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In Silico Analysis of miRNA in Type 2 Diabetes Melitus and Colorectal Cancer: Molecular Connections and Biomarker Potential

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia caused by insulin resistance and impaired insulin secretion, affecting 537 million adults worldwide in 2021 and projected to reach 783 million by 2045. T2DM increases the risk of malignancies, particularly colorectal cancer (CRC). MicroRNAs (miRNAs), small non-coding RNAs regulating gene expression, have emerged as molecular links between T2DM and CRC through their roles in proliferation, apoptosis, metabolism, and insulin signaling. Shared pathways, including PI3K/AKT/mTOR and IGF-1 signaling, support common pathogenic mechanisms. Due to their stability and disease-specific expression, miRNAs represent promising biomarkers. This study employs an in silico bioinformatics approach to identify shared dysregulated miRNAs, predict their target genes, analyze relevant molecular pathways, and evaluate their regulatory roles connecting T2DM with CRC development.

Methods: This study employed an in silico approach using miRNA expression data from GEO datasets (GSE262614, GSE185845, GSE115513, GSE156732), analyzed with R under the criteria $|Log2FC| > 1$ and $p < 0.05$. Differentially expressed miRNAs from each dataset were compared using a Venn diagram to identify consistently dysregulated miRNAs. Target gene prediction was conducted using miRTargetLink 2.0 and miRWalk, followed by validation with mRNA datasets GSE25724 and GSE44076. Pathway enrichment analyses were performed using GO and KEGG through ShinyGO and Enrichr

Results: Analysis revealed that hsa-miR-182-3p was the only miRNA consistently experiencing upregulation in both T2DM and colorectal cancer. From hsa miR-182-3p a total of 9 validated target genes were identified, and most of them are involved in MAPK, mTOR, cell cycle, and insulin signaling pathways which are key pathways implicated in both diseases.

Conclusion: This study indicates that hsa-miR-182-3p may serve as a molecular mediator linking the pathophysiological mechanisms of T2DM, such as insulin resistance and hyperinsulinemia, with colorectal cancer tumorigenesis, and may hold potential as a biomarker.

Keywords: Type 2 diabetes mellitus, Colorectal cancer, In silico, hsa miR-182-3p

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by hyperglycemia due to impaired insulin secretion or action. In 2021, approximately 537 million adults worldwide were affected, with projections reaching 783 million by 2045.[1] In Indonesia, the prevalence was reported at 19.47 million cases.[2] T2DM is associated with an increased risk of several malignancies, including colorectal cancer (CRC). Epidemiological studies have shown that patients with T2DM have a significantly higher risk of developing CRC.[3–5] CRC remains one of the most frequently diagnosed cancers and a leading cause of cancer-related mortality worldwide.[6]

MicroRNAs (miRNAs), small non-coding RNA molecules involved in post-transcriptional gene regulation, have emerged as important molecular links between T2DM and CRC. Dysregulated miRNAs contribute to cellular proliferation, apoptosis, and metabolic regulation, thereby influencing tumor development and insulin signaling.[7,8] Shared signaling pathways, including PI3K/AKT/mTOR and IGF-1, further connect the molecular mechanisms of both diseases.[9] Several miRNAs, such as miR-21, miR-34a, and miR-146a, have been reported to be aberrantly expressed in both T2DM and CRC, highlighting their potential as biomarkers and therapeutic targets.[10,11]

Biomarkers are objectively measurable biological indicators that reflect pathological processes or therapeutic responses.[12,13] Among emerging biomarker candidates, miRNAs are particularly promising due to their remarkable stability in biofluids, tissue specificity, and ability to reflect underlying molecular changes.[14] In T2DM, miRNAs have been explored as biomarkers for disease onset, progression, and complications; in CRC, circulating miRNAs have shown potential for early detection and prognosis. Nevertheless, efforts to identify miRNAs that capture the shared molecular basis of metabolic disorder and tumorigenesis are limited. A systematic in silico approach that integrates multiple datasets and bioinformatics tools can improve the identification of robust miRNA candidates that are relevant across diseases.

To address this gap, the present study employs an in silico bioinformatics strategy to identify miRNAs that are consistently dysregulated in T2DM and CRC. By integrating multiple publicly available miRNA expression datasets and applying stringent criteria for differential expression and cross-dataset overlap, we aimed to identify miRNAs with consistent dysregulation patterns. Predicted target genes of these miRNAs were further validated using

independent mRNA expression datasets, followed by functional enrichment analyses to characterize associated biological pathways. Through this multi-layered approach, we sought to elucidate miRNA-driven regulatory networks that may mechanistically link T2DM with CRC.

The novelty of this study lies in its integrative analysis across four independent expression datasets, rigorous validation of target genes using disease-specific mRNA profiles, and comprehensive pathway analysis to interpret biological relevance. Unlike previous studies that examine miRNAs within a single disease context, this research identifies miRNAs that concurrently associate with metabolic dysregulation and oncogenic signaling. This approach has the potential to reveal molecular mediators that contribute to the elevated CRC risk observed in individuals with T2DM and to uncover miRNA candidates with dual utility as biomarkers or therapeutic targets for both conditions.

Specifically, this study aims to identify miRNAs commonly associated with both T2DM and CRC, predict their target genes, analyze the significant molecular signaling pathways involving these targets, and evaluate the potential regulatory roles of miRNAs as molecular mediators linking the pathophysiology of T2DM to CRC development through gene regulation and tumorigenic pathway activation.

METHODS

Study Design

This research is an exploratory study employing an in silico approach

Data Acquisition

This study used publicly publicly available microRNA expression datasets obtained from the Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/gds). Two datasets representing type 2 diabetes mellitus (GSE262614 and GSE185845) and two datasets representing colorectal cancer (GSE25609 and GSE39833) were selected based on sample type, sample quality, and relevance. All the datasets were then analyzed using R software (version 4.5.1).

Identification of Dysregulated miRNAs

Differential expression analysis was performed with cutoffs set at $p < 0.05$ and $|Log2FC| > 1$ to ensure the identification of statistically significant and biologically meaningful miRNA changes. After obtaining the results from differential expression analyses, the lists of significantly dysregulated miRNAs from each dataset were compared to identify shared patterns between T2DM and CRC. Venn diagram analysis was used to visualize the overlapping miRNAs and determine which candidates

appeared consistently across all the datasets. This comparison helped narrow down the potential miRNAs that may play a meaningful regulatory role in their shared molecular mechanisms.

Identification of Target Genes

To investigate the regulatory effects of the identified miRNA candidate, predicted target genes were collected using two independent bioinformatics platforms: miRTargetLink 2.0 (https://ccb-compute.cs.uni-saarland.de/mirtargetlink2) and miRWalk (http://mirwalk.umm.uni-heidelberg.de).The combination of these tools generated a comprehensive list of genes potentially regulated by the selected microRNA.

Validation of Target Genes

Validation of the predicted target genes was performed using mRNA expression data from two additional GEO datasets: GSE25724, which contains pancreatic islet samples from individuals with T2DM, and GSE44076, which contains colorectal tissue samples from CRC patients. Genes that demonstrated consistent expression patterns across both mRNA datasets were considered validated targets of the candidate microRNA. This process ensured that the final set of targets reflected biologically relevant gene–miRNA interactions in the context of both diseases.

GO and KEGG Analyses

Functional enrichment analysis was carried out to explore the biological significance of the validated target genes. Gene Ontology (GO) analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis were performed using ShinyGO (https://bioinformatics.sdstate.edu/go) and Enrichr (https://maayanlab.cloud/Enrichr). These analyses identified enriched biological processes, molecular functions, cellular components, and canonical signaling pathways associated with the validated genes. The results provided insight into the molecular mechanisms that may link T2DM and CRC through the activity of the candidate miRNA.

RESULTS

MicroRNA Expression in T2DM and CRC

The analysis of the four GEO datasets revealed distinct patterns of microRNA dysregulation in both type 2 diabetes mellitus (T2DM) and colorectal cancer (CRC) as can be seen in **Table 1.** When the two datasets of T2DM are compared a total of 5 miRNAs were found upregulated in both GSE262614 and GSE185845, while no miRNA show consisten downregulation. Meanwhile fron the two datasets of CRC a total of 18 miRNA were found upregulated and 3 miRNA were found downregulated in both GSE25609 and GSE39833. The information of the overlapping

Table 1. Type 2 Diabetes Mellitus and Colorectal Cancer miRNA Datasets

No	Disease	Accession Number	Samples	Disease	Control	Up regulate	Down regulate	Total miRNA
1	Type 2 Diabetes Mellitus	GSE262614	Plasma exosomes	5	5	67	140	207
2		GSE185845	Blood serum	44	16	115	11	126
3	Colorectal Cancer	GSE25609	Plasma	20	20	35	11	46
4		GSE39833	Serum exosomes	88	11	1431	446	1.877

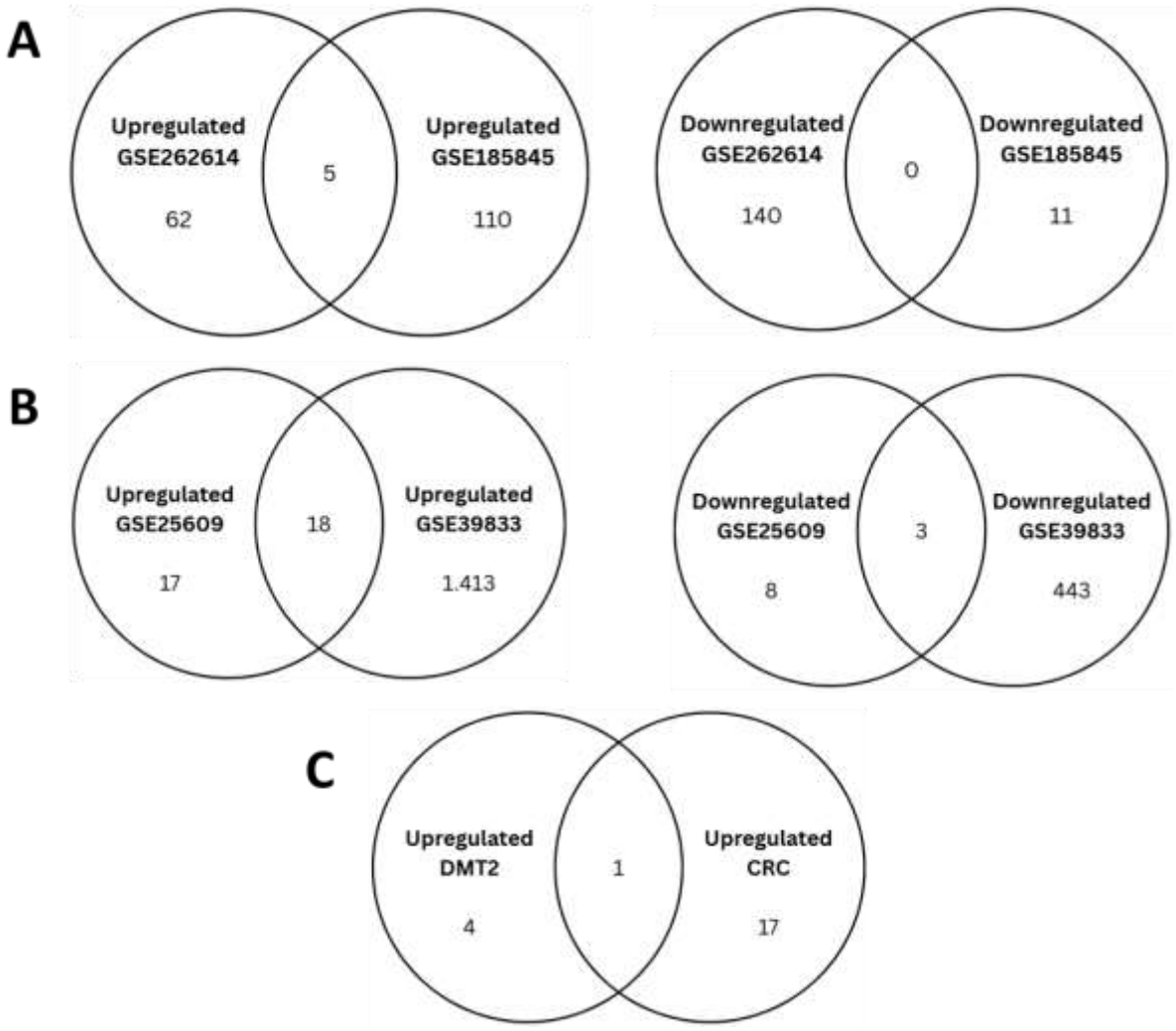

Fig 1. Venn diagram showing the overlapping microRNAs between two T2DM datasets (A) and two CRC datasets (B). The overlapped datasets from both T2DM and CRC are illustrated in (C).

miRNAs was visualized using a Venn diagram as displayed in Figure 1A,B. Considering there were no consistently downregulated miRNAs in T2DM datasets, further analyses will focused on upregulated miRNAs only. Among the 5 miRNAs upregulated in T2DM and 18 miRNAs upregulated in CRC, hsa-mir-182-3p emerged as the only miRNA consistently dysregulated in both T2DM and CRC datasets as can be seen in Figure 1C. This overlap indicates that hsa-miR-182-3p may play a central regulatory role in molecular pathways shared between the two diseases. Detailed dataset are presented as Figure 2

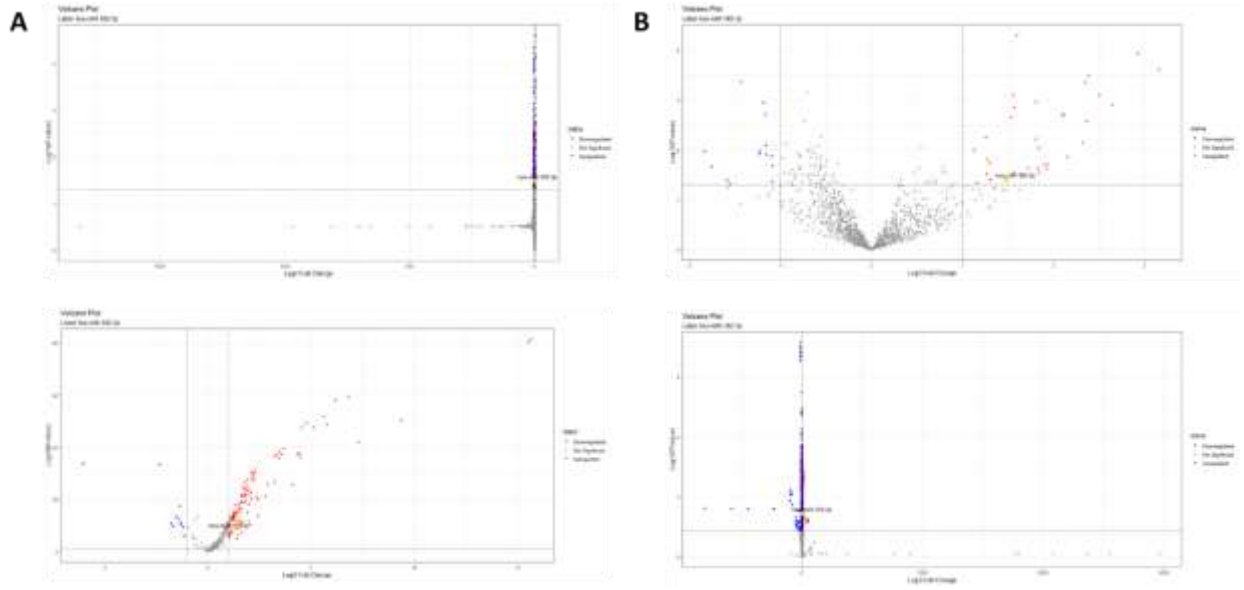

Fig 2. Volcano plot showing microRNAs expressions in T2DM datasets (A) and CRC datasets (B)

Target Gene Identification and Validation

Target gene prediction for hsa-miR-182-3p through miRTargetLink 2.0 and miRWalk initially yielded a total of 10,544 unique predicted genes as can be seen in **Table 2.** These genes were then subjected to further validation using the down regulated mRNA expression from GSE25724 (representing pancreatic islets from individuals with T2DM) and GSE44076 (representing colorectal tissue from CRC patients) as can be seen in **Table 3.** The two mRNA datasets were then compared using Venn diagram analysis resulting in 11 common gene as can be seen in **Figure 3A**. Through expression cross-referencing between the combined gene dataset from mRNA and predicted genes, 9 genes were confirmed as validated targets of hsa-miR-182-3p in both disease contexts as can be seen in **Figure 3B**. These validated genes include those involved in metabolic regulation, cellular proliferation, and inflammatory signaling—biological processes central to both T2DM pathogenesis and colorectal tumorigenesis.

Table 2. Gene Datasets of hsa-miR-182-3p from miRTargetLink 2.0 and miRWalk

No	In silico analysis platform	Total Gene
1	miRTargetLink2	40
2	miRWalk	10.531
3	Common data	27
4	Total unique data	10.544

Table 3. Gene Datasets of Type 2 Diabetes Mellitus and Colorectal Cancer Based on Their mRNA

No	Disease	Accession Number	Samples	Disease	Control	Total Gene
1	Type 2 Diabetes Mellitus	GSE25724	Pancreatic islets	6	7	84
2	Colorectal Cancer	GSE44076	Colorectal tissue	98	98	900

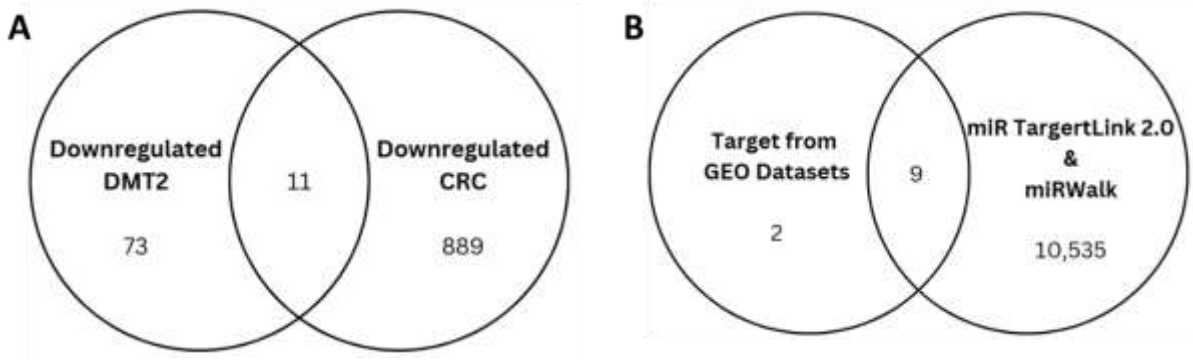

Fig 3. Venn diagram showing the overlapping gene that is downregulated in T2DM and CRC (A). The overlapped downregulated genes in DMT2 and CRC obtained from GEO are matched with predicted target of hsa-mir-182-3p based on both miR TargetLink and miRWalk (B).

GO and KEGG Analysis

Functional enrichment analysis of the 9 validated target genes revealed significant associations with several key biological functions and pathways. Gene Ontology (GO) analysis demonstrated enrichment in biological processes such as Peptidyl-tyrosine autophosphorylation, molecular functions including epidermal growth factor receptor activity, and cellular components such as Insulin receptor complex as can be seen in **Figure 4**. KEGG pathway analysis further highlighted the

involvement of the validated genes in major signaling pathways, including MAPK signaling, mTOR signaling, insulin signaling, and cell cycle regulation. Additionally, several cancer-associated pathways—such as those related to melanoma, prostate cancer, glioma, and breast cancer were strongly enriched as can be seen in **Figure 4** and **Table 4**. These findings suggest that hsa-miR-182-3p influences regulatory networks that intersect both metabolic dysfunction and oncogenic progression.

Table 4. Gene Datasets of Type 2 Diabetes Mellitus and Colorectal Cancer Based on Their mRNA

No	Name	Adjusted P-Value
1	Proteoglycans in cancer	0,00005642
2	Ras signaling pathway	0,00005642
3	Adherens junction	0,00005642
4	Melanoma	0,00005642
5	Prostate cancer	0,0001110
6	Breast cancer	0,0003216
7	Hepatocellular carcinoma	0,0004106
8	Rap1 signaling pathway	0,0006976
9	MAPK signaling pathway	0,001676
10	Human papillomavirus infection	0,002138
11	PI3K-Akt signaling pathway	0,002175
12	Central carbon metabolism in cancer	0,002175
13	Glioma	0,002304
14	ErbB signaling pathway	0,002746
15	Parathyroid hormone synthesis, secretion and action	0,003940
16	HIF-1 signaling pathway	0,003940
17	Pathways in cancer	0,004977
18	FoxO signaling pathway	0,005040
19	Signaling pathways regulating pluripotency of stem cells	0,005571
10	Phospholipase D signaling pathway	0,005571
21	Gastric cancer	0,005571
22	Hepatitis C	0,005895
23	Focal adhesion	0,009160
24	Regulation of actin cytoskeleton	0,01029
25	Coronavirus disease	0,01115
26	Calcium signaling pathway	0,01146
27	Endocytosis	0,01213
28	Bladder cancer	0,03987
29	Ovarian steroidogenesis	0,04779

DISCUSSION

The present in silico analysis identifies hsa-miR-182-3p as a miRNA consistently upregulated in both T2DM and colorectal cancer (CRC), implicating it as a molecular intersection between metabolic dysfunction and tumorigenesis. Despite the greater abundance of literature on the miR-182 family's 5p strand, emerging evidence suggests that both arms of miR-182 can exert biological function through post-transcriptional regulation of key signaling pathways. In cancer, miR-182 has been widely characterized as an oncomiR, promoting proliferation, invasion, and chemoresistance across multiple malignancies, including CRC.[15,16] For example, miR-182 drives CRC cell proliferation and invasion by targeting *DAB2IP*, thereby facilitating activation of the PI3K/AKT/mTOR and Wnt/β-catenin pathways—major mediators of cell survival, motility, and growth.[15,17–19] This oncogenic mechanism aligns with our enrichment analyses showing involvement of MAPK, mTOR, and cell cycle pathways among validated target genes, reinforcing the idea that miR-182-3p modulates central tumorigenic signaling networks in CRC.

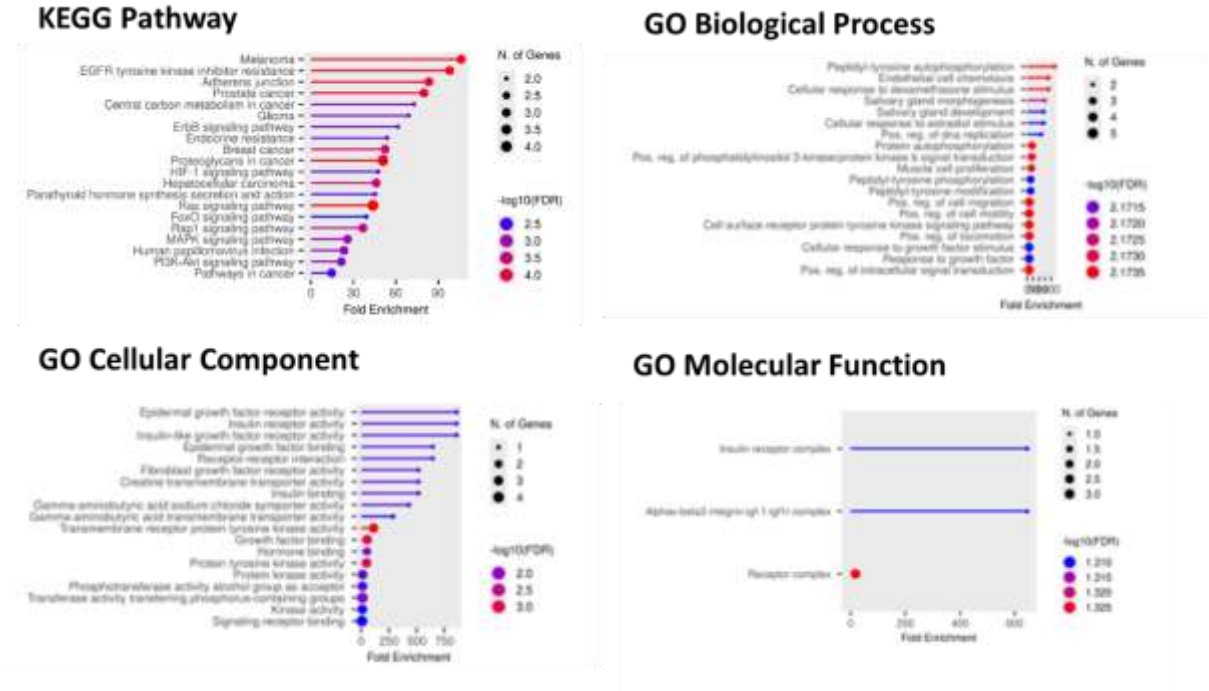

Fig 4. Results of KEGG pathway and Gene Ontology (GO) analysis on validated genes using ShinyGO 0.85

Mechanistically, miR-182 family members influence oncogenesis through diverse targets. In CRC, suppression of *ST6GALNAC2* by miR-182 enhances PI3K/AKT signaling, increasing migration, adhesion, and angiogenesis in malignant cells.[20] Beyond individual targets, miR-182 impacts pathways regulating cytoskeletal dynamics, apoptosis, and epithelial–mesenchymal transition (EMT) by modulating transcription factors and structural proteins.[21,22] Although most detailed functional characterizations focus on the 5p strand, the consistent upregulation of the 3p strand in both T2DM and CRC datasets suggests that hsa-miR-182-3p may have similarly potent effects on gene networks controlling cell proliferation and metabolic signaling, either by directly repressing target mRNAs or by complementing actions of miR-182-5p.

While miR-182's role in cancer is increasingly recognized, its involvement in metabolic disease, particularly T2DM, has only recently gained attention.[8] Dysregulated miRNA expression contributes to key pathogenic features of insulin resistance and β-cell dysfunction by targeting genes involved in glucose uptake, insulin signaling, metabolism of lipid, and inflammation.[23] Although specific functional studies on miR-182-3p in T2DM are limited, broader reviews implicate miR-182 family members in insulin resistance and metabolic regulation.[24] For instance, increased expression of miR-182 family members has been associated with altered insulin sensitivity and inflammatory responses in metabolic tissues, suggesting a role in the etiopathogenesis of T2DM.[25] These functional insights are concordant with our enrichment results implicating insulin signaling pathways among hsa-miR-182-3p targets, which provides a plausible biological link between miRNA dysregulation and impaired glucose homeostasis.

Biomarker discovery in both T2DM and CRC has evolved substantially over the last decade, with circulating miRNAs emerging as stable, non-invasive indicators of disease state and progression. In T2DM, miRNAs such as miR-126, miR-146a, and miR-375 have shown consistent associations with insulin resistance and β-cell failure in clinical cohorts, and alterations in these miRNAs often precede overt clinical onset.[26] In CRC, panels of miRNAs including miR-21, miR-29, and miR-92a have been evaluated as potential diagnostic markers, with some demonstrating sensitivity and specificity comparable to conventional markers like carcinoembryonic antigen (CEA).[27] Despite these advances, single miRNAs often lack disease specificity when evaluated in isolation because metabolic and oncogenic processes share common signaling pathways. The identification of hsa-miR-182-3p as a miRNA dysregulated in both conditions suggests that it could serve as a biomarker specifically reflecting the metabolic–oncogenic interface,

rather than being exclusive to either disease. This dual-disease association may confer unique clinical utility in contexts where T2DM heralds elevated cancer risk.

From a translational perspective, the integration of hsa-miR-182-3p into multi-analyte biomarker panels could improve risk stratification among patients with T2DM by identifying individuals with a molecular profile that predisposes them to CRC development. Because miRNAs are stable in circulating fluids and can be quantitatively measured by qRT-PCR or next-generation sequencing from blood or stool[28], hsa-miR-182-3p is a feasible candidate for non-invasive screening. Moreover, understanding the spectrum of its validated targets including genes involved in MAPK, cell cycle, and metabolic pathways supports the notion that modulation of hsa-miR-182-3p could influence disease mechanisms, making it an attractive therapeutic target. For example, antagomiRs or miRNA sponges could be designed to neutralize miR-182 activity, leading to restoring expression of tumor suppressor targets and attenuating oncogenic pathways. Similar approaches could be explored in metabolic tissues to improve insulin signaling or reduce inflammation.

Nevertheless, functional validation of hsa-miR-182-3p in experimental models of T2DM and CRC remains essential. Given that miRNAs exert context-dependent effects and can target hundreds of transcripts, integrated studies using cell lines, organoids, and in vivo models are necessary to dissect how hsa-miR-182-3p influences β-cell function, insulin resistance, tumorigenesis, and systemic metabolism. Such studies will clarify whether the 3p and 5p strands have overlapping, distinct, or even antagonistic roles—a consideration critical for therapeutic targeting. Additionally, longitudinal clinical studies that correlate circulating hsa-miR-182-3p levels with disease onset, progression, and response to therapy will determine its predictive and prognostic value in real-world populations.

CONCLUSION

This in silico study identifies hsa-miR-182-3p as a key miRNA potentially bridging the molecular mechanisms of T2DM and colorectal cancer. Its validated gene targets and involvement in crucial metabolic and oncogenic pathways suggest that hsa-miR-182-3p may serve as a biomarker and molecular mediator linking both diseases.

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CONFLICT OF INTEREST

There are no conflict of interest in this research.

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