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TITLE

THE PRESENCE OF MEMBRANE-BOUND PROGESTERONE RECEPTOR INDUCES GROWTH OF BREAST CANCER WITH NORETHISTERONE BUT NOT WITH PROGESTERONE: A XENOGRAFT MODEL

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ABSTRACT

Context WHI study indicates that increased risk of breast cancer in HRT is associated with progestogen. Recent research found that progesterone receptor membrane component 1 (PGRMC1) may be play an important role in tumor proliferation and increasing breast cancer risk.

Objective To compare the effects of progesterone and norethisterone (NET) on the growth of MCF7 and T47D tumor xenografts in nude mice considering the importance of PGRMC1 in the development of breast cancer for the first time.

Methods MCF7 cells were stably transfected with PGRMC1 expression plasmid (WT12) or empty vector (pcDNA-3HA). Nude mice were inoculated with Estradiol (E2) pellets before the injection of tumor cells into both flanks (n=6 per group), a norethisterone (NET), progesterone or placebo pellet was implanted 12-days following tumor cell injections and tumor volumes were monitored for 6-7 weeks. Tumor tissue was analyzed by immunohistochemical analysis. The experiment was repeated in a second xenograft model (T47D cells).

Results In an oestrogen-driven tumour context, progesterone did not increase oestrogen-induced tumor proliferation in MCF7 and T47D xenografts (neutral), whereas WT-12 significantly increased proliferation in response to progesterone compared with MCF7/pcDNA-3HA in vivo, and we observed the simlar trend in T47D xenograft models. WT12 and T47D/HA-PGRMC1 stimulated by sequential E2/NET regimen had a significant increase in tumor volume, PGRMC1 expression were higher than that in tumors with MCF7 and T47D containing the vector controls. Two breast cancer cells transfected with empty vectors did not respond to NET.

Conclusion We demonstrate that clinically-relevant progestins promote breast cancer growth that overexpressing PGRMC1 in vivo, even progesterone showed neutral in vitro. Such risk should be considered in the clinical practice.

INSTITUTE

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