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Editorial

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Intrinsic and Acquired Paclitaxel Resistance in Esophageal Squamous Cancer Cells

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Editorial

Single-cell transcriptomes analyses lead to a more accurate representation of cell-to-cell variations instead of the stochastic average reflected by bulk measurements [1]. It has been a promising technique to identify subpopulations in a multicellular system. In the paired paclitaxel sensitive and resistance cancer cell lines, Esophageal Squamous Cancer (ESCC) cell line KYSE-30 and Taxol-R-KYSE-30, single-cell and bulk transcriptome analysis were performed respectively, indicating that the categorization of cancer subpopulations with intrinsic and acquired paclitaxel resistance could be marked with the expression level of KRT19 and proteasome genes, respectively. This study provides a novel finding for the heterogeneity of esophageal cancer cells in response to paclitaxel treatment at single-cell transcriptome level, which could improve the understanding of molecular mechanisms involved in paclitaxel-resistance.

In primary KYSE-30 cancer cells, we identified and validated that KRT19 was a cell surface marker for the intrinsic paclitaxel resistance, which is consistent with the study from Qiao. YF et al. reporting that KRT19 mRNA level negatively correlated with prognosis of ESCC patients [2]. In addition, De Angelis PM. et al. reported that KRT19 was involved in response to 5-FU therapies [3]. We also found that KRT19 was related to worse prognosis in KIRC, LUAD and PAAD in database of OncoLnc (www.oncolnc.org), and the expression level of KRT19 was correlated with the survival of lung squamous carcinoma and gastric carcinoma which were treated with chemotherapy in the Kaplan Meier plotter (http://kmplot.com/). Another cell surface marker in the intrinsic paclitaxel resistant cancer cells was CD40, which can inhibit paclitaxel-induced apoptosis in breast cancer [4-6]. Furthermore, we analyzed all the highly expressed genes in intrinsic paclitaxel resistant cancer cells. These genes were significantly enriched in the signaling of pathway in cancer (p-value = 0.0075) and transcriptional dysregulation in cancer (p-value = 0.035). However, the contributory roles and detailed mechanisms to paclitaxel resistance of biomarkers (KRT19 and CD40) and affected signaling pathways still need to be assessed in the future studies.

In the resistant cancer cells (Taxol-R-KYSE-30), low level expression of HIF-1a signaling and high expression of proteasome signaling were identified to be responsible for their paclitaxel resistance. The expression level of proteasome genes was significantly enriched in the Taxol-R-KYSE-30, and the correlation of high proteasome activation and paclitaxel resistance was also reported in other studies [7-9]. We also found that diverse expression of proteasome genes in the TCGA database of ESCC patients (Figure A). Some ESCC patients have high expression level of proteasome genes, and they correlate with poor prognosis (Figure B), which may be due to the primary resistance to therapeutic treatments.

Taking together, although paclitaxel has been widely used as a first-line therapeutic strategy in ESCC, even in combination with other chemical drugs, the overall survival is still to be improved. In that case, more precise treatment for ESCC patients need be considered to avoid the intrinsic and acquired paclitaxel resistance (Figure C). The markers KRT19, CD40 and proteasome genes that we identified for intrinsic and acquired paclitaxel resistance of ESCC, should be investigated before the treatment of paclitaxel. Classification of ESCC patients into paclitaxel sensitive or resistant groups will lead to improved treatment. And for the intrinsic paclitaxel resistance, the combination of target therapy and proteasome inhibitors could be a novel approach for the clinical treatment of ESCC.

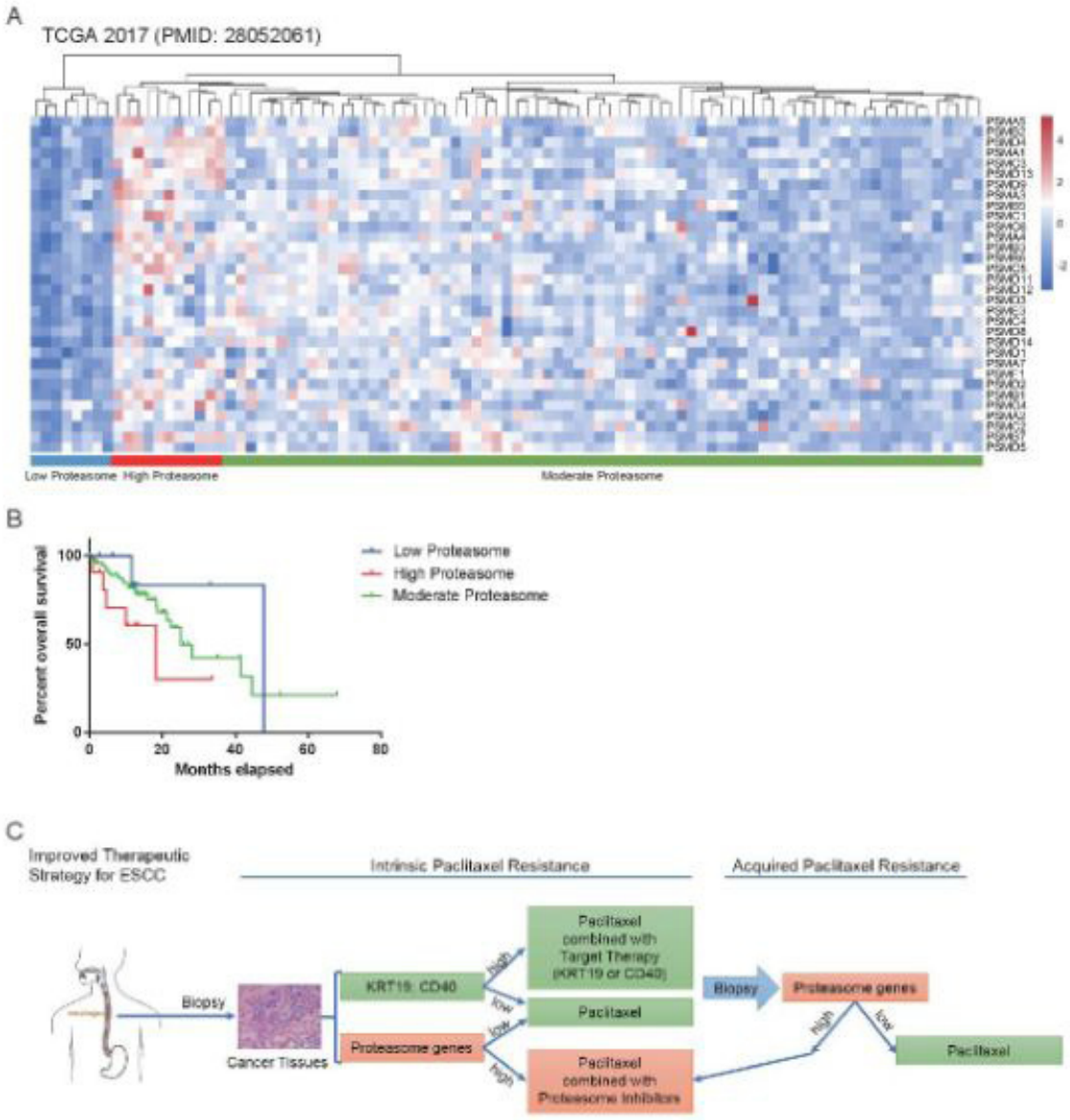

Figure 1: Precision treatment for ESCC.

A. A. RNA expression of proteasome signaling genes in TCGA database of ESCC (PMID: 28052061), Expression ratio = Log2(FPKM). The ESCC patients were clustered into three subgroups according to the expression level of proteasome genes (Low Proteasome, High Proteasome, and Moderate Proteasome). The majority of ESCC patients show moderate expression of proteasome genes.

B. B. Highly expressed proteasome genes correlate with poor prognosis and overall survival in TCGA. The overall survival of patients with moderate expression of proteasome genes were much longer than the patients with high expression of proteasome genes, but shorter than the patients with low expression of proteasome genes.

C. C. Suggested improved therapeutic strategies for ESCC treatment. Tumor tissues of ESCC patients were obtained with biopsy, and the expression of KRT19, CD40, and proteasome genes were investigated with qRT-PCR or RNA-seq or Immunohistochemistry. Patients with low expression of

KRT19, CD40 and proteasome genes can be directly treated with paclitaxel; patients with high expression of KRT19 and CD40 need to be treated with paclitaxel in combination with other targeted therapies (Targeting KRT19 or CD40); patients with high expression of proteasome genes need to be treated with paclitaxel in combination with proteasome inhibitors. After several rounds of treatments, tumor tissues could be investigated again on the expression of proteasome genes.

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