Radiation-induced injury responses and tumorigenesis

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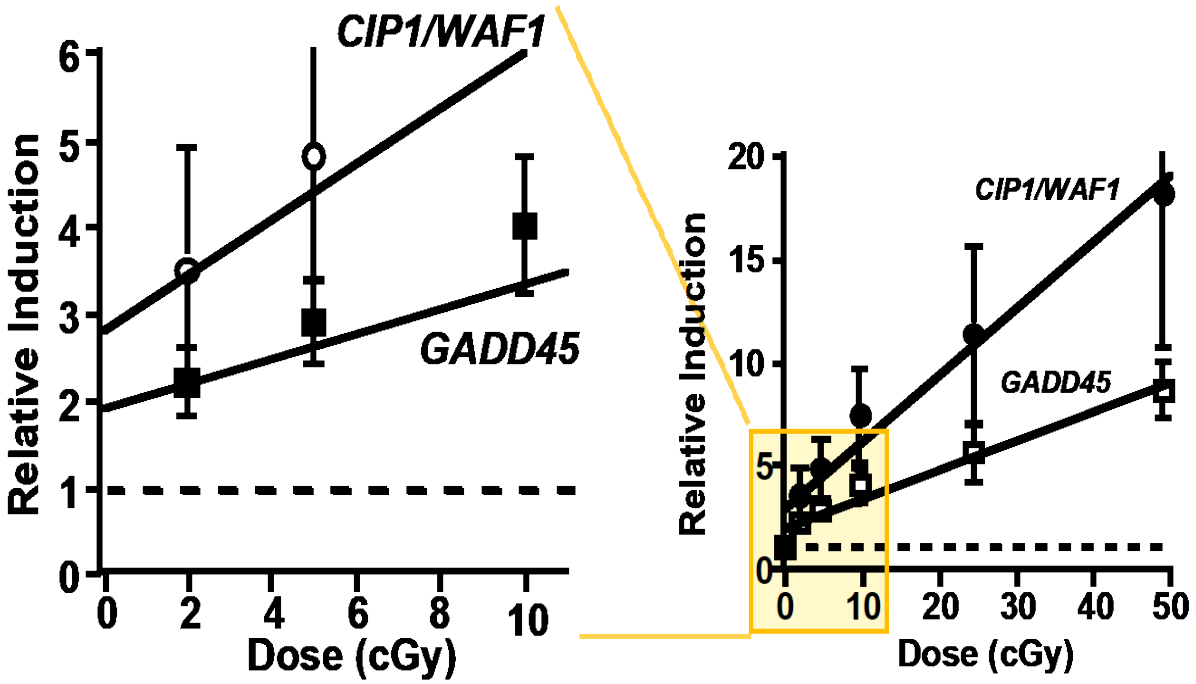
- *Low dose studies with γ rays*
- *Low dose studies with high LET radiation*

in vitro and *in vivo* responses to low dose radiation

Linear dose response with no threshold in ML-1 cells

Induction of *CDKN1A* and *GADD45A* mRNA



Amundson et al, 1999

Metabolic responses

- compromise of energy metabolism
- impacts on anabolic processes
- pro-inflammatory signaling
  - Senescent inflammatory response (SIR)
  - Senescence-associated secretory phenotypes (SASP)
  - Aging-related events
- variety of other perturbations in small molecules

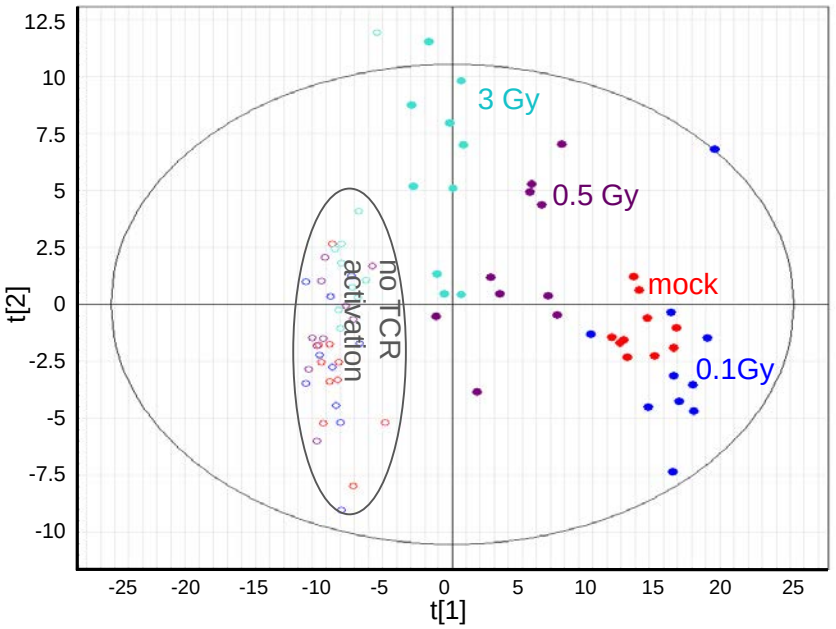
Li et al, 2015
Kumar et al, 2018 and 2019

How does radiation affect metabolism of viable cells?

T cell activation

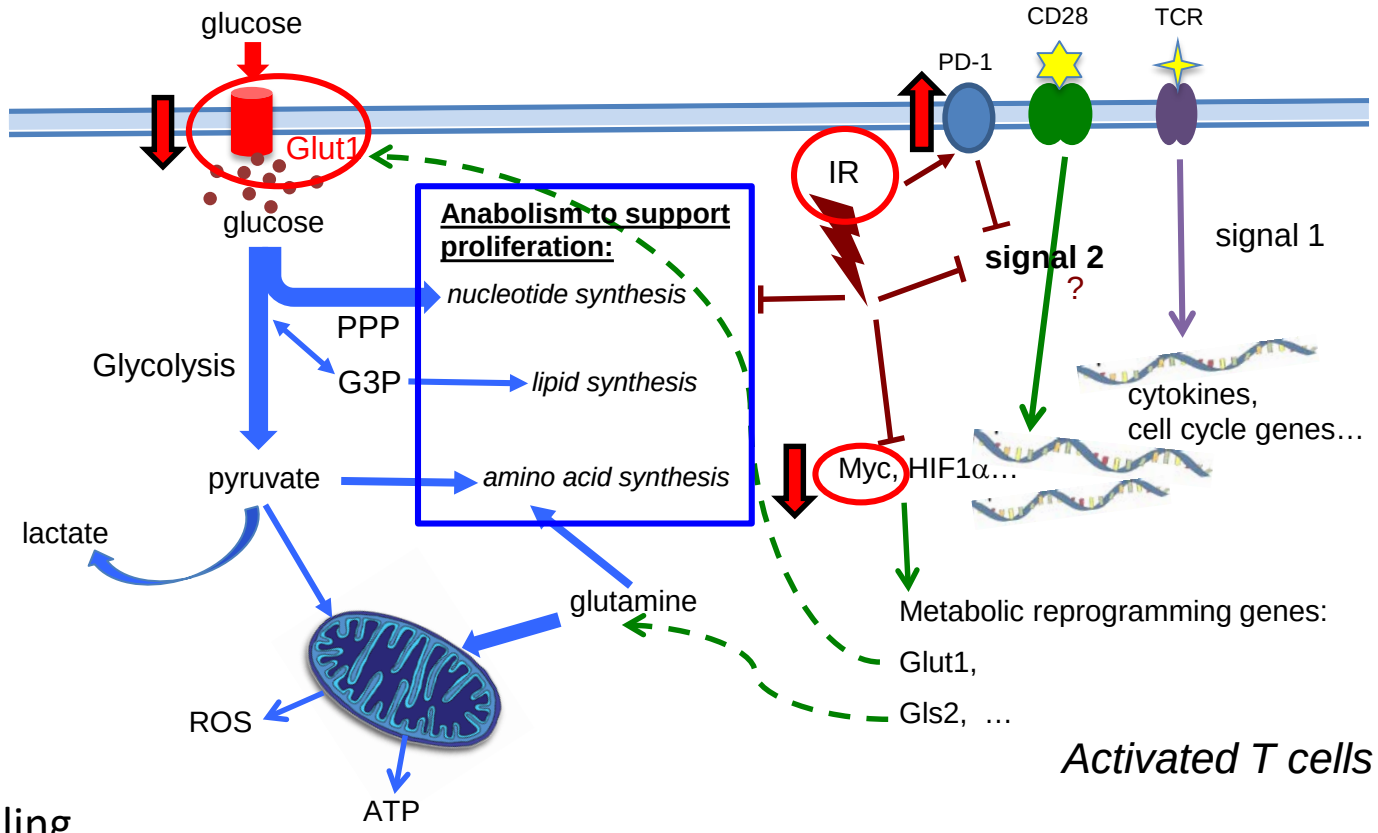
Metabolic Differences even at low doses

PCA



post-IR → TCR (0 – 4hr) → metabolomic profiling (for 72 hrs)

➠ Co-stimulation compromised:
decreased Glut1 decreases energy supply

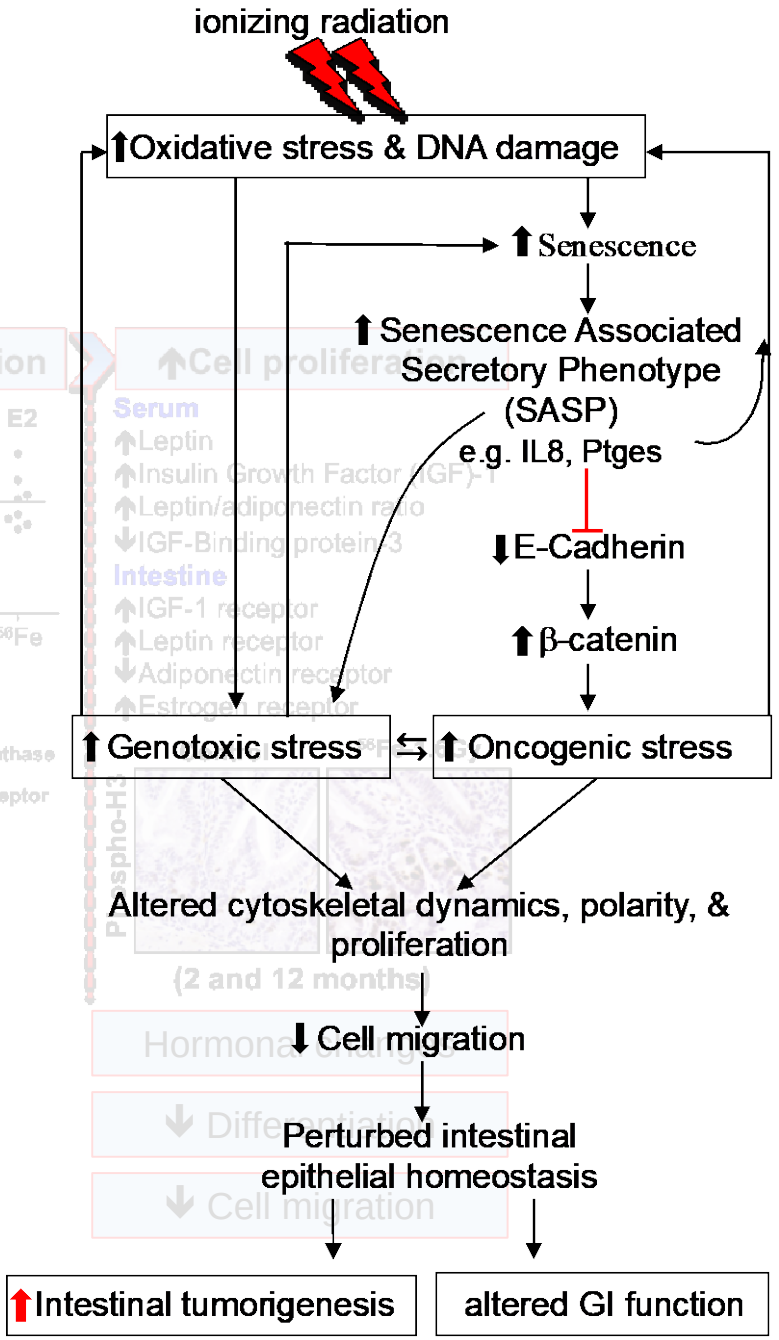


Li et al, 2015

Radiation triggers persistent (long-term) changes in GI (& many other) tissues

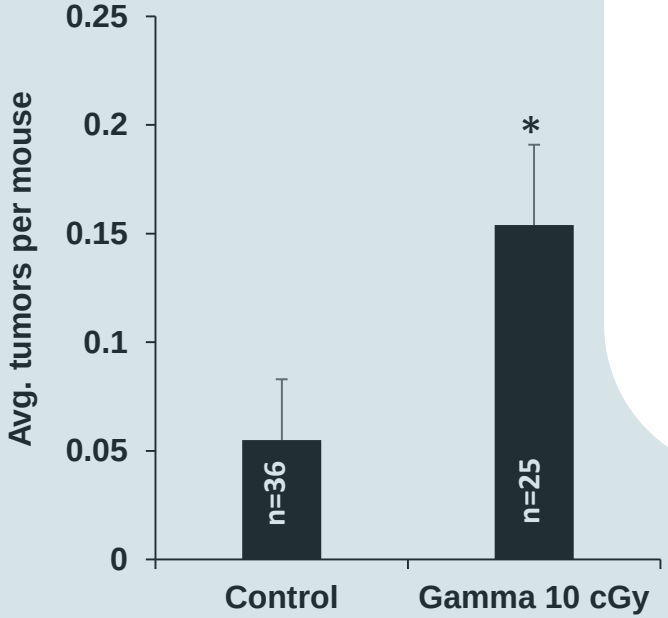
Stem cell damage

Senescent cells

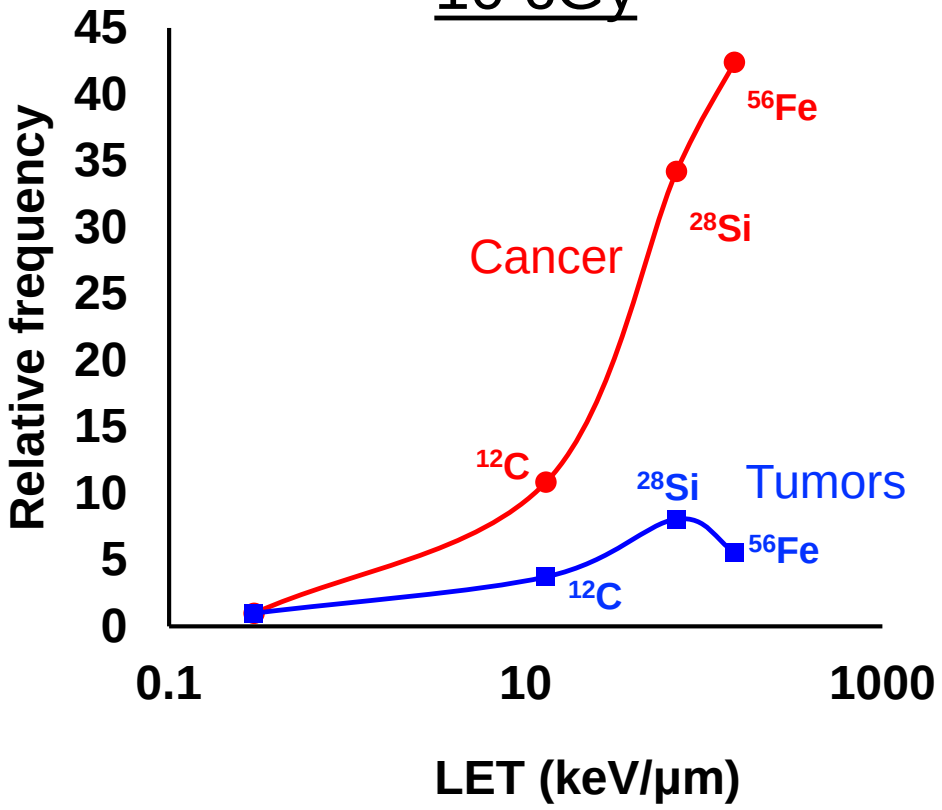


Low-dose radiation tumorigenesis

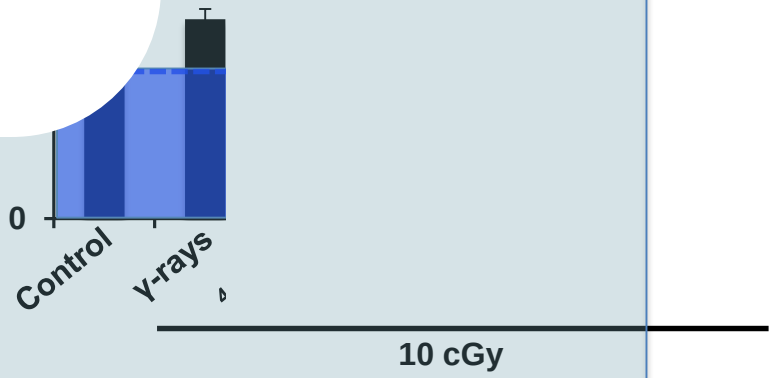
Mammary tumorigenes
Apc$^{Min/+}$ mice



10 cGy



	calculated cancer RBE		
Dose (cGy)	C	Fe	Si
4	58	182	117
9	26	81	53
49	6	16	10



Suman et al., Unpublished

Some priorities for low-dose radiation field going forward

- Early responses
  - myriad of signaling pathways to delineate further
  - impact on metabolism
- Long-term responses
  - tumorigenesis
    - initiation
    - progression – e.g. conversion from low grade (premalignant lesions) to high grade (cancer)
  - senescent cell signaling
    - positive feedback loop can drive adverse sequelae
      - pro-inflammatory
      - ROS & ongoing DNA damage
      - potential multi-organ and systemic consequences
    - myriad of secreted proteins & small molecules vary with injury & cell type
    - immunologic consequences
  - accelerated aging
  - what other long-term signaling events occur and mechanisms?

FACS sorting of senescent GI stem cells