Ovarian cancer cell death induced by non-genomic action of progesterone and its receptor agonist via membrane receptors

Takahiro Koyanagi[1], Yasushi Saga[1], Yoshifumi Takahashi[1], Kohei Tamura[1], Takahiro Yoshiba[1], Suzuyo Takahashi[1], Akiyo Taneichi[1], Yuji Takei[1], Hiroaki Mizukami[1], and Hiroyuki Fujiwara[1]

[1]Jichi Medical University

June 15, 2023

Abstract

Background and Aims: Progesterone therapy is a relatively inexpensive treatment option for endometrial and breast cancers, with few side effects. Two signaling pathways usually mediate the physiological effects of progesterone, namely genomic and non-genomic actions. Genomic action occurs slowly via the nuclear progesterone receptor (PR), whereas the membrane progesterone receptor (mPR) induces rapid non-genomic action. We investigated the effects of progesterone and various PR agonists on ovarian cancer cells. Methods: PR expression of six serous ovarian cancer cell lines was examined by western blotting, and mPR expression was examined by RT-qPCR. PR-negative and mPR-positive ovarian cancer cells were exposed to progesterone and seven types of PR agonists (medroxyprogesterone acetate [MPA], dehydroepiandrosterone, dienogest, levonorgestrel, drospirenone, pregnenolone, and allopregnanolone) at 10–400 μM, and viable cell counts after exposure for 30 min were measured using the water soluble tetrazolium (WST-1) assay. Ovarian cancer cell lines were exposed to 100 μM progesterone, and the expression of BAX, a pro-apoptotic protein, after 1-5 min was examined by western blotting. Results: Western blotting detected no PR expression in the six serous ovarian cancer cell lines. In contrast, RT-qPCR detected mPR expression in all six serous ovarian cancer cell lines. Progesterone and MPA induced cell death in all tested ovarian cancer cell lines in a concentration-dependent manner, whereas no effect was observed for other PR agonists. Western blotting revealed that pro-apoptotic protein BAX expression occurred 1 min after exposure to progesterone, suggesting that the cytocidal effects are mediated by rapid non-genomic action. Conclusions: MPA, like progesterone exhibited a rapid cytocidal effect on PR-negative ovarian cancer cells through non-genomic action. Progesterone and MPA could be novel treatment modalities for ovarian cancer. Keywords: genomics, medroxyprogesterone acetate, ovarian cancer, progesterone, progesterone receptor

Hosted file

`Main document for submission.docx` available at https://authorea.com/users/629117/articles/649493-ovarian-cancer-cell-death-induced-by-non-genomic-action-of-progesterone-and-its-receptor-agonist-via-membrane-receptors

Fig. 1 Top ↑

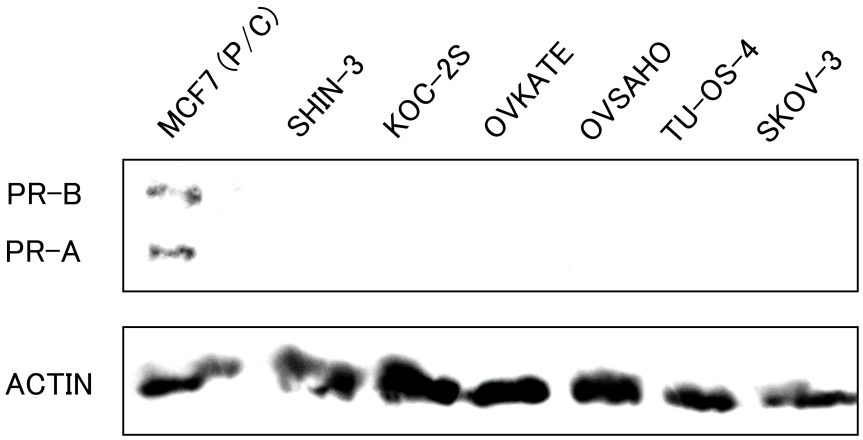

Fig. 2 Top ↑

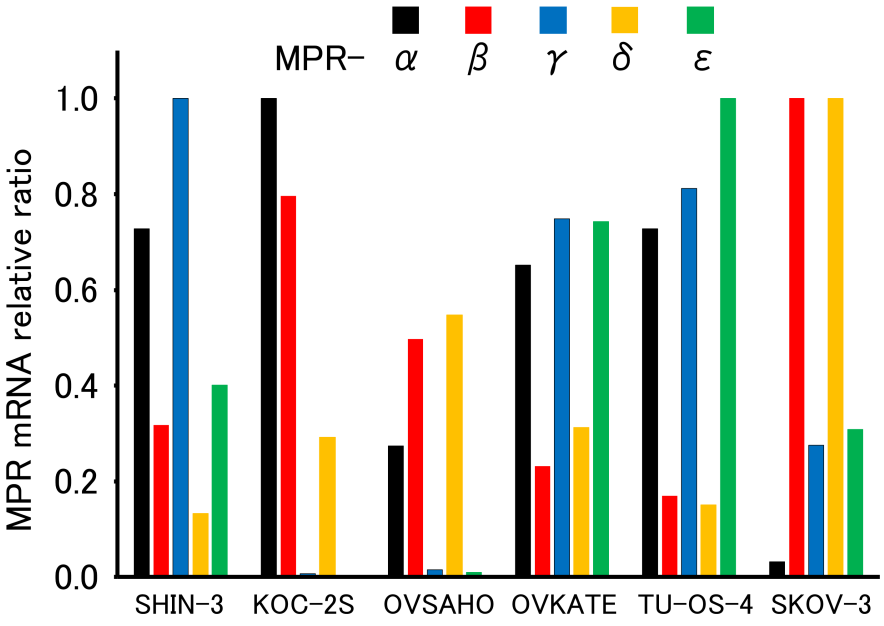

Fig. 3 Top ↑

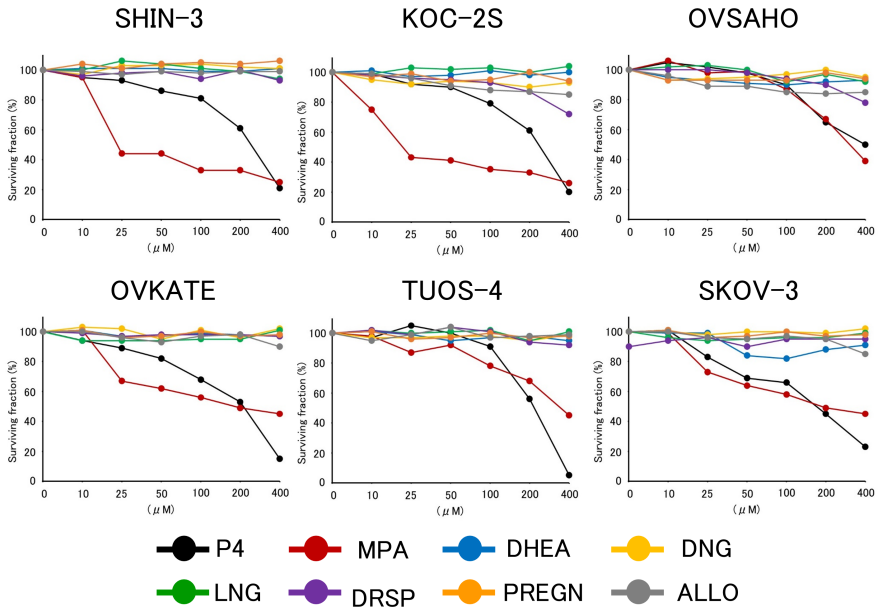

Fig. 4 Top ↑