Int J Clin Exp Med 2017;10(2):2188-2203
www.ijcem.com /ISSN:1940-5901/IJCEM0042038

*Original Article*

# Identification of the potential targets of miR-143-3p in colorectal cancer through bioinformatics analysis

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Received October 17, 2015; Accepted November 14, 2015; Epub February 15, 2017; Published February 28, 2017

**Abstract:** Background: Colorectal cancer (CRC) is a malignant tumor with a high incidence and mortality worldwide. However, traditional treatments are not satisfactory. Thus, novel therapeutic strategies are urgently required. Recently, microRNAs have been proven to be involved in various biological processes, such as cell differentiation, cell proliferation, apoptosis and tumorigenesis, which could have potential therapeutic value in CRC. Methods: In this study, we aimed to identify the target genes and potential molecular mechanism of miR-143-3p. GEO microarray GSE33420, which was generated using 2 colon cell lines, and 12 prediction databases were combined to seek the overlapping target genes of miR-143-3p in CRC. GO enrichment analysis and the KEGG pathway were respectively performed to explore the prospective pathways of miR-143-3p in CRC. The overlapping genes were further uploaded to the STRING 10.0 database for protein-protein interaction network (PPI) construction. All these work was conducted through computational database resources. Results: Forty-three overlapping candidate target genes of miR-143-3p in CRC were achieved through the GEO microarray and prediction databases. Nine genes (MAPK1, PTPN23, ERBB3, PKN2, KLF5, YARS, ETV6, PDPR and YWHAB) were shown as hub genes in the PPI network. Conclusions: In the present study, among the nine hub genes we discovered, KLF5 has been reported as a target gene of miR-143-3p in CRC. MAPK1, ERBB3, YWHAB, KLF5 and ETV6 have great potential to serve as key target genes of miR-143-3p, likely exerting a therapeutic effect in the treatment of CRC. Regarding PTPN23, PKN2, YARS and PDPR, research to support their roles in CRC is lacking. Nevertheless, further studies are required to confirm the results.

**Keywords:** Colorectal cancer, miR-143-3p, target gene, bioinformatics analysis

## Introducton

Colorectal cancer (CRC) ranked fifth in cancer incidence and mortality in China in 2015 [1]. However, it remains the third most frequent cancer and the third prominent cause of cancer-related mortality in the United States [2]. With the strong invasion and metastasis abilities of CRC cells, poor survival rates exist among CRC patients. Until now, colonoscopy, a direct screening tool of the gastrointestinal tract, combined with biopsy sample analysis, was defined as the gold standard for CRC diagnosis [3]. Thus, more accurate and non-invasive examination methods are needed to improve CRC diagnosis. Although the application of comprehensive treatments, such as surgery, radiotherapy and chemotherapy, have significantly improved the 5-year survival rate, the overall estimated mortality remains up to 50%-60% [4]. Consequently, a novel method with high diagnostic sensitivity, a non-invasive diagnosis and satisfactory treatments is urgently needed.

MicroRNAs (miRNAs) are endogenous small noncoding RNAs (20-25 nucleotides) that inhibit gene expressions post-transcriptionally. MicroRNAs perform the gene expression inhibition function by binding to the 3' untranslated region (3'UTR) of target messenger RNA (mRNA), resulting in either degradation or the inhibition of translation [5]. It has been reported that miRNAs are involved in the regulation of different physiological and pathological processes, such as cell differentiation, cell prolif-

eration, apoptosis and tumorigenesis [6, 7]. The abnormal expression of miRNA is correlated with human disease, especially with the development of cancer [8, 9]. For example, microRNA-217 inhibits CRC cell proliferation and invasion through AEG-1, thus acting as a prognosis predictor [10]. MicroRNA-302a can inhibit proliferation and invasion in CRC cells through regulating the MAPK and PI3K/Akt signaling pathways [11]. MiR-135b promotes CRC progression by targeting TGFBR2 [12].

Although some studies have shown associations between miRNAs and CRC, knowledge concerning the potential molecular mechanism of miRNAs in CRC is limited. Further studies are required to uncover the interaction mechanism between miRNAs and CRC. MiR-143-3p is a type of miRNA that was recently found to be involved in regulating proliferation and apoptosis in CRC [13]. It is located at a fragile site often deleted in cancers [14]. It has been found to be involved in several cancers, including osteosarcoma [15], esophageal squamous cell carcinoma [16], prostate cancer [17], breast cancer [18], human cervical cancer [19] and non-small cell lung cancer [20]. In recent years, it has been frequently reported that miR-143-3p was down-regulated in CRC [21, 22]. Numerous researches suggest that miR-143-3p is involved in colon carcinogenesis and prognosis, which indicted it as an onco-suppressor [23-26]. Some research groups applied in vitro models to identify targets of miR-143-3p. Target ARF6 was identified through vitro models [27]. Some targets of miR-143-3p, such as DNMT3A [28], KRAS [29] and MACC1 [30] were found in colon cancer cell lines. Although colorectal cancer is related with the under-expression of miRNA-143, the molecular etiology of the under-expression is unknown [13]. Therefore, it is still urgently necessary to uncover the underlying target genes of miR-143-3p and its corresponding signal pathways to further elucidate the molecular modulatory mechanism of miR-143-3p in CRC.

In recent years, with the development of modern biological technology and application of gene chip technology, the methods for microRNA target prediction have become increasingly diversified. With the widely used target gene prediction databases such as miRBase, Targetscan and PicTar-vert, the prediction of microRNA target genes has become more convenient. Combining the information of microarray with that of the prediction databases would enhance the specificity and accuracy [31]. Thus, in this study, we attempted to utilize bioinformatics methods to explore the target genes of miR-143-3p and their biological functions to uncover the potential molecular mechanism in CRC. Thus, the information gained might shed light on clinical diagnosis and treatment in the future.

## Materials and methods

### *Target genes prediction*

Twelve online prediction tools-miRBase, miRDB, miRWalk, PicTar-vert, PITA RNA22, Targetscan, miRNA.org, TarBase, mirTarBase, Targetminer, and PolymiRTS-were separately applied to predict the target genes of miRNA-143-3p. Next, we removed the repetitions and counted the frequency of each gene was predicted by the 12 prediction databases; only those predicted by five databases were included for further study. Those prediction tools are of good reputation in predicting targets. MiRBase is the main repository for all miRNA sequences and annotation. It integrated miRNA target predictions from different target predictions sites such as Targetscan, PicTar, TarBase and miRTarBase [32]. Harsh Dweep et al found that the precisions of miRDB, miRWalk, Pictar-vert, PITA, RNA22, Targetscan are over 97% [33]. PolymiRTS is a database that systematically identifies DNA polymorphisms in miRNAs and miRNA target sites. It integrates CLASH (cross linking, ligation and sequencing of hybrids) data, and therefore improve the accuracy of targets prediction [34]. Targetminer has 55.65% ACC (average classwise accuracy) which achieves significantly better accuracy than other 10 prediction softwares [35]. MiRTarBase v6.0 contains 3786 miRNAs and 22563 targets. And it can achieve the accuracy rate of 71.43% in the present retrieval system [36]. DIANA-TarBase v7.0, the first relevant database to index more than half a million interactions in 24 species, can identify thousands of miRNA: gene interactions by novel NGC (next generation sequencing) high-through miRNAs target identification techniques [37]. MiRNA.org uses miRanda algorithm to comprehensively achieve target predictions. It utilizes a weighted dynamic programming algorithm to calculate optimal sequence complementarity between mature

**Table 1.** Significant GO enrichment items of the 369 predicted genes

| Category | Term | Count | *P* Value |
|---|---|---|---|
| GOTERM_BP_FAT | GO:0007167~enzyme linked receptor protein signaling pathway | 22 | 1.25E-05 |
| GOTERM_BP_FAT | GO:0007169~transmembrane receptor protein tyrosine kinase signaling pathway | 16 | 8.47E-05 |
| GOTERM_BP_FAT | GO:0006793~phosphorus metabolic process | 37 | 0.000715 |
| GOTERM_BP_FAT | GO:0006796~phosphate metabolic process | 37 | 0.000715 |
| GOTERM_BP_FAT | GO:0040017~positive regulation of locomotion | 9 | 0.001099 |
| GOTERM_BP_FAT | GO:0010761~fibroblast migration | 3 | 0.001318 |
| GOTERM_BP_FAT | GO:0009890~negative regulation of biosynthetic process | 24 | 0.002467 |
| GOTERM_BP_FAT | GO:0040012~regulation of locomotion | 12 | 0.002599 |
| GOTERM_BP_FAT | GO:0030335~positive regulation of cell migration | 8 | 0.002758 |
| GOTERM_BP_FAT | GO:0050921~positive regulation of chemotaxis | 5 | 0.003063 |
| GOTERM_CC_FAT | GO:0008287~protein serine/threonine phosphatase complex | 7 | 1.41E-04 |
| GOTERM_CC_FAT | GO:0000159~protein phosphatase type 2A complex | 5 | 6.18E-04 |
| GOTERM_CC_FAT | GO:0017053~transcriptional repressor complex | 6 | 0.001357 |
| GOTERM_CC_FAT | GO:0005856~cytoskeleton | 43 | 0.004676 |
| GOTERM_CC_FAT | GO:0042827~platelet dense granule | 3 | 0.005814 |
| GOTERM_CC_FAT | GO:0031988~membrane-bounded vesicle | 22 | 0.005814 |
| GOTERM_CC_FAT | GO:0016023~cytoplasmic membrane-bounded vesicle | 21 | 0.008464 |
| GOTERM_CC_FAT | GO:0031982~vesicle | 23 | 0.017488 |
| GOTERM_CC_FAT | GO:0044430~cytoskeletal part | 30 | 0.017865 |
| GOTERM_CC_FAT | GO:0031410~cytoplasmic vesicle | 22 | 0.020959 |
| GOTERM_MF_FAT | GO:0019838~growth factor binding | 12 | 2.07E-05 |
| GOTERM_MF_FAT | GO:0019899~enzyme binding | 24 | 0.001413 |
| GOTERM_MF_FAT | GO:0004694~eukaryotic translation initiation factor 2 alpha kinase activity | 3 | 0.002857 |
| GOTERM_MF_FAT | GO:0016564~transcription repressor activity | 16 | 0.004654 |
| GOTERM_MF_FAT | GO:0008601~protein phosphatase type 2A regulator activity | 4 | 0.005833 |
| GOTERM_MF_FAT | GO:0015631~tubulin binding | 8 | 0.006799 |
| GOTERM_MF_FAT | GO:0030145~manganese ion binding | 10 | 0.007397 |
| GOTERM_MF_FAT | GO:0008092~cytoskeletal protein binding | 21 | 0.008748 |
| GOTERM_MF_FAT | GO:0003677~DNA binding | 68 | 0.012629 |
| GOTERM_MF_FAT | GO:0043167~ion binding | 113 | 0.014273 |

Only the top ten GO items were listed for each category.

miRNAs and mRNAs [38]. There is no doubt that each prediction tool has merits and demerits. Therefore, we integrate the 12 prediction tools to make the prediction more accurate and reliable.

*GEO microarray data extraction*

The gene expression profile GSE33420, deposited by Gregersen LH et al [39], was downloaded from the Gene Expression Omnibus database (GEO). https://www.ncbi.nlm.nih.gov/geo/. Based on the platform of the GPL570 [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array, the gene expression profile contained two samples, including four repetitions of colon cancer cell lines DLD-1 transfected with 50 nM of the miR-143-3p duplex and four repetitions of mock transfected DLD-1 cells. Total RNA was harvested after 24 hours of transfection and was analyzed by Affymetrix HG-U133 Plus 2.0 human arrays. The array contains 9,921 new probe sets representing approximately 6,500 new genes for the analysis of over 47,000 transcripts. GeneSpring-GX11.5 was applied to extract the microarray data. *In vitro* experiments were performed with miR-143-3p being over-expressed artificially for the purpose of seeking down-expressed targeted genes. A fold change (FC) <-0.2 was chosen for the threshold to screen the under-expressed genes.

*Protein-protein interaction (PPI) network construction*

The STRING (Search Tool for the Retrieval of Interacting Genes) database http://string-db.

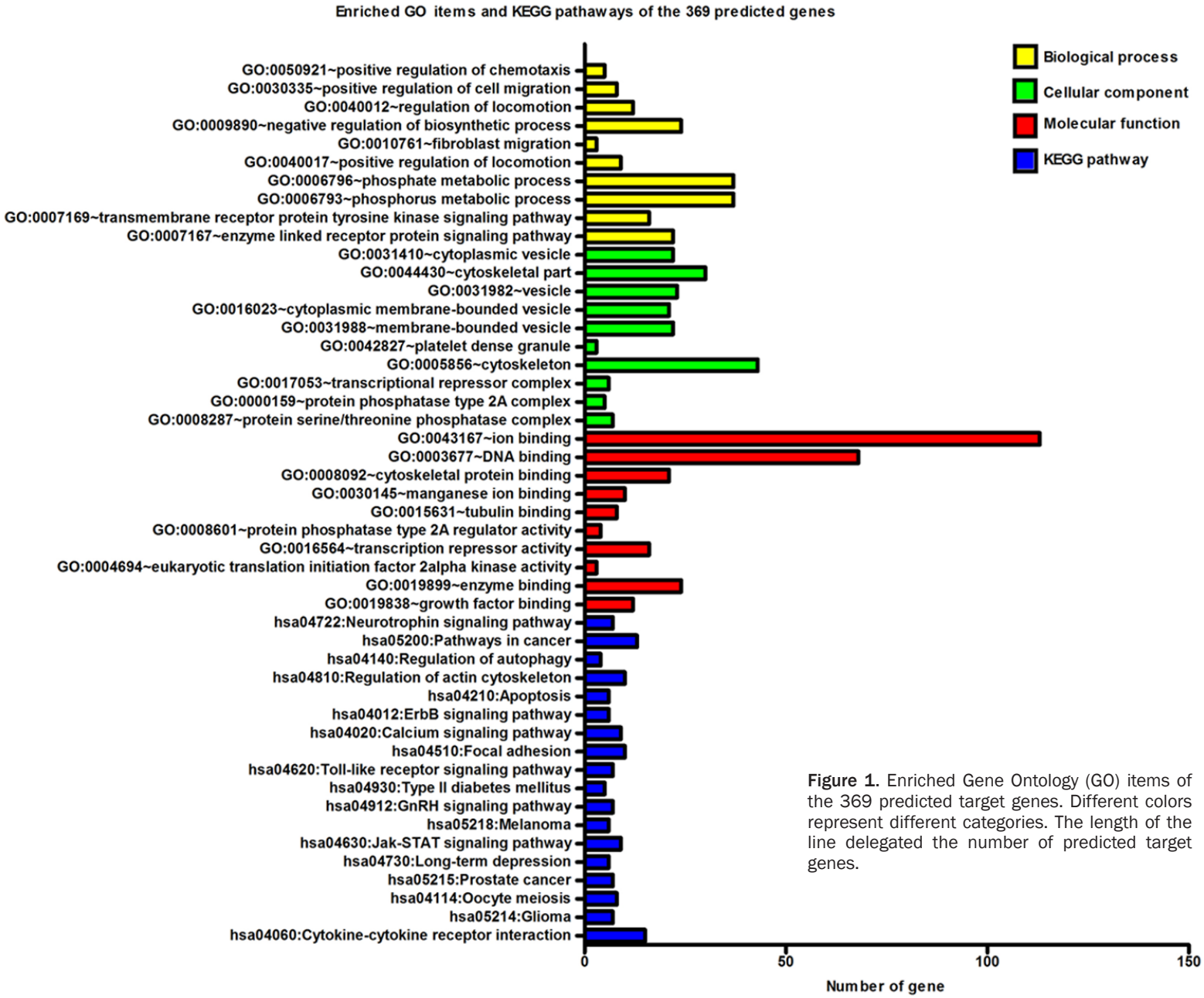


**Figure 1.** Enriched Gene Ontology (GO) items of the 369 predicted target genes. Different colors represent different categories. The length of the line delegated the number of predicted target genes.

**Table 2.** KEGG pathway of the 369 predicted genes

| Category | Term | Count | *P* Value |
|---|---|---|---|
| KEGG_PATHWAY | hsa04060:Cytokine-cytokine receptor interaction | 15 | 9.69E-04 |
| KEGG_PATHWAY | hsa05214:Glioma | 7 | 0.001846 |
| KEGG_PATHWAY | hsa04114:Oocyte meiosis | 8 | 0.007684 |
| KEGG_PATHWAY | hsa05215:Prostate cancer | 7 | 0.010217 |
| KEGG_PATHWAY | hsa04730:Long-term depression | 6 | 0.013995 |
| KEGG_PATHWAY | hsa04630:Jak-STAT signaling pathway | 9 | 0.015007 |
| KEGG_PATHWAY | hsa05218:Melanoma | 6 | 0.015693 |
| KEGG_PATHWAY | hsa04912:GnRH signaling pathway | 7 | 0.015932 |
| KEGG_PATHWAY | hsa04930:Type II diabetes mellitus | 5 | 0.016005 |
| KEGG_PATHWAY | hsa04620:Toll-like receptor signaling pathway | 7 | 0.01825 |
| KEGG_PATHWAY | hsa04510:Focal adhesion | 10 | 0.02355 |
| KEGG_PATHWAY | hsa04020:Calcium signaling pathway | 9 | 0.029677 |
| KEGG_PATHWAY | hsa04012:ErbB signaling pathway | 6 | 0.034355 |
| KEGG_PATHWAY | hsa04210:Apoptosis | 6 | 0.034355 |
| KEGG_PATHWAY | hsa04810:Regulation of actin cytoskeleton | 10 | 0.03439 |
| KEGG_PATHWAY | hsa04140:Regulation of autophagy | 4 | 0.035562 |
| KEGG_PATHWAY | hsa05200:Pathways in cancer | 13 | 0.039074 |
| KEGG_PATHWAY | hsa04722:Neurotrophin signaling pathway | 7 | 0.043969 |

org contains all of the known protein interactions predicted with a confidence score. Based on genome, high-throughput experiments, co-expression and prior knowledge, the interactions include direct (physical) and indirect (functional) associations. The new version 10.0 contains 9,643,763 proteins from 2,031 organisms [40]. To gain clear insight into the potential molecular mechanisms, STRING 10.0 was employed to determine the PPI association for the 43 overlapping genes. Adopting a confidence score >0.4 as the threshold to assess the associations, the PPI network was constructed.

*GO enrichment analysis and pathway analysis*

DAVID (Database for Annotation, Visualization and Integrated Discovery, http://david.abcc.Ncifcrf.gov/) offers a broad set of functional annotation tools to investigate the biological implication behind a great list of genes [41]. Thus, we used the DAVID Functional Annotation tool to perform Gene Ontology (GO) enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis to identify enriched biological items and metabolic pathways. The target genes predicted by five of the 12 prediction databases. and 43 overlapping genes were respectively uploaded to DAVID. The GO items and KEGG pathways whose *P* values are below 0.05 were selected as statistically significant terms.

## Results

*Predicted target genes of miR-143-3p*

Because miRNAs are very important in the regulation of the post-transcriptional expression of mRNAs, we tried to discover the putative targets of miR-143-3p through retrieval from the 12 prediction databases. Finally, integrating the results of the 12 online prediction tools, we chose 369 target genes [Supplementary File], which were predicted by 5 databases, to perform subsequent bioinformatics analysis. Significant GO annotation information of the 369 predicted genes were selected (P<0.05). There were 75 biological processes (BPs), including enzyme-linked receptor protein signaling pathway, transmembrane receptor protein tyrosine kinase signaling pathway and phosphorus metabolic processes. Additionally, there were 17 molecular functions (MFs)-for example, growth factor binding and enzyme binding. Moreover, 15 cellular components (CCs), including the protein serine/threonine phosphatase complex and protein phosphatase type 2A complex were identified. We only

**Table 3.** Significant GO enrichment items of the 43 overlapping genes

| Category | Term | Count | *P* Value |
|---|---|---|---|
| GOTERM_BP_FAT | GO:0046907~intracellular transport | 8 | 0.001262 |
| GOTERM_BP_FAT | GO:0006417~regulation of translation | 4 | 0.005248 |
| GOTERM_BP_FAT | GO:0010608~posttranscriptional regulation of gene expression | 4 | 0.016966 |
| GOTERM_BP_FAT | GO:0006605~protein targeting | 4 | 0.017829 |
| GOTERM_BP_FAT | GO:0007029~endoplasmic reticulum organization | 2 | 0.030621 |
| GOTERM_BP_FAT | GO:0032268~regulation of cellular protein metabolic process | 5 | 0.033053 |
| GOTERM_BP_FAT | GO:0006796~phosphate metabolic process | 7 | 0.03677 |
| GOTERM_BP_FAT | GO:0006793~phosphorus metabolic process | 7 | 0.03677 |
| GOTERM_MF_FAT | GO:0045309~protein phosphorylated amino acid binding | 2 | 0.028291 |
| GOTERM_MF_FAT | GO:0008483~transaminase activity | 2 | 0.049 |

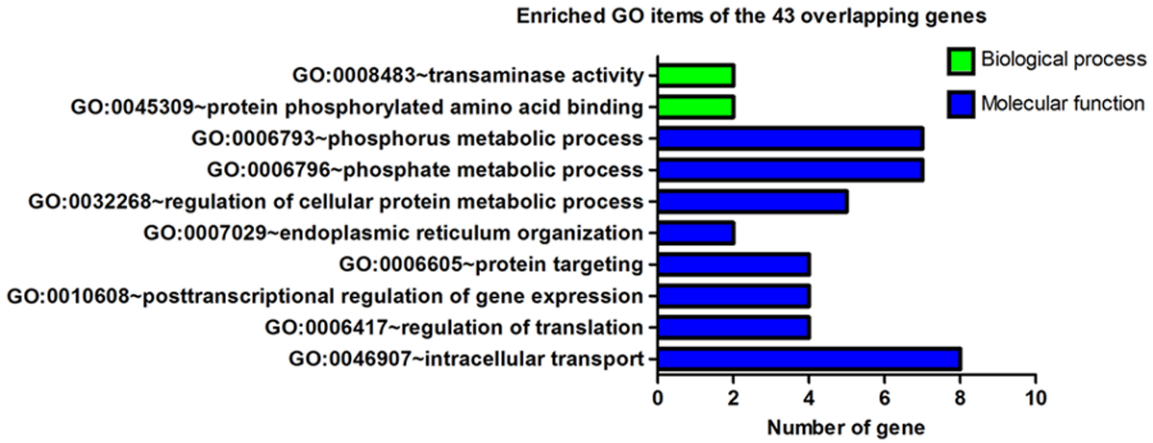


**Figure 2.** Enriched Gene Ontology (GO) items of the 43 overlapping genes. Different colors represent different categories. The length of the line delegated the number of overlapping genes.

listed the top ten GO items for each category in **Table 1** and **Figure 1**. Additionally, as shown in **Table 2** and **Figure 1**, KEGG pathway identified that there were 18 significant metabolic pathways (P<0.05), such as cytokine-cytokine receptor interaction, glioma and oocyte meiosis.

*GEO microarray*

To reduce the false positive rate of the predicted target genes, we further retrieved the GEO database and extracted the information regarding the microarray. GSE33420, our selected GEO microarray, was further analyzed to extract gene information. After miR-143-3p was over-expressed *in vitro*, we finally chose 821 genes of miR-143-3p that were down-expressed as our putative target genes. Only the genes with a fold change (FC) <-0.2 were selected for subsequent analysis. Therefore, 821 genes that met our criteria were finally screened out [Supplementary File].

*Overlapping genes*

Knowing that the most likely target genes of miRNA-143 should show in both the prediction database and GEO microarray, we integrated the results of the gene prediction databases and GEO microarray and extracted the overlapping genes. Forty-three overlapping genes were screened for the candidate target genes of miR-143-3p. Bioinformatics analysis were performed for the 43 overlapping genes. As shown in **Table 3** and **Figure 2**, the GO enrichment items of the overlapping genes were collected (P<0.05). There were eight biological processes (BPs), including intracellular transport, regulation of translation and posttranscriptional regulation of gene expression. Furthermore, two molecular functions (MFs)-pro-

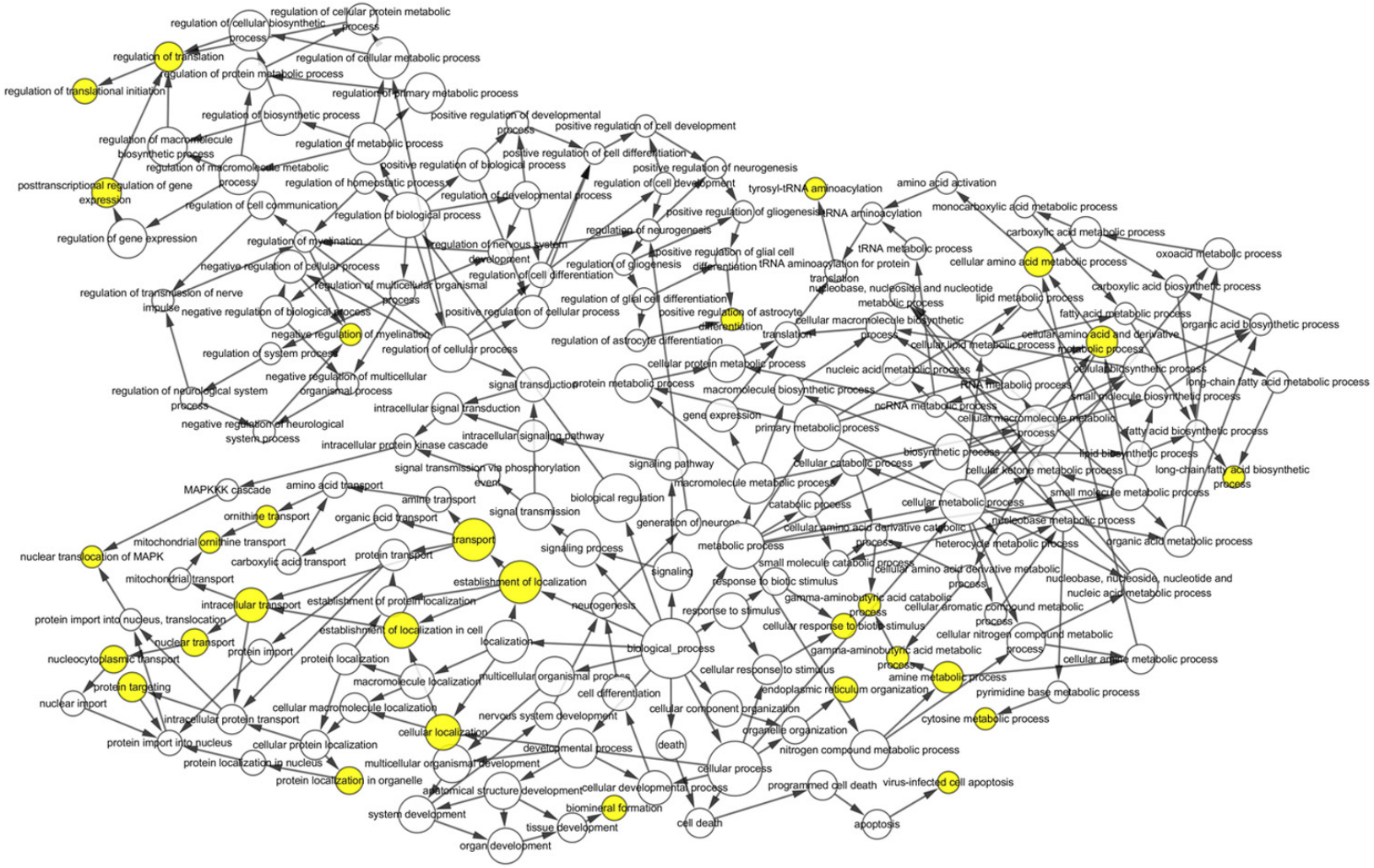


**Figure 3.** Biological process (BP) network of the 43 overlapping genes. Each node represents a GO item. The larger nodes indicate that more genes are involved in the GO item. All of the yellow nodes indicate statistical significance (P<0.18). White nodes are only involved in connecting the GO items, with no statistical significance.

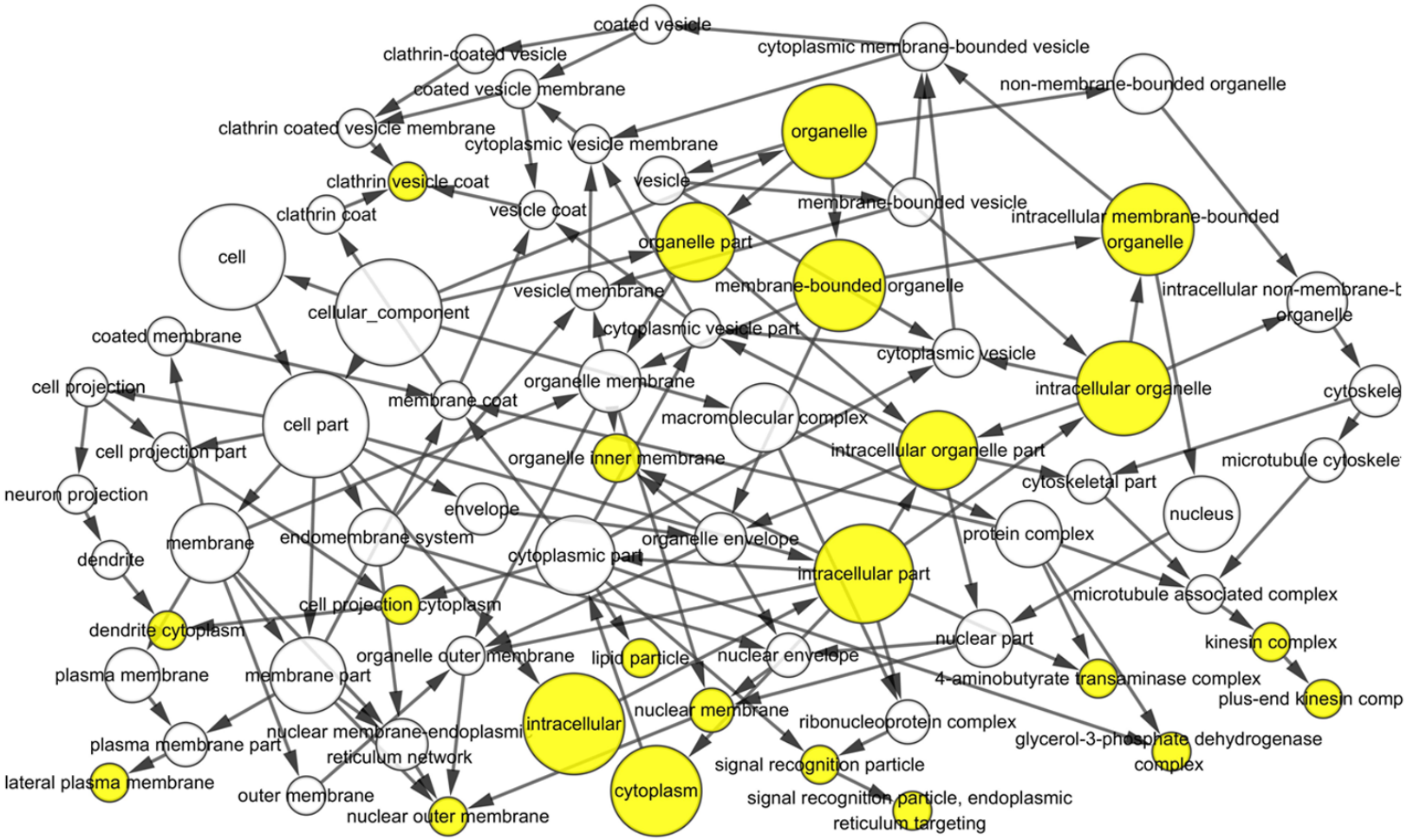


**Figure 4.** Cellular component (CC) network for the 43 overlapping genes. Each node represents a GO item. The larger nodes indicate that more genes are involved in the GO item. All of the yellow nodes indicate statistical significance (P<0.3). White nodes are only involved in connecting the GO items, with no statistical significance.

tein phosphorylated amino acid binding and transaminase activity-were found. However, no significant cellular component (CC) was found. Additionally, the GO enrichment networks of the 43 overlapping genes were constructed by the BINGO plugin in cytoscape 3.30. The biological process (BP), cellular component (CC) and molecular function (MF) network were shown in **Figures 3**-**5**, respectively. However, in the KEGG pathway analysis, no significant metabolic pathway was found.

*PPI network construction*

The aforementioned 43 overlapping genes were uploaded to the STRING 10.0 database to uncover potential protein-protein interactions, which could help us better understand the potential molecular mechanism. With the confidence score >0.4, the PPI network was constructed and is shown in **Figure 6**. We observed connections among the following genes: MAPK1, PTPN23, ERBB3, YWHAB, KLF5, ETV6, PKN2, YARS and PDPR. The results suggested that those genes were the key target genes of miR-143-3p in CRC.

## Discussion

As a high incidence and mortality cancer, colorectal cancer remains the third most common cancer in males and the fourth most frequent cancer in females; the mortality ranks third in both males and females in Asian Americans, Native Hawaiians and Pacific Islanders [42]. Thus, seeking novel potential therapeutic targets has become a promising area of research. In the present study, we sought to identify the target genes of miR-143-3p and then further explored the potential molecular mechanism in CRC. To that end, we applied 12 public prediction databases and microarrays to comprehensively screen the most likely target genes. As previously mentioned, we focused on 43 overlapping genes to mine the functions they might exert in CRC. Bioinformatics tools were adopted to analyze their biological functions.

GO enrichment analysis for the 43 overlapping genes showed that intracellular transport is the first GO term of BP, while protein phosphorylated amino acid binding is the first GO term of MF. This result indicated that intracellular transport and protein phosphorylated amino acid binding could play important roles in CRC. No significant CC GO term and KEGG metabolic pathway were found, so further study is needed. For the predicted genes, enzyme linked receptor protein signaling pathway, growth factor binding and protein serine/threonine phosphatase complex remained on top respectively in BP, MF and CC, which could probably be related to CRC. KEGG analysis showed that Cytokine-cytokine receptor interaction is the first metabolic pathway. It should be of great importance in the development of CRC. However, no research has elucidated the role of cytokine-cytokine receptor interaction in CRC. Thus, further study is needed to verify the speculation.

Through STRING functional protein association network construction, we found associations among nine genes (MAPK1, PTPN23, ERBB3, YWHAB, KLF5, ETV6, PKN2, YARS and PDPR). Those nine genes represent hub genes that may be the key genes of miR-143-3p in CRC. Thus, we focused on the nine genes for subsequent discussion.

MAPK1 (mitogen-activated protein kinase 1), which resides on chromosome 22q11.21, is also known as ERK2 or P42MAPK. It is a gene that encodes a member of the MAP kinase family and is involved in various cellular processes such as proliferation, differentiation, transcription regulation and development. Weng YR et al discovered that ERK2 plays a role in the carcinogenesis of CRC through inducing G0/G1 phase arrest in CRC cells [43]. Another study found that ERK1, along with ERK2, is related to a more aggressive type of CRC that may indicate a poor prognosis [44]. Furthermore, ERK1/2, which interacts with TRAPPC4, is involved in CRC cell proliferation and apoptosis [45]. Thus, combined with the studies above, MAPK1 could be the therapeutic target in CRC. However, there is still no study showing the relationship between MAPK1 with miR-143-3p. So it is required to perform experiments to validate if MAPK1 could be a target of miR-143-3p in CRC.

PTPN23 (protein tyrosine phosphatase, non-receptor type 23), also known as HD-PTP, belongs to the non-receptor class subfamily of the PTP family. PTPN23 is a candidate tumor suppressor involved in the tumorigenesis of various organs. In recent years, several functions of PTPN23 have been reported, including participation in the regulation of endothelial

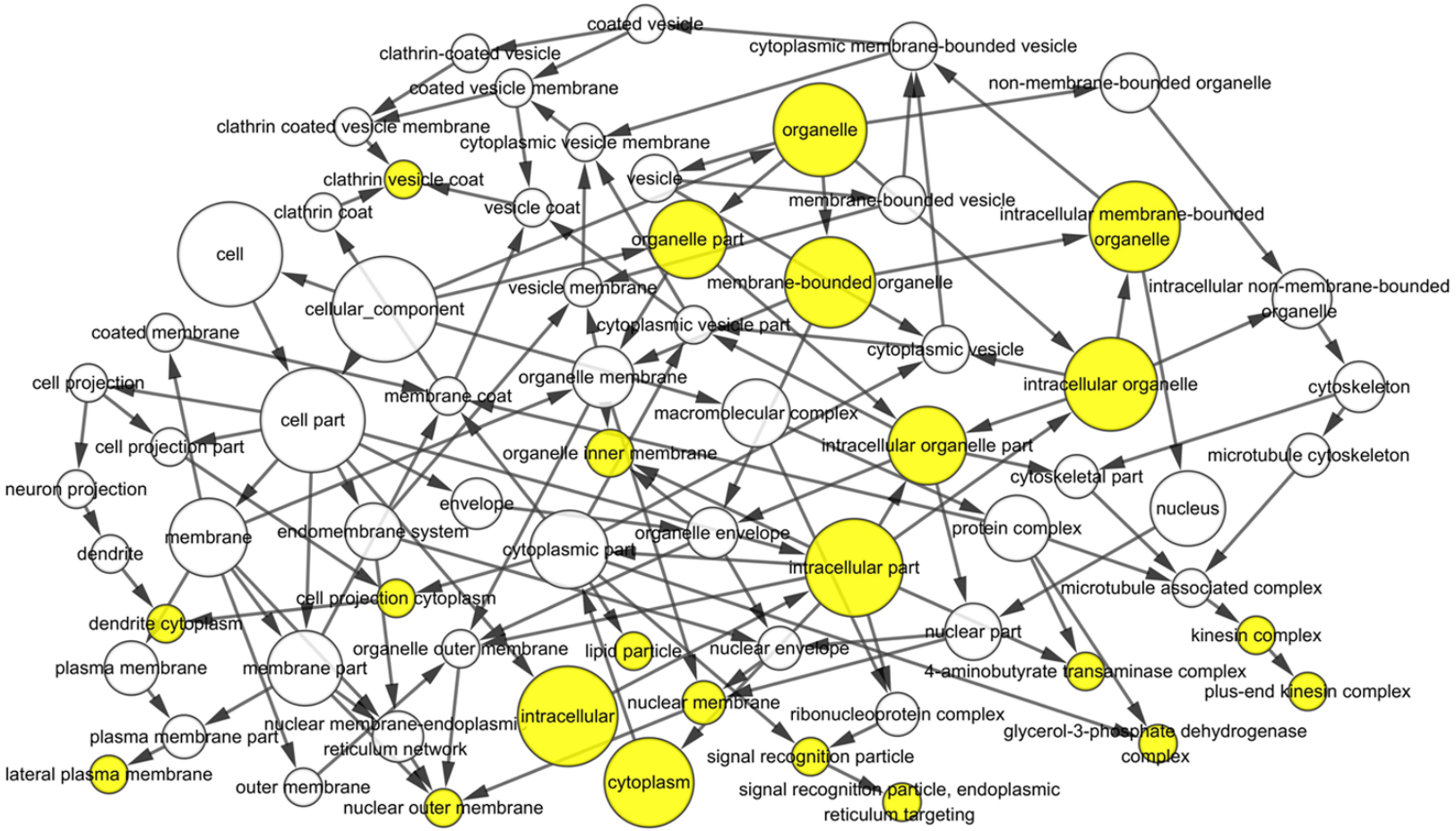


**Figure 5.** Molecular functions (MF) network of the 43 overlapping genes. Each node represents a GO item. The larger nodes indicate that more genes are involved in the GO item. All of the yellow nodes indicate statistical significance (P<0.1). White nodes are only involved in connecting the GO items, with no statistical significance.

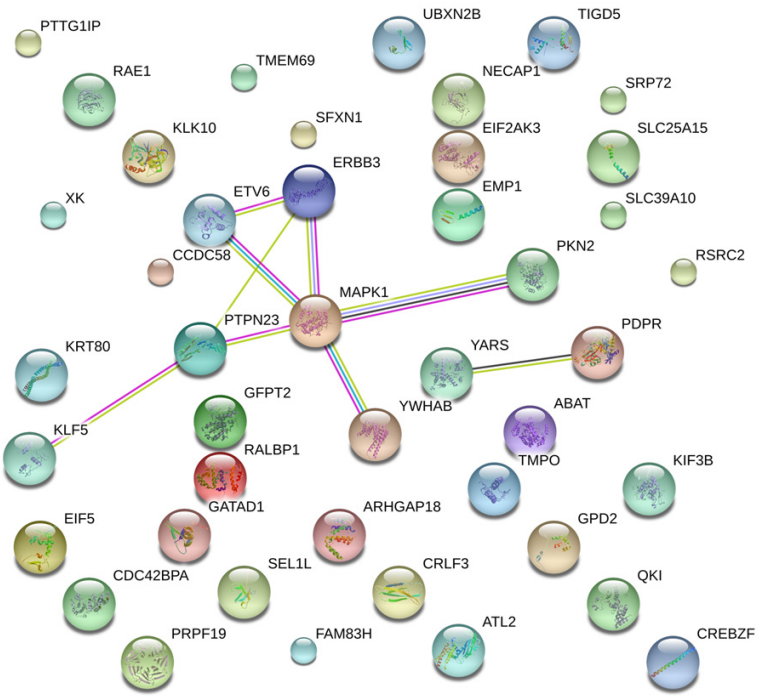


**Figure 6.** Protein-protein interaction network of overlapping genes constructed by STRING 10.0. Each node represents one protein encoded by genes. Small nodes represent the protein of unknown 3D structure while large nodes represent the protein of known or predicted 3D structure. Colored nodes mean query proteins and first shell of interactors while white color nodes mean second shell of interactors. The lines among nodes represent the associations of proteins. Line color indicates the type of interaction evidence. Interactions are based on the evidences such as experimentally determined, gene fusion, gene neighborhood, co-expression, etc.

cell motility by modulating the tyrosine phosphorylation of focal adhesion kinase (FAK) [46] and its interaction with SRC [47]. However, until now, no reports related to CRC or miR-143-3p has been found. To summarize, PPTPN23 is a tumor-related gene, although it has not been verified to be involved in CRC or miR-143-3p. Thus, more studies are needed to explore the functions of PTPN23 related to miR-143-3p in CRC.

ERBB3 (erb-b2 receptor tyrosine kinase 3), also known as HER3, is a member of the human epidermal growth factor receptor (HER) family. It contains an extracellular domain (ECD), a single-span transmembrane region, an intracellular tyrosine kinase domain that is functionally defective, and a C-terminal signaling tail. The ECD is a four-domain structure consisting of two L domains (I and III) and two cysteine-rich domains (II and IV) [48, 49]. Accumulated studies have shown that ERBB3 is deregulated, contributes to the development of several human malignancies and is mutated in a subset of cancers. In recent years, studies have found that ERBB3 is mutated in CRC [50, 51]. Additionally, ERBB3 is significantly increased in CRC tissues [52, 53]. Elevated levels of ERBB3 expression have been associated with decreased patient survival in colorectal cancer [54, 55]. Yan X et al found that ERBB3 is a target of miR-143-3p in breast cancer [56]. However, there is no research proving that ERBB3 could be associated with miR-143-3p in CRC. Overall, ERBB3 may be a target gene in CRC that has potential therapeutic values. But more studies are needed to validate its functions.

YWHAB (tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta) is also known as HS1 or GW128. It is a gene that encodes a protein belonging to the 14-3-3 family. Recently, Yi Hong et al found that YWHAB is one of the 54 genes in the molecular network that might be related to CRC [57]. Additionally, Zhao J et al observed that YWHAB is a differentially expressed scaffold protein in HCT-15 colon carcinoma cells after all-trans retinoic acid treatment [58]. Still, no literature is available to show the relationship between YWHAB and miR-143-3p. But with more experiments performed, there is still great possibility to prove that YWHAB could act as a target gene of miR-143-3p in CRC.

KLF5 (Krüppel-like factor 5), also known as intestinal-enriched Krüppel-like factor (IKLF), mainly exists in the proliferating crypt epithelial cells of the intestinal epithelium [59-61]. It belongs to the Krüppel-like factor (KLF) protein family that regulates the processes of cell differentiation, proliferation and apoptosis. Guo L et al found that KLF5, as a co-regulator to activate β-catenin, is involved in the proliferation of colon cancer cells [62]. Another study found that KLF5 activity is modulated by small-mole-

cule compounds, therefore inhibiting colorectal cancer proliferation [63]. Moreover, Pagliuca A et al found that KLF5 is a protein targeted by miR-143-3p in CRC [64]. Thus, considering the aforementioned findings, KLF5 can basically be considered as a target of miR-143-3p in CRC.

ETV6 (ETS variant 6), also named TEL, encodes an ETS family transcription factor that contains two functional domains: an N-terminal pointed (PNT) domain and a C-terminal DNA-binding domain. Located on 12p13, it is a leukemia-associated gene involved in different chromosomal translocations in myeloid and lymphoid malignancies [65]. Regarding CRC, C Deves et al found that ETV6 is slight down-regulated in CRC compared with that in adjacent normal tissues [66]. But the relationship between ETV6 and miR-143-3p has not been reported. Therefore, experiments are needed to further validate the association of ETV6 and miR-143-3p in CRC.

PKN2 (protein kinase N2), also named PRK2, belongs to the mammalian protein kinase N family of serine/threonine kinases. However, no study has been reported that PKN2 could be related to CRC or miR-143-3p. Thus, further studies are required to confirm the role of PKN2 in CRC and the relationship with miR-143-3p.

YARS (tyrosyl-tRNA synthetase) belongs to the class I tRNA synthetase family. It was observed that to exhibit cytokine activity for the human tyrosyl-tRNA synthetase. Little is known about the relationship between YARS and cancer. No study has been reported that YARS is involved in CRC or miR-143-3p. Consequently, more studies are needed to uncover the role of YARS in CRC.

PDPR, whose official full name is pyruvate dehydrogenase phosphatase regulatory subunit, is also known as PDP3. Until now, no report related to the association between PDPR and cancer or miR-143-3p has been found. Thus, it is imperative to further investigate the functions of PDPR in cancers.

We also searched the validated targets of miR-143-3p in CRC which have been specially reported in literatures in Pubmed. There are 34 target genes available: ERK5, KRAS, GMPSP, ANP32B, FSCN1, MDM2, ARF6 [27], MACC1 [30], HK2 [39], CD44, KLF5, BRAF [63], DNMT3A, ELK1, MYO6, Bcl-2 [67], PI3K, APC, TGFbRII, hMSH6 [68], c-Myc [69], API5,IRS-1 [70], FXYD3 [21] and CHEK2 [71]. Compared with the obtained prospective targets based on bioinformatics in our study (MAPK1, PTPN23, ERBB3, PKN2, KLF5, YARS, ETV6, PDPR and YWHAB), we found that KLF5 has been reported to be a target of miR-143-3p in CRC. This suggests the feasibility of our method to predict target genes through microarray and prediction programs. Although the rest eight targets (MAPK1, PTPN23, ERBB3, PKN2, YARS, ETV6, PDPR and YWHAB) have not been reported in literature according to our retrieve, with further experiments carried out, it still has great chance to be validated. Among those previously reported targets, ERK5 is of great importance. ERK5 belongs to MAP kinase family. It is involved in the regulation of cell proliferation and survival via activating multiple cellular proteins. Targeted by miR-143-3p, ERK5 can reduce protein steady-state levels and activation [67]. Overall, ERK5 plays an important role in CRC targeted by miR-143-3p.

However, there are several limitations in the present study. First of all, the expression of miR-143-3p in CRC has not been validated in clinic. Even though we have tried to utilize the TCGA CRC data to validate the expression of miR-143-3p, the normal samples were too limited and inadequate for statistical analysis. Therefore, further experimental validations are required. Besides, we only analyzed a single microarray which contained only two samples (4 repetitions for each sample). Small sample size limited the accuracy and reliability of the differential expression genes. We had expected microarrays with larger samples, however, this is the only, and most suitable microarray we could use based on the publicly available data. So further studies with larger samples are required to improve the weakness. Another limitation in this paper is that all the work is on computational level. Even though we adopted 12 prediction databases and achieved intersection of five prediction databases, the false positive results could inevitably exist. So experiments should be carried out to validate the target genes we predicted in the future. Nevertheless, the approach used in the present study could be applied to other miRNAs and cancers.

Target genes of miRNAs in other cancers can be predicted through similar method.

## Conclusions

In the present study, among the nine hub genes we discovered, KLF5 has been reported as a target gene of miR-143-3p in CRC. MAPK1, ERBB3, YWHAB and ETV6 showed great potential to serve as target genes of miR-143-3p and, thus, might exert therapeutic effects in the treatment of CRC. Further studies are required to confirm the findings. Regarding PTPN23, PKN2, YARS and PDPR, research is lacking to support their roles in CRC. Nevertheless, with more research investigations, there is still a great chance to uncover unknown roles of these genes in CRC.

## Acknowledgements

The study was supported by the Fund of Project of Future Academic Star in Guangxi Medical University, China (No. WLXSZX16003). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

## Disclosure of conflict of interest

None.

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