Adipose-derived mesenchymal stem cells drive endometrial cancer progression by establishing pro-tumorigenic metabolic crosstalk with tumor cells

P-30-131

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Obesity prevalence among women, especially those under 45, has significantly increased, correlating with a rise in endometrial cancer (EC), the most common gynecologic cancer in developed countries. This evidence highlights the need to better characterize the relations between obesity, aging, and EC progression. The molecular and metabolic interaction between adipose-derived mesenchymal stem cells (AD-MSCs), adipocytes, and EC cells remain underexplored. In this study, we characterized AD-MSCs and patient-derived organoids (PDOs) from patients undergoing EC surgery, along with commercial cell lines, setting up a co-culture system to study paracrine interactions between AD-MSCs and EC cells.

Estrogen-dependent (Ishikawa) and estrogen-independent (HEC1A) EC cells were co-cultured with AD-MSCs. Co-cultured EC cells showed a 1.5-fold increase in cell proliferation compared to controls, supporting the role of AD-MSCs in promoting EC cell growth. Spheroid formation and migration assays revealed enhanced 3D growth and migration potential in co-cultured EC cells. Additionally, HEC1A cells exhibited a 3-fold increase in chemoresistance after 20 hours of exposure to paclitaxel, further highlighting the pro-tumorigenic role of AD-MSCs.

Morphological analysis of co-cultures revealed significant lipid droplet accumulation in AD-MSCs, suggesting adipogenic differentiation. HEC1A cells exhibited increased expression of lipid metabolism-related genes, including diacylglycerol O-acyltransferase 2 and CD36, both linked to poor EC prognosis. Also, increased gene expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) and elevated mitochondrial membrane potential suggested a link between lipid metabolism and mitochondrial function in EC progression.

Our findings confirm that AD-MSCs significantly contribute to EC progression, validating the co-culture system's efficacy and supporting the ongoing development of a AD-MSCs and organoid biobank at UPO.