Summary: Radiation and Tissue Microenvironment

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Radiation and the Microenvironment-Tumorigenesis and Therapy
Mary Helen Barcellos-Hoff, Catherine Park, Eric Wright. *Nature Cancer Review*. 2005 Nov;5(11):867-75.

Definitions

TGFß- A protein secreted by many different cell types, stimulates wound healing but in vitro is also a growth inhibitor for certain cell types.

Radiation therapy- Ionizing radiation is energy capable of producing a state change called ionization in substances through which it passes. When a person is exposed to radiation, the energy interacts with macromolecules like DNA or protein, or with the water molecules that make up most tissue. The interaction with water molecules creates electrically charged atoms, or "ions" that are also highly energized and alter the macromolecules. Ionizing radiation is used for both diagnostic (very low dose) and therapeutic (high doses) medical applications, which means that people are exposed over a very large dose range. Cancer therapy may deliver cumulative doses of up to 80 Gy (Gy is a unit of dose) to the tumor, which diagnostic imaging results in doses of 0.03-0.001 Gy. Epidemiological studies of cancer incidence have shown significant risk for some cancers at doses above 0.5 Gy. Understanding the carcinogenic effect of radiation is one of the interests of Dr. Barcellos-Hoff

Extracellular Matrix- A matrix is a term used to describe the substance surrounding a cell, which is composed of proteins and complex sugars. It has recently become clear that the ECM can influence the behavior of cells quite markedly, an important factor to consider when growing cells in vitro: removing cells from their normal environment can have far reaching effects.

Background

Ionizing Radiation (IR) can act as both a carcinogen and a therapeutic agent. Low dose exposure can increase an individual's risk of developing cancer, while high doses are capable of slowing or halting tumor growth. Cancer research from the past two decades has revealed that IR has multiple multicellular effects since the behavior of any single cell is affected by its surrounding environment. The microenvironment of radiation-damaged tissues is being increasingly studied in an effort to learn more about epigenetic programming and tumorigenesis.

Investigations

This article reviews literature from the last decade examining the *in vitro* and *in vivo* effects of IR radiation on tissue damage. Specifically, the review outlines the most recent topics including the response of the microenvironment to IR damage, the actions and effects of transforming-growth factor ß, IR-induced inflammation, radiation induced carcinogenesis, and radiation therapy. Examples of post-IR induced alteration of the microenvironment are given while highlighting the role of IR in therapeutic intervention.

Results

IR alters the tissue microenvironment via two distinct mechanisms. The first, known as the *direct effect*, refers to the interaction of IR energy with matter, resulting in molecular ionization. Ionization is the process by which an atom or molecule loses or gains electrons, thereby acquiring an electric charge. Charged molecules are much more likely to react unfavorably with surrounding tissue in an effort to restore neutrality. The second cause of radiation damage stems from the *indirect effect*, which is due to the interaction of energy with water to create of reactive oxygen species. Indirect effects are estimated to cause 60% of all radiation damage since water is the most abundant molecule in the human body.

The Response of the Microenvironment: As starkly apparent during embryonic differentiation, the immediate environment of a maturing cell decidedly influences development. In most instances the microenvironment functions to keep cellular proliferation at bay; in tumorigenesis, however, the communication pathways between abnormally proliferating cells and regular stromal cells are disrupted. In addition, it has been observed that in localized tissue the stem-cell compartment is most sensitive to radiation damage.

The Action of Transforming Growth Factor ß: TGFß has previously been proposed to be the single most important mediator of microenvironmental response to ionization radiation damage. TGFß controls both homeostasis and apoptosis (programmed cell death, a good thing, since abnormal cells are selectively eliminated). In two recent studies, TGFß has been observed to protect the stem cell compartment from radiation damage. The notion that cancer is caused by an altered microenvironment and a disrupted cell signaling pathway (as opposed to DNA damage) is beginning to emerge.

IR-Induced Inflammation: Ionization radiation causes significant amounts of indirect damage, the result of which is the production of reactive oxygen species, a common cause of persistent inflammation. The potential consequence of inflammation is damage of epithelial cells by increasing DNA mutation and thus the probability of developing cancer. Some studies of Japanese survivors of the atomic bomb suggest that one consequence of IR might be that chronic IR-induced inflammation, and hence, ongoing, long-term oxidative damage.

Radiation-Induced Carcinogenesis: Various studies have shown that IR leads to a rapid and persistent activation of the microenvironment, suggesting a third class of carcinogenic mechanisms distinct from both mutation and mitotic disturbance. Experiments were performed to test this hypothesis and a higher rate of tumor production was observed when mammary epithelial cells were implanted into irradiated stroma (microenvironment) instead of unexposed stroma. Studies of leukemia and the bone-marrow environment confirm these results while implicating TGFß and the utility of functional signaling pathways.

Radiation Therapy- Radiation therapy utilizes high doses of radiation to eliminate cancer cells while attempting to spare normal tissue. Nonetheless, it is undeniable that significant and persistent remodeling of the extracellular matrix occurs that may contribute to therapeutic benefit. Analysis of breast tissue from patients who have undergone radiation therapy show epithelial abnormalities as well as vascular tissue changes. With this in mind, appropriate limits are set in order to minimize damage to healthy tissue.

Implications for Future Research
Appreciation that radiation acts beyond DNA damage leads to different ideas about how it acts as either a carcinogen or therapeutic agent. If persistent changes in the microenvironment via processes like inflammation are important to whether cancer develops after low dose exposure to radiation, then preventative agents can be administered to people exposed accidentally or therapeutically to reduce the risk of cancer.