Cell Interactions Mediating Radiation Responses and Carcinogenesis

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What can be achieved by identifying multicellular processes in radiation carcinogenesis?

- More complete understanding of radiation carcinogenesis feeds into biologically based cancer risk models for as yet unknown exposures, e.g. space travel
- Tests the biological veracity of LNT for low dose/dose rate where epidemiological data are uncertain
- Serves as a basis for assessing adequacy of protection standards
- Used to identify susceptible populations
- Could provide avenues for protection after radiation exposure
Properties of Cancer Cells

- Excessive proliferation
- Disrupted cellular architecture and morphogenesis
- Ability to subvert the microenvironment
  - Stimulate angiogenesis
  - Escape immune suppression
  - Provoke tissue remodeling
- Motility and invasion
Theories of Carcinogenesis

1900’s
Seed and Soil

1960-90’s
Somatic Mutation

2000
Cancer as an Evolutionary Process and a Ecological System
What distinguishes a complex system from a merely complicated one is that some behaviors emerge as a result of altered relationships between the elements.

http://www.biologydaily.com/biology/Systems_thinking
Is cancer an emergent phenomenon?

- Overexpression of stromelysin, a protease, induces mammary cancer (Cell, 98: 137-146, 1999).
- Deletion of TGFβ signaling in stroma results in epithelial cancer within 6 wk of birth (Science 303:848, 2004)
- Induction of skin cancer by large-T viral antigen, which blocks p53 and Rb, requires B-lymphocytes (Cancer Cell, 2006)
Impeding signaling between cells can cause cancer

- Mouse in which Tgfβ type II receptor is floxed in fibroblasts
- Loss of TGFβ stromal signaling results in epithelial cancer within 6 wk of birth

Bhowmick et al. Science 303:848, 2004
Radiation health effects are system, rather than component, driven.

That is, a property of the tissue rather than the cell.
Targeted vs Non-Targeted Radiation Effects

- Targeted effects are proportional to radiation dose, e.g. cell kill
  - Persistence through genetic sequence like mutation

- Non-targeted effects are responses to damage and often have little dose dependence: switches rather rheostats
  - Persistence by altered interactions or phenotype
We know how radiation can affect genotype

- Radiation has been an excellent probe to discover fundamental biology of genomic challenge:
  - Cell cycle and check points
  - DNA repair
  - DNA damage response
  - Mutagenic processes
  - Replication biology
  - Cell death mechanisms: apoptosis, mitotic catastrophe
Radiation also affects phenotype and cell interactions

- Radiation induced damage elicits network responses that affect:
  - Neighboring cells (e.g. ‘bystanders’)
  - Daughter cells (e.g. genomic instability)
  - Distant cells (e.g. immune and inflammatory systems)

- Which non-targeted radiation effects on phenotypes or cell and tissue interactions sufficiently persistent to affect the development of cancer?

- What are the mechanisms?
Cellular Mechanisms for Low-Dose Ionizing Radiation–Induced Perturbation of the Breast Tissue Microenvironment

Kelvin K.C. Tsai,¹ Eric Yao-Yu Chuang,² John B. Little,¹ and Zhi-Min Yuan¹
Cancer Res 2005; 65: (15). August 1, 2005

1 Radiation induces a senescent phenotype in fibroblasts

2 Senescent fibroblasts produce matrix metalloproteinases

3 Radiation induced senescent fibroblasts alter epithelial morphogenesis and growth

Zhi-Min Huang
Can Res 2006
Radiation Induced Phenotypic Switch

• Radiation primes the progeny of human epithelial cells to undergo epithelial-to-mesenchymal transition (EMT)
• Switch like dose function
• Persistent (weeks)
• Aberrant morphogenesis and increased motility typical of cancer cells

Andarawewa et al. 2008
Andarawewa Accepted 2010
Protection via Cell-Interactions: Selective Apoptosis of Aberrant Cells

- Low doses suppress in vitro transformation (Redpath, 2008)
- Transformed cells are selectively deleted by signaling from normal cells and low dose irradiation augments the efficacy of normal cells (Bauer, 1996; O’Neil, 2007)
- Radiation-induced TGFβ deletes genomically unstable cells in vitro and in vivo (Barcellos-Hoff, 2008)
- Low dose radiation suppresses recombination in vivo (Sykes, 2008)
Activated phagocytic cells produce genetic effects in co-culture

Mutation
Weitzman & Stossel, Science, 212, 546, 1981

Cytogenetic changes

Modification of DNA bases
Dizdaroglu et al., Cancer.Res, 53, 1269, 1993

Transformation
Weitzman et al., Science, 237, 1231, 1985

Radiation induces differentiation to an “activated” cell phenotype

Generates damage in neighbouring cell.

Process may be autocrine or juxtacrine or paracrine
Radiation Chimera Models

Kaplan et al., 1956, 58
Unirradiated thymus transplanted to irradiated mice form tumors

Barcellos-Hoff & Ravani, 2000
Mammary epithelial cells transplanted to irradiated hosts form tumors

Kupperwasser, 2004
Irradiating fibroblasts enable transplantation of human epithelium to mouse mammary stroma

Mancuso et al., 2008
Shielded brain develops tumors in irradiated *Ptch* mice
Oncogenic bystander radiation effects in Patched heterozygous mouse cerebellum

Mariateresa Mancuso*, Emanuela Pasquali†, Simona Leonardi*, Mirella Tanori*, Simonetta Rebessi*, Vincenzo Di Majo*, Simonetta Pazzaglia*, Maria Pia Toni‡, Maria Pimpinella‡, Vincenzo Covelli*, and Anna Saran*§

PNAS 106:12445, 2008
Genetic/Radiation Mammary Chimera

Remove epithelium at 3 wk

Irradiate at 3 mo

Transplant with oncogenic tissue.
Balb/c p53 null Mammary Model

- Aneuploidy, 8 months
- Ductal carcinoma in situ, 8 months
- Tumor latency, 12 months
- Highly heterogeneous histology

Jerry, D.J., et al. (2000). A mammary-specific model demonstrates the role of the p53 tumor suppressor gene in tumor development. Oncogene 19, 1052-
NTE mediated by specific signals affect the latency and features of cancer.
Challenges for Incorporating NTE into Risk Assessment

- Are NTE operational in vivo? YES
- Are NTE relevant to disease causation or modulation? YES
- What is the utility for including NTE in radiation protection and risk modeling?
Non-Targeted Effects are Critical Mechanisms in Radiation Carcinogenesis

- Predicting radiation health effects requires understanding the relationship between targeted and non-targeted radiation effects.

- Non-targeted effects are avenues for protection after exposure.

- A biological model of low (<10 mGy) dose cancer risk should incorporate systems biology principles of complexity and emergence.
The biological rationale for LNT is incomplete

- Cancer is two-compartment problem in which mutant cells must override a suppression by normal tissue.

- Radiation can augment carcinogenesis by acting on both compartments.

- While targeted effects like mutations are dose dependent, non-targeted effects act more like switches, which needs to be understood.
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