Low dose radiation effects: mechanisms and dose-response curves

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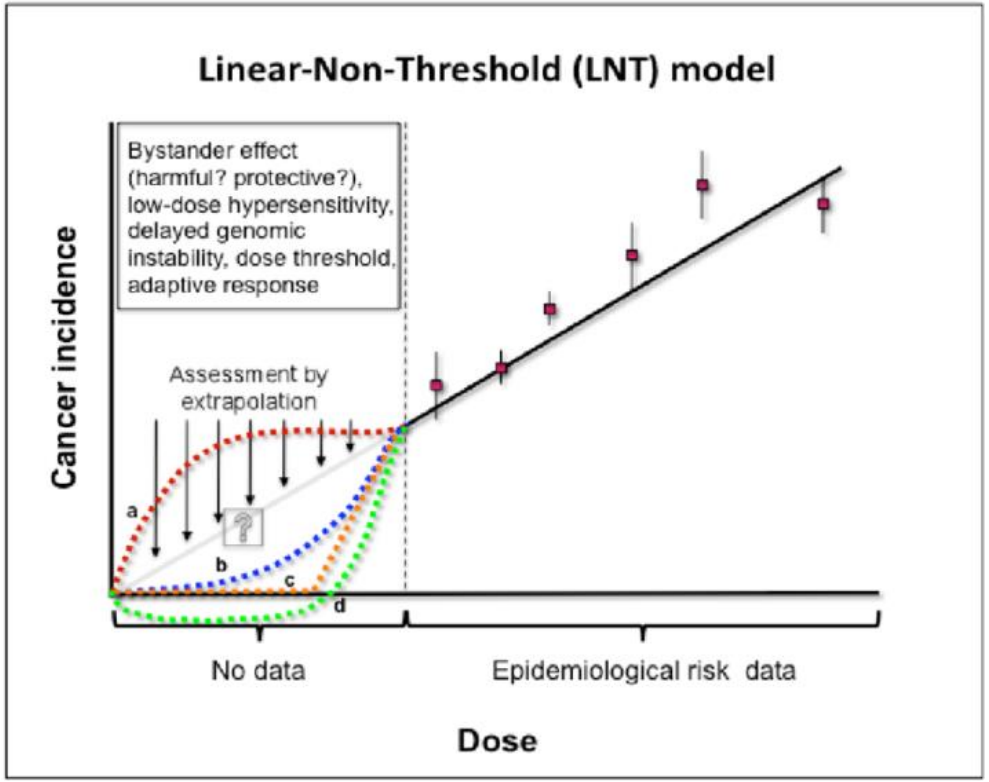
Does low dose IR cause disease?

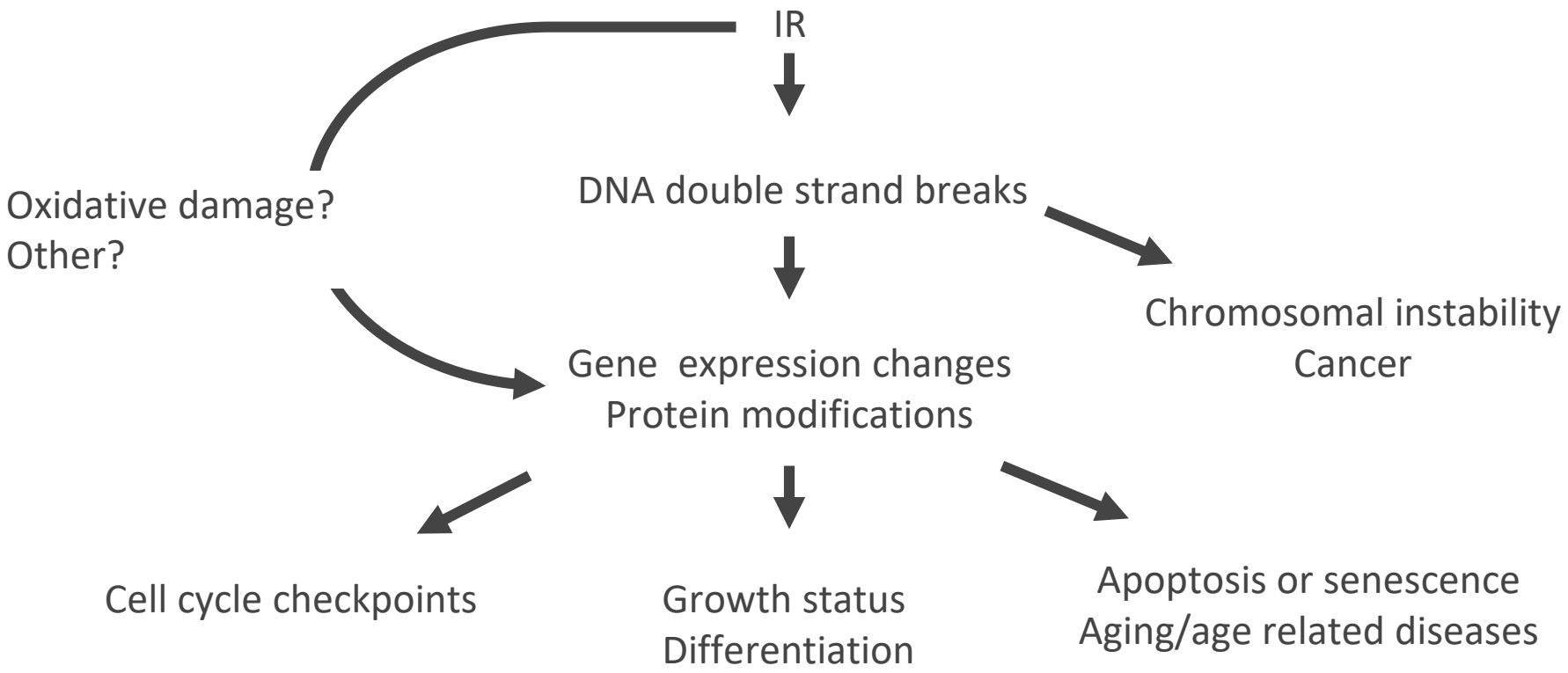


Low and high IR doses: linear or not?

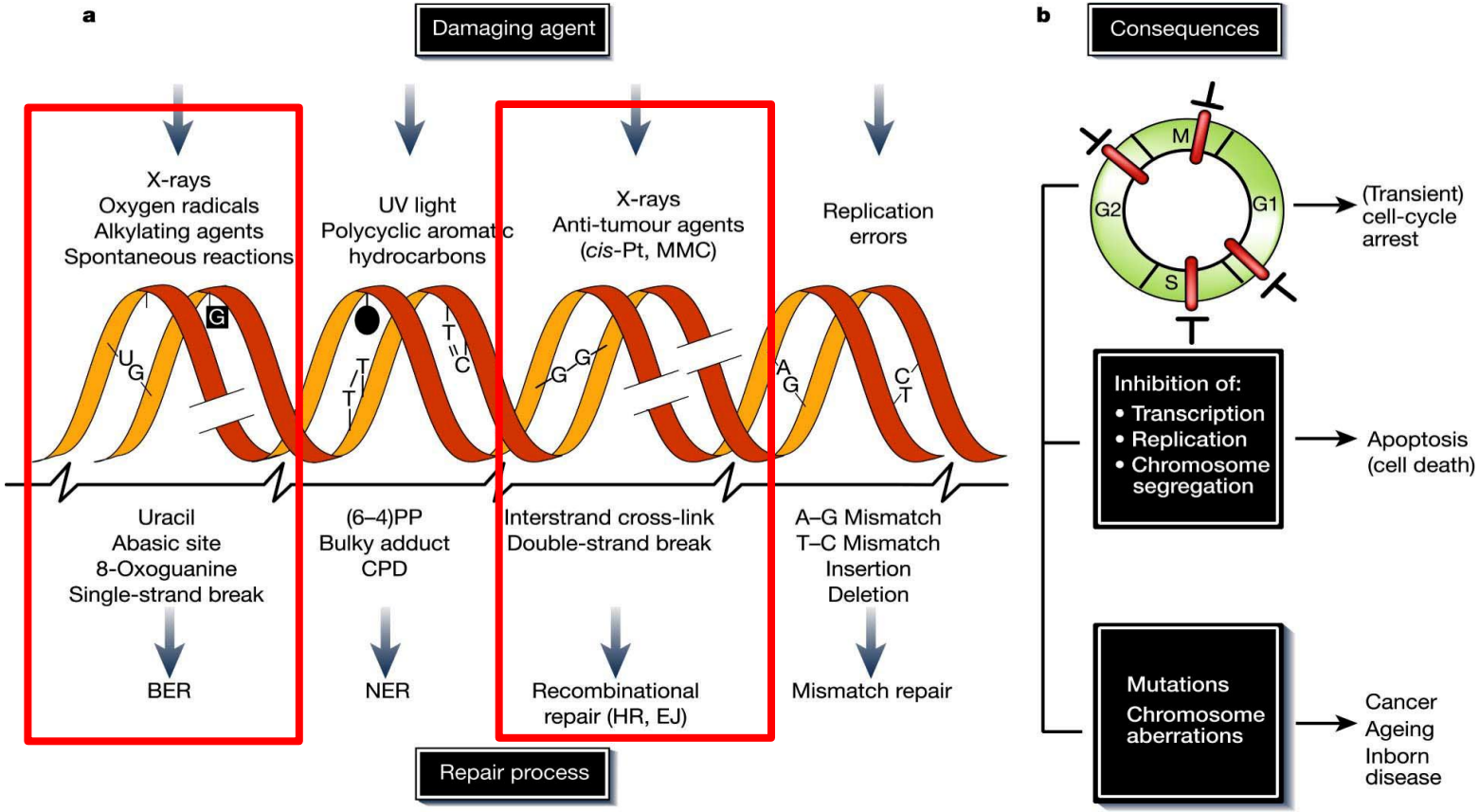
- IR induces DNA damage: breaks and oxidative
- Repaired by various repair pathways
- DNA damage induces various reactions:
  DNA damage response or DDR

Currently, we assume that responses are linear without a threshold: LNT
Is this correct?

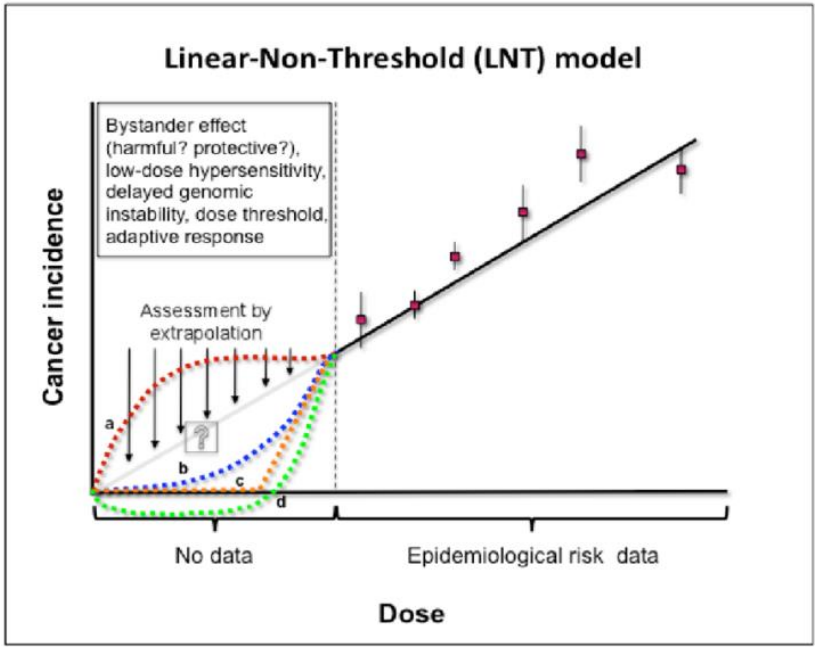
Regulation of the DNA damage response



DNA damage: Induction and repair



Does low dose IR cause cancer?



All depends on the question which model is correct

Why is extrapolation so difficult?

Cancer is a multifactorial process
Some processes are linear, others not

So, what will be the result?

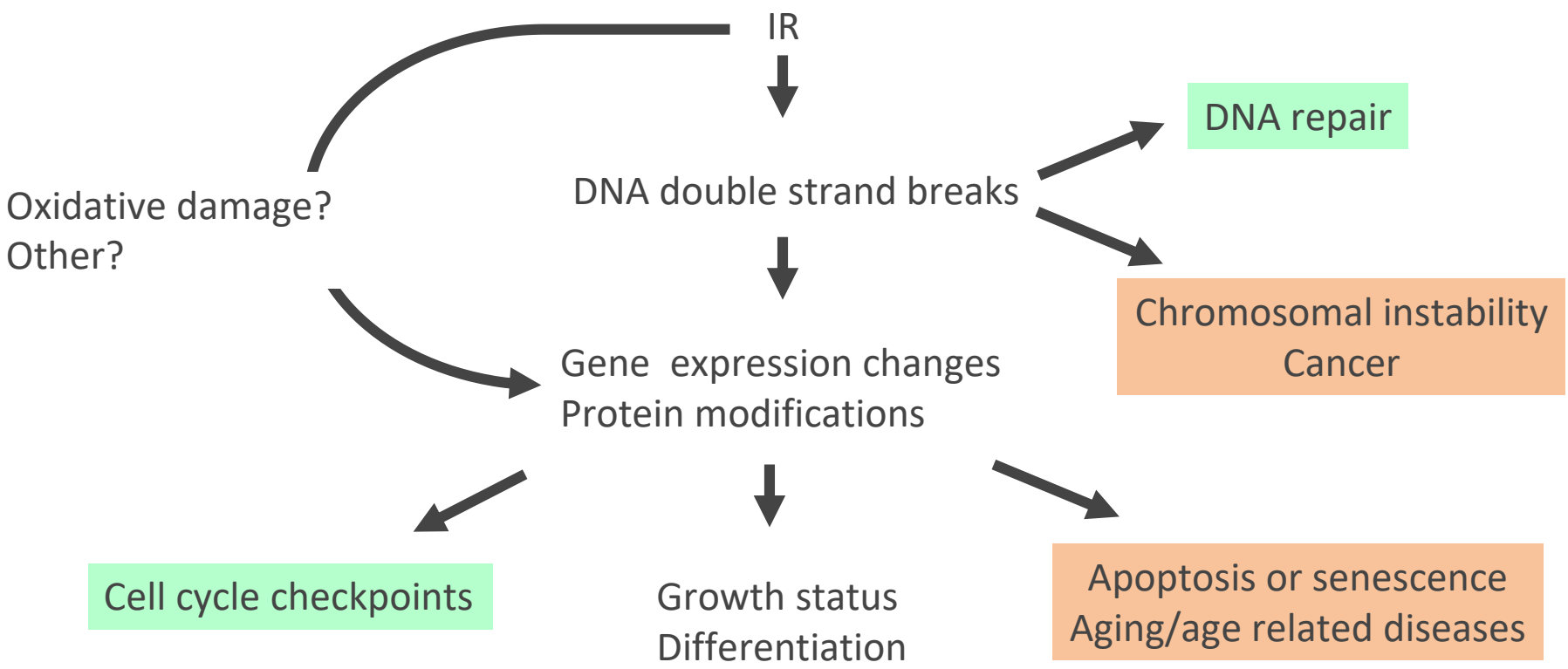
Version 1: Damage induction linear, mutations linear, so cancer risk linear
Version 2: Responses like transcription, apoptosis are not linear, so cancer risk not linear

Modeling of the dose-response curve

LNT, threshold, hypersensitive, hormesis?

Which processes could be important?
- DNA repair (mutations, chromosomal instability)
- cell cycle checkpoints
- transcriptional responses
- cell death and senescence
- differentiation

Regulation of the DNA damage response



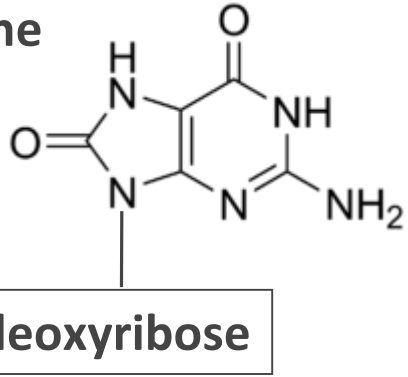
DNA repair

IR causes:

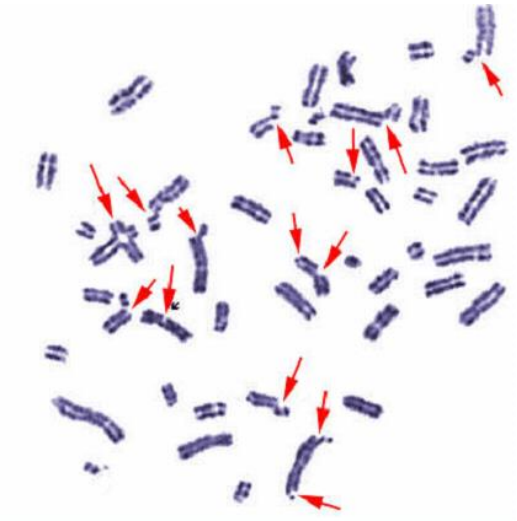
- DNA double strand breaks: chromosomal deletions and translocations

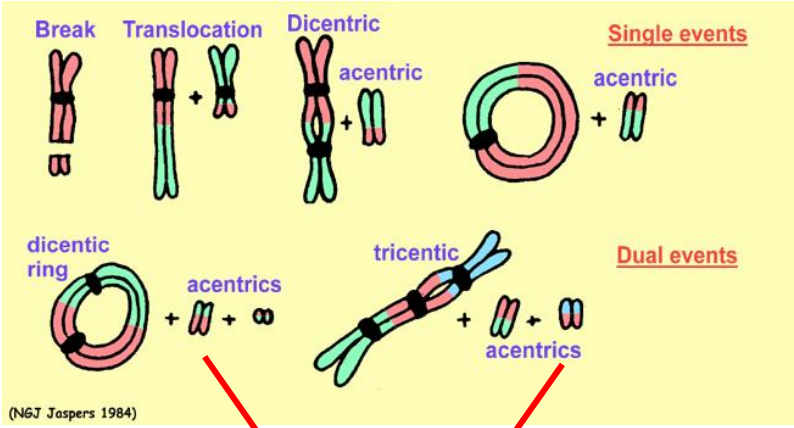
- Oxydative DNA lesions: influence on transcription, mutations

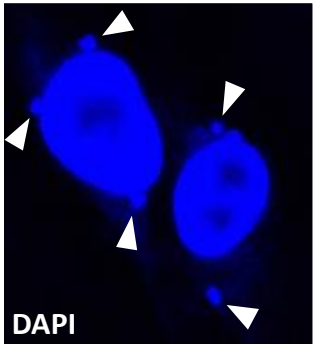
8-oxoguanine



DNA double strand breaks

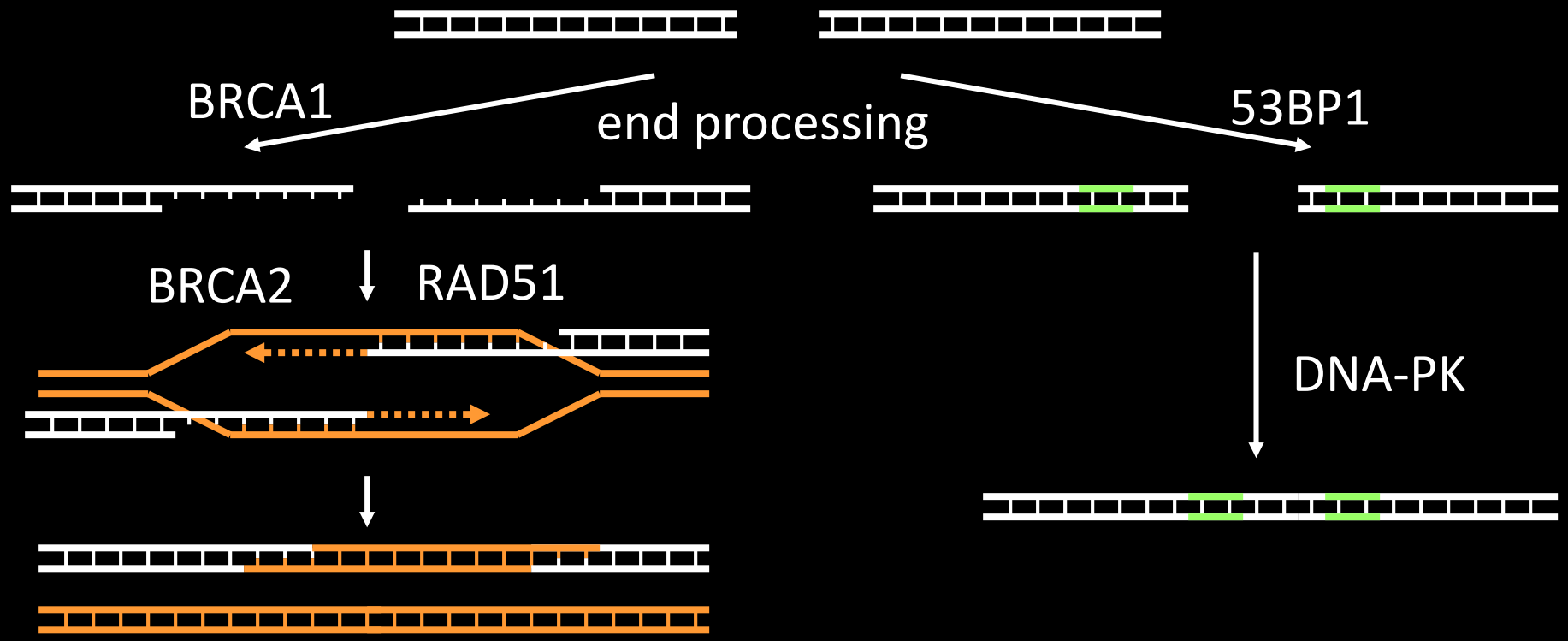






Breaks lead to deletions, translocations and micronuclei

Double-strand break repair pathways



Homologous Recombination

DNA end-joining (NHEJ)

DNA double strand breaks

Induction of DNA damage is linear with dose
Formation of micronuclei is linear with dose (down to 10 mGy)
Formation of chromosomal translocation is linear (down to 50 mGy)
DNA double strand break repair is linear (at least down to 10 mGy)
maybe not at very low doses (1 mGy)

Conclusion: DNA damage induction and repair is probably linear (LNT)

DNA double strand breaks

Is DNA damage induction and repair indeed linear?

Caviat 1: most knowledge has been obtained with fibroblasts or lymphocytes in cell culture (2D or suspension)

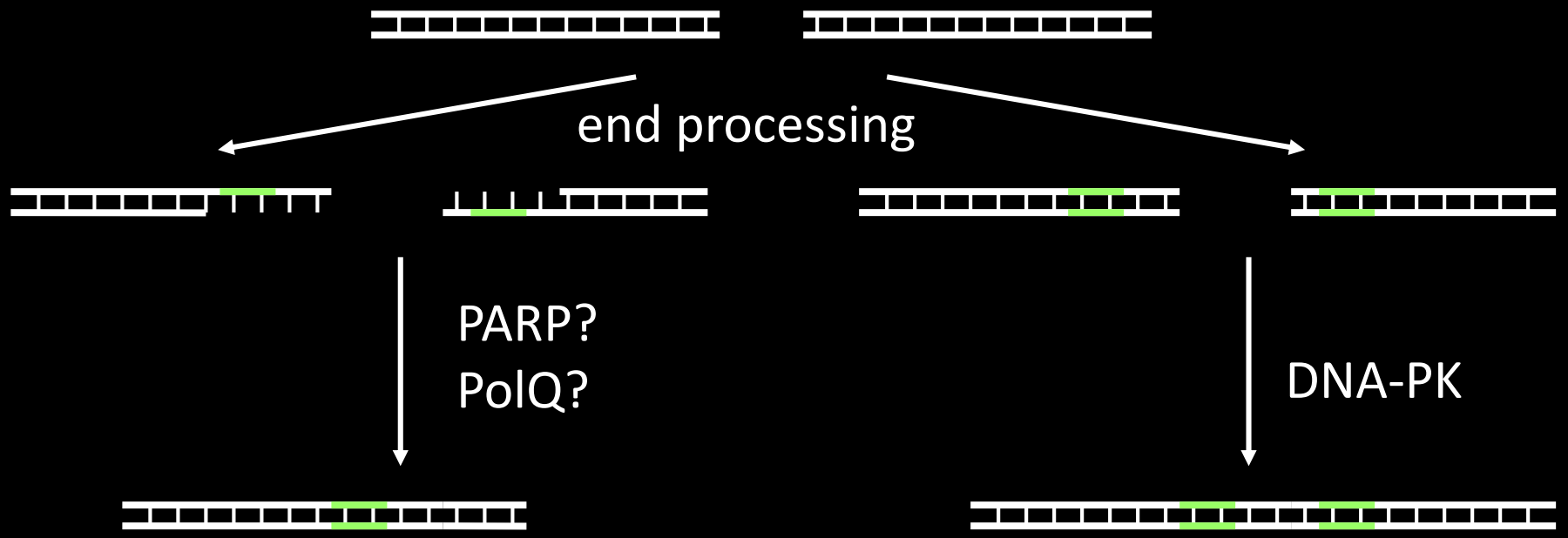
Caviat 2: we mainly assessed the kinetics of total DNA repair capacity
Subpathways of end-joining may have completely different cancer outcomes!

Classical and alternative NHEJ

Most DNA breaks are repaired by classical NHEJ, but alternative NHEJ may be the major factor determining cancer risk

The mechanism is not clearly defined, but mostly involved microhomologies

NHEJ pathways



Alternative end-joining (aNHEJ)

DNA end-joining (cNHEJ)

Balance between DNA break repair pathways

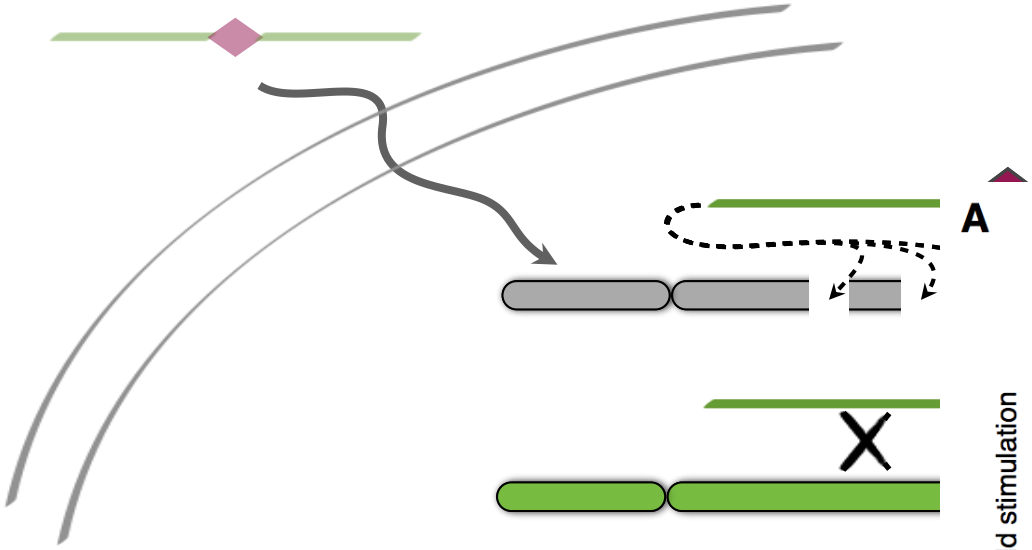
DNA damage induction and repair is probably linear (LNT)

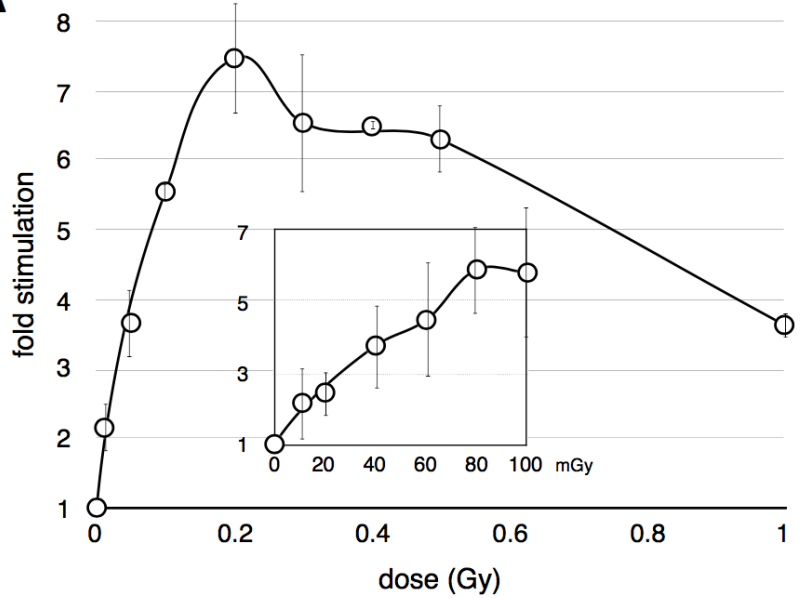
However, it is not always done in the same way

- sometimes alternative repair pathways are used
- sometimes extrachromosomal DNA is inserted (random integration)

Balance between pathways may be different at low and high doses

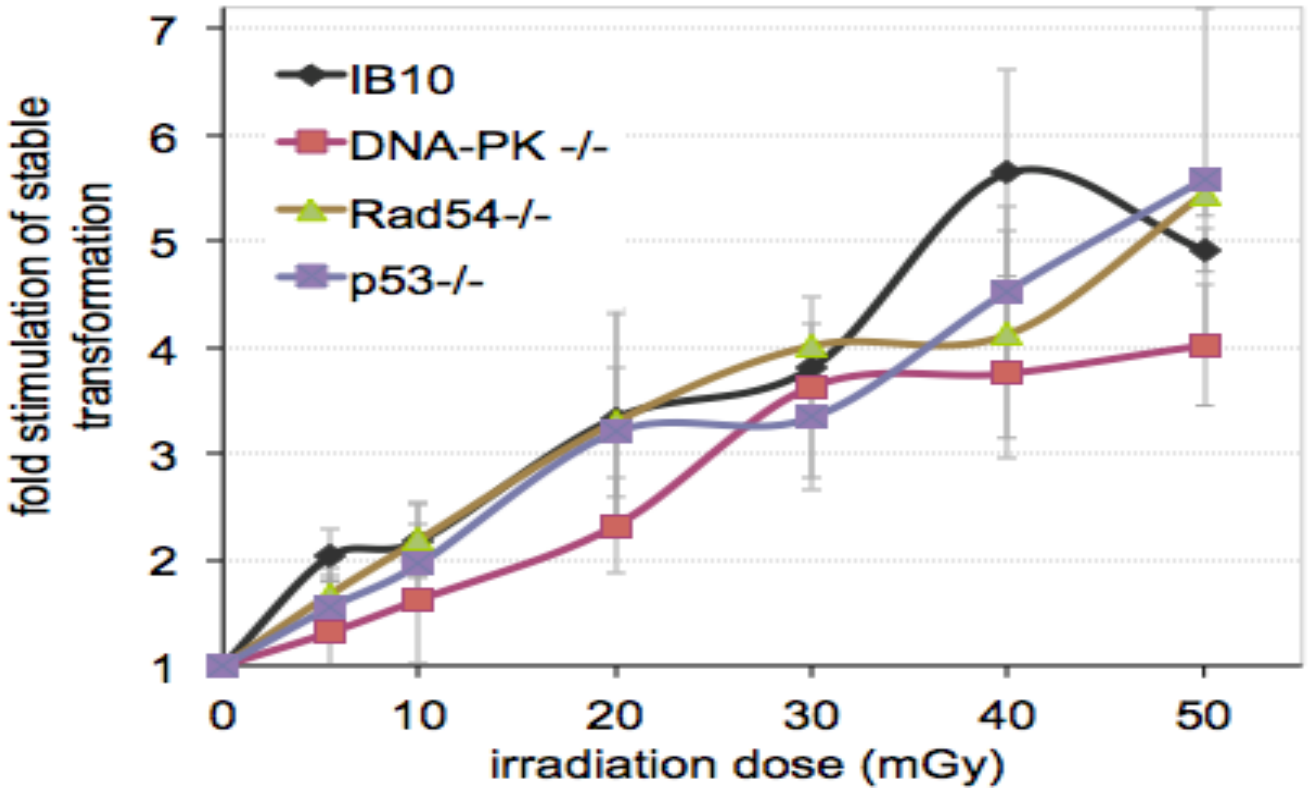
Random integration assay



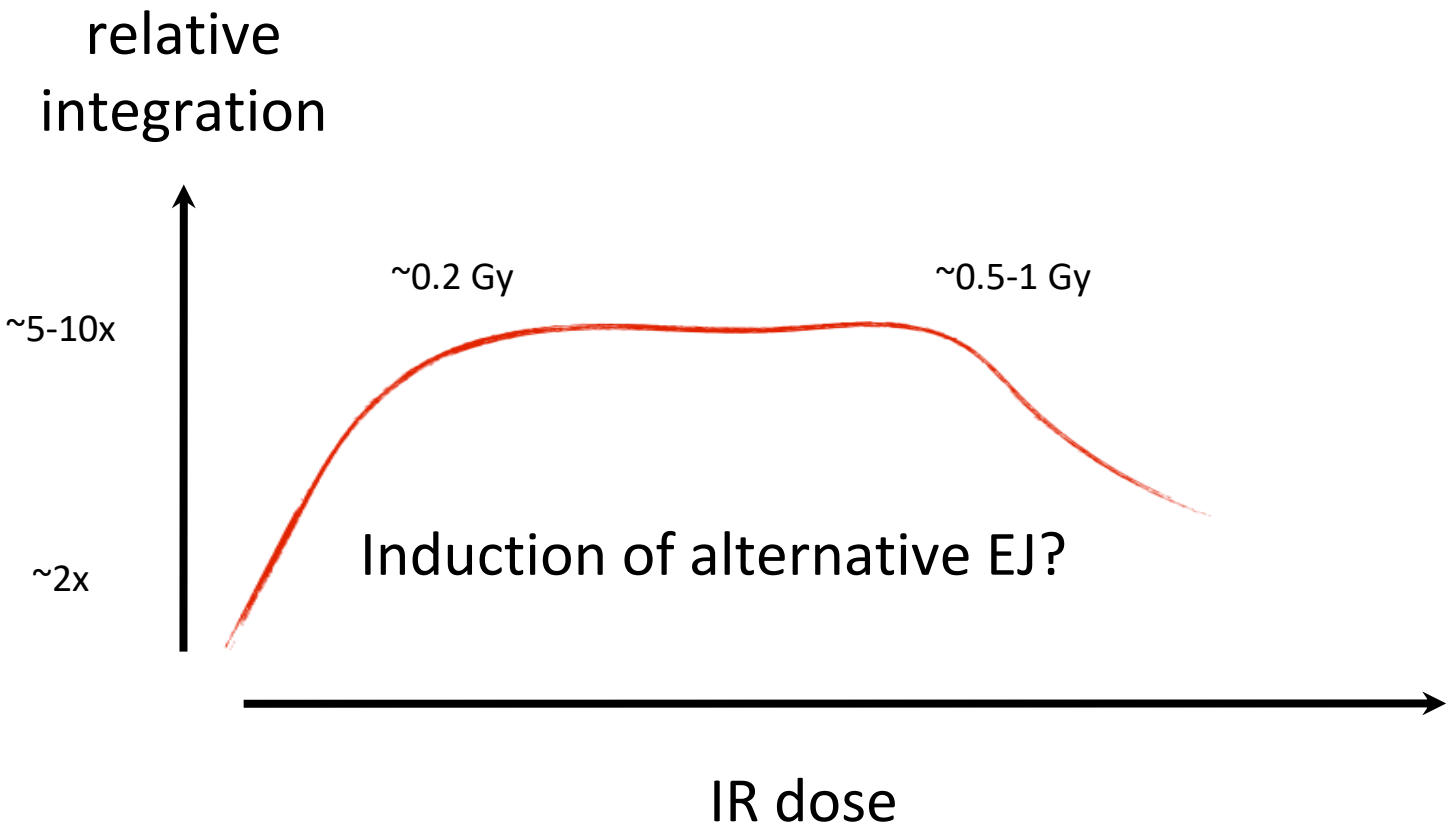


Alex Zelensky et al.

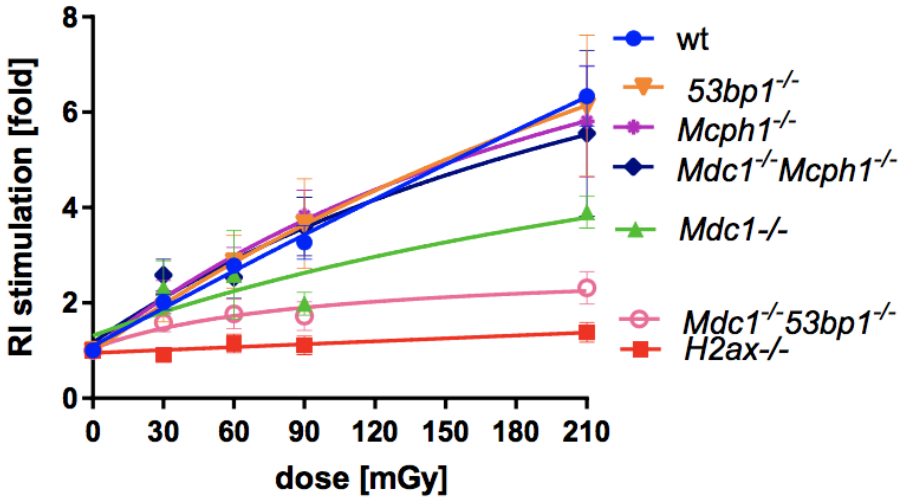
Repair mutants behave like wt

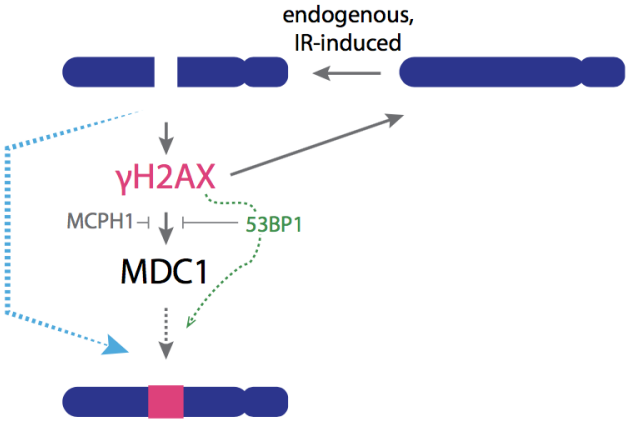


Random integration assay



Alternative EJ is required for stimulation





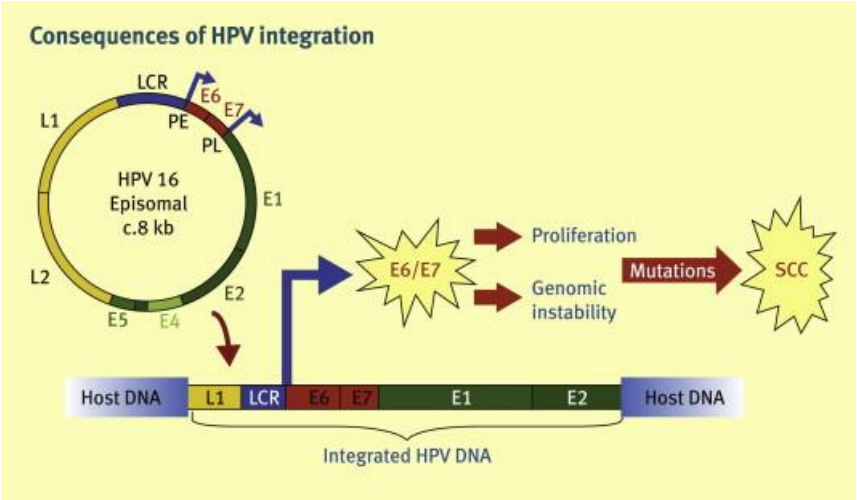
DSB induce alternative end-joining pathways

This alternative pathway is more prone to DNA integration

DNA integration and cancer risk?

In general, integration of extrachromosomal DNA is not very deleterious

However, viral DNA integration can be!



Interesting observation:
HPV+ oropharynx cancer is on the rise and this is positively correlated with income (US):
Relation with low dose IR from imaging?

DNA double strand breaks

Is DNA damage induction and repair linear (LNT)?

Repair kinetics yes
Chromosomal aberrations yes
More subtle differences no?
Risk of DNA integration (viruses) no?

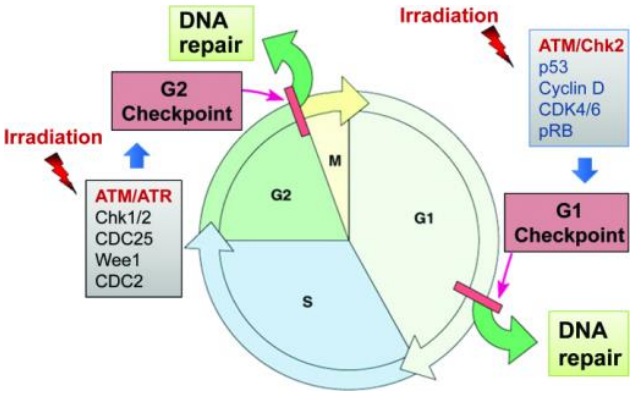
What does that mean for cancer risk???

Cell cycle checkpoints

DSB induce G2/M checkpoint

but only when several breaks are present (Löbrich and Jeggo labs)

Conclusion: this may be non-linear with a threshold, maybe not important at low doses



Cell death, scenescence and differentiation

Three ways to prevent uncontrolled growth and cancer development

Cell death by apoptosis (or necrosis) has threshold
In some cell types scenescence is induced, but not apoptosis
Other cell types start differentiation upon IR

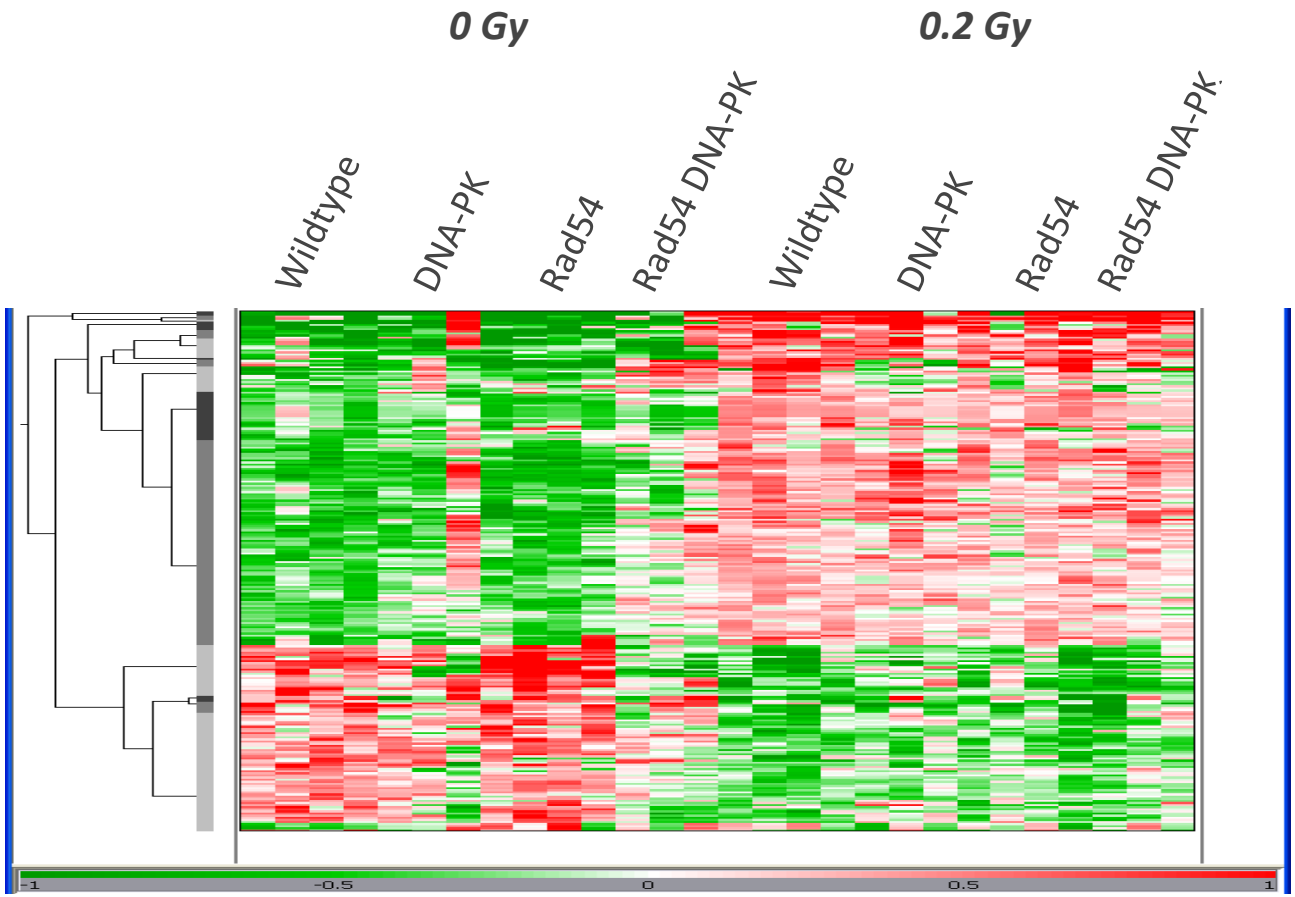
Conclusion: Induction of cell death, scenescence or differentiation is not linear with large differences between cell types/tissues
Probably not very important at low doses

Transcriptional responses

DNA damage activates transcription, e.g. via p53
Several pathways are activated and inactivated by DNA damage
Each pathway may have a different threshold and dose-response curve

Conclusion: transcriptional responses are non-linear, but it is not clear what is the right model

Low dose gene expression profiles



Mice irradiated 0.2 Gy, 0.2 Gy/hr
2 hours later, liver isolated
mRNA isolation
Micro array analysis
Significant genes

Non cell-autonomous effects

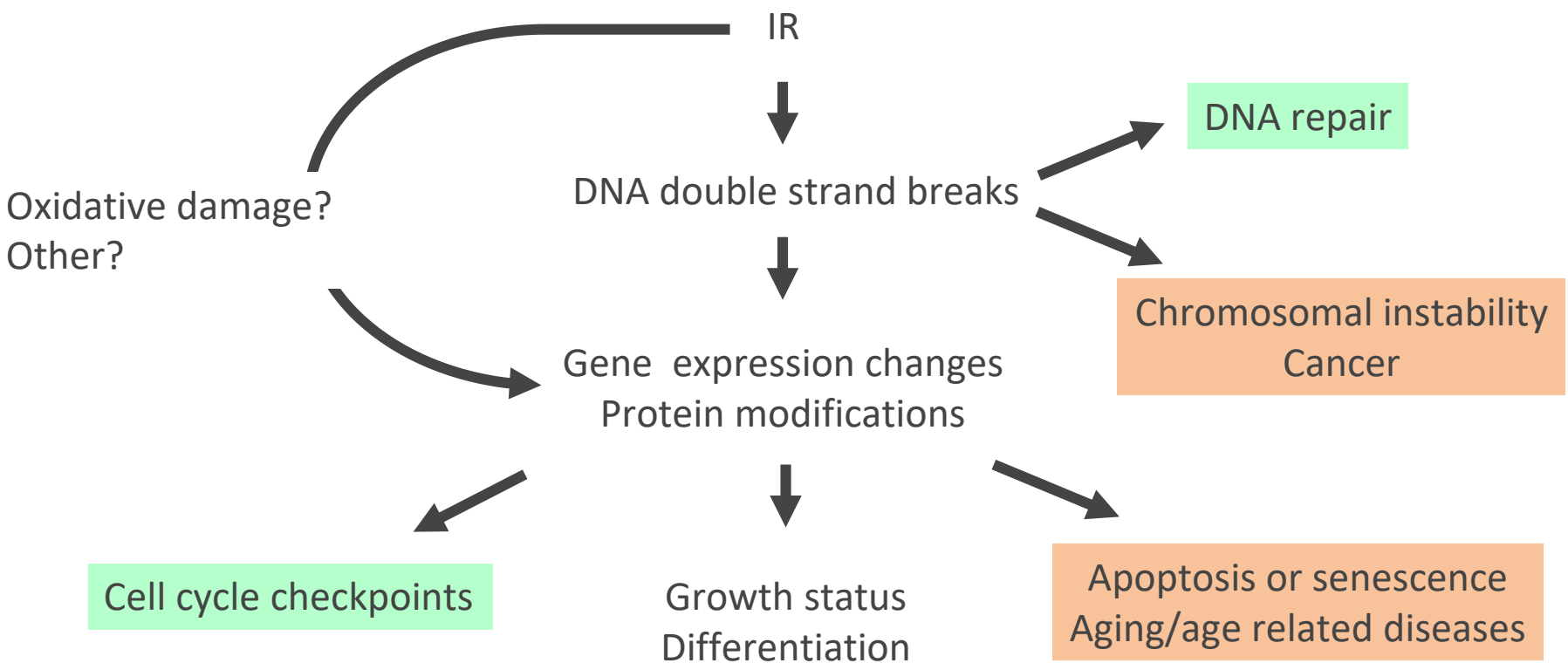
Some examples:

Inflammatory responses (cytokines)

Immune activation or inactivation

Hypoxia (e.g. by destroying blood vessels)

Regulation of the DNA damage response



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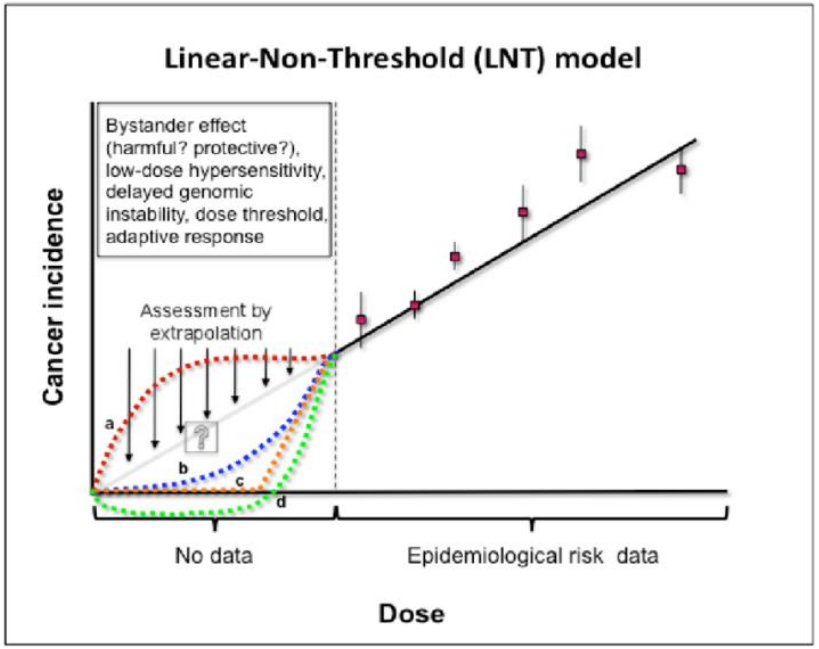

The jury is still out: we cannot yet predict this on the basis of known dose-response curves

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