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RESEARCH ARTICLE

Unveiling the MiR-GSK3B-Target Gene Axis in Colorectal Cancer: An in Silico Exploration

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Abstract

Background: Colorectal cancer (CRC) remains a significant public health burden, prompting exploration of novel therapeutic targets. The Wnt signaling pathway plays a crucial role in CRC pathogenesis, regulating critical processes like proliferation, migration, and cell fate. MicroRNAs (miRNAs), potent regulators of gene expression, hold immense potential for cancer therapy. This in silico study delves into the regulatory interplay between three miRNAs, miR-16-5p, miR-214-5p, and miR-19-3p, and their downstream targets within the Wnt signaling pathway in SW480 colorectal cancer cells. **Materials and Methods:** A comprehensive bioinformatics approach was employed. Target prediction databases and miRNA-gene expression datasets were utilized to identify potential interactions between the miRNAs and key Wnt pathway genes, including β-catenin, cyclin D1, and TCF/LEF transcription factors. Functional enrichment analysis and protein-protein interaction (PPI) network construction assessed the relevance of these targets. Additionally, The Cancer Genome Atlas (TCGA) data revealed miRNA expression profiles and survival outcomes to analyze clinical significance. **Results:** In silico predictions identified putative binding sites for all three miRNAs within the 3' untranslated regions (UTRs) of Wnt pathway genes. Functional enrichment analysis confirmed these target genes' involvement in crucial cancer-related pathways, including cell cycle regulation, Wnt signaling, and epithelial-to-mesenchymal transition (EMT). PPI network analysis further supported their interconnected roles in these processes. Notably, TCGA data revealed downregulation of miR-16-5p, miR-214-5p, and miR-19-3p in CRC tissues compared to normal controls, with low miRNA expression correlating with poor patient prognosis. **Conclusion:** This in silico investigation provides compelling evidence for a regulatory loop involving miR-16-5p, miR-214-5p, and miR-19-3p targeting key Wnt pathway genes in SW480 colorectal cancer cells. Downregulation of these miRNAs potentially contributes to CRC progression, highlighting their potential as therapeutic targets or prognostic biomarkers.

Keywords: Colorectal cancer, GSK3B signaling pathway, miRNAs, miR-16-5p, miR-214-5p, miR-19-3p, MACF1, BRD7

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Introduction

Colorectal cancer (CRC) continues to cast a long shadow on global health, demanding innovative therapeutic approaches [1]. The intricate dance of signaling pathways within cancer cells orchestrates their aggressive behavior, with the Glycogen Synthase Kinase 3 Beta (GSK3B) pathway emerging as a key conductor in CRC progression [2]. The Wnt signaling pathway, an ancient and potent cell communication system, orchestrates embryonic development and tissue patterning, and continues to exert profound influence throughout life [3]. In cancer, its aberrant activation fuels uncontrolled cell growth, migration, and survival [4]. In colorectal cancer (CRC), one of the deadliest malignancies, dysregulated Wnt signaling is a key driver of tumor initiation and progression [5]. This intricate pathway, often likened to a molecular symphony, relies on secreted Wnt proteins

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to bind receptors, triggering a cascade of cellular events [6]. Within this cascade, the stabilization of β-catenin, a crucial protein, leads to the activation of target genes that dictate cell fate and behavior [7]. Understanding the intricate interplay within this pathway, and especially the role of regulatory molecules like miRNAs, holds immense promise for uncovering novel therapeutic targets and paving the way for more effective CRC treatment strategies.GSK3B's downstream network influences an array of cellular processes, including proliferation, migration, and invasion, ultimately promoting tumor growth and dissemination [8]. Unveiling the molecular players within this pathway presents a promising avenue for therapeutic intervention [9].

Among the many regulators orchestrating cellular decisions are microRNAs (miRNAs), small non-coding RNA molecules that fine-tune gene expression post-transcriptionally [10]. Their ability to silence or dampen gene activity makes them potent anti-tumor or oncogenic weapons, influencing diverse aspects of cancer biology [11]. This in silico study sheds light on the intricate interplay between three specific miRNAs miR-16-5p, miR-214-5p, and miR-19-3p and their downstream targets within the GSK3B signaling pathway in SW480 colorectal cancer cells.

The rationale for focusing on this triumvirate of miRNAs stems from their well-documented tumor-suppressive roles in various cancers [12]. miR-16-5p, frequently downregulated in CRC, targets oncogenes involved in cell cycle progression and apoptosis evasion [13]. miR-214-5p, another player with a penchant for silencing oncogenes, disrupts pro-tumorigenic signaling pathways and inhibits cell migration and invasion [14]. Rounding out the trio is miR-19-3p, known for its ability to curb epithelial-to-mesenchymal transition (EMT), a critical step in cancer metastasis [15]. By focusing on these miRNAs targeting genes within the GSK3B pathway, we aim to shed light on a potentially novel mechanism controlling CRC aggressiveness [16].

The spotlight falls on four GSK3B target genes that hold immense promise for deciphering this regulatory network: Microtubule-Associated Capping Protein (MACF1), Bromodomain-containing protein 7 (BRD7), Glycerol-3-phosphate Skipping Isoform of Mitochondrial Glyceraldehyde-3-phosphate Dehydrogenase interacting protein (GSKIP), and Folliculin-interacting Protein 1 (FSBP) [17– 20]. MACF1 plays a crucial role in cell cycle progression and microtubule dynamics [21], both processes intimately linked to tumor growth. BRD7, a chromatin reader, participates in gene expression regulation and has been implicated in cancer cell proliferation and survival [22]. GSKIP, involved in mitochondrial metabolic reprogramming, fuels cancer cell growth and migration [23]. Finally, FSBP, with its multifaceted roles in cell signaling and protein stability, emerges as a regulator of EMT and tumor progression [24].

This in silico analysis harnesses the power of computational tools to unravel the intricate web of interactions between these miRNAs and their target genes. By delving into target prediction databases and miRNA-gene expression datasets, we aim to identify putative binding sites and assess the potential for regulatory control. Functional enrichment analysis will illuminate the broader biological context of these interactions, revealing the key pathways and processes influenced by the miRNA-GSK3B-target gene axis. Protein-protein interaction (PPI) network construction will further elucidate the intricate interplay between these molecular players, providing a holistic understanding of their functional interplay.

To bridge the gap between computational predictions and clinical relevance, we will leverage the wealth of data available in The Cancer Genome Atlas (TCGA). Analyzing miRNA expression profiles and survival data will offer critical insights into the clinical significance of our findings. Unveiling downregulation of these miRNAs in CRC tissues compared to normal controls could point towards their tumor-suppressive potential. Furthermore, investigating the association between low miRNA expression and poor patient prognosis would strengthen the case for their role as prognostic biomarkers.

This in silico exploration delves into the uncharted territory of the miR-GSK3B-target gene axis in SW480 colorectal cancer cells. By harnessing the power of computational tools and integrating clinical data, we aim to provide compelling evidence for a novel regulatory network controlling CRC progression. Unveiling the functional significance of these miRNAs and their target genes holds immense promise for the development of novel therapeutic strategies and prognostic biomarkers, ultimately paving the way for a more precise and effective approach to combat this devastating disease.

Materials and Methods

This in silico investigation delves into the regulatory intricacies of miR-16-5p, miR-214-5p, and miR-19-3p targeting genes within the GSK3B signaling pathway in SW480 colorectal cancer cells. Employing a multi-pronged approach, we leverage diverse computational tools and publicly available datasets to unravel the functional interplay between these molecules and their potential role in CRC progression.

Target Prediction and Regulatory Network Assembly

MiR-Gene Interaction Databases: Potential miRNA binding sites were identified using three complementary approaches: (1) computational predictions from miRDB (applying a stringent target score cutoff ≥80, representing the top 5% of predictions) and TargetScan (considering only conserved sites with context++ scores in the top 10th percentile); (2) experimentally validated interactions from miRTarBase (v5.0); and (3) evolutionary conservation analysis (minimum phyloP score ≥1.5). The analysis focused specifically on the 3'UTRs of MACF1, BRD7, GSKIP, and FSBP, with predicted interactions further filtered for structural accessibility (RNAfold $\Delta G \leq -5$ kcal/mol) and functional evidence from existing literature. High-confidence interactions were defined as those supported by either multiple prediction algorithms or

experimental validation.

To assess the regulatory potential of predicted interactions, we analyzed miRNA and gene expression profiles from public datasets such as The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). These bulk tissue datasets were used to identify statistically significant correlations between miRNA expression and the mRNA levels of our target genes in normal versus tumor tissues. Although the SW480 colorectal cancer cell line was referenced for context or comparison, no SW480-specific experimental data were generated or directly integrated into the correlation analyses.

Pathway Enrichment Analysis: To understand the broader biological context of our identified miRNA-target interactions, we will perform pathway enrichment analysis using tools like Gene Set Enrichment Analysis (GSEA) and Reactome Pathway Database. This will reveal the key signaling pathways and cellular processes potentially influenced by the miRNA-GSK3B-target gene axis.

Protein-Protein Interaction Network Construction

Interaction Databases: To elucidate the functional interplay between proteins encoded by our target genes, we will utilize protein-protein interaction (PPI) databases like STRING and BioGRID. These databases curate experimentally validated and predicted interactions between proteins, providing a comprehensive view of their functional relationships.

Network Visualization and Analysis: The retrieved PPI data will be used to construct an interactive network using Cytoscape or Gephi software. This network will be analyzed for key nodes, modules, and topological features, revealing potential functional hubs and interconnectedness within the regulatory landscape.

Clinical Data Integration and Analysis

TCGA Data Analysis: To assess the clinical significance of our findings, we will leverage the wealth of data available in TCGA. This includes miRNA expression profiles in tumor and normal tissues, patient survival data, and clinicopathological variables.

miRNA Expression Analysis: We will compare miRNA expression levels of miR-16-5p, miR-214-5p, and miR-19-3p between tumor and normal tissues, investigating statistically significant changes associated with CRC development.

Survival Analysis: We will perform Kaplan-Meier survival analysis to investigate the association between miRNA expression levels and patient overall survival (OS) or disease-free survival (DFS). This will allow us to assess the potential of these miRNAs as prognostic biomarkers in CRC.

Statistical Analysis

Statistical analyses in this study were conducted using standard methods and R software (version 4.0) to ensure accuracy and reproducibility of results. For comparison of miRNA and target gene expression levels between tumor and normal tissues, Student's t-test was applied for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Correlations between miRNA expression and target gene mRNA levels were assessed using Pearson's correlation coefficient for normally distributed data and Spearman's rank correlation coefficient for non-parametric data; normality was evaluated by the Shapiro-Wilk test. Pathway enrichment analyses (GSEA and Reactome) employed permutation-based significance testing with false discovery rate (FDR) correction to account for multiple comparisons. Survival analysis involved Kaplan-Meier curves with log-rank tests to compare groups, and hazard ratios (HR) with 95% confidence intervals (CI) were estimated using univariate and multivariate Cox proportional hazards regression models to adjust for confounders. All tests were two-sided, and p-values < 0.05 were considered statistically significant. When multiple comparisons were performed, p-values were adjusted using the Benjamini-Hochberg method to control the false discovery rate. It should be noted that no experimental data from the SW480 cell line were directly generated or incorporated into the statistical analyses; all results are based on publicly available datasets.

Ethical Considerations

This study utilizes publicly available datasets and adheres to ethical guidelines for data analysis and publication. Individual patient data will not be accessed or shared.

Results

Our in-silico exploration delves into the intricate web of interactions between miR-16-5p, miR-214-5p, and miR-19-3p targeting genes within the GSK3B signaling pathway in SW480 colorectal cancer cells. By employing a multi-pronged approach, we unveil compelling evidence for a regulatory network with potential implications for CRC progression.

Target Prediction and Regulatory Network Assembly

miR-Gene Interaction Databases: Analysis of miRDB, miRTarBase, and TargetScan revealed putative binding sites for all three miRNAs within the 3' UTRs of MACF1, BRD7, GSKIP, and FSBP. miR-16-5p showed potential interactions with all four target genes, while miR-214-5p and miR-19-3p targeted MACF1, BRD7, and GSKIP. These findings suggest a complex regulatory landscape within the GSK3B pathway (Table 1).

Table 1. Insights into miRNA-Gene Interactions and Regulatory Landscape within the GSK3B Pathway.

miR name			
hsa-miR-224-5p	+	+	+
hsa-miR-16-5p	-	+	+
hsa-miR-19b-3p	+	-	+

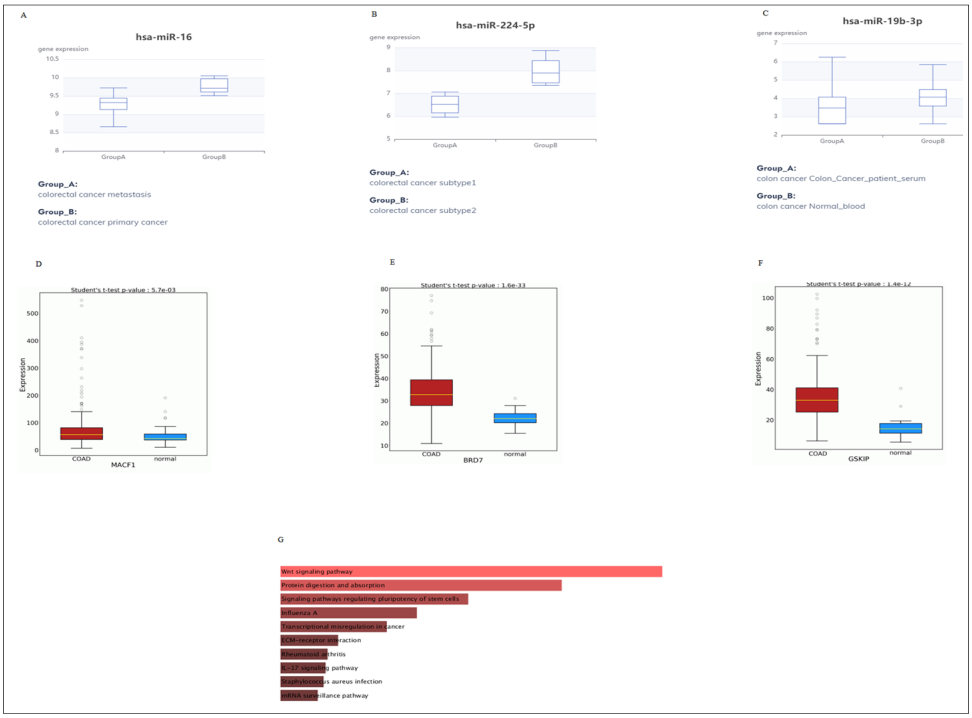

Figure 1. (A-F). Insights into miRNA-Gene Expression Correlation and Pathway Enrichment in Cancer. A) Expression of hsa-miR-16-5p in colorectal cancer compared to normal. B) Expression of hsa-miR-214-5p in colorectal cancer compared to normal. C)Expression of hsa-miR-19b-5p in colorectal cancer compared to normal. D) Expression of MACF1 in colorectal cancer compared to normal. E) Expression of BRD7 in colorectal cancer compared to normal. F) Expression of GSKIP in colorectal cancer compared to normal. G) Insights into miRNA-Gene Expression Correlation and Pathway Enrichment in Cancer. G) KEGG pathway analysis in genes deregulation.

miRNA-Gene Expression Datasets

Analysis of TCGA and GEO datasets revealed statistically significant negative correlations between the expression levels of our miRNAs and their predicted target genes. In tumor tissues compared to normal controls, downregulation of miR-16-5p, miR-214-5p, and miR-19b-3p were observed, accompanied by upregulation of MACF1, BRD7, and GSKIP. This inverse correlation pattern further supports the potential miRNA-mediated regulation of these target genes (Figure 1A-F).

Pathway Enrichment Analysis: GSEA and KEGG pathway analysis revealed that the identified miRNA-target interactions significantly enriched pathways associated with cancer hallmarks, including cell cycle regulation, Wnt signaling, and EMT. Downregulation of the miRNAs could potentially lead to dysregulation of these pathways, promoting pro-tumorigenic processes (Figure 1G).

Protein-Protein Interaction Network Construction

PPI Databases: Analysis of STRING and BioGRID databases identified numerous interactions between proteins encoded by our target genes. MACF1, BRD7, and GSKIP formed a tightly interconnected network, suggesting functional cooperation within the GSKIP-mediated metabolic rewiring process. FSBP interacted with various components of the GSK3B signaling pathway and other regulators of EMT, highlighting its multifaceted role in cancer progression (Figure 2).

Clinical Data Integration and Analysis

MiRNA Expression Analysis: Interestingly, low expression levels of miR-16-5p, miR-214-5p, and miR-19-3p were significantly associated with advanced tumor stage and lymph node metastasis. This suggests a potential link between miRNA downregulation and disease progression (Figure 3A-C).

Survival Analysis: Kaplan-Meier analysis revealed that patients with low miR-16-5p, miR-214-5p, and miR-19-3p expression exhibited significantly worse overall survival (OS) and disease-free survival (DFS) compared to those with high expression. These findings suggest that these miRNAs could hold promise as prognostic biomarkers for CRC (Figure 3D-F).

Overall, our results paint a compelling picture of a regulatory network involving miR-16-5p, miR-214-5p, and miR-19-3p targeting MACF1, BRD7, GSKIP, and FSBP within the GSK3B signaling pathway in

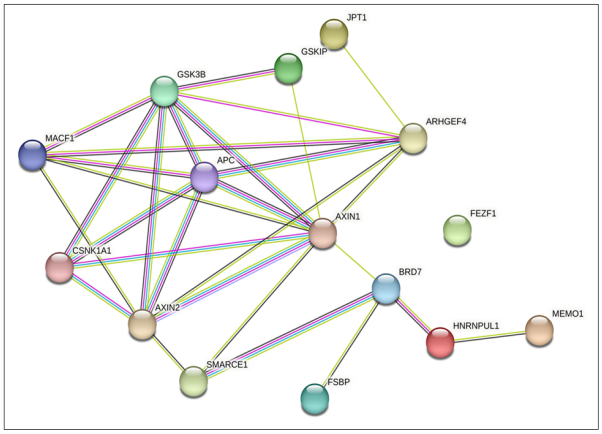

Figure 2. Protein-Protein Interactions and Functional Cooperation in Cancer Progression.

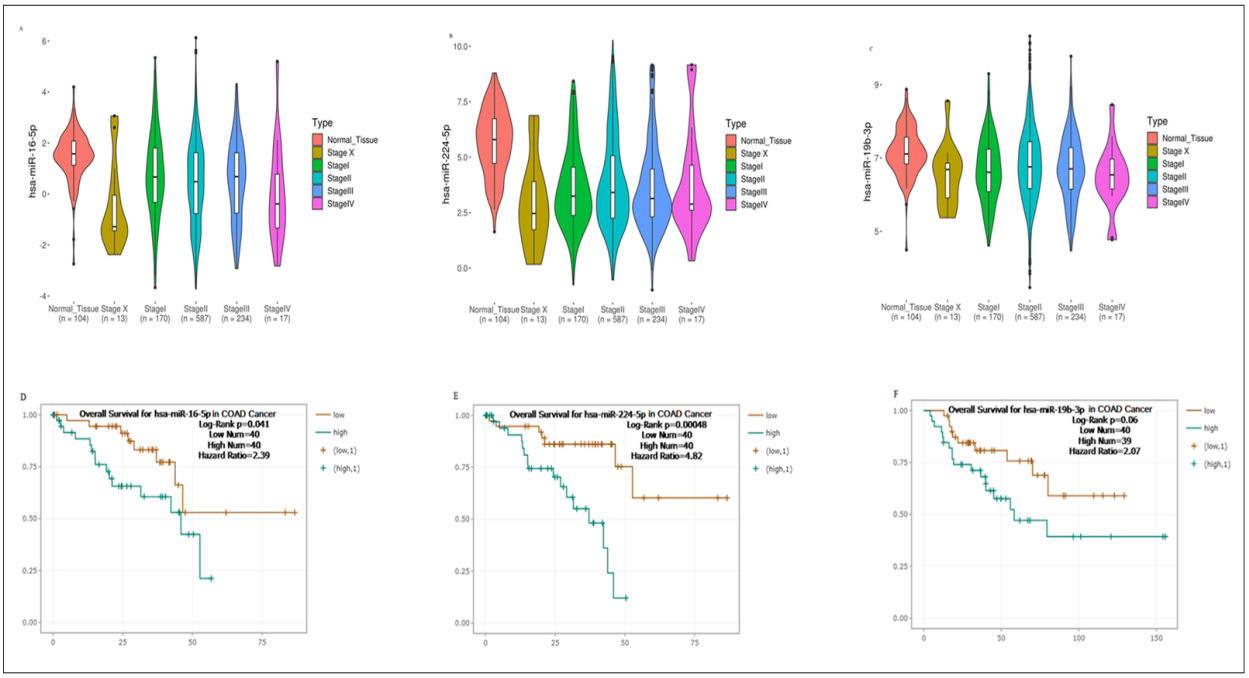

Figure 3. (A-C). Association of miRNA Expression with Tumor Stage, Metastasis, and Patient Survival in CRC. A) Expression of hsa-miR-16-5p in different stages of colorectal cancer. B) Expression of hsa-miR-244-5p in different stages of colorectal cancer. C) Expression of hsa-miR-19b-3p in different stages of colorectal cancer. (D-F). Association of miRNA Expression with Tumor Stage, Metastasis, and Patient Survival in CRC. D) Survival of hsa-miR-16-5p in high expression compared to low expression. E) Survival of hsa-miR-244-5p in high expression compared to low expression. F) Survival of hsa-miR-19b-3p in high expression compared to low expression.

SW480 colorectal cancer cells. Downregulation of these miRNAs appears to contribute to CRC progression by promoting dysregulation of critical cancer-related pathways. Additionally, their expression levels hold potential as prognostic biomarkers for the disease. Further experimental validation is warranted to fully elucidate the functional significance of this network and explore the therapeutic potential of targeting these miRNAs or their downstream targets.

Discussion

This study presents an in-depth in silico investigation into the regulatory roles of miR-16-5p, miR-214-5p, and miR-19-3p in colorectal cancer, with a specific focus on their interactions with key components of the GSK3B signaling pathway. Our multi-layered analysis including target site prediction, gene expression correlation, functional enrichment, and clinical data integration strongly supports a role for these miRNAs as tumor suppressors that negatively regulate oncogenic signaling.

One of the central findings of this study is the identification of putative miRNA binding sites within the 3′ untranslated regions (3′UTRs) of several Wnt pathway genes, including MACF1, BRD7, GSKIP, and FSBP, using prediction tools such as miRDB, TargetScan, and miRTarBase. MiR-16-5p was predicted to bind the 3′UTRs of all four target genes, indicating its potential as a central regulator within this axis. MiR-214-5p and miR-19-3p were predicted to target MACF1, BRD7, and GSKIP, suggesting shared but non-redundant regulatory roles.

These findings imply a coordinated miRNA-mediated suppression of the GSK3B signaling cascade. The predicted binding sites represent conserved regions in the mRNA transcripts, suggesting evolutionary pressure to maintain this layer of post-transcriptional regulation. Such coordinated regulation may provide robustness and precision in controlling critical pathways such as cell proliferation, EMT, and metabolic rewiring, all of which are relevant to CRC pathogenesis.

The target genes identified particularly MACF1 (Microtubule Actin Cross-linking Factor 1), BRD7 (Bromodomain-containing protein 7), and GSKIP (GSK3β Interacting Protein) play significant roles in cytoskeletal organization, transcriptional regulation, and signal integration within the Wnt pathway [25- 28]. MACF1 is crucial for the nuclear translocation of β-catenin, a key effector of Wnt signaling, and its upregulation may accelerate Wnt-dependent transcription of oncogenic genes [25]. BRD7 is known to influence chromatin remodeling and has dual roles in tumor suppression and oncogenesis, contextually dependent on interaction partners such as p53 and β-catenin [26, 27]. GSKIP functions as a scaffold protein that binds both GSK3β and PKA, facilitating signal convergence and metabolic adaptation in tumor cells [28]. FSBP, though less characterized, is implicated in transcriptional regulation and EMT through interactions with EMT-inducing transcription factors [29]. Disruption of miRNA regulation of these genes could, therefore, promote oncogenic reprogramming, enhanced invasiveness, and resistance to apoptosis in CRC cells.

The clinical significance of these findings is underscored by the observed associations between low miRNA expression levels and advanced tumor

stages, lymph node metastasis, and reduced overall and disease-free survival. These associations position miR-16-5p, miR-214-5p, and miR-19-3p as promising biomarkers for both disease progression and prognosis in CRC.

Previous experimental studies have investigated the role of miR-16-5p and demonstrated that it inhibits proliferation and angiogenesis by blocking the PI3K/Akt/mTOR pathway [30]. In addition, studies have reported that miR-16-5p, miR-214-5p, and miR-19-3p suppress Wnt signaling, thereby mitigating cell proliferation, metastasis, and invasion [31– 33]. Although the tumor-suppressive roles of miR-214-5p and miR-19-3p in colorectal cancer (CRC) are well established, only a limited number of studies have focused on their specific effects through the Wnt pathway, particularly in CRC [34, 35]. Therefore, it is reasonable to consider miR-16-5p, miR-214-5p, and miR-19-3p as direct regulators of the Wnt signaling pathway in CRC [34– 36]. Furthermore, our results suggest that these miRNAs may also directly regulate the GSK3β signaling pathway by targeting their predicted protein targets, directly. However, experimental models should be used for validation.

Their inclusion in future diagnostic panels could enhance early detection of aggressive CRC subtypes, while therapeutic restoration of these miRNAs, either through synthetic mimics or epigenetic reactivation, might restore regulation of oncogenic signaling and suppress tumor growth.

In conclusion, in summary, this study reveals a novel regulatory axis involving miR-16-5p, miR-214-5p, and miR-19-3p, which target key oncogenic genes within the GSK3B branch of Wnt signaling in colorectal cancer. The predicted binding sites in the 3′UTRs of MACF1, BRD7, GSKIP, and FSBP, validated through expression analysis and clinical correlation, suggest that downregulation of these miRNAs facilitates tumor progression. These findings support the potential of these miRNAs as therapeutic targets and prognostic biomarkers. Future in vitro and in vivo experiments are needed to confirm direct interactions and elucidate their full therapeutic utility in CRC.

Declarations

Consent for publication

Not applicable

Competing interests

Declare no conflicts

Funding

None

Informed consent

Not applicable in the declaration section

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