Cell Interactions mediating radiation responses and carcinogenesis

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Properties of cancer cells

- Disrupted architecture
- Excessive proliferation
- Ability to invade surrounding tissue
- Ability to evade the immune system

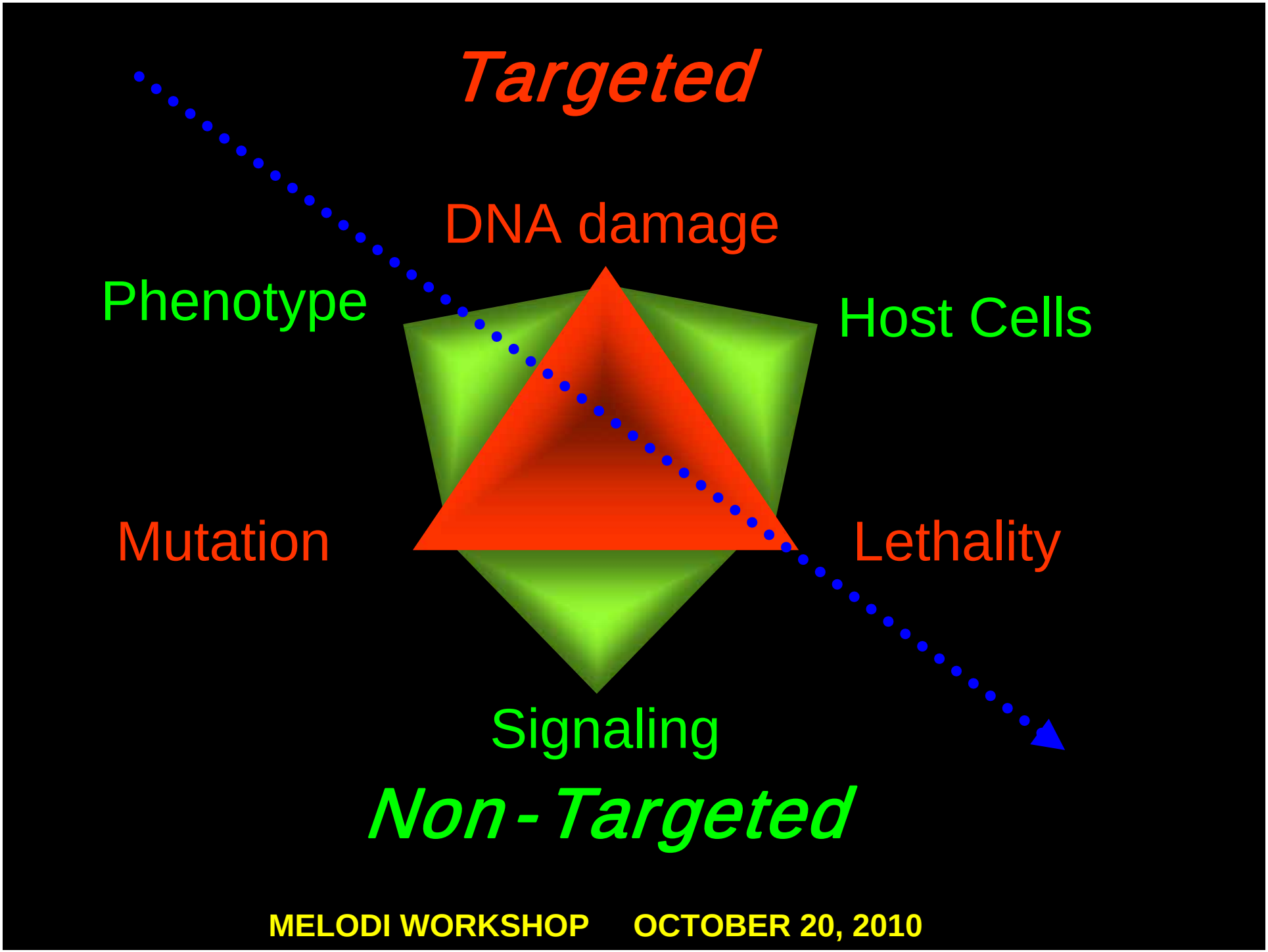
…but how do they do it??

Theories in Carcinogenesis

- Somatic mutation
  - Cancer arises due to DNA mutations
    - Oncogenes
    - Tumour suppressors
  - Cell behavior results from aberrant genetic controls
  - Provides a basis for clonality and transplantation

Either or Both??

- Field Cancerization
  - Cancers arise due to defective tissue organisation
  - Cancer cell behavior is dysregulated by aberrant surrounding cells


Targeted
DNA damage
Phenotype
Host Cells
Mutation
Lethality
Signaling
Non-Targeted

We know how radiation can affect genotype.

- Radiation biology has been instrumental in discovery of 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 is an excellent probe to discover biology!

How does radiation affect phenotype and cell interactions?

- Many NTE that mediate phenotypic changes and interactions between cells and tissues can be classified as processes that promotion.

- Radiation can be used to probe the essential biology of how tissues become cancers!

Questions that were raised:

- Does DNA damage → genetic changes contribute at very low doses?
  - Unknown at low doses
  - And questions remain at high doses

NTE: Cell-Cell Interactions

- Cell contact, cell communication mediated by secreted or transferred molecules
- Which cells?
- Which models and from which tissues?
  - normal cells, cancer cell lines, stem cells, cancer stem cells,
  - 3D models…. Organotypic culture, spheroids
  - In vivo… KO
- Doses and dose rates
- Early effects… late effects (weeks…)
- Mechanisms
  - Candidate approaches: TGFβ , Death receptor ligands
  - Non-biased approaches: Proteomic, metabolomic … small molecules!
- Relationship between early and long term effects
- Relationship between effects and risk?

NTE: Cell Phenotype

- Which phenotypes?
  - Activated vs Quiescent
  - Self-renewal vs differentiation
- Which models and from which tissues?
  - normal cells
  - 3D model
  - In vivo
- Mechanisms
  - Chronic oxidative stress
  - Epigenetic regulation
  - miRNA
- Transient/ permanent effects
- Reversible effects
- Selection / induction
- Contribution to long term risk

NTE are mediated
by specific signals
that affect the latency and
features of cancer.

Questions that were raised:

- How do NTE persist?
  - Crosstalk between systems and signals
    - Macrophage –BM stem cell induced GIN
  - What is the role of inflammation? When and where and what type? Pro or anti-tumor?
  - Epigenetic or transcriptional or extracellular reprogramming ?

Challenges for evaluating NTE

- Relevance to disease causation or modulation
- Operational in vivo
- Validity of extrapolation from models to humans
- Utility for radiation protection and risk modeling

Questions that were raised:

- What is THE signal (s)?
  - Is it cell-type specific?
  - Is it dose dependent?
  - Does it persist?
- If there are many signals, depending on dose, cell type, organ and genetic background, which are important and when?
- Which NTE have primary effects on cancer risk and which are secondary?

Questions that remain

- Do early NTE events/processes/signals contribute to cancer risk?
- How do NTE persist?
- Which NTE have primary effects on cancer and which are secondary?

What can be achieved by identifying how and when NTE contribute to radiation carcinogenesis?

- More complete understanding of radiation carcinogenesis feeds into biologically based cancer risk models.
  - Testing the veracity of LNT
  - Identify susceptible populations
  - Serve as a basis for adequate protection standards
  - Provide avenues for protection after exposure