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Consideration of EphA2 in relation to epithelial-mesenchymal transition in uterine endometrial cancer

To the editor: For decades, the mechanisms of cancer cell metastasis have been critical subject in the field of cancer research. Among them, the epithelial-mesenchymal transition (Emt) and mesenchymal-epithelial transition (MET) have been, currently, acknowledged as a crucial process by which carcinoma cells are acquired metastatic phenotype such as invasion of vessels and distant colonization, as well as a physiologic process during embryonic development.

In the volume 25 January, a research article regarding the correlation between the overexpression of epidermal growth factor receptor (EGFR) and EMT makers in endometrial cancer gave us the result that mesenchymal markers (N-cadherin and vimentin) was overexpressed in advanced stage and high grade tissue specimens of patients and also the upregulation of mesenchymal markers was observed in KLE cells and Ishikawa cells transfected with EGFR [1].

EphA2, a member of the biggest subfamily of RTKs, could be recognized as a molecular target based on the growing evidence that high levels of it promote various aspects of malignant phenotype, including proliferation, invasion, angiogenesis and survival of cancer cells. My previous research showed that high EphA2 expression and high angiogenesis makers were significantly associated with shorter disease-specific survival in tissue specimens of patients with endometrial cancer, and also the therapy using EphA2 agonist monoclonal antibody led to tumor inhibition over controls in murine orthotopic xenograft model made by Hec1A and Ishikawa cells [2].

Interestingly, several research papers regarding the correlation between EphA2 and EMT were currently published. Huang et al. [3] reported that EphA2 promotes EMT in gastric cancer cells and demonstrated that the promoting effect of EphA2 on EMT was made through the Wnt/β-catenin pathway based on the experiments employing the inhibitor and activator of that pathway. Additionally, Giannoni et al. [4] reported that mesenchymal-amoeboid transition, a second type of motility shifting process in cancer cells induced by endothelial progenitor cells, was mediated through the bidirectional ephrinA1/EphA2 signaling. Thereby, EphA2 could be also considered as a regulator in relation to epithelial-mesenchymal transition in endometrial cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Yang WN, Ai ZH, Wang J, Xu YL, Teng YC. Correlation between the overexpression of epidermal growth factor receptor and mesenchymal makers in endometrial carcinoma. J Gynecol Oncol 2014;25:36-42.
2. Merritt WM, Kamat AA, Hwang JY, Bottsford-Miller J, Lu C, Lin YG, et al. Clinical and biological impact of EphA2 overexpression and angiogenesis in endometrial cancer. Cancer Biol Ther 2010;10:1306-14.
3. Huang J, Xiao D, Li G, Ma J, Chen P, Yuan W, et al. EphA2 promotes epithelial-mesenchymal transition through the Wnt/β-catenin pathway in gastric cancer cells. Oncogene 2013 Jun 10 [Epub]. http://dx.doi.org/10.1038/onc.2013.238.
4. Giannoni E, Taddei ML, Parri M, Bianchini F, Santosuosso M, Grifantini R, et al. EphA2-mediated mesenchymal-amoeboid transition induced by endothelial progenitor cells enhances metastatic spread due to cancer-associated fibroblasts. J Mol Med (Berl) 2013;91:103-15.

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Reply to JY Hwang

We are grateful to Dr. Hwang for the interest and comment on our research "Correlation between the overexpression of epidermal growth factor receptor and mesenchymal makers in endometrial carcinoma." [1].

As you mentioned, lots of researches have proved the epithelial-mesenchymal transition (EMT) of cancer cells, which can severely affect the prognosis of patients. The purpose of our study was to discover the EMT situation of the epidermal growth factor receptor (EGFR) overexpressing endometrial carcinoma cells no matter they were KLE cells or Ishikawa cells transfected with EGFR. Meanwhile using RNA interference to inhibit EGFR gene expression could partially reverse the expression of EMT related genes in endometrial carcinoma cells [2]. It was verified by determining the expression of epithelial cell markers (E-cadherin and α-catenin) and mesenchymal cell markers (N-cadherin and vimentin). Clinical studies also indicated the expression of EMT markers were related to histologic grade and stage, myometrial invasion, lymph node metastasis and survival rate. Thus we suggested EGFR could be an indicator for the assessment of prognosis and could be used in gene therapy. However our study has not gone far enough to describe how EGFR works on signal transduction or the EGFR activating mechanism to make cancer cells EMT. We will continue to work on this.

As EphA2 gains more attention in cancer researches, some researchers start to focus on the correlation between EphA2 and cancer cell EMT [3]. Further studies found that the overexpression of EGFR could regulate EphA2 to affect cancer cells [4]. Larsen et al. [5] reported that EphA2 expression in cultured cells *in vitro* was determined by the activating of EGFR, mitogen activated protein kinase kinase (MEK) and Src family kinases (SRC). Inhibiting the EGFR ligand system favoring Ras/MAPK signaling pathway could decrease cell viability. Thus, they proposed that inhibiting EGFR activating and EphA2 expression could change the cell viability in human cancer cells. Another research indicated the higher expression of EphA2 and ephrin-A1 in non-small cell lung cancer (NSCLC) patients was more related to the female sex, reduced smoking status, adenocarcinoma, well differentiated carcinomas, p-stage IA, and EGFR gene mutations. The expression of EphA2 and ephrin-A1 in NSCLC patients was related to the prognosis [6].

Therefore we have reasons to believe that EphA2 is related to cancer cell EMT. EphA2 expression may be influenced by EGFR expression through regulating Ras/MAPK signaling pathway and may eventually affect the prognosis and survival rate. However we still need further researches to provide evidence for this conclusion.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Yang WN, Ai ZH, Wang J, Xu YL, Teng YC. Correlation between the overexpression of epidermal growth factor receptor and mesenchymal makers in endometrial carcinoma. J Gynecol Oncol 2014;25:36-42.
2. Xu W, Wang J, Xu YL, Ma L, Ai ZH, Teng YC. Influence of inhibition of EGFR gene expression by RNA interference on epithelial-mesenchymal transition in endometrial carcinoma cells. Shanghai Jiao Tong Da Xue Xue Bao Yi Xue Ban 2013;33:415-20.
3. Fan M, Liu Y, Xia F, Wang Z, Huang Y, Li J, et al. Increased expression of EphA2 and E-N cadherin switch in primary hepatocellular carcinoma. Tumori 2013;99:689-96.
4. Larsen AB, Pedersen MW, Stockhausen MT, Grandal MV, van Deurs B, Poulsen HS. Activation of the EGFR gene target EphA2 inhibits epidermal growth factor-induced cancer cell motility. Mol Cancer Res 2007;5:283-93.
5. Larsen AB, Stockhausen MT, Poulsen HS. Cell adhesion and EGFR activation regulate EphA2 expression in cancer. Cell Signal 2010;22:636-44.
6. Ishikawa M, Miyahara R, Sonobe M, Horiuchi M, Mennju T, Nakayama E, et al. Higher expression of EphA2 and ephrin-A1 is related to favorable clinicopathological features in pathological stage I non-small cell lung carcinoma. Lung Cancer 2012;76:431-8.

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