32) completely abolished m2R- or EGFR-induced RGS16 phosphorylation, suggesting that, in these cells, EGFR is the kinase primarily responsible for RGS16 phosphorylation. Recombinant purified RGS16 mutant proteins Y168F and Y168/177F, but not the RGS16Y177F, demonstrated diminished GAP activity on Gai1.However, all three mutant proteins were unable to inhibit m2R-induced MAP kinase activation in HEK 293T cells. Purified EGFR kinase enhanced the catalytic activity of RGS16 in vitro. These results suggest that EGFR and/or src tyrosine phosphorylation of both residues may regulate the activity of RGS16 in mammalian cells. This study also provides the first evidence that receptor tyrosine kinase pathways may negatively regulate activity of G protein-coupled signaling pathways.

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Testosterone inhibits estradiol's mitogenic effects upon primate mammary epithelium in vivo

In normal cycling women, the ovary produces balanced amounts of estrogen, androgen and progesterone. Years ago, it was found that 'replacing' estradiol alone in menopausal or oophorectomized women led to uterine hyperplasia and cancer, and that this effect could be prevented by giving progesterone, which opposes estrogen's proliferative effect upon uterine cells. Unfortunately, progesterone does not oppose and may even augment estrogen's stimulatory effect upon mammary epithelium. Estrogen is thought to increase the risk of breast cancer primarily by increasing mammary epithelial proliferation (MEP). Observing the anti-mammogenic effects of androgens in many clinical situations, we hypothesized that androgens may oppose estrogen's mitogenic effects upon the mammary epithelium. To test this hypothesis, we treated ovariectomized rhesus monkeys with sc pellets containing vehicle (7), estradiol (E2, n=4), E2 & progesterone (E2/P, n=5) or E2 plus testosterone (E2/T, n=5). The MEP index, assayed by Ki67 immunoreactivity, was increased 7-fold in both E2 and E2/P groups ($P<0.0001$). The E2/T group, however, showed only a 3.5-fold increase in MEPI, despite estradiol levels that were significantly higher than the other active treatment groups. Thus, addition of testosterone to the hormone replacement treatment (HRT) significantly attenuated E2's mitogenic effects. We repeated the study using physiological rather than pharmacological doses of ovarian steroids. In this experiment, E2 alone and E2/P increased MEPI compared to placebo controls by ~4-fold, while the E2/T combination did not significantly increase the MEPI above control values (E2 levels were similar in the 3 active treatment groups). To determine if endogenous testosterone normally inhibits endogenous estradiol's proliferative effects, intact, cycling monkeys were treated with flutamide, an androgen receptor antagonist or placebo. The MEPI was increased by ~2-fold in the flutamide group ($P = 0.03$). These data suggest that testosterone may serve as a natural, endogenous protector of the breast and limit estrogen's mitogenic and cancer promoting effects on mammary epithelium. Unfortunately, in giving menopausal women oral estrogen for HRT, we may inadvertanly aggravate estrogen-induced risk, since oral estrogens decrease testosterone production and availability. Thus, we propose clinical trials evaluating testosterone as a component of menopausal hormone replacement

Federica Dipalma, NIDCD

Identification of the Varitint-Waddler gene: a link between deafness and pigmentation defects.

Positional cloning of mouse deafness mutations has proven an important means for