Estradiol up-regulates antiapoptotic Bcl-2 messenger ribonucleic acid and protein in tumorigenic ovarian surface epithelium cells.

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摘要

Abstract

Most epithelial ovarian tumors appear to arise from the ovarian surface epithelium (OSE). Even though it has been suggested that estrogen may be associated with ovarian tumorigenesis, the exact role of estrogen in the regulation of apoptosis in neoplastic OSE cells remains uncertain. Immortalized OSE (IOSE) cell lines were generated from human normal OSE. These cell lines represent early neoplastic (IOSE-29), tumorigenic (IOSE-29EC), and late neoplastic (IOSE-29EC/T4 and IOSE-29EC/T5) transformation stages from human normal OSE. The present studies demonstrated that both mRNAs and proteins of estrogen receptor (ER) alpha and beta were expressed in IOSE cell lines. No difference was observed in normal OSE and IOSE-29 cells, whereas treatment with 17beta-estradiol (E(2); 10(-8)-10(-6) M) resulted in an increased thymidine incorporation and DNA content per culture in IOSE-29EC cells. This effect of E(2) was attenuated with tamoxifen treatment (10(-6) M), the estrogen antagonist, suggesting that the effect of E(2) is mediated through specific ERs. There was no stimulatory effect on thymidine incorporation before day 6, but after 6 days of E(2) treatment, thymidine incorporation was significantly increased. Because the ratio of thymidine incorporation to DNA content per culture did not change, this E(2) effect does not appear to indicate stimulation of proliferation but, rather, inhibition of apoptosis. In addition, treatment with tamoxifen (10(-6) M) induced apoptosis up to 3-fold in IOSE-29EC cells, whereas cotreatment with E(2) (10(-8)-10(-6) M) plus tamoxifen attenuated tamoxifen-induced apoptosis in a dose-dependent manner. Both proapoptotic bax and antiapoptotic bcl-2 at messenger RNA (mRNA) and protein levels were expressed in IOSE cell lines. Interestingly, treatments with E(2) resulted in a significant increase of bcl-2 mRNA and protein levels (2- and 1.7-fold, respectively), whereas no difference

was observed in bax mRNA level. Thus, E(2) may enhance survival of IOSE-29EC by up-regulating bcl-2, and antiapoptotic bcl-2 may be a dominant regulator of apoptotic pathway in these cells. In conclusion, the present study indicates that early neoplastic (IOSE-29), tumorigenic (IOSE-29EC), and late neoplastic (IOSE-29EC/T4 and T5) OSE cells expressed both ERalpha and ERbeta at the mRNA and protein levels. In addition, E(2) prevented tamoxifen induced-apoptosis through ERs. The mechanism of E(2) action may be associated with up-regulation of bcl-2 gene at mRNA and protein levels. These results suggest that estrogen may play a role in ovarian tumorigenesis by preventing apoptosis in tumorigenic OSE cells.

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