Mechanisms Underlying Low Dose γ-Ray-Induced Adaptive Responses

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Plan:

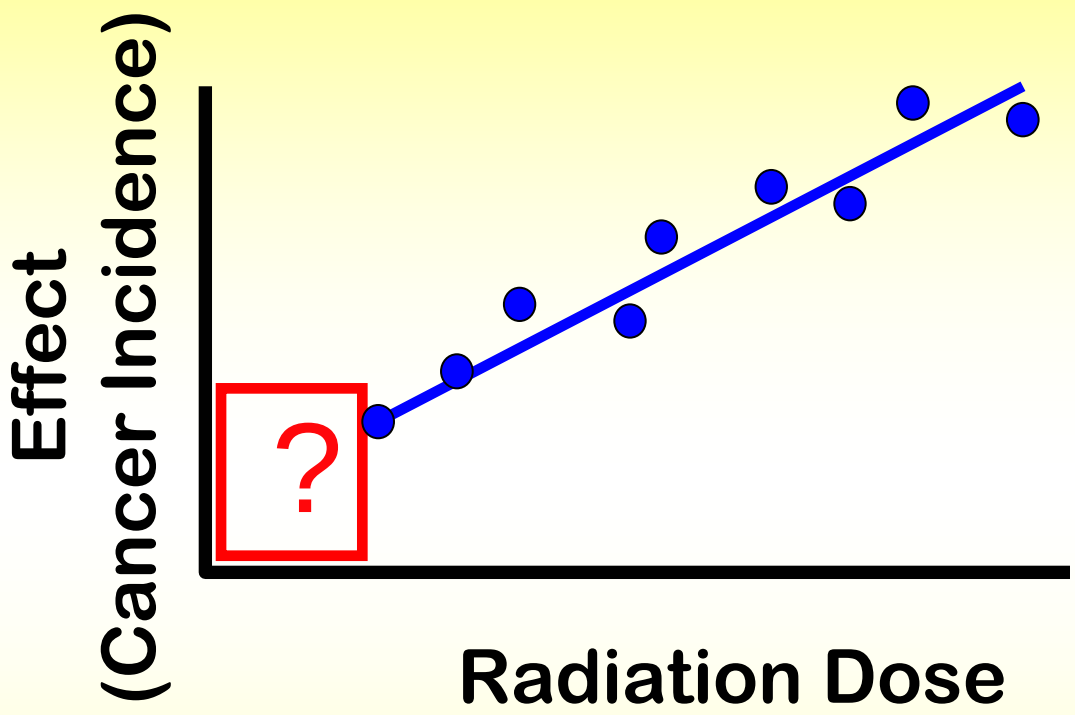
- Evidence for adaptive responses induced by low dose/low dose-rate ^{137}Cs-γ rays in G_0/G_1 **normal human fibroblasts**
- Evidence for mediating mechanisms
- Discussion:

  Biological factors modify the cellular response to energy deposition events

The frequency of human exposure to low level ionizing radiation is on the increase

Thus, the evaluation of risks for human health at low dose/low dose rates is an important issue in radiation protection

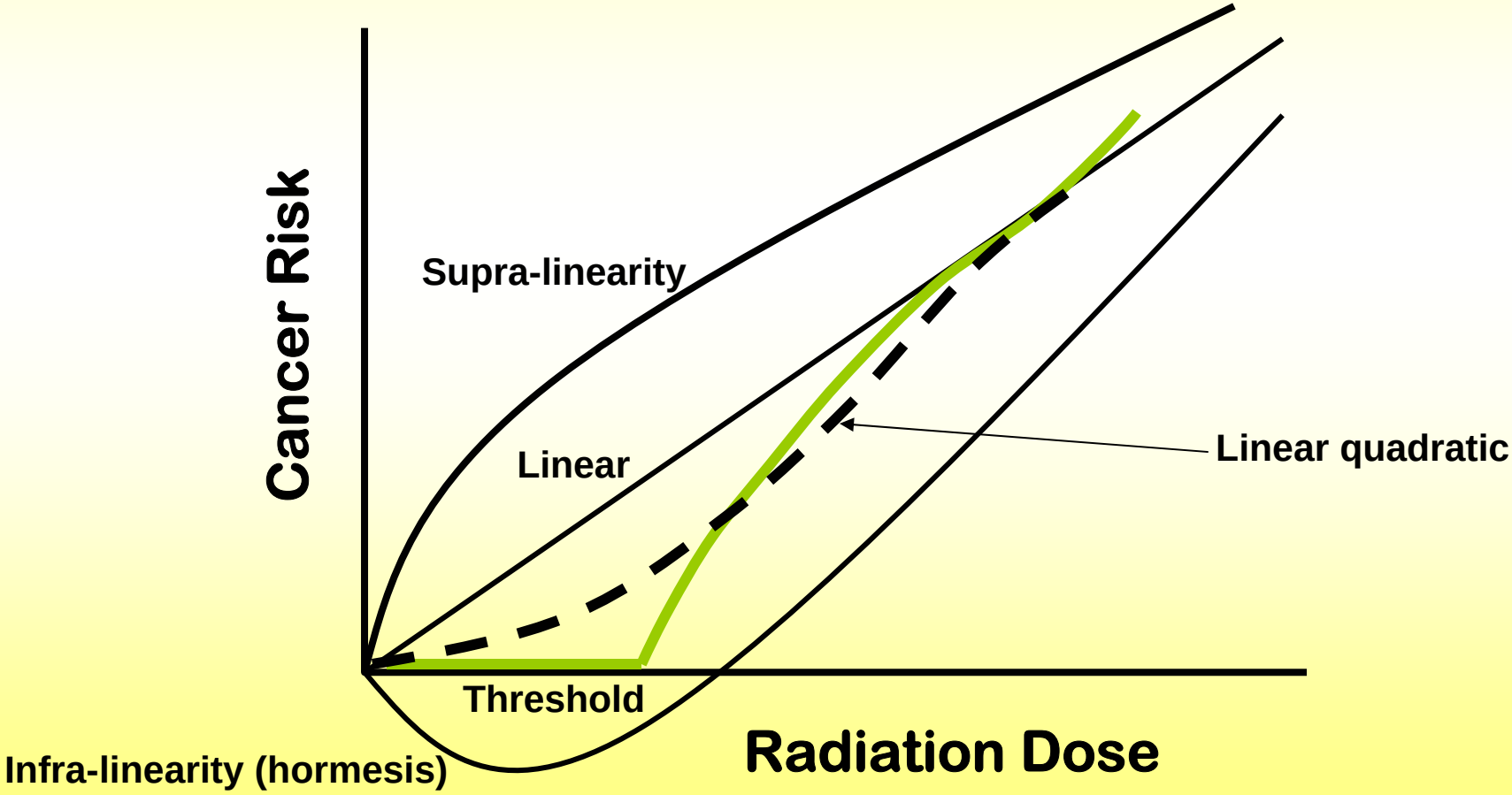
Health Risk and Dose



Japan 1945

Whereas high doses effects are well-characterized, those caused by low doses are extrapolated from effects at high dose

Possible extrapolations of radiation-induced cancer risk to doses where epidemiology cannot go



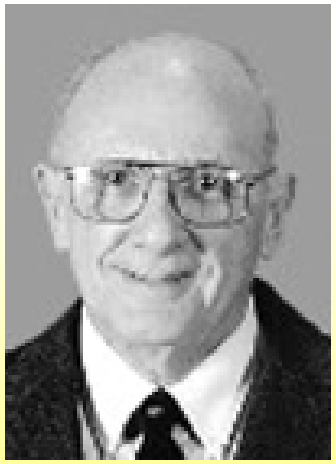
A BEIR VII Conclusion

Knowledge on adaptive/hormetic responses and their underlying mechanisms, which may act to alter radiation cancer risk was judged to be insufficient to be incorporated into modeling of epidemiological data

The Adaptive Response **is a phenomenon induced by low dose/low LET radiation that protect cells and whole organisms against endogenous damage or damage due to a subsequent dose of radiation**

$$\gamma$$

$$\gamma \longrightarrow \gamma$$

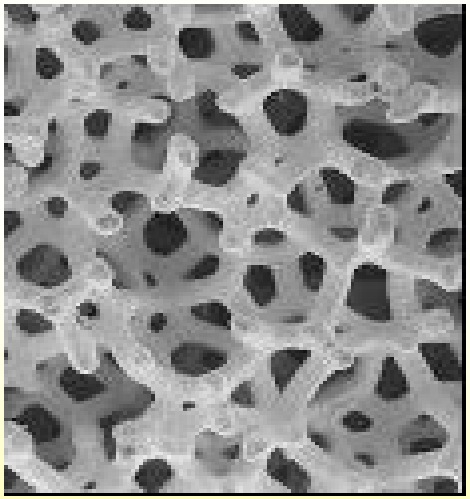


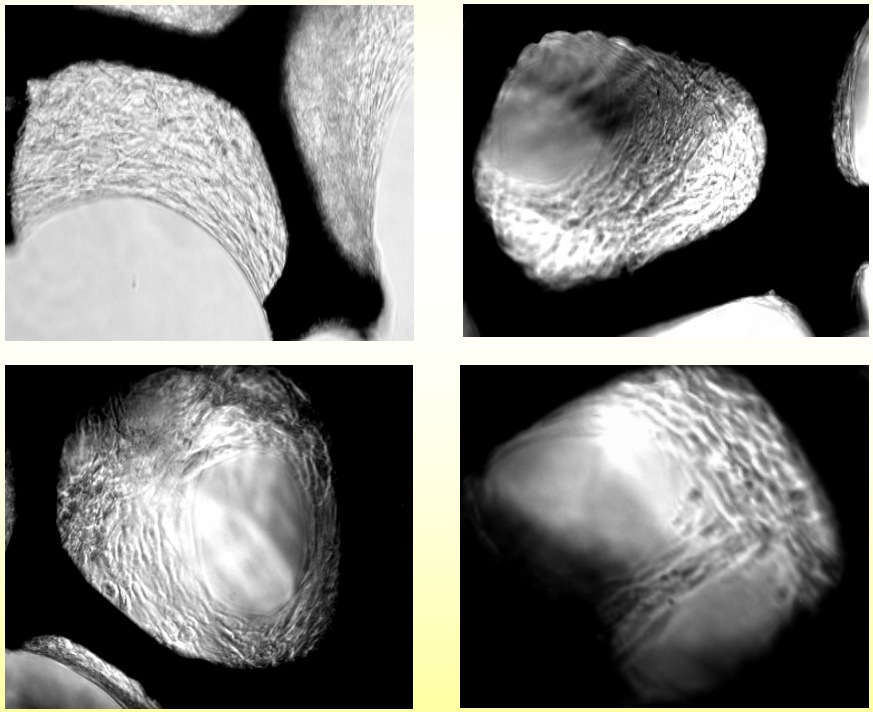
"Adaptive response of human lymphocytes to low concentrations of radioactive thymidine"
Olivieri G, Bodycote J, Wolff S.
***Science*, 223:594-7, 1984**

Treatment	***# Genetic Lesions***
None	0
[^{3}H]dThd (0.1 μCi/ml)	5
150 cGy	36
[^{3}H]dThd (0.1 μCi/ml) + 150 cGy	13

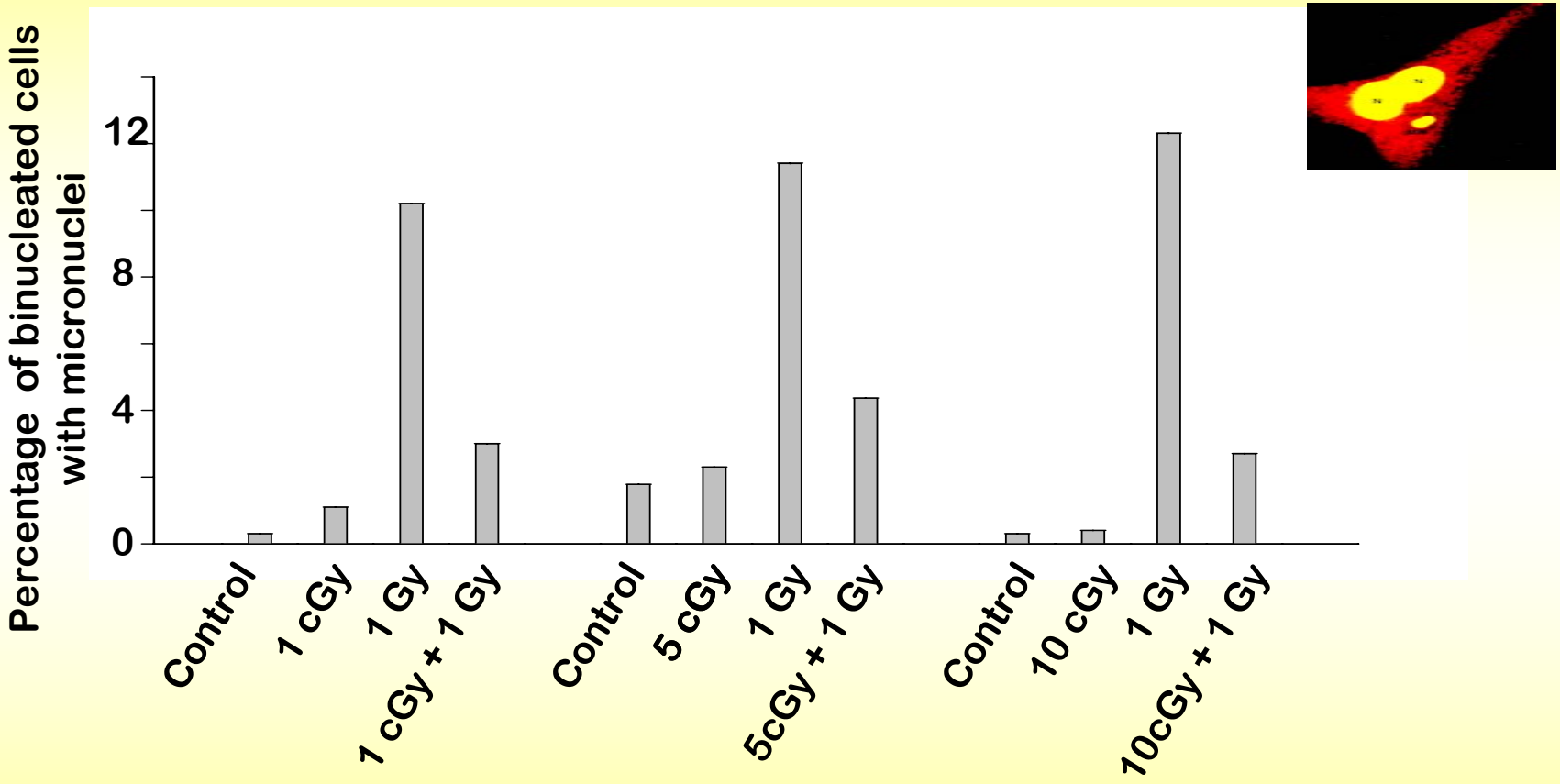
Normal Human Fibroblasts Growing in a Three-Dimensional Architecture

(to mimic *in vivo* growth)



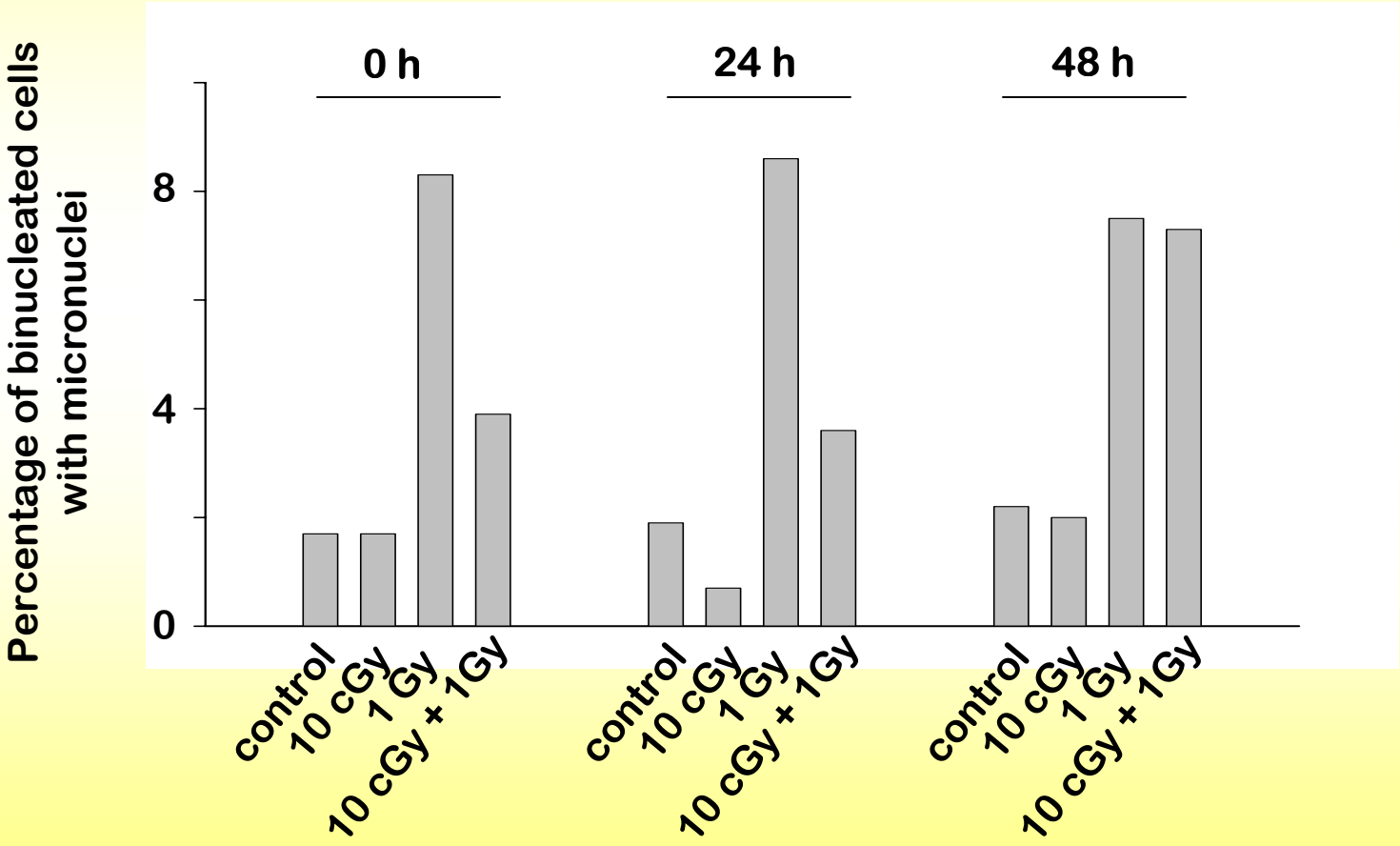


Effect of a priming dose of γ-rays (0.2 cGy/h) on modulation of the cellular response to a subsequent acute challenge dose



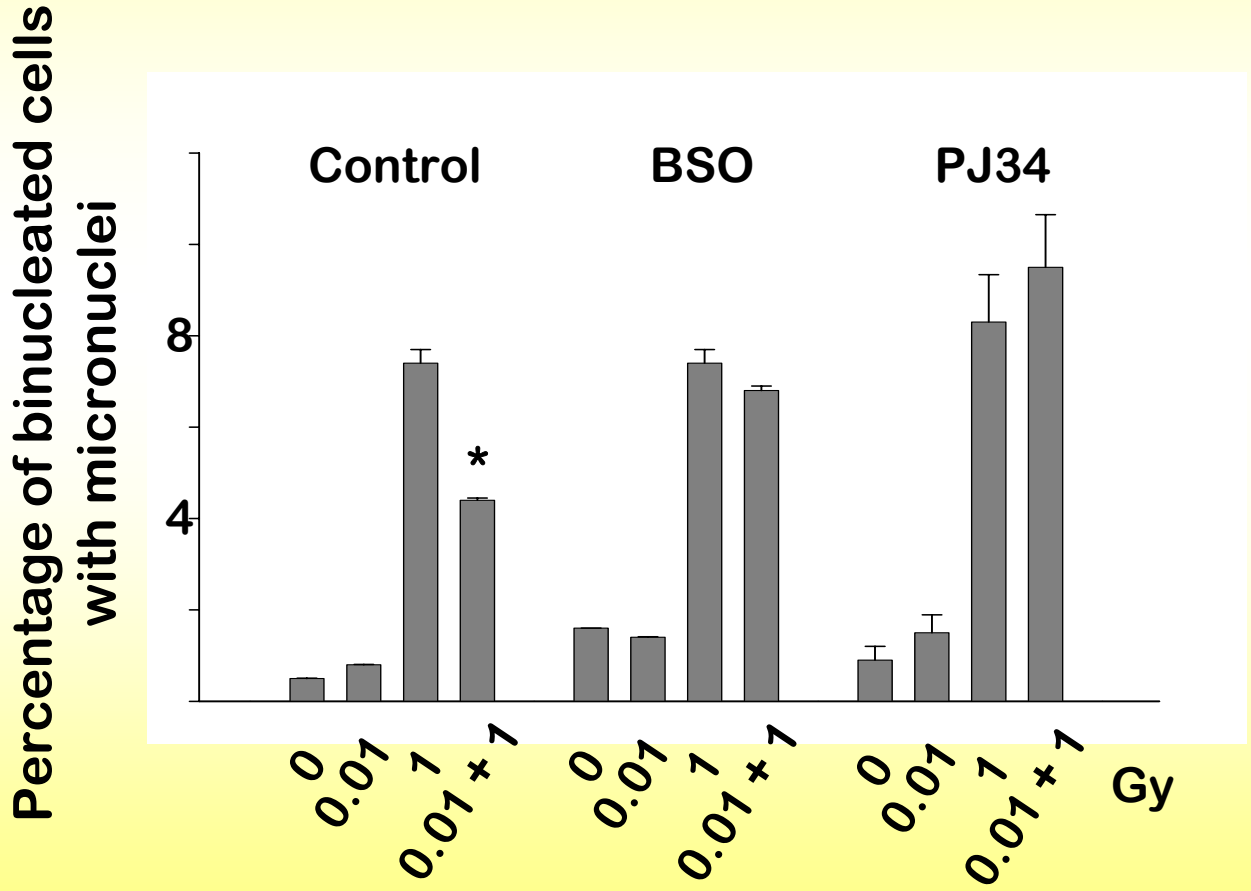
Protective responses are observed following exposure to adapting doses as low as 1 cGy

γ-ray induced adaptive responses are transient

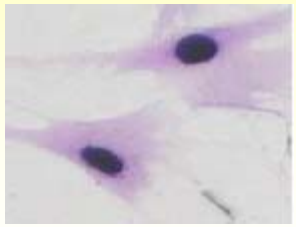


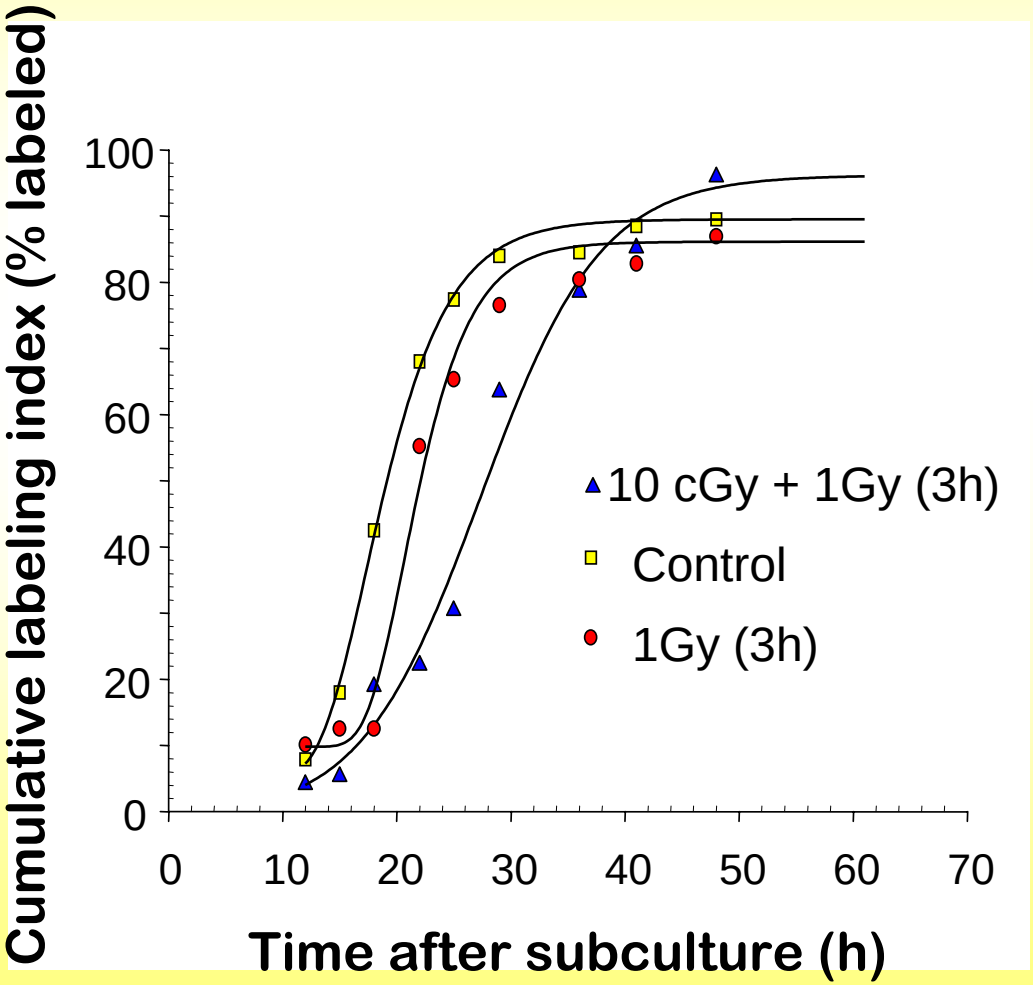
Mechanisms Underlying Low Dose γ-Ray Induced Adaptive Responses

Oxidative metabolism and DNA repair capacity mediate expression of adaptive responses induced by low dose/low dose-rate γ-rays



Involvement of Cell Cycle Checkpoints in Expression of the Adaptive Response

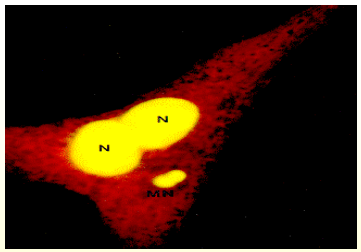


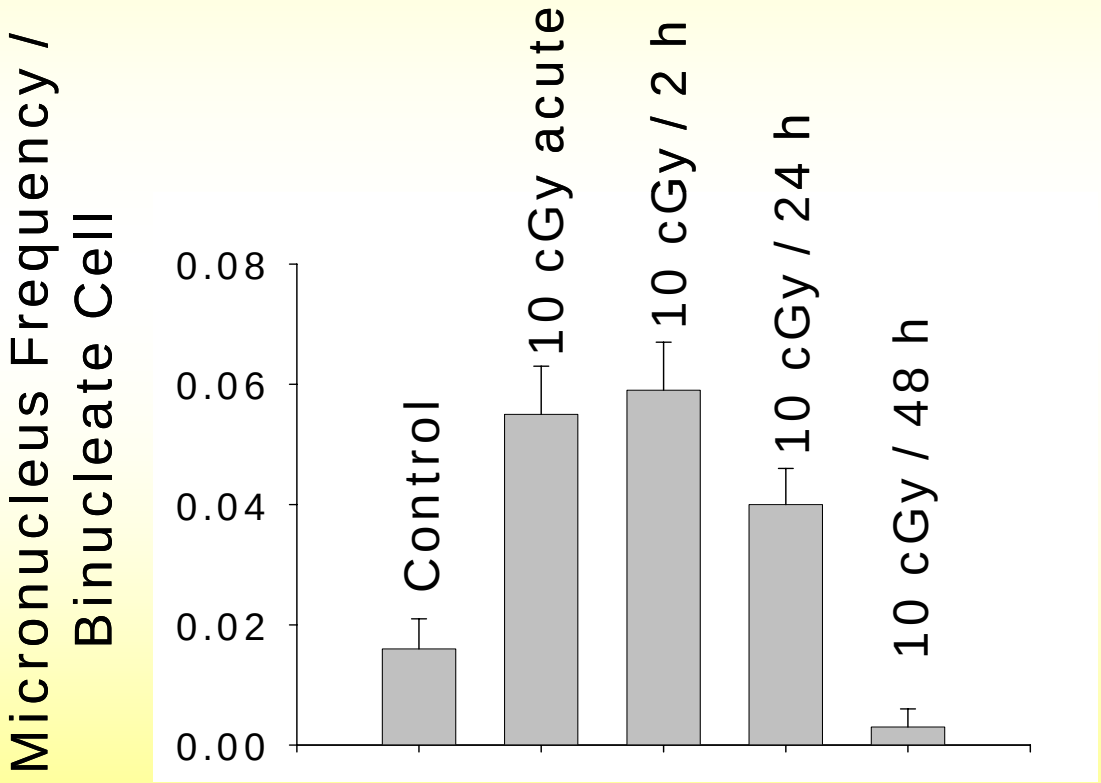


Other Mediating Mechanisms

- Oxidative metabolism
- Up-regulation of DNA repair
- Induction of cell cycle checkpoints
- Intercellular communication
- Apoptosis
- Altered chromatin conformation

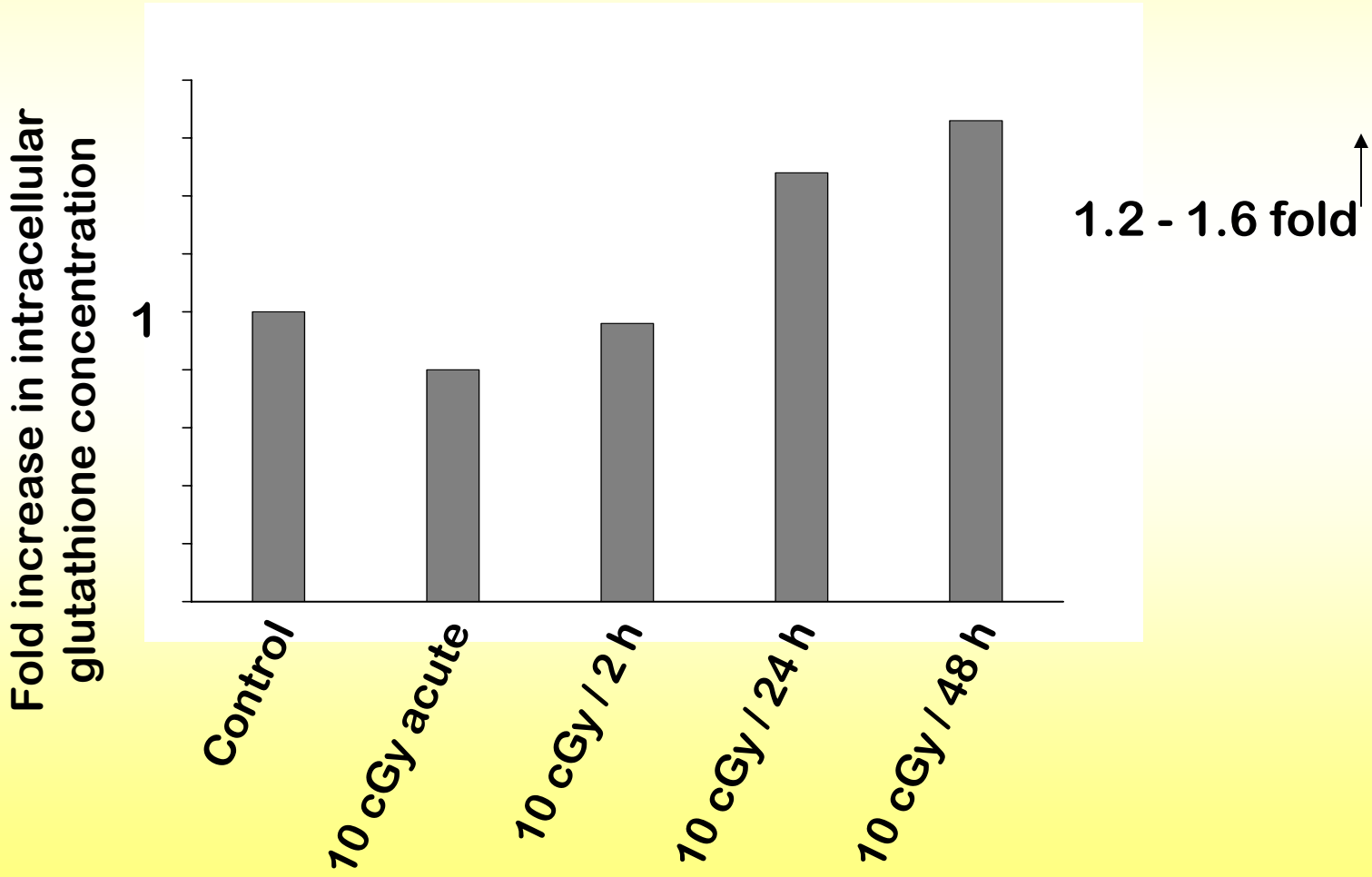
Effect of a Single low Dose of γ-Rays Delivered at Various Dose-Rates on DNA Damage in Normal Human Cells Growing in 3-D





De Toledo et al., *Rad. Res.,* 2006

The Role of Oxidative Metabolism: Exposure to Low Dose/Low Dose Rate γ–Rays Up-Regulates the Antioxidant Glutathione



Adaptive Responses and oxidative metabolism

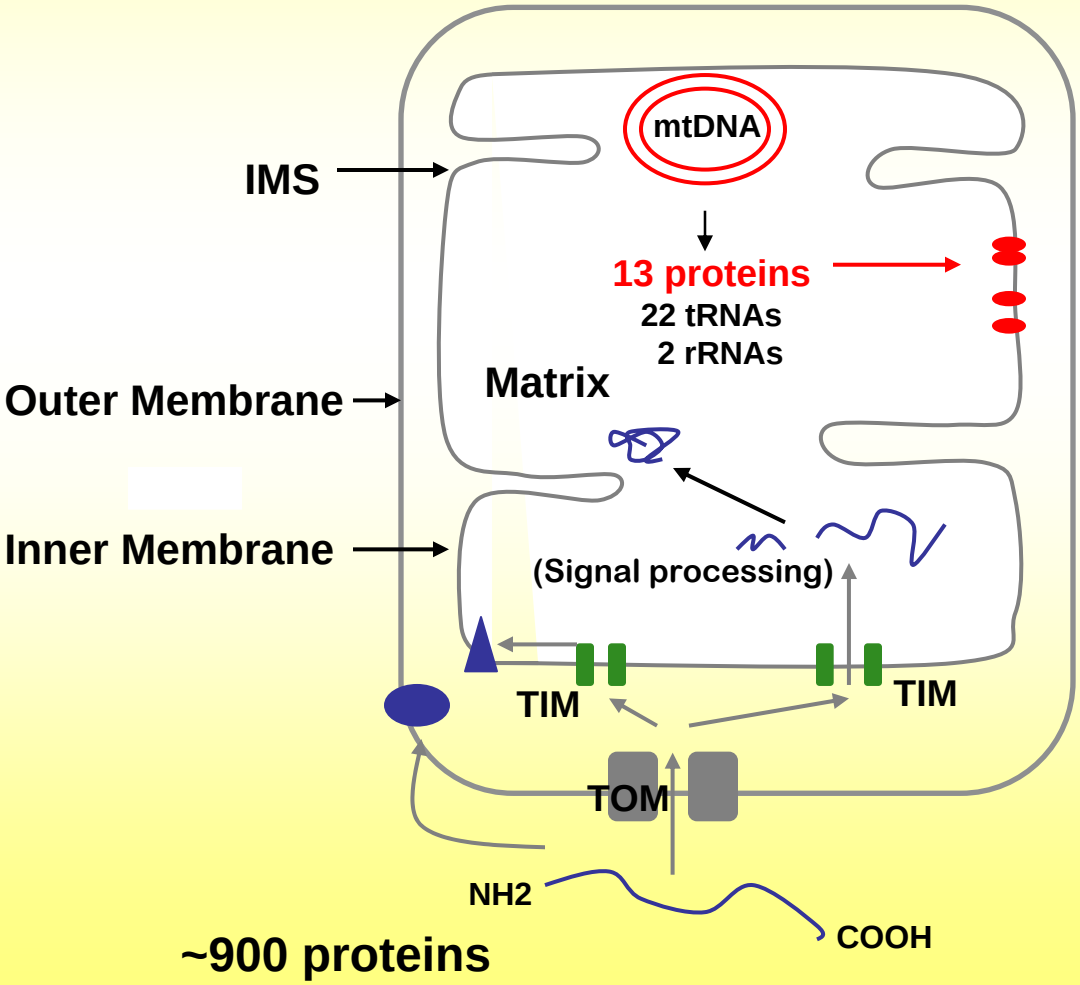
- Up-regulations of superoxide dismutase
- Up-regulation of thioredoxin
- Modulation of NFκB

Low Dose γ-Rays and Gene Expression

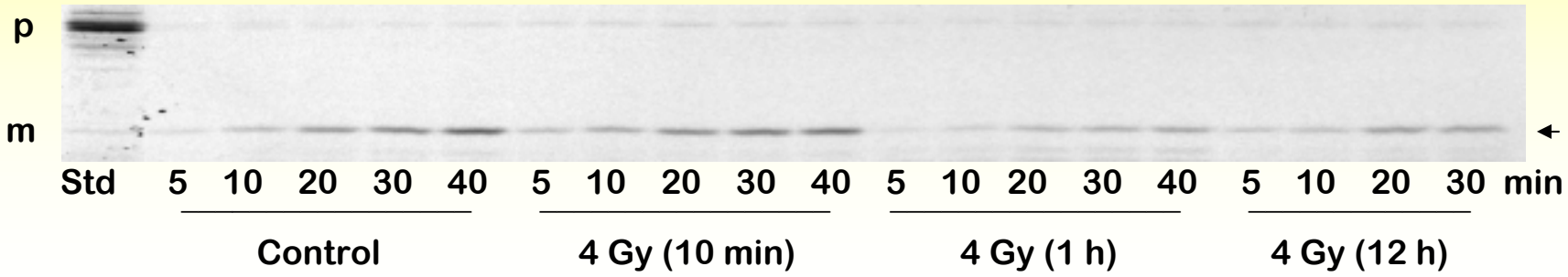
Our cDNA microarray & proteomics data indicate upregulation by low dose of genes related to aa activation, translation machinery and down-regulation of genes involved in glycolytic pathway

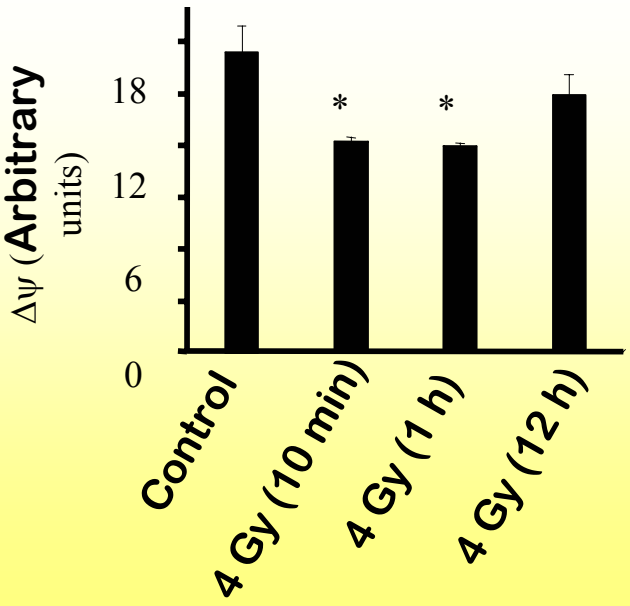
They reveal up-regulation in mitochondria of redox sensitive pro-survival proteins by low dose/low dose rate and *not* high dose/ high dose-rate γ-rays

Low Dose γ-Rays & Modulation of mitochondrial function



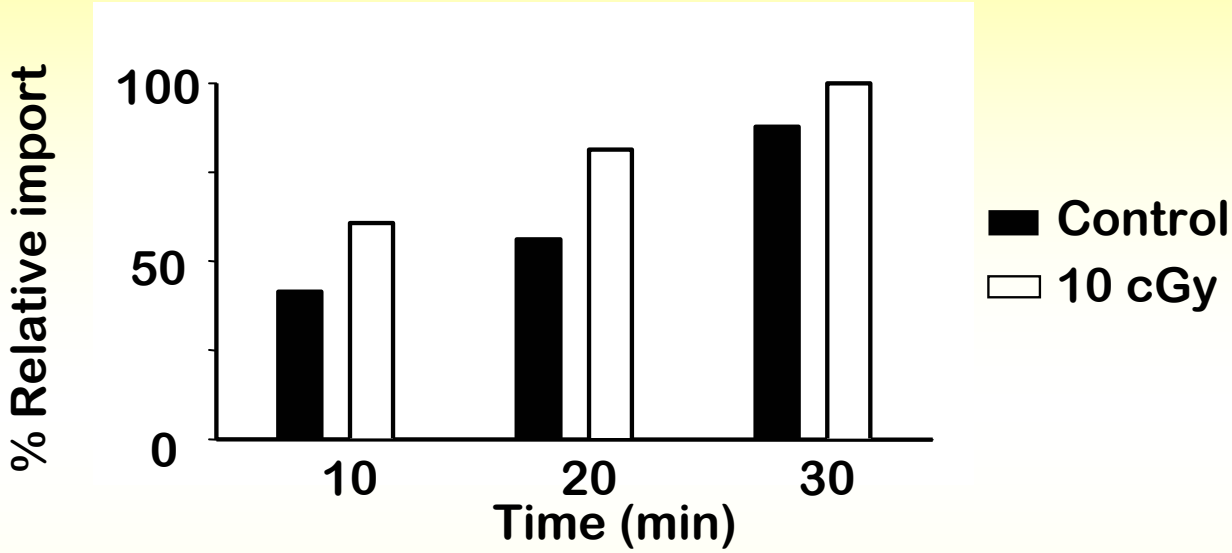
High dose γ-rays decreases mitochondrial protein import and mitochondrial membrane potential

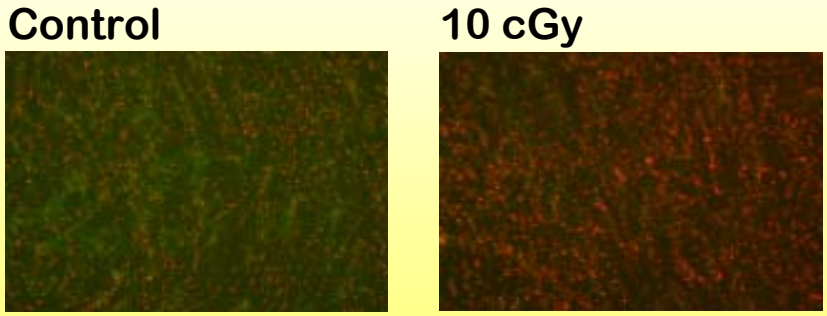




Pandey *et al.*, 2006

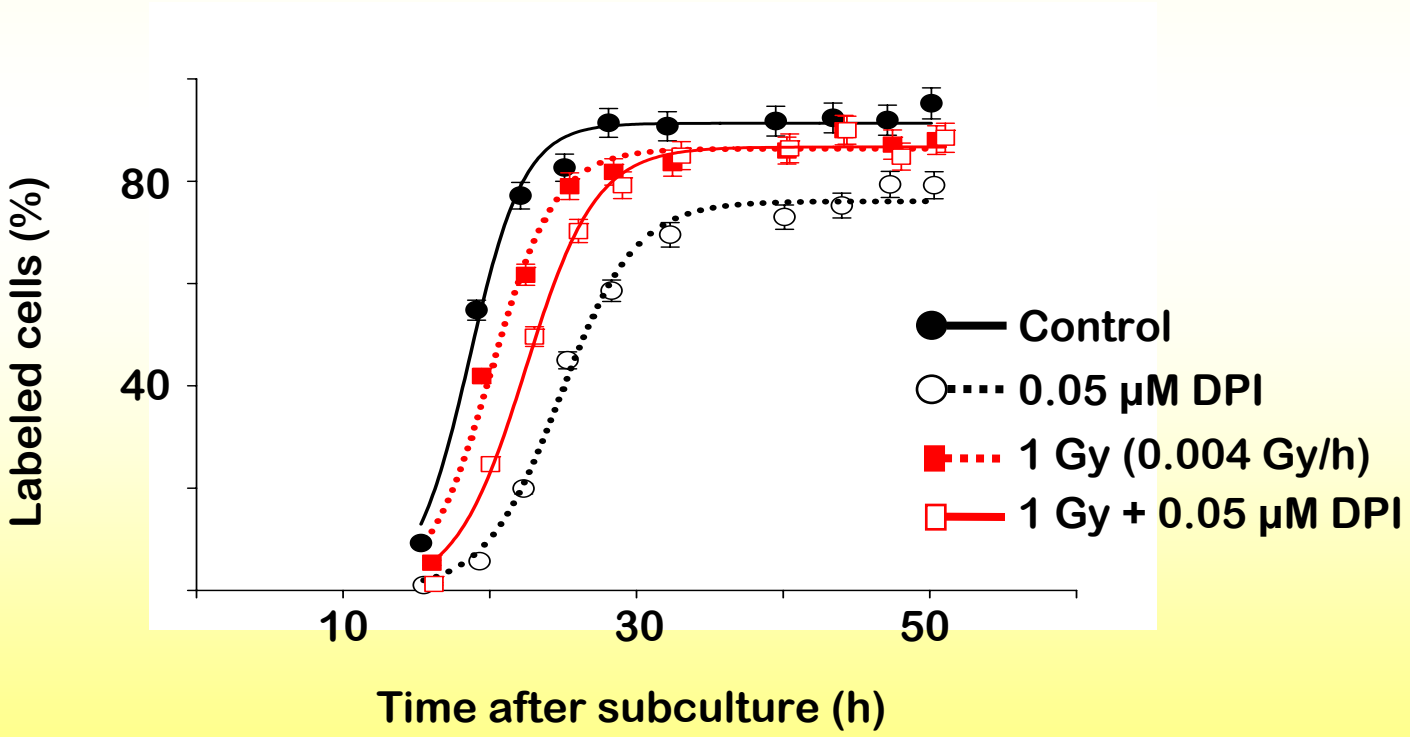
Low dose γ-rays increases mitochondrial protein import and mitochondrial membrane potential





Pandey *et al.*, 2006

Oxidation/reduction reactions induced by low dose rate ionizing radiation are similar to those caused by endogenous metabolism

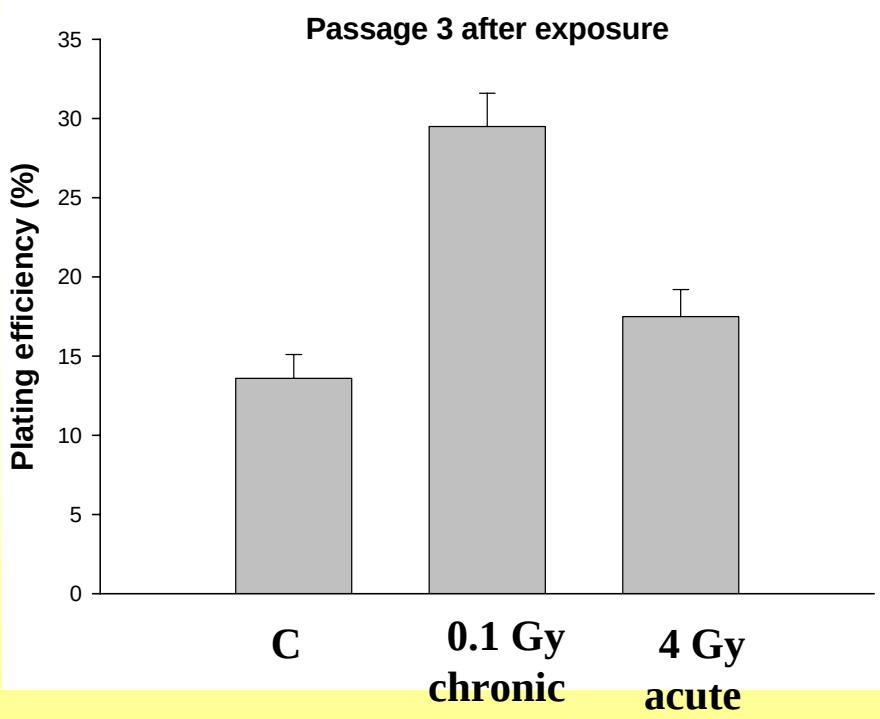


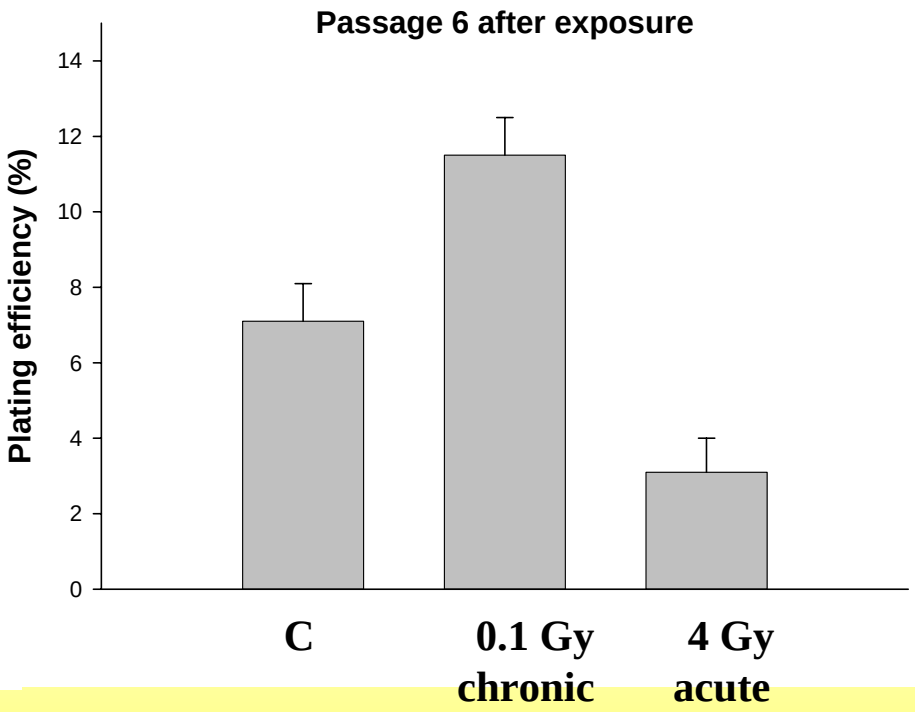
Low Dose γ-Rays and Risk

Effects in Progeny cells

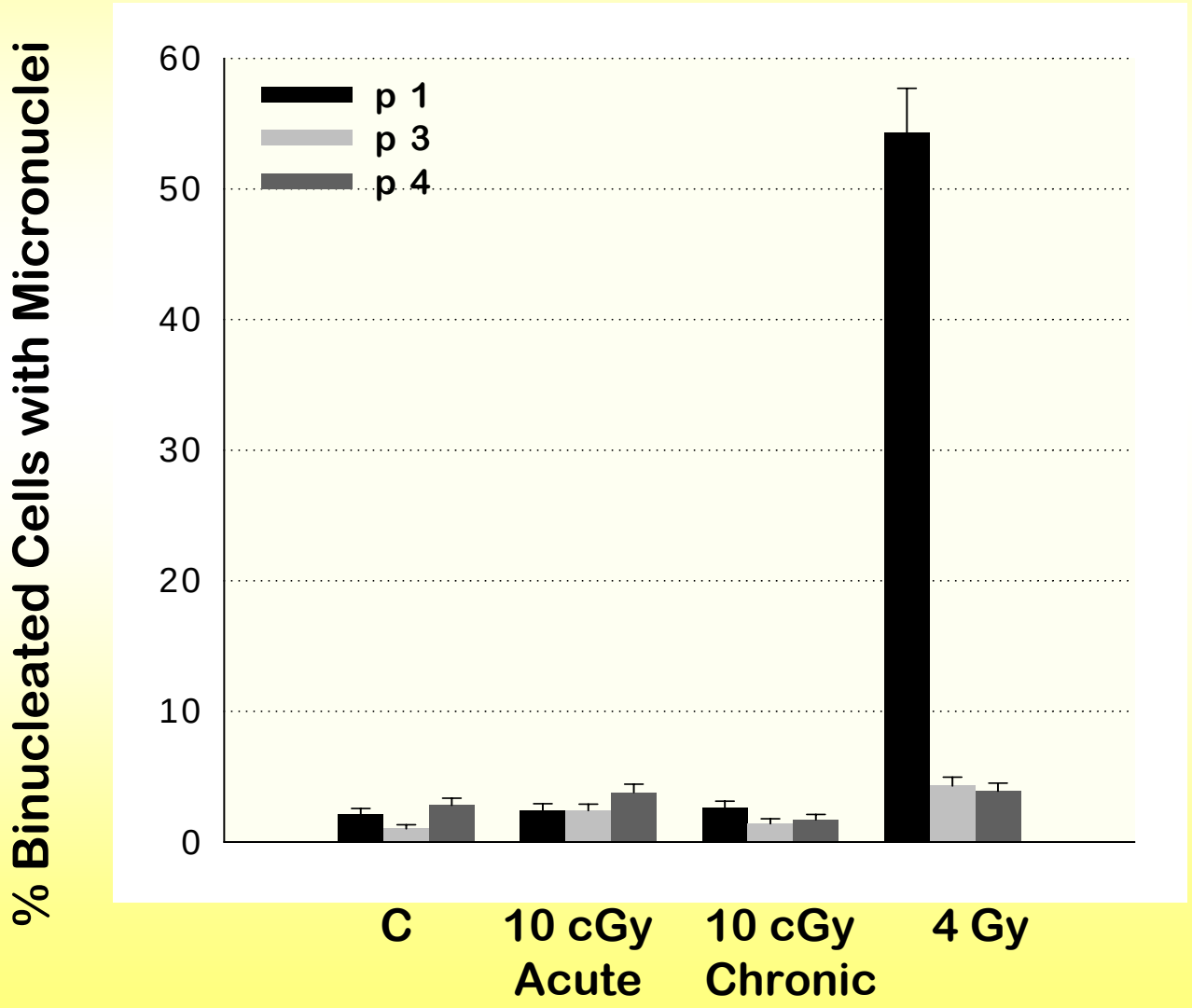
Induced stress (Physiological or genetic change) is of significance to risk assessment only if it persists and is transmitted to daughter cells.

Cloning Efficiency of the Progeny of Irradiated Cells





Residual Micronuclei in Progeny of γ-Irradiated Cells

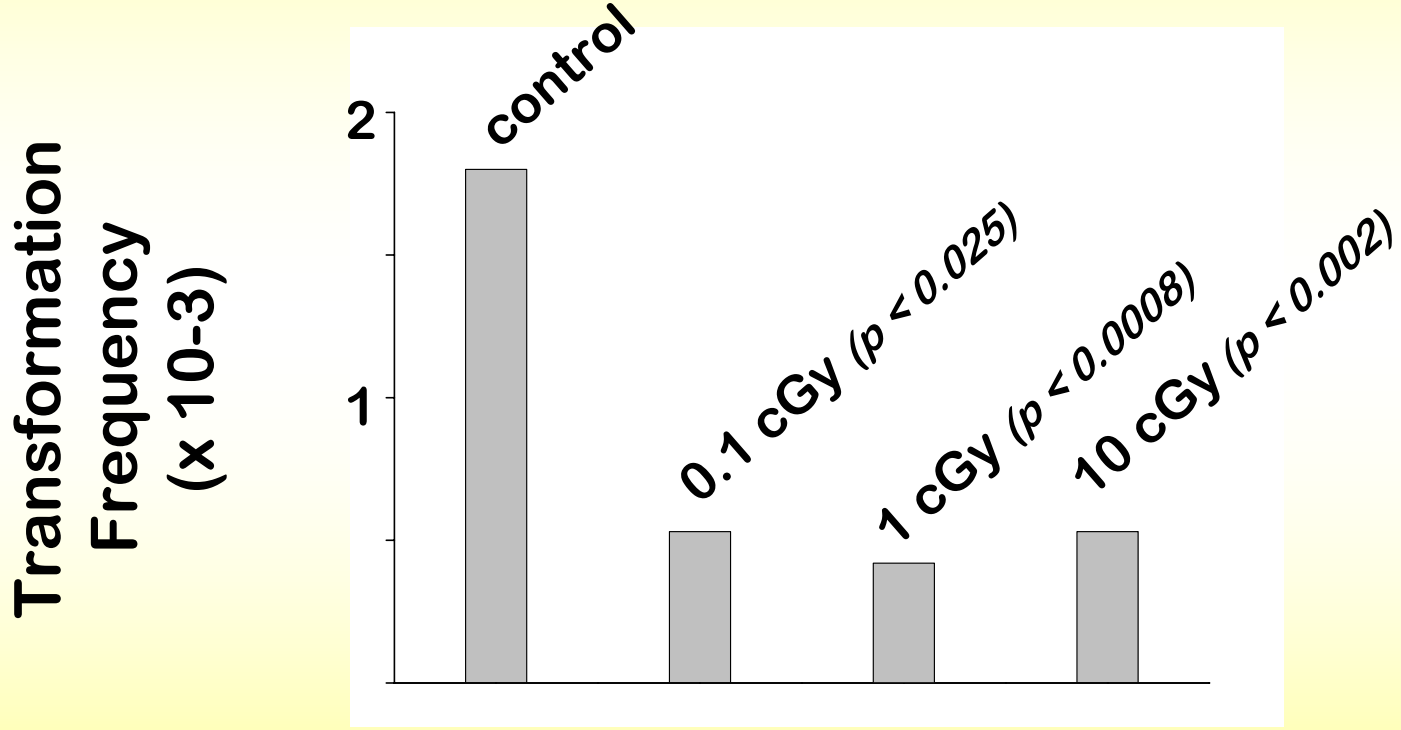


Adaptive response and Risk of Neoplastic Transformation

Neoplastic transformation assay using mouse embryo cells

Control Irradiated

Low Dose γ-Rays Reduces the Spontaneous Transformation Frequency in Mouse Embryo Cells



Azzam et al., 1996

In vitro adaptive responses observed for many biological endpoints:

Chromosomal aberrations

Sister chromosome exchanges

Mutations

Gene expression

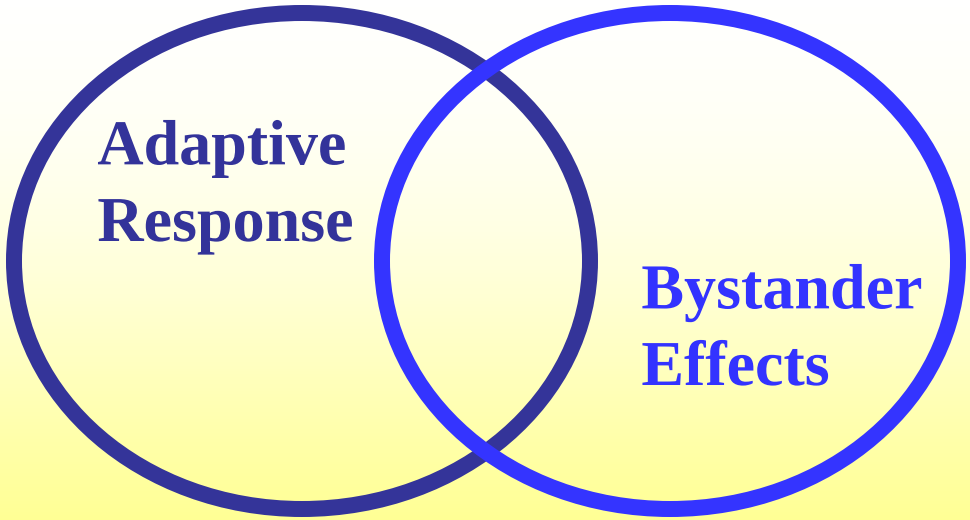
Survival

…

Often detected by multiple endpoints in the same experiment

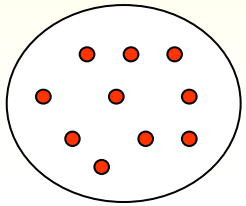
However, above observations are not universal

Propagation of ionizing radiation-induced adaptive responses from exposed to non-exposed cells

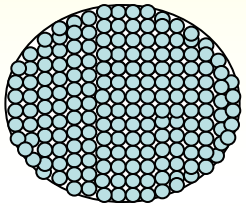


Co-Culture of tritiated-thymdine labeled cells and bystander cells

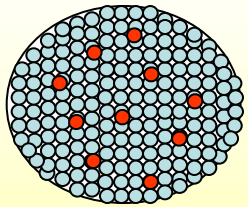
^{3}H-Thymidine Labeled cells



Bystander cells



Co-culture



5:95 Labeled to unlabeled

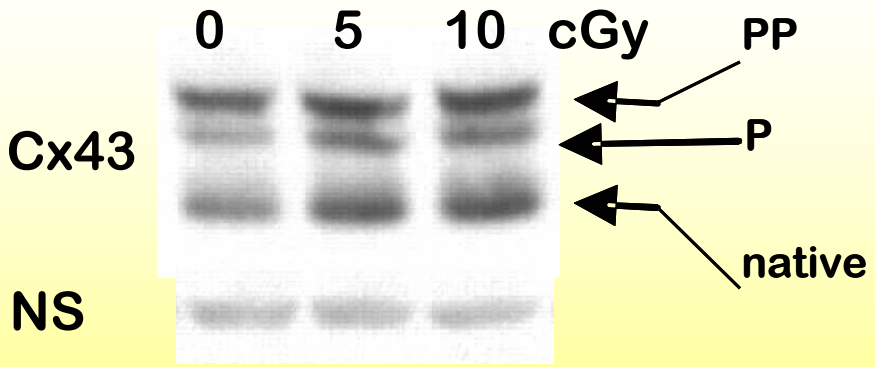
^{3}H-Thymidine Concentration μCi/ml	Micronucleus Frequency
0	0.012 ± 0.003
4	0.028 ± 0.005
0.04	0.004 ± 0.001

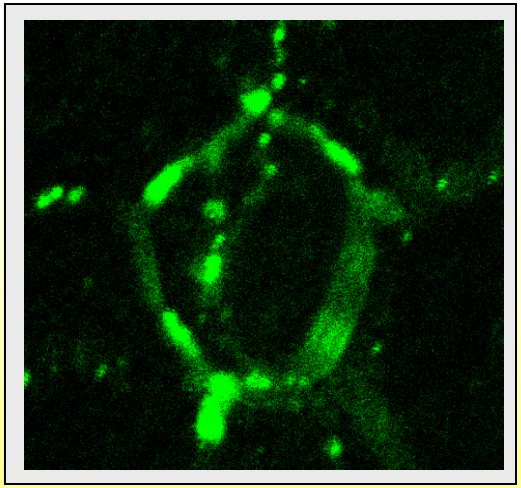
These data indicate that protective and damaging effects can be propagated in a bystander manner

Absorbed dose seems to be a determining factor

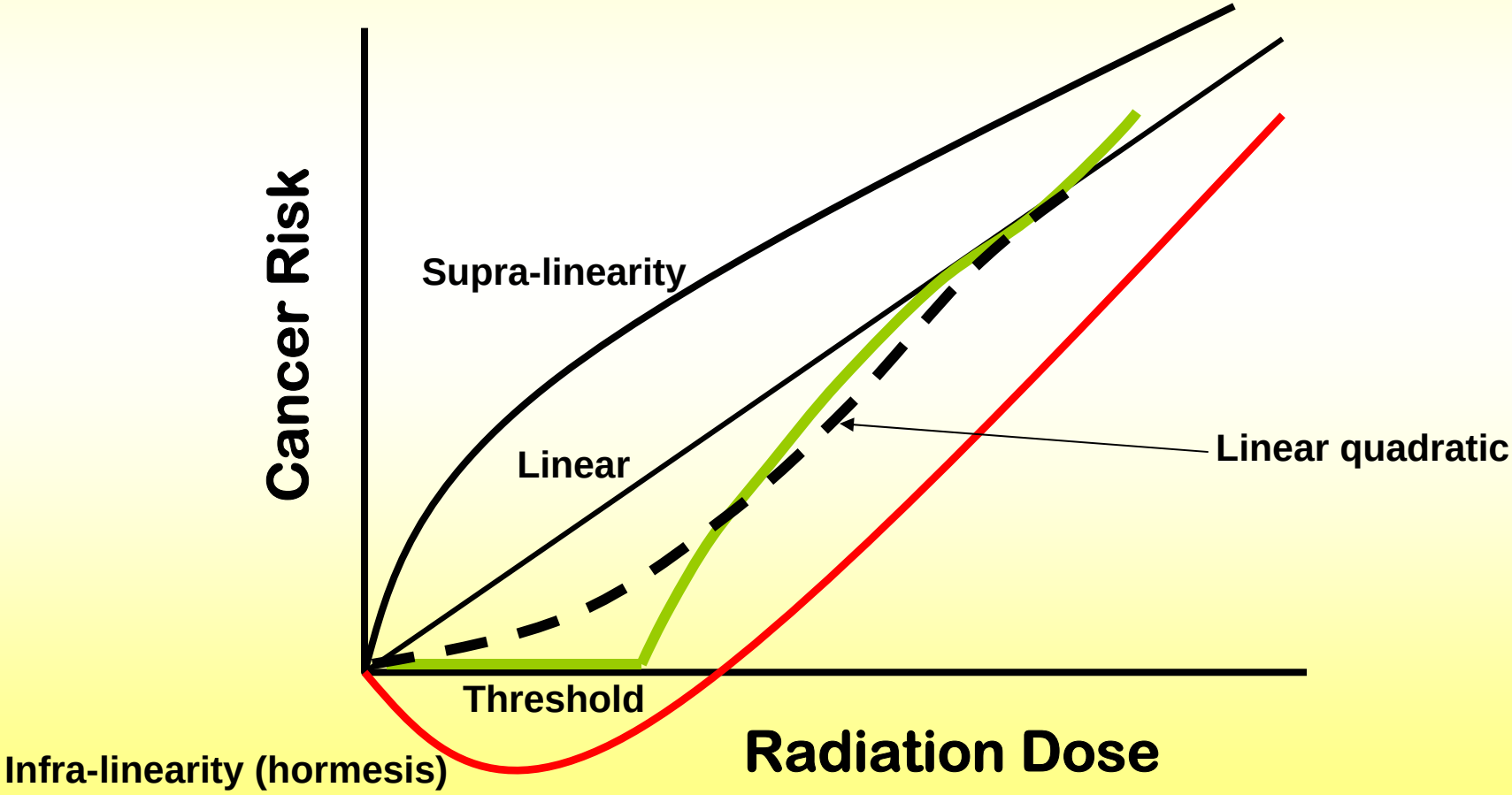
Low Dose γ-Ray induced Adaptive Responses Correlate with Induction of Connexin 43 (a constitutive protein of gap junctions)

Up-regulated connexin43 localizes in specific membrane Regions





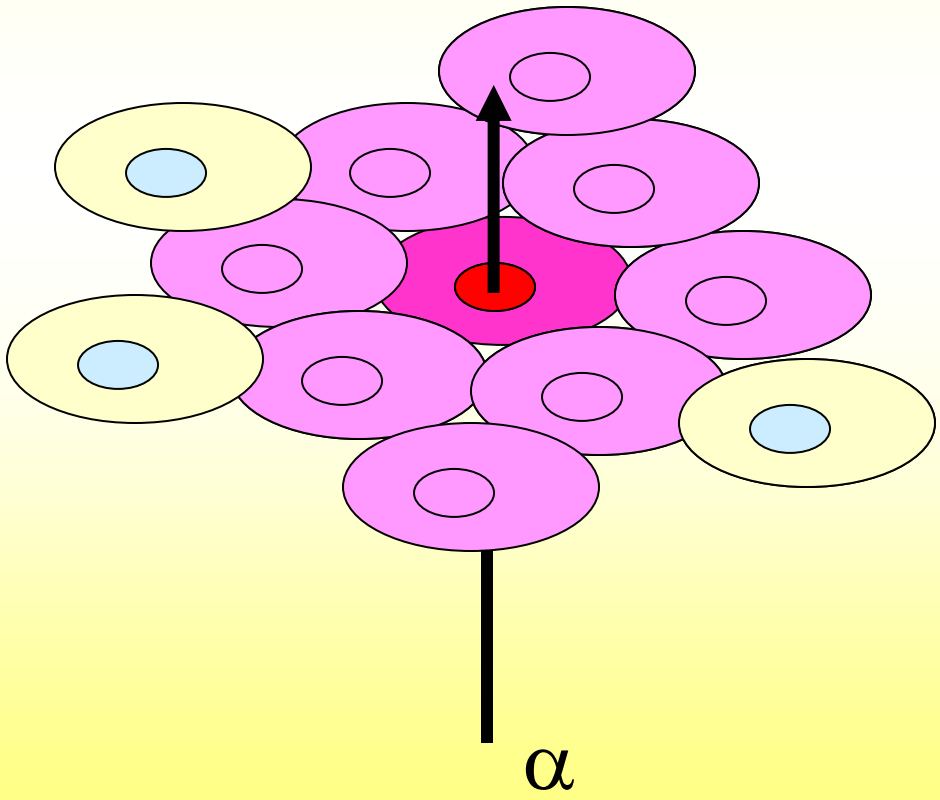
Possible extrapolations of radiation-induced cancer risk to doses where epidemiology cannot go



Biophysical argument in BEIR VII

Increases in dose simply increase the probability that a given cell in tissue will be intersected by an electron track which will have a non-zero probability of inducing a biological effect. Therefore, at these very low doses, linearity of response is almost certain

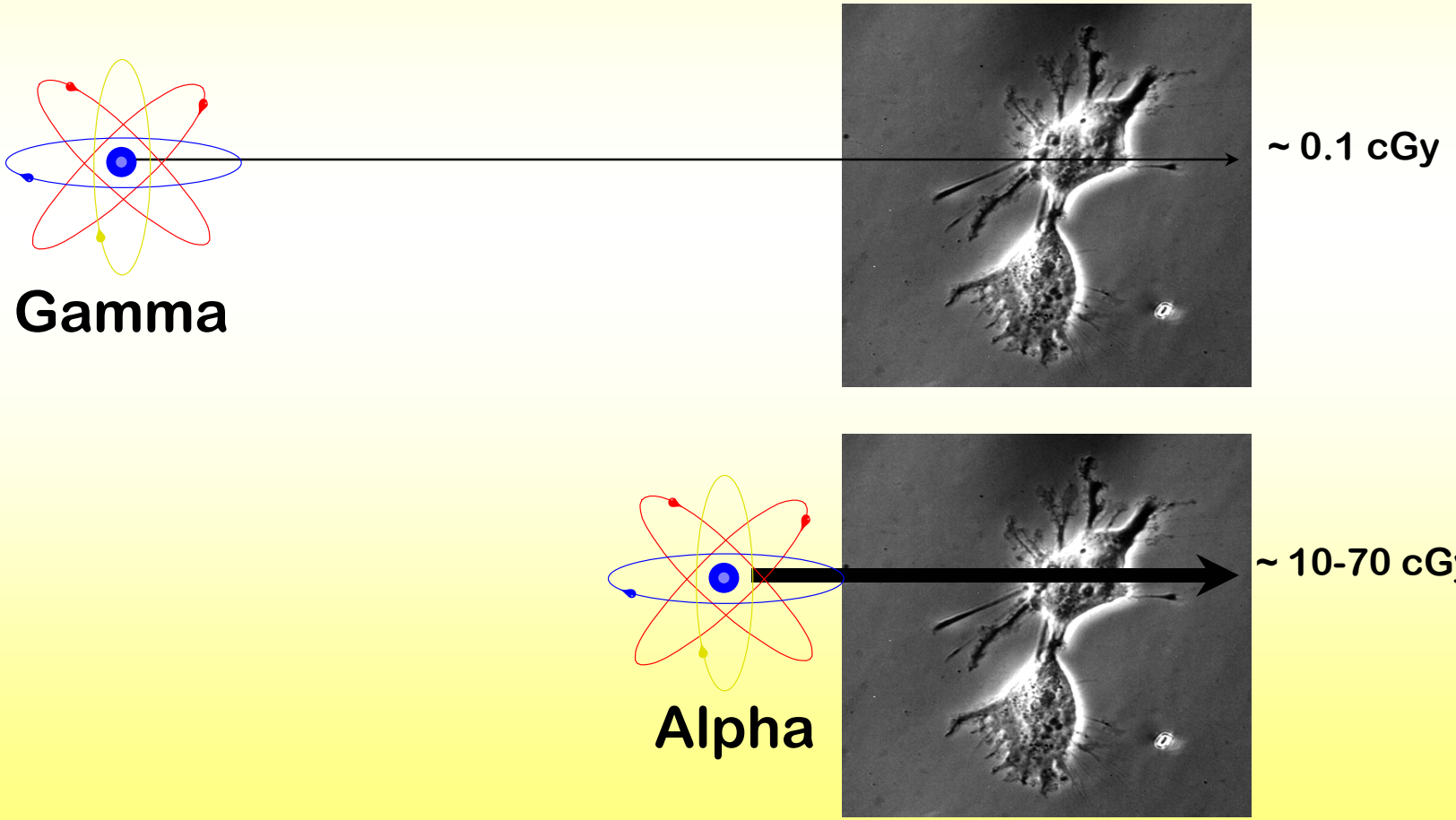
Radiation-induced bystander effect in cell cultures exposed to low fluences of α-particles

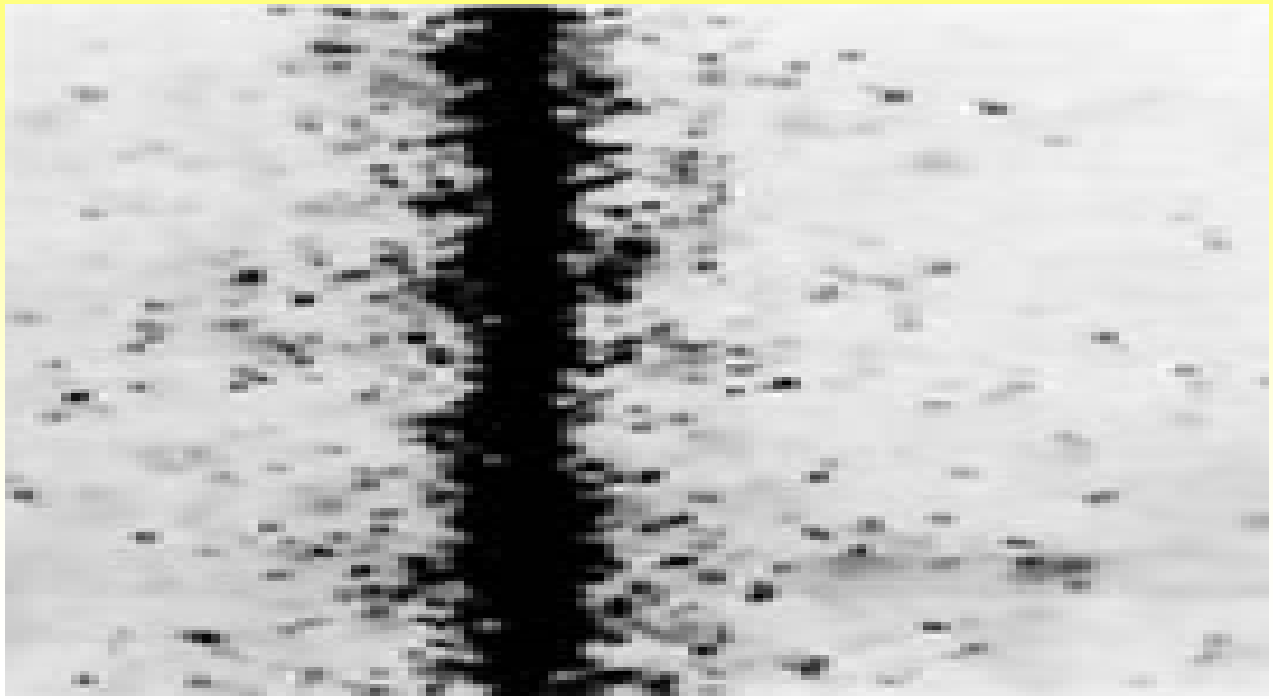


Genetic changes
Gene expression
Biochemical changes
Survival

Dosimetry

Approximate dose to the cell nucleus from a single track





Macroscopic dose from 1 α-particle track is ~ 0.15 Gy/ human fibroblast. The specific energy deposited in a directly hit area (e.g. nucleosome) is several dozen Grays

Cucinotta *et al*., 2000

Acknowledgement

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