The role of SGOL1 in the prognosis of skin cutaneous melanoma (SKCM)

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Abstract

Objective To analyze the expression of SGOL1 in skin cutaneous melanoma(SKCM) and its relationship with prognosis.

Methods The expression of SGOL1 in SKCM and normal tissues was analyzed by TCGA database. Kaplan-Meier curve was used to analyze the relationship between SGOL1 expression and prognosis of SKCM. Mann-Whitney U test and Kruskal-Wallis test were used to analyze the relationship between SGOL1 and clinicopathological features.

Results SGOL1 was over expressed in SKCM ($P < 0.05$). The overall survival of SGOL1 high expression group was lower than low expression group ($P < 0.05$). There was no difference in the expression of SGOL1 between gender or age groups, but there were different in the expression of SGOL1 between Clark grades, tumor stages and survival status.

Conclusion High expression of SGOL1 in SKCM may be related with poor prognosis.

Key words Skin Cutaneous Melanoma; SGOL1; TCGA

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Introduction

Skin cutaneous melanoma (SKCM) is a major public health problem worldwide. Skin is one of most common site of melanoma in China, skin cutaneous melanoma (SKCM) is a highly malignant tumor originating from melanocytes and a number of patients increased continuously[1]. SKCM has a poor prognosis and is prone to metastasis in the early stage. Although there are different treatments, such as chemotherapy and targeted therapy, the prognosis of advanced and metastatic cutaneous melanoma is not ideal[2]. Therefore, it is still very important to study the molecular mechanism of skin melanoma.

Shugoshin-like protein (SGOL1), also known as SGO1, is one of the human homologs of yeast shugoshin[3]. The protein encoded by this gene is a member of the shugoshin protein family[4]. This protein is believed to protect centromere fibronectin from being cleaved at the prophase of mitosis by preventing phosphorylation of

fibronectin subunits[5]. SGOL1 regulates accurate chromosome segregation during mitosis[6].The decrease of SGOL1 expression will lead to premature loss of centromere cohesion, erroneous separation of sister chromatids and mitosis arrest. The mutation of SGOL1 is related to chronic atrial and intestinal arrhythmia (CAID) syndrome, and the complex of SGOL1 and mucin plays a certain role in mediating the rhythm integrity of human heart and intestine[7]. Some studies shown that SGOL1 also played an important role in the occurrence and development of tumors[3, 5, 6, 8-10]. But the role of SGOL1 in SKCM is not clear.

Methods

SGOL1 expression and survival analysis

The cancer genome atlas (TCGA) is a project jointly launched by the National Cancer Institute of the United States and the National Human Genome Institute of the United States in 2006. It contains relevant data of various tumors and is an important data source for tumor research. For comparison of the SGOL1 expression in SKCM and normal tissues, the Gene Expression Profiling Interactive Analysis (GEPIA) database (http://gepia.cancer-pku.cn/index.html) was used. We selected 461 cases of SKCM and 558 cases of normal tissues from TCGA and GTEx database by using GEPIA (http://gepia.cancer-pku.cn/index.html) to analyze the expression of SGOL1 in SKCM and normal tissue. TIMMER (https://cistrome.shinyapps.io/timer) is a tool that can provide the differential expression of genes in TCGA tumors between tumors and adjacent normal tissues. We use TIMER to analyze the expression of SGOL1 in different tumors and normal tissues.

The gene expression RNA - Seq (HTSeq - FPKM) and clinical information of 472 patients with SKCM in TCGA were collected from the University of California Santa Cruz (UCSC) Xena (https://xenabrowser.net/datapages/). Eliminate samples without Clark grade or tumor stage, 457 patients with SKCM were obtained. Kaplan-Meier survival curve was drawn with R software "Survive" R package. The statistical analysis method and R software package used in this paper are processed by the R Statistical language (version 4.0.3), and p values of less than 0.05 are considered statistically significant.

Correlation analysis of clinical features

Mann-Whitney U test was used to evaluate the expression of SGOL1 gender and age groups ("< 60 years old" and "≥ 60 years old"). After excluding the cases without Clark grade or tumor stage information, Kruskal-Wallis test was used to evaluate the expression of SGOL1 among Clark grades, tumor stages and survival status.

Immunohistochemical expression

The Human Protein Atlas (https://www.proteinatlas.org/) provides tissues and cellular distribution information of all 24000 human proteins. The immunohistochemical (IHC) staining data of SGOL1 were retrieved from HPA database to detect the protein

expression of SGOL1 in melanoma and normal tissue. Protein expression score is based on immunohistochemical data manually scored with regard to staining intensity (negative, weak, moderate or strong) and fraction of stained cells (<25%, 25-75% or >75%). Each combination of intensity and fractions is automatically converted into an protein expression level score as follows: negative - not detected; weak <25% - not detected; weak combined with either 25 - 75% or 75% - low; moderate <25% - low; moderate combined with either 25 - 75% or 75% - medium; strong <25% - medium, strong combined with either 25 - 75% or 75% - high.

Result

SGOL1 expression

To better understand the role of SGOL1 in SKCM, we compared the expression of SGOL1 between SKCM (461samples) and normal tissues (558samples) in GEPIA database. The expression of SGOL1 in SKCM was increased compared to the normal tissues. Compared with primary cutaneous melanoma, the expression of SGOL1 in metastatic cutaneous melanoma was increased (Fig. 1), suggesting that it may be related to the progression of cutaneous melanoma. Comparing with normal tissues, SGOL1 was highly expressed in bladder urothelial carcinoma, invasive breast carcinoma, cholangiocarcinoma, colon cancer, esophageal cancer, head and neck squamous cell carcinoma, renal clear cell carcinoma, renal papillary cell carcinoma, hepatocellular carcinoma, lung cancer, lung squamous cell carcinoma, prostate cancer, rectal cancer, gastric cancer, thyroid carcinoma and endometrial carcinoma (Fig. 2).

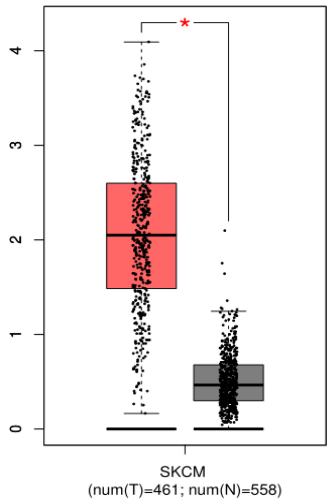

Fig.1: Expression of SGOL1 in SKCM and normal tissues.

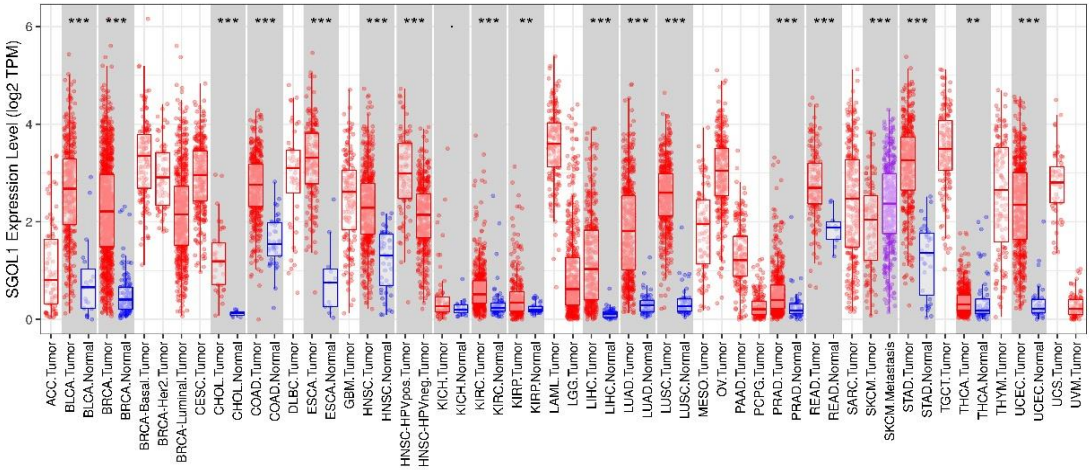

Fig.2: Expression of SGOL1 in different types of human tumors and normal tissues in TIMER database. p values: 0 ≤ *** < 0.001 ≤ ** < 0.01 ≤ * < 0.05 ≤ . < 0.1

Survival analysis

It was divided into low expression (n = 229) and high expression (n = 228) groups using the median of SGOL1 expression. The Kaplan-Meier curve indicated that patients in the high expression group had a significantly worse OS than their low expression counterparts (Fig. 3, P< 0.05).

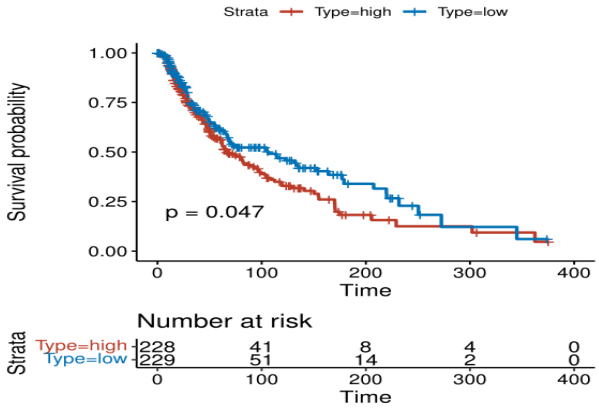

Fig.3: Kaplan-Meier curves for the OS of patients in the high expression group and low expression group in the TCGA cohort.

Correlation analysis of clinical features

The expression of SGOL1 was not associated with gender or age, but associated with Clark grade, tumor stage and survival status(Table 1).

Table 1 :SGOL1 expression and clinicopathological features in SKCM based on TCGA database

Characteristis	n	percentage	P value
Gender	457		0.057
Male	285	62.36%	
Fmale	172	37.64%	
Age	457		0.470
＜60	242	52.95%	
⩾60	215	47.05%	
Clark grade	315		0.042
Ⅰ	5	1.59%	
Ⅱ	18	5.71%	
Ⅲ	76	24.13%	
Ⅳ	164	52.06%	
Ⅴ	52	16.51%	
Stage	406		0.005
Ⅰ	77	18.97%	
Ⅱ	136	33.50%	
Ⅲ	170	41.87%	
Ⅳ	23	5.66%	
status	456		0.014
alive	235	51.54%	
dead	221	48.46%	

Immunohistochemical expression

IHC staining data were retrieved from HPA database to study the expression of SGOL1 at protein level. In normal skin tissue, SGOL1 expression was localised in the nuclei of squamous epithelium in the basal layer, while langerhans cells, myofibroblasts and melanocytes were negative. Ten cases of melanoma were detected by SGOL1 immunohistochemistry. Most cases (7/10) were positive, five cases were medium, two cases were low. Only three cases were not detected (3 / 10) (Fig. 4).

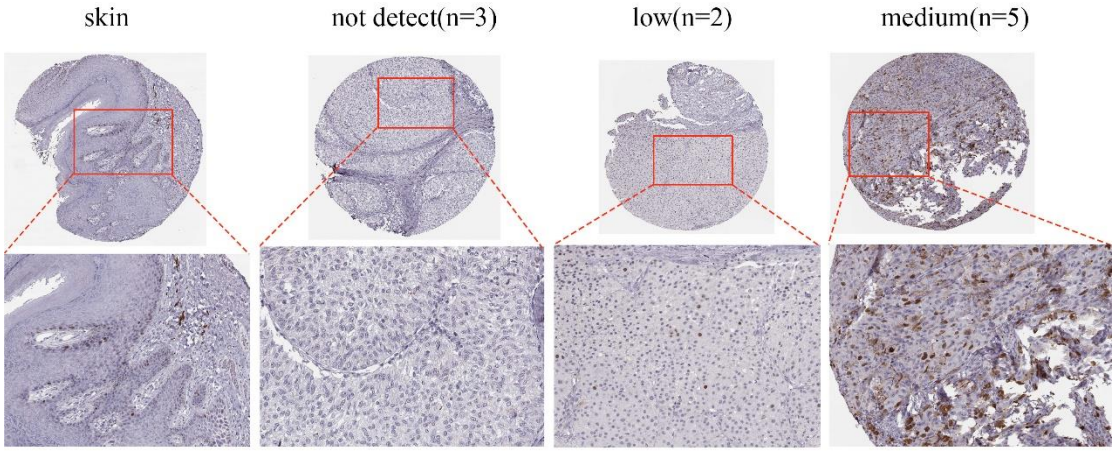

Fig. 4: Immunohistochemical expression of SGOL1 in skin and melanoma.

Discussion

Research by American Cancer Institute shows that the incidence of SKCM is on the rise[11]. Cutaneous melanoma is a deadly skin tumor, and is easy to metastasize. Advanced melanoma has high malignant degree and poor prognosis. Metastatic melanoma is a major challenge for treatment. Therefore, it is very important to study the molecular mechanism of SKCM and find new therapeutic targets. Shugoshin (Sgo) protein was a protector of centromeric cohesion in meiosis. SGOL1, also called hSgo1, was one of the two human Sgo proteins (hSgo1 and hSgo2). SGOL1 has been shown to be essential to accurate chromosome segregation during both mitosis and meiosis[12, 13]. Previous studies have shown that the expression of SGOL1 was decreased in colorectal adenocarcinoma and SGOL1 downregulation leads to chromosomal instability in colorectal cancer[14]. M Iwaizumi et al expected that hSgo1 dysfunction may induce CIN through G2/M arrest. In NSCLC, SGOL1 expression is upregulated and that the upregulation of SGOL1-B(one of the splicing variants of SGOL1) is associated with ominous clinical feature such as having WT EGFR and focal copy number amplification[3].

SGOL1 mRNA was expressed at higher levels in hepatocellular carcinoma, and high SGOL1 expression experienced worse overall survival[10]. SGOL1 is a druggable target that may enhance the efficacy of sorafenib

Treatment in hepatocellular carcinoma[10]. JingYang et al found that Acute myelogenous leukemia (AML) cells possessed significantly higher levels of SGOL1 than normal PBMCs and BMMCs[6].

In our study, we found that SGOL1 is highly expressed in SKCM, and the expression of metastatic melanoma is higher than the primary skin melanoma, suggesting that SGOL1 may be related to the occurrence and development of tumors. Statistical analysis of clinical pathological features showed that the expression of SGOL1 was associated with Clark grade, tumor stage and survival status. The Kaplan-Meier curve showed that the high expression of SGOL1 was related to the poor prognosis of SKCM.

Immunohistochemical results showed that the melanocyte SGOL1 in normal skin was negative, while most cases (7/10) of melanoma were positive, which further confirmed that the expression of SGOL1 in melanoma was up-regulated compared with normal tissues. At the same time, it is suggested that SGOL1 may have potential value in the differential diagnosis of melanoma, benign nevus and atypical nevus. To sum up, our research firstly emphasize the important role of SGOL1 in the metastasis of SKCM and SCKM. The high expression of SGOL1 is related to the poor prognosis of skin melanoma, suggesting that SGOL1 may be a new immune target for the treatment of skin melanoma.

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Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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