Pathophysiological Role of Estrogen Metabolism in Breast Cancer

Original title / Originaltitel
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Summary / Zusammenfassung
Breast cancer is one of the leading causes of premature death in women worldwide and approximately 1 in 8 women will develop this disease during their lifetime. Increased exposure to estrogen is an established risk factors for the development of breast cancer in both young women and postmenopausal taking hormone therapy (HT). Even after years of intense research, the mechanisms of breast cancer progression and metastasis are not fully understood. Although, estrogens play an important role in the development of normal mammary glands, however, they are also implicated in the development of breast cancer by simultaneously stimulating cell proliferation and gene expression via the estrogen receptor (ER) and by causing DNA damage potentially via their genotoxic catechol estrogen metabolites. The fact that ERs are expressed in breasts of most women, however, not all get estrogen-induced cancer suggests that an alternative pathway which counteracts the carcinogenic effects of estrogens may be active in them and lack of this pathway may make women more susceptible to estrogen induced breast cancer. In this context, endogeneous estradiol is sequentially metabolised by cytochrome-P450 (CYP450) and Catechol-O-methyltransferase (COMT), respectively, to methoxyestradiol, a potent anticarcinogenic and antimitogenic agent. Since CYP450 and COMT are present in the breast cells, the local conversion of estradiol to methoxyestradiol may serve a pathway to counteract, suppress or regulate the ER-mediated proliferative actions of estradaiol on breast. Moreover, dysfunction or decrease in the formation of methoxyestradiol from estradiol may shift the balance solely towards estrogen-induced proliferative effects and abnormal proliferation or cancer. Even though, methoxyestradiol is known to inhibit growth of several types of cancer, very little attention has been focused on the role of sequential metabolism of estradiol in breast in regulating the proliferative as well as carcinogenic and mutagenic effects. On going research in our laboratory provides evidence that local metabolism of estradiol to methoxyestradiol plays a key role in preventing vasoocclusive disorders by inhibiting abnormal growth of vascular cells. Since, abnormal growth is a common feature of both cancer and vasoocclusive disorders, we hypothesize that the sequential metabolism to estradiol by CYP450 and COMT to methoxyestradiol plays a key role in counteracting its ER-dependent proliferative actions, thereby, defining its overall, normal and/or carcinogenic, growth effects in breast cells. Hence, using specific molecular (gene silencing) and pharmacological approaches, the objective of this proposal is to explore whether in breast cells the sequential conversion of 17beta-estradiol to non-estrogenic methoxyestradiol by cytochrome P450 (CYP450) and catechol-O-methyltransferase (COMT), respectively, is an intrinsic growth inhibitory pathway which counteracts the ER-dependent proliferative actions of 17beta-estradiol.

Weitere Informationen unter http://www.nih.gov

Publications / Publikationen

Induced Antimitogenesis in Human Cardiac Fibroblast. J Clin Endocrinol Metab. 90:247-255.
Weitere Informationen unter http://www.pubmed.com

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metabolism, estrogen, cancer, hormone therapy, polymorphism

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