Radiobiology of radionuclide therapy

Prof Sarah Baatout
Sarah.Baatout@sckcen.be

Head of the Radiobiology Unit, SCK•CEN
Faculty of Biosciences Engineering, Universiteit Gent, Belgium
Faculté des Sciences, Université de Namur, Belgium
Many definitions

Definition (used by ASC):

- *Cancer is a large group of diseases characterized by the uncontrolled growth and spread of abnormal cells.*
- *If the spread is not controlled, it can result in death.*
- *Treatment requires a multidisciplinary approach*
It is thought that several mutations need to occur to give rise to cancer.

**Mutations** of normal genes:
- **oncogenes** linked to accelerated cell proliferation
- **tumour suppressor genes** linked to decreased cell death.

over 100s forms of cancer
What causes cancer?

- Cells that are old or not functioning properly normally self destruct and are replaced by new cells.
- However, cancerous cells do not self destruct and continue to divide rapidly producing millions of new cancerous cells.

**Normal Cell**
- Obeys strict rules
- Divides only when told to
- Dies rather than misbehaving
- Stays close to home
- Careful with chromosomes

**Cancer Cell**
- Disobeys rules
- Divides at will
- Bad behavior doesn’t kill
- Wanders through body
- Careless with chromosomes

At least 5 mutations
Cancer cure = minimum killing of 99.9% cells
**Situation in Belgium**

- **In 2013**, 65,847 new cancer diagnoses in Belgium
  - 34,542 in men (53%)
  - 30,945 in women (47%)

- Before 75th anniversary
  - 59% ♂️ 69% ♀ are still alive 5 years after diagnosis
  - 3% of the Belgian population is living with cancer or has been diagnosed with cancer in the last 10 years
  - 13% of patients with cancer have multiple tumours

- **Estimation for 2025**
  - 12,000 more new diagnoses than in 2013. Estimated total = 78,000
  - In 2025, the risk as high in women as in men (due to smoking habits).
  - This increase of cancers will mainly be due to ageing, growth of the population & new diagnosis.
“In terms of sensitivity to radiation, all *humans* are created equal,...but some *humans* are more equal than others”

The risk of radiation-induced effect (cancer and other) is not distributed equally within the population.

---

**Interindividual sensitivity to ionising radiation**

**STRONG NEED FOR PRECISION THERAPY**
Deterministic & stochastic effects

- **Deterministic**
  - severity dependent ("determined") on the dose
  - manifestation specific
  - effect only when exposure exceeded threshold
  - damage of large amount of cells
  - onset rather close to the exposure (short latency)

- **Stochastic**
  - probability increases with the dose (not the severity!)
  - manifestation non-specific
  - gradual increase of the risk without "safe" threshold
  - damage of the single cell enough to cause effect
  - manifestation delayed (typically years)

**LETHAL EFFECT ON CELLS**

**SUBLETHAL/MUTATION EFFECT ON CELLS**
Direct and indirect effects

Both actions will produce reactive species that will interact and damage DNA.

If the ion pairs and free radicals are produced in a biological target (DNA) then - this is direct action.

If water or other atoms or molecules are ionized, diffusible free radicals can act as intermediaries to cause damage - this is indirect action (75% hydroxyl radicals (OH)).
Damage in DNA

- Low-LET radiation = produce ionizations within single electron track

- High-LET radiation = somewhat larger number of ionizations that are closer together

- **Direct** action of radiation is dominant process for **high-LET** (neutrons or α-particles) and more complex damage

- For **low-LET** radiation, **direct** action represents about 20%, and **indirect** action is about 80%.
Estimation of numbers of radiation-induced different types of DNA lesions after 1 Gy irradiation with low-LET radiation (UNSCEAR)

<table>
<thead>
<tr>
<th>Damage type</th>
<th>Amount of damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base Damage (BD)</td>
<td>1000 - 2000</td>
</tr>
<tr>
<td>Deoxyribose damage</td>
<td>1200</td>
</tr>
<tr>
<td>SSBs</td>
<td>1000</td>
</tr>
<tr>
<td>AP sites</td>
<td>250</td>
</tr>
<tr>
<td>DSBs</td>
<td>40</td>
</tr>
<tr>
<td>DPCs</td>
<td>150</td>
</tr>
</tbody>
</table>

Stochastic effects if DNA not properly repaired

- DPC: DNA protein crosslinks
- AP sites: apurinic/apyrimidinic site
Targeted and non-targeted effects of radiation

- **Targeted Effects**
  - DNA
    - Base lesions
    - Intercalation
    - Strand breaks
    - Micronuclei formation
    - Sister chromatid exchange
  - Lipid
    - Lipid peroxidation
    - Changes in membrane viscosity and dynamics
  - Protein
    - Amino acid conversions
    - Inter and Intra-strand cross linking
    - Cleavage
    - Oxidation
    - Carbonylation

- **Non-targeted Effects**
  - Free radical generation
  - Bystander phenomenon
    - Mediated via release of GFs, cytokines, Interleukin, ROS, etc.

- **Intracellular damage**
- **Damage to ECM/neighbouring cells**

- **Cell cycle arrest**
- **Genomic Instability**
- **DNA Repair**
- **Apoptosis**
Sequence of events by which ionizing radiation affects living systems

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>10-18 s</td>
<td>Absorption of Ionizing Radiation</td>
</tr>
<tr>
<td>10-16 s</td>
<td>Physical Events</td>
</tr>
<tr>
<td></td>
<td>Ionization</td>
</tr>
<tr>
<td></td>
<td>Excitation</td>
</tr>
<tr>
<td>10-12 s</td>
<td>Physicochemical Events</td>
</tr>
<tr>
<td></td>
<td>Free radical formation</td>
</tr>
<tr>
<td></td>
<td>Breakage of chemical bonds</td>
</tr>
<tr>
<td>10-12 – 10-6 s</td>
<td>Chemical Events</td>
</tr>
<tr>
<td></td>
<td>Reactions of radicals</td>
</tr>
<tr>
<td>Minutes to hours</td>
<td>Biochemical/Cellular Processes</td>
</tr>
<tr>
<td></td>
<td>Repair</td>
</tr>
<tr>
<td></td>
<td>Division delay</td>
</tr>
<tr>
<td></td>
<td>Chromosome damage</td>
</tr>
<tr>
<td></td>
<td>Loss of reproductive capacity</td>
</tr>
<tr>
<td>Days to months</td>
<td>Tissue Damage</td>
</tr>
<tr>
<td></td>
<td>Central Nervous System, Gastro-Intestinal, Bone marrow syndromes</td>
</tr>
<tr>
<td></td>
<td>Late tissue damage</td>
</tr>
<tr>
<td></td>
<td>Birth defects from in utero exposure</td>
</tr>
<tr>
<td>Years</td>
<td>Late Somatic Effects</td>
</tr>
<tr>
<td></td>
<td>Cataracts</td>
</tr>
<tr>
<td></td>
<td>Carcinogenesis</td>
</tr>
<tr>
<td>Generations</td>
<td>Genetic Effects</td>
</tr>
</tbody>
</table>
Cell death following radionuclide therapy

- **APOPTOSIS (cell suicide)** = programmed (I-131, Xe-33, Ir-192, Sr-89)
- **NECROSIS (cell explosion)** = results from trauma or injury (I-131, W-188, Sr-89)
- **AUTOPHAGY (auto cell digestion)** = due to nutrient deficiency (Nobel prize 2016 to Yoshinori Ohsumi)
Cell death following radionuclide therapy

- **MITOTIC CATASTROPHE** = inappropriate entry into mitosis
- **ANOIKIS** = cell detachment from tissue and degradation

- **OTHER FORMS:**
  - CORNIFICATION (cell death to the eyes)
  - PYROPTOSIS (wrong killing from immune system)
  - FERROPTOSIS (iron dependent cell death)
  - NECROPTOSIS/APONECROSIS (combined apoptosis and necrosis)
  - ERYPTOSIS (suicidal erythrocyte death)

Deterministic effects if high cell death in a tissue
Review

Ionizing radiation biomarkers in epidemiological studies – An update

Janet Halla,*, Penny A. Jeggo, Catharine West, Maria Gomolka, Roel Quintens, Christophe Badie, Olivier Laurent, An Aerts, Nataša Anastasov, Omid Azimzadeh, Tamara Azizova, Sarah Baatout, Bjørn Baselet, Mohammed A. Benotmane, Eric Blanchardon, Yann Guéguen, Siamak Haghdooost, Mats Harms-Ringdahl, Julia Hess, Michaela Kreuzer, Dominique Laurier, Ellina Macaeva, Grainne Manning, Eileen Pernot, Jean-Luc Ravanat, Laure Sabatier, Karine Tack, Soile Tapio, Horst Zitzelsberger, Elisabeth Cardis

a Centre de Recherche en Cancérologie de Lyon, INSERM 1052, CNRS 5286, Univ Lyon, Université Claude Bernard, Lyon 1, Lyon, F-69424, France
b Genome Damage and Stability Centre, School of Life Sciences, University of Sussex, Falmer, Brighton, BN1 9RQ, United Kingdom
c Translational Radiobiology Group, Institute of Cancer Sciences, The University of Manchester, Manchester Academic Health Science Centre, Christie Hospital, Manchester, M20 4BX, United Kingdom
d Federal Office for Radiation Protection, Department of Radiation Protection and Health, D-85764 Neuerberg, Germany
e Radiobiology Unit, Belgian Nuclear Research Centre, SCK-CEN, B-2400 Mol, Belgium
f Cancer Mechanisms and Biomarkers group, Radiation Effects Department, Centre for Radiation, Chemical and Environmental Hazards, Public Health England, Chilton, Didcot, United Kingdom
g Institut de Radioprotection et de Sûreté Nucléaire, F-92260 Fontenay-aux-Roses, France
h Helmholtz Zentrum München, German Research Center for Environmental Health GmbH, Institute of Radiation Biology, D-85764 Neuerberg, Germany
i Southern Ural Biophysics Institute, Clinical Department, Chelyabinsk, Russia
j Cell Systems and Imaging Research Group, Department of Molecular Biotechnology, Ghent University, B-9000 Ghent, Belgium
k Pole of Pharmacology, Institut de Recherche Expérimentale et Clinique, Université catholique de Louvain, B-1200 Brussels, Belgium
l Centre for Radiation Protection Research, Department of Molecular Biosciences, The Wenner-Gren Institute, Stockholm University, SE 106 91 Stockholm, Sweden
m INSERM U897, Université de Bordeaux, F-33076 Bordeaux cedex, France
n Laboratoire des Lésions des Acides Nucleiques, Univ Grenoble Alpes, INAC-SCEB, F-38000 Grenoble, France

* Corresponding author.
** Change history:

Hall, Mut. Res., 2017
General considerations
Classifications of biomarkers

- Biomarkers of exposure
- Biomarkers of susceptibility
- Biomarkers of persistent effects
- Biomarkers of late effects

Exposed persons with increased susceptibility
eg young age or carrying (epi)genetic variants

Persons with pre-pathological state

Diseased person

BM of exposure

BM of late effects

BM of persistent effects (>1 year)

Radiation
General considerations
Characteristics of a good biomarker

- Sensitivity
- Specificity
- Reproducibility
- Known variability in the general population
- For use in large scale molecular epidemiological studies
  - particularly in young people, the possibility of using non-invasive procedures for collection of biological samples
- Cheap
## Biomarker detectability with time

<table>
<thead>
<tr>
<th>Biomarker Category</th>
<th>Detectable</th>
<th>Potentially detectable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic biomarkers (dicentrics/chromosome aberrations)</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Chromosomal rearrangements</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Micronucleated reticulocytes</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Radiation induced DNA lesions</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>gammaH2AX</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Circulating DNAs</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Radiation induced mutation profile</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Changes in RNA profiles</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Radiation induced alternative splicing</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Changes in protein profiles</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Radiation induced protein post-translational modifications</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>miRNA and non-coding RNAs expression profiles</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Epigenetic markers</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>RedOx imbalance</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Metabolomics</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Biophysical markers</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Mitochondrial biomarkers (oxidation/phosphorylation)</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Mitochondrial biomarkers (common deletions)</td>
<td>Red</td>
<td>White</td>
</tr>
<tr>
<td>Biomarkers of internal exposure (radio-isotopes)</td>
<td>Red</td>
<td>White</td>
</tr>
</tbody>
</table>
Difficulties

- Interindividual difference
- Confounding markers:
  - Age
  - Gender
  - Ethnicity
  - Mutations
- Cancer-related potential confounders:
  - Smoking status
  - Exposure to occupational carcinogens and medical treatment
- Confounders related to cardio-vascular diseases:
  - Blood pressure
  - Overweight
  - Cholesterol
Potential use for targeted radiotherapy

- There are number of biological biomarkers.
- The best established and validated markers are markers of exposure.
- Validation of potential markers of susceptibility and late and persistent effects still needed.
- Multidisciplinary approach for a better precision therapy.
25 years of Belgians in Space

Contribution to human spaceflights: towards a better protection of astronauts for future human space exploration

Friday, October 6, 2017

SCK•CEN | Boeretang 200 | 2400 Mol | Lakehouse

Marie Curie: 150th birthday celebration
November 7, 2017

Registration