

Biological Response to Radiation Mediated through the Microenvironment and Multicellular Interactions

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Modeling multicellular radiation responses coordinated via extracellular signaling could have a significant impact on the extrapolation of human health risks from high dose to low dose/rate radiation exposure. We propose that the cell biology of irradiated tissues reveals a coordinated multicellular damage response program in which individual cell contributions are primarily directed towards suppression of carcinogenesis and reestablishment of homeostasis (1, 2).

We identified transforming growth factor β 1 (TGF β) as a pivotal signal in irradiated tissues. Recently we have shown that TGF β suppresses genomic instability by controlling the intrinsic DNA damage response and centrosome integrity. However, TGF β also mediates disruption of microenvironment interactions, which drive epithelial to mesenchymal transition in irradiated human mammary epithelial cells. This apparent paradox of positive and negative controls by TGF β evident in single cell type culture models may manifest differentially as a result of interactions of multiple cell types in tissues.

There are many examples that homeotypic and heterotypic cell-cell interactions can either suppress or promote epithelial carcinogenesis. Many studies have shown that recruitment and/or subversion of normal fibroblasts, vascular, immune and inflammatory function are requisite in oncogenic mouse models (reviewed in (3-6). Bauer and colleagues have shown that transformed fibroblasts are eliminated in cell populations through intercellular induction of apoptosis (7). Terzaghi-Howe demonstrated that normal epithelial cells suppress transformed phenotypes induced by radiation in an ex vivo trachea (8), while Clifton et al. showed that normal epithelial cells inhibit irradiated rat mammary epithelial cells from undergoing neoplastic progression (9). Normal stromal cells suppress neoplastic potential, but our laboratory has shown that high dose radiation alters the stroma to promote tumorigenesis of non-irradiated epithelial cells (10).

Together these data underscore the complexity of tissue responses to damage and the multicellular nature of cancer as a disease process. The many non-deterministic forks in the road from damage to disease, particularly at low doses, should provide further impetus to rethink the extrapolation of carcinogenic risk based on linear induction of damage.

References

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