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Recent Biological Results Against the Validity of the LNT Hypothesis

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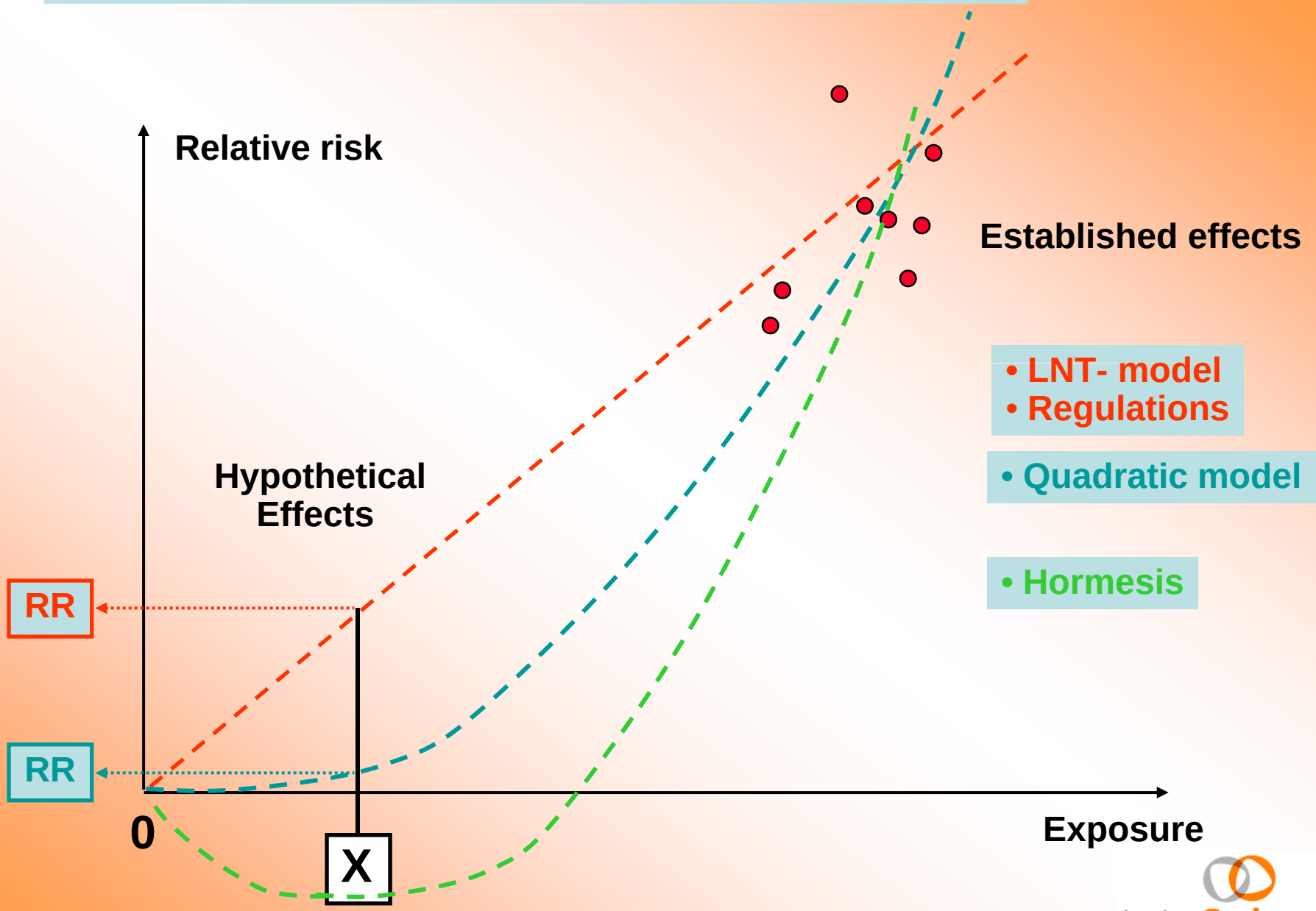
Introduction

- **The biological or health impacts of ionizing radiation are conditioned by the physically determined energy deposition and corresponding radiochemical events with free radical formation as well as by the biological reactivity of cells and tissues.**

- **Most studies have been focussed on high dose ionizing radiation induced deterministic and stochastic (mutation, cancer) effects which have been in line with the concept of linearity between radiation dose and biological effects.**
  This linear no-threshold concept (LNT) has been used to establish the international rules and standards in radioprotection (see ICRP recommendations).

Risk evaluation for ionizing radiation



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Limits of epidemiological studies

- During lifetime human beings are exposed only to **low dose ionizing radiation** (IR), with the exception of radiation therapy or radiation accidents.(Natural background IR: 2.4 mSv/year)
- **Epidemiological studies** are usually lacking sufficient statistical power to determine risks from very low dose exposures.
- Therefore, **fundamental mechanistic studies** are essential to understand the mechanisms associated with low dose exposures and the possible human health risks involved.

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Change in radiobiological paradigms and concepts

- Recent using new research tools have led to new findings that put into question some of previously established **radiobiological paradigms and concepts and the validity of the LNT-model.**

- This has been especially highlighted by the **Report of the French National Academies of Science and Medicine 2005, somewhat in contrast to the BEIR VII report 2006.**

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Recent concepts

- Existence of specifically IR-induced DNA lesions (locally multiply damaged sites or **LMDS**), responsible for deleterious IR effects (see BEIR VII report)
- Existence of effective cellular defence systems:
  1. Antioxidants and DNA repair pathways
  2. Elimination of damaged cells by apoptosis or mitotic death
  3. Immunological defences

Modern concepts

- Effectiveness of cellular defence systems is not constant with IR dose
- Probabilities of DNA repair and apoptosis vary with dose.
- Furthermore, there are phenomena ,especially influencing low dose responses, adaptive responses and non targeted effects, i.e. bystander effect, low dose hypersensitivity, genomic instability….

Ionizing radiation-induced DNA damage

Recent theoretical and biophysical findings show that:

1. High LET- and low LET ionizing radiation can give rise to **locally multiply damaged sites (LMDS)** in DNA (*Goodhead DT IJRB 1994;65:7-17; Nikjoo H. et al. Radiat. Res. 2001;156:577-583*) and may involve processes such as
2. **K-shell activation** by low LET IR where the emission of two energetic Auger electrons (250 and 360 eV) can induce complex DNA damages like DNA double-strand breaks (DSBs) *(Boissière A. et al. J Environ Pathol Toxicol Oncol. 2004; 23(2):107-115, Gobert FN et al IJRB 2004;80:135-145)*

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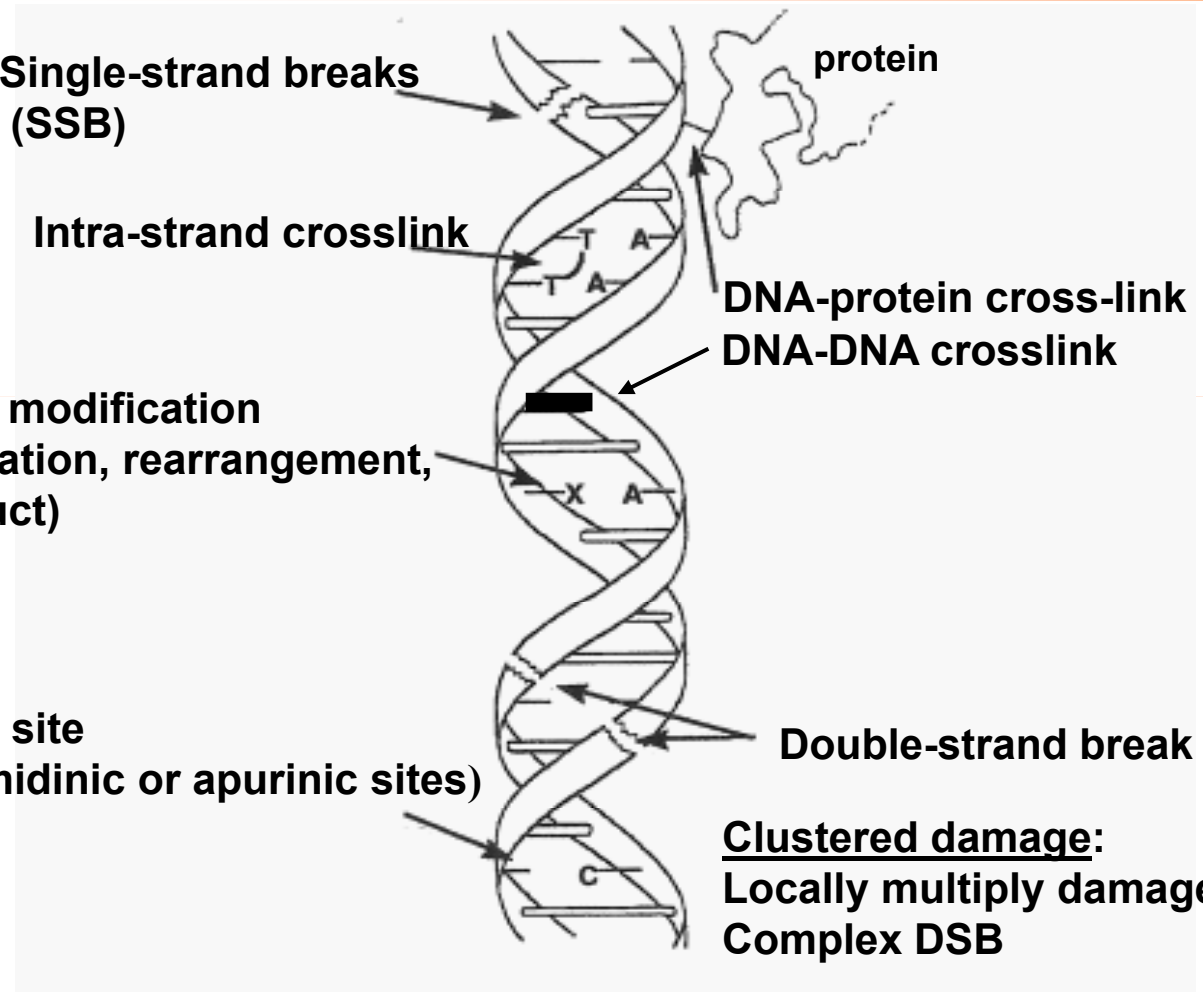
DNA damage



DNA

Differences between endogenously and IR-induced DNA lesions

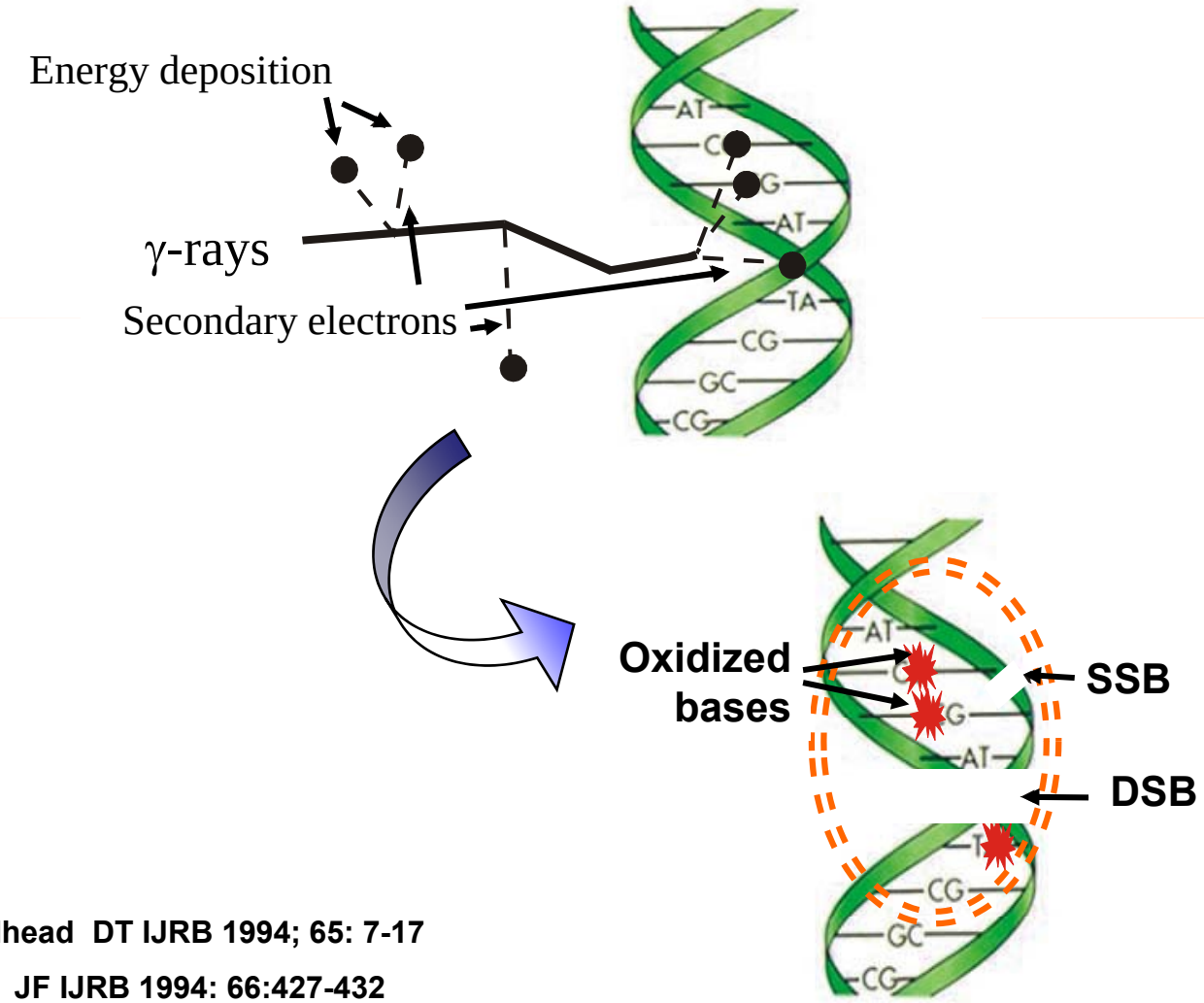
- **Endogenously**, due to cellular metabolism, one finds many SSBs and modified bases, however, **very few DSBs or complex lesions**.

  -----> *Single lesions are expected to be readily taken care of by cellular DNA repair systems.*

- **IR-induced** lesions in DNA include **considerable amounts of DSBs** and clustered lesions such as complex DSBs and **LMDS**, consisting of SSBs together with base damages.

  -----> *These lesions are considered highly deleterious*.

Formation of locally Multiply Damaged Sites (LMDS) at the end of radiation-induced electron tracks



Goodhead DT IJRB 1994; 65: 7-17

Ward JF IJRB 1994: 66:427-432

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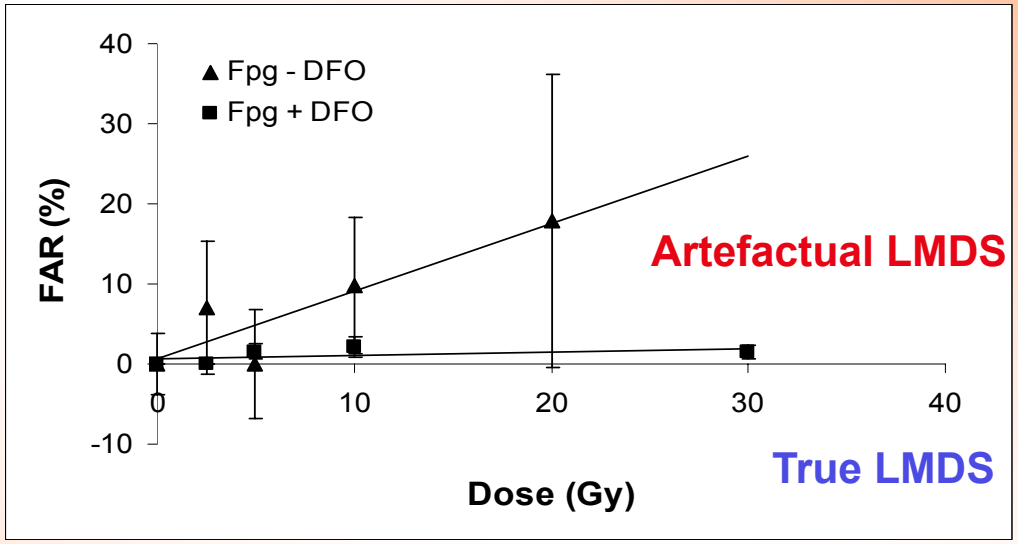
Search for IR-induced LMDS in mammalian cells



- **Using a classical approach, quite high amounts of LMDS are found** (3-4 fold more than DSBs)(*Sutherland B et al. ,PNAS 2000; 97(1):103-108*).
- **When limiting artefactual oxidation of DNA during analysis, we found very low yields of LMDS close to the level of DSBs in mammalian cells after low and high LET-irradiation** (*Boucher et al. 2006 Radiat. Environ.Biophys.*, 2006;45(4):267-276)

⇨**Clustered lesions (LMDS) are likely to consist of complex DSBs with oxidized endings ('dirty DSBs') which have been found difficult to repair by mammalian cell extracts** *(Budworth H et al. J.Mol.Biol 2005;351(5):1020-1029).*

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LMDS and radiation risk

- On the contrary to what is said by the BEIR VII report 2006 (p54): 'LMDS (clustered damage) may be viewed as complex lesions associated with IR and not with endogenous oxidative processes. If they are refractory to repair, the risk to humans posed by IR may be viewed as greater than that posed by endogenous oxidative stress.'

  Our results indicate that the amount of IR-induced LMDS may be confounded with the amount of DSBs.
- ----> In most cases, clustered lesions are found to be refractory to repair, showing mostly **lethal** and no mutagenic potential.
- ⇨ **LMDS are thus unlikely to contribute significantly to mutagenic and carcinogenic risk of IR for humans, especially at low doses.**

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Response to ionizing radiation (IR)

- ***Signaling***
- *Gene induction*
- ***Cell cycle arrest***

Cell death

DNA repair

Error-prone

Error-free

Mutation

Survival

Genetic instability

Cell transformation

Carcinogenesis

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Breakthrough finding (1)

Cellular signaling directs cellular responses

1. Cells react very sensitively to IR:

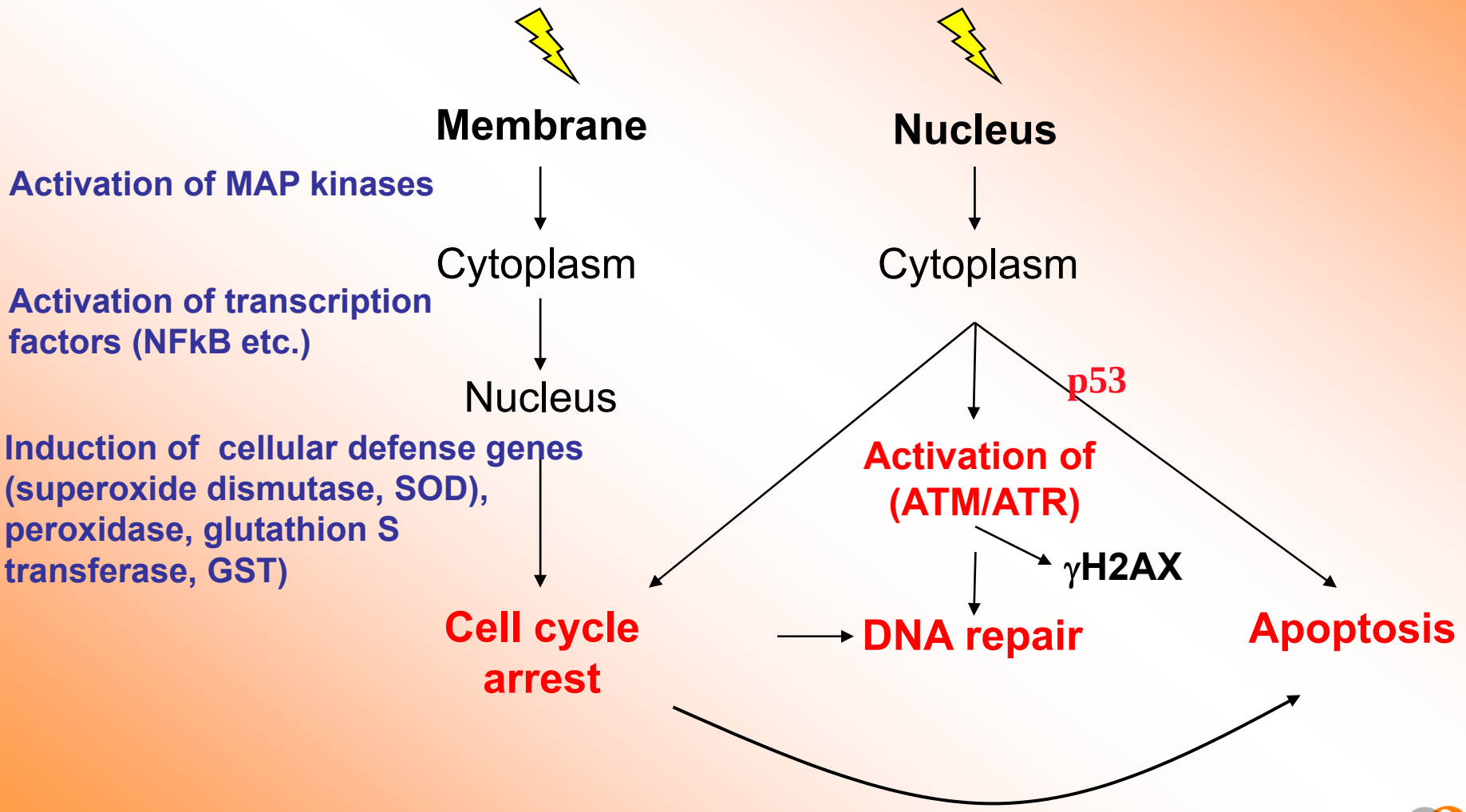
- Activation of **cellular signaling occurs** (including gene induction) with **activation of cellular defence systems**:

  ---> Activation of MAP kinases and antioxidant defences

  ---> Activation of phosphoinositidyl 3 kinases to activate DNA repair and/or apoptosis

Cellular signaling after IR and genotoxic stress

Activation of several pathways



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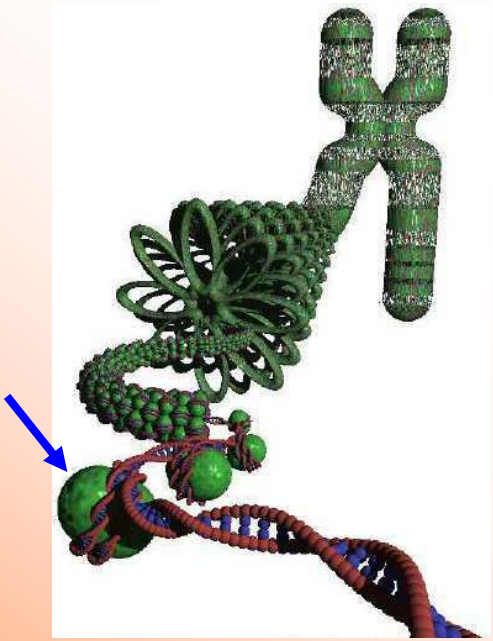
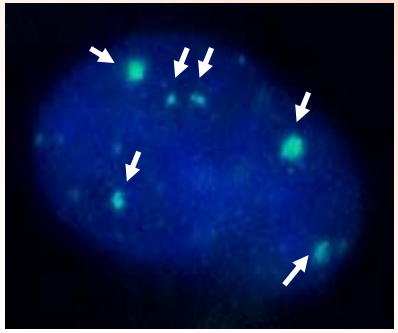
DNA damage signaling determines cell cycle arrest, DNA repair and apoptosis

----> DSB detection by γH2AX labeling



- **H2AX protein is part of the histone complex, and is phosphorylated in the presence of DSB by kinases ATM, ATR and DNA-PKcs *(Bakkenist, Kastan 2004, Shiloh 2003).***

- **γH2AX foci at DSB sites are quantified by immunofluorescence labeling. *(Brenner, Löbrich)***



➢ **The quantification of γH2AX foci is a very sensitive method for measuring DSBs (down to ~1 mGy) and is an indicator of DNA damage signaling.**

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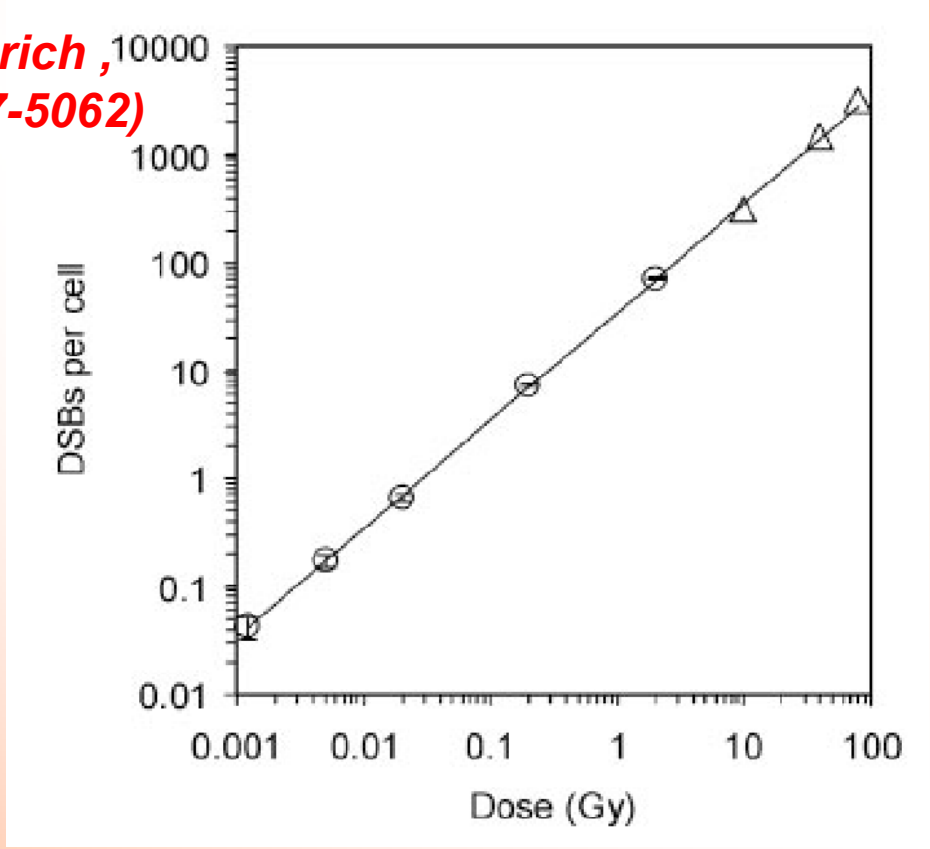
Detection of IR-induced DSBs by PFGE and γ-H2AX foci formation in mammalian cells

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)



⇨ **It is largely admitted that IR-induced DSBs directly correlate with formation of γ-H2AX foci** *(Sedelnikova OA et al. Radiat. Res. 2002;158:486-492)*

⇨ **In primary human fibroblasts the induction of DSBs is linear with IR-dose down to 1.2 mGy .**

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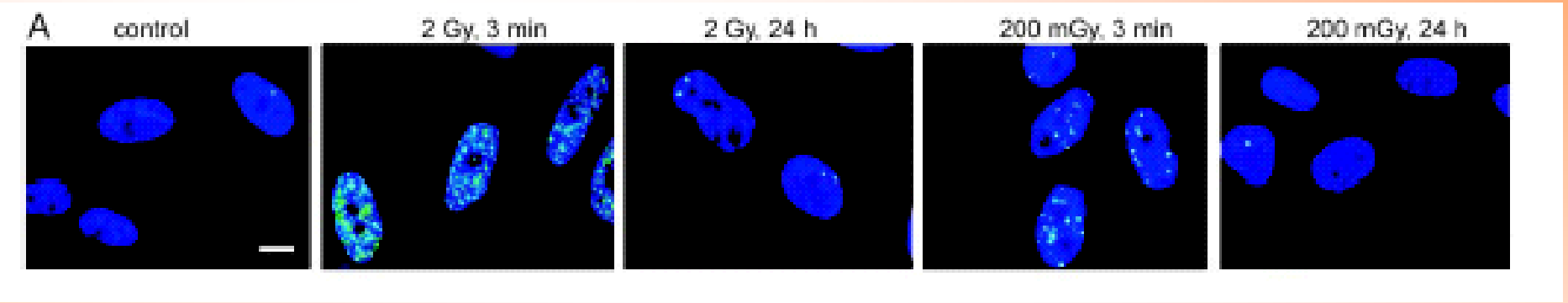
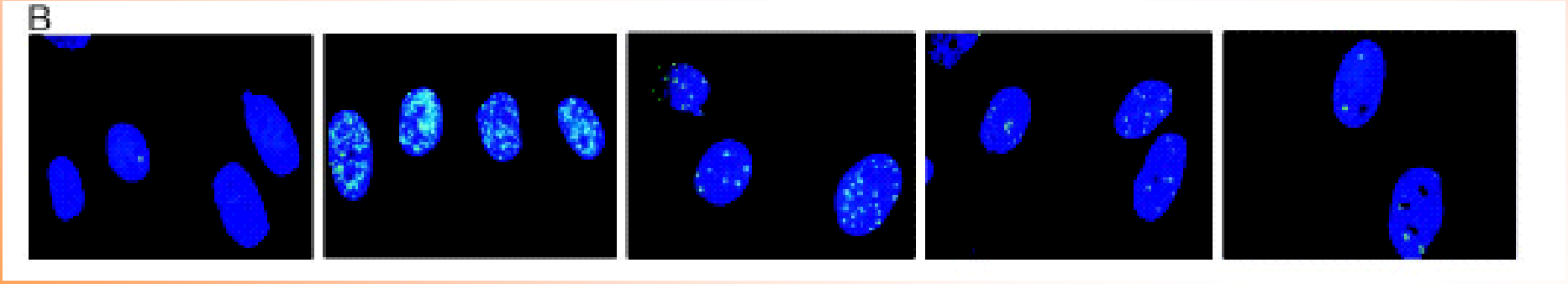
Induction and repair of DSBs as visualized by γ-H2AX in human cells

(Rothkamm K, Löbrich M, Proc Natl Acad Sci USA 2003,100:5057-5062).

MRC5 cells



180BR cells



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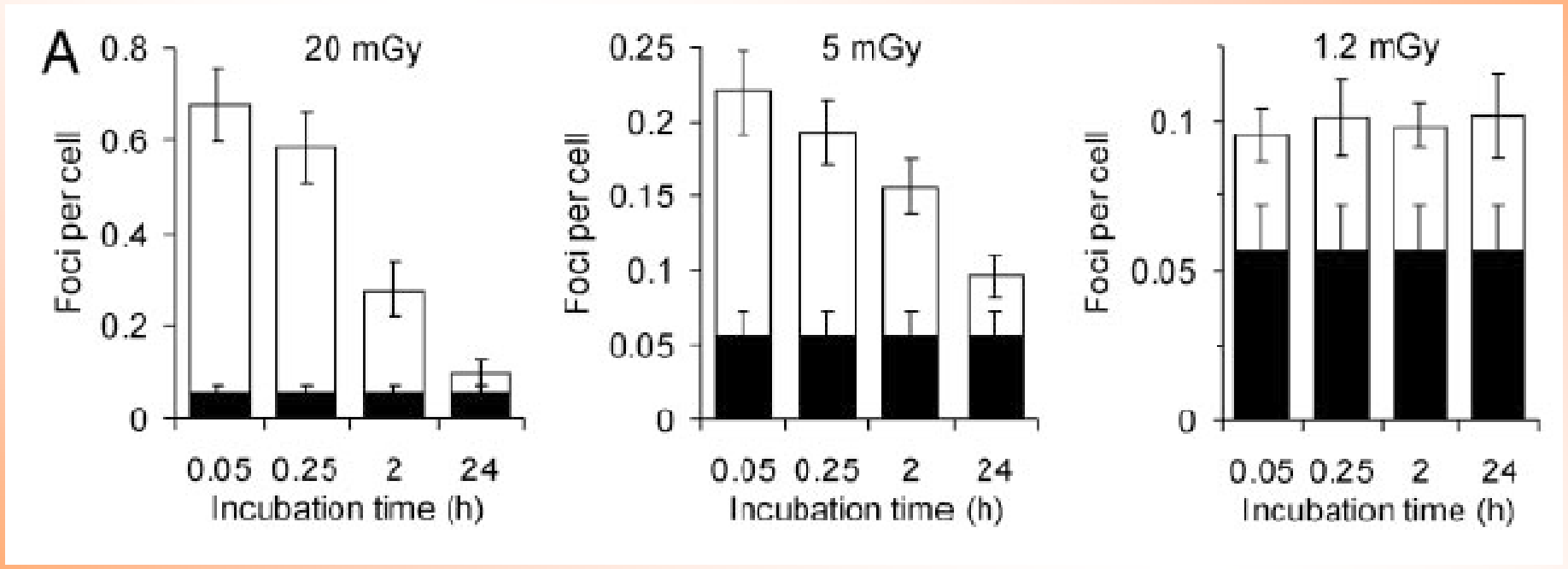
Repair of DSBs in human fibroblasts depends on IR dose

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)



⇨**Absence of repair at 1.2 mGy**

⇨ **Presence of repair at 5 mGy and 20 mGy**

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Cellular reactions and DNA repair depend on the dose level of IR

(Rothkamm and Löbrich , PNAS 2003;100:5057-5062)

- At very low dose (1 mGy), cells are going to die (probably because of no DNA signaling), and there is no initiation of DNA repair of DSBs (or other complex lesions)
- At slightly higher doses (5-20 mGy), DNA repair is initiated (5 mGy: 1 electron track/cell ⇨ 5-10 damaged bases, 2.5-5 SSBs and 0.25 DSBs, see BEIR VII report)

- At higher doses, DNA repair may start to be counteracted by apoptosis.

DNA repair can be error-prone and mutagenic which may enhance the risk of cancer.

⇨**Extrapolations from high to low dose effects do not correspond to the actual reactions of living cells to IR-exposure.**

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Possible consequences at the tissue level

Since mammalian cells are usually inbedded in tissues,

- **at very low IR doses**, tissue functions may **not be compromized** if a few IR-damaged cells do not survive and are eliminated.

- **at higher doses**, a substantial fraction of cells is damaged. Thus, normal tissue functions **cannot be anymore assured**.

- DNA repair allows cells to survive (even as mutated cells) and fulfil some of their tissue functions. However, the presence of mutations may allow **genomic instability, malignant transformation and cancer** to occur.

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Breakthrough finding (2)

Dose and dose-rate dependent cellular signaling

- At very low dose (1 mGy) cells do not turn on DNA repair, and the few damaged cells are eliminated.

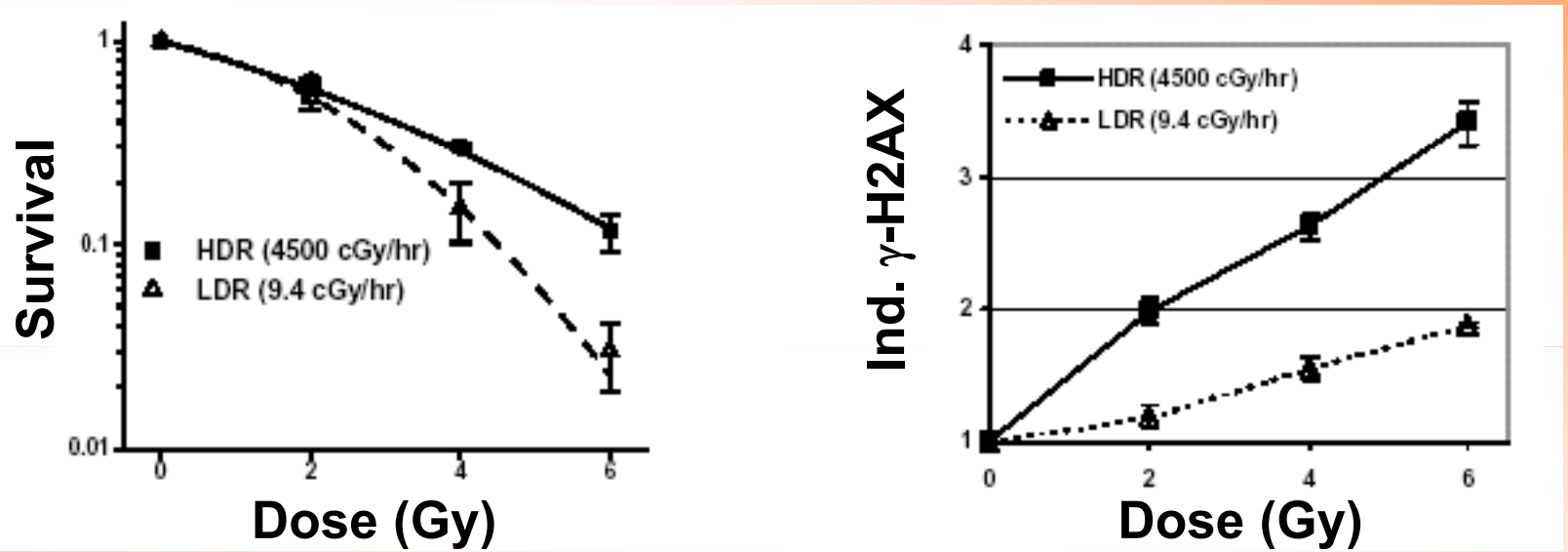
  (Rothkamm and Löbrich , PNAS 2003;100:5057-5062)

- At very low dose rate (1.5mGy/min) cells do not activate DNA repair, and affected cells are dying off.

  (Collis et al. JBC 2004; 279:49624-49632)

Absence of ATM activation and DNA damage signaling at very low dose rate

(Collis et al. JBC 2004; 279:49624-49632)



Taking γ**H2AX** as indicator for radiation-induced DSBs, Collis et al. (2004) have shown that at a very low dose-rate (94 mGy/h), **DSBs are recognized** by detector proteins (MRE11-RAD50-NBS1) **but not repaired** because of an absence of activation of ATM.

⇨ **Signaling of DNA damage (DSB) and DNA repair depend on dose-rate.**

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The effect of dose-rate

•**DSBs signaling** via ATM and H2AX phosphorylation was found to be **absent at a very low dose-rate** (1.5 mG/min) - and associated with lethality – but **present at slightly higher dose-rate** (4 mGy/min) and at high dose-rate (750 mGy/min)

(Collis et al. JBC 2004; 279:49624-49632)

⇨**there appears to be a threshold for ATM dependent signaling and DNA repair**. Because **at dose-rates > 4 mGy/min, DNA damage signaling is taking place.**

⇨**IR-exposures at very low dose levels of chronic radiation may cause more cell killing than that estimated from extrapolation from higher dose-rates.**

⇨ **This clearly questions the general application of a constant DDREF value of 2 for high dose rate exposures proposed by IRCP .**

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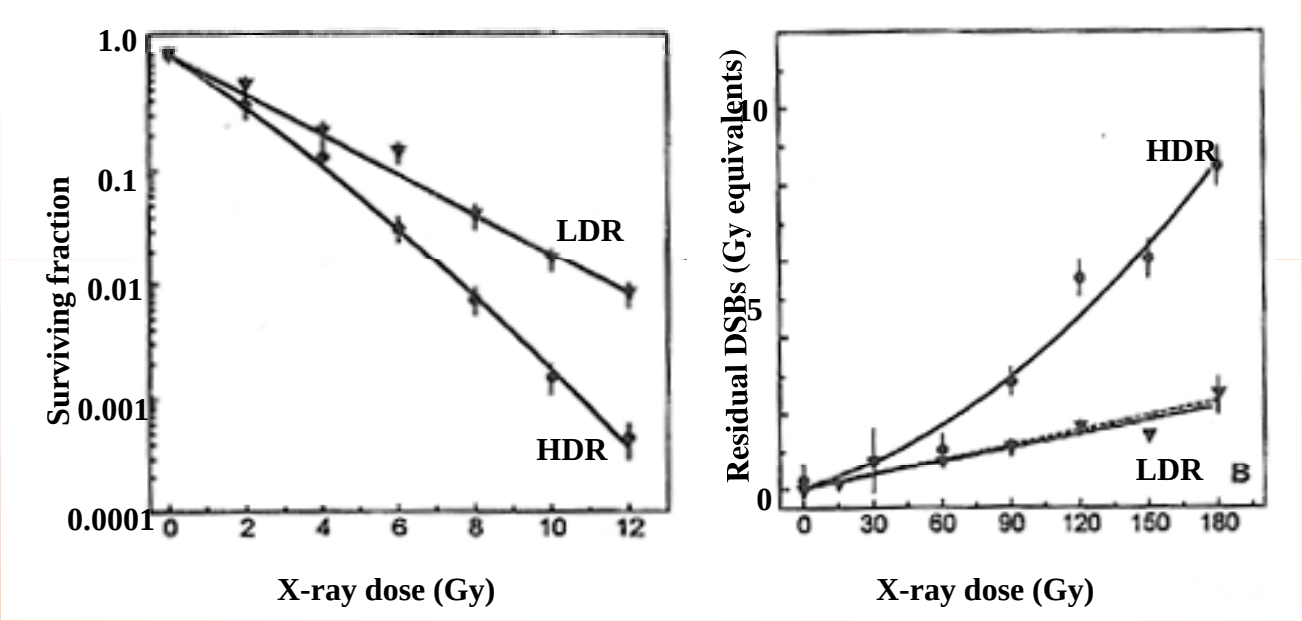
Dose-rate effects on cell survival and the induction of DSBs in mammalian cells



HDR= 4 Gy/min, LDR= 40 mGy/min

(E. Dikomey, I. Brammer, IJRB 2000; 76:773-781)

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The dose-rate effect on the induction of DSBs in mammalian cells depends on ATR signaling

(D. Boucher et al. 2007, in preparation)

- In a study of low dose-rate effects on DSB induction using γ-H2AX for measuring DSBs, we showed that the reduction in DSB at low dose rate does not depend on ATM signaling but involves instead **ATR-dependent signaling**. ATM is important at high dose rate of IR.

- ATR is known to be involved in the signaling of blocked replication forks.

--->**At a given dose-rate, there appears to be a switch from ATM to ATR signaling.**

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Dose-rate effects observed on different biological endpoints : Mutation induction

Mutation induction depends on dose-rate (*Vilenchik and Knudson PNAS 2000;97:5381-5386; PNAS 2003;100(22):12871-12876*):

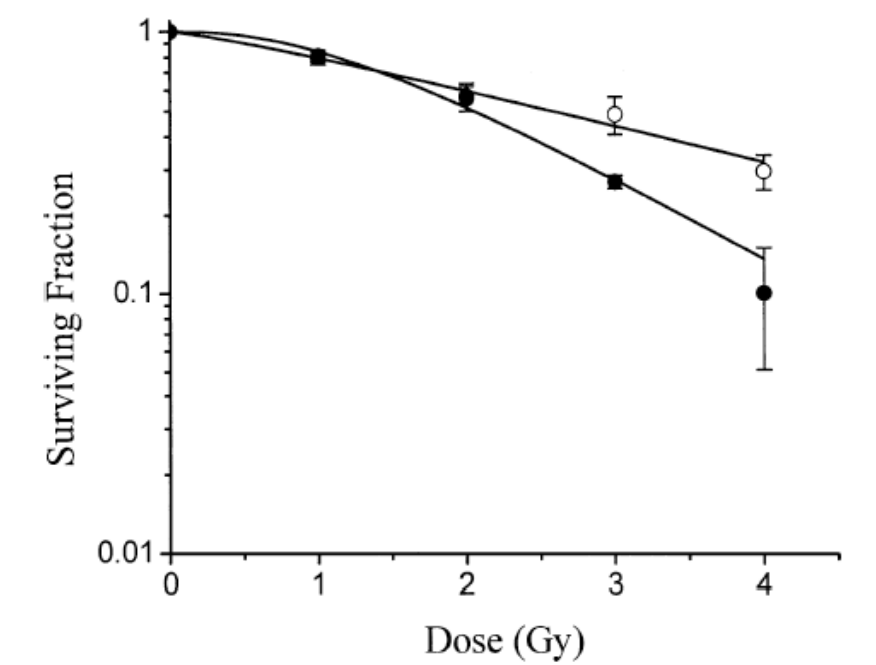
In Chinese hamster cells the mutagenic effect is 2-4 fold less at low dose rate than at high dose rate *(Thacker et al. Nucl Acids Res 1992;20:6183-6188)*

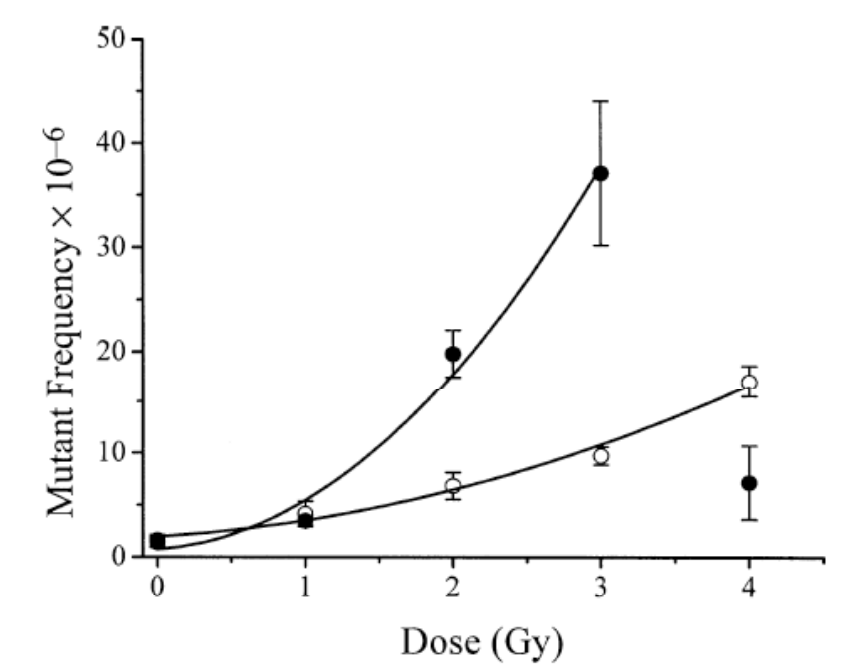
In rodent cells , at dose rates below 0.5 mGy/min an absence of dose rate effects as well as inverse dose rate effects have been described*(Vilenchik and Knudson PNAS 2000;97:5381-5386*).

An inverse dose rate effect has also been found with high LET radiation (neutrons). Cell cycle progression and DNA repair are thought to be involved in these phenomena *(Collis SJ et al. J Biol Chem 2004;279:49624-49632).*

Dose-rate dependent induction of HPRT mutations in human lymphocytes

(Kumar P.R.V. et al. 2006 Radiat. Res.165;43-50)





Dose and dose-rate effectiveness factor (DDREF)= 3.4

at 4 Gy HDR=840mGy/min, LDR= 1.4 mGy/min γ-rays

G_0 lymphocytes human

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Dose-rate effects observed on cell transformation in vitro

Neoplastic cell transformation in vitro in C3H 10T1/2 cells was shown to decrease at low dose rate below the spontaneous frequency *(Redpath JL et al. Radiat. Res 2003;159:433-436).*

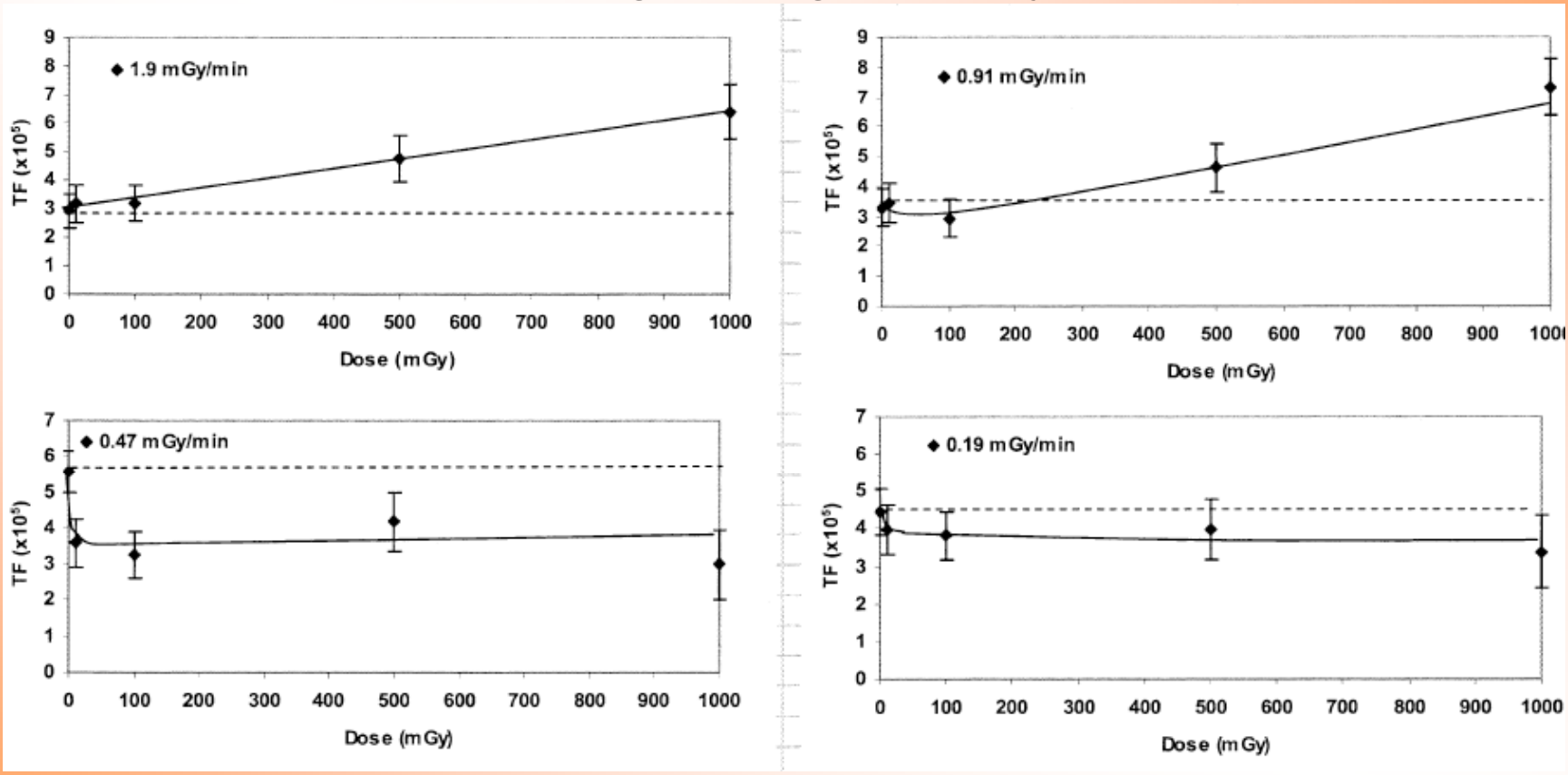
In human non tumor cells CGL1 exposed to 30 keV photons (125I) neoplastic transformation is found to be lower than background at dose-rates of 0.19 and 0.47 mGy/min and radiation doses up to 1 Gy *(Elmore E et al. Radiat Res 2006;166:832-838).*

---> Thus, there is no linear dose-response relationship at these low dose-rates.

Dose-rate effects observed on different biological endpoints : cell transformation in HeLa x Skin fibroblast hybrid cells *in vitro*

(Elmore E et al. Radiat Res 2006;166:832-838).

Low to high dose range of ^{125}I decays



----> at a dose of 1 Gy at dose-rates 1.9 and 0.91 mGy/min neoplastic transformation is significantly different from background.

---> IR-induced cell transformation appears to be lower than spontaneous background at very low dose rates (0.47mGy/min and 0.19 mGy/min of ^{125}I) (36 keV X rays +31 keV electrons)

Dose-rate effects

- Recent results suggest that

  it is not adequate to use a DDREF of 2 for **risk evaluation at very low dose rate** exposures.

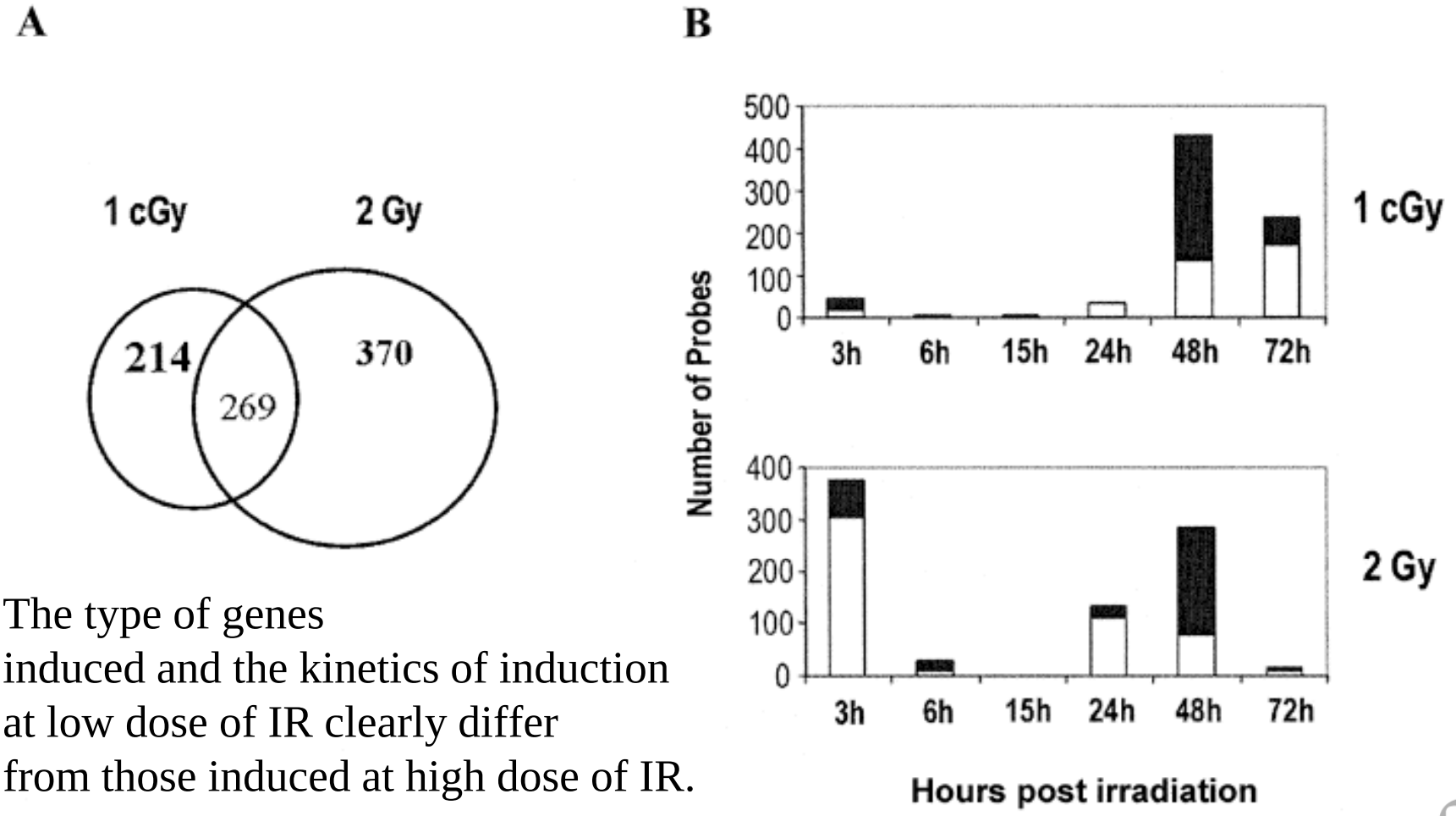
Breakthrough finding (3)
Induction of genes

- At low doses different genes and gene families are induced than at high doses.

- The induction of some genes is also dose-rate dependent (mechanism?).

Induction of specific genes at low dose

(Franco N et al. Radiat. Res. 163, 2005)



The type of genes
induced and the kinetics of induction
at low dose of IR clearly differ
from those induced at high dose of IR.

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Microarray analysis of cellular responses (primary keratinocytes) after low (10 mGy) or high doses (2 Gy) of gamma rays. *(Franco N. et al. Radiat. Res. 2005; 163: 623-635)*

Among 853 modulated genes:

- 214 modulated at low dose, mostly at late incubation times (48 h and 72 h)
- 370 modulated at high dose, mostly at early incubation times (3 h)

Low dose specific genes (140 known genes) include mostly genes
of homeostasis, cell communication, signaling, membrane, cytoskeleton, RNA and protein synthesis, chromatin, energy metabolism, stress, cell death and transport **but rarely DNA repair genes**.

⇨ The radiation response at low dose is rather specific and quite different from that obtained at high dose.

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Different phosphoproteomic profiles in human fibroblasts after low- and high-dose X-irradiation

(Yang F et al. J Proteome Res. 2006;5:1252-1260)

Ionizing radiation activates (by phosphorylation) important proteins involved in **cell cycle checkpoint** control, **DNA damage signaling**, DNA **repair and apoptosis**.

⇨ **This is specific to high dose radiation (4 Gy)**

⇨**At low dose (2 mGy), a more general spectrum of proteins is phosphorylated** (cyclin dependent kinase, 6-fold) and not specific genotoxicity-related proteins).

A **high dose (4 Gy) activates 3-phosphoinositide-dependent protein kinase-1** (PDK1) and AKT/RSK motifs 8.5 and 5.5 fold, respectively.

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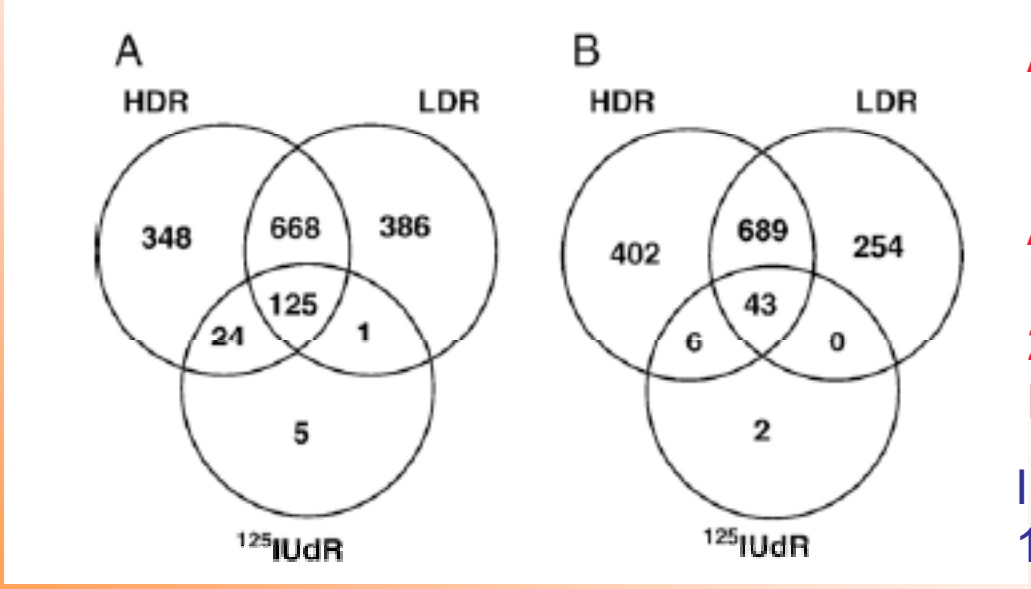
Dose-rate dependent gene expression in normal human lung fibroblasts(1)

(Sokolov MV et al. Gene 2006;382:47-56)

External irradiation:
Cells were exposed to 1 Gy
of γ -irradiation
at dose-rates: HDR= 1 Gy/min
LDR= 0.7 mGy/min

Internal irradiation:
decay of ^{125}I (emission of Auger electrons)
in ^{125}IUdR-labelled cells



After HDR: 1163 genes induced
1134 genes repressed

After LDR: 1180 up-regulated
987 down-regulated
2/3 of the genes were the same at HDR and LDR

Internal exposure induced
10 x less and repressed 20 x less genes than external exposures.

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Influence of dose-rate on gene activity

(Amundson et al. Mol Cancer Res.2003; 1:445-452).

Dose-rates affect genes involved in different cellular functions :

- ⇨ **Genes of IR-induced apoptosis (APO-1,TRAIL,TRID etc.) but not genes of cell proliferation (MDM2,BTG2,ELK4, SNK, etc.).**
- ⇨ **DNA repair genes such as XPC, and DDB2, but not ERCC1 and MDM2**

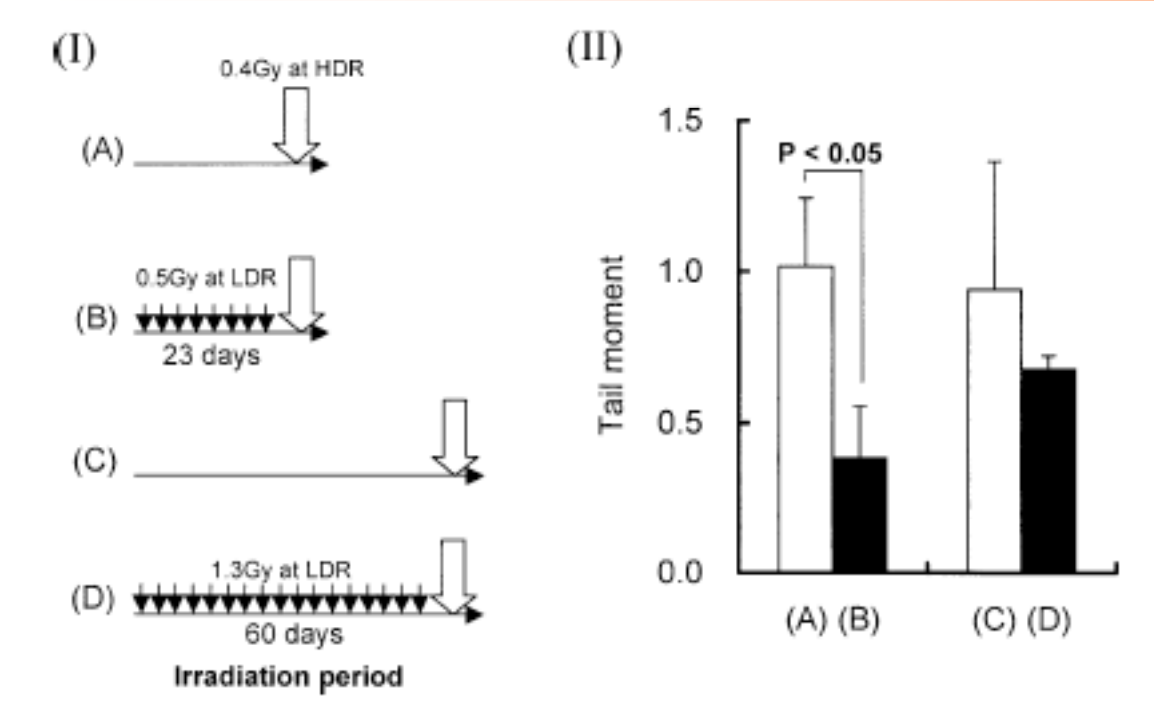
Breakthrough finding (4)

Low dose and low dose-rate cellular responses include:

- **Adaptive responses** may lead to reduced DNA damage, reduced mutation and cell transformation *(see Tapio S, Jacob V. Radiat. Environ Biophys 2006)*
- **Low dose hypersensitivity** appears to reflect absence of functional DNA repair at low doses *(Wykes SM et al. Radiat Res. 2006;165:516-524)*
- **Bystander effect** involves either direct intercellular communication via intercellular gap junctions and/or medium mediated effects. It may lead to increased cell killing *(Mothersill and Seymour, Nature 2004; 4: 256-63; Mutat Res. 2006 May 11;597(1-2):5-10)* or cell differentiation *(Belyakov OV et al. Mutat Res. 2006:597 (1-2)43-9)*

Adaptive response of γ-irradiation on the induction of DNA strand breakage in mice

(Otsuka K et al. Radiat Res 2006;166(3)474-478)



Induction of DNA strand breaks in the spleen by HDR= 1.6 Gy/min (A) or by an adaptive treatment: LDR= 0.5 Gy delivered over 23 days (B) plus a challenging dose of 0.4 Gy at HDR.
Challenging dose after 60 days sham irradiation C),
60 days LDR treatment followed by challenging dose (D)

----> less DNA strand breaks in cells pre-treated at LDR (B)

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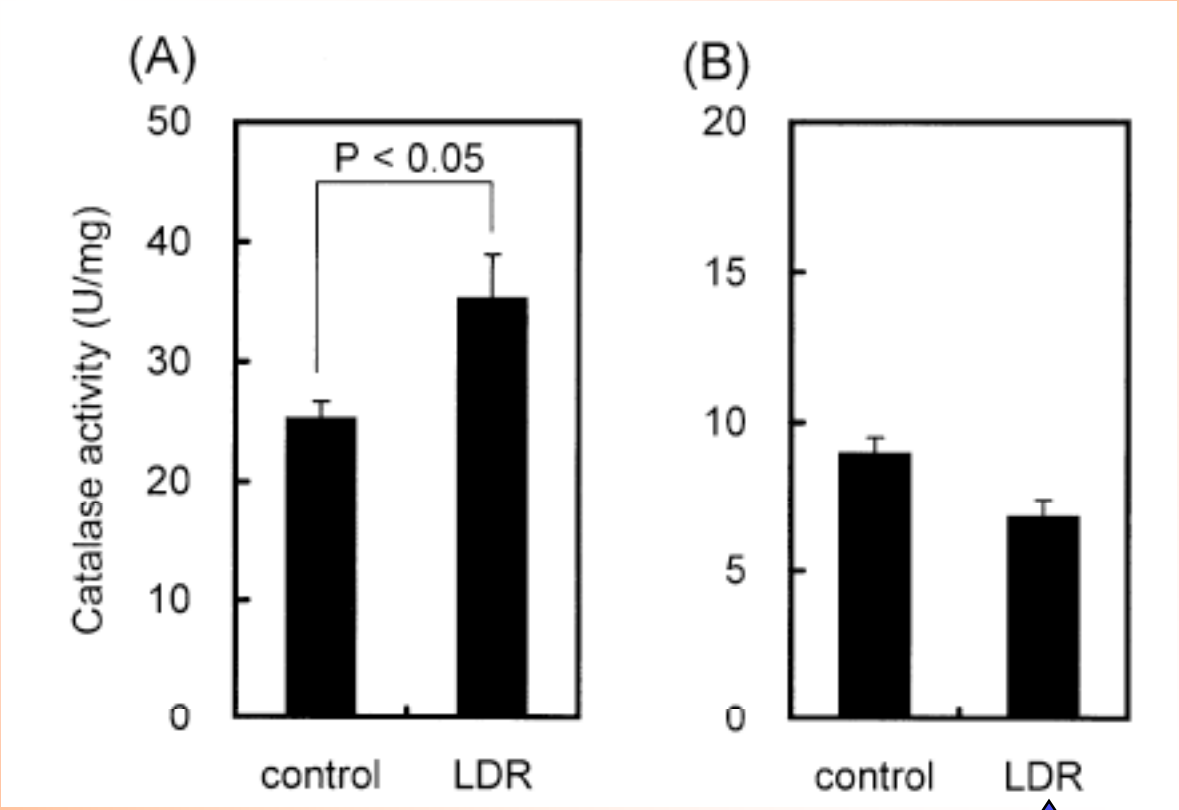
Low dose-rate effect on the induction of catalase in mouse spleen cells

(Otsuka K et al. Radiat Res 2006;166(3)474-478)



---> maximum induction of catalase in 23 days LDR

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Breakthrough finding (5)

- Elimination of precancerous cells by effective signaling from irradiated non transformed cells
- ***(D.I. Portess et al. Cancer Res. 2007; 67(3):1246--1253)***

Low-dose radiation-induced selective removal of precancerous cells via intercellular induction of apoptosis (1)

(D.I. Portess et al. Cancer Res. 2007; 67(3):1246--1253)

Table 1. Comparison of percent apoptosis scored in nonirradiated *src* transformed cells following 65-h coculture with irradiated 208F cells

Experimental conditions	Dose (Gy)	% Apoptosis (±SD)
LET comparison	Negative control*	14.52 (±0.90)
γ-Rays	0 †	26.70 (±1.54)
	0.5	47.15 (±1.66)
α-Particles	0 †	27.24 (±2.47)
	0.5	48.69 (±2.24)

---> Radiation of nontransformed cells 208F leads to increased levels of apoptosis in unirradiated transformed 208F*src3* cells in coculture.

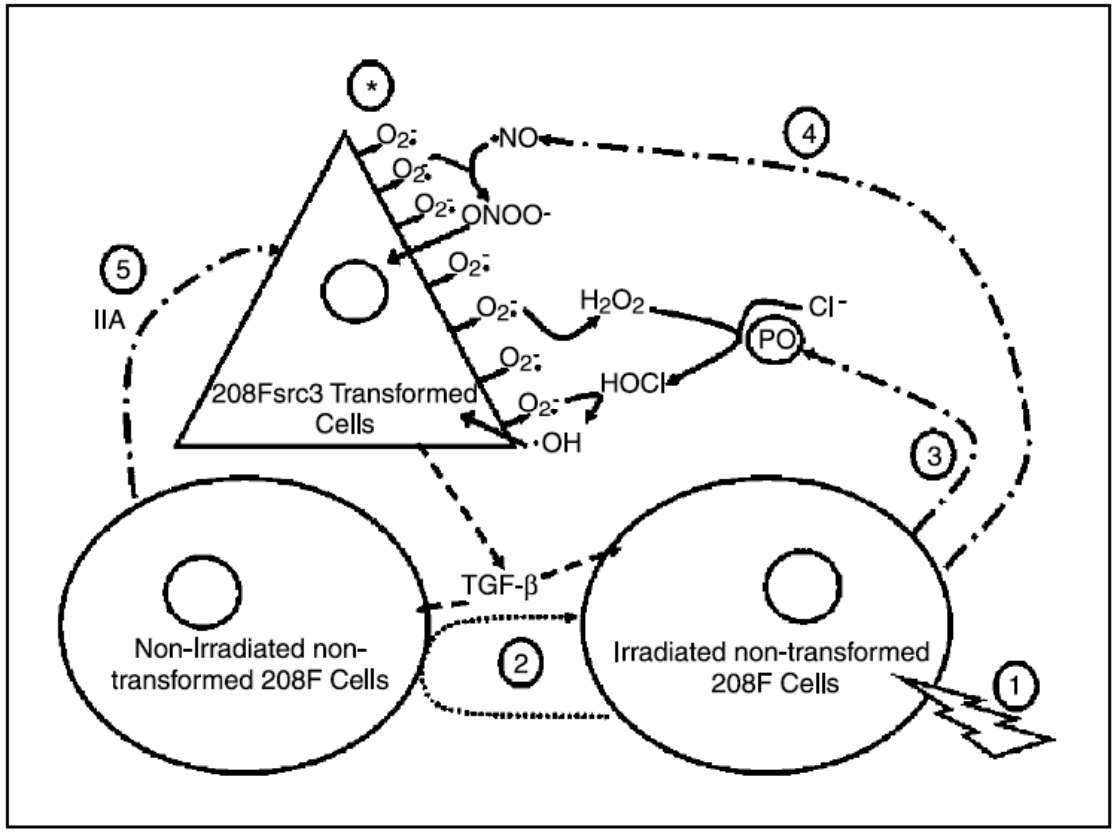

Figure 4. Proposed mechanism for radiation-stimulated intercellular induction of apoptosis. *1,* 208F cells exposed to ionizing radiation. At low doses of α-particles, this will result in some cells receiving an α-particle track, whereas others remain unirradiated. *2,* irradiated cells increase the amount of active TGF-β present in the media either through increased activation of existing latent TGF-β present in the media or through secretion of latent TGF-β, which is subsequently activated. *3* and *4,* TGF-β acts in an autocrine fashion to stimulate the irradiated cell to produce PO and •NO, which in turn leads to ROS/RNS signaling culminating in transformed cell apoptosis. *5,* the active TGF-β released into the media by the irradiated cells will also stimulate nonirradiated neighbor cells to produce PO and •NO (*steps 3* and *4*). *, key to the selectivity of the signaling system is superoxide produced by membrane-bound NADPH oxidase expressed constitutively in the transformed cells. The nontransformed cells are not susceptible to apoptosis induction as they do not produce the superoxide required to produce the final apoptosis-inducing ROS (•*OH* and $ONOO^-$).

Transformed cells show O2- production.
TGF-b signaling from transformed irrad. Cells forces transformed cells into apoptosis.

(D.I. Portess et al. Cancer Res. 2007; 67(3):1246--1253)

Killing of early transformed cells by non transformed neighbours at low IR doses prevents cells of becoming tumorigenic

(D.I. Portess et al. Cancer Res. 2007; 67(3):1246--1253)

•High or low LET IR-induced TGF-beta signaling occurs at very low doses and stimulates intercellular induction of apoptosis to selectively remove transformed cells in coculture.

•This may be related to positive effects of low dose IR (**radiation hormesis**) showing a reduction in transformation frequency after low doses *(Redpath et al. Radiat. Res 2003,2006; Azzam EI et al. Radiat. Res. 1996).*

•The low-dose saturation of radiation-induced apoptosis in pretransformed cells has potential implications for the effect of low doses of ionizing radiation on a naturally occurring anticancer defence mechanism.

--->These effects are not compatible with the linear-no-threshold model !

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Dose response relationship for radiocarcinogenesis

There is a general consensus from epidemiological studies (A-bomb survivors, accidental exposures) that the **cancer risk increases above doses of 100-200 mGy.**

However, environmental and clinical exposures concern much lower doses.

--> discussion on radiation risks from exposures outside the main field in conformational radiotherapy or diagnostic exposures (tomography..)

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Epidemiological studies (1)

Hiroshima-Nagasaki
76.000 ; M 200 mSv

Leukaemia threshold 150 mSv
Solid cancers NS < 100 mSv
Solid tumours : curvi-linear

IARC1995
96.000 Nuclear workers

Leukaemia NS < 400 mSv
Solid cancers NS

IARC 2007
407 391 Nuclear workers
19.4 mSv/yr

ERR leukaemia : 1.93/Sv
(1-2% deaths due to IR ?)
--->smoking as confounder ?

Radiologists > 1960
220.000 ; 10 - 50 mSv / yr

Leukaemia NS
Solid cancers NS

Air crews
47.000 ; 1,5 - 6 mSv / yr

Leukaemia NS
Solid cancers NS
Melanoma

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IARC study: Risk of cancer after low doses of IR

(Cardis E. et al. BMJ Online First 29 June 2005)

	15 country study		**A-bomb surv. (20-60)**	
	Cancer	Risk/Sv	Cancers	Risk/Sv
Cancers w/o leukaemia	5024	0.97 (0.14- 1.97)		
Solid cancers	4770	0.87 (0.03 -1.88)	3246	0.32(0.01-0.5)
Leukaemia w/o CLL				
LNT model	196	**1.93**(0-8.47)	83	3.15 (1.85-5.67)
linear-quadr.		-		1.54 (-1.14-5.33)

Overall average cumulative dose: 19.4 mSv
90% workers : < 50mSv
<0.1% workers: >500mSv

---> 1-2% deaths from cancer among nuclear workers may be due to IR!

---> Values should be much lower since confounding factor smoking could not yet be taken into account !

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IARC study:Risk of cancer after low doses of IR

(Cardis E. et al. BMJ Online First 29 June 2005)

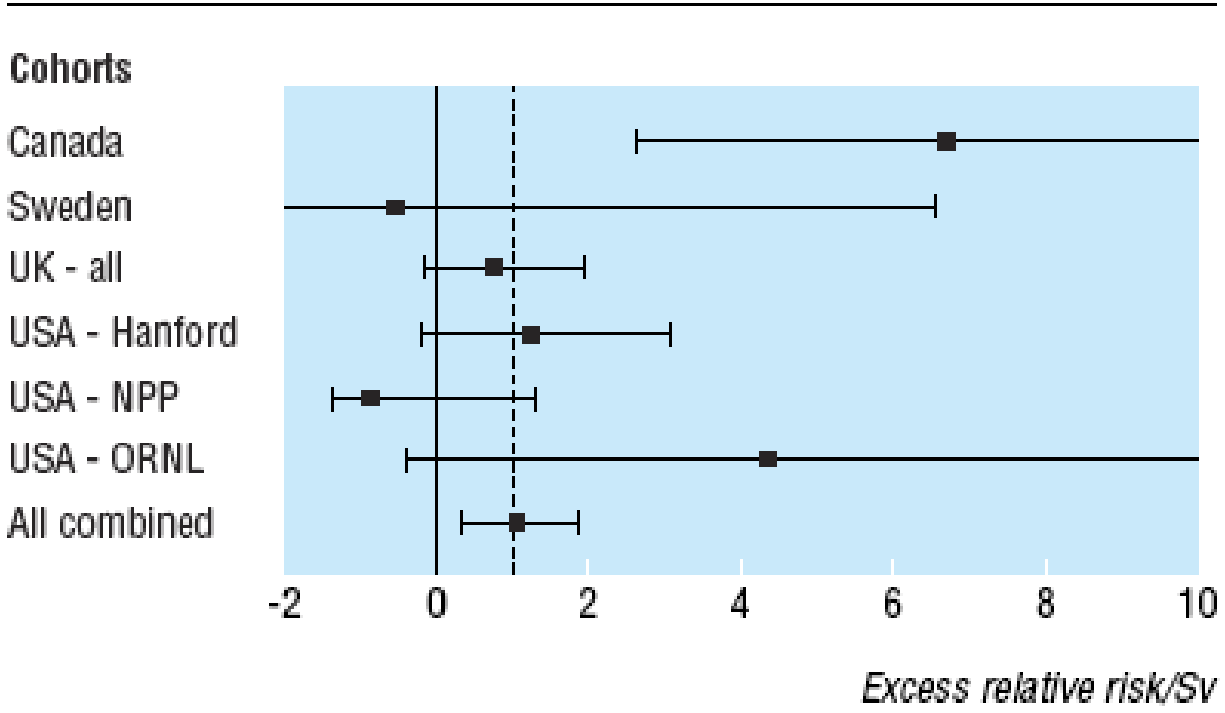

Fig 2 Excess relative risks per Sv for all cancer excluding leukaemia in cohorts with more than 100 deaths (NPP=nuclear power plants, ORNL=Oak Ridge National Laboratory)

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Radon in homes

(S. Darby et al. BMJ 2004, 330, 233-240)
BMJ Online First Bmj.com pp.1-6

7148people/14208controls from 13 European case-control studies

--->proportionate increase in lung cancer risk for radon.

Increase in risk per 100Bq/m^3 was 31.2% for small cell lung cancer

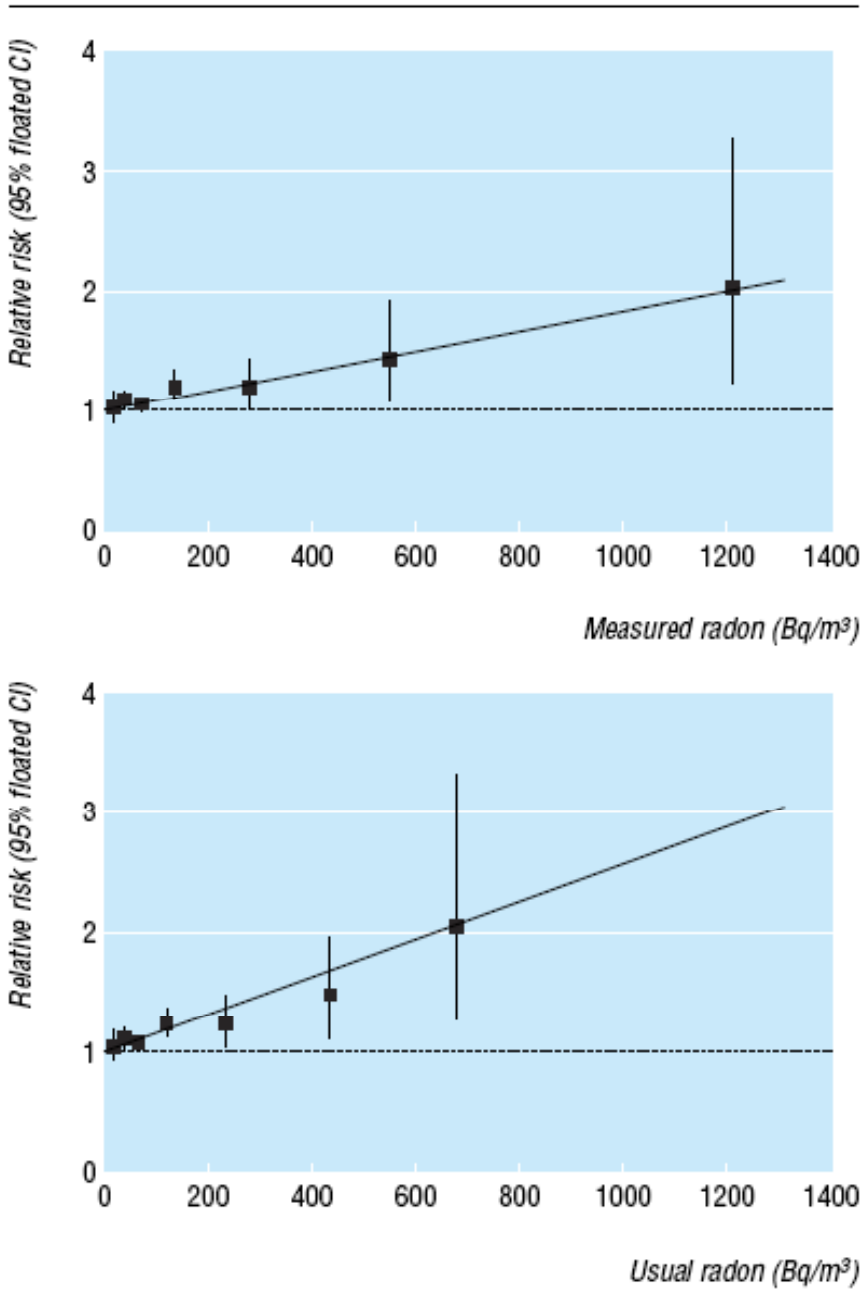

Fig 1 Relative risk of lung cancer according to measured residential radon concentration and usual residential radon concentration, with best fitting straight lines (risks are relative to that at 0 Bq/m^3)

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Radon in homes

(S. Darby et al. BMJ 2004, 330, 233-240)
BMJ Online First Bmj.com pp.1-6

If the risk of lung cancer increases by about 16% par 100 Bq/m^3 usual radon, regardless of smoking status, at 0, 100, 400 and 800 Bq/m^3
the cumulative absolute risk of lung cancer by age of 75 years would be, respectively,

0.41%,0.47%, 0.67% and 0.93% in lifelong non-smokers and

10.1%,11.6%, 16% and 21.6% in cigarette smokers.

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A Word on Hormesis

1. Hormesis has been reported in 40% of animal experiments (Duport P. Int.J. Low Radiation 2003;1:120131.)
2. There is evidence for hormesis (Calabrese EJ. Toxcol Appl Pharmacol 2004;197:125-136) and there is a mechanistic basis for hormesis . (Feinendegen LE Br J Radiology 2005;78:3-7)
3. Tanooka's meta-analysis shows a practical threshold for virtually all experimental tumors (Tanooka H, Int J Radiat. Biol 2001;77:541-551.)
   ---> The introduction of the DDREF and the LNT model cannot account for this.
   ---> Dose-rate or fractionation effects on animal carcinogenesis are too complex to be fitted this way.

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Conclusions

1. Cells possess a remarquable capacity to react to internal and external stresses.
2. Several cellular defence systems are activated upon low IR exposure.
3. At very low doses and dose rates IR-damaged cells are eliminated.
4. At higher doses and dose rates, DNA repair is activated and also apoptosis is induced.
5. DNA damage signaling differs at low doses and dose rates from that at high doses and dose rates. Different gene families are induced at these exposure levels. **This clearly contradicts the LNT-model.**
6. A general dose-and dose-rate effectiveness factor (2) does not appear justified.
6. Cellular responses to low exposures also include hormetic and adaptive radiation responses, some interfere with cell transformation and growth of precancerous cells.
7. Several epidemiological studies on IR-induced cancers lack precision for low dose exposures. The presence of confounding factors (smoking..) may account for some low dose responses.

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Joint report n° 2 of
the Academie des Sciences (Paris)
and the Academie Nationale de Medecine.

Dose-effect relationship and estimation of the carcinogenic effects of low doses of ionizing radiation.
M. Tubiana et al.

March 30, 2005, Editions Nucléon, pp. 1-94

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Thank your for your attention!