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Effects of medroxyprogesterone acetate (MPA) in activating progesterone receptor signaling in benign and cancer-associated fibroblasts of the endometrium

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Medroxyprogesterone acetate (MPA) is used for conservative treatment for endometrial cancer (EC); however, patients often develop progesterone resistance. Most typical and atypical endometrial hyperplasia shows regression after MPA treatment. Primary type 1 EC responds moderately to MPA therapy (50-70%). Yet, MPA treatment only offers 10-20% response rates and survival of less than one year in advanced and recurrent EC. It was shown that secretion from normal fibroblast cells inhibit while cancer fibroblasts cells promote the proliferation of EC cells. Interestingly, a recent study showed that progesterone receptor (PR) expression in normal fibroblast is important for progesterone inhibitory effects on cancer cells. It has also been shown that estrogen is responsible for increasing PR expression. However, it is still largely unknown, if and how, fibroblasts from endometrial cancers modulate EC response to progesterone. BAF and CAF were isolated from human endometrial primary cultured cells using antibody-conjugated magnetic beads. Fibroblast and epithelial markers expression, and progesterone receptor (PR) expression were determined using quantitative real-time PCR (qRT-PCR) and western blotting. PR nuclear translocation was determined using immunofluorescence assay. Cell viability was determined using MTT assay. Fibroblasts expressed high levels of fibroblast markers but not epithelial cell markers indicating minimal epithelial cells contamination. Both BAF and CAF expressed varied levels of PR expression. PR nuclear translocation occurs within 6 hours of 10 nM MPA treatment in BAFs and CAFs. Their response to MPA growth inhibition was similar (20% growth inhibition when compared to vehicle) after treated with 1-400 nM MPA for 72 hours. The cell viability was 22% and 9% lower in BAFs and CAFs, respectively following 100 nM MPA treatment in the presence of 10 nM E2 compared to MPA alone. Our data suggests that PR signaling in CAF can be activated, and but has lower response to combination of MPA and estrogen treatment.

Biography

Ivy Chung is an Associate Professor at Department of Pharmacology, Faculty of Medicine, University of Malaya, Malaysia. She is trained as a Cancer Pharmacologist and interested in tumor microenvironment research. She has published numerous articles on tumor angiogenesis and cancer-associated fibroblasts. Her current interest is to study hormonal and survival pathways that are activated in the tumor-host cell interaction that could contribute to aggressiveness of the cancer as well as to development of therapy resistance.

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