# MICROENVIRONMENTAL REGULATION OF OVARIAN CANCER DISSEMINATION VIA ACTIVATION OF THE WNT SIGNALING PATHWAY

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ABSTRACT

Disseminating single cells and multicellular aggregates (MCAs) and experience compressive forces exerted upon them by ascites fluid and are exposed to lysophosphatidic acid, aberrantly adhesive mesothelium and a collagen-rich submesothelial matrix. This work investigates the ***hypothesis*** that microenvironmental forces (increased fluid pressure/compressive force, lysophosphatidic acid, and integrin engagement) facilitate successful metastasis via Wnt signaling activation. Short-term (8-hour) increased fluid pressure, applied using an Instron 8215, enhances cell proliferation and up-regulates expression of Wnt target genes. Integrin engagement and LPA signaling down-regulate E-cadherin leading to dissolution of MCAs and initiating the epithelial to mesenchymal transition (EMT), characteristic of disseminating EOCs at this stage. β1 integrin engagement, modeled using anti-β1 integrin antibody adsorbed on 3-micron microspheres, leads to accumulation of free cytoplasmic β-catenin. And subsequent activation β-catenin target genes. These data suggest a novel Wnt ligand-independent mechanism for activation of the Wnt signaling pathway in ovarian carcinoma, and correlates with research and clinical observations of alterations in Wnt signaling by addressing mutation-independent activation of the signaling pathway.