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Original Article

CRNDE and Myc affect metastasis of melanoma via modulating cell migration

Yifei Yang[1], Fang Wang[2], Ke Tian[3], Lei Wang[4], Chunxia Yao[4], Xiaohua Wang[5], Guoying Miao[1]

[1]Dermatology of Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China; [2]Respiration of Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China; [3]CT Scan Rooms of Affiliated Hospital of Hebei University of Engineering, Handan, Hebei Province, China; [4]Pathology of School of Medicine, [5]Nursing of School of Medicine, Hebei University of Engineering, Handan, Hebei Province, China

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Abstract: Melanoma is one of the deadliest cancer developing from the pigment-containing cells. It strikes tens of thousands of people every year, being one of the fastest rising cancers around the world. Metastasis is the most deadly stage in the development of melanoma. We conducted a series of bioinformatics analysis to the transformation potential of primary cervical cancer melanoma and metastatic malignant melanoma cells in a xenograft model. The analysis consisted of differential analysis, co-expression analysis, enrichment analysis, and ncRNA prediction and TF prediction. The differential analysis highlighted 5395 differential genes. Using WGCNA to further analyze these differential genes, we obtained eight potentially relevant dysfunction modules. Thereafter, GO function and KEGG enrichment analysis demonstrated many signal pathways closely related to tumor growth and metastasis including nuclear division, focal adhesion, epithelial cell proliferation, and epithelium migration. Finally, the analysis of transcripts and ncRNAs of the dysfunction module showed transcription factors such as Myc and its family members MYCN and CRNDE, and ncRNAs such as FENDRR may be involved in the regulation of multiple module genes. Moreover, it also revealed that CRNDE can regulate the expression level of Myc, and ultimately regulate the proliferation and migration of cancer cells. In conclusion, we believe that CRNDE may affect melanoma metastasis by regulating cancer cell migration, and CRNDE may be a potential therapeutic target for melanoma cells.

Keywords: Melanoma, CRNDE, cell migration, WGCNA

Introduction

Melanoma is a clinically common skin mucosa and pigmented membrane tumor. It is one of the fastest-growing tumors. According to the degree of metastasis, melanoma can be divided into stages 0, I/II, III and IV. In stage 0, it is in situ, while metastasis has not occurred. In stage I/II, it is invasive melanoma. In stage III it exhibits regional metastasis, and in stage IV, it causes distant metastasis. According to statistics, the incidence of males is higher than that of females, and the incidence of whites is significantly higher than that of other races [1]. Besides, the highest incidence of melanoma occurs in Australia and New Zealand in the world, while the low incidence takes place in Africa, Asia, and Latin America. In 2015, there were approximately 3.1 million melanoma patients worldwide, with an annual growth rate of 3% to 5%. Approximately 60,000 patients died of melanoma each year (Siegel et al. 2014). The 5-year survival rate of melanoma in situ is about 98%, while the 5-year survival rate of metastatic malignant melanoma is only 15-20%. Clinically, the diagnosis of melanoma mainly depends on visual detection. Its early symptoms are mainly characterized by an abnormal shape of nevus, color change, or abnormal mass on the surface of the skin. The changes in nevus mainly are manifested as asymmetrical shapes, irregular edges, large diameters, constant changes, and funny looking, as well as itch, ulcers, and bleeding probably in the later period. The abnormal mass is mainly manifested as an apparent and tough lump on the surface of the skin with continuous growth. In metastatic malignant melanoma, other abnormal clinical manifestations may also be exhibited [2]. Besides, ugly duckling, biopsy and other methods combined with dermoscopic imaging methods can provide a very high detec-

tion rate [3]. Lactate dehydrogenase (LDH) testing is commonly used to detect whether the tumor has progressed to metastatic malignant melanoma. It is now believed that melanoma is mainly caused by long-term exposure to ultraviolet radiation in people with low skin pigment content. These ultraviolet rays also stem from the sun, tanning beds, etc. [4]. Repeated severe sunburn can significantly increase the risk of developing sunburn into melanoma. Also, a family history of melanoma can significantly increase the risk. Multiple genes, including MC1R, BRCA, p53, CDKN2A, and other mutations are closely related to the occurrence of melanoma.

Metastasis refers to the growth of cancer cells of malignant tumors in organs other than the initial site. It is one of the important markers for distinguishing between benign and malignant tumors. Once metastasis occurs, it refers to the late stage of tumor or a higher degree of malignancy. After that, the operation is difficult and the recurrence rate after surgery is high. Metastasis is the leading cause of death in cancer patients, accounting for more than 90% of the total number of deaths. However, little is known about the specific mechanism of metastasis [5-7]. The biological processes of metastasis are listed as follows: cell loses adhesion, increases motility and invasiveness, survives in the circulation, enters into new tissues, and eventually colonizes in the distal position [7, 8]. In their molecular spectrum analysis of cancer, Weigelt et al. found that cancer metastasis and recurrence may be closely related to various tumorigenic genes [9]. Metastatic malignant melanoma with a low 5-year survival rate is difficult to cure and is prone to recurrence. Therefore, many studies are trying to find more suitable diagnostic biomarkers, treatments, and markers. Mutations in genes such as BRAF, NRAS, β-catenin, E-cadherin, and HIF-1α are biomarkers of melanoma metastasis through genetic screening [10, 11]. Besides, clinical trials have shown that the use of Dabrafenib, a selective inhibitor of V600-mutant BRAF, can increase the progression-free survival of melanoma patients [12].

This study further explored the differentially related genes of metastatic malignant melanoma and melanoma in situ to look for genes closely related to melanoma metastasis. It predicted that these mechanisms may regulate ncRNA and transcription factors to further understand the mechanism of melanoma metastasis.

Materials and methods

Data resource

The data for gene expression in this study was derived from the Gene Expression Omnibus (GE). GEO is an international public database for archiving and free distribution of high-throughput gene expression and functional genes. Up to now, GEO has accepted high-throughput data for a variety of research, including gene methylation, chromosome structure, and interactions between genes and proteins. GSE8401 is a database downloaded in the GEO database. It compares the metastatic potential of metastatic invasive malignant melanoma with melanoma in situ. We performed a differential analysis of the genetic data of GSE8401 to find the potential genes that affect the metastasis of metastatic malignant melanoma [13].

Variance analysis

In this study, we used the R language limma package to analyze the genes in the database to find the metastatic potential related genes of malignant melanoma [14]. After background calibration and standardization, differential genes were screened ($p<0.05$). At the same time, we also used volcano maps to analyze genes to look for genes that are up-regulated, down-regulated, and not significantly altered. The volcano map was experimentally analyzed with a comprehensive analysis of fold change (FC) and *p* values. Its Y-axis setting is based on -log10 (*P*-value) and the X-axis setting is based on log2 (fold change). Concerning candidate genes, we set the threshold value of the absolute value of log2 (FC) and -log (*p*-value) greater than 0.5.

Identification of dysfunction modules

To further investigate the genes involved in metastatic potential, we analyzed the differential expression of differential genes in melanoma in situ and metastatic malignant melanoma, using WGCNA In the process, we assume that the connections between all genes in the network are subject to scale-free network distribution. It makes the analysis method more

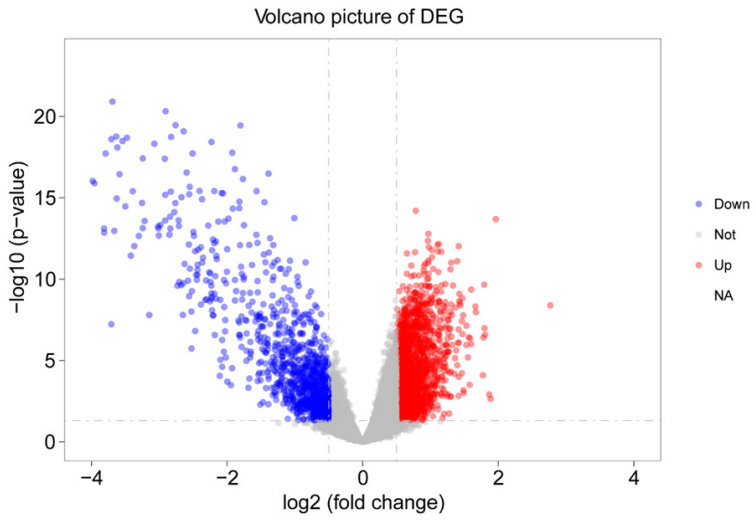

Figure 1. Differential gene volcano map. Blue dots refer to down-regulated genes, red dots stand for up-regulated genes, and gray dots stand for genes that have not changed significantly.

meaningful in terms of biology. In this study, we analyzed the correlation between any two differential genes, obtained the heat map of all genes in the co-expression network. All the genes were clustered using the hierarchical clustering tree method. We got 19 co-expressing modules, using diverse colors to represent various dysfunction modules. Besides, we analyzed the correlation between any two modules for a dysfunctional module with coordinated expression. Finally, based on the size of each gene in the module, we identified key genes that contribute to the dysfunction of the module. We believe they may be key genes for malignant melanoma metastasis.

Functional and path enrichment analysis of differential genes

Exploring the function and signaling pathways involved in differential genes contributes to the study of the molecular mechanisms of disease. In this study, GO function and KEGG pathway enrichment analysis were conducted on 8 functional modules. Based on the UNI gene GO function annotation, we annotated the differential genes screened [15]. Then, we respectively performed GO analysis of the differential genes in the 8 modules using the R language. We (http://kobas.cbi.pku.edu.cn/home.do) performed KEGG path enrichment analysis on the differential genes [16] (p-value <0.01) and plot the bubble with the application of KOBAS2.0.

Pivot regulator

Transcription factors and ncRNA have significant regulatory effects on gene transcription and post-transcriptional regulation. In this study, we scientifically predicted and tested the relationship between dysfunction modules of metastatic melanoma-expressing genes and transcription factors and ncRNAs. On request, the number of targeted adjustments between each transcription factor and module is greater than or equal to 2. Meanwhile, the target enrichment in each module is significant (p-value <0.01). Also, in this study, we only showed in-depth research and analysis concerning the ncRNA with the largest number of regulatory modules. Based on the TF and ncRNA target data as a background set, the pivotal regulator of regulatory dysfunction module was finally predicted.

Result

Identification of differential expressed genes in metastatic tumor

Many studies have been conducted on the occurrence, migration, and treatment of melanoma, and have found a variety of potential genes and microRNAs for melanoma. However, little is known about the link between these potential genes, microRNA complex molecules and the overall effect. It is well known that metastasis is the most deadly stage in the development of melanoma. But not much is known about the genes involved in metastasis. To find potential genes for melanoma metastasis, we compared and analyzed the metastatic potential of melanoma in situ and metastatic invasive malignant melanoma cells, based on the human GSE8401 gene database. As a result, we found 12 and 548 genes. To further identify differential gene expression in these melanoma metastatic potentials, we got 5,395 differentially expressed genes (DEGs) involved in melanin transfer. Besides, we integrated these genes and mapped the volcano, according to the P values and fold changes of these genes (**Figure 1**).

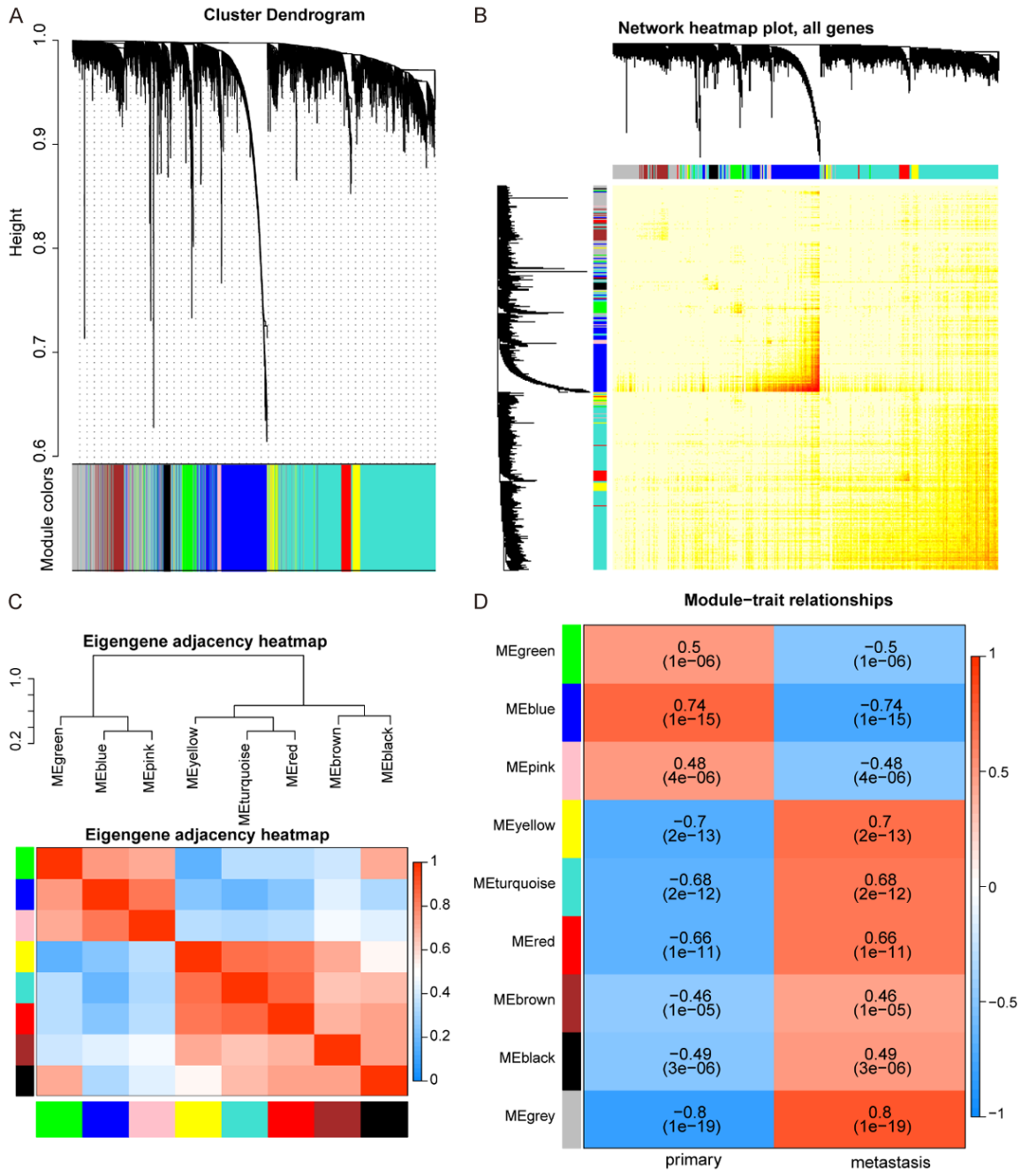

Figure 2. Synergistic expression of differential genes in primary and metastatic malignant melanoma. A. 8 dysfunction modules through the cluster. 8 colors represent 8 modules. B. Here are heat maps of all genes expressed in the co-expression network, whose expression behavior is clustered into 8 co-expression modules. C. The module and the module co-express the calorimetric map. Each color represents a module. The color of each cell is mapped by the corresponding correlation coefficient. The value ranges from 0 to 1, and the color transitions from blue to white and red. D. Each row stands for a module, and each column represents a phenotype, and the cell color reflects the corresponding correlation coefficient. The correlation increases from blue to white to red.

Recognition of melanoma metastasis functional disorder module through weighted gene co-expression network analysis

We explored the underlying pathogenesis of disease through biological networks. In an undirected network, a module consisting of a series of highly related genes represents a potential mechanism. The dysregulation of the Hub gene may cause abnormal function of multiple genes in the module and global dysfunction. It eventually leads to the occurrence or progression of

Table 1. Hub genes of each module

colour	HubGenes	Module
turquoise	XPO1	m1
blue	S100A14	m2
brown	PSG9	m3
yellow	CALU	m4
green	IL32	m5
red	RRM2	m6
black	LAIR1	m7
pink	DCN	m8

the disease. To identify the melanoma metastasis dysfunction module, we analyzed 5,395 differential genes and their interaction genes involved in melanoma metastasis. They were used to construct an expression profile matrix in the sample. Then, the weighted gene co-expression network analysis (WGCNA) revealed that these genes had significant group co-expression in the samples (**Figure 2A**, **2B**). To further analyze the possible synergistic relationship of these co-expressed genes, we put these co-expressed genes into the same module. We got 8 dysfunction modules and identified the key genes of each module with XP01 8, S100A14, PSG9 and other 8 Hubgene obtained (**Table 1**). Then, the correlation map between the modules reflect the correlation between the expression of the vector gene in each module and the expression of the gene in the entire module (**Figure 2C**). It is obtained by clustering the inter-gene expression amount.

GO function and KEGG pathway enrichment analysis (enrichment of DEGs)

The occurrence and development of each disease are closely related to different pathways. Exploring the GO function and KEGG pathway enrichment analysis showed that the dysfunction module gene may contribute to the comprehension of the upstream and downstream relationship of this pathway. It links various biological pathways to disease occurrence, which is a vital issue for the study of the underlying molecular mechanisms of disease. In this study, we performed GO function and KEGG pathway enrichment analysis on 8 dysfunction modules. It resulted in 32,887 biological processes, 4,055 cell components, 6,494 molecular functions, and 1,655 KEGG pathways. Based on functional analysis of GO and KEGG, we found that several issues may be closely related to metastasis of melanoma. They are adhesion factors, cell proliferation, migration, immunity, and various cancer-related signaling pathways, especially nuclear division, focal adhesion, epithelial cell proliferation, epithelium migration, viral carcinogenesis, etc. (**Figure 3A**, **3B**).

TF and ncRNA regulating melanoma metastasis

It is well known that the expression, transcription, and transcription of genes in vivo are strictly regulated. The transcription and post-transcriptional regulation of genes may be closely related to the occurrence and development of various diseases. It is generally believed that both TF and ncRNA are salient regulators during and after transcription. Analysis and prediction of transcription factors that regulate dysfunction modules will help us further explore the transcriptional regulation mechanisms of melanoma metastasis. In this study, we found a total of 86 TFs involving 91 TF-module target pairs, using TF pivot analysis. Of them, we selected transcription factors linked to more modules and found that MYC is involved in the regulation of three dysfunctional module genes. MYCN, SP1, and JUND are involved in the regulation of two dysfunctional module genes (**Figure 4A**), while MYCN is one of the family members of MYC. Therefore, we believe that MYC may affect the metastasis of melanoma. We analyzed the targeted regulatory relationships between ncRNA and dysfunction module genes for co-expression of modular genes, using the pivot software. This was to explore key ncRNAs that regulate melanoma metastasis. The analysis showed a total of 1,272 ncRNAs involved 1,642 ncRNA-module regulatory pairs. Of them, CRNDE was involved in the regulation of six functional modules, while FENDRR and miR-149-5p participated in the regulation of five dysfunctional module genes (**Figure 4B**). Therefore, we believe that the above three ncRNAs are important parts of the development of melanoma metastasis. We identified these potential regulatory factors as dysfunctional molecules during melanoma metastasis.

Discussion

Melanoma, a tumor produced by melanocytes, mainly occurs in the skin, meninges, mucous

A
GO-Function terms
regulation of I−κB kinase/NF−κB signaling
nuclear division
nuclear chromosome segregation
mitotic nuclear division
Golgi vesicle transport
focal adhesion
epithelium migration
epithelial cell proliferation
epithelial cell migration
chromosome segregation
cell chemotaxis
cell adhesion molecule binding
cell−substrate junction
cell−substrate adherens junction
cadherin binding
20
30
40
50
Count
−log10(FDR)
50
40
30
20
10
Count
20
30
40
50
B
KEGG Pathway Terms
Viral carcinogenesis
Ubiquitin mediated proteolysis
Thyroid cancer
Spliceosome
RNA transport
RNA degradation
Proteoglycans in cancer
Protein processing in endoplasmic reticulum
Human T−cell leukemia virus 1 infection
Focal adhesion
Epstein−Barr virus infection
Cushing syndrome
Central carbon metabolism in cancer
Cell cycle
Arachidonic acid metabolism
5
10
15
20
count
count
5
10
15
20
−log(pvalue, 10)
20
15
10
5

Figure 3. Functional analysis and pathway enrichment analysis of modular genes. A. Analysis of GO gene function of the module gene. B. Analysis of KEGG signaling pathway set. The color and size of each circle correspond to the enrichment significance and number of GO function entries. From blue to purple, the enrichment gradually increases. From small circle to large, the number of GO function entries gradually increases.

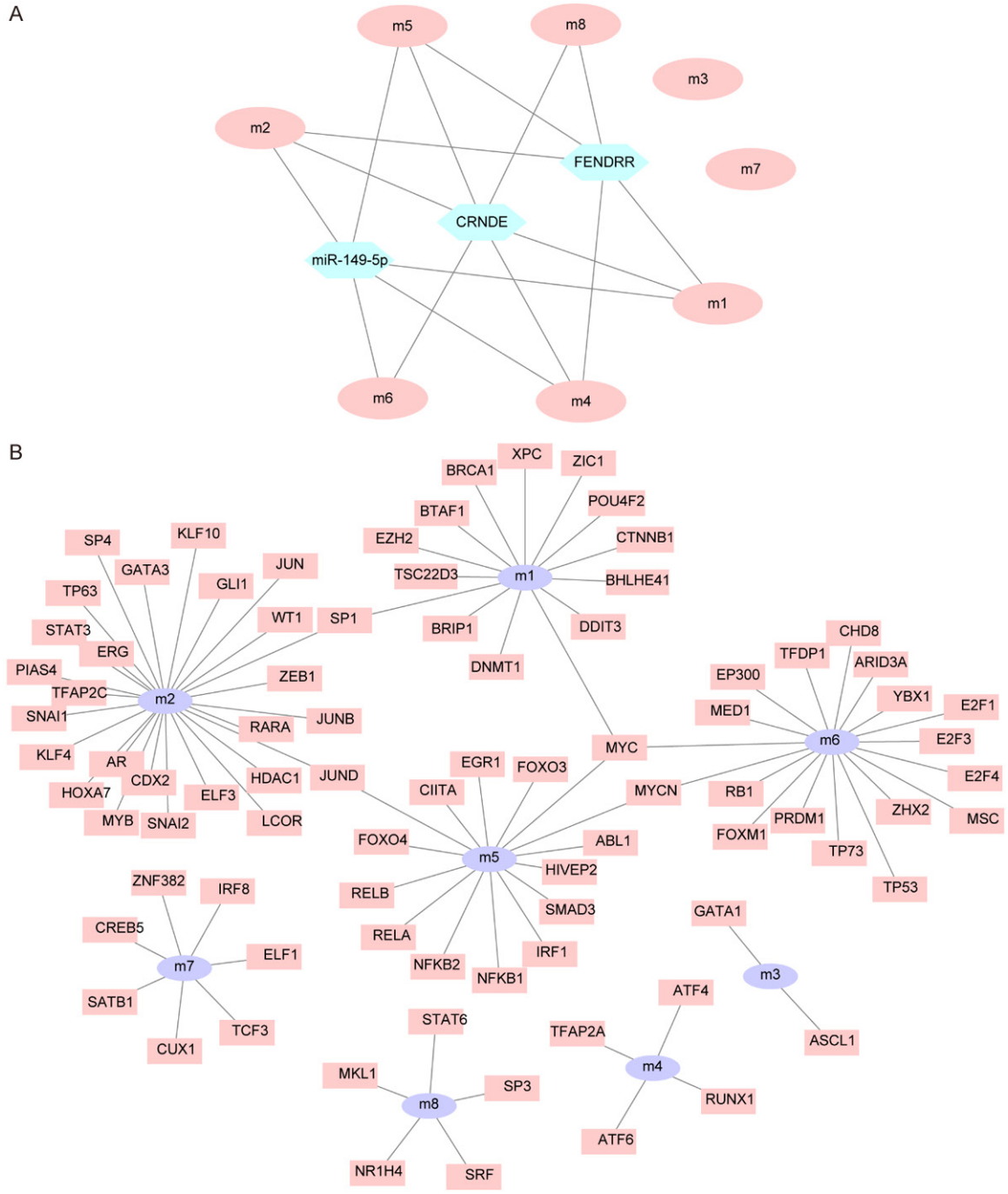

Figure 4. The regulation of the Pivot regulator on the dysfunction module. A. Cyan hexagon represents ncRNA, and pink oval stands for the module. B. Blue oval represents a module, and a pink square represents a transcription factor.

membranes, and soft tissues in the upper part of the esophagus. The metastatic malignant melanoma is in stage IV of melanoma with high malignancy. The short median survival of pa-

tients and low survival rate within 5 years, has received more and more attention. It is generally believed that metastatic malignant melanoma cannot be treated with surgical resection. Clinically, the treatments of malignant melanoma mainly consist of radiation treatment, chemotherapy, immunotherapy, etc. [11]. Also, adoptive cell therapy and gene therapy are still under investigation [17]. However, the mechanism of melanoma cell metastasis is not clear. Thus, these treatments can only increase the median survival and survival rate within 5 years.

To further understand the mechanism of melanoma metastasis, we collected GSE8401 in the GEO database. After comparing the metastatic potential of in situ melanoma and metastatic malignant melanoma, we obtained 8 dysfunction modules. Meanwhile, we performed the GO function and KEGG analysis and found significant changes in the nuclear division, focal adhesion, epithelial cell proliferation, epithelium migration, viral carcinogenesis, etc. with cell proliferation, adhesion change, endothelial cell proliferation, metastasis and various pathway associated with cancers. Changes in adhesion, exercise, and increased invasiveness are important biological changes in the process of cancer metastasis. Increased cell proliferation is one of the basic characteristics of the malignant tumor. Also, we have found significant changes in a variety of cancer-associated pathways and NF-κB, a recognized tumor-related pathway. After further analysis of the functions and modules of the genes of interest, we found MYC is involved in the regulation of three dysfunctional modules, and SP1, MYCN, and JUND are involved in the regulation of two dysfunctional modules. After further analysis of the regulated TFs involved in 2 or 3 dysfunctional modules, we found that MYCN is a member of the MYC family. It is well known that myc, also called c-myc, is a recognized oncogene which is crucial to metastasis of various cancers [18]. In the study of prostate cancer, it was found that Myc can inhibit Akt through Phlpp2 and promote the metastasis of prostate cancer [19]. Activation of PI3K and BRD4 significantly inhibits Myc and cancer cell proliferation and migration [20]. Like these studies, our study indicates that Myc may play a large role in the process of cancer metastasis. We analyzed the targeted regulatory relationships between ncRNA and dysfunction module genes for co-expression of modular genes, using the pivot software. This was to explore key ncRNAs that regulate melanoma metastasis. The analysis showed a total of 1,272 ncRNAs involved 1,642 ncRNA-module regulatory pairs. Of them, CRNDE is involved in the regulation of six functional modules. FENDRR and miR-149-5p are involved in the regulation of five dysfunctional modules. Let-7b-5p and let-7i-5b are involved in the regulation of four dysfunctional modules. Among these identified ncRNAs, CRNDE regulates most dysfunctional modules. Moreover, cancer research has also shown that CRNDE is closely related to the occurrence and metastasis of various cancers. In the study of pancreatic cancer, people revealed that its expression in cancer tissues is significantly higher than that in normal tissues, and CRNDE can promote the growth and metastasis of pancreatic cancer by regulating miR-384 [21]. In colorectal cancer, it has been found that CRNDE regulates miR-181a-5p and Wnt/β-catenin signaling pathways to promote colon cancer cell proliferation and migration [22]. Additionally, we also found that CRNDE can promote Myc expression in breast cancer cells. But knockdown of CRNDE expression by siRNA can significantly inhibit Myc expression. These results suggest that CRNDE and myc may affect the migration of melanoma cells by regulating cancer cell migration.

In summary, our work provides new insights into the mechanisms of melanoma metastasis. In particular, the CRNDE and myc identified in this study may be closely related to the metastasis of melanoma. This will not only help us further understand the mechanism of melanoma metastasis, but also provide potential therapeutic targets for its drug development. In summary, TF and ncRNA based on functional block analysis provide an effective method for mechanistic studies and therapeutic target prediction of melanoma and other diseases.

Disclosure of conflict of interest

None.

Address correspondence to: Xiaohua Wang, Nursing of School of Medicine, Hebei University of Engineering, No. 81 Congtai Road, Congtai District, Handan, Hebei Province, China. E-mail: yubingwei74703037@163.com

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