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The Regulation of ARE Activity and HO-1 Expression by Estrogen In Human Endometrial Epithelial Cells

The transcription factor Nrf2 regulates basal and inducible expression of detoxifying and antioxidant genes. This is known to occur via binding of Nrf2 to a regulatory motif known as the Antioxidant Response Element (ARE) in the promoter of these genes. Heme oxygenase 1 (HO-1) is an enzyme that catalyzes the degradation of heme and is inducible in response to Nrf2 activation. It has been suggested that HO-1 in placenta and endometrial cells may be involved in supporting normal fetal development and local control of endometrial function. The goal of this research was to study the regulation by estrogen of HO-1 in human endometrial epithelial cells. Immortalized human endometrial epithelial (HEE) cells derived from normal endometrium by stable transfection with a telomerase expression vector were used for this study. These cells were transiently transfected with an ARE-luciferase reporter plasmid and cultured in the absence or presence of various concentration of estrogen. Results showed that 10 nM estrogen induced a 5-fold increase in luciferase activity. When estrogen was combined with the known Nrf2 activator, TBHQ, reporter activity increase up to 15-fold. These results coincided with a 2- and 3.3-fold induction in HO-1 mRNA expression by estrogen and estrogen + TBHQ, respectively as assessed by quantitative RT-PCR. Sulforaphane is a compound found in broccoli that has know anticancer properties. When estrogen was combined with sulforaphane (.2 μM) there was a 20-fold increase in luciferase activity; which also coincided with a 13.1- fold increase in HO-1 mRNA expression by estrogen +sulforaphane. Together, these results demonstrate the ability of estrogen either alone or combined with a Nrf2 activator to upregulate HO-1 expression. This activity may be instrumental in the protection of a developing embryo from free radical or other oxidative stresses.