Stromal Mitochondrial Changes in High-Grade Serous Ovarian Carcinoma

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Ovarian cancer is the deadliest gynecological cancer, with a five year survival rate that still barely exceeds 50%. Mesenchymal stem cells (MSCs) are a stromal cell population in the tumor microenvironment that strongly influence the metastasis, growth, and chemoresistive nature of high-grade serous ovarian carcinoma. Carcinoma-associated MSCs (CA-MSCs), a pro-tumorigenic phenotype of MSCs, have been shown to donate mitochondria, altered in morphology and function, to ovarian cancer (OC) cells, leading to increased respiration. However, the underlying factors causing these changes in CA-MSC mitochondria remain unknown. This study investigates stromal mitochondrial changes between patient derived normal MSCs (nMSCs) and CA-MSCs that influence OC progression. To identify genes impacting metabolic differences in CA-MSCs versus nMSCs, differential expression analysis and gene set enrichment analysis were performed on bulk RNA sequencing data. Genes of interest were validated using reverse transcription quantitative PCR, and changes at the protein level were confirmed by western blotting. CA-MSCs were found to exhibit significant differences in expression of PDK4, CYP24A1, TSPO, MTFR2, and DNA2 genes, and ATP5a protein, and these changes were more dramatic when cells were starved in media without FBS. Pathway analysis also revealed oxidative phosphorylation (OXPHOS) as the top altered pathway. These results suggest that changes in CA-MSC mitochondria are influenced by a shift from glucose utilization towards fatty acid oxidation. This study allows for a deeper understanding of alterations in CA-MSC mitochondria that aid in OC progression and treatment resistance, and also presents possible biomarkers for early detection and diagnosis along with potential therapeutic targets.

Awards Won:
Fourth Award of $600
Zydus Pharmaceuticals USA Inc.: Second Place Cellular and Molecular Biology