Original Article

B7-H3 regulates migration and invasion in salivary gland adenoid cystic carcinoma via the JAK2/STAT3 signaling pathway

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Abstract: B7 Homolog 3 (B7-H3), a newly identified member of the B7 family, is over-expressed in various human cancers and plays a vital role in tumor progression. To identify the expression pattern of B7-H3 in human salivary adenoid cystic carcinoma (AdCC) and its underlying mechanisms, we characterized B7-H3 expression in AdCC tissues microarrays using immunohistochemical staining, and analyzed potentially associated molecules. The results showed that B7-H3 was highly expressed in salivary AdCC, compared with normal salivary glands. Statistical analyses of immunohistochemical staining showed that B7-H3 was closely correlated with Slug and p-STAT3. Functional studies showed that knockdown of B7-H3 in AdCC cell lines using RNA interference did not influence cell growth and apoptosis, but decreased migration and invasion in vitro. Further mechanism studies suggested that B7-H3 influenced the migration and invasion of AdCC cells by regulating the epithelial-mesenchymal transition via JAK2/STAT3 pathway components. Collectively, these findings suggested that B7-H3 may be a potential therapeutic target for AdCC.

Keywords: B7-H3, adenoid cystic carcinoma, epithelial-mesenchymal transition, JAK2, STAT3

Introduction

Adenoid cystic carcinomas (AdCC) are rare variants of adenocarcinoma that most often arise in the salivary glands [1]. Clinical studies indicated that salivary AdCC were characterized by invasive local growth and a high incidence of lung metastasis [2]. Patients with lung metastasis of the salivary AdCC have poor prognoses [3]. However, the precise mechanisms underlying invasion and metastasis in AdCC are not known. Therefore, there is an urgent need to develop new agents and strategies with high efficacy for the treatment of salivary AdCC.

B7 homolog 3 protein (B7-H3), a transmembrane protein with an immunoglobulin-like structure [4], is known to have immunoregulatory properties, with both inhibitory and stimulatory effects on the activation of T cells [5, 6]. As a tumor-associated antigen, B7-H3 is not only involved in tumor immunity, but also plays a non-immunological role in cancer progression. A recent report suggested that over-expression of B7-H3 promoted cutaneous malignant melanoma cell migration and invasion [7]. In addition, the functional knockdown of B7-H3 suppressed the proliferation, colony formation, migration, and invasion in human esophageal cancer [8]. These results strongly suggest that B7-H3 is involved in cancer progression and metastasis.

The epithelial-mesenchymal transition (EMT) process consists of a set of rapid changes in the cellular phenotype during which epithelial cells experience a molecular switch from a polarized, epithelial phenotype to a highly motile, non-polarized mesenchymal phenotype [9, 10]. The EMT is frequently observed at the invasive front of advanced tumors and significantly correlated with metastasis in tumor progression [11-13]. However, whether B7-H3 influ-
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ences the EMT in salivary AdCC remains unclear.

In the present study, B7-H3 and EMT molecules expression in salivary AdCC tissue were observed based on serial sections. Tissue microarrays were used to explore the associated molecules. In addition, we determined the function and mechanism of B7-H3 using in vitro knockdown assays of B7-H3.

**Materials and methods**

**Cell lines, antibodies and reagent**

Human salivary AdCC cell lines SACC-83 and SACC-LM were obtained from the China Center for Type Culture Collection, and grown in RPMI 1640 medium (HyClone) containing 10% FBS (fetal bovine serum) [14]. Chemical reagents for experiment were purchased from Sigma-Aldrich (St. Louis, MO), unless otherwise specified. B7-H3 siRNAs were purchased from Sigma-Aldrich with 2 different sequences. Primary antibody against human B7-H3, E-cadherin, N-cadherin, Vimentin, Slug and p-STAT3 were purchased from Cell Signaling Technology (Danvers, MA).

**B7-H3 siRNA transfection**

To further analyze the role of B7-H3 in AdCC malignancy, human SACC-83 and SACC-LM cell lines were transfected with B7-H3 siRNA using lipofectamine 2000 (Invitrogen, Carlsbad, CA) as previously been described [14]. The sequences of the B7-H3 are 5'-TGAAACACTCTGGACAGAAAGATGA-3' (siB7-H3-1) and 5'-AGCACATGTGGTTCTGCCTCACA-3' (siB7-H3-2). The validated non-targeted control (negative control) sequence was 5'-GCACTACCAGAGCTAACT-3', while mock transfections (Mock) were carried out with lipofectamine 2000 transfection reagent only. After 48 h, transfected cells were harvested for Western blotting analysis.

**Cell proliferation by MTT assay**

The MTT assay was used to study the effect of B7-H3 RNA interference on AdCC cell viability as previously described [15]. Briefly, cells were suspended at a density of 5 × 10^3 cells per well in 200 μl of RPMI 1640 medium in 96-well plates, and continue cultured overnight. The medium was replaced with 100 μl fresh medium containing 0.5 mg/ml MTT (Sigma, USA) at indicated time points. Four hours after the co-culture with MTT, the supernatants were removed and discarded. 150 μl of dimethylsulfoxide (DMSO, Sigma) was added to each well to dissolve the crystals. Cell viability was determined by scanning with a microplate reader at a wavelength of 490 nm. Each experiment was performed in triplicate and repeated at least three times.

**Wound healing assay**

In vitro wound healing assay was performed as described previously [16]. Briefly, SACC-83 and SACC-LM cell lines were seeded in 6-well plates (Corning Life Sciences, USA) at 1.0 × 10^5 cells/well. When the cells reached 80% confluence, the center of each well was scratched with a sterile pipette tip to generate a constant gap. The cells were continued incubated with serum free medium for additional 24 hours. The cells were photographed under phase microscopy and counted after fixation as previously described [16].

**Transwell migration assays**

In vitro migration assay was performed using 8 μm pore size Transwell® inserts (#3422, Corning, Albany, NY) as described previously [17]. Briefly, 10^4 cells were placed on the top of the Transwell® chamber inserts. Serum (5%) was used as the chemoattractant. To rule out the effect of cell proliferation, 2 μg ml^-1 mitomycin C was added to the cells. Cells on the lower surface of the inserts were stained and counted using a light microscope.

**Cell immunofluorescence**

SACC-83 and SACC-LM cell lines were seeded onto coverslips at a density of 10^5/mL and cultured in a 6-well plate for 24 hours with the indicated treatment. After treatment, cells were washed twice in PBS and fixed in 4% paraformaldehyde for 30 minutes. Then cells were permeabilized in 0.2% Triton X-100 in PBS for 15 minutes, and blocked by non-immune goat serum for 60 minutes at room temperature. Then cells were incubated with indicated primary antibody at 4°C overnight respectively.

The next day, slides were incubated with fluorochrome conjugated secondary antibodies (PerCP-Cy5.5 anti-rabbit, Jackson ImmunoRe-
search, USA) and mounted in Vectashield with 4', 6-diamidino-2-phenylindole (DAPI; Vector Laboratories). Fluorescence images were then captured using a CLSM-310, Zeiss fluorescence microscope.

**Western blot analysis**

Western blot analysis was performed as previously described [18]. Briefly, SACC-83 and SACC-LM cell lines were transfected with B7-H3 siRNA (100 nM, Sigma-Aldrich), mock, and negative control siRNA. The cells were lysed in a T-PER buffer containing 1% phosphatase inhibitors and complete mini cocktail (Roche) 48 h after transfection. Proteins from each sample were denatured and then loaded in each lane of 12% SEMS polyacrylamide gel electrophoresis. Subsequently, proteins were transferred onto a polyvinylidene fluoride membrane (Millipore, Billerica, MA) and blocked with 5% non-fat milk for 1 hour, then incubated with following primary antibody B7-H3, JAK2, p-JAK2, STAT3, and p-STAT3 at 1:1000 dilution. After overnight incubation at 4°C, membranes were washed for three times and then incubated with second antibody for 1 h at room temperature and visualized with enhanced chemi-luminescence.

**Human salivary AdCC tissue microarray**

The human salivary gland AdCC specimen tissue microarrays used in the present study were obtained from the Department of Oral and Maxillofacial Surgery, School and Hospital of Stomatologiy Wuhan University (PI: Zhi-Jun Sun) [14]. All patients histologically diagnosed as AdCC by two independent pathologists were included in the present study. The classification of the World Health Organization was used to determine the histologic phenotype. The AdCC cohort consisted of 72 AdCCs (cribriform pattern: 28, tubular pattern 24, solid pattern 20), 12 PMAs and 18 NSGs as previously described [14].

**Immunohistochemistry, digital pathology and scoring system**

The methods and processes of immunohistochemistry were previously reported [19]. Briefly, all AdCC tissue microarrays were cut into 4-µm sections. The slides were deparaffinized and rehydrated. The sections were boiled in 0.01 M citric acid buffer solution (pH 6.0) or 1 mM EDTA buffer solution (pH 8.0) for 1.5 min at high pressure. Subsequently, the samples were incubated with 3% hydrogen superoxide for 20 minutes to quench endogenous peroxidase activity, and 10% goat serum was used to block non-specific binding. The sections were incubated with anti-human B7-H3 (1:200), Slug (1:200), p-STAT3 (1:200). A positive slide was set at each experiment. Subsequently, an avidin-biotin peroxidase reagent was added onto the slides. After washing with phosphate buffer saline, 3,3'-diaminobenzidine tetrachloride was added to the sections, followed by counterstaining with Mayer’s hematoxylin.

The immunohistochemical staining was scanned using an Aperio ScanScope CS whole slice scanner (Vista, CA, USA) with background subtraction as previously described [21]. The membrane, nuclear, or pixel immunohistochemical staining was quantified using Aperio Quantification software. The histoscore of the membrane and nuclear staining quantification were assessed according to the formula (3 + percent cells) × 3 + (2 + percent cells) × 2 + (1 + percent cells) × 1, and the formula total intensity/total cell number was used to assess the histoscore of pixel quantification. In this case, the normalized score is between 0 and 300. This method has previously been described [22]. The immunohistochemical staining histoscores were converted to the range of -3 to 3 using Microsoft Excel software as previously described [23]. Cluster 3.0 with average linkage based on Pearson’s correlation coefficient was used for hierarchical analysis, and the results were visualized using Java TreeView 1.0.5.

**Statistical analysis**

All values are expressed as the means ± SEM. The statistical data analysis was performed using GraphPad Prism 5.03 (GraphPad Software, Inc., La Jolla, CA) statistical package. The differences in immunostaining and protein levels among each group were analyzed by the one-way ANOVA followed by the post-Tukey multiple comparison tests. Student’s t-test was used for two-group analysis. All experiments were independently repeated in triplicate. P < 0.05 was regarded as statistical significance; all tests were two-sided and no correction was applied.
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A

NSG | PMA | AdCC
---|---|---
B7-H3

B

Histoscore of B7-H3

C

Histoscore of B7-H3

D

E

Histoscore of p-STAT3

F

Cluster 1 | Cluster 2
---|---
B7-H3 | Slug | p-STAT3
B7-H3 regulates AdCC metastasis via JAK2/STAT3 pathway

Figure 1. B7-H3 immunoreactivity is significantly increased in salivary AdCC, which is correlated with expression of Slug and p-STAT3. A. Representative immunohistochemical staining of B7-H3 in human AdCC tissue (right panel) compared with normal salivary gland (NSG, left panel) and pleomorphic adenoma (PMA, middle panel) (Scale bars = 50 μm); B. Quantification of B7-H3 immunohistochemical expression levels in human NSG, PMA and AdCC tissue as indicated by histoscore (***P < 0.01; ****P < 0.001, One-way ANOVA with GraphPad Prism 5.0); C. Comparison between different pathological types of B7-H3, expression of B7-H3 was not statistically different between cribriform, tubular and solid type of human salivary AdCC. D. Representative hematoxylin-eosin staining (HE) and immunohisostaining of B7-H3, Slug and p-STAT3 in human salivary AdCC tissue (Scale bars = 50 μm); E. B7-H3 was found to be closely associated the Slug (P < 0.001, r = 0.4211) and p-STAT3 (P < 0.05, r = 0.2316) immunoreactivity. F. Hierarchical clustering presents the protein expression correlation of B7-H3, p-STAT3 and Slug in human AdCC tissue microarrays.

Results

B7-H3 immunoreactivity was significantly increased and correlated with Slug and p-STAT3 in salivary AdCC

Immunohistochemistry for B7-H3 was performed on tissue microarrays, including human AdCC (n = 72), common salivary gland benign tumor polymorphic adenoma (PMA, n = 12), and normal salivary glands (NSG, n = 25). The results indicated that B7-H3 immunoreactivity was weakly expressed in NSG and PMA tissues, whereas AdCC showed strong protein expression in the tumor cells, especially at the invasive front (Figure 1A). To more precisely determine the difference, we quantified the expression using Aperio ImageScope software, version 12.0 (Leica Biosystems, Buffalo Grove, IL, USA). The results showed that B7-H3 was significantly increased in AdCC compared with PMA (P < 0.01) and NSG (P < 0.001; Figure 1B). However, B7-H3 was not associated with the pathological parameters of different subtypes (cribriform, tubular and solid type) of AdCC (Figure 1C). To investigate the possible relation of B7-H3 with EMT marker Slug and p-STAT3, the immunostaining of Slug and p-STAT3 were performed based on serial section of tissue microarrays (Figure 1D). Quantification of immunohistochemistry of AdCC and normal oral mucosa tissues indicated by histoscores showed that B7-H3 was statistically associated with p-STAT3 (P < 0.05, r = 0.2316; Figure 1E) and Slug (P < 0.001, r = 0.4211; Figure 1E) as assessed by the Spearman’s rank correlation coefficient test and the linear regression tendency test. Notably, the expression of B7-H3, p-STAT3, and Slug, in most of the AdCC cases (cluster 2), were distinct from those of the normal mucosa (cluster 1), the hierarchical cluster reflecting the correlation of in B7-H3 with Slug staining in AdCC (Figure 1F).

Knockdown of B7-H3 showed no effect on AdCC cell proliferation

To characterize the role of B7-H3 in AdCC, two different siRNAs were designed for knockdown of B7-H3 (Figure 2A, 2B). The knockdown efficiency of B7-H3 was > 70% (Figure 2A, 2B). We then measured the cell proliferation rate in vitro using the MTT assay. The results showed that there was no difference in cellular proliferation between the B7-H3 knockdown group and the control group in both the SACC-83 and SACC-LM cell lines (Figure 2C, 2D).

Knockdown of B7-H3 by RNA interference decreased AdCC cell migration and invasion

To further determine the relationship of B7-H3 with cell migration and invasion, we employed wound healing assays to examine the cytochemical effects of B7-H3 on the migration ability of AdCC cells, and Transwell® invasion assays to determine the key factors involved in malignant progression and metastasis during B7-H3 downregulation. The knockdown of B7-H3 significantly decreased the cell mobility of SACC-83 (P < 0.01, Figure 3A) and SACC-LM (P < 0.01, Figure 3B) cells as indicated by in vitro wound healing assay 24 hours between the negative control group and the B7-H3 siRNA treatment group. Likewise, the results of the Transwell® assay also showed that knockdown of B7-H3 significantly decreased the transmembrane cell numbers compared with that of the negative control group, in SACC-83 and SACC-LM cells without (migration assay, Figure 3C) or without Matrigel coating (invasive assay, Figure 3D).
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Knockdown of B7-H3 by siRNA suppressed the invasion and migration of AdCC cells by regulating the EMT via the JAK2/STAT3/Slug signaling pathway.

On the basis of the correlation between B7-H3 and the EMT marker (Slug), we hypothesized that B7-H3 influenced the EMT progression. siRNA was used to knock down B7-H3, and changes in EMT were determined by Western blotting of the putative EMT markers. The results showed that B7-H3 was involved in the EMT of AdCC cells. After knockdown of B7-H3, the expression of E-cadherin was upregulated, while N-cadherin, Slug, and vimentin were downregulated in the B7-H3 silenced groups compared with the negative control group in both the SACC-83 cells (Figure 4A) and the SACC-LM cells (Figure 4B). Furthermore, we detected the expression in the cell lines using immunofluorescence microscopy. Similar results were observed in SACC-83 cells (Figure 4C).
B7-H3 regulates AdCC metastasis via JAK2/STAT3 pathway

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Cell migration assay

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Cell invasion

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B7-H3 regulates AdCC metastasis via JAK2/STAT3 pathway

4C) and SACC-LM cells (Figure 4D), with decreased vimentin and increased E-cadherin after knockdown of B7-H3. These results suggested that B7-H3 regulated the progression of EMT in AdCC.

The JAK2/STAT3 pathway is critical for cytokine and growth factor-mediated responses that regulate the EMT in fibrogenesis and cancer [20-22]. Because of the reported relationship between STAT3 and AdCC [17], and the role of STAT3 in cell motility and the EMT [22, 23], our study sought to directly examine the role of this pathway in B7-H3-induced EMT in AdCC cells. After transfection with B7-H3 siRNA, the phosphorylation of STAT3 and JAK2 was dramatically reduced in SACC-83 and SACC-LM cells, compared to that seen in the negative control group (Figure 4E, 4F). However, the protein levels of JAK2 and STAT3 were not significantly changed (Figure 4E, 4F). These results could explain, at least partially, the regulation of the EMT process by B7-H3, as being via the activation the JAK2/STAT3/Slug signaling pathway.

Discussion

In this study, we showed that the B7-H3 expression was significantly upregulated in human salivary AdCC, which was not associated with a subtype of salivary AdCC. On the basis of the AdCC tissue microarray results, we found that B7-H3 correlated with the levels of Slug and p-STAT3. Furthermore, in vitro functional studies suggested that knockdown of B7-H3 in AdCC cells decreased cell migration but had no effect on cell viability and apoptosis. Additionally, B7-H3 may have promoted the AdCC EMT via the JAK2/STAT3/Slug signaling pathway.

The remarkable clinical successes obtained from blocking the B7 superfamily of ligands, such as CTLA-4 and PD-1, have shown potential for cancer immunotherapy by inhibiting more recently discovered checkpoint ligands and receptors [24]. However, the tumor-associated antigen, B7-H3 has not only been attributed to tumor immunity but also may play a non-immunological role in cancer progression [4, 25-28]. Recent studies have reported that B7-H3 over-expression was observed in various cancers [8, 28, 29]. Consistent with these findings, immunohistochemical staining indicated that aberrant positive expression of B7-H3 in human salivary AdCC was observed in comparison with that of normal salivary glands, although B7-H3 expression was the same among cribriform, tubular, and solid subtypes of AdCC.

EMT is frequently observed at the invasive front of advanced tumors and significantly correlates with metastasis in tumor progression [11, 12]. EMT is a key event for cancerous cells to acquire the capability of migration and invasion [30, 31]. These processes are tightly temporally and spatially regulated by the expression and activation of many signal molecules [32-34]. A recent report suggested that Slug is the key molecule regulating EMT programming in cancer [35]. We have previously reported that Slug-mediated EMT plays an important role in the process of metastasis [16]. In addition, the replacement of E-cadherin by N-cadherin during the EMT promoted the invasiveness and metastasis of tumor cells [36]. When we determined the variation of EMT markers, the results showed up-regulation of an epithelial marker, whereas the down-regulation of the mesenchymal markers N-cadherin and Slug were as predicted.

Our previous study demonstrated that targeting STAT3 reduced the migration and invasion of AdCC cells [17]. In present study, we found that the expression of B7-H3 was positively associated with p-STAT3 level. We also observed that p-JAK2 and p-STAT3 were down-regulated after the knockdown of B7-H3. In agreement with previous findings, B7-H3 regulated JAK2/STAT3 signaling in colorectal cancer and hepatocellu-
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Figure 4. Knockdown of B7-H3 suppresses the EMT via JAK2/STAT3/Slug signaling. A, B. Knockdown of B7-H3 using siRNA decreased the EMT in SACC-83 and SACC-LM cell lines, as indicated by increased E-cadherin and decreased N-cadherin, Vimentin and Slug by Western blotting. GAPDH was used as a loading control. The quantification of blotting are presented as the means ± SEM by 3 different experiments. One-way ANOVA with post-Tukey analysis was performed using GraphPad Prism5. *P < 0.05; **P < 0.01; ***P < 0.001 versus the negative control group (NC, n = 3); Mock, mock transfection. C, D. The representative immunofluorescence of B7-H3, E-cadherin and Vimentin of B7-H3 knockdown in SACC-83 and SACC-LM cell lines compared with negative control (NC) and mock counterpart (Scale bars = 50 μm); E, F. Knockdown B7-H3 decreased JAK2/p-STAT3 signaling in SACC-83 and SACC-LM cell lines as indicated by the JAK2, p-JAK2, STAT3 and p-STAT3T705 Western blotting. GAPDH was used as a loading control. The values are presented as the means ± SEM. One-way ANOVA with post-Dunnett analysis was performed using GraphPad Prism5. *P < 0.05, **P < 0.01; versus the negative control group (n = 3) Mock, mock transfection.

lar carcinoma [32, 37]. Based on these results and those from previous reports, we confirmed the close relationship between B7-H3 and JAK2/STAT3 signaling.

In conclusion, this study demonstrated that B7-H3 was up-regulated in the salivary AdCC. B7-H3 knockdown inhibited the EMT process, and the JAK2/STAT3 signaling pathway played an important role in this process. These findings supported the possibility of using B7-H3 as a target for anti-metastatic therapy in salivary AdCC.

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Disclosure of conflict of interest

None.

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