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(Article begins on next page)

## Modulation of cellular proliferation and immediate early genes in normal and tumor-derived mammary cells by kinase inhibitors of the EGFR, IGFR, ERK1/2 and PI3K pathways.

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In the mammary gland, during the different phases of the reproductive cycle, moments of tissue growth with increased cellular proliferation are followed by moments of tissue involution, with augmented cellular apoptosis. These phases are regulated by endocrine hormones (estrogens, progesterone, etc) and local acting growth factors (EGFs, IGFs, etc). An altered cellular response to these signals may cause deregulated proliferation within this tissue, with increased cancer susceptibility.

We used tumorigenic and non-tumorigenic mammary cells obtained from different species to examine how inhibitors of tyrosine kinase receptors (EGFR, IGFR) and downstream signaling pathways (ERK1/2 and PI3K-Akt) important during mammary growth, could alter proliferation and modulate the immediate early genes (IEGs) EGR1, JUN and FOS.

IGF-1 RTK inhibitor cyclolignan PPP blocked growth of all mammary cells lines, induced G2/M block, but did not modulate any IEGs. This result possibly reflects an aspecific effect of this molecule. Inhibiting the PI3K-Akt pathway with wortmannin did not influence cellular proliferation nor IEGs expression. EGFR inhibition with AG1478 and ERK1/2 inhibition with UO126 acted similarly. Cell proliferation was reduced to a various extent and there was an accumulation in the G0/G1 phase of the cycle. EGR1 and FOS IEGs were decreased but JUN expression was unaltered. Mammary cells that were less sensitive to EGFR-ERK1/2 inhibition, showed higher levels of basal FOS mRNA expression together with complete FOS recovery after 8h of treatment with the inhibitors. Therefore, in mammary cells, EGFR seems to be a mayor modulator of both EGR1 and FOS by acting through ERK1/2.