Hormonal Regulation of Catechol-O-Methyl Transferase Activity in Uterine Leiomyoma

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Objectives: Catechol-O-methyltransferase (COMT) plays an important role in estrogen metabolism. COMT converts catechol estrogens into their methoxy derivatives. Two promoters control the expression of human COMT isoforms: membrane-bound COMT and soluble COMT, which are under the control of two distinct promoters (COMTP2 and COMTP1, respectively). Regulation of human COMT gene expression may be important in the pathophysiology of various estrogen-related disorder.

Methods and Results: RNA microarray analysis indicated that COMT exhibits about 3.4 fold higher expression in leiomyoma tumor tissues compared with adjacent normal myometrium. Immunohistochemical staining with anti-COMT specific polyclonal antibodies confirmed stronger COMT protein expression in leiomyomatous tumor tissues compared to normal myometrial tissue from same uterus. Analysis of COMTP1 and COMTP2 indicated that both promoters harbor half sites of estrogen response element (TGACCT) and glucocorticoid response element (TGTTCT), suggesting that these promoters might be regulated by estrogen and glucocorticoids. Indeed, treatment of ELT3 rat leiomyoma cells with 17-ß-estradiol (10^{-10} - 10^{-6}M) resulted in downregulation of COMT protein expression in western blot analysis. Similarly, in ELT3 cells cotransfected with COMT promoter-luciferase reporter, 17-beta-estradiol down-regulated both COMTP1- and COMTP2-luciferase activities in a dose-dependent manner. Contrary to estradiol, progesterone as well as dexamethasone (10^{-10} -10^{-6} M) upregulated COMT protein expression and COMTP1-and COMTP-luciferase activities in a dose dependent manner.

Conclusion: Our findings present a molecular mechanism for the interactive effect of different steroid hormones in the pathophysiology of uterine leiomyoma.