Novel Keap1-Nrf2 Direct Inhibitors Reduce Estrogen-Induced Effects in Estrogen Receptor-Positive Breast Cancer

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Estrogen-mediated signaling promotes cell proliferation and tumor growth in estrogen receptor-positive breast cancers. Estrogen metabolism produces quinone adducts which cause oxidative DNA damage and potential carcinogenicity. Activation of the transcription factor Nrf2 and downstream cytoprotective genes initiates antioxidant responses and detoxifies xenobiotics. Nrf2 activation can be achieved by inhibiting the protein-protein interaction (PPI) between Keap1 and Nrf2, which activates antioxidant responsive element (ARE) pathway and defends cells against oxidative damage. The purpose of this study was to investigate whether the novel direct inhibitors of Keap1-Nrf2 PPI could reduce estrogen receptor (ER) response in MCF-7, human ER-positive breast cancer cells. MCF-7 cells were treated with 100 pM of estrogen or 10 µM of Keap1-Nrf2 PPI inhibitors (LH601A, LH1092, LH1093, LH1095 and LH1101) with estrogen. mRNA was extracted after 48-hour treatment and RT-qPCR analysis was performed to compare gene expression levels. Our results showed that mRNA level of PGR (progesterone receptor) was increased by estrogen treatment, and this upregulation was reduced by the Keap1-Nrf2 PPI inhibitors. In addition, the Keap1-Nrf2 PPI inhibitors increased the mRNA levels of NQO1 (NAD(P)H quinone oxidoreductase 1) and HO-1 (heme oxygenase-1), which were decreased by estrogen treatment. Our findings suggest that the novel Keap1-Nrf2 PPI inhibitors have an anti-estrogenic effect and antioxidant activity by activating Nrf2. The Keap1-Nrf2 PPI inhibitors may serve as chemopreventive agents in estrogen-stimulated breast cancer. Supported by R25ES020721, Busch Grant and New Jersey Health Foundation.