

CARCINOGENESIS

Know your enemy

In order to defend yourself, it's important to know what weapons your enemy has at their disposal. In the fight against cancer, information about the mechanisms by which carcinogens promote tumour development is essential for developing treatments that can protect against or counteract their effects. A paper by Barcellos-Hoff and colleagues now indicates that ionizing radiation can cause cancer by epigenetic mechanisms as well as by mutagenesis, providing a new insight into how best to protect against this carcinogen.

Although the ability of ionizing radiation to induce DNA damage is the accepted basis for its carcinogenic properties, there is evidence to indicate that it might also contribute to tumour progression by disrupting normal cell–cell and cell–matrix interactions. The loss of such interactions is crucial for the development of tumours, as it removes the constraints on growth and motility that are usually imposed on a cell by its surroundings. Barcellos-Hoff and co-workers tested whether exposing human mammary epithelial cells (HMECs) to ionizing radiation induces morphological changes that might promote tumour progression independently of DNA damage. They exposed HMECs to sublethal doses of ionizing radiation and studied the effects on cellular interactions and morphogenesis in colonies that were produced from the irradiated cells.

The authors saw a severe disruption of the organization of these cells into the acinar structures that are usually formed in mammary epithelial tissue. Importantly, this was seen in the progeny of irradiated cells for several generations after irradiation. The expression patterns of several proteins that are crucial for mediating normal cellular interactions were also abnormal in these colonies. E-cadherin and β -catenin, which are vital for

cell–cell adhesion, and connexin 43, a component of gap junctions, were present at decreased levels at their normal sites of localization, indicating that ionizing radiation disrupts normal cellular contacts.

These changes are unlikely to be due to the mutagenic effects of irradiation, as they were seen in almost all surviving cells — far more than would be expected to show these effects because of mutation. This indicates that ionizing radiation induces heritable changes in cellular organization that could promote tumour development independently of its mutagenic properties, predisposing cells to further malignant progression. These results indicate that therapies that are used to prevent tumour development caused by exposure to ionizing radiation should include agents that prevent or counteract the disruption to cellular organization, providing a new line of defence against this carcinogen.

Louisa Flintoft

References and links

ORIGINAL RESEARCH PAPER Park, C. C. *et al.* Ionizing radiation induces heritable disruption of epithelial cell interactions. *Proc. Natl Acad. Sci. USA* **100**, 10728–10733 (2003)

FURTHER READING Bissell, M. J. & Radisky, D. Putting tumours in context. *Nature Rev. Cancer* **1**, 46–54 (2001)

WEB SITE

Mary Helen Barcellos-Hoff's lab:
http://www.lbl.gov/lifesciences/labs/barcellos-hoff_lab.html



TRIAL WATCH

Advance for aromatase inhibitors

A large international clinical trial has led to the discovery that postmenopausal survivors of early-stage breast cancer who take the drug letrozole after completing 5 years of tamoxifen therapy have a significantly reduced risk of cancer recurrence.

Tamoxifen is widely used to prevent breast cancer recurrence in postmenopausal women with hormone-responsive tumours. It initially functions as both an antagonist and a partial agonist of the oestrogen receptor, but over time, its agonistic action increases, which is believed to reduce its antitumour activity. Additional treatment approaches are therefore needed. Aromatase inhibitors, which prevent oestrogen synthesis, are good candidates, as they have been shown to be effective in treating women with metastatic disease that progresses despite tamoxifen therapy.

In the 6 November issue of the *New England Journal of Medicine*, Goss *et al.* analysed the efficacy of the aromatase inhibitor letrozole as a second-line therapy in women with oestrogen-responsive breast cancer. In a Phase III double-blind clinical trial that involved 5,187 women, they found that letrozole, when taken after 5 years of tamoxifen therapy, significantly improves the odds for disease-free survival. In total, 132 women in the placebo group experienced disease recurrence, compared with 75 women on letrozole. The 4-year disease-free survival rate for women who received letrozole was 93%, compared with 87% of the women in the placebo group. Women who received letrozole had a reduction in the number of recurrences of cancer in their previously affected breast, a reduction in the number of new cancers in the opposite breast and also a reduction in metastatic tumours.

The side effects of letrozole, which was taken once a day in pill form, are very similar to those experienced by women undergoing menopause. More women in the letrozole group experienced low-grade hot flashes, arthritis, arthralgia and myalgia. Furthermore, they developed osteoporosis and fractures more frequently than women in the control group. As aromatase inhibitors decrease oestrogen levels, they are likely to reduce bone-mineral density.

The clinical trial was halted early, after a median follow up of only 2.4 years, because of the positive results. However, in an accompanying editorial, John Bryant and Norman Wolmark state that the short period of follow-up diminishes the clinical utility of the data. They point out that an overall survival effect, which was not statistically significant in this trial, might never be documented. Furthermore, nothing is known about optimal duration of treatment beyond 2–3 years, or about the long-term side effects of letrozole therapy. Less than 1% of women in the trial received over 4 years of letrozole therapy.

In a second editorial, Harold Burstein also warns that these data should not be interpreted as a recommendation for the use of aromatase inhibitors as primary adjuvant therapy. Several other trials are underway to compare aromatase inhibitors with tamoxifen as adjuvant therapy for the first 5 years after diagnosis.

ORIGINAL RESEARCH PAPER Goss, P. E. *et al.* A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N. Engl. J. Med.* 9 Oct 2003 (doi: 10.1056/NEJMoa032312)

FURTHER READING Bryant, J. & Wolmark, N. Letrozole after tamoxifen for breast cancer: what is the price of success? *N. Engl. J. Med.* 9 Oct 2003 (doi: 10.1056/NEJMe038167) | Burstein, H. Beyond tamoxifen: extending endocrine treatment for early-stage breast cancer. *N. Engl. J. Med.* 9 Oct 2003 (doi: 10.1056/NEJM038174)