Tamoxifen and gonadal steroids inhibit colon cancer growth in association with inhibition of thymidylate synthase, survivin and telomerase expression through estrogen receptor beta mediated system

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Estrogen receptor beta (ERbeta) mediated system was tested in three colon cancer cell lines with different sensitivities. These cell lines express ERbeta and androgen receptor (AR) but not the classic estrogen receptor ERalpha. Combinations of ERbeta ligands such as estradiol (E(2)), 17 epiestriol (17E(3)), quercetin (Q) with tamoxifen (TMX) showed marked growth inhibition. The IC(50) were: 2. 0+/-.03x10(-15), 3.0+/-.3x10(-10) and 1.2+/-.5x10(-14) M for DLD-1, DLD-1/5FU and DLD-1/FdUrd, respectively (TMX+E(2) treatment, mean+/-.SD, n=3). The IC(50) of TMX+17E(3) were 3.5+/-.8x10(-8), 2. 6+/-.9x10(-8) and 1.4+/-.1x10(-14) M and that of TMX+Q treatment were 3.4+/-.1x10(-9), 3.6+/-.2x10(-9) and 2.6+/-.1x10(-9) M, respectively. This inhibition was significantly different from single agent treatment at the probability level of P<0.002. Thymidylate synthase expression and survivin expression were also markedly inhibited. The inhibition was highest with TMX+Q and lowest with TMX+dehydroepiandrosterone (DHEA). The expression of telomerase was also inhibited by TMX but combination with ERbeta agonists reversed the inhibition. The cellular sensitivity to 5FU was increased: TMX+E(2), TMX+17E(3) and TMX+Q were 1.7+/-.5x10(-5), 8. 4+/-.2x10(-8), 8.2+/-.2x10(-8) and 6.3+/-.3x10(-8) M for DLD-1 cells and 7.7+/-.8x10(-5), 9.1+/-.9x10(-7), 1.5+/-.3x10(-9) and 5.7+/-.2x10(-8) M for DLD-1/5FU. DLD-1/FdUrd cells had IC(50) of 8. 5+/-.6x10(-5), 1.8+/-.8x10(-8), 37+/-.1x10(-9) and 1.6+/-.1x10(-9) M (mean+/-.SD) for the control, TMX+E(2), TMX+17E(3) and TMX+Q. The present data indicate that ERbeta ligands in combination with TMX may have tumor static effects on colon cancer cells.

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