Methods Medroxyprogesterone acetate (MPA)-resistant endometrial cancer cells were established through continuous treatment of endometrial cancer cells (RL95–2 and Ishikawa) with gradually escalating doses of MPA. RNA-seq was performed on both original and MPA-resistant EC cells to evaluate DEGs. Gene-set enrichment analysis (GSEA) was also performed to find biologic processes or pathways in relation to MPA resistance. Further validation was undertaken by real-time polymerase chain reaction (RT-PCR) on selected genes.

Results The profiles of DEGs were substantially different between RL95–2 and Ishikawa cells. In MPA-resistant RL95–2 cells, the enriched hallmark gene sets include KRAS signaling, down, myogenesis, and late estrogen response. In MPA-resistant Ishikawa, hallmark gene sets of TNFα signaling via NFκB, hypoxia, and late estrogen response were significantly enriched. Common hallmark gene sets in both MPA-resistant RL95–2 and Ishikawa include late estrogen response and myogenesis. In addition, common gene ontology biological processes include cellular response to corticosteroid stimulus and epithelial cell differentiation.

Conclusions We identified DEGs and several pathways enriched in MPA-resistant endometrial cancer cells as potential therapeutic targets of progesterone resistance, which need further validation.