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CARCINOGENESIS

Know your enemy

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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.

References and links

ORIGINAL RESEARCH PAPER
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FURTHER READING
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WEB SITE
Mary Helen Barcellos-Hoff's lab