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Funding Source: NIH grant to M.S Stack

Lysophoshatidic acid regulation of cell surface-associated proteases

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Lysophosphatidic acid (LPA) is a potential biomarker of ovarian cancer and is thought to promote early stages of cancer progression through the stimulation of two cell surface associated proteases. The affects of LPA on the expression and cell surface association of two proteolytic enzymes associated with ovarian cancer progression, matrix metalloproteinase-9 (MMP-9) and urokinase-type plasminogen activator (uPA), were analyzed. Both MMP-9 and uPA have been linked with cancer cell invasion due to their proteolytic activity. The cell surface association and activation of MMP-9 is a chief mechanism by which cells invade collagen rich barriers, whereas the increased binding of uPA to its cell surface receptor promotes the conversion of plasminogen to plasmin which also promotes cell invasion. LPA was shown to increase the expression of the MMP-9 protease in a concentration dependent manner in both OVCA 429 and OVCA 433 ovarian cancer cell cultures at concentrations well below those normally found in ascites fluids (≤ 1 μM). LPA treatment (80 μM) showed as much as a 3.5 fold increase in MMP-9 expression. Further, LPA treatment increased the expression of MMP-9 over MMP-2 in conditioned media of both OVCA 429 and OVCA 433 cells. Stimulation of uPA activity was also shown in culture medium but required the elevated concentrations (≥ 20 μM) often found in the ascites of ovarian cancer patients. Inhibitor studies showed that inhibition of PI-3K signaling (most evidently in OVCA 433 cells) and p38 MAPK (namely in OVCA 429 cells) repressed LPA stimulation of MMP-9 expression in a dose-dependent fashion. Future studies involving matrigel invasion assays will evaluate the functional consequence of LPA-stimulated MMP-9 expression and enhanced cell surface proteolysis on ovarian cancer cell invasive activity.