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DOSE-DEPENDENT EFFECT OF ESTETROL (E4) ON ANGIOGENESIS AND BREAST TUMOR GROWTH

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Hormone replacement therapies (HRT) based on estrogen preparations are the most powerful treatments to prevent menopause symptoms. However, they are associated to an increased risk of breast cancer and they sustain the development of Estrogen Receptor Î±-positive tumors (ERÎ±+). In addition, we have previously observed that estradiol (E2) can promote the growth of ERÎ±-negative (ERÎ±-) tumors, by increasing tumor angiogenesis that subsequently improves oxygen and nutrients delivery, thereby preventing hypoxia and necrosis. To identify new and safe drugs for the development of HRT presenting a better benefice/risk ratio, it is therefore necessary to evaluate the potential impact of new candidates on both ERÎ±+ and ERÎ±- tumors. In this context, estetrol (E4), a natural estrogen exclusively produced by the fetal liver, is a promising candidate. The aim of this study was to evaluate the impact of different doses of E4 on ERÎ±+ and ERÎ±- tumor progression mediated by direct and indirect effects on tumor cells and microenvironment, respectively.
Using ovariectomized MMTV-PyMT mice and human MCF7 xenografts, we evaluated the impact of E4 on ERÎ±+ tumor development and lung metastatic dissemination. We tested a range of E4 doses starting at 0.3 mg/kg/day that matches to the therapeutic dose that could be used in human. Interestingly, E4 used at 0.3 mg/kg/day did not modify neither mammary primary tumor nor lung metastasis. However, E4 used at 3 or 7 mg/kg/day increased the tumor progression as well as lung metastasis occurrence. Using a mouse model of ERÎ±- cancer cells grafted subcutaneously into syngeneic ovariectomized immunocompetent mice, we studied the impact of E4 on tumor progression and microenvironment, more specifically on angiogenesis. We observed that E4 used at 0.3 mg/kg/day did not modulate tumor growth, intratumoral vessel density, nor tumor hypoxia and necrosis.
In conclusion, when used at 0.3 mg/kg/day, E4 does not promote tumor growth, while it already prevents menopause symptoms in animal models. However, when used at high doses, E4 promotes both ERÎ±+ and ERÎ±- tumor development. Altogether, these results highlight that it is crucial to be cautious with the dose to use E4 as a menopause treatment.

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