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# The Expression of Actin-Related Protein 2/3 Complex Subunit 5 (ARPC5) Expression in Multiple Myeloma and its Prognostic Significance

Authors' Contribution:  
Study Design A  
Data Collection B  
Statistical Analysis C  
Data Interpretation D  
Manuscript Preparation E  
Literature Search F  
Funds Collection G

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**Background:** The aim of this study was to analyze the prognostic value of ARPC5 in patients with multiple myeloma (MM).





**Material/Methods:** MM gene expression studies GSE6477, GSE31162, GSE24080, and GSE19784 were obtained and analyzed. The expression of ARPC5 was assessed in normal plasma cells, baseline MM cells, and relapsed MM cells. Univariate and multivariable analyses were used to determine the relationship between ARPC5 expression and clinical characteristics and survivals of MM patients. Quantitative PCR was used to detect the expression ARPC5 in bone marrow mononuclear cells of MM patients and normal controls. GSEA was conducted to identify associated mechanisms.

**Results:** ARPC5 expression was significantly increased in baseline MM cells compared to normal plasma cells ( $P=0.0414$ ). Meanwhile, ARPC5 was significantly increased in relapsed MM cells compared to baseline MM cells ( $P<0.0001$ ). ARPC5 expression was significantly associated with  $\beta 2$ -microglobulin ( $P=0.047$ ), serum lactate dehydrogenase ( $P=0.007$ ), and rates of aspirate plasma cells ( $P=0.007$ ). Meanwhile, patients in the ARPC5 high expression group were associated with poor overall survival ( $P=0.0027$ ) and event-free survival ( $P=0.0102$ ) compared to those in the ARPC5 low expression group. Multivariable analysis indicated that ARPC5 was an independent prognostic factor for MM patients. Quantitative PCR demonstrated that ARPC5 was significantly increased in MM patients. GSEA results indicated that ARPC5 might affect cellular growth of myeloma cells through mammalian target of rapamycin (mTOR)C1 signaling pathway.

**Conclusions:** ARPC5 could be treated as an independent biomarker for patients with MM.

**MeSH Keywords:** **Actin-Related Protein 2-3 Complex • Multiple Myeloma • Prognosis**

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## Background

Multiple myeloma (MM), the second most frequent hematologic malignancy after non-Hodgkin lymphoma, is characterized by the clonal expansion of malignant plasma cells in the bone marrow [1,2]. Nearly 1–5 cases in 1000 persons are diagnosed with MM annually. MM represents about 20% of mortalities of all blood cancers [3]. The availability novel agents including bortezomib, carfilzomib, thalidomide, lenalidomide, and pomalidomide has significantly improved the response rates and survival rates of patients with MM [4–6]. Although MM patients initially respond to treatment, they inevitably relapse due to acquired drug resistance [7]. Although the 5-year survival rate for patients with MM is about 49%, the survival rate of patient with high-risk features is dismal [8]. Therefore, accurate identification of this subset of patients is crucial to the diagnosis, treatment, and prognosis of patients with MM.

ARPC5, also known as actin related protein 2/3 complex subunit 5, encodes 1 of 7 subunits of the human Arp2/3 protein complex [9,10]. Several studies demonstrated that ARPC5 was involved in tumor growth or metastasis of head and neck squamous cell carcinoma and lung squamous cell carcinoma, and cell differentiation [11-12]. Herein, we analyzed the relationship between ARPC5 expression and demographic and tumor characteristics of patients with MM.

## Material and Methods

### Identification of MM microarray studies

MM microarray GSE24080 [13,14] was contributed by the Myeloma Institute for Research and Therapy at the University of Arkansas for Medical Sciences. Pretreatment bone marrow plasma cells of 559 newly diagnosed MM patients in trial TT2 [15,16] and TT3 [17] were collected and gene expression profiling was conducted for these cases with Affymetrix Human Genome U133 Plus 2.0 gene chip. Demographic and tumor characteristics including age, gender, race, isotype, serum  $\beta$ -2 microglobulin, CRP, creatinine, lactate dehydrogenase, albumin, hemoglobin, rates of aspirate plasma cells, rates of bone marrow biopsy plasma cells, number of magnetic resonance imaging (MRI)-defined focal lesions, cytogenetic abnormalities, event-free survival and overall survival were well documented. GSE6477 [18b19] was contributed by Fonseca et al. A total number of 73 cases of newly diagnosed MM and 15 cases of normal donor were included. Gene expression profiling was conducted for these cases with Affymetrix Human Genome U133A gene chip. GSE31162 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE31162>) included gene expression data of 780 newly diagnosed MM and 258 relapsed MM. GSE19784 [20], contributed by Broyl et al., was comprised of 328 previously

untreated MM samples and annotated with Affymetrix Human Genome U133 Plus 2.0 Array. We used GSE14784 to perform gene set enrichment analysis (GSEA) [21,22].

### Data analysis

To evaluate the expression of ARPC5 in baseline MM, normal plasma, and relapsed MM, 2-sample *t*-test was conducted and relative expression of ARPC5 was presented as mean  $\pm$  standard deviation. To determine the correlation between ARPC5 expression and demographic and tumor characteristics of patients with MM, patients in GSE24080 were divided into ARPC5 low expression group and ARPC5 high expression group based on the median of ARPC5 (the corresponding probe ID is 1555797\_a\_at) expression in GSE24080, and then chi-square test and logistic regression analysis were performed. To investigate the prognostic value of ARPC5 in MM patients, Kaplan-Meier survival analysis and multivariable Cox proportional hazards analysis were conducted. If *P* values were less than 0.05, the differences were considered statistically significant. Finally, to characterize potentially relevant mechanisms for ARPC5 affected MM cells, GSEA was conducted.

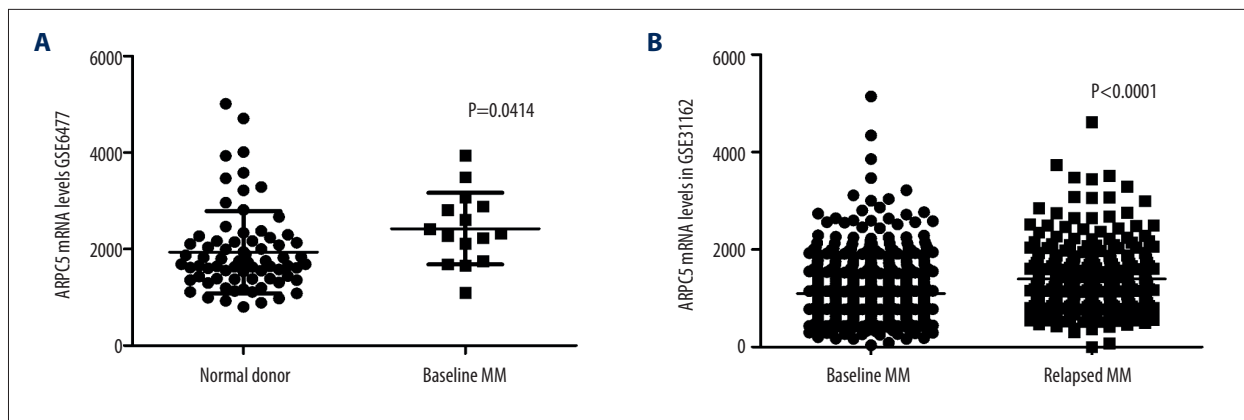
### MM sample collection, mononuclear separation, and quantitative PCR

Pretreatment bone marrow aspirates were obtained from 10 newly diagnosed MM patients and 10 patients who were finally excluded based on the diagnosis of hematological malignancies at Jingzhou Central Hospital. The collection of bone marrows was approved by the Ethics Committee of Jingzhou Central Hospital and the informed consents of the included participants were obtained. Bone marrow mononuclear cells were isolated by using the Ficoll-Hypaque density gradient protocol according to the manufacturer's protocols. Total RNAs were isolated with TRIzol reagent (Invitrogen) according to manufacturer's instructions. After the synthesis of cDNA, quantitative PCR was performed using SYBR Premix ExTaq (TaKaRa, Japan) on an ABI7500 real-time PCR instrument (ABI Company, Oyster Bay, NY, USA) according to the manufacturer's instructions. Homo  $\beta$ -actin was treated as an internal control. The PCR detection was performed 3 times. Primers used in this study were as follows: ARPC5 forward: 5'-AAGTTCGTG GACGAGGAGG-3', ARPC5 reverse 5'-GTAGGGCAGCGGTCATGTTTC-3';  $\beta$ -actin forward: 5'-AGCGAGCATCCCCAAAGTT-3', reverse 5'-GGGCACGAAGGCTCATCATT-3'.

## Results

### ARPC5 was significantly upregulated in baseline MM and relapsed MM

To explore whether ARPC5 was associated with carcinogenesis of MM, we analyzed the expression of ARPC5 in normal plasma



**Figure 1.** Relative expression of ARPC5 in normal plasma cells, baseline myeloma cells, and relapsed myeloma cells.

cells, baseline MM cells, and relapsed MM cells using GSE6477 and GSE31162. As shown in Figure 1, the expression of ARPC5 was significantly increased in baseline MM cells ( $n=73$ ) as compared to that in normal plasma cells ( $n=15$ ) ( $2425 \pm 744.58$  vs.  $1935 \pm 850.61$ ,  $P=0.0414$ , Figure 1A). Meanwhile, the expression of ARPC5 was significantly increased in relapsed MM cells ( $n=258$ ) as compared to that in baseline MM cells ( $n=780$ ) ( $1397 \pm 703.46$  vs.  $1096 \pm 552.62$ ,  $P<0.0001$ , Figure 1B).

#### Correlations between ARPC5 expression and demographic and tumor characteristics of patients with MM

Then, we analyzed the relationship between ARPC5 expression and clinical characteristics of MM patients. As shown in Table 1, univariate analysis (chi-square test) suggested that pretreatment ARPC5 was associated with gender ( $P=0.014$ ), serum  $\beta 2$ -microglobulin ( $P<0.0001$ ), serum creatinine ( $P=0.019$ ), serum lactate dehydrogenase ( $P=0.019$ ), hemoglobin ( $P=0.001$ ), rates of aspirate plasma cells ( $P=0.022$ ), and number of magnetic resonance imaging (MRI)-defined focal lesions ( $P=0.049$ ). Multivariable analysis (logistic regression analysis) demonstrated that ARPC5 expression was significantly associated with  $\beta 2$ -microglobulin ( $P=0.047$ ), serum lactate dehydrogenase ( $P=0.007$ ), and rates of aspirate plasma cells ( $P=0.007$ ). These results indicated that higher expression of ARPC5 expression was associated with poor tumor characteristics of patients with MM.

#### Higher expression of ARPC5 was associated with poor survivals of patients with MM

We analyzed the prognostic significance of ARPC5 for MM patients in GSE24080. Patients in GSE24080 were divided into ARPC5 low expression group and ARPC5 high expression group based on the median of ARPC5 expression in GSE24080. Results of Kaplan-Meier survival analyses indicated that patients in the ARPC5 low expression group ( $n=280$ ) were associated with more superior event-free survival (HR=0.718, 95% CI: 0.5577–0.9245,  $P=0.0102$ , Figure 2A) and overall survival

(HR=0.6279, 95% CI: 0.4634–0.8508,  $P=0.0027$ , Figure 2B) compared with patients in the ARPC5 high expression group ( $n=279$ ). Multivariable Cox proportional hazard analysis demonstrated that ARPC5 expression was an independent prognosis factor for event-free survival ( $P=0.006$ , HR=1.351, 95% CI: 1.092–1.672) and overall survival ( $P=0.020$ , HR=1.356, 95% CI: 1.05–1.75) of patients with MM (Table 2).

#### ARPC5 was significantly increased in MM patients

As stated earlier, we detected the expression of ARPC5 in bone marrow mononuclear cells of MM patients and normal donors who were excluded based on hematological malignance. These 10 MM patients included 6 males and 4 females, the median age was 63.5 years; 5 cases were IgG MM, 3 cases were IgA MM, 1 case was light chain MM, and 1 case was IgD MM (Supplementary Table 1). As shown in Figure 3, mRNA levels of ARPC5 were significantly increased in the bone marrow mononuclear cells of these 10 MM patients compared with that in patients with non-malignant bone marrow mononuclear cells ( $0.8160 \pm 0.136$  vs.  $0.4167 \pm 0.074$ ,  $P<0.0001$ ).

#### Results of gene set enrichment analysis

In order to identify related molecular mechanisms involved in the function of ARPC5 in MM cells, GSEA analysis was conducted using another independent MM microarray study GSE19784 (MM samples in GSE19784 were divided into ARPC5 low expression group and ARPC5 high expression group according to the median of ARPC5 expression), as shown in Figure 4, the MM samples in ARPC5 mammalian target of rapamycin (mTOR)C1 signaling were: nominal  $P<0.0001$ , FDR=1.47%, enrichment score=0.57, normalized enrichment score=1.75. This result indicated that ARPC5 might promote the growth of MM cells through mTORC1 signaling.

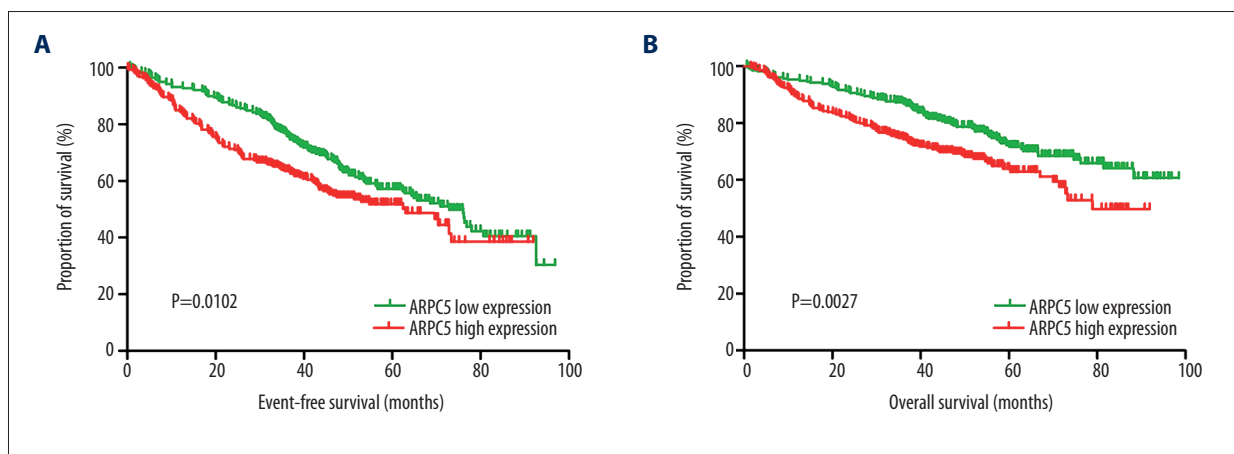
**Table 1.** Correlations between ARPC5 expression and tumor characteristics of multiple myeloma patients.

Characteristics	ARPC5 expression		Univariate analysis		Multivariable analysis		
	High (n=279)	Low (n=280)	Chi-square	P value	OR(95% CI)	P value	
Age (years)							
≤60	166	157	0.214	0.644	0.986	(0.966–1.007)	0.192
>60	113	123					
Gender							
Male	154	183	6.025	0.014	0.779	(0.511–1.188)	0.246
Female	125	97					
Race							
White	246	251	0.307	0.58	0.901	(0.471–1.723)	0.752
Other	33	29					
M protein*							
IgG	141	172	8.408	0.078	0.389	(0.34–4.631)	0.462
IgA	77	56					
FLC	47	37					
IgD	2	1					
NS	3	5					
β2-microglobulin (mg/mL)*							
<3.5	138	181	15.42	P<0.0001	1.091	(1.001–1.188)	0.047
3.5–5.5	67	58					
≥5.5	73	41					
CRP (mg/L)*							
<5.8	151	173	3.782	0.052	0.998	(0.987–1.009)	0.704
≥5.8	127	104					
Creatinine (mg/dL)*							
<1.2	174	200	5.522	0.019	0.93	(0.707–1.225)	0.608
≥1.2	104	78					
LDH (U/L)							
<170	150	178	5.544	0.019	1.005	(1.001–1.009)	0.007
≥170	129	102					
ALB (g/dL)							
<3.5	46	31	3.451	0.063	0.759	(0.508–1.136)	0.18
≥3.5	233	249					
HGB (g/dL)							
<11	142	105	10.169	0.001	0.916	(0.798–1.050)	0.207
≥11	137	175					

**Table 1 continued.** Correlations between ARPC5 expression and tumor characteristics of multiple myeloma patients.

Characteristics	ARPC5 expression		Univariate analysis		Multivariable analysis	
	High (n=279)	Low (n=280)	Chi-square	P value	OR(95% CI)	P value
ASPC* (%)						
<40	139	116	5.244	0.022	0.983 (0.972–0.996)	0.007
≥40	123	153				
BMPC (%)*						
<50	143	131	1.554	0.213	0.999 (0.988–1.01)	0.864
≥50	126	143				
MRI (Magnetic resonance imaging (MRI)-defined focal lesions (skull, spine, pelvis)*						
Yes	200	180	3.87	0.049	1.01 (0.999–1.028)	0.078
No	61	81				
Cytogenetic abnormalities						
Yes	104	103	0.014	0.904	0.98 (0.64–1.502)	0.927
No	175	177				

CRP – C-reactive protein; LDH – lactate dehydrogenase; ALB – albumin; HGB – hemoglobin; ASPC – aspirate plasma cells; BMPC – bone marrow biopsy plasma cells; \* indicates that the corresponding data for that clinical phenotype has some missing values.



**Figure 2.** Event-free survival (A) and overall survival (B) of patients in the ARPC5 low expression group and the ARPC5 high expression group.

### Discussion

Although significant improvements have been made regarding the diagnosis and treatment of patients with MM, the disease remains incurable due to acquired drug resistance [23]. In the present study, we demonstrated that ARPC5 might be an independent risk factor of patients with MM.

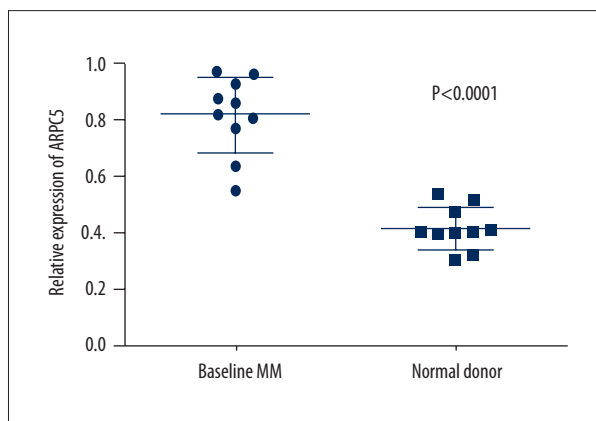
The inclusion criteria for MM microarray studies resulted in a total number of 4 MM gene expression microarray studies that included more than 2055 participants who were selected

for our analysis. GSE6477 included 73 samples of newly diagnosed MM and 15 samples of normal donor, thus, it was used to evaluate the expression of ARPC5 normal plasma cells and myeloma cells. GSE31162 included a great number of relapsed and newly diagnosed MM samples (780 relapsed MM and 258 newly diagnosed MM), thus, it was used to evaluate the expression ARPC5 in relapsed MM cells and newly diagnosed MM cells. Thanks to the large quantity of pretreatment MM samples and detailed clinical information of MM patients, GSE24080 was selected to analyze the relationship between ARPC5 expression and clinical features of patients with MM.

**Table 2.** Multivariable Cox proportional hazard analysis on Overall survival and event free survival of patients with multiple myeloma.

Characteristics	Overall survival			Event free survival		
	P value	HR (95% CI)		P value	HR (95% CI)	
ARPC5	0.02	1.356	(1.05–1.75)	0.006	1.351	(1.092–1.672)
Age	0.271	1.01	(0.992–1.028)	0.633	0.996	(0.982–1.011)
Sex	0.515	1.125	(0.79–1.602)	0.274	1.176	(0.879–1.572)
Type	0.884			0.023		
Type (1)	0.889	1.153	(0.157–8.481)	0.143	0.415	(0.128–1.348)
Type (2)	0.995	1.006	(0.136–7.45)	0.168	0.435	(0.133–1.42)
Type (3)	0.887	0.863	(0.113–6.582)	0.019	0.231	(0.068–0.789)
Type (4)	0.955	<0.0001	(<0.0001–<0.00001)	0.034	0.085	(0.009–0.835)
B2M	<0.0001	1.098	(1.056–1.142)	<0.0001	1.088	(1.05–1.127)
CRP	0.489	0.997	(0.988–1.006)	0.489	0.997	(0.99–1.005)
Creatinine	0.262	0.917	(0.788–1.067)	0.604	0.965	(0.845–1.103)
LHD	<0.0001	1.005	(1.003–1.007)	0	1.004	(1.002–1.006)
ALB	0.06	0.747	(0.552–1.012)	0.407	0.900	(0.701–1.155)
HGB	0.892	1.008	(0.904–1.123)	0.38	0.959	(0.873–1.053)
ASPC	0.797	0.999	(0.989–1.009)	0.413	0.997	(0.988–1.005)
BMPS	0.875	1.001	(0.991–1.01)	0.711	1.001	(0.994–1.009)
MRI	0.076	1.010	(0.999–1.02)	0.279	1.005	(0.996–1.015)
CA	0.001	0.549	(0.388–0.777)	0.003	0.645	(0.483–0.863)
RACE	0.846	0.948	(0.554–1.623)	0.116	1.482	(0.908–2.420)
Treatment	0.32	1.244	(0.809–1.913)	0.004	1.691	(1.178–2.428)

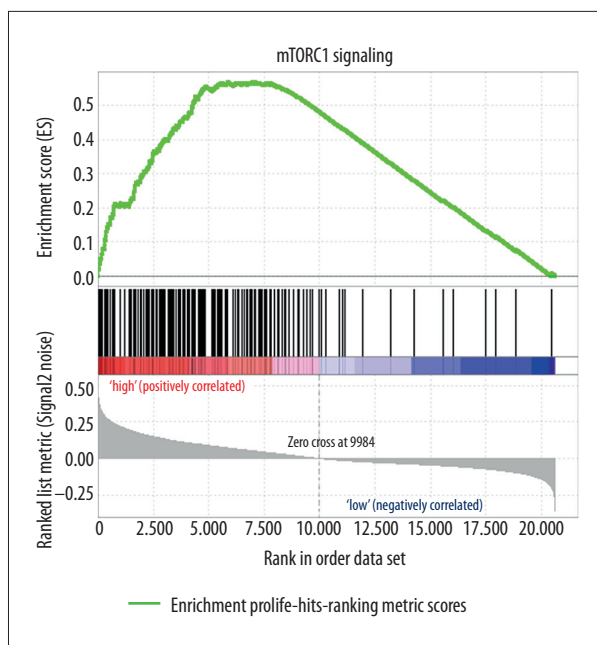
CRP – C-reactive protein; LDH – lactate dehydrogenase; ALB – albumin; HGB – haemoglobin; ASPC – aspirate plasma cells; BMPS – bone marrow biopsy plasma cells; CA – cytogenetic abnormalities.



**Figure 3.** ARPC5 expression in bone marrow mononuclear cells from newly diagnosed myeloma patients and normal donors.

The reason that GSE19784 was selected to perform GSEA analysis was attributed to the relative large number of MM samples in this dataset. In summary, the results of our study were based on the relative large number of participants in corresponding analyses.

Our results showed that ARPC5 was increased in baseline MM cells relative to normal plasma cells, and it was also increased in relapsed MM cells when compared with that in baseline MM cells, indicating that ARPC5 was associated with the carcinogenesis and progression of MM. The results of our correlation analysis, survival analysis, and clinical validation were in accordance with this conclusion. Results of GSEA indicated that ARPC5 might affect the proliferation of MM cells through mTORC1 signaling.



**Figure 4.** Samples in ARPC5 high expression group were significantly enrichment in mTORC1 signaling pathway.

Moriya et al. suggested that the knockdown of microRNA-133a was associated with downregulation of ARPC5, knockdown of ARPC5 inhibited the proliferation of lung squamous cell carcinoma and they concluded that ARPC5 might function as oncogenes in the development of lung squamous cell carcinoma [24]. Liu et al. demonstrated that microRNA-141 inhibited the proliferation of prostate cancer stem cells by regulating ARPC5 as well as other Rho GTPase family members including (CDC42, CDC42EP3, RAC1) [11]. Kinoshita et al. suggested that ARPC5 was a candidate target of miR-133a, and ARPC5 was significantly increased in head and neck squamous cell carcinoma compared with that in non-cancer tissues, and ARPC5 was also significantly increased in invasive cancer cells. Thus, they concluded that ARPC5 contributed to cancer cell migration and invasion in head and neck squamous cell carcinoma and this gene was directly regulated by miR-133a [12]. In human osteosarcoma, Bernardini et al. demonstrated that the SI-83 induced dephosphorylation of ARPC5L, a subunit of the actin related Arp2/3 complex, and the decrease of other cytoskeleton proteins [25]. These studies indicated that ARPC5 might play a role as oncogene in prostate cancer and head and neck squamous cell carcinoma.

Mammalian target of rapamycin (mTOR) represents a downstream serine/threonine kinase of the PI3K/Akt pathway that integrates signals from the tumor microenvironment to regulate multiple cellular processes, and TORC1 was comprised of the mTOR catalytic subunit and 3 associated proteins, raptor, PRAS40, and mLST8/GβL [26]. Maiso et al. demonstrated that downregulation TORC1 was associated with significant suppression of the growth of myeloma cells [26]. Xiang et al. demonstrated that MK2206 combined with bufalin inhibited the proliferation and stimulated apoptosis of myeloma cells through the inhibition of the AKT/mTOR pathway [27]. Yang et al. demonstrated that polydatin inhibited cell proliferation and induced apoptosis and autophagy of myeloma cells through the mTOR/p70s6k signaling pathway [28]. These results indicated that the inhibition of mTOR signaling pathway was associated with cellular growth of MM cells. Our GSEA results indicated that ARPC5 might inhibit the proliferation of MM cells through regulation of mTORC1 signaling pathway. Taking all these results into consideration, it could be speculated that ARPC5 might affect the growth of myeloma cells through regulation of mTOR signaling pathway.

Although several previous studies have evaluated the expression of some molecular using bone marrow mononuclear cells from MM patients and those conclusions have been widely accepted, our study has limitations. We analyzed the expression of ARPC5 in bone marrow mononuclear cells rather than CD138+ MM cells from MM patients; the expression of ARPC5 in bone marrow mononuclear cells might not fully reflect its expression in MM cells. Thus, the conclusions of clinical validation should be interpreted with caution, and we suggest future studies should detect ARPC5 expression in CD138+ MM cells.

## Conclusions

Our results indicated that ARPC5 was increased in myeloma cells, correlated with tumor characteristics of myeloma cells, therefore, ARPC5 could be treated as an independent risk factor of patients with MM.

## Conflicts of interest

None.

## Supplementary Table

**Supplementary Table 1.** The clinical characteristics of ten MM patients.

Patients ID	Gender	Age	M-protein type	ISS stage	Bone marrow biopsy plasma cells (%)	Relative expression of ARPC5
1	Female	68	IgA-Kap	3A	88	0.547445
2	Male	70	IgA-Kap	3A	70	0.63868
3	Male	64	IgA-Lam	2B	73	0.767532
4	Female	59	IgD-Lam	3B	75	0.861735
5	Male	51	IgG-Kap	3B	59	0.923884
6	Female	60	IgG-Kap	3A	60	0.805834
7	Female	63	IgG-Kap	3A	65	0.870867
8	Male	64	IgG-Kap	3A	90	0.816188
9	Male	48	IgG-Lam	3A	85	0.95939
10	Male	66	Light Chain-Lam	3A	68	0.96821

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