Title

Shutting down EpCAM kills tumor cells and prevents their escape from immune surveillance

Abstract

Epithelial cell adhesion molecule (EpCAM) is highly expressed in solid tumors, but its role in cancer progression remains to be elucidated. Our recent study has advanced our knowledge of how EpCAM acts to promote cancer cell growth and how that process can be stopped. We found that the extracellular domain of EpCAM (EpEX) activated EGFR and downstream ERK1/2 signaling to promote colon cancer cell migration and proliferation, as well as tumor growth. Mechanistically, we discovered that EpEX-EGFR-ERK1/2 signaling positively regulated intramembrane proteolysis (RIP) of EpCAM and shedding of the intracellular domain (EpICD). EpEX binds EGFR, activating both AKT and MAPK signaling to respectively inhibit FOXO3a function and stabilize PD-L1 protein. Treatment with the EpCAM-neutralizing antibody, EpAb2-6, developed by our lab, could inhibit AKT and FOXO3a phosphorylation, increase FOXO3a nuclear translocation, and upregulate HtrA2 expression to promote apoptosis, while decreasing PD-L1 protein levels to enhance the cytotoxic activity of CD8+ T cells. The combination of EpAb2-6 with Atezolizumab, an anti-PD-L1 antibody, almost completely eliminated tumors. Moreover, the number of CD8+ T cells in combination-treated tumors was increased compared to Atezolizumab alone. Therefore, the recent findings suggest an exciting new combined treatment strategy for cancer immunotherapy in patients with EpCAM-expressing tumors.