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An in vitro breast cell immortalisation assay

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Keywords

Chemopreventive agent, immortalization, Li-Fraumeni syndrome, telomerase

Context

In most normal human cells there is a progressive shortening of chromosomal telomeres with successive cell divisions, leading ultimately to cell senescence. Cellular immortalisation is thought to occur by the reactivation of a telomerase which prevents telomere shortening and consequent growth arrest. As telomerase activity has been detected in 90% of cancers tested, it may be a good target in cancer treatment. Early-onset breast cancer is prevalent amongst patients with Li-Fraumeni syndrome (LFS). In previous studies, the authors demonstrated that normal breast epithelial cells from women with LFS immortalise spontaneously in culture. Normal breast epithelial cells were used in an in vitro assay to investigate the effects of chemopreventive and antitelomerase agents on telomerase activity and the immortalisation process.

Significant findings

Treatment of breast epithelial cells with established chemopreventive agents, such as oltipraz, tamoxifen, 9-*cis*-retinoic acid, 13-*cis*-retinoic acid and difluoromethylornithine, resulted in fewer spontaneous immortalisation events than those compared with solvent-treated controls. This treatment was only significant, however, for treatment with tamoxifen, 9-*cis*-retinoic acid and 13-*cis*-retinoic acid. Transfection with antisense or dominant-negative telomerase RNA had a similar inhibitory effect on the incidence of spontaneous immortalisation. Telomerase activity was absent in all preimmortal cells and present in all clones of spontaneously immortalised cells.

Comments

This study describes a good model system for testing the effects of chemopreventive agents, and begins to address the molecular basis of their activity. As the reactivation of telomerase is an early event in cancer it makes sense to design drugs that target it specifically. Whether these agents work by inhibiting telomerase activity is an important question and is the subject of ongoing work by this laboratory. The retinoic acid analogues were particularly successful in this study so it will be interesting to see them investigated further. The effect of tamoxifen is an important finding, especially with respect to the prophylactic tamoxifen trials that are ongoing. However, the effect is also intriguing since these normal cells do not contain significant amounts of the oestrogen receptor. My only criticism is the use of mixed breast cell populations in MCDB 170 media, which encourages the growth of the basal myoepithelial cell type, not of the luminal epithelial cells that become malignant.

Methods

Cell culture, retroviral infection, transfection, PCR, fluctuation analysis

Additional information

Cells from LFS patients may be difficult to come by and human mammary epithelial cells, which are commercially available, may provide a useful alternative. These have spontaneously immortalised in culture but whether they exhibit a sufficient frequency of events would need to be studied.

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