Summary: How Radiation Damages the Extracellular Environment and Why It Is Important

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Integrative radiation carcinogenesis: interactions between cell and tissue responses to DNA damage
Mary Helen Barcellos-Hoff. *Seminars in Cancer Biology.* 2005 Apr;15(2):138-48.

Definitions

Neoplasia- Literally means "new growth." Neoplasia in cancer research refers to abnormal and uncontrolled growth of new cells, and thus has the same meaning as tumor. The neoplasia may be benign or malignant.
TGFß- Secreted by many different cell types, stimulates wound healing but in vitro is also a growth inhibitor for certain cell types.
Immunofluorescent- Any method in which a fluorescent-labeled antibody is used to determine the location or detect the presence of the corresponding antigen.
Murine- Of or relating to members of the rodent family; includes rats and mice.
Fat pads- An accumulation of connective tissue which has been specialized to store fat.

Background

Recent research regarding the mechanistic aspects of cancer origin and growth has repeatedly called attention to the multicellular dynamics between the target cells and the stromal environment. It has become widely accepted that disruption of cell-cell interactions as well as tissue architecture can act as a primary driver of carcinogenesis. An encompassing model of cancer as a "phenomenon of tissues," rather than divergent individual cells, is changing the approach of scientists. This paper investigates changes in the extracellular environment of irradiated mammary tissue in an effort to identify abnormal signaling interactions and neoplastic activation.

Methods

Literature addressing the hypothesis that ionizing radiation acts in a non-mutational manner to promote cancer is reviewed. Studies from the author used mouse models and human cells in culture to evaluate radiation effects.

Results

Experiments that show radiation causes changes in the extracellular matrix and stroma are reviewed. Some effects are rapid, such as unmasking of a key microenvironmental signaling molecule, TGFß, is evident within an hour of radiation exposure and is persistently detected for no less than one week. Studies showed that TGFß controls the activity of p53, a classic tumor suppressor molecule. This result is both "surprising and unprecedented," as p53 has long been thought to be the master of its own engagements. The team proposes TGFß to be an extracellular sensor of damage in charge of orchestrating diverse multicellular fates, while p53 manages the individual cell response. Confirming these findings, several other studies have linked p53 status and TGFß responsiveness in cancer cells and shown that such cells exhibit a very high incidence of p53 mutation and disrupted TGFß signaling. Appropriate p53 and TGFß signaling responses support genomic stability as well as a healthy microenvironment.

Transplantation studies of murine mammary epithelial cells into irradiated and non-irradiated stromal fat pads show irradiated stroma drastically increasing the likelihood of tumor development, regardless of the fitness of the epithelial tissue. Tumor incidence was 2-4 fold greater and tumors were up to five times larger when epithelial cells were allowed to proliferate in a previously irradiated mouse. This study indicates that the irradiated stroma can promote neoplastic progression in unirradiated epithelial cells.

The response of human mammary epithelial cells to ionizing radiation was determined to be negative, as the irradiated tissue displayed pronounced disorganization and superfluous cellular growth. Notably, radiation exposure appears to induce a heritable derangement of pathways, exhibited in the daughters of irradiated cells. Thankfully, there is some evidence that restoration of the microenvironment to its customary state may be a promising therapeutic tool.

Discussion

An awareness of cancer as a multifaceted, complex mechanism of cellular interaction has evolved from a naive sense of the sole involvement of one class of cells. This study, amid numerous others published

in the last five years, has revealed cancer as a disturbance of the tissue rather than abnormal cells. The carcinogenic effect of ionizing radiation in terms of both non-mutagenic, via disruption of microenvironmental signaling, promotes cancer progression. Approaching cancer as a disease of the tissue offers opportunities for both novel therapeutic techniques and explorational research.

Implications for Future Research

The studies show that the composition of the irradiated microenvironment is a function of tissue type, radiation dose, and radiation intensity. Presently, relatively little is known about the extracellular factors that affecting appropriate regulatory responses. Further research will identify such factors. Will these findings present potential targets for chemoprevention?

The new human mammary epithelial model used in this study presents numerous opportunities for more research concerning the specific mechanisms at work in the microenvironment of mammary tissue. The team is currently working to understand how the stromal microenvironment might elicit the genetic instability which ultimately leads to cancer. Future plans are directed towards defining the molecular mechanisms of normal and irradiated mammary tissue.