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Original Article

ITGA8 accelerates migration and invasion of myeloma cells in multiple myelomas

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Abstract: Multiple myeloma is cancer of the plasma cells and is the second most common cancer of the blood system, which is characterized by increased calcium levels, renal insufficiency, anemia, bone disease, and susceptibility to infection due to suppression of immunoglobulin production. Early diagnosis of multiple myeloma is difficult as it has no symptoms until it reaches an advanced stage. Therefore, key genes involved in the pathogenesis of multiple myeloma might be significant markers for early diagnosis and treatment of the disease. We analyzed the differentially expressed genes in patients with multiple myeloma using sequencing microarrays from the GEO database. Combined with GO and KEGG analysis, we identified ITGA8 as a key target in the pathogenesis of multiple myeloma, and further verified the differential expression of ITGA8 in myeloma cell lines by rtPCR experiments. Our study contributes to a better understanding of the development of multiple myeloma and advances the application of bioinformatics in clinical diagnosis.

Keywords: ITGA8, migration, invasion, myeloma cells, multiple myelomas

Introduction

Multiple myeloma, a hematologic malignancy derived from differentiated end-stage plasma cells, accounts for approximately 10% of patients with hematologic malignancies in the United States, second only to non-Hodgkin's lymphoma [1]. It is typically characterized by infiltration with malignant plasma cells in the patient's bone marrow as well as the presence of a monoclonal protein in blood or urine that is produced by abnormal plasma cells [2]. The typical clinical manifestation of multiple myeloma is end stage organ damage caused by cancer cells as well as monoclonal proteins and cytokines secreted by tumor cells, and patients may present with renal insufficiency, anemia, and pathological fractures [3].

In the last decade, the pathogenesis and individualized treatment of multiple myeloma have been greatly improved. New therapeutic approaches have been developed with good efficacy, such as protease inhibitors and immunomodulatory drugs, which, together with autologous hematopoietic stem cell transplantation, have greatly reduced patients' pain and improved their quality of life [4].

However, accurate diagnosis and treatment were often made after patients showed signs of end-stage organ damage, when disease progression had already caused irreversible damage [5]. In addition, due to the high heterogeneity of multiple myeloma, individual differences among patients, adverse reactions and different sensitivities of diagnostic criteria [6], it is of great significance to investigate the molecular mechanisms and pathways related to multiple myeloma and to seek biomarkers for early diagnosis and more effective target therapy of multiple myeloma.

Microarray analysis is gaining importance in the field of medical oncology, which can detect thousands of genetic alterations simultaneously, greatly enhancing the efficiency of scientific research [7]. Combined with other bioinformatics technologies and medical knowledge, microarrays are now an indispensable tool in medical research, with unique advantages in cancer taxonomy, molecular diagnosis and prognosis prediction, and with great potential in clinical applications.

In this study, we used gene expression microarrays from patients with multiple myeloma and healthy controls to systematically compare differentially expressed genes (DEGs), analyze the relevant biological functions and signaling pathways involved in DEGs, and make inferences about the causative genes and related pathways.

Materials and methods

Microarray data

The Gene Expression Omnibus (GEO, http://www.ncbi. nlm.nih.gov/geo/) is a public repository of genomic data that provides publicly available gene chip and sequencing data [8]. Query DataSets for GSE113736 uploaded by Fernando et al. based on the GPL17629 platform (Affymetrix Human Exon 1.0 ST Array) contain results of RNA expression from four untreated patients with multiple myeloma and four healthy controls [9].

Identification of DEGs

GEO2R is an online interactive tool for analyzing GEO data and can be used to compare differentially expressed genes between two groups or among more groups. We used the GEO2R website to obtain differentially expressed genes in bone marrow-derived mesenchymal stem cells from patients with multiple myeloma and healthy controls. The Benjamini and Hochberg false discovery rate method was used by default to correct possible false positives of adjusted *P*-value (adj *P*-value). Inclusion criteria for DEG were adj *P*-value < 0.05 and logFC < -1 (down-regulated gene) or > 1 (up-regulated gene expression). Based on this criterion, a total of 14 DEGs were found, including 2 up-regulated genes and 12 down-regulated genes.

Gene ontology and KEGG pathway analysis

With the development of bioinformatics, there are various software and platforms available to help medical researchers analyze the functions and pathways of the genes of interest. GO (gene ontology) is an online site that provides enrichment results for three aspects of target genes: cellular components, molecular function, and biological pathways [10]. Kyoto Encyclopedia of Genes and Genomes (KEGG) can show the network of interactions and reactions between molecules by mapping pathways [11]. We entered all DEGs into the DAVID online site for GO and KEGG analysis (https://david.ncifcrf.gov/). $P < 0.05$ indicated significantly difference.

PPI network

PPI information was obtained from the Search Tool for the Retrieval of Interacting Genes (STRING, http://www.stringdb.org/) database, and we screened for experimentally validated genes with a score of 0.4 or higher (out of 1) to construct interaction networks.

Cell line, and quantitative real-time PCR

The P3X63Ag8.653 cell line (mouse myeloma cells) was purchased from Procell (Wuhan, China) and cultured with 10% FBS and 1% P/S RPMI-1640 medium (purchased from Procell, Wuhan, China), the OP9 cell line (mouse bone marrow stromal cells) was purchased from Procell and cultured in MEMα medium containing 20% FBS and 1% P/S (Procell). The cell culture environment was set as 95% air + 5% CO_2 at 37°C. Total RNA was analyzed using TRIzol reagent (purchased from Thermo Fisher Scientific, Waltham, MA, USA). Reverse transcription of mRNA was performed using the RevertAid RT Reverse Transcription Kit (Thermo Fisher Scientific, Waltham, MA, USA). Quantitative real-time PCR was performed on the basis of the instructions of the Hieff® qPCR SYBR Green Master Mix (No Rox) kits (Shanghai, China). β-actin is the internal reference. Each sample was repeated three times. The specific primers were synthesized by Tsing Ke (Beijing Qing Ke Xin Ye Biotechnology Co., Ltd, Wuhan, China), and the primer sequences were: ITGA8 forward primer: ACAGCAACTTCGAGCGTGTA; reverse primer: TTCTTTCTCTTGAGGAACGTGT; β-actin, forward primer: 5'-TGGCA-

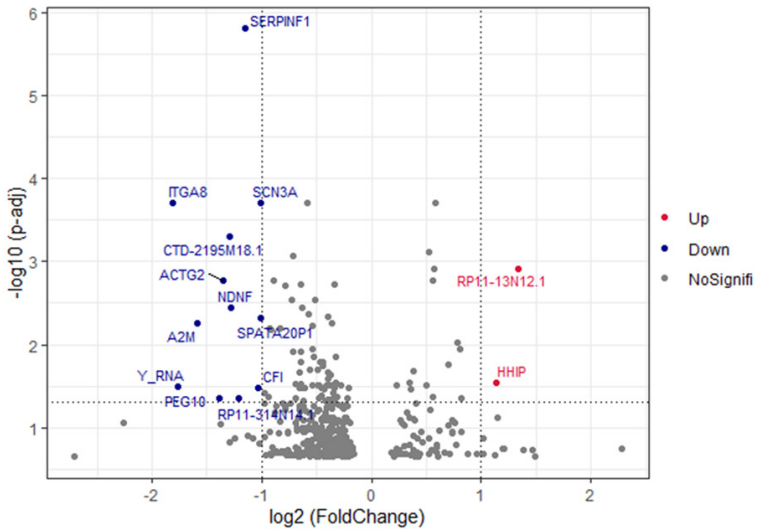

Figure 1. Volcano plot of total 14 DEGs from GSE113736. The red dots stand for 2 up-regulated DEGs, while the blue dots represent 12 down-regulated DEGs. The grey dots denote the no-differentially expressed genes.

CCCAGCACAATGAA-3', reverse primer: 5'-CTAAGTCATAGTCCGCCTAGAAG CA-3'.

Statistical analysis

All data are expressed as mean ± SD, and all data analysis was performed using SPSS 19.0 and GraphPad Prism 8.0 software. $P < 0.05$ was considered to be statistically significant.

Results

Identification of DEGs

The liquid marrow samples were collected from four patients with multiple myeloma and four healthy controls were included in micro-assays. A total of 14 DEGs, including 12 down-regulated and 2 up-regulated expression genes, were identified by GEO2R online analysis. The DEG screening results are shown in the volcano plot (**Figure 1**). DEG results are shown in **Table 1**. The 12 down-regulated expression genes are ITGA8, Y_RNA, A2M, PEG10, ACTG2, CTD-2195M18.1, NDNF, RP11-314N14.1, SERPINF1, CFI, SPATA20P1, SCN3A, and the two down-regulated expression genes are HHIP, RP11-13N12.1. Among them, CTD-2195M18.1, RP11-314N14.1, RP11-13N12.1 are long non-coding RNAs.

Go function and KEGG pathway enrichment analysis

To investigate the biological functions and related signaling pathways of differentially expressed genes, we used the DAVID database to analyze all DEGs and derive GO function and KEGG pathways. We selected GO and KEGG results ranked first in GeneRatio for analysis. Specifically, according to biological processes (BP) (**Table 2**), DEG is mainly concentrated in extracellular matrix organization, extracellular structure organization, renal system development, urogenital system development, muscle organ development, reproductive structure development, reproductive system development, regulation of peptide secretion, muscle system process, and regulation of protein secretion. From cell component (CC) analysis (**Table 3**), DEG is mainly concentrated in collagen-containing extracellular matrix, cell-substrate junction, focal adhesion, endosome membrane, lysosomal membrane, lytic vacuole membrane, vacuum membrane, secretory granule lumen, cytoplasmic vesicle lumen, and the vesicle lumen. From molecular function (MF) analysis (**Table 4**), DEG mainly is concentrated in actin binding, endopeptidase activity, ion channel activity, channel activity, passive transmembrane transporter activity, cation channel activity, gated channel activity, metal ion transmembrane transporter activity, cell adhesion molecule binding, and phospholipid binding.

PPI network

PPI information among DEGs was obtained from the Search Tool for the Retrieval of Interacting Genes (STRING, http://www.stringdb.org/) database [12]. STRING is a database that provides known and predicted protein-protein interactions. Protein-protein interactions include both direct (physical) and indirect (functional) correlations. From the PPI results (**Figure 2**), we found that ITGA8 is the most central DEG and plays a major role in the PPI network. Therefore, IGTA8 was chosen as the target gene for subsequent analysis.

Validation of ITGA8 in vitro

To reconfirm the conclusions of the bioinformatic analysis, we examined the expression

Table 1. Selected DEGs with the criteria of logFC < -1 or logFC > 1 and adj. *P*-value < 0.05

ENSEMBL	adj.*P*.Val	*P*.Value	LogFC	SYMBOL
ENSG00000132386	0.0000	0.0000000	-1.15408152	SERPINF1
ENSG00000153253	0.0002	0.0000000	-1.00915265	SCN3A
ENSG00000077943	0.0002	0.0000000	-1.81122099	ITGA8
ENSG00000250056	0.0005	0.0000001	-1.2917	CTD-2195M18.1
ENSG00000163017	0.0017	0.0000005	-1.35108021	ACTG2
ENSG00000173376	0.0036	0.0000017	-1.2830245	NDNF
ENSG00000231123	0.0048	0.0000026	-1.01229347	SPATA20P1
ENSG00000175899	0.0055	0.0000032	-1.58440266	A2M
ENSG00000201282	0.0325	0.0000515	-1.76791083	Y_RNA
ENSG00000205403	0.0327	0.0000541	-1.03385521	CFI
ENSG00000250102	0.0438	0.0000882	-1.214285	RP11-314N14.1
ENSG00000242265	0.0438	0.0000929	-1.39315255	PEG10
ENSG00000253496	0.0012	0.0000003	1.33606083	RP11-13N12.1
ENSG00000164161	0.0282	0.0000348	1.13900401	HHIP

levels of ITGA8 mRNA in mouse myeloma cell lines. The results of PCR experiments confirmed the significant reduction of ITGA8 expression in the myeloma cell line compared to controls (**Figure 3**).

Discussion

In this study, bone marrow samples from multiple myeloma patients and healthy controls of Gene Expression Microarray GSE in the GEO database was analyzed, and the differentially expressed genes obtained were screened for further biological function and pathway analysis, and ITGA8 was finally identified as a key gene locus in the pathogenesis of multiple myeloma by establishing the PPI network. In cellular experiments, ITGA8 was significantly under-expressed in mouse myeloma cells, confirming the crucial role of this gene. In recent years, there have been significant advances in the therapeutic research of multiple myeloma; nevertheless, it is still a relapse-prone, incurable disease with unknown pathogenesis [13, 14]. This study provides new insights into key genes and pathways in the pathogenesis of multiple myeloma and through a combination of bioinformatics and cellular experiments.

The integrin family is widely expressed on the cell surface of several cancers, including multiple myeloma [15, 16]. It plays a key role in tumor proliferation, progression, and metastasis by mediating the onset, migration, and invasion of tumor cells [17-19]. VLA-4 and VLA-5 have been reported to promote the development of multiple myeloma by mediating the adhesion and migration of myeloma cells [20]. It has also been demonstrated that integrin-7 enhances the adhesion of myeloma cells to the bone marrow and promotes the production of vascular endothelial growth factor (VEGF), resulting in drug resistance [21]. The integrin α subfamily has also been reported to play an important role in the pathogenesis of colorectal adenocarcinoma and the expression levels are closely related to the onset and prognosis. ITGA family genes are significantly enriched in cell adhesion- and integrin-mediated signaling pathways and are co-expressed with each other. Clinical specimen validation revealed that the expression level of ITGA8 was significantly higher in paracancerous tissues than in cancerous tissues [22]. However, the role of ITGA8 in multiple myeloma has been seldom studied. Some studies found that the expression level of ITGA8 was significantly increased in patients with multiple myeloma who had a shorter progression-free survival compared with those who had a longer progression-free survival [23]. By inducing overexpression of ITGA8, myeloma cells exhibit epithelial mesenchymal transition. Epithelial mesenchymal transformation (EMT) is the process of trans differentiation of epithelial cells to motor mesenchymal cells, a change that is essential in development, wound healing, and stem cell behavior, and that promotes fibrosis and cancer progression during pathology [24]. It has been shown that myeloma cells under hypoxic conditions might invade other areas of the

Table 2. Gene ontology analysis in biological processes of DEGs associated with MM

Description	Gene Ratio	gene ID	Count
extracellular matrix organization	23/305	ITGA8/LOXL3/NDNF/A2M/ITGB8/ITGA2/KAZALD1/DPP4/OLFML2A/VWA1/DDR1/AGT/CRISPLD2/MMP15/HAS3/COL14A1/PDPN/FOXC1/LAMA2/ITGA1/FMOD/ERCC2/SERAC1	23
extracellular structure organization	23/305	ITGA8/LOXL3/NDNF/A2M/ITGB8/ITGA2/KAZALD1/DPP4/OLFML2A/VWA1/DDR1/AGT/CRISPLD2/MMP15/HAS3/COL14A1/PDPN/FOXC1/LAMA2/ITGA1/FMOD/ERCC2/SERAC1	23
renal system development	16/305	SERPINF1/ITGA8/FRAS1/ASS1/EMX2/ACE/KLF15/CTSH/ARID5B/AGT/FAT4/FGFR2/NFIA/FOXC1/SPRY1/SDC1	16
urogenital system development	16/305	SERPINF1/ITGA8/FRAS1/ASS1/EMX2/ACE/KLF15/CTSH/ARID5B/AGT/FAT4/FGFR2/NFIA/FOXC1/SPRY1/SDC1	16
muscle organ development	16/305	JPH2/SHOX2/ASS1/HEY2/SGCE/KCNK2/ARID5B/LARGE1/BCL9L/FGFR2/FZD2/FOXC1/LAMA2/MYOM1/BTG2/POU6F1	16
reproductive structure development	16/305	SERPINF1/ITGB8/HEY2/TLR3/ARID5B/HOXA10/PTN/BOK/VDR/FZD5/FGFR2/FOXC1/SDC1/ASB1/ZFP36L1/ETNK2	16
reproductive system development	16/305	SERPINF1/ITGB8/HEY2/TLR3/ARID5B/HOXA10/PTN/BOK/VDR/FZD5/FGFR2/FOXC1/SDC1/ASB1/ZFP36L1/ETNK2	16
regulation of peptide secretion	16/305	KCNN4/SYT11/DPP4/LRP5/CD200/SIDT2/CACNA1C/CCN4/NR1H3/FZD5/C1QTNF3/F2RL1/CARD16/EFNA5/MYOM1/CD74	16
muscle system process	15/305	ACTG2/ITGA2/PDE5A/HEY2/MYL4/DSG2/KLF15/AGT/KCND3/CACNA1C/LMOD1/CHRNE/SNTB1/ITGA1/MYOM1	15
regulation of protein secretion	15/305	KCNN4/SYT11/DPP4/LRP5/CD200/SIDT2/CACNA1C/CCN4/NR1H3/FZD5/C1QTNF3/F2RL1/CARD16/EFNA5/MYOM1	15

Table 3. Gene ontology analysis in cell component of DEGs associated with MM

Description	Gene Ratio	gene ID	Count
collagen-containing extracellular matrix	17/317	SERPINF1/FRAS1/A2M/KAZALD1/VWA1/SERPING1/CTSH/AGT/PTN/CLEC3B/COL14A1/ANGPTL2/FGFR2/PODN/LAMA2/EFNA5/FMOD	17
cell-substrate junction	17/317	ITGA8/ITGB8/ITGA2/CORO2B/LPXN/CNN2/ENAH/DPP4/SYNPO2/ASAP3/AJUBA/PLAUR/HSPB1/FZD2/SNTB1/ITGA1/CIB2	17
focal adhesion	16/317	ITGA8/ITGB8/ITGA2/CORO2B/LPXN/CNN2/ENAH/DPP4/SYNPO2/ASAP3/AJUBA/PLAUR/HSPB1/FZD2/SNTB1/ITGA1	16
endosome membrane	15/317	RHOD/SORT1/GRB14/TLR3/CLIP3/HLA-DMA/ATP9A/BOK/MARCHF2/HLA-DRB1/MCOLN3/FZD5/RAB11FIP2/NTRK2/HSD17B6	15
lysosomal membrane	13/317	SORT1/DPP4/TLR3/SIDT2/SLC7A14/HLA-DMA/ATP8A1/MARCHF2/HLA-DRB1/MCOLN3/RNF152/CYB561/CD74	13
lytic vacuole membrane	13/317	SORT1/DPP4/TLR3/SIDT2/SLC7A14/HLA-DMA/ATP8A1/MARCHF2/HLA-DRB1/MCOLN3/RNF152/CYB561/CD74	13
vacuolar membrane	13/317	SORT1/DPP4/TLR3/SIDT2/SLC7A14/HLA-DMA/ATP8A1/MARCHF2/HLA-DRB1/MCOLN3/RNF152/CYB561/CD74	13
secretory granule lumen	12/317	A2M/ARSA/CNN2/SERPING1/CTSH/ALDOC/CLEC3B/CRISPLD2/ISLR/SELENOP/ADA2/PLAC8	12
cytoplasmic vesicle lumen	12/317	A2M/ARSA/CNN2/SERPING1/CTSH/ALDOC/CLEC3B/CRISPLD2/ISLR/SELENOP/ADA2/PLAC8	12
vesicle lumen	12/317	A2M/ARSA/CNN2/SERPING1/CTSH/ALDOC/CLEC3B/CRISPLD2/ISLR/SELENOP/ADA2/PLAC8	12

Table 4. Gene ontology analysis in molecular function of DEGs associated with MM

Description	Gene Ratio	gene ID	Count
actin binding	17/301	CORO2B/MYL4/CNN2/ENAH/MLPH/EPB41L1/SYNPO2/AJUBA/HIP1/HCLS1/LMOD1/PDLIM2/DAAM2/MTSS2/ABLIM1/SNTB1/MYOM1	17
endopeptidase activity	13/301	CPS1/CFI/CORIN/C1RL/DPP4/ACE/CTSH/C1R/MMP15/C2/USP9Y/ADAM22/ADAMTS7	13
ion channel activity	13/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/CHRNE/CLCA2/TRPV2/ASIC1/SCN2A/KCNS1	13
channel activity	13/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/CHRNE/CLCA2/TRPV2/ASIC1/SCN2A/KCNS1	13
passive transmembrane transporter activity	13/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/CHRNE/CLCA2/TRPV2/ASIC1/SCN2A/KCNS1	13
cation channel activity	12/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/CHRNE/TRPV2/ASIC1/SCN2A/KCNS1	12
gated channel activity	12/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/CHRNE/CLCA2/ASIC1/SCN2A/KCNS1	12
metal ion transmembrane transporter activity	11/301	SCN3A/JPH2/KCNN4/KCNK2/KCND3/CACNA1C/MCOLN3/TRPV2/ASIC1/SCN2A/KCNS1	11
cell adhesion molecule binding	11/301	ITGB8/ITGA2/CNN2/DSG2/CDH18/PTN/CCN4/PTPRD/STK38/ADAM22/CIB2	11
phospholipid binding	10/301	JPH2/CPS1/SYT11/JCHAIN/ANXA10/AMPH/SYTL2/HIP1/MTSS2/OSBPL1A	10

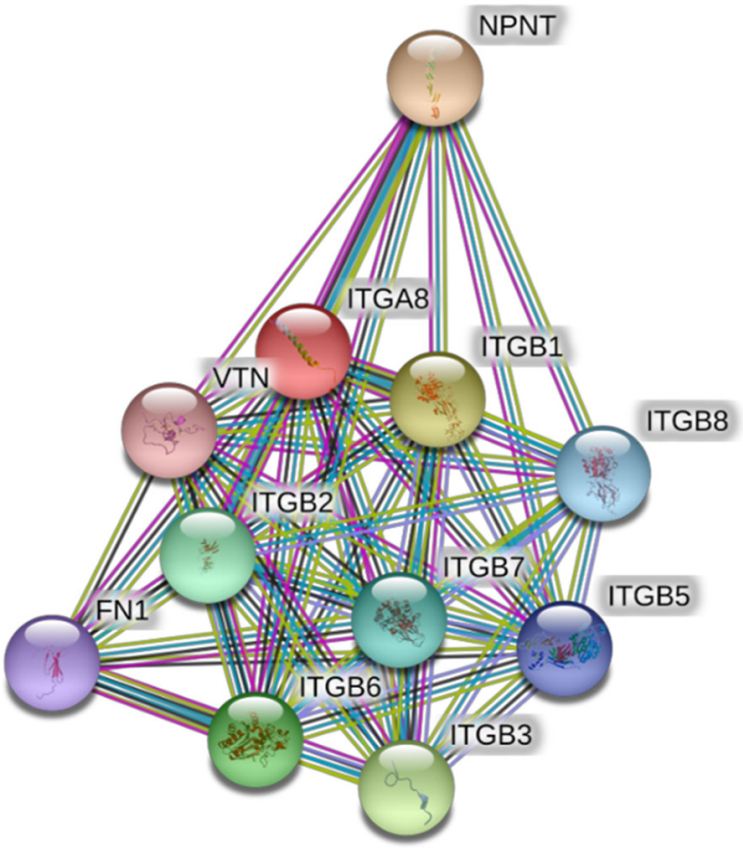

Figure 2. PPI network of all DEGs based on STRING database. The analysis shows that ITGA8 is the core gene in the interaction.

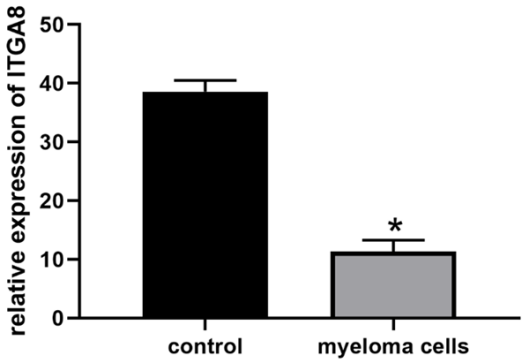

Figure 3. The relative mRNA expression is significant lower in the myeloma cell line, compared to normal cell line. *$P < 0.05$ is regarded statistically different.

bone marrow through EMT, and spread into the peripheral circulation [25]. This transformation under experimental conditions is consistent with the relapse-prone characteristics of multiple myeloma. Therefore, we believe that dysregulated expression of ITGA8 enhances the migration and invasion of myeloma cells, thereby promoting the onset, progression and relapse of multiple myeloma. Through bioinformatics analysis, we obtained results consistent with the clinical features. ITGA8 expression levels can be used as an indicator and therapeutic target for the clinical testing of multiple myeloma.

This research provides new insights for the pathogenesis and therapeutic targets of multiple myeloma. However, there are some limitations: (1) Microarray data are scarce, and the differences between individual patients are not specifically analyzed. (2) Lack of relevant clinical specimens and validation. At present, the team has collected the specimens and the relevant experiments are underway. (3) Since the microarray information of multiple myeloma is not included in the TCGA database, only GEO database was analyzed in the study.

Disclosure of conflict of interest

None.

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