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Prognostic Value of Dynactin mRNA Expression in Cutaneous Melanoma

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Background: Dynactin (DCTN) is a multi-subunit protein encoded by *DCTN* genes for 6 subunits. In different diseases the *DCTN* genes may have different roles; therefore, we investigated the prognostic potential of *DCTN* mRNA expression in cutaneous melanoma (CM).

Material/Methods: Data for *DCTN* mRNA expression in CM patients were obtained from the OncoLnc database, which contains updated gene expression data for 459 CM patients based on the Cancer Genome Atlas. Kaplan-Meier analysis and a Cox regression model were used to determine overall survival (OS) with calculation of hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: The multivariate survival analysis showed that individually low expression of *DCTN1*, *DCTN2*, and *DCTN5* and high expression of DCTN6 were associated with favorable OS (adjusted *P*=0.008, HR=0.676, 95% CI=0.506–0.903; adjusted *P*=0.004, HR=0.648, 95% CI=0.485–0.867; adjusted *P*=0.011, HR=0.686, 95% CI=0.514–0.916; and adjusted *P*=0.018, HR=0.706, 95% CI=0.530–0.942, respectively). In a joint-effects analysis, combinations of low expression of *DCTN1, DCTN2*, and *DCTN5* and high expression of *DCTN6* were found to be more highly correlated with favorable OS (all *P*<0.05).

Conclusions: Our findings suggest that downregulated *DCTN1*, *DCTN2*, and *DCTN5* and upregulated *DCTN6* mRNA expression in CM are associated with favorable prognosis and may represent potential prognostic biomarkers. Moreover, use of the 4 genes in combination can improve the sensitivity for predicting OS in CM patients.

MeSH Keywords: Dynactin • Melanoma • Prognosis

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Background

Cutaneous melanoma (CM) is one of the most aggressive tumors of the skin and mucosa [1], accounting for 6380 out of 9250 skin cancer-related deaths in the United States in 2017 [2]. With improved awareness and treatment options, the 5-year relative survival rate has reached 92% and the 10-year relative survival rate has reached 89% [3]. Still, early detection is important, as the prognosis is much better if the cancer is detected early. The primary treatment for CM is surgery, and adjuvant immunotherapy, immunotherapy, and targeted therapy drugs also are used to treat various stages of melanoma [3].

Dynactin (DCTN) is a multi-subunit protein that drives retrograde transport in cells [4–7]. The 6 subunits of DCTN are referred to as dynactin 1–6 (DCTN1–6). All subunits of DCTN are critical to the structure and function of DCTN [4,8–10]. DCTN1 was shown to act as a fusion partner in some but not all Spitz tumors [11] as well as in non-small cell lung cancer (NSCLC) [12]. DCTN1 and DCTN3 are upregulated in sporadic ALS [13]. DCTN2 is upregulated in the osteosarcoma SJSA-1 cell line, but a link between its altered expression and the prognosis of CM has not been reported [14]. Another study showed that the intronic regions of *DCTN6* pre-mRNA interact with the *SPRIGHTLY* long non-coding (lnc)RNA of melanoma [15]. Based on this evidence for pathogenic roles of mutations in DCTN subunits, we questioned whether mutations in DCTN genes are associated with CM.

According to these previous studies, *DCTN1* and *DCTN2* are expressed in human epidermal melanocytes [16]. However, the relationships between *DCTN* family members and CM patients have not been investigated. Therefore, in the present study, we investigated the prognostic value of the mRNA expression levels of individual DCTN subunits and conducted a joint-effects analysis using data from 459 CM patients available in the OncoLnc database based on the Cancer Genome Atlas.

Material and Methods

Patient and disease characteristics

We used The Metabolic gEne Rapid Visualizer (MERAV: *http://merav.wi.mit.edu/*, accessed by November 5, 2017) to generate boxplots of the expression levels of DCTN subunits in normal tissue and primary CM tissue [17]. The Cancer Genome Atlas (*http://tcga-data.nci.nih.gov/tcga*, accessed by November 7, 2017) and OncoLnc (*http://www.oncolnc.org/*, accessed by November 8, 2017) [18] were searched to obtain the clinical information of 459 CM patients, including sex, age, body mass index (BMI), TNM stage, events, survival time, death status, and mRNA expression levels of *DCTN1*, *DCTN2*, *DCTN3*, *DCTN4*, *DCTN5,* and *DCTN6* according to 50% cutoff values.

Correlation analysis and functional enrichment analysis

Pearson correlation coefficient analysis was used to identify correlations among DCTN family genes. The Database for Annotation, Visualization, and Integrated Discovery (DAVID) v.6.8 (*https://david.ncifcrf.gov/tools.jsp*, accessed November 10, 2017) [19,20] was used for analyses of functional enrichment, including gene ontology (GO) functional analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway

Table 1. Grouping according to 2 selected genes.

Group	Composition	Group	Composition
I	Low *DCTN1* + low *DCTN2*	X	Low *DCTN2* + low *DCTN5*
II	Low *DCTN1* + high *DCTN2*	XI	Low *DCTN2* + high *DCTN5*
	High *DCTN1* + low *DCTN2*		High *DCTN2* + low *DCTN5*
III	High *DCTN1* + high *DCTN2*	XII	High *DCTN2* + high *DCTN5*
IV	Low *DCTN1* + low *DCTN5*	XIII	Low *DCTN2* + high *DCTN6*
V	Low *DCTN1* + high *DCTN5*	XIV	Low *DCTN2* + low *DCTN2*
	High *DCTN1* + low *DCTN5*		High *DCTN2* + high *DCTN6*
VI	High *DCTN1* + high *DCTN5*	XV	High *DCTN2* + low *DCTN6*
VII	Low *DCTN1* + high *DCTN6*	XVI	Low *DCTN5* + high *DCTN6*
VIII	Low *DCTN1* + low *DCTN6*	XVII	Low *DCTN5* + low *DCTN6*
	High *DCTN1* + high *DCTN6*		High *DCTN5* + high *DCTN6*
IX	High *DCTN1* + low *DCTN6*	XVIII	High *DCTN5* + low *DCTN6*

DCTN – dynactin.

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Table 2. Grouping according to 3 selected genes.

Group	Composition	Group	Composition	Group	Composition
i	Low *DCTN1* + low *DCTN2* + low *DCTN5*	iv	Low *DCTN1* + low *DCTN2* + high *DCTN6*	vii	Low *DCTN2* + low *DCTN5* + high *DCTN6*
ii	High *DCTN1* + low *DCTN2* + low *DCTN5*	v	High *DCTN1* + low *DCTN2* + high *DCTN6*	viii	High *DCTN2* + low *DCTN5* + high *DCTN6*
	Low *DCTN1* + high *DCTN2* + low *DCTN5*		Low *DCTN1* + high *DCTN2* + high *DCTN6*		Low *DCTN2* + high *DCTN5* + high *DCTN6*
	Low *DCTN1* + low *DCTN2* + high *DCTN5*		Low *DCTN1* + low *DCTN2* + low *DCTN6*		Low *DCTN2* + low *DCTN5* + low *DCTN6*
	High *DCTN1* + high *DCTN2* + low *DCTN5*		High *DCTN1* + high *DCTN2* + high *DCTN6*		High *DCTN2* + high *DCTN5* + high *DCTN6*
	High *DCTN1* + low *DCTN2* + high *DCTN5*		High *DCTN1* + low *DCTN2* + low *DCTN6*		High *DCTN2* + low *DCTN5* + low *DCTN6*
	Low *DCTN1* + high *DCTN2* + high *DCTN5*		Low *DCTN1* + high *DCTN2* + low *DCTN6*		Low *DCTN2* + high *DCTN5* + low *DCTN6*
iii	High *DCTN1* + high *DCTN2* + high *DCTN5*	vi	High *DCTN1* + high *DCTN2* + low *DCTN6*	ix	High *DCTN2* + high *DCTN5* + low *DCTN6*

DCTN – dynactin.

analysis. GO functional analysis included molecular function (MF), cellular component (CC), and biological process (BP). A gene function prediction website (GeneMANIA: *http://genemania.org/*, accessed November 15, 2017) [21] was used to analyze interactions among *DCTN* family members.

Survival analysis

For each *DCTN* mRNA, patients were divided into high- and low-expression groups according to a 50th percentile cutoff. The prognosis of CM was evaluated based on overall survival (OS). The Kaplan-Meier estimator with a log-rank test was used to identify correlations between the 6 *DCTN* mRNAs and patient survival. Adjustment was made for race, age, sex, and TNM stage in the Cox proportional hazards regression model.

Joint-effects analysis

A joint-effects analysis was performed for the combination of genes identified as significant by the survival analysis. Groups were formulated by summarizing the selected expression of genes associated with better OS in one group, worse OS in another group, and others in the last group, as outlined in Tables 1–3.

Statistical analyses

Kaplan-Meier survival analysis and the log-rank test were used to calculate OS and *P* values for all associations. The Cox proportional hazards regression model was used for uni- and

Table 3. Grouping according to 4 selected genes.

Group	Composition
1	High *DCTN1* + high *DCTN2* + high *DCTN5* + low *DCTN6*
2	High *DCTN1* + high *DCTN2* + high *DCTN5* + high *DCTN6*
	High *DCTN1* + low *DCTN2* + high *DCTN5* + high *DCTN6*
	High *DCTN1* + high *DCTN2* + low *DCTN5* + high *DCTN6*
	Low *DCTN1* + high *DCTN2* + high *DCTN5* + high *DCTN6*
	Low *DCTN1* + low *DCTN2* + high *DCTN5* + high *DCTN6*
	Low *DCTN1* + high *DCTN2* + low *DCTN5* + high *DCTN6*
	Low *DCTN1* + high *DCTN2* + high *DCTN5* + low *DCTN6*
	High *DCTN1* + low *DCTN2* + low *DCTN5* + high *DCTN6*
	High *DCTN1* + low *DCTN2* + high *DCTN5* + low *DCTN6*
	High *DCTN1* + high *DCTN2* + low *DCTN5* + low *DCTN6*
	Low *DCTN1* + low *DCTN2* + high *DCTN5* + low *DCTN6*
	Low *DCTN1* + high *DCTN2* + low *DCTN5* + low *DCTN6*
	High *DCTN1* + low *DCTN2* + low *DCTN5* + low *DCTN6*
	Low *DCTN1* + low *DCTN2* + low *DCTN5* + low *DCTN6*
3	Low *DCTN1* + low *DCTN2* + low *DCTN5* + high *DCTN6*

DCTN – dynactin.

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Table 4. Demographic and clinical data for 459 CM patients.

Variables	Patients (n=459)	No. of events (%)	MST (days)	HR (95% CI)	Log-rank *P*
Race					**0.004**
White	436	208 (47.7%)	2470	Ref.	
Others	13	8 (61.5%)	636	0.347 (0.170–0.707)	
Missing	10				
Sex					0.259
Male	284	146 (51.4%)	2454	Ref.	
Female	175	72 (41.1%)	2030	0849 (0.638–1.128)	
Age (years)					**0.001**
≥60	240	116 (48.3%)	3564	Ref.	
<60	219	102 (46.6%)	1860	1.619 (1.227–2.136)	
TNM stage					**<0.001**
0+I+II+I/II nos	232	108 (46.6%)	3259	Ref.	
III+IV	191	91 (47.6%)	1960	1.673 (1.253–2.235)	
Missing	36				
BMI (kg/m^2)					0.437
>25	80	25 (31.3%)	2101	Ref.	
≤25	160	61 (38.1%)	3136	0.830 (0.519–1.327)	
Missing	219				

MST – median survival time; HR – hazard ratio; CI – confidence interval.

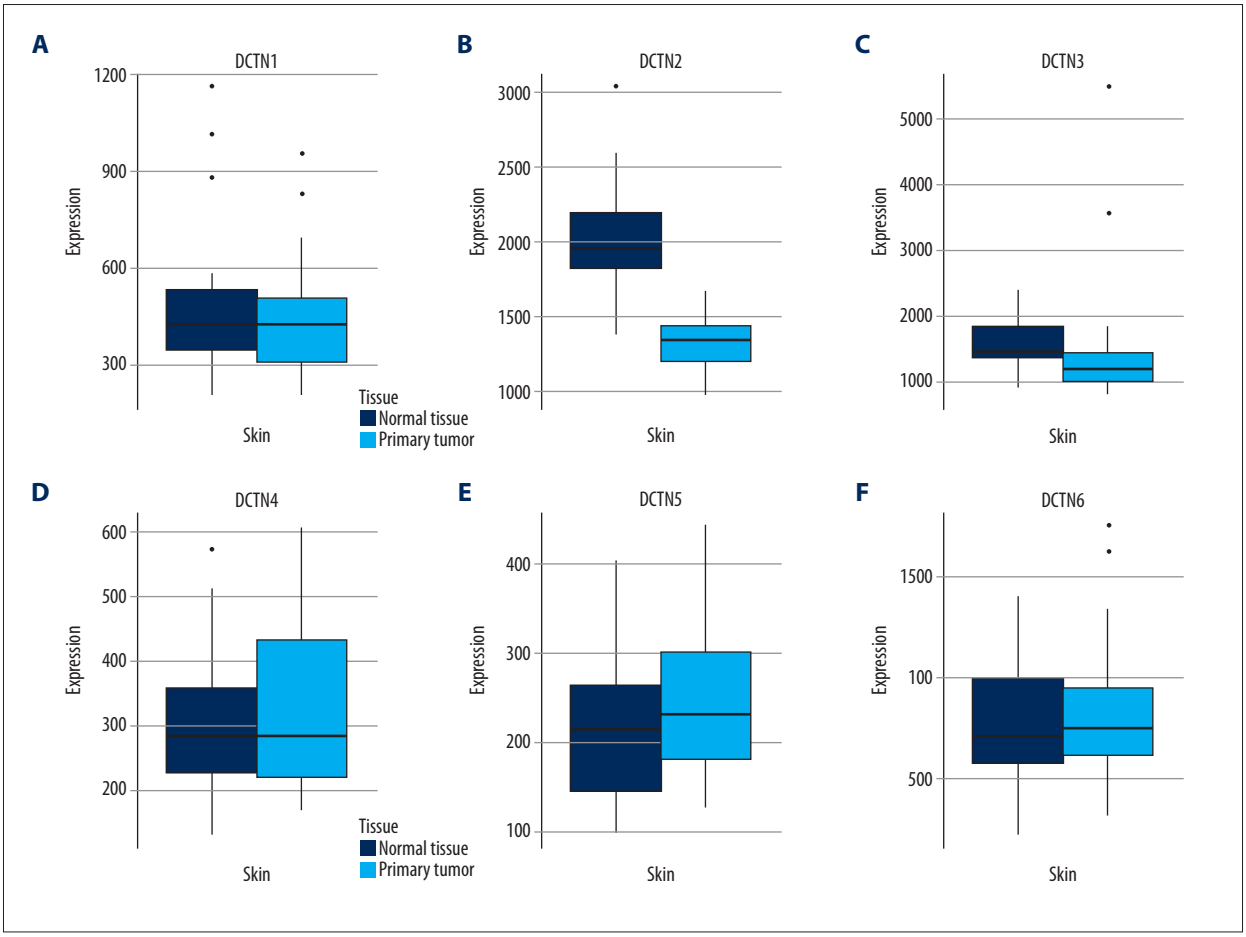

Figure 1. MERAV boxplots for *DCTN* gene expression in normal skin tissue and primary CM tissue: (**A**) *DCTN1* expression; (**B**) *DCTN2* expression; (**C**) *DCTN3* expression; (**D**) *DCTN4* expression; (**E**) *DCTN5* expression; and (**F**) *DCTN6* expression.

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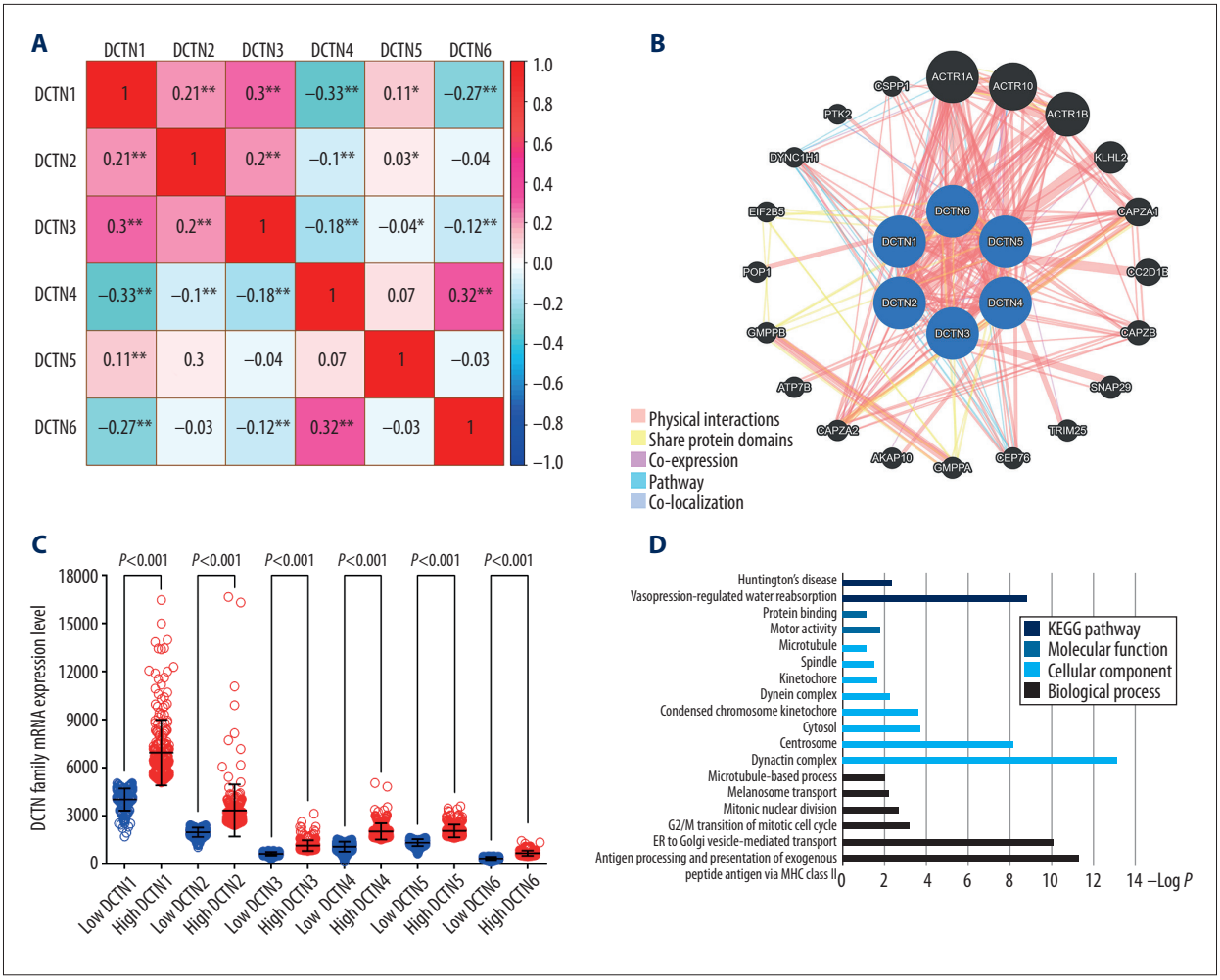

Figure 2. (**A**) Pearson's correlation coefficients for *DCTN1*, *DCTN2*, *DCTN3*, *DCTN4*, *DCTN5*, and *DCTN6* gene expression levels; (**B**) gene interaction networks among selected genes generated by GeneMANIA; (**C**) scatter plots for *DCTN1*, *DCTN2*, *DCTN3*, *DCTN4*, *DCTN5*, and *DCTN6* gene expression levels in The Cancer Genome Atlas; and (**D**) analysis of enriched GO terms and KEGG pathways for *DCTN* genes obtained using DAVID. ** *P*<0.05, *** *P*<0.001.

multivariate survival analyses. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated with the Cox proportional hazards regression model with adjustment for influential clinical characteristics such as race, sex, age, TNM stage, and BMI. *P*<0.05 was considered statistically significant. Statistical analyses were carried out using SPSS v.22.0 software (IBM, Chicago, IL, USA). Vertical scatter plots and survival curves were generated in GraphPad Prism v.7.0 (La Jolla, CA, USA).

Ethics statement

All data used in this study were obtained from a public database; therefore, approval of the study by an ethics committee was not required.

Results

Patient characteristics influencing survival and differential DCTN expression in CM

The detailed demographic and clinical data for the 459 included patients are provided in Table 4. Race, age, and TNM stage were significantly associated with median survival time (MST; *P*=0.004, *P*=0.001, and *P*<0.001, respectively; Table 4). Boxplots illustrating differences in the expression of the 6 *DCTN* genes in normal skin tissue versus primary CM tissue were generated using MERAV (Figure 1). The median expression levels of *DCTN2* and *DCTN3* were higher in normal skin tissue than in primary CM tissue, whereas the median expression levels of *DCTN5* and *DCTN6* were higher in primary CM tissue than in normal skin tissue. The median expression levels of *DCTN1* and *DCTN4* did not differ significantly between normal skin tissue and primary tumor.

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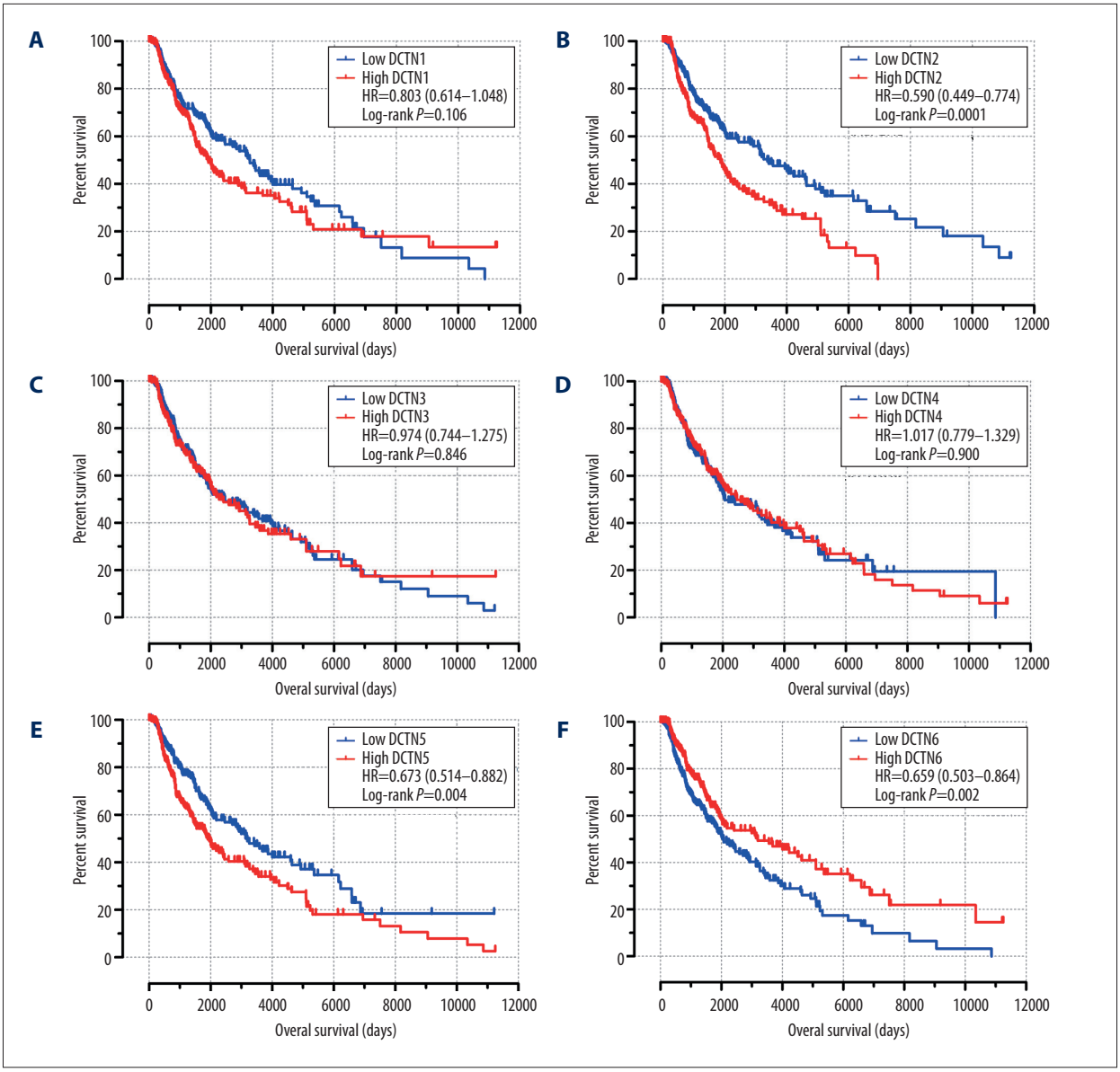

Figure 3. Prognostic value of *DCTN* expression for OS. (**A–F**) Kaplan-Meier survival curves for all CM patients according to *DCTN1* (**A**), *DCTN2* (**B**), *DCTN3* (**C**), *DCTN4* (**D**), *DCTN5* (**E**), and *DCTN6* (**F**) expression (n=459).

Correlations among expression levels of DCTN genes and functions of DCTN genes

Correlations among the expression levels of individual *DCTN* genes were identified by Pearson correlation coefficient analysis. For *DCTN1*, *DCTN2*, *DCTN3,* and *DCTN4*, the expression level of each gene was correlated with that of each of the other genes (all $P<0.05$), but not with the expression levels of *DCTN5* and *DCTN6*. *DCTN5* expression was only correlated with *DCTN1* expression ($P<0.05$). *DCTN6* expression was correlated with *DCTN1*, *DCTN3,* and *DCTN4* expression (all $P<0.001$; Figure 2A). Interactions among the expression levels of *DCTN1*, *DCTN2*, *DCTN3*, *DCTN4*, *DCTN5,* and *DCTN6* are shown in Figure 2B. Scatter plots for the expression of the 6 genes according to the 50th percentile cutoff are shown in Figure 2C.

The biological functions of the *DCTN* genes were evaluated according to the BP, MF, and CC categories for GO functional analysis (Figure 2D), and the results of KEGG pathway analysis are shown in Figure 2D.

Survival influence of differential DCTN gene expression

The results of univariate survival analysis were showed as Figure 3A–3F. The results showed that low expression levels of *DCTN2* and *DCTN5* separately were significantly associated

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Table 5. Prognostic survival analysis according to high or low expression of DCTN family genes.

Gene	Patients (n=459)	No. of events (%)	MST (days)	Crude HR (95% CI)	Crude P	Adjusted HR* (95% CI)	Adjusted P*
DCTN1					0.106		**0.008**
High	229	112 (48.9%)	1910	Ref.		Ref.	
Low	229	105 (45.9%)	3259	0.803		0.676	
Missing	1			(0.614–1.048)		(0.506–0.903)	
DCTN2					**<0.001**		**0.004**
High	229	111 (48.5%)	1860	Ref.		Ref.	
Low	229	107 (46.7%)	3379	0.590		0.648	
Missing	1			(0.449–0.774)		(0.485–0.867)	
DCTN3					0.846		0.437
High	229	94 (41.0%)	2273	Ref.		Ref.	
Low	229	124 (54.1%)	2454	0.974		0.893	
Missing	1			(0.744–1.275)		(0.671–1.188)	
DCTN4					0.900		0.140
High	229	114 (49.8%)	2470	Ref.		Ref.	
Low	229	104 (45.4%)	2071	1.017		0.806	
missing	1			(0.779–1.329)		(0.606–1.073)	
DCTN5					**0.004**		**0.011**
High	229	123 (53.7%)	1910	Ref.		Ref.	
Low	229	94 (41%)	3195	0.673		0.686	
Missing	1			(0.514–0.882)		(0.514–0.916)	
DCTN6					**0.002**		**0.018**
Low	229	125 (54.6%)	2071	Ref.		Ref.	
High	229	92 (40.2%)	3195	0.659		0.706	
Missing	1			(0.503–0.864)		(0.530–0.942)	

* Adjustment for race, sex, age, and TNM stage. *DCTN* – dynactin; MST – median survival time; HR – hazard ratio; CI – confidence interval.

with favorable OS in CM patients ($P<0.01$ and $P=0.004$, respectively; Figure 3B, 3E). High expression of *DCTN6* also was significantly associated with favorable OS ($P=0.002$; Figure 3F). The multivariate Cox proportional hazards regression analysis identified associations of sex, race, age, and TNM stage with the prognosis of CM patients. The multivariate survival analysis showed that, individually, low expression levels of *DCTN1*, *DCTN2*, and *DCTN5* and high expression level of DCTN6 were associated with favorable OS (adjusted $P=0.008$ HR=0.676 95% CI=0.506–0.903; adjusted $P=0.004$, HR=0.648, 95% CI=0.485–0.867; adjusted $P=0.011$, HR=0.686, 95% CI=0.514–0.916; and adjusted $P=0.018$, HR=0.706, 95% CI=0.530–0.942, respectively; Table 5).

Survival influence of combinations of DCTN gene expression

Based on the *DCTN* genes identified as influential by the multivariate survival analysis, a joint-effects model was used to determine the combined effects of *DCTN* genes on the OS of CM patients. The different groups for this analysis were generated according to the expression of *DCTN1*, *DCTN2, DCTN5,* and *DCTN6* (Tables 1–3). The Kaplan-Meier estimator with a log-rank test was used to evaluate the prognostic value of the gene expression combinations represented by each group (Figures 4, 5). In the analysis of low *DCTN1, DCTN2, and DCTN5* expression with high *DCTN6* expression, the combinations in groups I, IV, XII, X, XIII, XVI, i, iv, vii, and 1 were found to be more highly correlated with favorable OS (all $P<0.05$; Table 6). On the contrary, in the analysis of high expression of *DCTN1, DCTN2, and DCTN5* and low *DCTN6* expression, the combinations in groups III, VI, IX, XIII, XV, XVIII, iii, vi, ix, and 3 were found to be more highly correlated with poor OS (all $P<0.05$; Table 6).

Discussion

The 6 *DCTN* genes are known to encode the 6 subunits of DCTN, which are all essential for the DCTN activity of driving retrograde transport in cells [4–7]. Specific functions of individual DCTN subunits have also been reported. In human epidermal melanocytes, *DCTN1* expression was detected in the dendrite tips, and *DCTN2* expression was also localized in the perinuclear area and dendrite tips [16]. Notably, overexpression of

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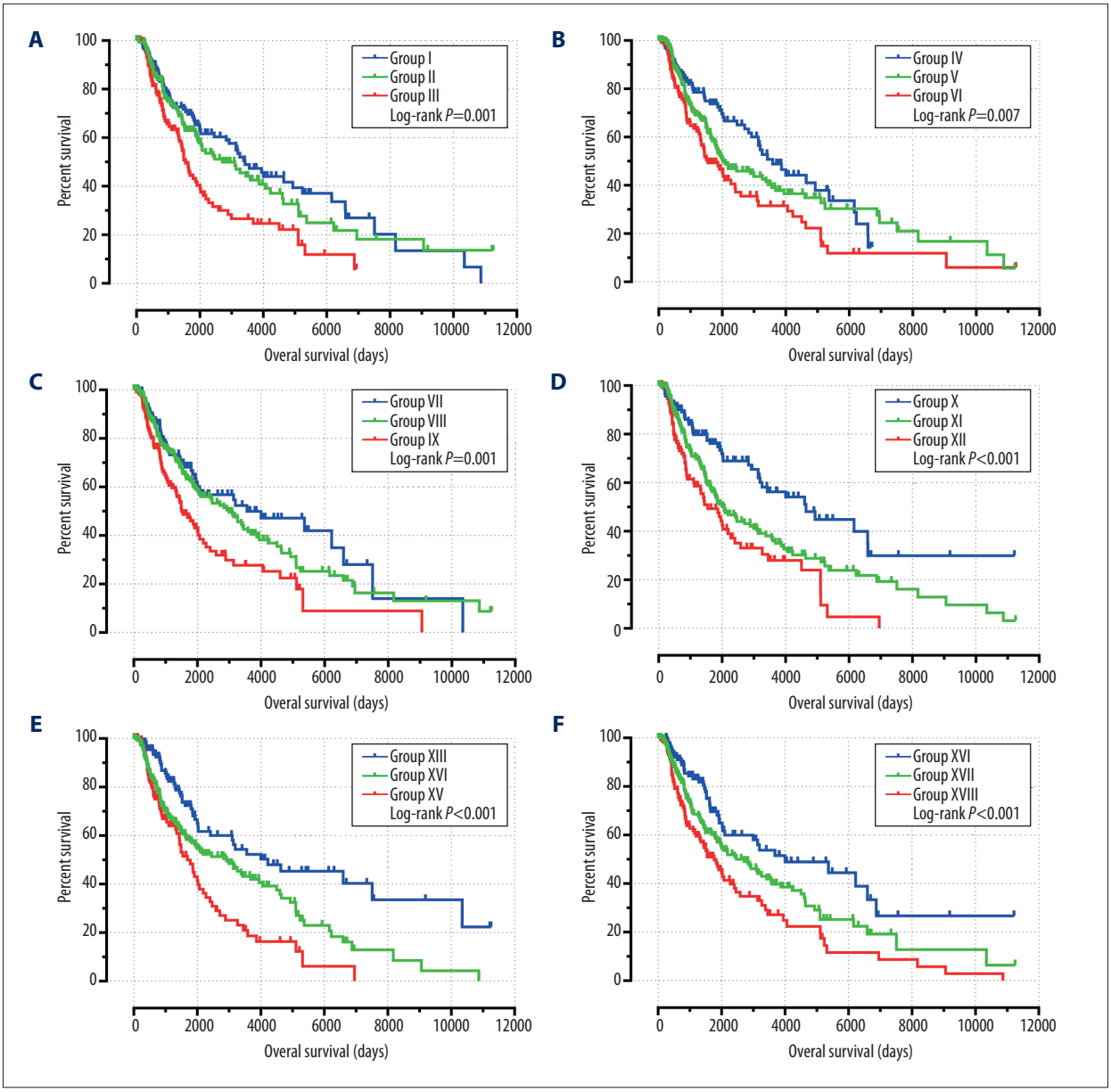

Figure 4. Joint-effects analysis of the influence of combined *DCTN* gene expression on OS with stratification according to 2 selected *DCTN* genes among *DCTN1*, *DCTN2*, *DCTN5,* and *DCTN6*. (**A**) *DCTN1* and *DCTN2*, (**B**) *DCTN1* and *DCTN5*, (**C**) *DCTN1* and *DCTN6*, (**D**) *DCTN2* and *DCTN5*, (**E**) *DCTN2* and *DCTN6*, and (**F**) *DCTN5* and *DCTN6*. I, low *DCTN1*+low *DCTN2*; III, high *DCTN1*+high *DCTN2*; IV, low *DCTN1*+low *DCTN5*; VI, high *DCTN1*+high *DCTN5*; VII, low *DCTN1*+high *DCTN6*; IX, high *DCTN1*+low *DCTN6*; X, low *DCTN2*+low *DCTN5*; XII, high *DCTN2*+high *DCTN5*; XIII, low *DCTN2*+high *DCTN6*; XV, high *DCTN2*+low *DCTN6*; XVI, low *DCTN5*+high *DCTN6*; XVIII, high *DCTN5*+low *DCTN6*; II, V, VIII, XI, XIV, and XVII correspond to other combinations of genes as detailed in Table 1.

DCTN3 is lethal to cells, and overexpression of *DCTN2* leads to the disruption of the Golgi apparatus [6,22]. Mutations of *DCTN1* have been identified in many serious motor neuron diseases, including ALS, ALS-frontotemporal dementia ALS/FTD, and PS [23–28], and a mutation in *DCTN4* was linked to Pa airway infection, chronic Pa infection, and mucoid Pa in cystic fibrosis patients [29,30]. Finally, the interaction between DCTN4 and the P-type ATPase (ATP7B) is a key component of Wilson disease [31].

Most studies to date have investigated associations between *DCTN* genes and nervous system diseases, infection diseases, both through functional studies and mutational studies. Only a few reports have been published on connections between *DCTN*

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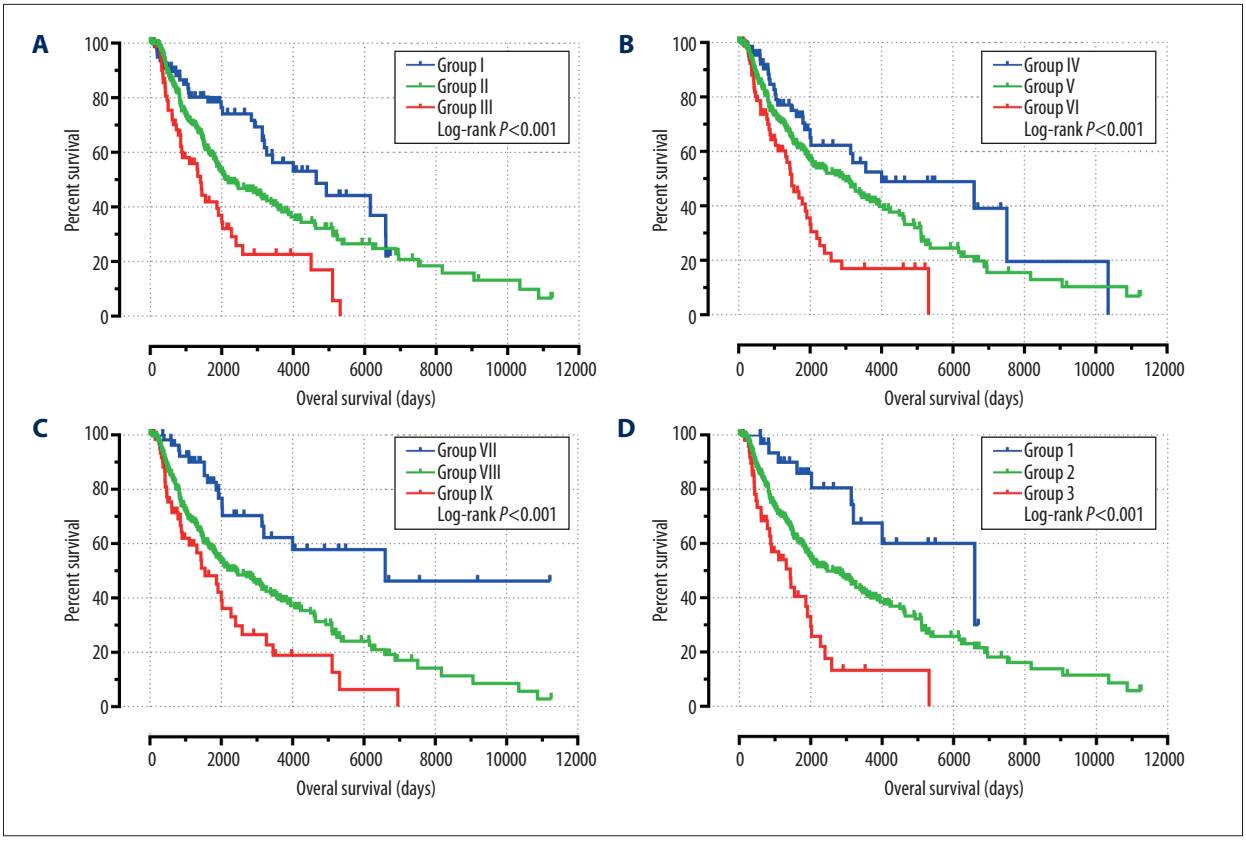

Figure 5. Joint-effects analysis of the influence of combined *DCTN* gene expression on OS with stratification according to 3 or 4 selected *DCTN* genes among *DCTN1*, *DCTN2*, *DCTN5,* and *DCTN6*. (**A**) *DCTN1*, *DCTN2, and DCTN5*; (**B**) *DCTN1, DCTN2,* and *DCTN6* (**C**) *DCTN2, DCTN5* and *DCTN6*, (**D**) *DCTN1*, *DCTN2*, *DCTN5,* and *DCTN6*. i, low *DCTN1*+low *DCTN2*+low *DCTN5*; iii, high *DCTN1*+high *DCTN2*+high *DCTN5*; iv, low *DCTN1*+low *DCTN2*+high *DCTN6*; vi, high *DCTN1*+high *DCTN2*+low *DCTN6*; vii, low *DCTN2*+low *DCTN5*+high *DCTN6*; ix, high *DCTN2*+high *DCTN5*+low *DCTN6*; 1, high *DCTN1*+high *DCTN2*+high *DCTN5*+low *DCTN6*; 3, low *DCTN1*+low *DCTN2*+low *DCTN5*+high *DCTN6*; ii, v, viii, and 2 correspond to other combinations of genes as detailed in Tables 2 and 3.

genes and cancer, although the *DCTN* family may play a crucial role in some cancers via their effect of the function and structure of DCTN. For example, it was reported that DCTN1 and DCTN2 could coprecipitate with human EB1, which may be correlated with human adenomatous polyposis coli *in vivo* [32]. Most relevant to our study, the intronic regions of *DCTN6* pre-mRNA were shown to interact with the *SPRIGHTLY* lncRNA of melanoma [15]. Still, there were no reports about the connection between *DCTN* mRNA expression and the prognosis of CM. Here, we used data for *DCTN* mRNA expression and clinical information in CM patients from the OncoLnc database according to the Cancer Genome Atlas to investigate the correlation of *DCTN* family mRNA expression and prognosis in CM patients and assess whether expression of any *DCTN* genes, individually or in combination, could be used as biomarkers for predicting prognosis in CM.

In our study, we found high expression levels of *DCTN2* and *DCTN5* in normal tissue, while the Kaplan-Meier curves from univariate survival analysis showed that low expression of *DCTN2* and *DCTN5* in tumor tissue was correlated with favorable OS in all CM patients, suggesting that *DCTN2* and *DCTN5* act as oncogenes in CM. In contrast, *DCTN6* was highly expressed in primary skin tumor tissue, and high expression of *DCTN6* was found to be correlated with favorable OS. This may be because *DCTN6* can act as a tumor suppressor. *DCTN2* was downregulated in CM but upregulated in the SJSA-1 osteosarcoma cell line [14], indicating that *DCTN2* may have different roles in different cancers.

Multivariate survival analysis confirmed the results of the univariate survival analysis, except for *DCTN1*. Multivariate survival analysis showed that a low expression of *DCTN1* was correlated with favorable prognosis, whereas in univariate survival analysis, neither low nor high expression of *DCTN1* was found to be correlated with OS. This may be due to adjustment in the Cox proportional hazards regression model, which indicated that *DCTN1* expression affects CM prognosis. Expression of both *DCTN1* and *DCTN2* was previously found in

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Table 6. Joint-effects analysis of the prognostic value of combinations of *DCTN1*, *DCTN2*, *DCTN5,* and *DCTN6* expression in CM.

Group	Patients (n=459)	MST (days)	Crude *P*	Crude HR (95% CI)	Adjusted *P**	Adjusted HR* (95% CI)
I	141	3424	**0.001**	Ref.	**0.001**	Ref.
II	176	2711	0.415	1.146 (0.826–1.589)	0.509	1.118 (0.803–1.558)
III	142	3733	**<0.001**	1.855 (1.323–2.601)	**<0.001**	1.859 (1.315–2.629)
IV	130	3587	**0.007**	Ref.	**0.003**	Ref.
V	199	2030	0.201	1.248 (0.888–1.754)	0.277	1.803 (1.255–2.590)
VI	130	1544	**0.002**	1.749 (1.220–2.509)	**0.001**	1.210 (0.858–1.705)
VII	124	3564	**0.001**	Ref.	**<0.001**	Ref.
VIII	210	2993	0.289	1.206 (0.853–1.704)	0.341	1.186 (0.835–1.686)
IX	125	1506	**0.001**	1.895 (1.304–2.752)	**<0.001**	2.012 (1.375–2.944)
X	114	4648	**<0.001**	Ref.	**<0.001**	Ref.
XI	231	2071	**0.001**	1.785 (1.256–2.536)	**0.004**	1.680 (1.180–2.391)
XII	114	1544	**<0.001**	2.567 (1.729–3.812)	**<0.001**	2.307 (1.542–3.452)
XIII	115	4222	**<0.001**	Ref.	**<0.001**	Ref.
XIV	228	2927	**0.002**	1.765 (1.238–2.516)	**0.005**	1.673 (1.170–2.392)
XV	116	1691	**<0.001**	2.643 (1.776–3.933)	**<0.001**	2.443 (1.628–3.665)
XVI	119	4000	**<0.001**	Ref.	**0.001**	Ref.
XVII	220	2711	**0.016**	1.559 (1.088–2.234)	**0.018**	1.546 (1.078–2.217)
XVIII	120	1766	**<0.001**	2.185 (1.495–3.193)	**<0.001**	2.089 (1.421–3.071)
i	78	4648	**<0.001**	Ref.	**<0.001**	Ref.
ii	302	2184	**0.020**	1.598 (1.076–2.374)	**0.036**	1.531 (1.028–2.281)
iii	79	1413	**<0.001**	2.999 (1.873–4.802)	**<0.001**	3.013 (1.870–4.857)
iv	68	4000	**<0.001**	Ref.	**<0.001**	Ref.
v	307	2927	0.056	1.503 (0.990–2.281)	0.104	1.422 (0.931–2.171)
vi	84	1486	**<0.001**	2.780 (1.659–4.422)	**<0.001**	2.679 (1.630–4.404)
vii	56	6598	**<0.001**	Ref.	**<0.001**	Ref.
viii	339	2421	**<0.001**	2.530 (1.513–4.231)	**0.001**	2.354 (1.403–3.949)
ix	64	1544	**<0.001**	4.088 (2.226–7.375)	**<0.001**	3.572 (1.955–6.524)
1	34	6598	**<0.001**	Ref.	**<0.001**	Ref.
2	373	2470	**0.008**	2.493 (1.275–4.875)	**0.009**	2.451 (1.248–4.816)
3	52	1429	**<0.001**	5.271 (2.500–11.113)	**<0.001**	5.216 (2.455–11.080)

* Adjustment for race, sex, age, and TNM stage. Bold type highlights statistically significant values ($P \leq 0.05$). *DCTN* – dynactin; MST – median survival time; HR – hazard ratio; CI – confidence interval.

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human epidermal melanocytes [16], suggesting that the mutations of *DCTN1* and *DCTN2* are important components of CM, and downregulated expression of these 2 genes may predict a favorable prognosis in CM.

The joint-effects analysis showed that expression of *DCTN1*, *DCTN2*, and *DCTN5* at low levels and *DCTN6* at a high level were correlated with a favorable OS in CM patients. In contrast, high expression of *DCTN1*, *DCTN2*, and *DCTN5* and low expression of *DCTN6* were correlated with poor OS.

There were some limitations in our study. First, a larger sample size is required to increase the reliability of our results. Second, more clinical data are required from further studies, including smoke and alcohol history, main tumor size, tumor sites in areas exposed or not exposed to the sun, anti-therapy status, radical resection status, family history, and pathological diagnosis, as well as data for more races among Asian and African populations. Thirdly, the patient data in our study were exclusively from a single source; therefore, the results need to be validated in another group. Despite these limitations, our study is the first to report that downregulation of *DCTN1*, *DCTN2*, and *DCTN5* and upregulation of *DCTN6* in CM are associated with a favorable prognosis. These 4 genes may be used as a prognostic biomarker panel in CM patients.

Conclusions

Our study demonstrated that low mRNA expression of *DCTN1*, *DCTN2*, and *DCTN5* and high mRNA expression of *DCTN6* were individually and jointly correlated with favorable prognosis among CM patients. Those 4 genes may be used as potential prognostic biomarkers in CM patients. Due to the small sample size and limited clinical information available in this study, these results need to be confirmed in further studies.

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Conflicts of interest

None.

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