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Using small molecule estrogen receptor biomodulators to identify new pathways and as anticancer drugs

David J Shapiro
University of Illinois, USA

Estrogens, acting via estrogen receptor (ER), stimulate cell proliferation, and tumor growth. Endocrine therapy targeting these tumors using aromatase inhibitors to inhibit estrogen production, and tamoxifen and other antiestrogens that compete with estrogens for binding to ER, is a mainstay in breast cancer treatment. Selection and outgrowth of resistant tumors is common. Screening identified a lead non-competitive ER inhibitor. At sub-micromolar concentrations, the inhibitor blocked proliferation of ER positive breast, ovarian and endometrial cancer cells-including cells resistant to tamoxifen and Fulvestrant/Faslodex/ICI 182,780. The compound had no effect in ER negative cells. In a mouse xenograft model, the inhibitor was not toxic and induced rapid and substantial tumor regression. This unusual ER inhibitor is so effective because it targets multiple pathways. Independent of its other effects, the compound rapidly inhibits estrogen-ER induction and repression of gene expression. Chromatin immunoprecipitation (ChIP) shows the compound inhibits recruitment of ER to regulatory regions of estrogen responsive genes. The compound also acts outside the cell nucleus to regulate pathways not previously linked to ER action. Subsequent investigation revealed that the inhibitor distorts and amplifies a previously undescribed action of estrogen and ER, leading to death of the ER containing cancer cells. Our studies demonstrate the potential of targeted cell-based screening to reveal new pathways of action, coregulators and small molecule therapeutic candidates; even in a system as intensively studied as ER positive cancer. Supported by NIH DK-017909.

Biography

David J Shapiro received his Ph.D. from Purdue University, did postdoctoral work at Stanford University School of Medicine and was a Guggenheim Fellow in the Center for Cancer research at MIT. He is the author of more than 100 research papers and book chapters in the field of steroid hormone receptor action and has served on the Editorial Boards of the Journal of Biological Chemistry (JBC), Molecular Endocrinology and other journals. Most current research focuses on identification and characterization of novel steroid receptor biomodulators; using biomodulators to identify previously undescribed pathways and evaluating them as anticancer drugs.

djshapir@life.illinois.edu