Applications of paradigm breaking non-targeted effects for radiation protection and risk estimates

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System of radiation protection

- Present estimations of radiation risk is based on direct epidemiological evidence, as well as on radiation biology research.
- The system is designed to protect against both deterministic and stochastic effects.
- Linear-Non-Threshold (LNT) model is used for estimation of long-term health effects including carcinogenesis and genetic effects.
- A dose and dose-rate correction factor is used to relate the effects of acute exposures to chronic exposures (DDREF).
- Radiation dose is used as a surrogate for risk.
- The effects produced by different types of radiation are assumed to be qualitatively the same.
- Doses can be summed to predict overall risk.
Challenges of the present radiation protection system

• The main objective of the system is to protect the individual. The protection system is generally applicable, in the same fashion, to all age groups, males and females.

• The protection system include the principles of justification, optimisation and exposure restrictions.

• There is a broad international agreement among governmental bodies that the current system of radiation protection is effective, robust and adequately protects people and the environment.

• There are, however, scientific challenges that may bring into question various aspects of the current approach, and which may have significant policy, regulatory and operational implications.

• These challenges include non-targeted effects.
Target theory

• The *target theory* of radiation induced effects (Lea, 1946) postulates that cells contain at least one critical site or *target* that must be hit by radiation in order to kill a cell.

• Therefore, radiation damage *outside* of the target should not cause cell death.

• It is widely accepted that nuclear DNA is the *critical target* for radiation induced cell death.
Targeted and Non-Targeted effects of ionising radiation

**Targeted effects**

- **Classical paradigm of radiation biology**
  - DNA damage occurs during or very shortly after irradiation of the nuclei in targeted cells
  - The potential for biological consequences can be expressed within one or two cell generations

**Non-targeted effects**

- **New evidence**
  - Bystander effect
  - Radiation-induced genomic instability
  - Low dose hypersensitivity
  - Adaptive response
  - Abscopal (out-of-field) effects
  - Clastogenic factors
  - Delayed reproductive death
  - Induction of genes by radiation
“Non-targeted“ effects

A new paradigm of Radiation Biology

- An essential feature of "non-targeted" effects is that they do not require a direct nuclear exposure by irradiation to be expressed and they are particularly significant at low doses.
- Recent evidence for non-targeted effects suggests a new paradigm for radiation biology that challenges the universality of target theory.
- This new radiation biology paradigm would cover both targeted (direct) and non-targeted effects of ionising (and possibly non-ionising) radiation.


The radiation-induced bystander effect is a phenomenon whereby cellular damage is expressed in unirradiated neighboring cells near to an irradiated cell or cells.
Evidence for radiation induced bystander effects

- Increased p53 expression in epithelial cells exposed to $\alpha$-particles (Hickman et al., *Cancer Res*, 1994).
- Medium from $\gamma$-rays irradiated cells reduces the survival of unirradiated cells (Mothersill and Seymour, *Radiat Res*, 2001).
- Bystander effect after microbeam irradiation of a single cell (Belyakov et al., *BJC*, 2001).
- Induction of a bystander mutagenic effect after $\alpha$-particle microbeam irradiation (Zhou et al., *PNAS*, 2000).
- Increased bystander neoplastic transformation after treatment with medium from irradiated cells (Lewis et al., *Radiat Res*, 2001).
- Bystander effect and genomic instability under *in vitro* (Lorimore et al., *PNAS*, 1998) and *in vivo* conditions (Watson et al., *Cancer Res*, 2000).
Contribution of bystander and direct components to the radiation induced damage

Cellular damage

Total

Direct effects

Bystander effects

~0.2 Gy

Dose
Radiation-induced genomic instability is defined as a persistent elevation in the rate of de novo appearance of genetic changes within a clonal population.
Bystander effect and genomic instability are closely related

- **Bystander effect** and genomic instability are non-targeted effects of irradiation and might have common mechanisms (Kadhim et al., *Mutat Res*, 2004).

- **Chromosomal instability** could be induced in bystander cells (Lorimore et al., *PNAS*, 1998).

- There is a recent evidence that the **bystander effect** persists for many generations (Lorimore et al., *Cancer Res*, 2005).

- This evidence suggests that the initial cross-section for radiation damage is **increased** by the **bystander effect**, and cells that are affected by the bystander mechanism may remain at an increased risk of genetic change for many generations.
Non-targeted versus targeted effects

• Non-targeted effects do not contradict to “target theory” but increase size of the target in such extent that concept of “target” became meaningless.

• For example, bystander effect increases target spatially to the size of cell group, tissue or even organ.

• Genomic instability increases it temporarily by prolongation of damage over many cell generations or even transgenerationally.
LNT and uncertainties in extrapolation of radiation risk

Risk

Dose

Epidemiological risk data

LNT
Key question

Does the bystander effect increase or decrease low dose risk in relation to LNT?
The bystander effect might be harmful

- The bystander-induced mutagenesis
  Nagasawa and Little, *Rad Res*, 1999

- Bystander-induced transformation

- Chromosomal instability could be induced in bystander cells
  Lorimore *et al.*, *PNAS*, 1998
  Watson *et al.*, *Cancer Res*, 2000
The risk at low doses might be greater than predicted by LNT.
The bystander effect might be protective

• A gross bystander induced differentiation in the urothelial explant outgrowth after microbeam irradiation

  Belyakov et al., Mut Res, 2006

• Cell survival is increased after treatment with medium from irradiated cells

  Matsumoto et al., Radiat Res, 2001

• Increase in cell proliferation after low doses of α-particle exposure

  Iyer and Lehnert, Cancer Res, 2000

• Bystander effect is a mechanism of tissue integrity maintenance

  Barcellos-Hoff and Brooks, Rad Res, 2001
The risk at low doses might be \textit{less} than predicted by LNT.
## Summary

<table>
<thead>
<tr>
<th>Bystander effects:</th>
<th>RISK</th>
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<tbody>
<tr>
<td>cell death</td>
<td>-</td>
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<tr>
<td>mutation</td>
<td>-</td>
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<tr>
<td>chromosomal damage</td>
<td>-</td>
</tr>
<tr>
<td>malignant transformation</td>
<td>-</td>
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<td>premature differentiation</td>
<td>-</td>
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<tr>
<th>Other non-targeted effects:</th>
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<tr>
<td>genomic instability</td>
<td>-</td>
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<td>adaptive responses</td>
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Hypothesis - bystander effect is a protective mechanism

- Remove potentially damaged *functional group* of cells to decrease risk of *transformation*.
- Maximal at *low doses* when a small fraction of cells is exposed.
- Normal tissue *microarchitecture* amplifies the response.
- *Apoptosis* is an important contributor.
- *Irreversible differentiation* is a major pathway of removing potentially damaged cells from proliferating population.
A general scheme of radiation induced bystander effect in tissue systems

Sparse irradiation → Bystander signal → Tissue response

- Track
- Intercellular communication
- Targeted cell
- Potentially damaged cell
- Premature differentiated cell
- Apoptotic cell
Conclusions I

• The observation of the bystander phenomenon is preliminary in nature, and the applicability of any conclusion derived from in vitro studies to in vivo situation is still uncertain.

• The risk at low doses might be greater or less than predicted by a linear extrapolation of the high dose.

• However, the bystander effect will clearly result in an overall risk, which is a non-linear function of dose.

• It would be premature to consider revising current risk calculations on the basis of current studies of bystander phenomena.
On other hand, the LNT model is important for radiation protection as a simple method to optimise procedures and regulations. However, it should not be mistaken as a scientific model directly derived from the present state of knowledge of the processes involved in radiation risk estimations.
Implications for radiation protection

- Concept of dose as a surrogate of risk in conjunction with LNT model suggest that:
- every increment of dose and the associated risk can be assessed separately, irrespective of prior or future doses, as long as doses are below deterministic effects;
- a fixed dose increment is always associated with the same additional risk;
- doses received by an individual at different time points can be summed up (cumulative dose);
- collective dose can be used to predict risk at the population level.
Potential policy implications, in case if there would be a *significant* departure from LNT model

- The **conceptual basis** of the present system would be undermined.
- Use of dose as surrogate of risk would be seriously challenged.
- The relevance of dose and the **target theory** should be re-examined.
- We need to accumulate **new facts** and study mechanisms of non-targeted effects, new thinking and contingency planning ("what if") is required.
- We should build up on the **existing knowledge**, but be opened to **new evidences**.