Differential effects of estrogen exposure on steroid metabolizing CYP enzyme expression in estrogen receptor alpha versus beta positive breast cancer cell lines

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BACKGROUND

The estrogen receptors (ER) α and β, might serve as extra-hepatic regulators of CYP450 enzymes involved in drug and steroid hormone metabolism such as CYP1B1 and CYP2B6. The two cytosolic estrogen receptors form homo- and heterodimers upon binding of 17β-estradiol (E2) and translocate to the nucleus where they bind to estrogen response elements (ERE) in regulatory regions of target genes [1]. Alteration of CYP activity by estrogen signaling could have detrimental or beneficial effects on the development, progression, outcome and treatment of breast cancer [2].

AIM

The aim of this project was to investigate the effects of E2 treatment in breast cancer cell lines on the expression of ERα and ERβ, and their capability to modulate the expression of CYP450 enzymes, involved in steroid metabolism.

METHODS

We used commercially available ERα-positive (T47D, MCF-7) and -negative (SKBR3, MDA-MB-231) human breast cancer cell lines. The respective cell lines were treated with different concentrations of 17β-estradiol (E2) for 24 hours. The influence of the E2 treatment on CYP1B1 and CYP2B6 as well as ERα and ERβ expression was investigated by qPCR analysis.

RESULTS

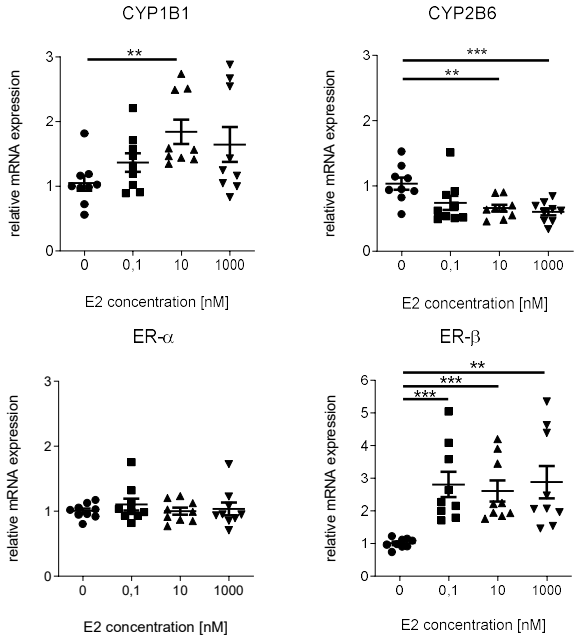

Figure 1: qPCR analysis of CYP1B1, CYP2B6, ERα and β mRNA expression in ERα-positive T47D cells. Cells were treated for 24 hours with increasing concentrations of E2. Shown are combined data from three different experiments with three biological replicates each. Values were normalized to the housekeeping gene *18S* and the untreated control cells. Significant changes in mRNA levels compared to control are indicated by unpaired student´s t-test. p-value: *<0.05, **<0.005, ***<0.001

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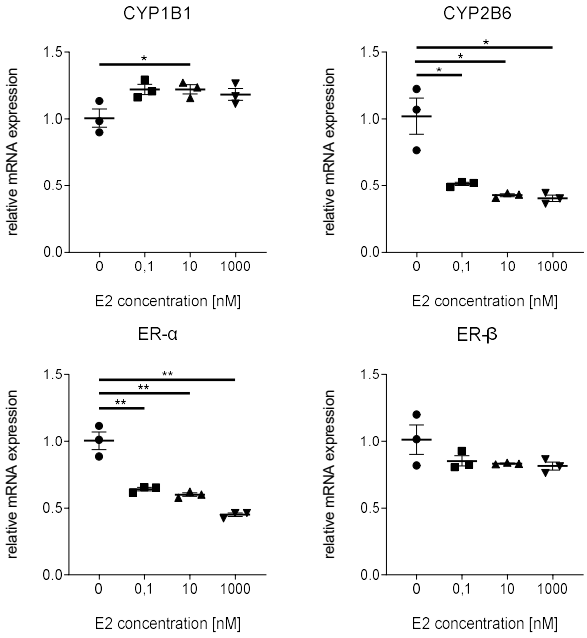

Figure 2: qPCR analysis of CYP1B1, CYP2B6, ERα and β mRNA expression in ERα-positive MCF-7 cells. Cells were treated for 24 hours with increasing concentrations of E2. Shown are data from a single experiment with three biological replicates. Values were normalized to the housekeeping gene *RPLP0* and the untreated control cells. Significant changes in mRNA levels compared to control are indicated by unpaired student´s t-test. p-value: *<0.05, **<0.005, ***<0.001

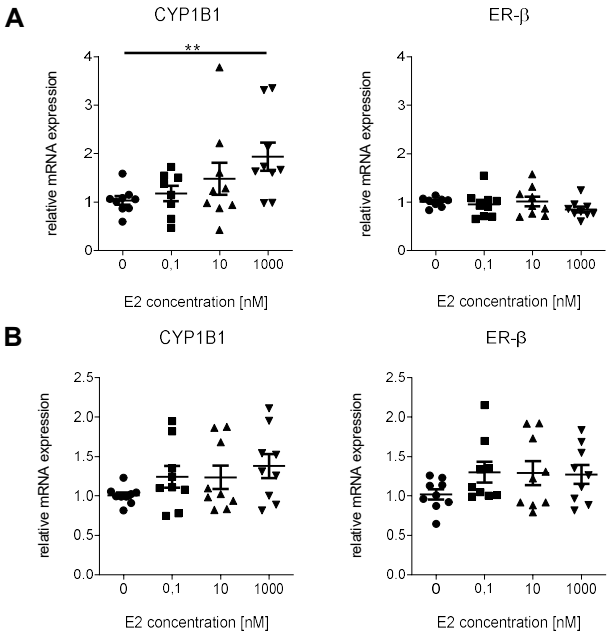

Figure 3: qPCR analysis of CYP1B1 and ERβ mRNA expression in ERα-negative SKBR3 and MDA-MB-231 cells. (A) SKBR3 and (B) MDA-MB-231 cells were treated for 24 hours with increasing concentrations of E2. CYP2B6 and ERα are not shown as they could not be detected in both cell lines. Shown are combined data from three different experiments with three biological replicates each. Values were normalized to the housekeeping gene *18S* and the untreated control cells. Significant changes in mRNA levels compared to control are indicated by unpaired student´s t-test. p-value: *<0.05, **<0.005, ***<0.001

CONCLUSION

We detected differential effects of E2 on CYP enzyme expression in ERα-positive and –negative cell lines. The most prominent estrogen metabolizing enzyme CYP1B1 showed a tendency to induction in all cell lines. CYP2B6 is known to be induced by ERα [3], and CYP2B6 mRNA could only be detected in ERα-positive cell lines as expected. Conversely, in both ERα-positive cell lines, the mRNA levels of CYP2B6 were decreased after E2-treatment. This could by explained by a decrease of ERα-levels in MCF-7 cells and increased levels of ERβ in T47D cells. In literature, ERβ is often described to be antagonistic to ERα in the regulation of many genes [4]. Hence, In the presence of ERα, ERβ might have an antagonistic effect on CYP2B6 induction.

Disclosure Statement of Financial Interest: The authors DO NOT have a financial interest or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation