DISRUPTION OF E-CADHERIN JUNCTIONAL INTEGRITY IN OVARIAN CANCER CELLS IS PROMOTED BY LPA-INDUCED MMP-9 ACTIVITY

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Approximately 22,000 U.S. women are newly diagnosed each year with epithelial ovarian cancer (EOC), 75% of whom present with existing metastases and peritoneal ascites. A key event in EOC metastasis is disruption of cell-cell contacts via modulation of intercellular junctional components such as cadherins. In contrast to most carcinomas, EOC actually gain expression of the cell-cell adhesion molecule E-cadherin. Ovarian cancer metastasizes via exfoliation of cells from the primary tumor to the peritoneal cavity, wherein free-floating cells and multi-cellular aggregates attach and invade to anchor growth of secondary lesions. Ascites is also rich in lysophosphatidic acid (LPA), a bioactive lipid that is a sensitive biomarker for ovarian cancer and may promote early events in ovarian cancer dissemination. The objective of this study was to determine whether LPA modulates E-cadherin junctional integrity. Immunofluorescence analyses were used to demonstrate a loss of junctional E-cadherin in OvCar3, OvCa429 and OvCa433cells exposed to LPA. LPA-induced loss of E-cadherin was concentration-and time-dependent. Surface labeling and western blotting showed that LPA promoted E-cadherin ectodomain shedding. Matrix metalloproteinase-9 (MMP9) expression was also induced by LPA treatment and inhibition of MMP9 activity blocked E-cadherin ectodomain shedding. Blocking LPA receptor signaling using the compound LPAR1 inhibited MMP9 expression and restored junctional E-cadherin staining. These data support a model wherein LPA induces MMP9 expression and MMP9-catalyzed E-cadherin ectodomain shedding, resulting in a loss of E-cadherin junctional integrity, facilitating metastatic dissemination of ovarian cancer cells.