Targeting Estrogen Signaling in Chemoprevention of Breast Cancer

Qun Zhou
University of Maryland, USA

Exposure to higher levels of estrogen produces genotoxic metabolites that can stimulate mammary tumorigenesis. Induction of NF-E2-related factor 2 (NRF2)-dependent detoxifying enzymes (e.g., NAD(P)H-quinone oxidoreductase 1 (NQO1)) is considered an important mechanism of protection against estrogen-associated carcinogenesis because they would facilitate removal of toxic estrogens. We found that estrogen-receptor (ER) signaling suppresses NRF2-dependent gene transcription. Inhibition of ERα expression by the novel antiestrogen shikonin reverses the inhibitory effect of estrogen on NQO1 expression. As a consequence, a chemoprevention study was undertaken to monitor the impact of shikonin on DNA lesions and tumor growth. Treatment of MCF-7 breast cancer cells with shikonin inhibits estrogen-induced 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of DNA damage. NQO1 deficiency promotes estrogen-dependent tumor formation, and shikonin inhibits estrogen-dependent tumor growth in an NQO1-dependent manner in MCF-7 xenografts. These results suggest that estrogen-receptor signaling pathway has an inhibitory effect on NRF2-dependent enzymes. Moreover, shikonin reverses the inhibitory effects of estrogen on this pathway and may contribute to breast cancer prevention.