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

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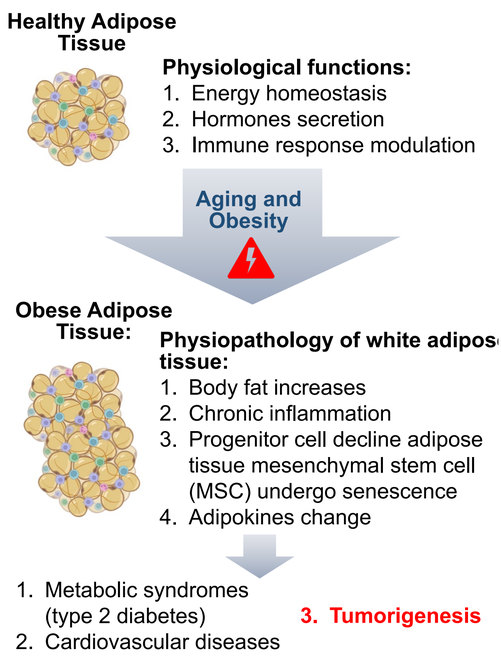
BACKGROUND

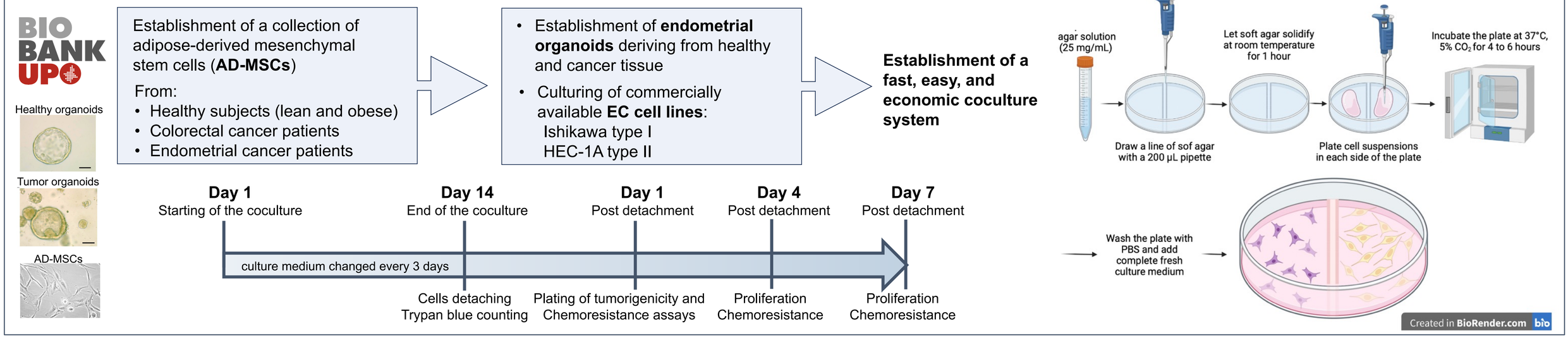
Obesity prevalence among women has significantly increased, correlating with a rise in endometrial cancer (EC), the most common gynecologic cancer in developed countries. This evidence highlights the need to better characterize the relations between obesity, aging, and EC progression. The molecular and metabolic interaction between adipose-derived mesenchymal stem cells (ADMSCs), adipocytes, and EC cells remains underexplored.

In this study, we characterized ADMSCs and patient-derived organoids (PDOs) from patients undergoing EC surgery, along with commercial cell lines, setting up a coculture system to study paracrine interactions between ADMSCs and EC cells.

Estrogen-dependent (Ishikawa) and estrogen-independent (HEC1A) EC cells were cocultured with ADMSCs. 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 cocultured 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 cocultures revealed significant lipid droplet accumulation in ADMSCs, suggesting adipogenic differentiation. HEC1A cells exhibited increased expression of lipid metabolism-related genes, including diacylglycerol O-acyltransferase 2 and CD36, both of which are linked to poor EC prognosis. Also, increased gene expression of peroxisome proliferator-activated receptor γ coactivator 1α (PGC1α) and elevated mitochondrial membrane potential suggested a link between lipid metabolism and mitochondrial function in EC progression.

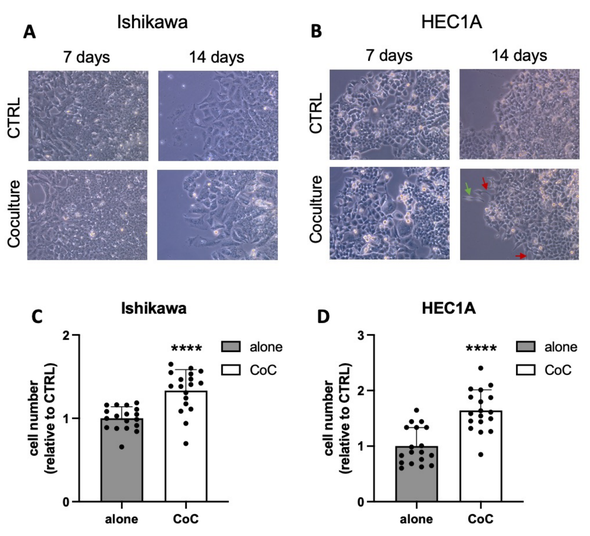


EXPERIMENTAL DESIGN



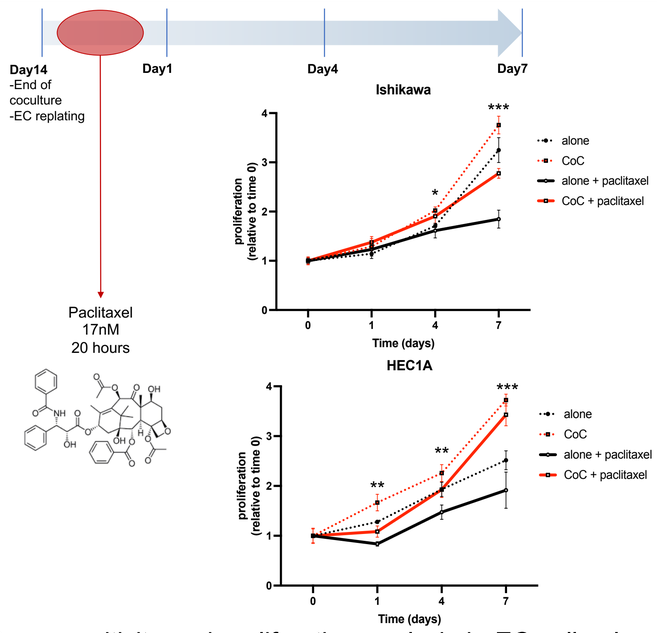
RESULTS

AD-MSCs sustain EC cells' proliferation in coculture



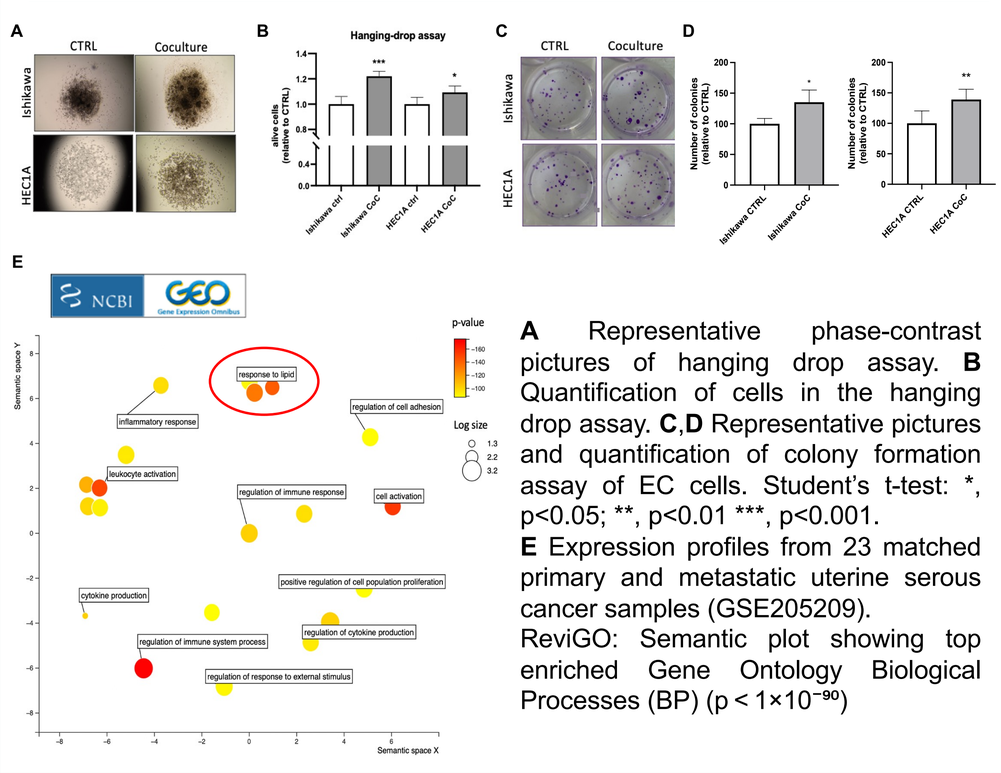
Phase-contrast pictures of EC cells alone or co-cultured for 7 and 14 days. **A** Ishikawa and **B** HEC1A cells cocultured for 7- and 14- days display an increase in the vesicular bodies (black spots). **C**, **D** Cell number quantification of cell number by trypan blue exclusion Student's t-test: ****, p<0.0001

Coc-EC cells retain higher proliferative potential and display chemoresistance



Drug sensitivity and proliferation analysis in EC cells alone or cocultured, 20 hours of exposure to 17 nmol/L paclitaxel, after washout, viability was monitored at days 1, 4, and 7. Student's t-test: *, p<0.05; **, p<0.01; ***, p<0.001

Coc-EC cells display increased tumorigenic features and lipid metabolism drives EC metastatic progression

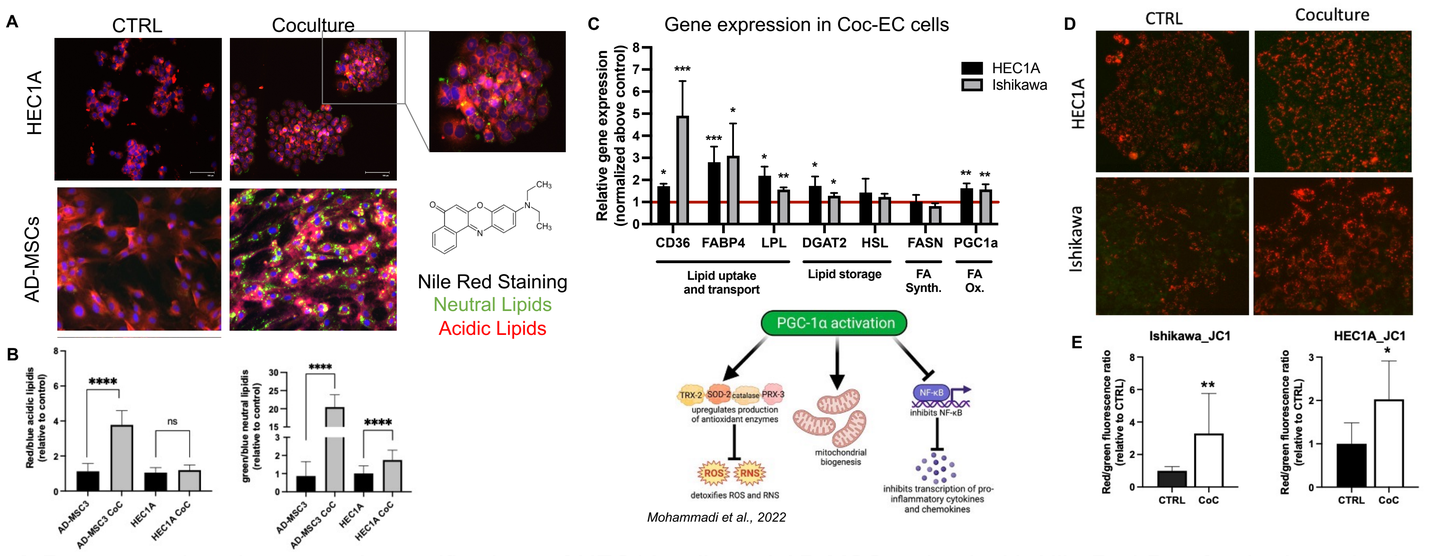


A Representative phase-contrast pictures of hanging drop assay. **B** Quantification of cells in the hanging drop assay. **C**,**D** Representative pictures and quantification of colony formation assay of EC cells. Student's t-test: *, p<0.05; **, p<0.01 ***, p<0.001.

E Expression profiles from 23 matched primary and metastatic uterine serous cancer samples (GSE205209).

ReviGO: Semantic plot showing top enriched Gene Ontology Biological Processes (BP) ($p < 1\times10^{-90}$)

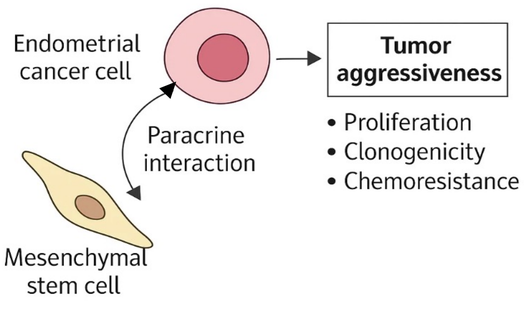
AD-MSCs and EC cells crosstalk results in lipid droplet accumulation and altered mitochondrial function



A Representative pictures and quantifications of HEC1A cells and AD-MSC stained with Nile Red Dye for the investigation of lipid droplet accumulation (red: acidic lipids, green: neutral lipids, blue: nuclei). **B** Quantification of Nile Red. **C** RT-PCR performed on EC cells, control or cocultured for 14 days with AD-MSCs. **D** Representative pictures displaying mitochondrial membrane hyperpolarization in Coc-EC cells (JC-1 Dye). Quantification of mitochondrial membrane potential in EC cells, control vs cocultured. Student's t-test: *, p<0.05; **, p<0.01; ****, p<0.0001.

CONCLUSIONS

Despite being the cancer most strongly linked to obesity, endometrial cancer remains poorly studied

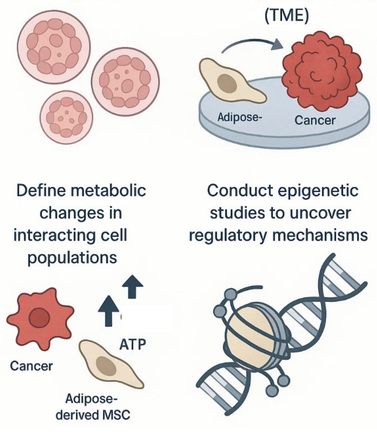


Metabolic symbiosis supporting cancer progression

Lipid metabolism

Altered mitochondrial activity

Future perspectives



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