EpCAM Enhances Gefitinib-induced Drug Resistance in Colon Cancer Cells

Chen, Yun-Chi (School: Taipei First Girls High School)

Gefitinib, which is a small molecule tyrosine kinase inhibitor (TKI) of epithelial growth factor receptor (EGFR), is currently under investigation for colon cancer treatment. However, some patients develop resistance to EGFR-TKIs in clinical trials. It has been found that colon cancer cells exhibit the highest frequency of high-level epithelial cell adhesion molecule (EpCAM) expression of any cancer, but the relation of EpCAM and EGFR-TKIs resistance has not been elucidated. In this study, we hypothesized that the extracellular domain of EpCAM (EpEX) enhances Gefitinib drug resistance by inhibiting FOXO3a-induced apoptosis pathway. To validate this hypothesis, EpCAM/EpEX's impact on Gefitinib drug resistance was first examined, and its molecular mechanism was then elucidated. HCT116 and COLO205 cells which express both EGFR and EpCAM protein were as the model systems in this study. MTT assay shows that EpCAM/EpEX indeed enhances the resistance to Gefitinib in colon cancer cells. Protein expression analyses indicate a potential mechanism of Gefitinib resistance that EpEX phosphorylates EGFR at tyrosine 845 site and leads to the phosphorylation of FOXO3a at S253 which in turn inactives its function by preventing its nuclear translocation. In addition, EpEX inhibits the expression of FOXO3a-downstream pro-apoptotic genes. Collectively, this study indicates a novel role of EpCAM/EpEX enhancing Gefitinib resistance by inhibiting FOXO3a-induced apoptosis pathway. This is the first study to show that EpCAM/EpEX enhances TKIs resistance and the findings can be applied to cancer combination therapy to overcome EGFR-TKIs resistance.

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