초청연제

Pharmacogenomics of Active Tamoxifen Metabolites

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4-hydroxy-tamoxifen (4-OH-Tam) has been for many years considered the active metabolite of tamoxifen; it is ~100-fold potent than tamoxifen. Recently, we have identified another active metabolite of tamoxifen, endoxifen, and demonstrated that it is equipotent to 4-OH-Tam with respect to estrogen receptor binding, anti-proliferative activity, and inhibition of gene expression. We have also evidence that this metabolite is more abundant in human plasma (up to 14-fold) than 4-OH-Tam and that its concentrations are controlled in part by cytochrome P450 2D6, a highly polymorphic enzyme. These data suggest that endoxifen may mediate a large portion of the antiestrogenic effects of tamoxifen. The purpose of the present work was to determine the effect of estrogen, active tamoxifen metabolites and their combinations on global gene expression in MCF-7 cells using DNA microarray analysis. Cells were treated for 24 hrs with vehicle, 10^{-10}M 17β-estradiol (E2), 10^{-7}M 4-OH-Tam, 10^{-7}M endoxifen, and various combinations. Of the 22,283 genes detected by the array Chip, 4,062 (1,924 up-regulated 2,138 down-regulated) were responsive to E2 treatment. The ratio of E2-induced to E2-suppressed genes was consistent regardless of the fold-change cutoff. In the presence of E2, 2,444 and 2,390 genes were affected by 4-OH-Tam or endoxifen, respectively. The majority of genes influenced by these tamoxifen metabolites were estrogen-responsive (74.4% and 73.3%, resp.). 4-OH-Tam and endoxifen had overlapping effects on 1,365 genes, but also brought about distinct patterns of gene regulation (830 vs. 776 genes were changed by 4-OH-Tam alone or endoxifen alone, resp.). Among the 1,365 genes coregulated by both 4-OH-Tam and endoxifen, there was a significant correlation between the fold-effects brought about by these two metabolites (R^2=0.99). Among E2-insensitive and tamoxifen metabolites regulated genes (625 for 4-OH-Tam and 638 for endoxifen), 249 genes were also shown to be coregulated by both tamoxifen metabolites and significant correlation between the fold-effects by these two metabolites was also found (R^2=0.99). Hierarchical clustering analysis showed a similar pattern of gene regulation by endoxifen and 4-OH-Tam. We verified the microarray data by real-time PCR and the results were generally consistent with the microarray data. These data suggest that 4-OH- Tam and endoxifen exhibits similar gene expression patterns in MCF-7 cells and the majority of genes influenced are estrogen-sensitive. Our data also raise the possibility that some effects of tamoxifen metabolites may involve estrogen-independent pathways. In conclusion, the data presented here, along with our previous findings, suggest that endoxifen is more important than 4-OH-Tam in mediating tamoxifen activity in vivo and that inherited polymorphisms in the CYP2D6 gene may alter individual responses to tamoxifen.