Retinoic Acid Up-Regulates Catechol-O-Methyl Transferase Promoters: Potential Mechanism for the Mitogenic Effect of Retinoic Acid on Leiomyomas Cells

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Introduction: Catechol-O-methyltransferase (COMT) is a key enzyme in metabolism of estrogens and therefore factors affecting COMT expression can indirectly affect the estrogenic milieu in situ. Retinoic acid has been proposed to promote the effect of estrogen in the guinea pig leiomyoma model. In addition, leiomyoma tissues express higher level of all-trans retinoic acid (ATRA) compared to adjacent normal myometrium. However, the mechanisms by which ATRA modulates estrogen activity and contributes to the pathophysiology of leiomyomas are not completely understood.

Methods: In the current study, we evaluate the effect of ATRA on the proliferation of cultured ELT3 rat leiomyoma cells. In addition, we tested the hypothesis that the effect of ATRA on ELT3 cells proliferation is mediated, in part, by altering the expression of COMT.

Results: Our data indicate that ATRA (10^{-8} and 10^{-7} M) significantly increased the proliferation of ELT3 cells (120% and 130%), respectively, from the control ($P<0.01$). Molecular mapping demonstrated that both COMT proximal (P1) and distal (P2) promoters are harboring Retinoic acid response element. Western blot analysis indicates that treatment of ELT3 cells with ATRA (10^{-8}, 10^{-7}, 10^{-6} M) resulted in concentration-dependent increase COMT protein expression. ATRA treatment (10^{-8}-, 10^{-7}, or10^{-6}, M) of ELT3 leiomyoma cells transfected with COMTP1- or COMTP2-luciferase (Luc) reporter resulted in significantly increased activity of both COMTP1-Luc (4-, 8- and 23- fold, respectively) and COMTP2-Luc (10-, 17-, and 21-fold, respectively) compared to untreated control.

Conclusion: ATRA exerts a mitogenic effect on ELT3 cells and this mitogenic effect may be attributed, at least in part, to up-regulation of COMT expression in these cells. This is the first report that ATRA up-regulates COMT expression. This finding has both therapeutic and toxicologic implications on the impact of ATRA on estrogen metabolism.