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Stromal-epithelial interactions lead to tumour formation in irradiated mice

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Keywords

COMMA-D, irradiated, mammary, stroma, tumour

Introduction

The disruption of epithelial-stromal interactions may facilitate the growth of genomically unstable epithelial cells leading to tumour formation. Ionising radiation is a known carcinogen of the human breast and it has previously been shown to lead to a rapid remodelling of the mammary gland extracellular matrix (ECM). Therefore, the possibility of an indirect tumorigenic effect of irradiation on epithelial cells via the stroma was investigated.

Aims

To examine the effects of transplanting the mouse mammary cell line, COMMA-D into cleared fat pads (CFPs) of irradiated mice.

Comments

This study explores the possibility that cancer may be a physiological response to an abnormal environment. It shows that genetic modification of epithelial cells by itself may be insufficient, but in the appropriate 'damaged' environment, may lead to tumour formation. This is a convincing and thought-provoking paper.

Methods

Known numbers of cultured COMMA-D mouse mammary epithelial cells (passage 15-24) were transplanted into the CFPs of either untreated or irradiated female BALB/c mice. Anaesthetised animals were used for hemibody irradiation. Tumour size and volume was measured. Vimentin, keratin, p53 and 4'-6-diamidino-2-phenylindole (DAPI) staining was carried out on cultured cells and on tumour sections. H&E and p53 staining was performed on paraffin-embedded whole mounts.

Results

Tumours arose in CFPs of irradiated mice as a function of cell number. In four experiments tumours grew in 30 of 36 irradiated hosts compared to 8 of 36 sham-irradiated animals. Tumours only occurred in sham-irradiated mice when greater than one million cells were injected and the resulting tumour size was significantly smaller than in irradiated mice. However, the transplant take of normal mammary tissue fragments was equivalent in both sets of mice. Tumour cells, but not cells in the surrounding stroma, stained for p53, vimentin and keratin, thus demonstrating their COMMA-D origin. Tumour incidence as a function of time showed the optimum time of transplantation to be 3 days post-irradiation. No tumours were found in non-irradiated fat pads of hemibody-irradiated mice.

Differential trypsinisation and selective cloning of COMMA-D cells gave rise to either spindle shaped, or flat polygon shaped, subpopulations of cells. The former stained more strongly for vimentin and the latter for keratin and both were p53-positive. The spindle shaped cells produced significantly more tumours in irradiated mice than the polygonal cells. However, although they gave rise to far fewer tumours in sham-irradiated hosts, these were of a similar size to those in the irradiated mice.

Discussion

This study demonstrated that ionising radiation may lead not only to genetic damage, but also to an altered microenvironment which facilitates the development of malignant tumours. This could be due to ECM remodelling, changes in cytokine production and activity, and receptor expression leading to modified cell-cell interactions. Since ionising radiation of mouse mammary tissue has previously been shown to induce transforming growth factor-β activation, a possible tumourigenic role for this growth factor was discussed.

References

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