-mir-607 / hsa_circ_0071106	Biomarkers in type 2 diabetes mellitus	(Su et al., 2022)
	Diabetic patients and PBM cells	Tug1/meg3/atf4 /chop	Endoplasmic reticulum stress	(Heydari et al., 2023)
	Peripheral blood of mice	Mir-29c-3p/pdgf-bb/wnt	Endothelial progenitor cell	(Li et al., 2020a, 2020b, 2020c)
	Diabetic patients	H19/tug1	Biomarkers	(Esawy et al., 2022a, 2022b)
	Mice	Tug1/mir-204	Brown remodeling	(Zhang et al., 2020)
	Hiec-6 / sw480	Tug1/ampk/sirt1	Intestinal epithelial cells damage	(Wei et al., 2022)
	Diabetic patients	Tug1/linc00657/mir-9/ mir-106a	Molecular biomarkers	(Abdelaleem et al., 2021)
	B-cell	A830019p07rik/malat1	B-cell mass and function modulators	(López-Noriega and Rutter, 2020)
	B cell	Ezh2/h3k27	Growth retardation	(Li et al., 2020a, 2020b, 2020c)
Diabetes induced nephropathy	Mice and hk-2 cells	Pu.1/rtn1	Lesions and apoptosis	(Meng et al., 2022a, 2022b)
	Diabetic mice and immortalized mouse podocytes	Pgc-1α */tug1*	Mitochondrial bioenergetics	(Long et al., 2016)
	Spf mice	tug1	Timp3-expression	(Wang et al., 2019)
	Rats	Iv/lncrna-tug1/traf5	Apoptosis	(Lei et al., 2018)
	Hk-2 cells	Tug1/mir-29c-3p/sirt1	Endoplasmic reticulum stress	(Wang et al., 2021)
	Hk2 cells	Mir-145-5p/dusp6	Fibrosis	(Wang et al., 2023a, 2023b)
	Rat	Tug1/ pi3k/akt	Proliferation and fibrosis	(Zang et al., 2019)
	Mouse podocytes	Chop/pgc-1α/tug1	Apoptosis	(Shen et al., 2019)
	Hk2 cells	Mapk1/erk/mettl14	Apoptosis	(Zheng et al., 2023a, 2023b)
	C57bl/ksj-db/db mice	Mirna-377/pai-1/tgf-β1	Extracellular matrix accumulation	(Duan et al., 2017)
	Patients	Rs3931283/pvt1g/ rs7158663/meg3 g/g	Polymorphisms	(Dieter et al., 2023a, 2023b)
	C57bl/6 j mice	Mir-188-3p/tug1	Mitochondrial injury	(Wang et al., 2022)
	Patients	Malat1/neat1	miRNAs expression	(Petrica et al., 2021)
	Patients	Tug1	Mitochondrial biogenesis	(Salazar-Torres et al., 2021)
Diabetes-induced cardiomyopathy	Mice	Tug1/mir-145a-5p/cfl2	Fibrosis	(Wang et al., 2023a, 2023b)
	Mice	Tug1/mir-499-5p	Hypertrophy and fibrosis	(Zhao et al., 2020)
Diabetes-induced retinal vascular dysfunction	Rat	Tug1/mir-524-5p	Vascular function	(Tian et al., 2022)
	Patients	Tug1/miat/malat1	Polymorphism	(Mohammad et al., 2021)
Diabetes-induced testicular damage	Mice	Tug1/clusterin/mettl3	Reduced blood glucose, oxidative stress, and testicular damage	(Tian et al., 2023)
Diabetes-induced atherosclerosis	HUVEC	Tug1/β-catenin/ Wnt/c-myc	Cell proliferation and migration	(Yan et al., 2018).

miR-204/SIRT1/AMPK/ACC pathway (Zhang et al., 2020, He et al., 2023). AMPK and SIRT1 are vital regulators of cellular energy metabolism and homeostasis. AMPK senses and responds to energy deficits, while SIRT1, a deacetylase, modulates various cellular processes, including metabolism, stress response, and longevity (Gan et al., 2018, Tang et al., 2023). Both AMPK and SIRT1 play pivotal roles in conditions like diabetes, obesity, and age-related disorders, positioning them as potential targets for therapeutic interventions (Tian et al., 2022). Wei et al. focused on the increasing rate of obesity and T2DM, particularly among younger individuals, and the effectiveness of sleeve gastrectomy (SG) as a treatment. The research examines the impact of lncRNA TUG1 on metabolic mechanisms. In T2DM patients and cells treated with HGHF, TUG1, and UCP2 appearance increased, while AMPK and SIRT1 levels decreased with SG. Underneath HGHF, cell viability decreased, apoptosis increased, and IL secretion changed. TUG1 overexpression countered HGHF effects, suggesting its involvement in mitigating metabolic damage. The TUG1/AMPK/SIRT1/UCP2 axis could have implications for T2DM treatment (Wei et al., 2022). LINC00657, a long non-coding RNA, is gaining prominence for its potential roles in numerous living processes and illnesses. While its precise purposes are still being elucidated, emerging research suggests its involvement in complex cellular pathways (Bhat et al., 2022a, 2022b, 2022c, Trewin et al., 2022, Tian et al., 2023, Zhou et al., 2023). Investigating LINC00657′s implications could provide valuable insights into its significance, potentially revealing its value as a diagnostic or therapeutic target in various health and disease contexts (Wang et al., 2019). Abdelaleem et al. focused on the capability of ncRNAs as biomarkers for stroke in diabetic patients. It investigates serum expression of miR-106a, TUG1, LINC00657, and miR-9 in diabetics with and without stroke. Elevated miR-9 and LINC00657 levels were observed in diabetics without stroke. However, diabetics with stroke showed increased TUG1, LINC00657, and miR-9 expression alongside decreased miR-106a. Strong associations among TUG1, miR-9, LINC00657, and stroke severity were noted, with miR-106a showing a negative correlation. These non-coding RNAs could serve as potential indicators of disease and potential targets for treatment in diabetes stroke patients (Abdelaleem et al., 2021). Diabetes mellitus is marked by β-cell loss and dysfunction, contributing to impaired insulin production and glucose regulation. The mechanisms underlying these β-cell alterations remain complex and multifaceted (Wang et al., 2023a, 2023b). Understanding the molecular pathways governing β-cell health and identifying factors that trigger their dysfunction is crucial for devising effective strategies for diabetes management and treatment (Wang et al., 2021). Noriega et al. investigated the importance of understanding ncRNA functions in β-cell biology to unravel diabetes pathogenesis. Despite numerous genetic studies, diabetes origins and treatments remain inadequately

understood. As diabetes-related genetic factors mostly inhabit noncoding genome regions, lncRNAs have appeared as key players. Studies reveal that lncRNAs like TUG-1 and MEG3 influence β-cell proliferation, compensation, apoptosis, and function. Some regulate β-cell-enriched transcription factors. The review highlights how deciphering lncRNA roles provides insights into diabetes development, offering a comprehensive perspective on β-cell maintenance and diabetes pathogenesis (Tang et al., 2018, López-Noriega and Rutter, 2020). IUGR refers to inadequate fetal development through pregnancy, leading to newborns with lower birth weights than expected for their gestational age (Wang et al., 2023a, 2023b). IUGR is associated with various maternal and fetal factors and can result in developmental complications, health risks, and a higher risk of developing chronic illnesses afterwards in life, including diabetes and cardiovascular disorders (Wang et al., 2022). Li et al. explored the part of the lncRNA Tug1 in islet dysfunction linked to IUGR. IUGR mice displayed smaller islets and pancreatic changes. Tug1 overexpression partially improved glucose tolerance and gene expression related to diabetes. Tug1 regulates Hes1 through requisite to EZH2, impacting insulin synthesis in islet cells. This study proposes Tug1′s potential as a biomarker and a novel target for diabetes treatment, emphasizing its importance in understanding islet dysfunction and diabetes pathogenesis (Li et al., 2020a, 2020b, 2020c, Huang and Zhou, 2023).

3. Role of TUG1 in diabetes-associated diseases

3.1. Diabetes-Induced nephropathy

Diabetes-induced nephropathy, also known as diabetic kidney disease, develops due to prolonged high blood sugar levels damaging the kidneys' blood vessels and filtering units (Wei et al., 2022). This leads to protein leakage into the urine, impaired filtration, and gradual kidney function decline. Inflammatory processes, oxidative stress, and metabolic changes further exacerbate kidney damage (Yan et al., 2018). Untreated nephropathy can progress to end-stage renal disease, highlighting the importance of tight blood sugar control and early intervention to mitigate diabetic nephropathy's impact on kidney health (Zang et al., 2019). Meng et al. investigated whether long noncoding RNA TUG1 could mitigate apoptosis and ERS in kidney tubule cells in DN. TUG1 was reduced in DN mice and overexpression reduced ERS and apoptosis markers in high glucose-treated cells. TUG1 lowered ERS by inhibiting reticulon-1 (RTN1) expression via suppressing PU.1 binding to RTN1 promoter. Injecting TUG1-overexpression adenovirus in mice improved tubular lesions and decreased Apoptosis markers, ERS, and RTN1., while PU.1 overexpression reversed these effects. TUG1 appears to alleviate DN by restraining ERS and apoptosis through PU.1 inhibition (Meng et al., 2022a, 2022b, Mao et al., 2023). Mitochondrial bioenergetics refers to the processes within cells' mitochondria that produce and manage energy. This energy, in the form of ATP, is crucial for cellular functions. Mitochondria play a central role in aerobic respiration, where nutrients are metabolized to generate ATP via oxidative phosphorylation and the electron transfer chain (Zhang et al., 2021, Bhat et al., 2023a, 2023b, 2023c). Disruptions in mitochondrial bioenergetics can lead to various health issues, including metabolic disorders and neurodegenerative diseases. Maintaining optimal mitochondrial function is essential for overall cellular and organismal health (Zhang et al., 2020). Long et al. revealed the functional interaction between the lncRNA Tug1 and the transcriptional coactivator PGC-1α in the context of DN. Using a diabetic mouse model, the study found that Tug1 was dysregulated in kidney glomeruli. In diabetic mice, podocyte-specific expression of Tug1 enhanced DN-related characteristics, unexpectedly rescuing PGC-1α expression and its targets. This improvement was associated with enhanced mitochondrial function in podocytes. It has been demonstrated that Tug1 and PGC-1α interaction enhances PGC-1α adherence to its supporter, highlighting their role in adjusting the bioenergetics of the mitochondria in the diabetes environment (Long et al., 2016, Zhou et al., 2022a, 2022b, 2022c). Tissue inhibitor of metalloproteinase 3 (TIMP3) is a protein that regulates extracellular matrix remodelling by inhibiting MMPs. It plays a vital role in maintaining tissue integrity and preventing excessive tissue breakdown (Zhao et al., 2019). TIMP3 is implicated in several biological and pathological events, such as inflammation, angiogenesis, and tissue repair. Dysregulation of TIMP3 has been related to several illnesses, such as cancer and cardiovascular diseases. Its intricate balance with MMPs makes TIMP3 a crucial factor in maintaining tissue homeostasis and proper cellular function (Zhao et al., 2020). Wang et al. aimed to understand the genetic mechanisms involving the long noncoding RNA (lncRNA) TUG1 in diabetic nephropathy (DN) renal fibrosis. TUG1 was downregulated in DN mice kidneys and high glucose-stimulated kidney cells. Overexpressing TUG1 inhibited fibrosis in these cells. TUG1 was predicted to target miR-21, which in turn targeted TIMP3, and these interactions were confirmed through experiments. Overexpressing TUG1 promoted TIMP3 expression by targeting miR-21, reducing cell and renal fibrosis. These findings suggest that TUG1 indirectly regulates TIMP3 via miR-21, potentially offering a strategy to mitigate DN-related fibrosis (Wang et al., 2019, Zhou et al., 2022a, 2022b, 2022c).

TRAF5 is a signaling protein involved in immune and inflammatory responses. Upon activation by various receptors, including cytokine receptors, TRAF5 interacts with downstream molecules, like NF-κB and MAP kinases, triggering cascades that regulate gene expression (Chen et al., 2022, Tang et al., 2022, Zheng et al., 2023a, 2023b). These pathways impact immunity, inflammation, and cell survival. TRAF5′s role in signal transduction makes it a critical mediator in various physiological and pathological processes, offering potential therapeutic targets for diseases linked to immune dysregulation and inflammation (Xu et al., 2020). Lei et al. investigated AS-IV as a protective mechanism against podocyte apoptosis in DN rats. Rats with diabetes who received therapy AS-IV showed reduced albuminuria and TRAF5 levels, enhanced TUG1 expression, and decreased cleaved-caspase-3 protein levels. AS-IV stimulated the upregulation of TUG1 in cells treated with high glucose. TUG1 and TRAF5 interacted, and TUG1 overexpression promoted the degradation of TRAF5 protein. TUG1 allowed AS-IV to regulate TRAF5, which in turn decreased podocyte apoptosis via the TUG1/TRAF5 pathway. In vivo, silencing TUG1 negated AS-IV's protective effects on DN. AS-IV safeguards against podocyte apoptosis in DN through the lncRNA-TUG1/TRAF5 pathway (Lei et al., 2018). The SIRT1 axis involves the Sirtuin 1 protein, an associate of the sirtuin family of enzymes. SIRT1 is a critical regulator of cellular processes like metabolism, DNA repair, and stress response (Chen et al., 2020). It modulates gene expression by deacetylating histones and transcription factors (DiNicolantonio et al., 2022). The SIRT1 axis influences various pathways, including those related to ageing, inflammation, and energy metabolism (Shen et al., 2021). SIRT1 dysregulation has been connected to several illnesses, making it a viable target for treatment in illnesses including cancer, metabolic diseases, and neurodegenerative disorders. (Tang, 2016, Yang et al., 2022, Yan et al., 2024). Wang et al. discovered the function of the lncRNA TUG1 in controlling apoptosis triggered by endoplasmic reticulum stress (ERS) in renal tubular epithelium cells were exposed to elevated glucose levels. High glucose led to apoptosis and ERS while reducing TUG1 expression. Overexpressing TUG1 countered apoptosis and ERS by inhibiting miR-29c-3p. Conversely, miR-29c-3p increased ERS and apoptosis under high glucose conditions. SIRT1 was identified as a direct miR-29c-3p target, contributing to its effects. TUG1 suppressed miR-29c-3p, mitigating its negative influence on SIRT1. Thus, TUG1 regulates SIRT1/ miR-29c-3p to alleviate renal epithelial cell injury caused by high glucose, possibly signifying a diagnostic marker for diabetic nephropathy (Wang et al., 2021). miR-145-5p is a microRNA that regulates gene expression by binding to messenger RNAs. It plays a crucial function in a range of physiological and pathological events, encompassing cellular growth, specialization, and inflammation (Chen et al., 2019, Ding et al., 2020). miR-145-5p's dysregulation has been related to several diseases, such as

cardiovascular disorders, cancer, and diabetes (Fu et al., 2021). Its ability to modulate multiple signaling pathways makes it an important regulator of cellular homeostasis, offering latent as a therapy target and diagnostic indicator for various conditions (Liang et al., 2022, Zhang et al., 2022). Wang et al. investigated the role of lncRNA TUG1 in diabetic nephropathy-related renal interstitial fibrosis. TUG1 downregulation due to hyperglycemia is examined in HK-2 cells treated with high glucose and the DN mouse model. TUG1 overexpression reduced kidney damage in vivo by lowering fibrosis and inflammation. In HK-2 cells, overexpression of TUG1 suppressed fibrosis and inflammation. TUG1 was found to directly interact with miR-145-5p, which targeted DUSP6. Elevating miR-145-5p and inhibiting DUSP6 reversed TUG1′s effects. This study highlights that TUG1 alleviates DN-associated kidney injury through the miR-145-5p/DUSP6 axis, potentially offering therapeutic insights (Wang et al., 2023a, 2023b). One essential cell signalling pathway that controls several functions, including survival, cell division, and metabolism, is the PI3K/AKT route. (Xia and Xu, 2015, Ediriweera et al., 2019). Phosphatidylinositol 3-kinase (PI3K) activation triggers the synthesis of PIP3, which results in the initiation of AKT activation (Chen et al., 2016). Activated AKT phosphorylates target proteins, impacting cell proliferation, apoptosis, and nutrient utilization (Ersahin et al., 2015). Dysregulation of the PI3K/AKT pathway is linked to numerous illnesses, such as cardiovascular disorders, diabetes, and cancer, making it a key target for therapeutic involvement (Xie et al., 2019, Wang et al., 2020). Zang et al. aimed to explore the role of the lncRNA TUG1 in DN progression and its mechanism. Using diabetic rat models and mesangial cells subjected to elevated glucose levels, the study found that TUG1 expression was reduced. TUG1 overexpression in diabetic rats lowered kidney damage markers. In mesangial cells, TUG1 overexpression decreased proliferation and extracellular matrix accumulation by inhibiting the PI3K/AKT pathway. TUG1 downregulation in DN contributes to disease progression, and its overexpression can be mitigated by focusing on the AKT/PI3K pathway, proliferation of cells and extracellular matrix formation can be achieved. (Zang et al., 2019). ERS is a cellular response to imbalances in protein folding and processing within the endoplasmic reticulum (Kong et al., 2018). Various factors, such as nutrient deprivation, oxidative stress, and genetic mutations, can trigger ERS (Lee and Lee, 2022). When the endoplasmic reticulum becomes populated with unfolded or misfolded proteins, ERS activates a signaling pathway called the UPR. UPR aims to restore proper protein folding and function or, if unsuccessful, induces apoptosis (Li et al., 2020a, 2020b, 2020c, Lee et al., 2022). ERS is implicated in several diseases, including diabetes, neurodegenerative disorders, and cardiovascular conditions, highlighting its significance in cellular homeostasis and pathology (Mustapha et al., 2021). Shen el al. aimed to understand how the lncRNA TUG1 In diabetic nephropathy, there are effects on the levels of CHOP and PGC-1α expression. TUG1 was found to control CHOP and PGC-1α levels, affecting podocyte apoptosis in diabetic nephropathy. High glucose led to elevated TUG1 and CHOP, and reduced PGC-1α levels, influencing podocyte apoptosis. TUG1 positively regulated PGC-1α expression and negatively regulated CHOP. Human participants with diabetic nephropathy also showed altered levels of these molecules. This study highlighted TUG1′s role in modulating podocyte apoptosis through the ERS-CHOP-PGC-1α pathway in diabetic nephropathy (Shen et al., 2019).

METTL14 is an enzyme responsible for m6A modification, a reversible RNA epigenetic modification that influences RNA metabolism and function (Li et al., 2021). METTL14 adds methyl groups to adenosine residues within RNA molecules, affecting their stability, translation, and interaction with other molecules (Lu et al., 2021). This modification, known as m6A, plays an essential function in varied cellular actions, including controlling the expression of genes (Meng et al., 2022a, 2022b). regulation, RNA splicing, and stress response (Su et al., 2022a, 2022b). Dysregulation of METTL14-mediated m6A modification has been a concern in numerous diseases, like cancer, neurodegenerative disorders, and metabolic conditions (Xu et al., 2021). Zheng et al. aimed to understand the role of METTL14 in diabetic kidney disease (DKD) progression and its mechanism involving endoplasmic reticulum stress (ERS). In DKD models, METTL14 knockdown reduced cell apoptosis and ERS marker expression. METTL14 affected the stability of lncRNA TUG1 through m6A modification, influencing its interaction with LIN28B and MAPK1/ERK signaling. The impact of METTL14 reduction on ERS and cell apoptosis was offset by TUG1 knockdown. Moreover, in DKD mice models, overexpression of TUG1 and METTL14 suppression defended renal tumours and fibrosis. This study highlights METTL14′s role in accelerating DKD progression through ERS and MAPK/ERK pathway activation via TUG1 modification (Zheng et al., 2023a, 2023b). The nuclear receptor PPARγ is essential for metabolism and cellular functions. It regulates genes involved in adipogenesis, insulin sensitivity, lipid metabolism, and anti-inflammatory responses (Cataldi et al., 2021, Fan et al., 2022). PPARγ activation influences glucose homeostasis and lipid storage, making it a target for diabetes and metabolic disorders treatment (Han et al., 2017). Additionally, PPARγ has been implicated in modulating pathways related to inflammation, cardiovascular health, and cell differentiation (Nunez Lopez et al., 2022). Duan et al. inspected the role of lncRNA TUG1 in diabetic nephropathy (DN). MiRNA-377 is identified as upregulated in DN mice, and its target is predicted to be PPARγ. MiR-377 overexpression under high glucose conditions promotes PAI-1 and TGF-β1 expression by inhibiting PPARγ. By acting as a reservoir for miR-377, TUG1 relieves PPARγ inhibition and downregulates miR-377. This decreases the formation of extracellular matrix in mesangial cells, shedding light on the pathophysiology of DN. TUG1′s role in DN involves modulating the miR-377-PPARγ axis to curb extracellular matrix buildup (Duan et al., 2017). The study by Dieter et al. examined the association between specific lncRNA gene polymorphisms and DKD in patients with T2DM. Higher urine albumin excretion levels and an increased risk of DKD have been associated with the rs3931283/PVT1 G/G genotype. On the other hand, a higher approximated glomerular filtration rate, better renal function indicators, and a decreased risk of severe DKD were associated with the rs7158663/MEG3 G/G genotype. No significant associations were observed for other studied polymorphisms. These findings suggest that certain lncRNA gene variants may contribute to DKD susceptibility and renal function in T2DM patients (Dieter et al., 2023a, 2023b). Mitochondrial injury refers to the impairment of the cellular powerhouse, mitochondria, which play a critical role in energy production, oxidative stress regulation, and cell survival (Bhargava and Schnellmann, 2017). Various factors like oxidative stress, genetic mutations, or toxic substances can disrupt Impaired mitochondrial function resulting in diminished energy generation and elevated synthesis of reactive oxygen species (Hamed, 2017, Han et al., 2018). This damage can contribute to various diseases, including neurodegenerative disorders, cardiovascular diseases, and metabolic disorders like diabetes, where mitochondrial injury can trigger apoptosis and cellular dysfunction (Wei and Szeto, 2019). Wang et al. explored the role of germacrone in type I DN by exploring its effects on mitochondrial function and podocyte apoptosis. In a type I DN animal model, germacrone decreased proteinuria, blood glucose, and nephrotic symptoms. It decreased the buildup of ROS, prevented mitochondrial damage, and increased glutathione peroxidase activity. Germacone mechanistically undid the elevated expression of miR-188-3p seen in type I DN mice. This miRNA contributed to podocyte apoptosis and mitochondrial damage. Germacrone showed potential in alleviating DN by limiting podocyte apoptosis, counteracting miR-188-3p's effects, and offering a possible therapeutic strategy for DN (Wang et al., 2022). Podocytes are specialized cells in the kidney responsible for forming the filtration barrier in glomeruli, preventing the loss of important proteins in urine (Fu et al., 2020a, 2020b, Gupta et al., 2023a, 2023b, Mohandes et al., 2023). Proximal tubule cells are part of the renal tubular system and play a critical role in reabsorbing filtered nutrients, ions, and water from the glomerular filtrate, helping to maintain the body's balance of fluids and electrolytes (Podgórski et al., 2019). Dysfunction of podocytes and proximal tubules can lead to kidney diseases like diabetic

nephropathy, affecting filtration and reabsorption processes, and ultimately impacting kidney function (Rogacka and Piwkowska, 2021). Petrica et al. examine the involvement of certain lncRNAs in tubular damage and podocyte damage in kidney disease linked with type 2 diabetes. They examined patients' urinary lncRNA levels along with podocyte and tubular injury markers. Results showed lncRNAs like MALAT1, NEAT1, MIAT, and TUG1 correlated with various injury markers and miRNA levels. These lncRNAs exhibited both detrimental and protective effects on kidney components. Overall, the findings suggested that lncRNAs contribute to DKD by interacting with miRNAs, irrespective of albuminuria or DKD stage (Petrica et al., 2021). Diabetes-induced glomerulonephritides refer to kidney inflammation and damage that result from persistently elevated levels of blood sugar in diabetic patients (AlYousef et al., 2020). The condition primarily affects the glomeruli, the filtering units of the kidneys. Persistent hyperglycemia triggers inflammation, oxidative stress, and altered immune responses, contributing to glomerular dysfunction (Anders et al., 2022, Barutta et al., 2022). Over time, this can lead to proteinuria, reduced kidney function, and eventually, diabetic nephropathy (Deng et al., 2022). Early detection, blood sugar control, and timely medical intervention are essential to prevent and manage the progression of these glomerulonephritides in diabetes (McQuarrie et al., 2022). Torres et al. focused on the role of the lncRNA TUG1 in non-diabetic patients with glomerulonephritides. TUG1 is known to regulate podocyte health and mitochondrial biogenesis. The study discovered that patients with glomerulonephritides, especially those with FSGS, had considerably lower levels of TUG1 expression in their urine sediment. The levels of TUG1 were linked to markers of podocyte function and mitochondrial biogenesis. The study suggests that decreased TUG1 expression could be indicative of FSGS and might serve as a non-invasive biomarker for assessing podocyte health (Salazar-Torres et al., 2021).

3.2. Diabetes-Induced cardiomyopathy

Diabetes-induced cardiomyopathy is a condition where prolonged elevated blood sugar levels lead to structural and functional changes in the heart (Dillmann, 2019). It involves impaired cardiac muscle contraction, relaxation, and fibrosis. The underlying mechanisms include oxidative stress, inflammation, and metabolic disturbances (Jankauskas et al., 2021, Gupta et al., 2023a, 2023b). These alterations contribute to reduced heart function, increased risk of cardiovascular complications and heart failure in diabetic patients (Jia et al., 2016). Wang et al. aimed to uncover the miR-145a-5p/Cfl2/lncRNA TUG1 axis in diabetic cardiomyopathy (DCM). DCM models were established in male mice using streptozotocin. In DCM cardiac tissues, miR-145a-5p was downregulated while lncRNA TUG1 and Cfl2 were increased. Lowering TUG1 improved cardiac function, reduced fibrosis, and lowered inflammation markers. Elevating miR-145a-5p showed similar benefits. MiR-145a-5p counteracted TUG1′s pro-fibrotic impact, and raising Cfl2 reversed TUG1′s anti-fibrotic effect. Mechanistically, TUG1 interacted with miR-145a-5p, which targeted Cfl2. This study demonstrates that TUG1 exacerbates DCM-induced fibrosis by sponging miR-145a-5p to promote Cfl2 (Wang et al., 2023a, 2023b, 2023c). miR-499-5p is a microRNA participating in the control of genetic expression. It is essential for several biological functions, including metabolism, muscular growth, and heart function. miR-499-5p is particularly associated with the heart, where it influences cardiac hypertrophy, contractility, and stress response (Pielok and Marycz, 2020, Thapa et al., 2023a, 2023b, 2023c). Dysregulation of miR-499-5p has been implicated in cardiovascular diseases, such as myocardial infarction and heart failure. Its intricate role in cardiac physiology makes it a promising candidate for therapeutic interventions targeting cardiac-related disorders (Wang et al., 2015, Zhao et al., 2020). Zhao et al. explored the role of lncRNA TUG1 in DCM-induced cardiac hypertrophy. TUG1 was found to be upregulated in diabetic mice cardiomyocytes. Inhibiting TUG1 improved diastolic dysfunction without affecting systolic function in DCM. TUG1 knockdown reduced fibrosis and cardiac hypertrophy in vivo. Mechanistically, TUG1 negatively controlled miR-499-5p. Overexpressing miR-499-5p counteracted TUG1 silencing's inhibitory effects on high glucose-induced cardiac hypertrophy in vitro. The findings suggest that TUG1 knockdown mitigated DCM-associated cardiac hypertrophy and dysfunction by upregulating miR-499-5p, highlighting TUG1 as a potential therapeutic target for DCM (Zhao et al., 2020).

3.3. Diabetes-Induced retinal vascular dysfunction

Diabetes-induced retinal vascular dysfunction is characterized by compromised blood vessels in the retina due to prolonged high blood sugar levels. It leads to abnormalities like microaneurysms, leakage, and non-perfusion of blood vessels (Azad et al., 2021). This dysfunction results from oxidative stress, inflammation, and impaired blood flow regulation (Kern and Barber, 2008). The retina's sensitivity to glucose fluctuations contributes to vision-threatening conditions such as diabetic retinopathy (Li et al., 2021). Tight glycemic control, regular eye examinations, and early intervention are crucial in preventing or managing diabetes-related retinal vascular complications (Wright et al., 2020). Tian et al. explored the role of lncRNA TUG1 in DR. TUG1 was elevated in DR rat models and high glucose-treated retinal cells. Inhibiting TUG1 reduced migration, cell proliferation, and angiogenesis. TUG1 acts as a sponge for miR-524-5p, which is downregulated in hyperglycemia. FGFR2 was identified as a target of miR-524-5p, with elevated expression in high glucose-treated cells. Suppressing TUG1 improved retinal vascular function in diabetes-induced impairment, indicating a potential therapeutic avenue for DR (Tian et al., 2022). Anti-VEGF therapy is a treatment approach that focuses on VEGF, a protein that promotes blood vessel development (Porta and Striglia, 2020). It is mainly employed in ailments such as AMD, diabetic retinopathy, and certain types of cancer (Tan et al., 2021). By inhibiting VEGF, this therapy aims to reduce abnormal blood vessel growth, leakage, and associated complications (Uludag et al., 2022, Bhat et al., 2023a, 2023b, 2023c). Commonly delivered through intravitreal injections, it has revolutionized eye disease management by slowing disease progression and improving visual outcomes. Regular follow-up is essential to monitor response and adjust treatment as needed (Wang and Lo, 2018). Mohammad et al. explored the link between specific lncRNA variants (TUG1, MIAT, MALAT1, and SENCR) and diabetic retinopathy (DR). Carriers of certain genotypes in TUG1 and MIAT had a higher risk of developing DR, while the MALAT1 variant offered protection. MIAT variant (T/T) correlated with more severe DR, while SENCR variant (T) was linked to better pre-treatment visual acuity. Carrying MIAT T/C or TUG1 A variants predicted an unfortunate response to aflibercept treatment. These lncRNA variants could aid in predicting DR susceptibility and guiding treatment response, pending further large-scale validation (Mohammad et al., 2021).

3.4. Diabetes-Induced testicular damage

Diabetes can lead to testicular damage due to impaired blood flow and oxidative stress. Elevated blood sugar levels in diabetes contribute to inflammation and reduced function of the testes, potentially causing hormonal imbalances and reduced sperm production (Abdel-Aziz et al., 2020, Huang et al., 2022, Thapa et al., 2022). Additionally, neuropathy and vascular complications associated with diabetes can further exacerbate testicular damage. Management of diabetes through proper blood sugar control and lifestyle adjustments may help mitigate the risk of such damage (Liu et al., 2021, Koroglu Aydın et al., 2022). Tian et al. investigated the role of METTL3 in the context of testicular damage induced by diabetes was investigated. The study employed diabetic mice and GC-1 spg cells treated with high glucose. Within diabetic testicular tissues and high glucose-treated cells, both METTL3 and long noncoding RNA TUG1 exhibited lowered expression. Introducing METTL3 overexpression resulted in decreased blood glucose levels, mitigated

oxidative stress, and ameliorated testicular damage. Furthermore, this intervention led to an augmentation in testosterone secretion. METTL3-mediated m6A methylation stabilized TUG1, which in turn stabilized clusterin mRNA via merging factor 1. On HG-stimulated cells, METTL3′s protective effects were undone by blocking TUG1/clusterin signalling. This work demonstrates how TUG1/clusterin signalling mediates the amelioration of diabetes-induced testicular damage by METTL3. (Tian et al., 2023).

3.5. Diabetes-Induced atherosclerosis

Diabetes-induced atherosclerosis is characterized by the accelerated development of fatty plaque buildup in arteries due to prolonged high blood sugar levels (Ye et al., 2022). Oxidative stress, chronic inflammation, and insulin resistance in diabetes contribute to the formation of arterial plaques, narrowing the vessels and restricting blood flow (Poznyak et al., 2020). This heightened atherosclerotic process upsurges the hazard of cardiovascular complications such as heart attacks and strokes in individuals with diabetes (Hasani et al., 2021). Management of blood sugar levels and cardiovascular risk factors is essential in preventing and mitigating diabetes-related atherosclerosis (Elfaki et al., 2018). Yan et al. aimed to examine the role of TUG1 in diabetic atherosclerosis. In CAD cells and blood vessels exposed to elevated hyperglycemia and TNF-α, TUG1 was overexpressed. TUG1 overexpression Increased proliferation, migration, and progression through the cell cycle of HUVECs have been augmented. It upregulated β-catenin and c-Myc proteins associated with the Wnt pathway. Inhibition of the Wnt pathway partially reversed the effects of TUG1 overexpression on HUVEC behaviour. These findings suggest that TUG1 contributes to diabetic atherosclerosis by promoting migration and endothelial cell proliferation through the Wnt pathway (Yan et al., 2018).

4. Conclusion and future perspective

Finally, the investigation into the epigenetic regulation of TUG1 in diabetes and its complications may offer significant insights into the complex molecular mechanisms underlying these conditions. The central involvement of TUG1 in epigenetic and gene expression regulation may emphasize its importance as a key regulator in the pathogenesis of diabetes, insulin resistance, and the subsequent development of diabetic retinopathy, nephropathy, and cardiovascular complications. Alteration of TUG1 expression through histone modifications, DNA methylation, and regulation by microRNAs may communicate with metabolic pathways, inflammation, and oxidative stress and influence the initiation and progression of diabetes and diabetic complications.

Understanding the epigenetic landscape of TUG1, combined with its interaction with key co-factors, will contribute to a more detailed understanding of the molecular basis of diabetes and its complications.

The instances of future opportunities are both numerous and bright. More research is needed to dissect the intricate web of epigenetics involving TUG1 in diabetes and complications. The use of advanced genomics, transcriptomics, and epigenomics technologies will uncover novel interacting partners and pathways as further targets affected by TUG1. In addition, the development of detailed computational modelling and bioinformatics tools can assist in the elucidation of these intricate networks and provide preferences for potential therapeutic targets. Conversely, innovation in the therapeutic application of the above discoveries is being contemplated. The modulation of TUG1 epigenetically provides a new and exciting avenue for therapeutics. Altering TUG1 levels by specific epigenetic therapeutics may allow for the development of new treatments which may not only slow the progression of diabetes but also alleviate complications. However, careful preclinical studies, as well as controlled clinical trials, will be necessary to investigate the safety, efficacy, and exactitude of these therapies – given the prominent and highly specific role of epigenetic modifications in normal cellular operation. An integrative approach is required. As a completely integrated view of the epigenetic regulation of TUG1 in diabetes is of utmost importance for its clinical transition, multiple fields, including genetics, molecular biology, bioinformatics, and clinical research, will need to work together. Burgeoning technological research will be effectively harnessed to develop patient-specific epigenetic regimens for diagnosing, preventing, and treating diabetes and its complications and much of the duplicate text across all sections can be resolved.

In conclusion, the epigenetic labyrinth of TUG1 in diabetes may catalyze the start of an era of precision medicine possibility, providing more streamlined care and a better quality of life for millions worldwide.

Declaration of competing interest

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

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