2nd GLOBAL CONFERENCE ON REPRODUCTION, FERTILITY AND GYNECOLOGY

April 29-30, 2025 | VIENNA, AUSTRIA

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Integrin-Linked Kinase–Frizzled 7 Axis: A Novel Target Bridging Cancer Stem Cells and the Tumor Niche

Abstract:

Ovarian cancer (OC) is the deadliest gynecological malignancy characterized by chemoresistance and peritoneal recurrence. This has been attributed partly to persistence of ovarian cancer stem cells (OCSCs) at the end of primary treatment. The plasticity of OCSC allows them to survive and to be enriched during disease progression as well as after chemotherapy. Therefore, development of novel therapeutic strategies exploiting key biological mechanisms regulating cancer progression will significantly impact outcomes of patients suffering the complications of this aggressive cancer. The focus of our research was to understand how integrin-linked kinase (ILK), an enzyme found to be active in ovarian tumors, protected OCSC and stimulated their growth. Our results demonstrated increased fibronectin, integrin β1, and active-phospho-ILK at Ser246 in spheroids and chemoresistant OC cells. Mechanistically, the Wnt receptor frizzled 7 (Fzd7) activated ILK and amplified Wnt-3A signals with increased β-catenin-TCF/LEF1 transcriptional activity. Fzd7 and ILK blockade in combination with carboplatin reduced β-catenin nuclear translocation and inhibited Akt activation with consequent increased levels of cleaved-caspase-3 compared to single agent alone, indicating sustained apoptotic damage, significant decrease in the expression levels of stemness-related genes, spheroid proliferation, and tumorigenicity in mice.

Keywords: frizzled 7, integrin-linked kinase, tumor microenvironment, cancer stem cells

Biography: Dr. Condello is an Assistant Professor (tenure track) in the Department of Obstetrics and Gynecology at Indiana University School of Medicine in the subspecialty of Gynecology Oncology. His ongoing research is focused in identifying and validating oncogenic pathways and metabolic pattern alterations correlated with ovarian cancer stem cells survival and proliferation, with the final aim to find new functional target genes and test novel therapeutics.

doi.org/10.51219/URForum.2025.Salvatore-Condello

ISBN: 978-1-917892-03-2