DTL promotes melanoma progression through rewiring cell glucose metabolism

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Background: To investigate the role of *DTL* in the development of skin cutaneous melanoma (SKCM) and possible mechanisms.

Methods: We examined the expression of *DTL* in SKCM in The Cancer Genome Atlas (TCGA) and Oncomine database and analyzed the relationship between *DTL* expression and melanoma prognosis. Furthermore, we silenced the *DTL* gene by RNA interference in A375 cells and investigated the effect of *DTL* silencing on the biological function of melanoma cells.

Results: The expression of *DTL* in SKCM was upregulated in the tumor tissues compared with the paired normal tissues. Survival analysis showed that higher *DTL* expression in SKCM patients was associated with poor clinical outcome compared with the lower *DTL* expression group. Silencing of *DTL* in A375 cells significantly inhibited the melanoma cell growth and proliferation ability, and also significantly decreased the total glucose consumption and lactate production. Gene set enrichment analysis (GSEA) showed that MYC targets gene set pathway was highly enriched in the *DTL* high expression group. The expression levels of some MYC targets-related oncogenes, including *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGCR*, were reduced in the A375 cells with knockdown *DTL* and upregulated in SKCM tissues with high *DTL* expression, and there was a positive correlation between them.

Conclusions: An important role is played by *DTL* in promoting melanoma cell growth and glucose metabolism, possibly through activation of the *MYC* target pathway.

Keywords: Skin cutaneous melanoma (SKCM); *DTL*; glucose metabolism

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Introduction

Skin cutaneous melanoma (SKCM) is the most malignant skin cancer, accounting for more than 75% of skin cancer deaths (1). Despite great advances in targeted therapy and immunotherapy for SKCM over the past decade, the overall survival (OS) rate for SKCM remains low, especially for advanced SKCM. Therefore, exploring the mechanisms of SKCM development is of great benefit to understand the biological behavior of SKCM and to find new treatments.

The *DTL* gene, also known as *CDT2*, *DCAF2*, or *RAMP*, is a denticleless E3 ubiquitin protein ligase. It plays an important role in regulating *CDT1* proteolysis, DNA replication, and cell cycle (2,3). Functional abnormalities of *DTL* are involved in the development of many human malignancies. Elevated *DTL* expression has been found in a variety of human malignancies including breast cancer, colorectal cancer, lung cancer, and hepatocellular

carcinoma, and elevated *DTL* expression is positively associated with poor prognosis of these malignancies (4-7). In *in vitro* experiments, silencing *DTL* could significantly impair tumor cell growth and invasion capability, and induce apoptosis (8). The *DTL* gene is also critical in the development of SKCM. It has been found to be frequently overexpressed in SKCM tissues, and its overexpression has been associated with poor outcome (9,10). *In vitro* analysis has demonstrated that silencing *DTL* could inhibit melanoma cell proliferation via inducing DNA rereplication and senescence (10). However, the role and mechanisms of *DTL* in SKCM are still far from being elucidated.

In this study, we examined the expression of *DTL* in SKCM in The Cancer Genome Atlas (TCGA) and Oncomine database and analyzed the relationship between *DTL* expression and SKCM prognosis. Furthermore, we silenced the *DTL* gene by RNA interference in a melanoma cell line and investigated the effect of *DTL* silencing on the biological function of melanoma cells. Our aim was to reveal the role and possible mechanisms of *DTL* in melanoma and to initially establish an association between *DTL* and melanoma cell metabolic rewiring which shows good promise in the treatment of melanoma.

We present the following article in accordance with the MDAR reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6648/rc).

Methods

DTL expression analysis from the TCGA and Oncomine database

The messenger RNA (mRNA) expression levels of *DTL* in SKCM patient tissues were analyzed from TCGA (https://tcga-data.nci.nih.gov/publications/tcga) and Oncomine database (https://www.oncomine.org/resource/main.html). A total of 461 SKCM tumor specimens and 558 normal tissues were available from TCGA normal, Genotype-Tissue Expression (GTEx) data, and the Oncomine cohorts including the Riker melanoma (n=14, tumor tissues; n=4, normal tissues) and Talantov melanoma (n=45, tumor tissues; n=7, normal tissues). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Kaplan-Meier survival analysis of the prognostic value of DTL

We obtained SKCM patient tissues containing patient survival information from TCGA database (https://tcga-data.nci.nih.gov/publications/tcga). In line with the *DTL* expression median value in the SKCM patient tissues, they were classified into two groups: *DTL* high expression group and *DTL* low expression group.

Cell culture and stable cell lines

The A375 cell line was obtained from the Cell Bank of Shanghai Institutes of Biological Sciences, Chinese Academy of Sciences (Shanghai, China). The A375 cells were passaged in Dulbecco's modified Eagle's medium (DMEM; Life Technologies, Carlsbad, CA, USA) supplemented with 10% fetal bovine serum (FBS; Life Technologies), 1× penicillin/streptomycin, and 4 mM L-glutamine and incubated at 37 ℃ in 5% CO_2. To knockdown the expression of *DTL*, short hairpin RNA (shRNA; shDTL-1: GCCTAGTAACAGTAACGAGTA and shDTL-2: CTGGTGAACTTAAACTTGTTA) was cloned in pLKO.1 plasmid. For lentivirus production, HEK293T cells were transfected with the lentiviral vectors and helper plasmids DR8.91 and VSVG. At 48 h after transfection, virus-containing media were collected. The A375 cells were transduced using lentivirus for 24 h, and then selected with puromycin.

Cell proliferation assay

Cell proliferation was measured with a Cell Counting Kit-8 (CCK-8) kit. The A375 cells stably expressing vector (A375-SCR) or shDTL (A375-shDTL-1 and A375-shDTL-2) (3,000 cells/well) were seeded into 96-well plates. The A375-SCR, A375-shDTL-1, and A375-shDTL-2 cells were cultured at 37 ℃ in 5% CO_2 for 24, 48, 72, and 96 h, then the medium of each well was replaced with 10% CCK-8 solution in fresh medium. The above cells were then incubated for 2 h, following which absorbance at 450 nm was measured using a microplate reader.

Colony formation assay

The A375-SCR, A375-shDTL-1, and A375-shDTL-2 cells were seeded respectively in 6-well plates at a density of 200 cells/well at 37 ℃ in a 5% CO_2 humidified environment. After incubation for about 14 days, the plates were washed with phosphate-buffered saline (PBS) and fixed with methanol for 30 min, then stained with Giemsa solution (Sigma-Aldrich, St. Louis, MO, USA) for 30 min.

Afterwards, the plates were washed with clean water and the number of the above cell colonies were counted.

Gene set enrichment analysis (GSEA) of DTL

GSEA was performed using RNA-seq data sets from TCGA-SKCM (https://tcga-data.nci.nih.gov/publications/TCGA-SKCM). According to the mRNA expression median level of *DTL* gene in the SKCM patient tissues, the tissues were divided into two groups: *DTL* high expression group (DTL-high, n=236) and *DTL* low expression group (DTL-low, n=237).

Statistical analysis

Statistical analysis was performed with the software SPSS 20 (IBM Corp., Armonk, NY, USA). Kaplan-Meier survival analysis, Pearson's test, and Student's *t*-test were used to compare the difference of the variables. A P value <0.05 was considered statistically significant.

Results

Upregulation of DTL in SKCM is associated with worse clinical outcomes

To reveal the clinical relevance of *DTL* in human SKCM, we analyzed the expression of *DTL* in the SKCM-TCGA database and found that *DTL* mRNA levels were significantly increased in the SKCM tumor tissues compared with the normal adjacent tissues (*Figure 1A*). Moreover, we further examined the expression of *DTL* in the SKCM data from the Oncomine database and also found that *DTL* expression in the Riker melanoma and Talantov melanoma were notably upregulated in the tumor tissues compared with the paired normal tissues (*Figure 1B,1C*), suggesting the potential oncogenic activity of *DTL*. We then analyzed the *DTL* expression level in tumor tissues derived from 458 post-operative SKCM patients from TCGA database. These SKCM patient tissues were grouped under high *DTL* expression or low DTL expression according to their *DTL* mRNA levels. Next, we evaluated the relationship between *DTL* expression level and patient OS and disease-free survival (DFS) by Kaplan-Meier survival analysis. Survival analysis revealed that higher *DTL* expression in SKCM patients was associated with poor clinical outcome as well as shorter DFS times compared with the lower *DTL* expression group (*Figure 1D,1E*). Taken together, these results indicated that upregulation of *DTL* contributes to cancer development and can serve as a novel indicator for poor prognosis in SKCM.

DTL promotes cell growth and glucose metabolism in SKCM

To evaluate the function of *DTL* in the progression of SKCM, we firstly constructed the *DTL* high or low expression SKCM cell lines, knocked down *DTL* expression in the A375 cells with the lentivirus expressing *DTL* shRNA precursor (A375-shDTL-1 and -2), and used the real-time polymerase chain reaction (PCR) assay to confirm the knockdown efficiency of *DTL* in the A375-shDTL-1 and -2 cells compared with the control cells (A375-SCR) (*Figure 2A*). The above cells were used to evaluate *DTL* influence on SKCM progression. Using the CCK-8 assay, we found that knockdown of the expression of *DTL* in the A375 cells significantly inhibited the cell proliferation ability (*Figure 2B*). Furthermore, we also revealed that *DTL* knockdown notably impaired the tumor cell colony formation ability (*Figure 2C,2D*). We then analyzed glucose metabolism upon *DTL* knockdown in A375 cells. As expected, *DTL* silencing significantly decreased total glucose consumption and lactate production in the A375 cells (*Figure 2E,2F*). Collectively, these results demonstrate that *DTL* promotes SKCM cell growth and enhances glucose metabolism.

DTL expression levels positively correlate with the MYC targets pathway and SKCM progression

To explore the mechanism underlying *DTL*'s promotion of SKCM cell growth and glucose metabolism, we firstly made an analysis of the RNA-seq data of SKCM patient tissues (n=473) from TCGA database, and then divided the into a *DTL* high expression group (DTL-high, n=236) and *DTL* low expression group (DTL-low, n=237). Moreover, we performed GSEA for the RNA-seq data between the DTL-high and DTL-low group, and found that cell cycle and Jaeger metastasis up gene pathways were significantly enriched in the SKCM patient tissues of the *DTL* high expression group (*Figure 3A,3B*), which were similar to the results of *DTL*'s promotion of SKCM progression. Furthermore, *MYC* targets V1 and *MYC* targets V2 gene set pathways were also highly enriched in the *DTL* high expression group (*Figure 3C,3D*), suggesting *DTL* may promote glucose metabolism via activating *MYC* targets

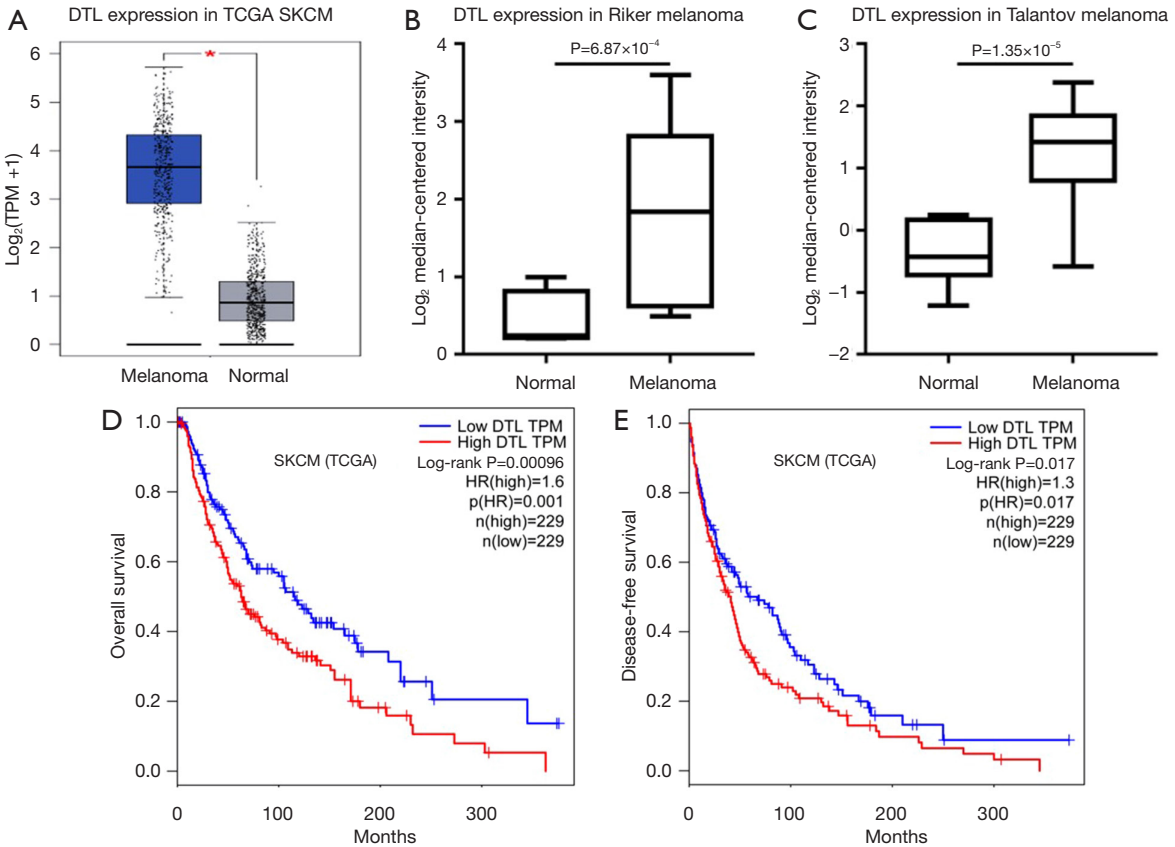

Figure 1 Upregulation of *DTL* in SKCM is associated with worse clinical outcomes. (A) The expression of DTL between SKCM tumor specimens (n=461) and 558 normal tissues (n=558) from the TCGA normal and GTEx data. *P<0.01. (B,C) The mRNA levels of *DTL* in the Riker melanoma (n=14, tumor tissues; n=4, normal tissues) (B) and Talantov melanoma (n=45, tumor tissues; n=7, normal tissues) (C) from the Oncomine database (https://www.oncomine.org/resource/main.html). The expression of *DTL* was up-regulated in the melanoma tissues comparing with the normal tissues. (D,E) Kaplan-Meier curves of OS (D) and DFS (E) of SKCM patient according to *DTL* expression levels in the SKCM tissues. The OS and DFS was significantly reduced in the *DTL* high expression group (n=229) compared with the *DTL* low expression group (n=229). The SKCM patients data come from TCGA database (https://tcga-data.nci.nih.gov/publications/tcga). Log-rank P values were shown. SKCM, skin cutaneous melanoma; TCGA, The Cancer Genome Atlas; GTEx, Genotype-Tissue Expression; mRNA, messenger RNA; OS, overall survival; DFS, disease-free survival; TPM, transcripts per million; HR, hazard ratio.

V1–2 gene set pathway. In addition, the G2M checkpoint, E2F targets, mitotic spindle, and mTORC1 signaling gene set pathways were notably enriched in the *DTL* high expression group compared with the *DTL* low expression group (*Figure 3E-3H*). Thus, these findings indicate that *DTL* promotes the *MYC* targets pathway and SKCM progression.

DTL drives the cell glucose metabolism reprogramming in SKCM

Next, we investigated whether *DTL* could active the *MYC* targets pathway to promote tumor cell glucose metabolism reprogramming. Firstly, we detected several *MYC* targets-related oncogenes expressions (*c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGCR*) in the *DTL* knockdown A375 cells and the real-time PCR results showed that knockdown of the expression of *DTL* could reduce the above genes' mRNA levels (*Figure 4A*). Moreover, we also found that *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGCR* expression levels were upregulated in the *DTL* high expression SKCM patient tissues compared with the *DTL* low expression group (*Figure 4B*). Furthermore, a positive correlation

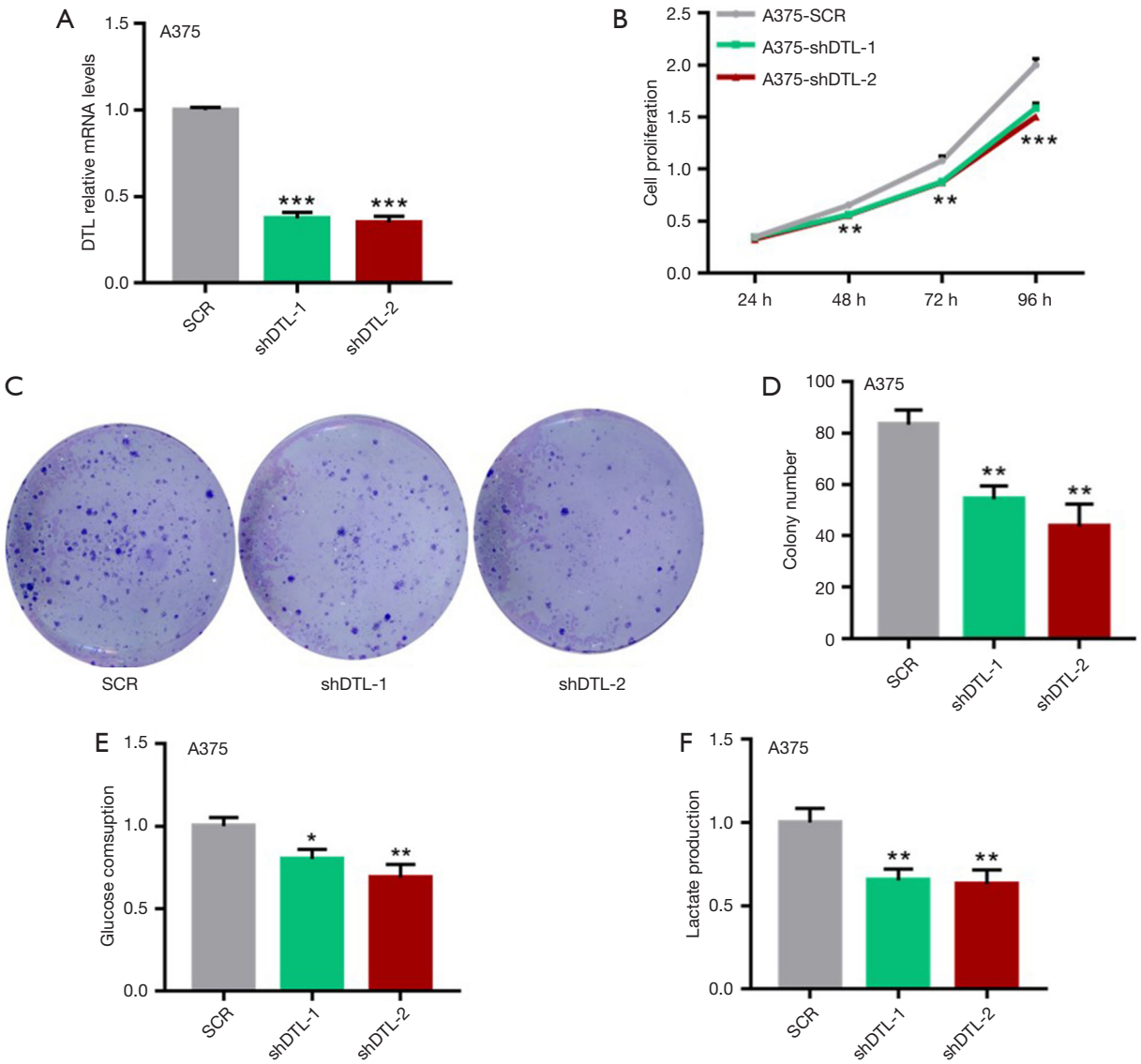

Figure 2 *DTL* promotes cell growth and glucose metabolism in SKCM. (A) Knockdown expression of *DTL* in the A375 cells infected with lentivirus as indicated. The efficiency of *DTL* knockdown in the A375 cells were assessed by real-time PCR. (B) Using the CCK-8 assays to examine the A375 cell proliferation ability as the indicated. (C,D) The cell colony formation assay of A375 cells infected with shRNA targeting *DTL* and the control (Giemsa staining). (E,F) Glucose consumption (E) and lactate production (F) of A375 cells infected with shRNA targeting *DTL* (shDTL-1 and -2) were determined. The data represent the mean ± SD. Significant differences were determined using two-tailed Student's *t*-test, *P<0.05; **P<0.01; ***P<0.001. SKCM, skin cutaneous melanoma; PCR, polymerase chain reaction; CCK-8, Cell Counting Kit-8; shRNA, short hairpin RNA; SD, standard deviation.

was found between the *DTL* expression and *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGCR* expression levels in the SKCM tissues from TCGA database (*Figure 4C-4K*). These results suggest that *DTL* promotes cell glucose metabolism reprogramming in both SKCM tissues and cell lines.

Discussion

This study illustrated that *DTL* expression levels are significantly higher in SKCM tissues than in normal tissues, and that OS and DFS are significantly lower in SKCM patients with high *DTL* expression than in those with low

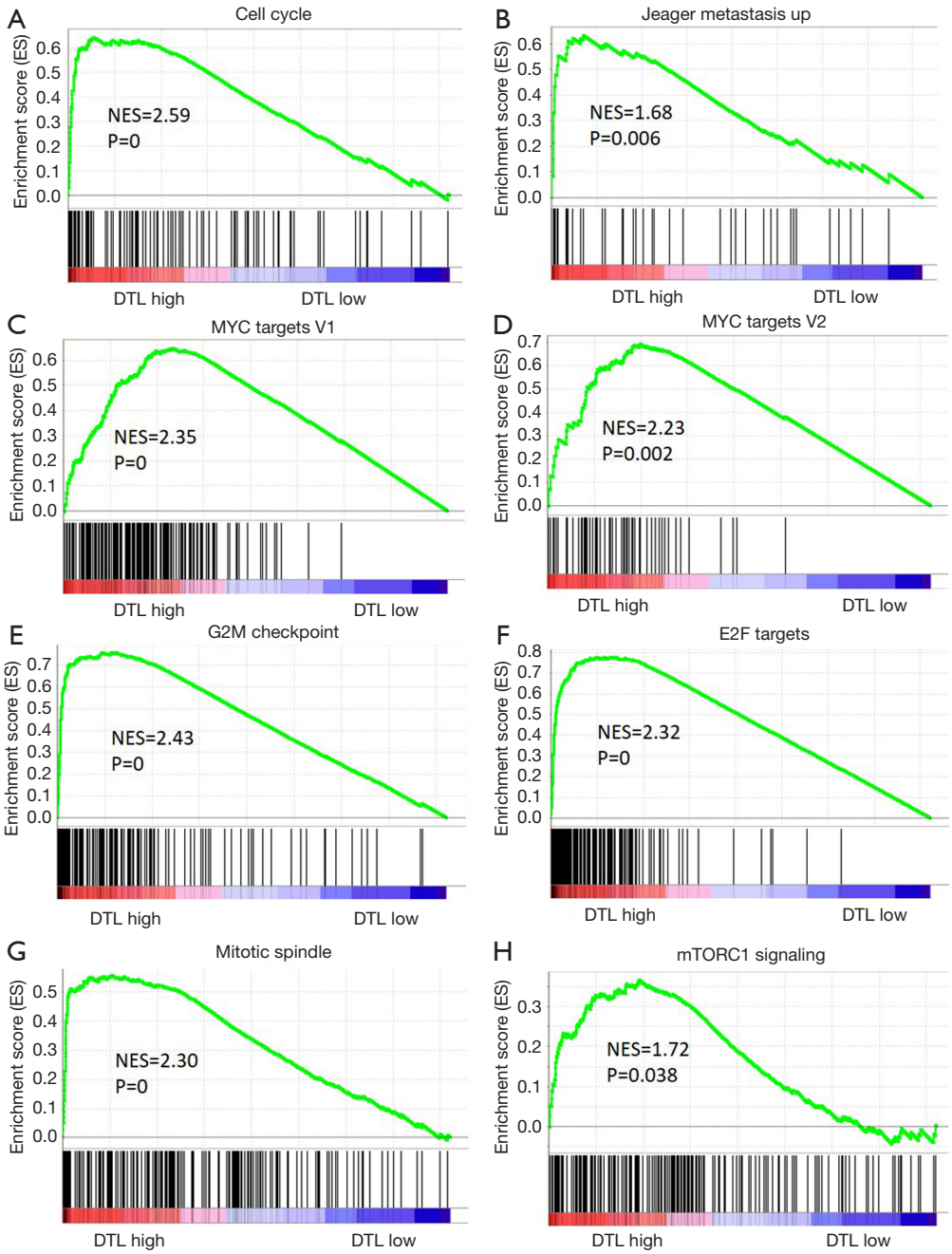

Figure 3 *DTL* expression levels positively correlates with the MYC targets pathway and SKCM progression. (A-H) Analysis the RNA-seq data of SKCM patient tissues from TCGA, according to the mRNA expression median level of *DTL* gene in the SKCM patient tissues, which were divided into two groups: *DTL* high expression group (*DTL*-high, n=236) and *DTL* low expression group (DTL-low, n=237). and then followed using GSEA analysis. GSEA analysis indicated that pathways including cell cycle (A), Jaeger metastasis up (B), MYC targets V1 (C), MYC targets V2 (D), G2M checkpoint (E), E2F targets (F), mitotic spindle (G), and mTORC1 signaling (H) were highly enriched in the SKCM patient tissues with *DTL* high expression group (DTL-high) compared with the *DTL* low expression group (DTL-low). SKCM, skin cutaneous melanoma; TCGA, The Cancer Genome Atlas; mRNA, messenger RNA; GSEA, gene set enrichment analysis; NES, normalized enrichment score.

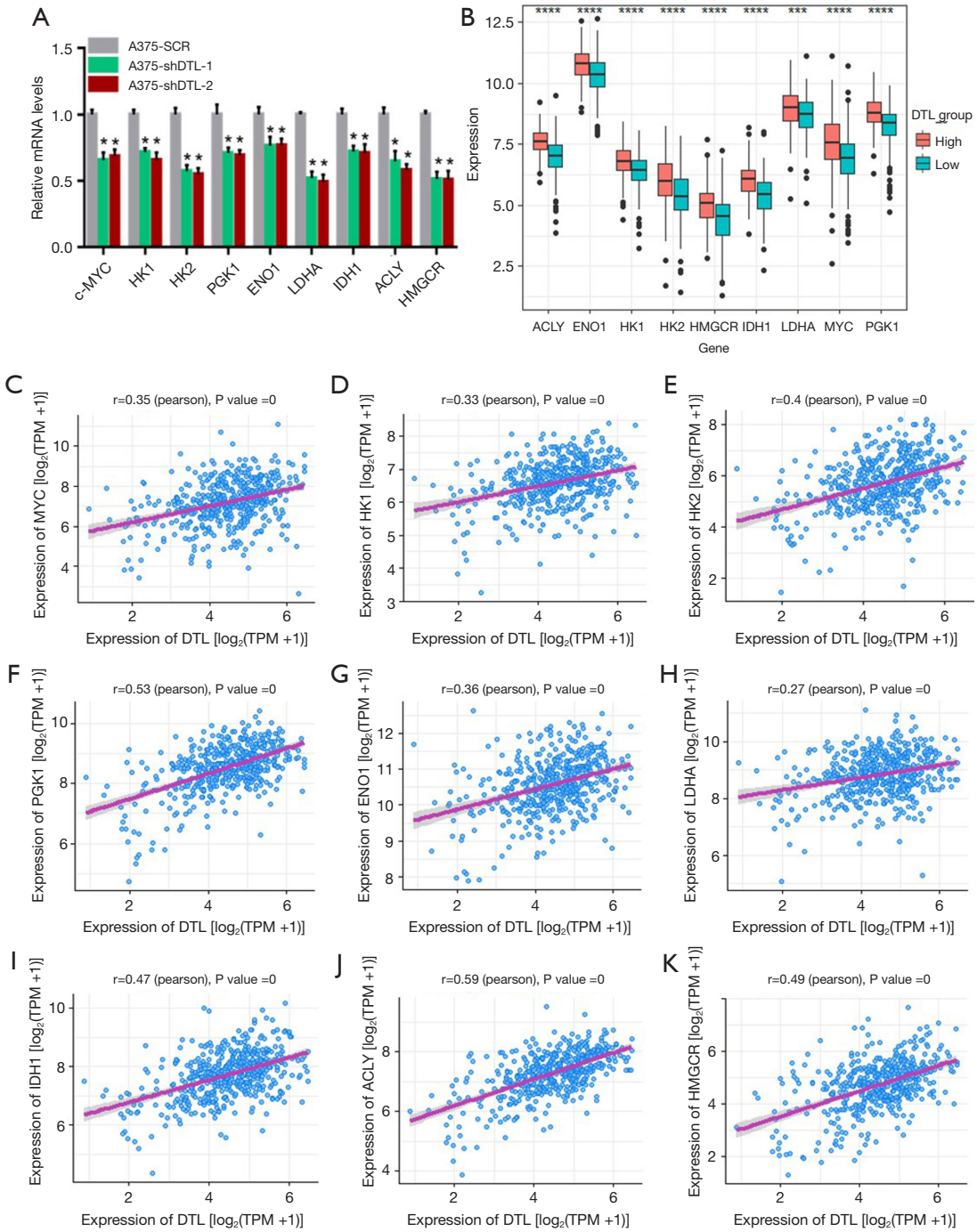

Figure 4 *DTL* drives the cell glucose metabolism reprogramming in SKCM. (A) The expression of *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY* and *HMGCR* in the A375 cells were measured using the real-time PCR. Means ± SD from three independent experiments were presented. Significant differences were determined using Student's *t*-test, *P<0.05. (B) The expression levels of *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGCR* between in the *DTL* high expression group (DTL-high, n=236) and *DTL* low expression group (DTL-low, n=237) from SKCM-TCGA database. ***P<0.001; ****P<0.0001. (C-K) A positive correlation were found between the levels of *c-MYC* (C), *HK1* (D), *HK2* (E), *PGK1* (F), *ENO1* (G), *LDHA* (H), *IDH1* (I), *ACLY* (J), and *HMGCR* (K) with *DTL* expression in the SKCM tissues. The SKCM tissues data come from TCGA. SKCM, skin cutaneous melanoma; PCR, polymerase chain reaction; SD, standard deviation; TCGA, The Cancer Genome Atlas; mRNA, messenger RNA; TPM, transcripts per million.

DTL expression. *In vitro* experiments showed that silencing *DTL* could significantly impair the growth ability and invasive ability of melanoma cells. Silencing *DTL* also significantly reduced glucose consumption and lactate production in melanoma cells. These findings suggest that *DTL* can promote the growth and glucose metabolism of melanoma cells and play a vital role in the development of melanoma.

Abnormal glucose metabolism is one of the important features of cancer and plays an important role in promoting the development of melanoma (11). Studies have shown that melanoma cells have abnormally high levels of glucose metabolism, producing large amounts of lactic acid while consuming large amounts of glucose. Melanoma cells, especially the more metastatic ones, are able to take in excess lactic acid, which allows them to increase the production of antioxidants, thus contributing to their survival in the bloodstream (12,13). These metabolic alterations facilitate malignant tumor proliferation and adaptation to unfavorable survival environments, thereby promoting disease progression. Enhanced metabolic activity of tumor cells can also resist melanoma response to adoptive T cell therapy, which is one of the important reasons for the failure of melanoma immunotherapy (14). Therefore, limiting the metabolic pathways of melanoma cell growth would provide a basis for targeted metabolic therapy for melanoma. In this study, we found that inhibition of *DTL* expression significantly attenuated the glucose consumption level as well as the lactate production level in melanoma, suggesting that *DTL* is also involved in the glucose metabolic process of melanoma and that it may promote melanoma progression by altering the its glucose metabolic process. This needs to be supported by more studies.

Metabolic rewiring is an adaptive response process of tumor cells in a low nutrient and hypoxic conditions in the tumor microenvironment (15). Studies have shown that many signaling pathways are partially involved in the process of metabolic changes through genetic and epigenetic alterations. These signaling pathways and molecules include the RAS/MAPK pathway, the AKT pathway, *RSK* and *SOX4* (16,17). Targeting metabolic rewiring process could increase the efficiency of target therapy and the sensitivity to immunotherapy in melanoma (18). Thus, the discovery of additional molecules that regulate metabolic rewiring offers promising prospects for therapies that target metabolic rewiring. The present study mainly provides an association between *DTL* and metabolic rewiring, although the pathway through which *DTL* promotes melanoma glucose metabolism is currently unknown. As a ubiquitin ligase, *DTL* may act by the ubiquitination pathway of degrading tumor suppressor proteins or by directly activating related oncogene pathways. In this study, we found that *MYC* targets gene set pathway was highly enriched in the *DTL* high expression group, and inhibition of *DTL* expression could downregulate the expression levels of some important *MYC* targets-related oncogenes. In addition, the expression levels of *MYC* targets-related oncogenes including *c-MYC*, *HK1*, *HK2*, *PGK1*, *ENO1*, *LDHA*, *IDH1*, *ACLY*, and *HMGC* were upregulated in SKCM tissues with high expression of *DTL*, whereas the expression levels of the above *MYC* targets-related oncogenes were downregulated in melanoma cell lines with knockdown of *DTL*. These results suggest that *DTL* may promote melanoma cell glucose metabolism reprogramming by activating *MYC* target pathway.

In summary, our study revealed that *DTL* plays an important role in promoting melanoma cell growth and glucose metabolism, possibly through activation of the *MYC* target pathway. Additionally, *DTL* may serve as a potential therapeutic target for the future development of drugs for melanoma treatment.

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Footnote

Reporting Checklist: The authors have completed the MDAR reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6648/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6648/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6648/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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