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LETTER TO EDITOR

Elevated Expression of CD109 in Esophageal Squamous Cell Carcinoma

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To the Editor,

Esophageal squamous cell carcinoma (ESCC) accounts for approximately one-sixth of all cancer-related mortality, occurring at a higher incidence in Asian countries [1]. Though the effectiveness of surgical treatments has significantly improved, the prognosis of ESCC remains poor, with a 5-year survival rate of less than 10 % [1]. Recent studies suggest that the transforming growth factor-β (TGF-β) signaling may involve in malignancy development of ESCC [2, 3]. Altered expression of TGF-β receptors contributes to ESCC progression, and elevated expression of inhibitory proteins of TGF-β signaling correlates with poor prognosis of ESCC [2]. CD109, a member of the α2-macroglobulin/complement family, is a co-receptor of TGF-β1 [4]. CD109 suppresses TGF-β signaling by promoting internalization of TGF-β receptors [4]. The transcription of CD109 is up-regulated in some ESCC samples [5]. However, the protein level of CD109 in ESCCs has not yet been examined. In this limited study, CD109 expression in ESCCs was determined by immunohistochemistry on tissue microarrays (TMA).

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The TMAs were purchased from US Biomax, Inc (Rockville, MD), which include specimens of esophagus from 79 ESCC patients and 3 healthy donors. The information of the ESCC specimens including TMN stage and differentiation level was provided by the manufacturer (http://www.biomax.us/tissue-arrays/Esophagus/ES1021). The TMAs were stained using a rabbit anti-CD109 antibody (HPA009292, Sigma-Aldrich, St. Louis, MO) with appropriate controls, and photographed by OLYMPUS FSX100 imaging system (Olympus, Tokyo, Japan). The images were analyzed by ImagePro Plus (Media Cybernetics, Silver Spring, MD, USA), and intensity of cytoplasmic staining (ICS) was calculated for evaluation of CD109 expression as previously described [6].

In the non-diseased esophageal tissue, CD109 expression was restricted in cytosol of the stratified epithelial cells at a weak level (Fig. 1a). In all the ESCC samples, strands of malignant squamous epithelial cells displayed strong brownish CD109 staining in the cytosol (Fig. 1b, c, d). No positive staining was observed in other cell types. The ICS of CD109 is significantly higher in ESCCs than in normal esophagus (0.04±0.003 vs. 0.007±0.001, $p<0.05$) (Fig. 2a). For tumor grade, CD109 expression was higher in well- and moderately-differentiated ESCCs than the poorly differentiated ones (ICS: 0.054±0.006 vs. 0.025±0.004, $p<0.05$;0.042±0.004 vs. 0.025±0.004,$p<0.05$) (Fig. 2b). No statistical difference of ICS was found between well- and moderately-differentiated ESCCs ($p=0.12$). CD109 expression was not significantly correlated with gender ($p=0.25$), age ($p=0.52$), and invasion depth ($p=0.43$).

To our knowledge, this is the first report showing elevated CD109 protein expression in ESCCs. Higher

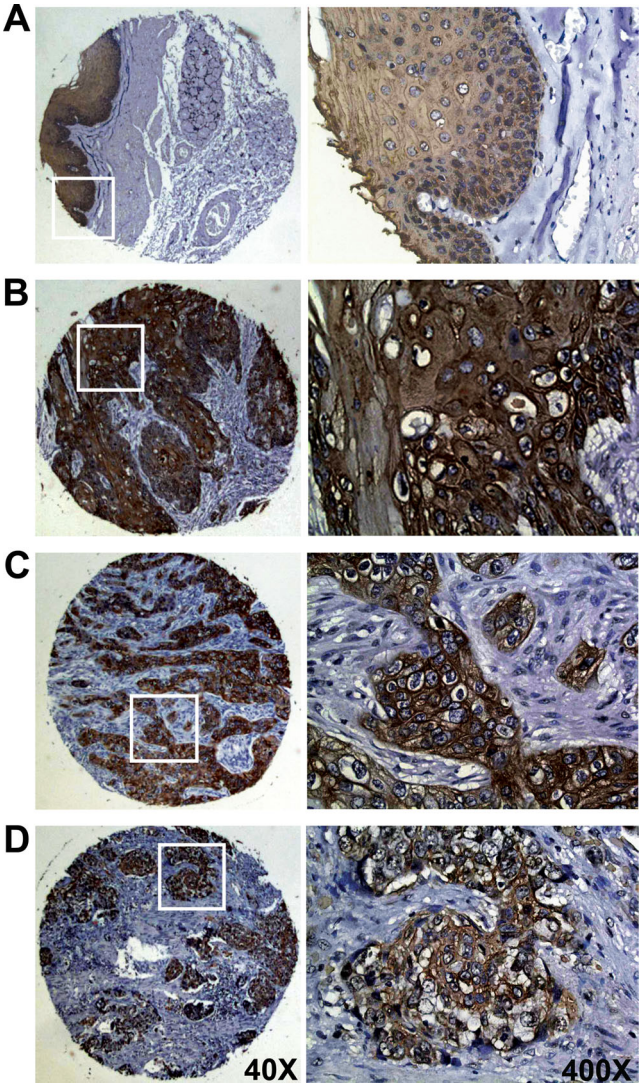

Fig. 1 Expression pattern of CD109 in ESCC. **a**–**d** Representative images of CD109 immunostaining on normal esophageal tissue (**a**), well-differentiated ESCC (**b**), moderately-differentiated ESCC (**c**), and poorly-differentiated ESCC (**d**) at 40× and 400× magnification

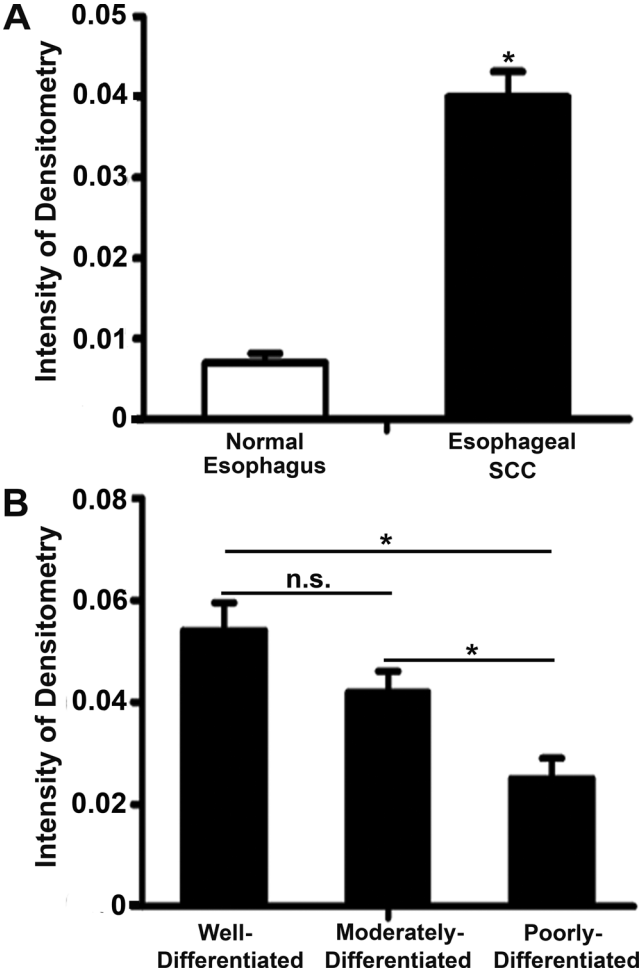

Fig. 2 Analyses of CD109 expression in ESCC. **a** Analyses of CD109 expression level in normal esophagus and ESCC; *, $p<0.05$; **b**, CD109 expression level in well-, moderately-, and poorly differentiated ESCC; *, $p<0.05$; n.s., non-significant. *Error bars* represent standard error of the mean

level of CD109 protein expression was also observed in SCCs of lung, vulva, uterine cervix and oral cavity [7–9, 6]. Thus, malignant transformation of squamous cells might up-regulate CD109 expression. Our results are also consistent with the previous studies demonstrating a negative correlation between CD109 expression and tumor grade of SCCs [6, 10]. By repressing TGF-β signaling, CD109 may participate in the regulation of progression and differentiation of ESCC. In addition, we found that CD109 expression is restricted in squamous cells of ESCCs. As a receptor on cell surface, CD109 is a potential target for developing new therapeutics for ESCC. Further studies are needed to determine the detailed role of CD109 in ESCC and the underlying molecular mechanisms.

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Specific author contributions:

FD, FL, YS, XL: Data collection, analysis and interpretation; drafting the manuscript; final approval of the version to be published.

ZJ, JL: project conception/initiation; experimental design; drafting of the manuscript; critical revision; final approval of the version to be published.

Conflict of interest None

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