GMR
The Original

THE ROLE OF TUG LONG NON-CODING RNA IN BREAST CANCER AND TYPE 2 DIABETES: A SYSTEMATIC REVIEW OF MOLECULAR MECHANISMS, REGULATORY NETWORKS, AND CLINICAL IMPLICATIONS

Haider Yabr Lafta[1], Hossein Fallahi[*1], Majeed Arsheed Sabbah[2], Abdul-Sahib Kadhim Ali[3]

[1]Department of Biology, School of Sciences, Razi University, Baq-e-Abrisham, Kermanshah, I.R. of Iran. Postal Code: 6714967346, Email:h.fallahi@razi.ac.ir
[2]Forensic DNA Center for Research and Training, Al-Nahrain University, Al-Jadriyah Bridge, Baghdad, Iraq, 64074, Email:majeedbio@gmail.com
[3]Laboratories Directorate, Radiological and Nuclear Application, IAEC, Iraq, Email: sahib1966@yahoo.com
Corresponding author: Dr. Hossein Fallahi, h.fallahi@razi.ac.ir

ABSTRACT
Long non-coding RNAs (lncRNAs) are essential members of the human transcriptome that regulate all forms of gene expression during the body's normal and disease situations. The regulatory role of taurine upregulated gene 1 (TUG1) in gene expression has been established during tumor formation and the regulation of metabolism. In this review, we critically integrate findings from experimental models, patient-based studies, and bioinformatics analyses to clarify how TUG1 regulates molecular networks common to breast cancer and type 2 diabetes mellitus. Relevant information was extracted from PubMed, Scopus, and Web of Science databases following the PRISMA 2020 guidelines for systematic review. Relevant studies were considered to contain the expression of TUG1, regulation of TUG1, functional predictions, pathway(s) of signal transduction, and clinical aspects. Evidence from in vitro and in silico studies was combined and presented descriptively.
TUG1 is known to regulate gene expression through epigenetic modifications, regulation of transcription, and post-transcriptional control processes, which involve specific microRNAs and their corresponding target genes. TUG1-associated gene networks involve main signaling pathways of cancer and metabolic diseases, including PI3K/AKT, MAPK, insulin signaling, inflammation, and cell cycle. Studies have shown that changes in TUG1 expression correlate with tumor progression, negative clinical impacts, insulin resistance, and chronic inflammation/ inflammatory processes. The studies reviewed here suggest that TUG1 operates at the crossroads of metabolic and cancer signaling pathways and, therefore, could be considered as a variable for the translational studies, and might be used as a marker and target for cancer diagnosis or therapy.

KEYWORDS: Breast Cancer; Type 2 Diabetes Mellitus; TUG lncRNA; Functional Enrichment; Bioinformatics Analysis; Molecular Biomarkers.

1. INTRODUCTION

Advances in transcriptomic profiling have revealed that transcription across the human genome is far more extensive than previously appreciated, with only a few numbers produce protein-coding transcripts. The non-coding RNAs, which constitute the bulk of the transcriptome, include long non-coding RNAs that are being acknowledged as important modulators of gene expression and balance of the cell [1,2]. LncRNAs are defined as transcripts that are greater than 200 nucleotides in length and are typically non-coding, with a diverse regulatory function. They regulate gene expression, modulate the chromatin status, are involved in the transcription process, and the stability of RNA, and form complexes with RNAs that are bound with regulatory proteins [2,3]. LncRNAs are vital in the control of cellular differentiation and responses to stress. Their irregular expression has been implicated in the onset and progression of various diseases [3,4].
Breast cancer is the most common cancer among women and is one of the leading causes of cancer deaths worldwide. The breast cancer molecular landscape is complex and the result of an interplay of environment, epigenetics, hormones, and genetic alterations. On the other hand, Type 2 diabetes (T2DM) is a chronic metabolic disorder caused by a combination of factors, including insulin resistance, chronic inflammation, and an aberrant glucose and lipid metabolism. From a biological and clinical point of view, the onset and progression of both breast cancer and T2DM are linked to common chronic inflammation, altered metabolic states, cell stress, and growth signaling. Epidemiological studies describe a bidirectional relation between progression and outcomes of diabetes and cancer risk, implying the presence of similar mechanisms [5-9].

Recent studies have identified long non-coding RNAs (lncRNAs) as potential molecular mediators linking metabolic dysregulation with oncogenic processes. By operating at the interface of epigenetic control, transcriptional regulation, and post-transcriptional processing, lncRNAs are uniquely positioned to integrate metabolic and environmental signals and coordinate gene regulatory responses. Among these regulatory lncRNAs, taurine upregulated gene 1 (TUG1) has attracted particular scientific interest. TUG1 lncRNA was the very first lncRNA to be documented in taurine-stimulated retinal cells where it was thought to be important to regulation of the development of the retina and the differentiation of retinal cells [10] yet in the years following the initial characterizations, the lncRNA was shown to be relevant in several other pathological conditions such as neoplasms, disorders of metabolism, inflammation and so on.

Accumulating evidence indicates that TUG1 plays context-dependent roles in cancer-related processes, including cellular proliferation, apoptosis, invasion, epithelial–mesenchymal transition, and metastasis. Concurrently, emerging evidence suggests that TUG1 is involved in the regulation of insulin signaling, glucose homeostasis, endoplasmic reticulum stress, and inflammatory responses in metabolic disease contexts [11–13]. These findings demonstrate that TUG1 has multiple biological functions, which are likely a function of the particular cell type, the type of disease, and the specific regulatory mechanisms present.

Some researchers have suggested that TUG1 has the power to regulate gene expression through several ways, controlling the transcription through epigenetic alterations, binding with chromatin to organize protein complexes, and acting as a competitive endogenous RNA which works to modulate the levels of microRNA and gene expression. With regards to the activities of signaling TUG1, such as the PI3K/AKT, MAPK, inflammatory, and metabolic signaling pathways, all of which are directed toward key hubs that progress BC and the T2DM pathways. These are the pathways of converging metabolic stress and inflammatory signaling, along with those of the oncogenic processes, and it is here where the connective role of TUG1 with metabolic and oncogenic disease processes becomes clear.

Despite the expanding body of literature on TUG1, current understanding remains fragmented due to disease-specific study designs, methodological heterogeneity, and limited integrative analyses. Much of the work is based on high-throughput transcriptomic datasets with functional role predictions made via bioinformatics network analyses. While these approaches expose valuable system and functional level roles, they frequently remain unconnected and unreported in an integrative fashion across diseases. To date, no systematic review has comprehensively integrated molecular, bioinformatics, and clinical evidence to examine the role of TUG1 across both breast cancer and type 2 diabetes mellitus.

Accordingly, this systematic review aims to integrate and critically synthesize available experimental, clinical, and bioinformatics-based evidence to clarify the molecular mechanisms, regulatory networks, and clinical relevance of TUG1 in breast cancer and type 2 diabetes mellitus. Identification of overlapping as well as disease-specific regulatory pathways may help in understanding the position of TUG1 at the cross-section of metabolic and oncogenic disorders and assessing TUG1 lncRNA's potential to serve as a diagnostic, prognostic, and therapeutic biomarker of breast cancer and T2DM [14].

2. **METHODS**

2.1 **Study Design and Reporting Framework**

The methodological framework of this review followed the reporting principles outlined in the PRISMA 2020 statement, ensuring transparency and reproducibility across all stages of study selection and synthesis [15]. The review design was structured to integrate experimental, clinical, and bioinformatics-based evidence, reflecting the multidisciplinary nature of long non-coding RNA research.

2.2 **Review Protocol**

Before the literature search and study selection could begin, a series of methodological protocols had to be put in place. Even though the protocols were not registered in the PROSPERO database, in order to avoid selection bias and to allow for consistency in the analysis, all critical methodological components, including the research question and the inclusion and exclusion criteria, data extraction elements, and synthesis methods, were established a priori. During the review process, no changes to the protocols were made post hoc.

2.3 Information Sources and Search Strategy

A thorough examination of the literature was completed using 3 different databases: PubMed, Scopus, and Web of Science. Various combinations of the search terms, including: TUG1, long non-coding RNAs, breast cancer, type 2 diabetes mellitus, and bioinformatics, including functionality enrichment analysis, pathway analysis, and ceRNA network construction, were applied using both thesaurus and free text strategies, and Boolean operators were utilized to achieve both search sensitivity and specificity. Searches were unbounded geographically, and to find any missing studies, the reference lists of relevant articles were manually inspected. Only articles published until the end of March, 2025 were included.

2.4 **Study Selection Criteria**

This research focuses on characterizing the expression patterns, biological functions, and regulatory scopes of TUG long non-coding RNA (lncRNA) in breast cancer and Type 2 diabetes mellitus (T2DM), as well as in both comorbidities concurrently. Also considering explanatory, clinical, or bioinformatics methods, the studies

advancing or analyzing regulatory relations, mechanistic links, or pathway relevance with clinical dimensions were accepted. For studies describing the order of events, without leaning on mechanisms or analyses, and where the research did not have a disease focus or were TUG lncRNA in breast cancer and T2DM, they were considered and archived.

2.5 Data Collection and Synthesis

Information was gathered from the selected studies as per the outlined parameters. For each study, information was grouped as per the predetermined study designs, medical conditions, biological and patient models, expression profiles of TUG lncRNA, converging microRNAs and their targets, enriched biological processes and pathways, and correlational study's findings. Given the wide variation in the study design, analytical methods, and outcomes reported, it was not possible to carry out a quantitative synthesis. Therefore, qualitative data synthesis was used to collate the findings from different studies.

2.6 Assessment of Study Quality and Sources of Bias

Even though there was no formal application of quantitative risk modeling tools, some consideration was given to the methodological quality and possible sources of bias in the synthesis, and the bias was systematically addressed while drawing the evidence. Differences in experimental models, sample size, and data processing and validation approaches were noted across studies. In bioinformatics studies, some other factors of heterogeneity were also present, i.e., differences in normalization approaches, statistical cut-offs, and prediction algorithms. All these factors were considered to ensure careful and systematic evaluation of the evidence.

2.7 Presentation of Study Characteristics

Data on TUG1 lncRNA and its relation to both breast cancer and type 2 diabetes mellitus, including the studies that were a part of this assessment, along with their primary characteristics and contributions, are organized and presented in Table 1. This overview allows for a cross-study comparison, even when studies differ in their methodology and analysis.

Table 1: Key studies investigating the role and regulatory functions of TUG lncRNA in breast cancer and type 2 diabetes mellitus.

2.7 Handling of Conflicting Evidence

Discrepancies in the literature prompted an increased reliance on studies that featured larger sample sizes as well as tightly controlled experimental or clinical designs, and integrated analyses that melded experimental and bioinformatics approaches. Such studies incorporated several tiers of analyses completed in conjunction with several layers of biological interpretation, allowing for more thorough and expanded analyses.

Conflicting conclusions were analyzed in the framework of the heterogeneity of clinical disease, biological models, and diverse methodologies, including the analytical, validation, and statistical thresholds employed. Instead of simply viewing the variation as weak points, the differences among the studies were appreciated as informative because of the context-dependent and distinct disease TUG lncRNA regulatory roles.

Table 1: Key studies investigating the role and regulatory functions of TUG lncRNA in breast cancer and type 2 diabetes mellitus.

Author (Year)	Disease	Study Type / Model	Main Findings	Analysis Type
Zhao et al. (2016) [8]	Breast cancer	In vitro & tissue expression (MCF-7 cells)	High TUG1 expression promotes cell proliferation and inhibits apoptosis via miR-9 regulation; TUG1 knockdown reduces proliferation and increases apoptosis.	qRT-PCR, cell viability, luciferase assay
Li et al. (2017) [9]	Breast cancer	Clinical + expression study	TUG1 is overexpressed in breast cancer tissues and promotes cellular proliferation and metastatic potential.	Tissue expression profiling
Fan et al. (2017) [10]	Breast cancer	In vitro / cell lines	Downregulation of TUG1 is associated with reduced proliferation, migration, and invasion in breast cancer models.	Cell-based assays
Heydari et al. (2023) [13]	Type 2 diabetes mellitus	Clinical patient study	Elevated TUG1 expression in T2DM patients correlates positively with glycemic control parameters and ER stress markers.	Expression profiling, correlation analysis
Su et al. (2022) [14]	Type 2 diabetes mellitus	Clinical T2DM cohort	TUG1 is upregulated in T2DM patients and exhibits potential diagnostic value within circRNA/lncRNA/miRNA regulatory networks.	qRT-PCR, ROC analysis

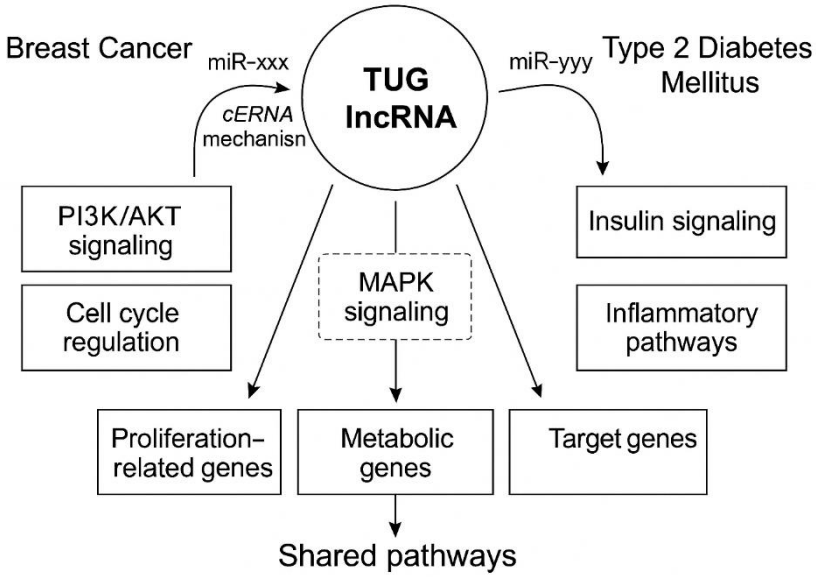

Figure 1: PRISMA 2020 flow diagram depicting the study selection process for the systematic review

3. Molecular and Biological Functions of TUG lncRNA

3.1 Mechanistic Modes of Action

Aside from transcriptional regulation, TUG lncRNA mediates a number of context-dependent processes as well. TUG lncRNA helps to control chromatin structure, as well as post-transcriptional regulation, thereby affecting a variety of cellular activities [18,20].

The regulatory roles of TUG lncRNA are multilayered and operate across multiple levels of gene regulation. The variety of potential regulatory roles TUG lncRNA has is greatly influenced by being specific to the tissue, cellular context, disease state, surrounding metabolic system, and interacting biomolecular components [21]. Overall, one can conclude that the processes that TUG lncRNA can regulate that are associated with DNA and RNA are anything but simple and are heavily influenced by the context surrounding those processes.

Furthermore, TUG lncRNA appears to function as an integrative regulatory scaffold linking chromatin-associated complexes, microRNAs, and downstream effector genes. Through this network-oriented mode of action, TUG coordinates gene expression programs governing cell proliferation, metabolic adaptation, cellular stress responses, and survival. These characteristics support the classification of TUG lncRNA as a central regulatory node within complex gene regulatory networks rather than a single-pathway effector [22,23].

3.2 Functional Enrichment and Pathway Analysis

Functional enrichment analyses of TUG-associated gene sets consistently identify pathways related to cell cycle regulation, apoptosis, glucose metabolism, insulin signaling, inflammation, and oxidative stress as prominently represented [24–26]. Cellular growth, metabolism, immunity, and stress, as well as related processes, are frequently indicated as enriched in the Gene Ontology metabolic processes component, while the molecular function subcategories of transcription regulation, protein, and RNA binding are often highlighted [27].

At the pathway level, both KEGG and Reactome identify the PI3K/AKT and MAPK pathways as being conclusively responsible for the control of cell growth, survival, and metabolism and are major contributors to the progression of breast cancer and the metabolic syndrome of diabetes TUG lncRNA regulatory networks converging to these pathways supports the hypothesis that TUG lncRNA participates in the molecular interrelation of oncogenic and metabolic disorders [30].

From a systems biology perspective, functional enrichment and pathway analyses provide a contextual framework for interpreting transcript-level changes rather than direct evidence of causality. In the case of TUG lncRNA, these analyses consistently point toward the involvement of coordinated biological processes and signaling pathways, suggesting that TUG-associated gene networks may participate in interconnected regulatory programs rather than isolated molecular effects. Collectively, these findings support the biological plausibility of TUG lncRNA involvement in coordinated signaling pathways, as summarized in Table 2 [24–30].

Table 2:Key biological processes and signaling pathways associated with TUG lncRNA identified through functional enrichment analyses

Category	Enriched Terms	Disease Context
GO: BP	Cell cycle, apoptosis	Breast cancer
KEGG	PI3K/AKT, MAPK	BC & T2DM
GO: MF	Protein binding	BC & T2DM

4. TUG lncRNA in Breast Cancer

4.1 Expression Patterns and Tumor Biology

Dysregulation of the lncRNA TUG has been identified in the independent samples of breast cancer tissues in comparison to adjacent normal tissues in a couple of studies [8-10]. Along with that, increased expression of TUG is also related to more advanced stages of the cancers, increased involvement of lymph nodes, higher proliferative index, and more aggressive cancer types [8,10]. These observations suggest that elevated TUG expression may contribute to tumor growth and disease progression of cancers. However, tumor expression subtypes of breast cancer have been noted to have a differing expression of TUG, which may suggest TUG may have differing biological functionality with the presence of different hormone receptors, a unique genetic background, and variant tumor microenvironments [12].

The differences above demonstrate the need for stratified and subtype-specific analyses of the breast cancer samples when determining the potential oncogenic relevance of TUG lncRNA. More simply, these differences suggest that it may be an oversimplified hypothesis to propose TUG as an uncontrolled oncogenic metric; rather, they suggest a contextual model of TUG in the biology of breast cancer [13].

4.2 ceRNA Networks and Post-Transcriptional Regulation

The importance of TUG lncRNA being involved in ceRNA networks has been highlighted in relation to breast cancer in multiple studies [14,31]. In the ceRNA networks, TUG functions as a molecular sponge of the tumor-suppressing miRNAs, thus sequestering these miRNAs and, in turn, modulating the expression of the oncogenic genes that are involved in the proliferation of the cells, their invasion, the epithelial-mesenchymal transition, as well as in the development of resistance to anticancer therapies [31–33].

Based on bioinformatics and in the context of the ceRNA network, TUG has been shown to focus on key survival, migratory, and metabolic pathways [34]. These results demonstrate that, transcript-wise, TUG lncRNA's role was more than regulatory but integrative as well. In saying that, it should also be noted that the existence of ceRNA frameworks is limited as a result of an array of factors, and therefore, the networks need confirming experiments to be valid [35].

4.3 Prognostic Relevance and Clinical Outcomes

Expressed evidence indicates that high-level TUG lncRNA expression shows considerable signs in negative breast cancer survival (decreased total survival and disease-free survival), and prediction of unfavorable outcomes of breast cancer is not rare, indicating that TUG lncRNA expression is a negative prognosticator in breast cancer [36-38]. Analyzing TUG-related gene signatures via ROC curve showed a moderate diagnostic ability and a sufficiently accurate prognostic capability, indicating that TUG's related gene signatures can be described as clinically relevant [39]. Cohort and treatment diversity and variation in methodology used in analyzing the data explain the lack of concentration in separating the heterogeneity present across the studies.

Importantly, most evidence supporting the prognostic relevance of TUG lncRNA in breast cancer is derived from retrospective analyses and publicly available transcriptomic datasets. This highlights the need for well-designed prospective clinical studies to validate the prognostic value of TUG lncRNA and to determine its potential utility in guiding personalized therapeutic strategies [40].

5. TUG lncRNA in Type 2 Diabetes Mellitus

5.1 Metabolic Regulation and Insulin Signaling

Regarding type 2 diabetes mellitus, TUG lncRNA has been associated with managing the expression of certain genes, namely, those engaged in the modulation of insulin signaling, glucose transport, lipid metabolism, and the equilibrium of energy in the cells [13, 14]. Analysis of TUG expression and its insulin-related signaling cascade effects, in the negative regulatory sense, indicates that it could be one of the factors of the metabolic disturbance and the deterioration of glucose homeostasis [41]. These findings will fit the developing concept of some lncRNAs modulating chronic low-grade inflammation and metabolic changes.

Although direct mechanistic studies of TUG lncRNA in metabolic tissues remain limited, available evidence suggests that TUG may be integrated into regulatory networks governing key metabolic pathways, including those related to endoplasmic reticulum stress, and supports the integration of far-range network integration in metabolic pathways. These elements can be the baseline for experimentally driven studies that will aim to demonstrate the direct links of TUG lncRNA to insulin resistance and metabolic alterations [42].

5.2 Inflammatory and Stress-Response Pathways

Chronic low-grade inflammation is the pathophysiology of T2DM's main characteristic. There is a TUG-related gene network concomitant with enrichments present in inflammation and cellular stress response pathways [43,44]. Immune response signal, oxidative stress, and stress mechanisms are pathways contributing to the development of metabolic deterioration. Functional enrichment profiles of TUG lncRNA–associated networks highlight a strong involvement in inflammatory and metabolic signaling pathways [45].

5.3 Methodological Insights from Bioinformatics-Based Investigations

Many of the integrated bioinformatics studies reviewed here incorporated the analysis of TUG lncRNA-affiliated regulatory networks. These studies included some or all of the following components: differential expression analysis, functional enrichment, construction of ceRNA networks, principal component analysis, ROC curve

analysis, and survival analysis [46–48]. These studies/frameworks do not employ traditional hypothesis formation and statistical testing, but are aimed at providing biological and systems-level insight.

Particularly, the functional enrichment and pathway analyses served to place alterations in the expression of genes and RNAs within the context of particular biological processes and networks of signal transduction. This context, provided by the particular biological processes and networks of signal transduction, is critical to the understanding of the findings arising from high-throughput studies and emphasizes the role of bioinformatics, in conjunction with experimental verification, to decipher the biological roles of TUG lncRNA [27,28,49].

Given that the primary objective of this review was the biological and functional interpretation of gene- and RNA-associated datasets using bioinformatics-based approaches, rather than the quantitative pooling of clinical effect sizes, the application of a meta-analysis was not appropriate [50]. Accordingly, functional enrichment, pathway analysis, and network-based strategies were emphasized to elucidate disease-relevant biological processes and regulatory mechanisms associated with TUG lncRNA.

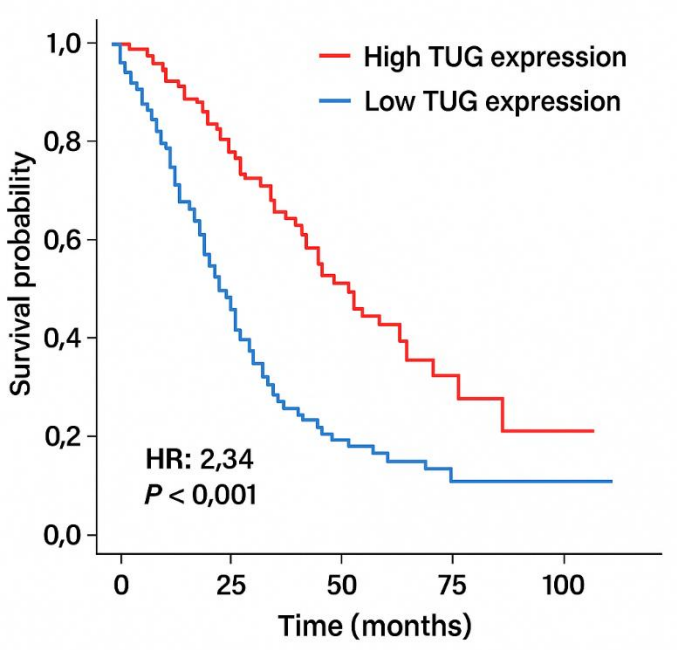

Figure 2: Survival Analysis of patients with high and low TUG expression. The results indicate at least two times increased associated risk with high expression.

6. Shared Molecular Pathways Linking Breast Cancer and T2DM

The fact that TUG-regulated molecular pathways converge in breast cancer as well as in type 2 diabetes mellitus raises the possibility that this lncRNA functions as a molecular bridge connecting metabolic dysregulation and the disease processes of diabetes-related cancer [30,51]. Instead of being restricted to disease-specific pathways, TUG lncRNA seems to be a part of the regulatory circuits that modulate core regulatory processes within the cells common to the two diseases, and to be a part of the integrating circuits that account for the well-known epidemiological associations between metabolic diseases and cancers.

Among the most consistently implicated pathways are those related to insulin and insulin-like growth factor signaling, which play central roles in both metabolic regulation and tumor biology. Dysregulation of these signaling axes contributes to metabolic imbalance and promotes malignant progression. TUG lncRNA has been reported to modulate convergent regulatory networks centered on the PI3K/AKT pathway, a key regulator of cell survival, proliferation, and metabolic homeostasis. Aberrant activation of PI3K/AKT signaling is a hallmark of breast cancer and is also critically involved in the development of insulin resistance and metabolic dysfunction in type 2 diabetes mellitus [7,9].

Inflammatory signaling represents another major point of convergence between breast cancer and type 2 diabetes mellitus. Chronic low-grade inflammation is a defining feature of metabolic disease and is increasingly recognized as a driver of tumor initiation and progression. Bioinformatics analyses of TUG-associated gene networks consistently reveal enrichment of inflammatory cascades, cytokine signaling pathways, and cellular stress-response mechanisms. These findings suggest that TUG lncRNA may contribute to a pro-inflammatory cellular environment that links metabolic dysfunction with oncogenic processes, rather than acting as a direct causal driver [7,9].

At the systems level, incorporated metabolic cues along with inflammatory stimuli and signals through TUG lncRNA coordinate gene expression programs and influence processes related to disease. TUG's involvement in the regulation of epigenetics and in ceRNAs gives TUG the potential to fine-tune several downstream effectors and amplify the total biological consequence of interconnected pathways. Such cross-scale regulation is in

opposition to the notion of complex multi-system dysregulation in biological systems such as T2DM and cancer, which perturbs through interconnected regulatory pathways, and is instead purely systemic in molecular dysregulation.

Current evidence indicates that the functional role of TUG lncRNA varies across disease contexts and experimental settings. While several studies associate TUG expression with disease progression, existing data—largely derived from associative and bioinformatics-based analyses—do not yet allow definitive conclusions regarding causality. It therefore remains unclear whether TUG lncRNA functions primarily as a downstream molecular marker or as an active driver of disease pathogenesis. Addressing this question will require well-designed longitudinal studies and integrative multi-omics approaches to clarify the temporal and functional roles of TUG lncRNA across metabolic and oncogenic conditions [52].

Integrated analyses of TUG-associated signaling pathways across breast cancer and type 2 diabetes mellitus reveal a shared involvement of metabolic and oncogenic regulatory processes. These novel potential pathways associated with TUG suggest that TUG lncRNA is involved in disease mechanisms, such as cancer and diabetes. These findings have great potential as lncRNA TUG-associated pathways could lead to integrated diagnostic and prognostic and lncRNA TUG therapies at the cancer diabetes interface metabolic–oncogenic disease continuum.

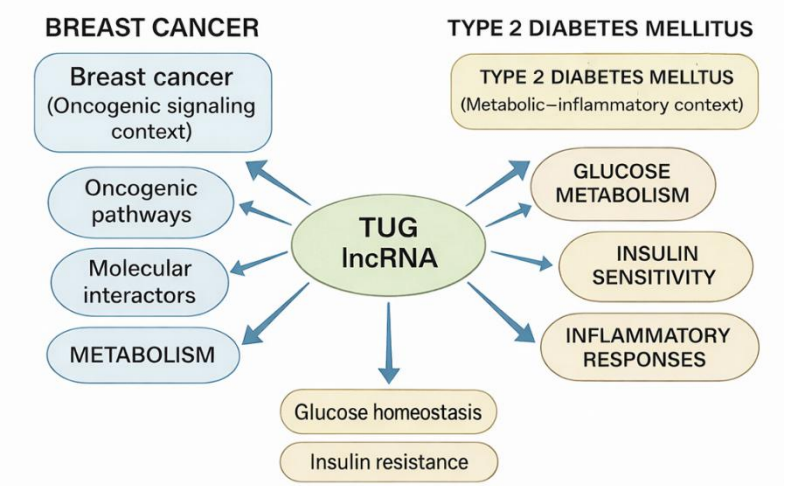

Figure 3: Schematic overview of TUG lncRNA regulatory mechanisms and associated molecular pathways in breast cancer and type 2 diabetes mellitus.

6.1 Conceptual Model of TUG lncRNA Integration Across Metabolic and Oncogenic Pathways

Emerging evidence supports a conceptual model in which TUG lncRNA functions as an integrative regulatory node linking metabolic and oncogenic signaling networks. At the epigenetic level, TUG modulates chromatin-associated complexes and transcriptional programs that influence cell proliferation and metabolic adaptation. In parallel, TUG participates in competitive endogenous RNA (ceRNA) networks, sequestering regulatory microRNAs and fine-tuning the expression of downstream target genes. These layers of regulation all focus on the fundamental pathways in signaling, particularly the PI3K/AKT and MAPK pathways, which regulate growth, survival, and cellular responses to insulin, as well as inflammation. TUG LncRNA, through the multi-layered regulatory structure, via cross-talk between the metabolic stress and the oncogenic pathway, could serve as an integrator of the pathways that lie on the nexus of breast cancer and type 2 diabetes mellitus.

7. Clinical Implications and Translational Potential

Given the context-dependent activity of TUG regulatory networks across multiple diseases, therapeutic targeting of TUG requires careful consideration to minimize potential off-target and systemic effects [55]. In regard to diagnostics, TUG lncRNA may provide opportunities for early disease detection and risk stratification due to aberrant expression being detectable in tissues and/or circulation. In cancer and metabolic disease, the diagnostic test may become more sensitive and specific by combining TUG lncRNA expression with other molecular markers [39].

Prognostically, several investigators report that TUG lncRNA-associated gene signatures may add to the understanding of the disease, its progression, and the response to treatment, as well as the overall outcomes of the patients. Receiver Operating Characteristic (ROC) curves show that these TUG lncRNA profiles may have moderate to high accuracy, and therefore, are useful in prediction and in clinical guidance [54]. The prognostic impact of TUG lncRNA is, however, context-dependent, emphasizing the need to evaluate disease and subtype-specific TUG lncRNA prognostic impact.

Targeting TUG-associated lncRNA TUG regulatory networks (and maybe downstream from effectors or upstream from regulators) would be a novel way to impact the course of the disease and become a candidate to consider therapeutically. This is particularly the case in patients with paradoxical metabolic and oncological diseases and

comorbidities, where molecular networks paradoxically determine the complexity of the disease and the overall impact of the disease burden. And while TUG regulatory networks work on a wide variety of diseases in a context-dependent way, TUG targeting therapeutically is a sensitive instrument, and caution will be most advised to eliminate the possibility of off-target effects and overall systemic effects [55].
The complexity of the observations will lead to TUG lncRNA participating in the systems of precision medicine, to a greater extent, in the developed prognosis, diagnostics, and therapy.

8. Strengths of This Review

This systematic review integrates experimental, clinical, and bioinformatics-based evidence to provide a cross-disease synthesis of TUG lncRNA function in breast cancer and type 2 diabetes mellitus. Beyond descriptive summarization, the review emphasizes functional enrichment, pathway-level interpretation, and regulatory network analyses to offer a systems-level perspective on TUG-mediated regulation. Through comparative analysis across disease contexts, the review highlights both shared and disease-specific molecular mechanisms, illustrating how metabolic and oncogenic processes may converge on common regulatory architectures. This cross-disease perspective extends beyond disease-restricted analyses and supports the relevance of the present review to translational and precision medicine research.

9. Limitations, Knowledge Gaps, and Future Directions

Despite the growing body of literature addressing the involvement of TUG lncRNA in breast cancer and type 2 diabetes mellitus, several important knowledge gaps and methodological limitations remain. Most available studies are based on associative analyses derived from retrospective datasets, which limits the ability to draw causal or mechanistic conclusions regarding the role of TUG lncRNA in disease initiation and progression.
Although bioinformatics-driven approaches provide valuable systems-level insights, their findings cannot be interpreted in isolation and require experimental validation to support biological relevance. Substantial heterogeneity is evident across studies with respect to experimental models, patient cohorts, analytical methodologies, and validation strategies. Variations in data preprocessing pipelines, normalization procedures, statistical thresholds, and target prediction algorithms further contribute to inconsistent findings and hinder direct comparison between studies. Moreover, a considerable proportion of bioinformatics-based predictions lack sufficient experimental confirmation, restricting their translational applicability.
The tissue-specific and disease-context–dependent functions of TUG lncRNA also remain incompletely characterized. Differences across cancer subtypes, metabolic states, and inflammatory microenvironments highlight the need for carefully designed functional studies that account for biological context. Future research should prioritize standardized analytical frameworks, rigorous experimental validation, and the integration of multi-omics approaches, including transcriptomics, epigenomics, proteomics, and metabolomics. In addition, well-designed prospective and longitudinal studies are required to clarify the temporal dynamics of TUG expression and to assess its potential clinical utility. Finally, definitive gain- and loss-of-function studies in disease-relevant biological models are essential to establish the causal roles of TUG lncRNA in oncogenic and metabolic disease processes.

10. CONCLUSION

This systematic review compiles and analyzes the experimental, clinical, and bioinformatics-based evidence regarding the role of TUG lncRNA in breast cancer and type 2 diabetes mellitus. The data we have indicate that TUG lncRNA is involved in the regulation of interrelated molecular pathways with cellular proliferation, metabolic, and inflammation-related stress disease processes in oncogenic and metabolic diseases.
Since TUG lncRNA is involved in the regulatory networks of cancer and metabolic dysfunction, it probably is not a disease-specific regulator but a common molecular entity. This regulatory overlap of TUG lncRNA strengthens the case for its use as a potential biomarker, but also calls for a close understanding of the circumstances under which TUG lncRNA acts.
Most importantly, the body of evidence synthesized in this systematic review highlights the value of integrated methodological approaches that combine molecular biology, bioinformatics, and molecular medicine for elucidating the mechanisms underlying complex diseases. Future investigations employing standardized analytical frameworks and integrated bioinformatics and molecular biology approaches will be essential to further define the biological and clinical relevance of TUG lncRNA at the intersection of oncogenic and metabolic disease processes.

10.1. Data Availability Statement

The current study did not generate or analyze any data. All data that support this study were obtained from other studies that have been published and are therefore already present in the references.

11. REFERENCES

1. Esteller M. Non-coding RNAs in human disease. Nat Rev Genet. 2011;12(12):861–874.
2. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016;17(1):47–62.
3. Schmitt AM, Chang HY. Long noncoding RNAs in cancer pathways. Cancer Cell. 2016;29(4):452–463.
4. Bhan A, Soleimani M, Mandal SS. Long noncoding RNA and cancer: a new paradigm. Cancer Res. 2017;77(15):3965–3981.
5. Polyak K. Heterogeneity in breast cancer. J Clin Invest. 2011;121(10):3786–3788.
6. DeFronzo RA, Ferrannini E, Groop L, et al. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015;1:15019.
7. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–867.
8. Zhao XB, Ren GS. Long non-coding RNA TUG1 promotes breast cancer cell proliferation and inhibits apoptosis via targeting miR-9. Eur Rev Med Pharmacol Sci. 2016;20(24):5364–5371.
9. Zhang Y, Song X, Wang X, et al. Long noncoding RNA TUG1 promotes breast cancer cell proliferation and invasion through epigenetic repression of tumor suppressor genes. Cancer Cell Int. 2018;18:38.
10. Xu Y, Wang J, Qiu M, et al. Upregulation of lncRNA TUG1 promotes breast cancer progression via miRNA-mediated regulatory networks. J Cell Mol Med. 2020;24(7):4150–4162.
11. Katsushima K, Natsume A, Ohka F, et al. Targeting the Notch-regulated lncRNA TUG1 for glioma treatment. Nat Commun. 2016;7:13616.
12. Li Z, Shen J, Chan MT, Wu WK. TUG1: a pivotal oncogenic long non-coding RNA in human cancers. Cell Prolif. 2020;53(8):e12833.
13. Heydari M, Yousefi H, Namdar A, et al. Expression analysis of long non-coding RNA TUG1 in patients with type 2 diabetes mellitus. J Diabetes Metab Disord. 2023;22:23–31.
14. Su Y, Zhang T, Zhang L, et al. Integrated analysis of circRNA–lncRNA–miRNA networks reveals potential biomarkers in type 2 diabetes mellitus. BMC Endocr Disord. 2022;22:265.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
16. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. Wiley; 2019.
17. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses (PRISMA). PLoS Med. 2009;6(7):e1000097.
18. Quinn JJ, Chang HY. Unique features of long non-coding RNA biogenesis and function. Nat Rev Genet. 2016;17(1):47–62.
19. Yao RW, Wang Y, Chen LL. Cellular functions of long noncoding RNAs. Nat Cell Biol. 2019;21(5):542–551.
20. Mattick JS, Amaral PP, Carninci P, et al. Long non-coding RNAs: definitions, functions, and challenges. Nat Rev Mol Cell Biol. 2023;24:430–447.
21. Ulitsky I, Bartel DP. lincRNAs: genomics, evolution, and mechanisms. Cell. 2013;154(1):26–46.
22. Kopp F, Mendell JT. Functional classification and experimental dissection of long noncoding RNAs. Cell. 2018;172(3):393–407.
23. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol. 2021;22(2):96–118.
24. Ashburner M, Ball CA, Blake JA, et al. Gene ontology: a tool for the unification of biology. Nat Genet. 2000;25(1):25–29.
25. Kanehisa M, Goto S. KEGG: Kyoto Encyclopedia of Genes and Genomes. Nucleic Acids Res. 2000;28(1):27–30.
26. Kanehisa M, Furumichi M, Tanabe M, Sato Y, Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. Nucleic Acids Res. 2017;45(D1):D353–D361.
27. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach. Proc Natl Acad Sci USA. 2005;102(43):15545–15550.
28. Manning BD, Toker A. AKT/PKB signaling: navigating the network. Cell. 2017;169(3):381–405.
29. Samatar AA, Poulikakos PI. Targeting RAS–ERK signalling in cancer. Nat Rev Drug Discov. 2014;13(12):928–942.
30. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer—viewpoint of the IARC. N Engl J Med. 2016;375:794–798.
31. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language. Cell. 2011;146(3):353–358.
32. Tay Y, Rinn J, Pandolfi PP. The multilayered complexity of ceRNA crosstalk. Nature. 2014;505(7483):344–352.
33. Thomson DW, Dinger ME. Endogenous microRNA sponges: evidence and controversy. Nat Rev Genet. 2016;17(5):272–283.
34. Barabási AL, Gulbahce N, Loscalzo J. Network medicine: a network-based approach to human disease. Nat Rev Genet. 2011;12(1):56–68.

35. van Rooij E, Kauppinen S. Development of microRNA therapeutics is coming of age. EMBO Mol Med. 2014;6(7):851–864.
36. Zhang Y, Wang F, Chen G, et al. Prognostic value of long noncoding RNAs in breast cancer. Oncotarget. 2017;8(21):34556–34565.
37. Li J, Tian H, Yang J, et al. Prognostic role of lncRNA TUG1 in cancers: a meta-analysis. Oncotarget. 2017;8(59):100527–100535.
38. Zhou Y, Zhang X, Klibanski A. Genetic and epigenetic regulation of long noncoding RNAs in cancer. Trends Endocrinol Metab. 2012;23(12):568–576.
39. Pepe MS, Etzioni R, Feng Z, et al. Phases of biomarker development for early detection of cancer. J Natl Cancer Inst. 2001;93(14):1054–1061.
40. Altman DG, Royston P. The cost of dichotomising continuous variables. BMJ. 2006;332(7549):1080.
41. Morán I, Akerman I, van de Bunt M, et al. Human β-cell transcriptome analysis uncovers lncRNAs involved in type 2 diabetes. Cell Metab. 2012;16(4):435–448.
42. Ruan Y, Lin N, Ma Q, et al. Circulating long noncoding RNAs as potential biomarkers in metabolic diseases. Mol Metab. 2020;32:1–10.
43. Donath MY, Shoelson SE. Type 2 diabetes is an inflammatory disease. Nat Rev Immunol. 2011;11(2):98–107.
44. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome, and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141–150.
45. Hotamisligil GS, Erbay E. Nutrient sensing and inflammation in metabolic diseases. Nat Rev Immunol. 2008;8(12):923–934.
46. Love MI, Huber W, Anders S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 2014;15(12):550.
47. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for functional enrichment analysis. OMICS. 2012;16(5):284–287.
48. Shannon P, Markiel A, Ozier O, et al. Cytoscape: a software environment for biomolecular interaction networks. Genome Res. 2003;13(11):2498–2504.
49. Robinson MD, McCarthy DJ, Smyth GK. edgeR: a Bioconductor package for differential expression analysis. Bioinformatics. 2010;26(1):139–140.
50. Egger M, Davey Smith G, Altman DG. Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd ed. BMJ Publishing Group; 2001.
51. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. Diabetes Care. 2010;33(7):1674–1685.
52. VanderWeele TJ. Explanation in causal inference: methods for mediation and interaction. Oxford University Press, 2015.
53. Calin GA, Croce CM. MicroRNA signatures in human cancers. Nat Rev Cancer. 2006;6(11):857–866.
54. McShane LM, Hayes DF. Publication of tumor marker research results. J Clin Oncol. 2012;30(34):4223–4232.
55. Matsui M, Corey DR. Non-coding RNAs as drug targets. Nat Rev Drug Discov. 2017;16(3):167–179.