HUMAN CYP1B1 IS A NEW TARGET GENE OF ESTROGEN RECEPTOR

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Human CYP1B1 is a key enzyme in the metabolism of 17beta-estradiol (E2). CYP1B1 is mainly expressed in endocrine-regulated tissues, such as mammary, uterus, and ovary. Since many CYP enzymes are likely to be induced by the substrates themselves, we examined whether the human CYP1B1 expression is regulated by E2 in the present study. Real-time RT-PCR analysis revealed that treatment with 10 nM E2 for 12 h induced CYP1B1 mRNA expression in estrogen receptor (ER)-positive MCF-7 cells. Luciferase reporter assays showed a significant transactivation up to 7 fold by E2 with a reporter plasmid containing a region from -152 to +25 of the human CYP1B1 gene. Specific binding of ER to the putative estrogen responsive element (ERE) between -63 and -49 was demonstrated by ChIP assays and gel shift analyses. Since endometrial tissue is highly regulated by estrogens, the expression pattern of CYP1B1 protein in human endometrial specimens was examined by immunohistochemistry. The staining of CYP1B1 was stronger in glandular epithelial cells during a proliferative phase than those during a secretory phase, being consistent with the pattern of estrogen secretion. These findings clearly indicated that the human CYP1B1 is regulated by E2 via ER. Because 4-hydroxyestradiol produced by CYP1B1 from E2 is estrogenically inactive but toxicologically active, our findings suggest a clinical significance in the estrogen-regulated CYP1B1 expression for the homeostasis of estrogens as well as estrogen-dependent carcinogenesis.