THE EFFECTS OF THE SELECTIVE ESTROGEN RECEPTOR MODULATORS MPP AND RALOXIFENE IN NORMAL AND CANCEROUS HUMAN AND MURINE UTERINE TISSUE

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ABSTRACT

The goal of this research was to determine the \textit{in vitro} and \textit{in vivo} effects of the Selective Estrogen Receptor Modulators (SERMs), methyl-piperidino-pyrazole (MPP), raloxifene, ICI 182,780 and 17β-estradiol on endometrial carcinoma cells in culture and on murine uterine tissue. These SERMs have been developed to target and understand the role of estrogen receptor action in estrogen-responsive organs. Based on their antagonistic actions, SERMs have both real and potential value in treating estrogen-responsive cancers, including endometrial cancer. The studies described herein verify that the SERMs MPP and raloxifene demonstrate partial agonistic effects in ovariectomized wild-type and ER-β knockout (ERβKO) mice but also induce apoptosis and proliferation \textit{in vitro} in cultured endometrial cell lines, Ishikawa and RL-95. Thus, MPP and raloxifene exert apparently contrasting \textit{in vitro} and \textit{in vivo} effects due to their mixed agonist/antagonist action on murine uterine estrogen receptor \textit{in vivo}. In addition to these data, I report gene expression changes in the uterus of mice treated individually or with the combination of 17β-estradiol and the SERMs, MPP, raloxifene, ICI 182,780 are reported herein. A greater number of genes showed up- or down regulation when the
mice were co-treated with estrogen and one of the SERMs than when dosed with one of the compounds alone. A combination of a SERM and 17β-estradiol resulted in a combinatorial or synergistic effect. These data may be explained by the fact that dual administration of a SERM with β-estradiol allows the compounds to bind combinatorially to heterodimers as well as homodimers of the two receptors ERα and ERβ. These studies provide a framework of how 17β-estradiol and various SERMs act in the uterus and might result in future therapies for gynecological maladies, including endometrial cancer.