Loss of Connective Tissue Growth Factor Expression Promotes Remodeling of the Extracellular Matrix and Epithelial-to-Mesenchymal Transition in Ovarian Cancer

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Loss of Connective Tissue Growth Factor Expression Promotes Remodeling of the Extracellular Matrix and Epithelial-to-Mesenchymal Transition in Ovarian Cancer

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Background: Ovarian Cancer (OC) is the leading cause of death from gynecologic malignancies in the United States largely due to the advanced stage at the time of diagnosis. Epithelial-to-mesenchymal transition (EMT) is a key biological process implicated in the pathophysiology of the metastatic spread of OC. Discovering the “trigger/s,” its downstream targets, and therapeutic targeting are essential to substantively improve the survival of women with OC. The objective of our study is to evaluate the role of Connective Tissue Growth Factor (CTGF) in EMT in OC.

Methods: R182 and R2615 are well-described epithelial OC cell and MR182 and MR2615 are the mesenchymal counterparts. R182/R2615 CTGF knock outs (KO) were derived utilizing a Cas9/CRISPR-Cas9 lentivirus plasmid vector and verified by indel sequencing. Invasion, anoikis resistance, and chemosensitivity assays were performed in wild-type (WT) and KO cells. RNA sequence analysis was performed and analyzed using iPathway guide. Top five upregulated and downregulated genes involved in ECM organization pathway were validated by quantitative PCR (qPCR). Immunofluorescence was performed for F-actin.

Results: CTGF was expressed in the epithelial and not in the mesenchymal OC cell lines. Loss of CTGF was associated with anoikis resistance, where KO and WT cells displayed 75% and 10% viability, respectively. KO cells were significantly more invasive than WT cells. Administration of exogeneous CTGF in KO cells decreased invasion in a dose dependent manner. No change was seen in chemosensitivity to Cisplatin in KO cells. RNA seq analysis identified ECM organization as the biologic process most affected by loss of CTGF. Upregulated (FREM2, LAMC2, ITGB4) and downregulated (SPP1, SV2A, RELN, COL6A3, COL4A6) extracellular matrix genes were validated by qPCR. Immunofluorescence staining of F-actin demonstrated increased cytoskeleton expression of F-actin in CTGF KO cells.

Conclusion: Our data suggests that CTGF expression maintains the epithelial phenotype in OC. Loss of CTGF may be one of the early triggers of EMT in OC through extracellular matrix remodeling affecting anoikis and adhesion characteristics, thus acquiring a more migratory and invasive phenotype.