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tamoxifen. These Est(+) cells are also more resistant to apoptosis induced by Est and aromatase inhibitors. The mechanisms by which ER+ breast cancers can become independent of Est are not well understood. We have found that hypoxia or hypoxia mimetic compounds, which reduce oxygen availability, significantly increase the growth rate and survival of Est+ cells. We hypothesize that increased cell survival and proliferation during hypoxia is caused, in part, by increased HIF-1/NfKB expression, and that increased NfKB expression in Est+ cancers confers a growth advantage independent of Est. To test this hypothesis, we will use pharmacologic and molecular strategies to modulate NfKB in Est+ cells; assess the effects of NfKB on Est+ growth and survival; and we will determine the role of NfKB in driving Est+ cancer growth in vivo. In addition, we will determine the role of estrogen in regulating NfKB expression and NfKB function. The specific objectives of this proposal are (1) to evaluate the role of NfKB in estrogen-independent growth of Est+ cancer cells, (2) to determine the effects of NfKB inhibition on Est+ breast tumor growth and survival in xenograft mouse models, and (3) to determine the effects of estrogen on NfKB expression and function. The goal of the proposed study is



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