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Investigating the MicroRNA 10b Regulatory Network: A Bioinformatic Approach to Transcription Factor Binding and Cancer Implications

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ABSTRACT: miR-10b, that stands for microRNA 10 in bovine serum protein refers to a subgroup of small molecules belonging to the body especially involved in physiological processes with regard cancers initiation and progression as well cellular differentiation. An understanding of the regulation miR-10b along with identification of its corresponding transcription factors (TFs) that bind to the so-called mirR-10b Regulated-DNA Sequence (MRDS) as well discovering potential targets serves a powerful tool not only in elucidation but also pharmacological arsenal targeting miRNAs. In this work, two bioinformatics databases (JASPAR and PROMO) were used to suggest the putative TFs that can interact with miR-10b MRDS. Most interestingly, among the set of TFs common to both databases were a number have previously associated with histone modification. Since the function of miR-10b is well known, we focused only on TFs with documented associations to regulation by this particular miRNA. These TFs were E2F1, P53, SP1 and NFKB. In an attempt to investigate the regulatory network of TFs involved TFs associated with miR-10b, STRING database was utilized to study the interactions among the identified TFs and their functional enrichments. Through this analysis, we found important Gene Ontology terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways linked with different kinds of cancer, the transcriptional regulation, and gene expression. This study aims to provide an inclusive analysis of TFs that control miR-10b by applying bioinformatics predictions and validate these findings over existing literature evidence. This method will deepen our knowledge towards miR-10b regulatory network and its implications in cancer biology and eventually discovering new treatment interventions.

Keywords: Cancer, JASPAR, miR-10b, PROMO, STRING, Transcription Factors

1. INTRODUCTION

MicroRNAs are short non-coding RNAs that are identified as oncogenes or tumor suppressors. [1] [2], [3] These molecules have the ability to target the mRNAs by degrading or suppressing them during their translation [4]. One of these miRNAs is miR-10b, that is situated on chromosome 2q31 and received a special focus for its role in various cancer-related activities, including metastasis, tumor initiation, and progression. [5].

In clinical cases, miR-10b showed a linked to cancer [6]. Since miR-10b has been expressed in high levels in the patients' blood or cancer tissues that have been linked with poor prognosis and high probability of metastasis, including breast, glioblastoma, and pancreatic cancer, it has been determined as a potential diagnostic and prognostic biomarker for cancer. [7]. Consequently, measuring miR-10b levels could assist in early detection and monitoring of cancer development serving in disease progression prediction and patient survival [8].

Furthermore, it has been established that miR-10b links with critical signaling pathways such as PI3K/Akt and MAPK/ERK that play vital roles in cell survival and proliferation. By activating these pathways, miR-10b boosts tumor growth and resistance to apoptosis, ultimately assisting in cancer progression and metastasis [9], [10].

The molecular mechanisms regulating miR-10b expression need to be understood to shape its role in cancer biology and develop a possible targeted treatment strategy. Transcription factors (TFs), the regulatory proteins bind to certain DNA sequences, control the DNA transcription to RNA [11], [12], [13]. Detecting the TFs binding to the MRDS can

deliver perceptions into the regulatory networks that control its expression. In this study, we employed two bioinformatics databases, JASPAR and PROMO to predict the potential TFs that bind MRDS. JASPAR and PROMO are common databases used for anticipating transcription factor binding sites and TFs binding to specific genes [14]. They contain a high-quality, organized assemblies of TF binding profiles taken from experimental data [15], [16]. By analyzing MRDS using PROMO and JASPAR, we identified multiple TFs that may significantly impact its expression. Key TFs such as E2F1, P53, SP1, and NFKB1 that were well documented to play a dynamic role in cancer related transcriptional regulation were emphasized. Afterward, we evaluated the effectiveness and possible relationships mediated by these TFs using STRING database an online resource platform that enables comprehensive designing and interpretation of protein–protein interaction networks along with functional enrichment. In order to shed light on the transcriptional regulation of MRDS involved in different cancers, we also predicted which TFs binding these allow using PROMO and JASPAR databases, as well as their interaction networks by utilizing STRING database [17], [18].

2. MATERIALS AND METHODS

2.1 RETRIEVAL OF MRDS

We obtained the human MRDS from the National Center for Biotechnology Information (NCBI) GenBank database assemblage of sequences that are associated with a specific protein and have been annotated after being clearly defined according to their position on Chromosome (Gene ID:406903). Promoter region is the area upstream of transcription start site (TSS), and Ensemble databases Genome Browser were used to locate TSS for miR-10b, we then extracted whole gene sequence as well promoter sequences - 2000 bp up-stream and 2 kbp downstream around TTS.

2.2. USING BIOINFORMATICS DATABASES TO PREDICT TFS.

PROMO and JASPAR were used to predict the Transcription Factor (TFs) that may bind to the "MRDS" in our study.

2.2.1. PROMO DATABASE ANALYSIS:

PROMO is a virtual tool for predicting TF binding sites in DNA sequences based on species-specific binding sites and transcription factor binding motifs. The analysis was conducted via submitting the MRDS into PROMO (Figure 1). The analysis was accomplished using the default matrix similarity threshold of 85% to identify potential TF binding sites. The output yielded a number of TFs predicted to bind to the MRDS, along with the corresponding binding sites and matrix similarity scores (Table 1).

2.2.2. JASPAR DATABASE ANALYSIS:

JASPAR, a database of transcription factor binding profiles, is an open-access database of curated, non-redundant transcription factor binding profiles derived from published experimental data. The analysis was conducted by submitting the MRDS into in the JASPAR database. The search involved transcription factor binding profiles from the core vertebrate database and the output comprised a list of TFs with significant matrix similarity scores to the MRDS (Figure2).

2.3. THE PREDICTED TFS VALIDATION

To confirm the predicted TFs, an extensive search of scientific literature was performed with specific keywords linked to each TF and miR-10b (e.g., “NF-KB miR-10b regulation,” were used to search for related literature. The assessment focused on the documented relationships and functional relevance. For instance, articles and studies that reported a straight contact or regulatory role of the predicted TFs with miR-10b were employed in addition to the studies exploring the functional inferences of the interaction between TFs and miR-10b in numerous biological frameworks, mainly cancer progression and metastasis.

2.4. INTEGRATION OF DATA AND ANALYSIS

The predicted and validated TFs that potentially bind to the MRDS were compared between PROMO and JASPAR to identify common results. The shared TFs were cross-referenced with literature evidence to assess their documented involvement in regulating miR-10b. Bioinformatics predictions and literature validation were combined to create the definitive list of TFs.

2.5. PROTEIN-PROTEIN INTERACTION (PPI) NAETWORK ANALYSIS

STRING database was used to explore the protein-protein inter-actions and identify common Kyoto Encyclopedia of Genes and Genomes pathways (KEGG) between the predicted and validated TFs. STRING database offers extensive information about how proteins had been functionally connected.

3. RESULTS AND DISCUSSION

miR-10b is one of the crucial microRNAs identified to implicate in various biological processes, cancerarious transitions and evolution [4]. An important goal towards this end is to understand the regulatory mechanisms that control miR- 10b expression in these processes and identify potential therapeutic targets. Therefore, this study predicts the

transcription factors (TFs) binding to the MRDS and confirms interactions between those predicted TFs using two bioinformatics databases, PROMO and JASPAR.

PROMO (an online tool for the prediction of transcription factor binding sites in an upstream region) was used to scan MRDS. We performed the analysis with default settings using matrix similarity threshold of 85%. PROMO located 83 putative transcription factors binding sites with respect to the MRDS (Figure1).

For the validation of predicted TFs, we used JASPAR database (containing collection of transcription factor binding profiles) to check whether observed regulatory elements have potential for binding or not. JASPAR analysis focused on the matrix similarity score and percentage of consensus motif in leads with MRDS (Figure 2).

The preliminary analysis identified 20 TFs common to both PROMO and JASPAR predictions, including GATA1, GATA2, GATA3, E2F1, IRF1, USF1, P53, MEF2A, TBP, PAX5, YY1, AHR, CEBPA, ELK1, SP1, AR, HNF1A, SRY, NFKB1, and HNF4A. This wide-ranging list of TFs from both databases highlights the latent complexity and the potential significance of the regulatory network controlling miR-10b expression.

In a literature review, we found that four of the TFs from our listing are highly related to miR-10b legal guidelines. These TFs described to interact with miR-10b, include E2F1, P53 SP1 and NFKB imputed in the pathway bioinformatics analysis were major regulators of miR-10b-expression (Figure 5A). E2F1 is considered to be a prominent activator for miRNA transcription and, as an example are known to be involved in cancer-related pathways that constitute the central function of miR-10b. Comparativ analysis of The Cancer Genome Atlas (TCGA) project revealed that miR-10b participates to the regulation E2F1-dependent network gene in glioblastoma and low-grade [19].

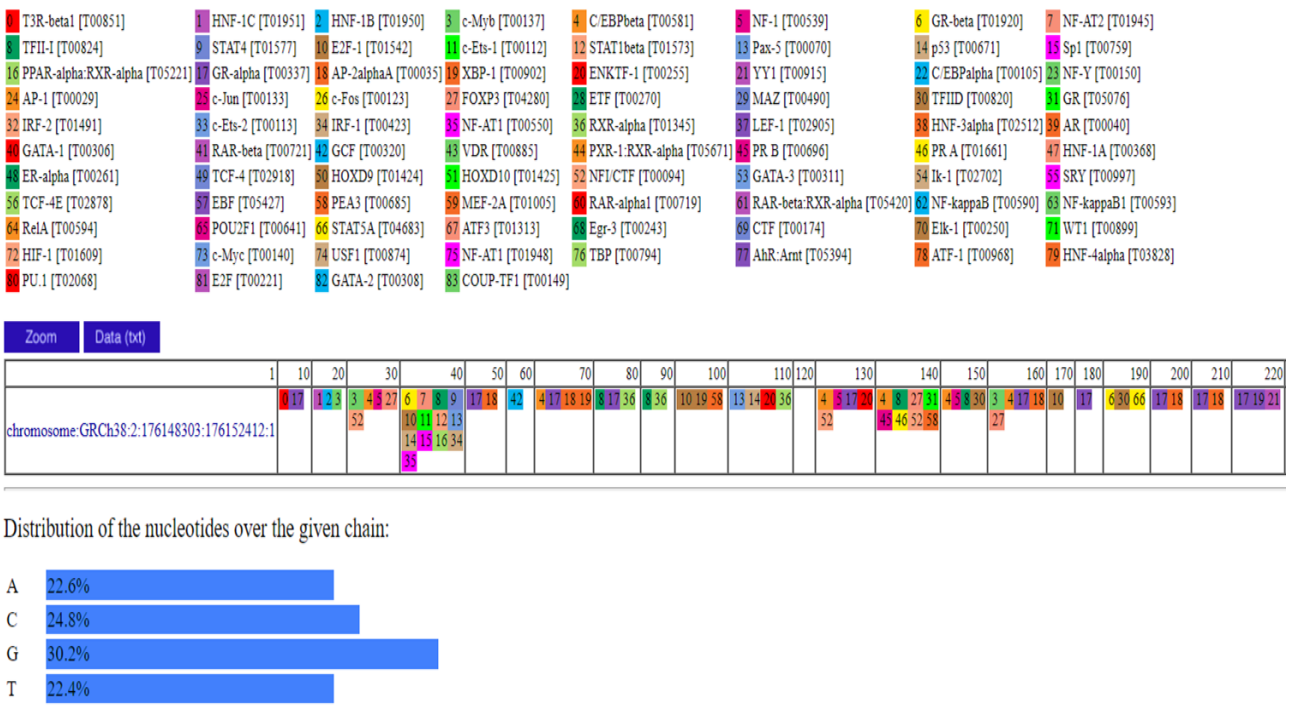


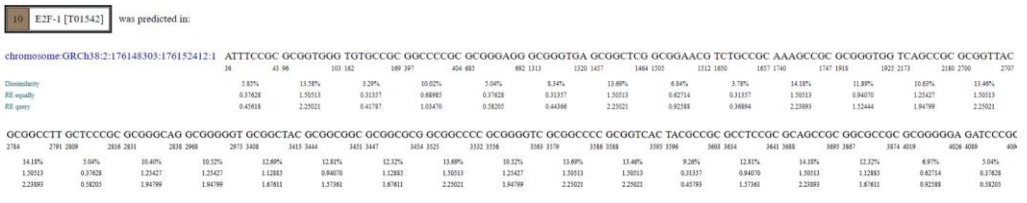
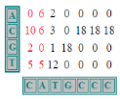
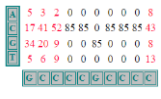
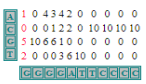
FIGURE 1. Transcription Factors Predicted within a dissimilarity margin less than or equal to 15%

More concordantly, p53 induces miR-10b as well. A research study has identified miR-10b as a novel target of p53, and demonstrated that it is regulated by expression from a cis-acting element. The most significant association is that of miR-10b, and p53 and its tumor-suppressor role [20].

Evidence suggested that SP1 is associated with miR-10b as well. Consistent with it in different contexts, our data demonstrate that miR-10b expression is regulated by SP1. SP1 can bind on the promoter region of miR-10b and upregulate its level, subsequently influences cancer metastasis. A research study showed that miR-10b promoter region includes Sp1 binding site located at the −324 position in the hippocampus cells, which was associated with an increase in miR-10b-5p expression [21].

As for NF-κB, it has been found that miR-10b contributes to the proliferation and metastasis of gastric cancer (GC) cells by targeting CSMD1 and promotes the epithelial mesenchymal transition (EMT) through the NF-κB signaling pathway. NFKB1's contribution in inflammatory and cancer processes lines up with miR-10b's known functions, supporting the potential regulatory association between NFKB1 and miR-10b [22].

Table 1. Transcription factor binding sites and TFs predicted by PROMO database

Predicted Transcription Factors	Consensus sequence and matrix
	
	
	
	

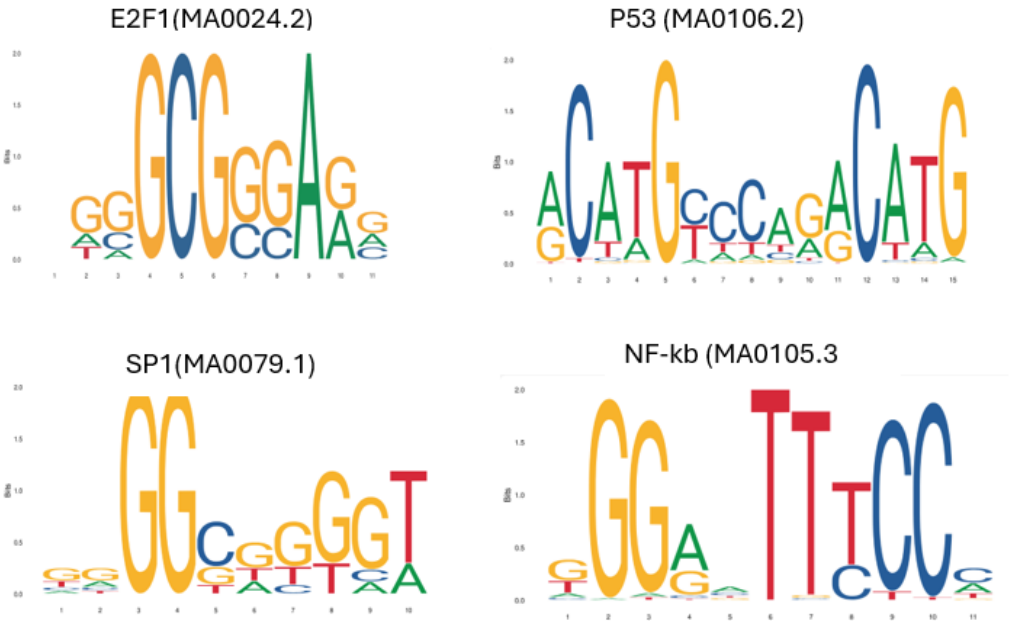


FIGURE 2. Sequence logos and matrix IDs of transcription factors predicted by JASPAR database.

In contrast, there is no much literature evidence for the remainder 16 TFs to show a direct link to miR-10b. This lack of such evidences is due to the fact that there is no significant role in miR-10b regulation. Also, it could suggest that their interactions with miR-10b are yet to be revealed or categorized or these TFs interact with miR-10b via indirect pathways. However, some of these TFs showed a connection with other microRNAs. For instance, the androgen receptor (AR) can downregulate or upregulate certain miRNAs by directly binding to specific DNA sequences, named androgen response elements (AREs), in the regulatory regions of the target genes leading to the transcriptional activation or repression of these genes. In a different study, AR displayed upregulation expression of miR-4496 by directly binding to the AREs of the miR-4496 promoter and decreasing the expression of β-catenin by targeting the $3'$ UTR of the β-catenin-miRNA [23], [24]. Current studies on GATA1 have verified that it controls erythropoiesis via regulating miRNAs [25], [26]. In another study, microarray screening showed miR-144 and miR-451 as miRNAs regulated by GATA1 [27]. These results point to the fact that miRNAs act right downstream of GATA factors, suggesting a new mechanism by which GATA factors stipulate cell destiny and the regulation of miRNA loci might be key components to the function of these transcription factors [28], [29]. Investigation on ELK1 showed that it could be a direct target of miR-150 according to an experimental fact that knocking down ELK1 eliminated the anti-apoptotic effect of the miR-150 inhibitor [30]. USF1 can activate miR-483 in an indirect manner. In a study conducted by Emmerling et al., 2016 proposed that the miR-483 can enhance the expression of itself in human HeLa cells by a positive feedback loop including an independent promoter that is activated by the USF1 transcription factor [31].

To more elucidate the regulatory network of miR-10b, STRING database was utilized to analyze the interactions between the identified and validated TFs. The STRING analysis revealed a network with four nodes and six edges, resulting in an average node degree of three and an average local clustering coefficient of 1.0. The observed number of edges significantly exceeded the expected number (3 edges), with a PPI enrichment p-value of 0.0317, indicating that the network has significantly more interactions than expected by chance. This enrichment implies that the proteins interact with each other's more than what would be anticipated for a random set of proteins of the same size and degree distribution drawn from the genome, which may collaboratively regulate miR-10b expression and function. Such an enrichment suggests that the proteins share biological connections as a group (Figure 3).

Gene Ontology analysis discovered a significant enrichment in processes associated with the transcriptional regulation activity across all transcription factors, DNA-binding transcription factor binding, and RNA polymerase II cis-regulatory region sequence-specific DNA binding (Table 2).

KEGG pathway analysis on the other hand, emphasized significant enrichment in pathways such as the transcriptional misregulation in cancer, pathways in cancer, MAPK signaling pathway, PI3K-Akt signaling pathway, apoptosis, and different types of cancer, including breast, prostate, pancreatic, bladder, and gastric cancer (Table 3).

Future work should contain experimental validation, such as Chromatin Immunoprecipitation proceeded by sequencing (ChIP-seq), to confirm transcription factor binding to the MRDS in addition to the luciferase reporter assay which is commonly used to study gene expression at the transcriptional level.

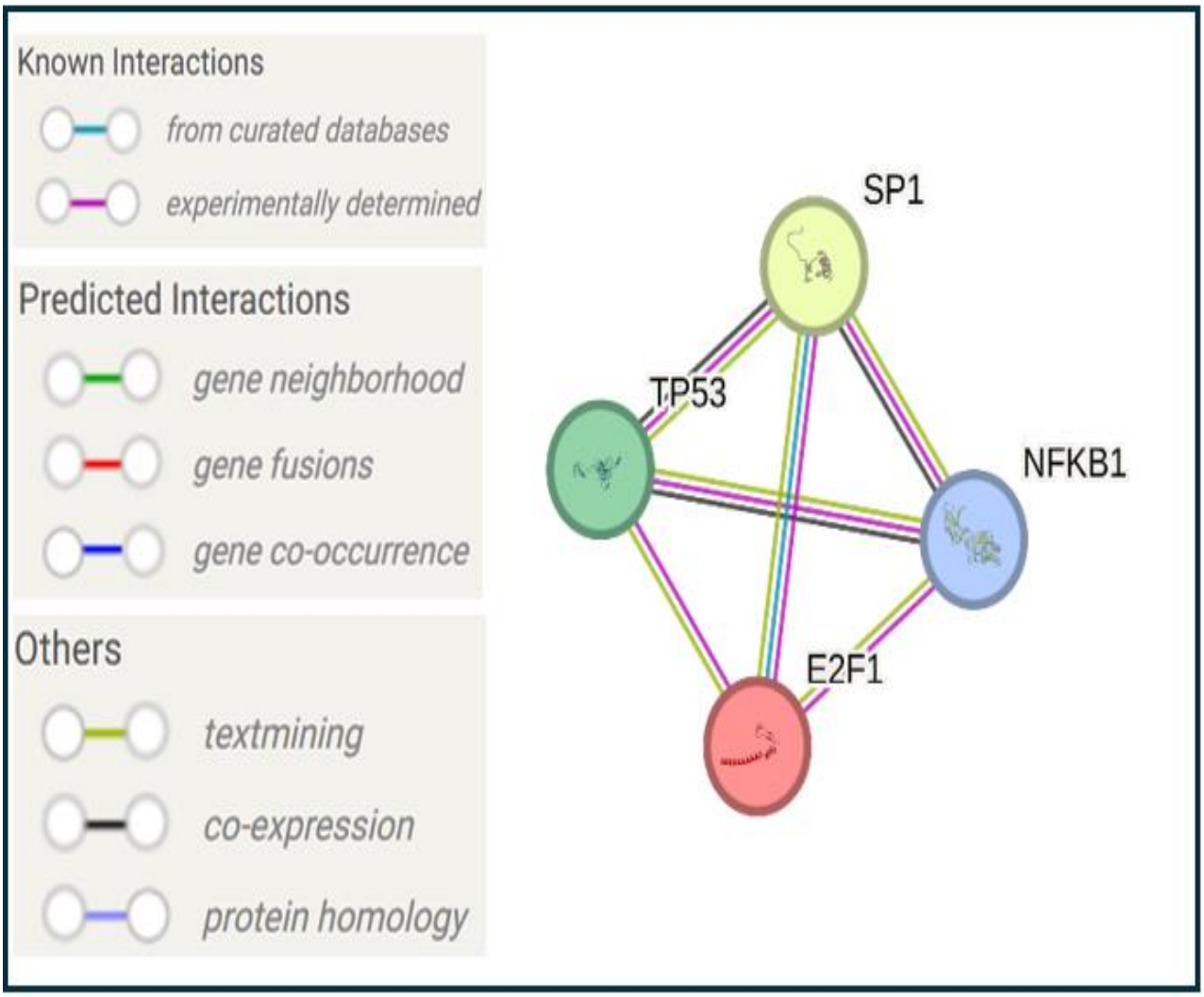


FIGURE 3. Protein-protein interaction network and functional enrichment construct in predicted transcription factors binding to miR-10b using STRING database.

Table2. Molecular function and significantly enriched gene ontology terms (GO) in transcription factors network involved in miR-10b regulation.

Gene Ontology	Term Description	Count in Network	Enrichment Strength	FDR
GO:0001216	DNA-binding transcription activator activity	4	1.63	0.0015
GO:0008134	Transcription factor binding	4	1.53	0.0020
GO:0001228	DNA-binding transcription activator activity, RNA polymerase II-specific	3	1.51	0.0206
GO:0140297	DNA-binding transcription factor binding	3	1.48	0.0206
GO:0000978	RNA polymerase II cis-regulatory region sequence-specific DNA binding	4	1.22	0.0169
GO:0000981	DNA-binding transcription factor activity, RNA polymerase II-specific	4	1.16	0.0192

Table3. KEGG Pathways of transcription factors network involved in miR-10b regulation.

Pathway	Description	Count in network	Enrichment Strength	FDR
hsa05219	Bladder cancer	2	2.39	0.00047
hsa05212	Pancreatic cancer	3	2.32	2.52e-05
hsa05220	Chronic myeloid leukemia	3	2.29	2.52e-05
hsa05222	Small cell lung cancer	3	2.21	2.91e-05
hsa05215	Prostate cancer	3	2.18	2.91e-05
hsa05218	Melanoma	2	2.14	0.0013
hsa05214	Glioma	2	2.14	0.0013
hsa05224	Breast cancer	3	2.01	6.29e-05
hsa05206	MicroRNAs in cancer	3	1.97	6.38e-05
hsa05202	Transcriptional misregulation in cancer	3	1.94	6.46e-05
hsa04210	Apoptosis	2	1.88	0.0032
hsa05226	Gastric cancer	2	1.83	0.0037
hsa05225	Hepatocellular carcinoma	2	1.79	0.0042
hsa05203	Viral carcinogenesis	2	1.73	0.0053
hsa05200	Pathways in cancer	4	1.58	2.91e-05
hsa04010	MAPK signaling pathway	2	1.54	0.0120
hsa04151	PI3K-Akt signaling pathway	2	1.45	0.0168

4. CONCLUSIONS

miR-10b, a vital microRNA, is concerned in numerous biological processes, including cancer metastasis, progression, and cellular differentiation. The regulatory mechanisms directing miR-10b expression is important to be comprehended for emerging therapeutic strategies. In this study, we employed PROMO and JASPAR as bioinformatics databases to identify (TFs) that may bind to the MRDS. Our analysis identified a range of potential TFs that are common to both databases. An extensive literature review was utilized to validate the identified TFs. These validated TFs were well-documented to influence miR-10b expression and are implicated in cancer-related pathways, supporting their potential importance as regulators of miR-10b. STRING database elucidated the regulatory network of miR-10b and analyze the interaction among the identified TFs binding to it. The significant enrichment of PPI suggests a solid interconnection among the predicted TFs. This network of interaction may indicate a complex regulatory connection that are essential for adjusting miR-10b function in distinct cellular processes, especially those associated with cancer.

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