LIFE IN LOW RADIATION ENVIRONMENT: BIOLOGICAL RESPONSE AND ROLE OF BACKGROUND RADIATION

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INFN LNGS

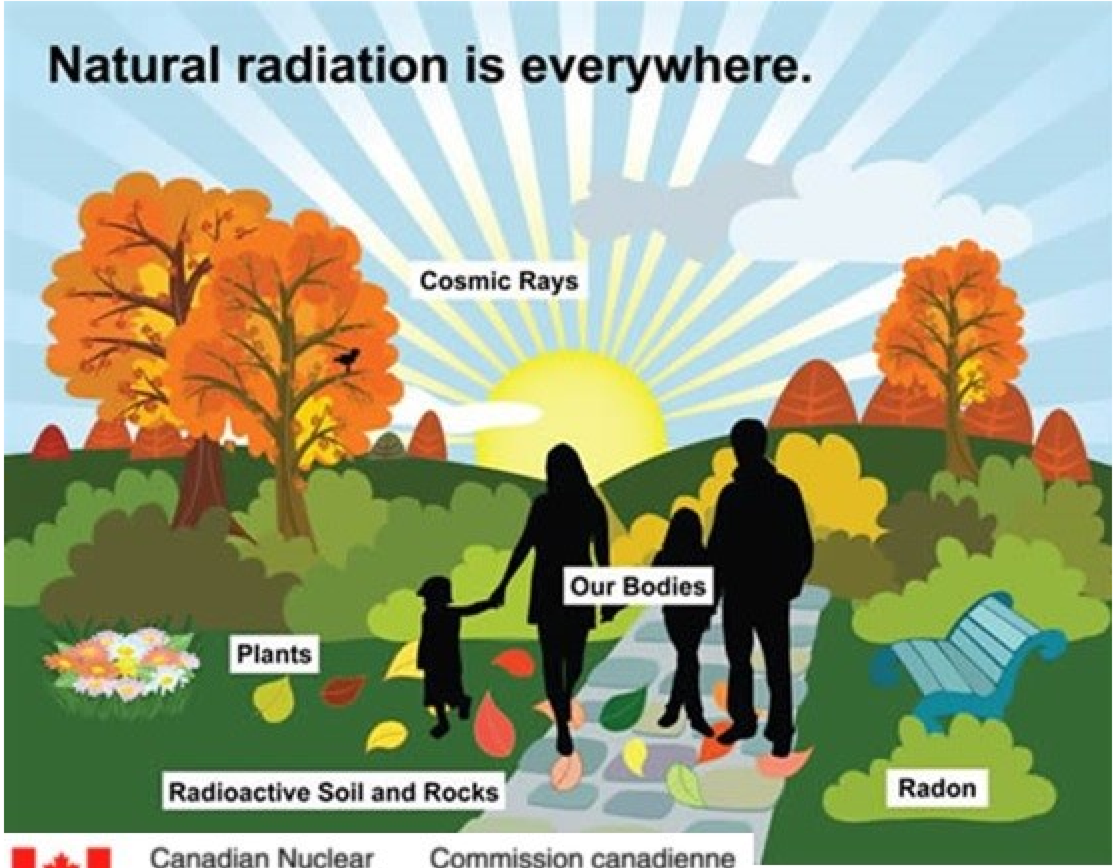
HEALTH RISKS AND BIOLOGICAL EFFECTS AT LOW DOSES OF IONIZING RADIATION:

SCIENTIFIC BACKGROUNDS, HYPOTHESES, AND ROLE OF UNDERGROUND EXPERIMENTS

OUTLINE

1. The ionizing radiation background
2. Biological response and health risks: the low dose issue
3. The radiobiological bases of LNT hypothesis: conventional paradigm and its limitation
4. Epigenetic mechanisms
5. Role of underground experiments and perspectives

Radiation is everywhere



Canadian Nuclear Safety Commission   Commission canadienne de sûreté nucléaire

Life has evolved on Earth for about 4 billion years in the presence of the natural background of ionizing radiation (even if it was not always the same as today).

Without it, life on Earth could not have existed or would not exist in the present form.

Cosmic radiation

Origin: galactic + solar

- **deep interstellar space**
- **sun especially during solar flares**

Life on the Earth's surface is protected from cosmic rays by:

- **The Earth's atmosphere layer**
- **The Earth's magnetic field**

…….but some radiation reaches the biosphere

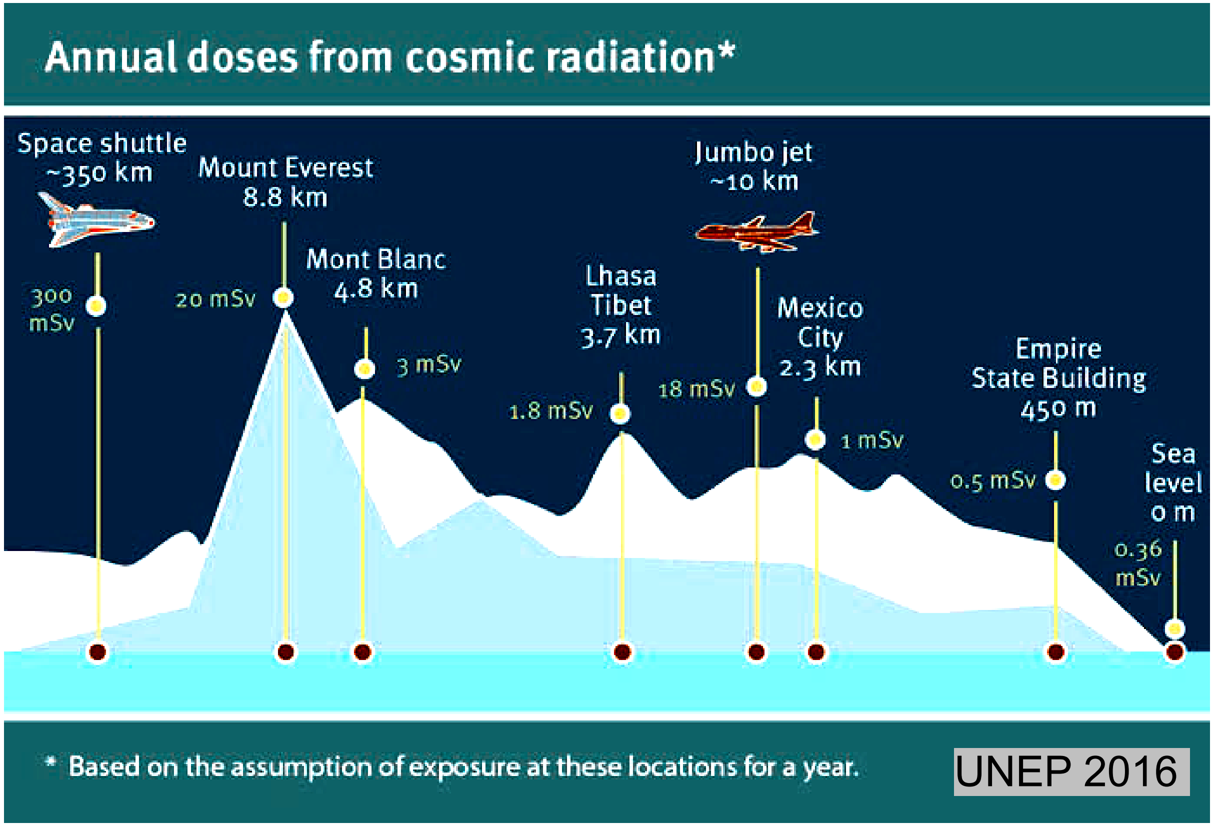
Cosmic radiation field at ground altitude

⇓

mainly secondary particles originated from galactic radiation

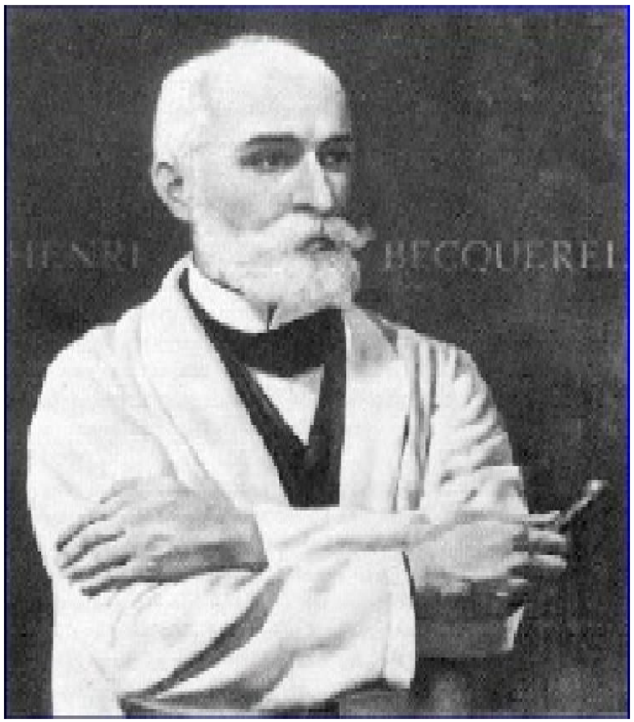
- High-LET component (neutrons)
- Low-LET component (charged particles, photons)

Cosmic rays are a major natural source of external exposure to radiation

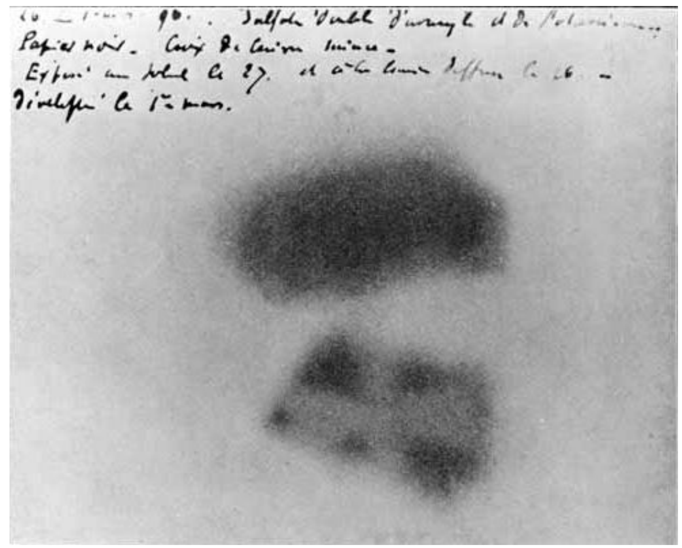


cosmic ray field depends on the location (latitude and altitude)

The discovery of natural radioactivity (1896)

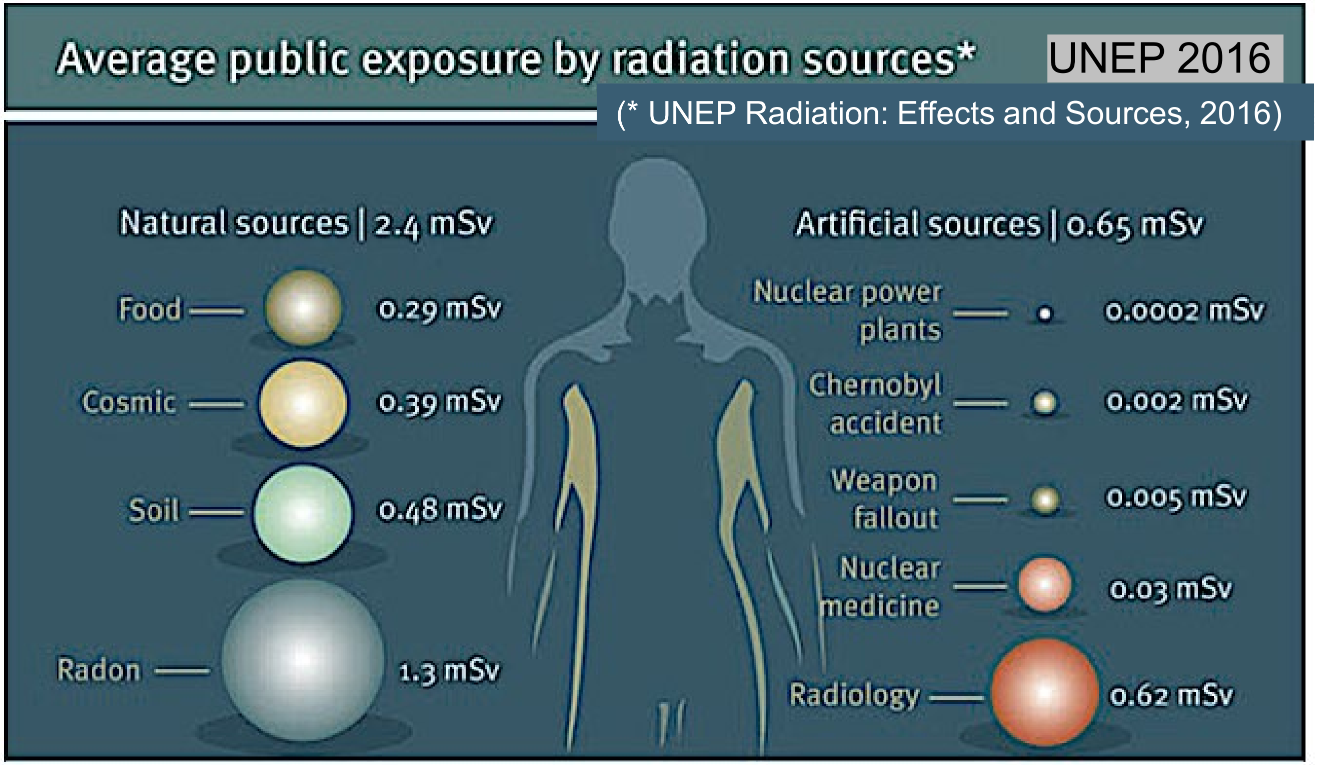


Antoine Henry Bequerel



First photographic plate by Becquerel impressed by the radioactivity of uranium salt (Feb 24, 1896)

World average annual (effective) dose



natural sources: ≈ 2.4 mSv

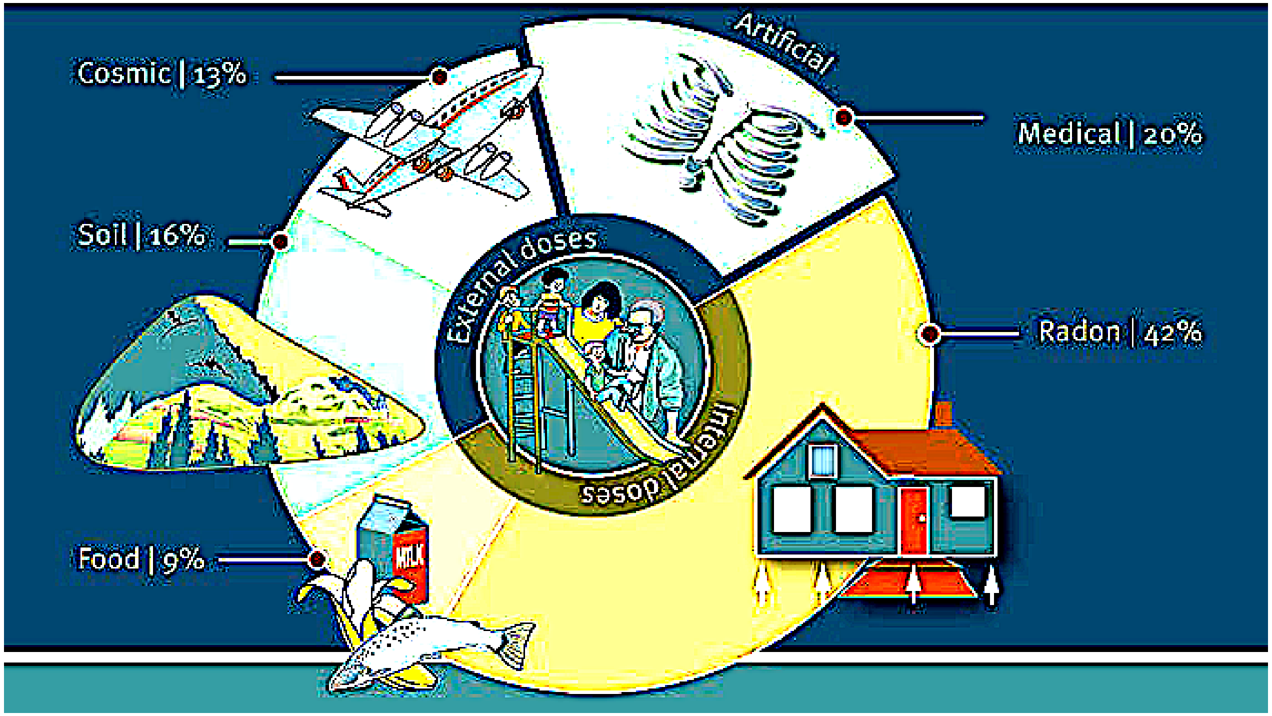
(this value ranges from about 1 to more than 10 mSv depending on where people live

artificial sources (mainly diagnostic medicine exposure) : ≈ 0.4 mSv

(values up to 1 mSv occur in industrialized countries with more resources for medical care)

(UNSCEAR 2008 Report Vol. I *Sources of Ionizing Radiation*)

Worldwide distribution of radiation exposure



Average annual dose due to natural background ≈ 1.1 mSv

(cosmic contribution slightly less than the terrestrial one)

For humans in addition radon contribution ≈ 1.3 mSv

(it is not the same for all organisms. In humans it targets the lungs as consequence of air inhalation – does not apply to cell cultures !)

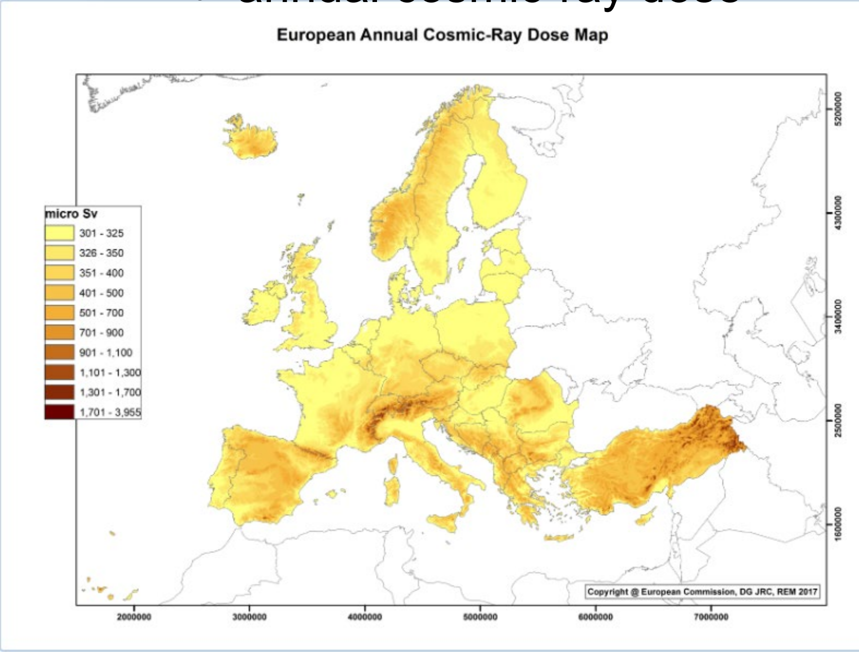
Total from natural background ≈ 2.4 mSv

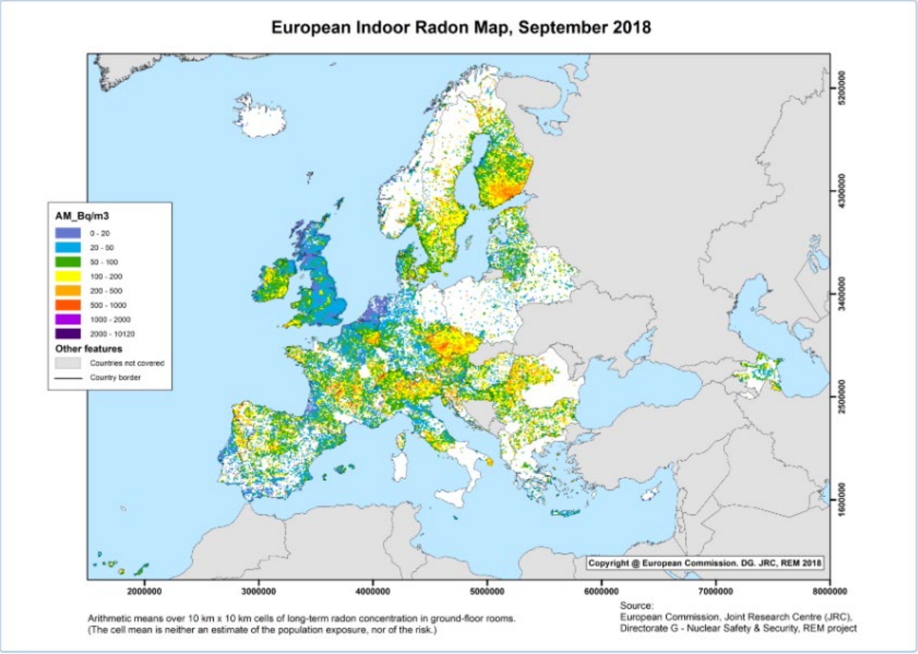
M. Belli – 2nd DULIA-bio 2019

• Radiation background variability

- Natural background typically ranges from 1 to 13 mSv per year. Some particular areas of the world, such as Guarapan in Brazil, Ramsar in Iran and Kerala in India, have greater values than the country-wide average.

  - **European natural radioactivity maps, 2017**
    - annual cosmic-ray dose
    - annual indoor radon concentration





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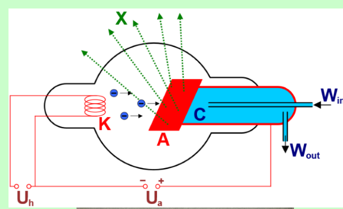
The low dose biological response and radiation protection

Our knowledge about the response of living organisms to low dose of ionizing radiation is mainly related to radiation protection needs, where the focus is on **detrimental** effects.

Our scientific community has become aware of ionizing radiation just over 100 years ago ! Radiation science is a quite recent field.

Wilhelm Conrad Röntgen at the time of its discovery of X-rays (1895)



Röntgen's first X-ray, of his wife's hand, taken on 22 December 1895.

Even if harmful effects were reported soon after the discovery, scientists were slow to understand them.

- Report of X-ray-induced dermatitis (EH. Grubbe,1896)
- First radiation-induced cancer (Freiben, 1902)

A historical note: mutagenic potential of X-rays

- In 1926, the American genetist Muller discovered that, by exposing the fruit fly *Drosophila melanogaster* to high levels of radiation (such as X-rays or gamma rays from radioactive materials), the mutation rate in their offspring can be increased by as much as 150 times.

- For this discovery he was awarded the 1946 Nobel Prize in medicine and physiology.

- His work convinced him that the vast majority of **mutations were deleterious** and consequently that exposure to radiation should be strictly controlled

What is a «low dose» of ionizing radiation ?

Several different definitions

Pragmatic definition (ICRP, HLEG):

Such as doses typically encountered in the workplace, in the environment and in diagnostic medicine.
Also irradiation of normal tissues in radiotherapy may be included in this type of exposure.

In this context, low dose $\leq \approx$ 10 mSv (mGy)

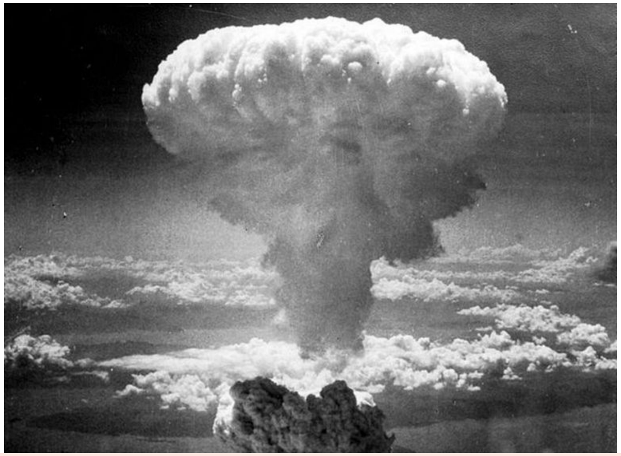
A typical annual dose from natural background of 3 mSv, corresponds to a low dose rate of 3/8760 $\approx$ 0.3 μSv/h (0.3 μGy/h)

Note: for low-LET (sparsely ionizing) radiation 1 mGy = 1 mSv

Health effects: the low dose issue

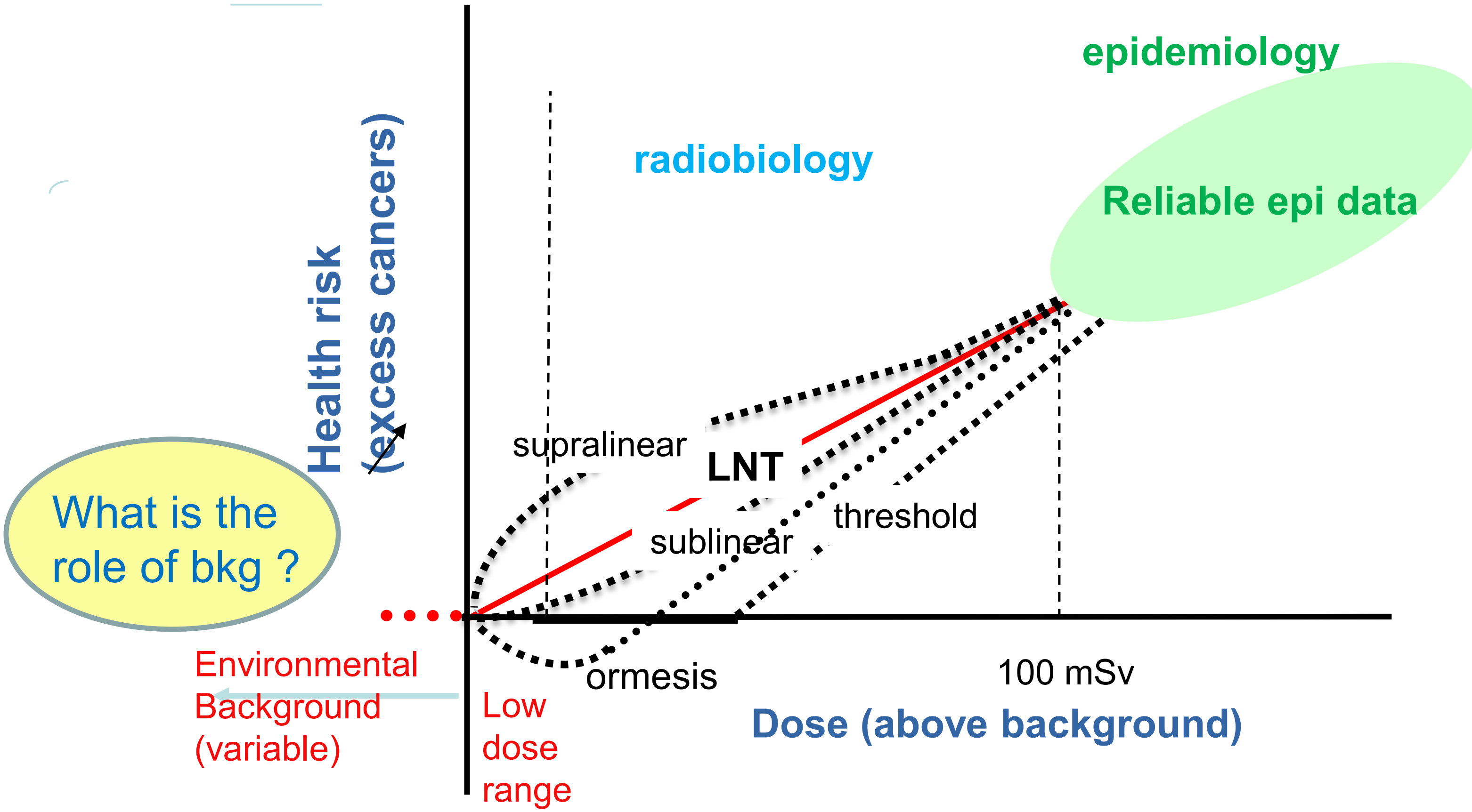
- The main health risk at moderate and low doses (i.e., doses not causing acute/deterministic effects) is induction of **solid tumors** and **leukemias**.

- The most important long-term evaluation of populations exposed to radiation is the epidemiological study of the Hiroshima and Nagasaki survivors of the atomic bombing **(Life Span Study, LSS**, a cohort of about **120,000** subjects followed since 1950)



- **However, below an absorbed dose of about 100 mGy from low-LET* radiation), the statistical uncertainties associated with epidemiological studies become increasingly large and tend to mask any possible effect.**
- **It is estimated that a cohort size of 629,000 is needed to detect an excess risk associated to 10 mGy**

Extrapolation of epi data: the LNT assumption



International Commission for Radiological Protection assumed linear-no threshold extrapolation of excess stochastic risk to low dose (ICRP 103, 2007). LNT assumption makes radiation protection relatively easy and manageable (doses are additive, dose is an index of risk).

Statistical power limitation of epidemiological studies

NO epidemiological evidence of a carcinogenic effect in humans for doses below 100 mSv
(100 mGy for low LET radiation).

This value. **below which it is not possible to detect adverse health effects,** is often used in as an epidemiology-based definition of low dose.

Warning:
no evidence of epidemiological effects
≠
evidence of **no** epidemiological effects
!!!!

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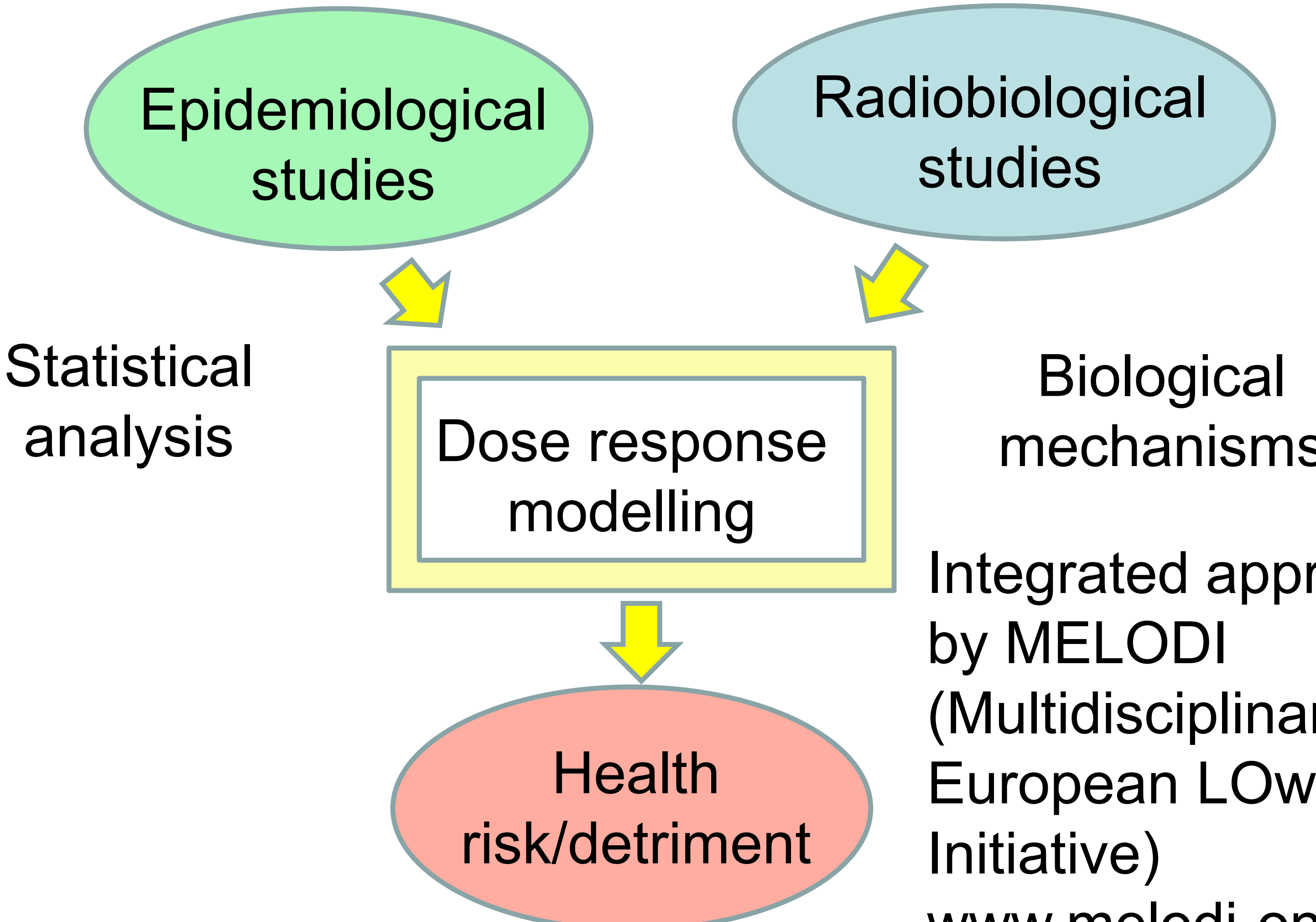
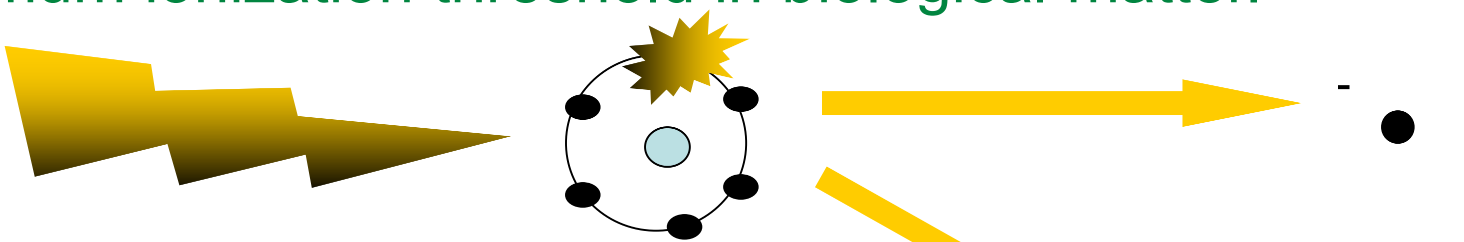
Health risk assessment: the shape of dose-response relationship

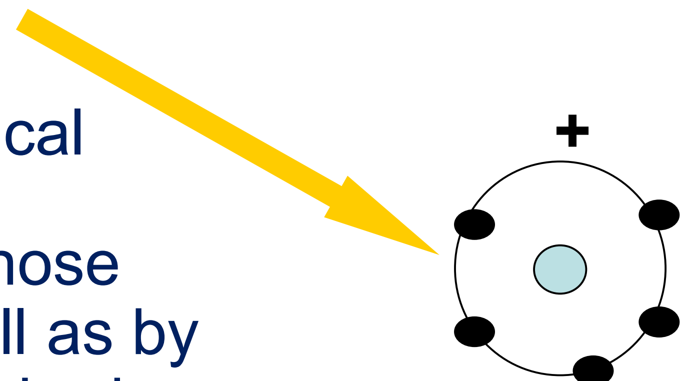


Integrated approach by MELODI (Multidisciplinar European LOw Dose Initiative)
www.melodi-online.eu

How does ionizing radiation injure people?

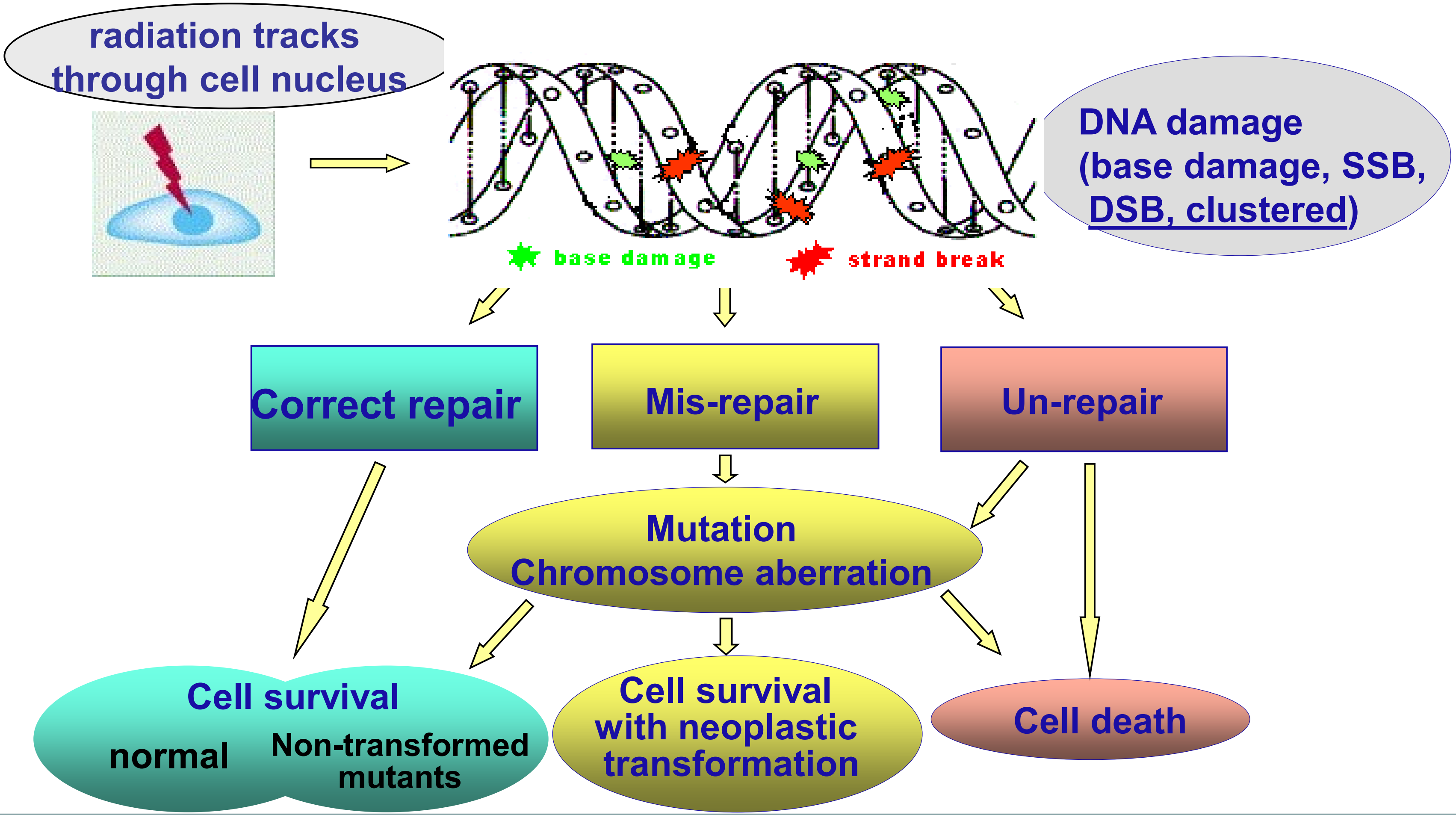
In radiobiology a radiation is **ionizing** when it is capable to ionize biological matter → deposit E > 12.4 eV, the minimum ionization threshold in biological matter.





- Ionizing radiation breaks chemical bonds.
- This creates free radicals, like those produced by other insults as well as by normal cellular processes in the body.
- The free radicals can change biomolecules in the the body's cells, changing cell function.
- The most important cell target is the **DNA**.

From DNA damage to cell effects



Un-repaired or mis-repaired DNA lesions cause genetic mutations, most likely to be detrimental. Even at low doses they are generally assumed to increase both the probability of developing cancers and the rates of hereditary diseases.

Conventional paradigm of Radiobiology

i) The DNA damage in directly exposed cells is the main event for biological effects

ii) DNA damage occurs during, or very shortly after, irradiation of the nuclei in targeted cells

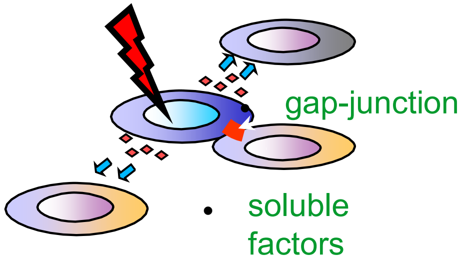
iii) The potential for biological consequences can be expressed within one or two cell generations

iv) At low doses the biological effect is in direct proportion to the energy deposited in nuclear DNA (this is the rational basis for assuming a Linear No-Threshold (LNT) relationship between risk and dose).

Effects outside the conventional paradigm: non-targeted effects (NTE)

NTE: Radiobiological processes that do not follow the conventional paradigm ⟶ NON LINEAR effects !!!
Seen especially at low doses

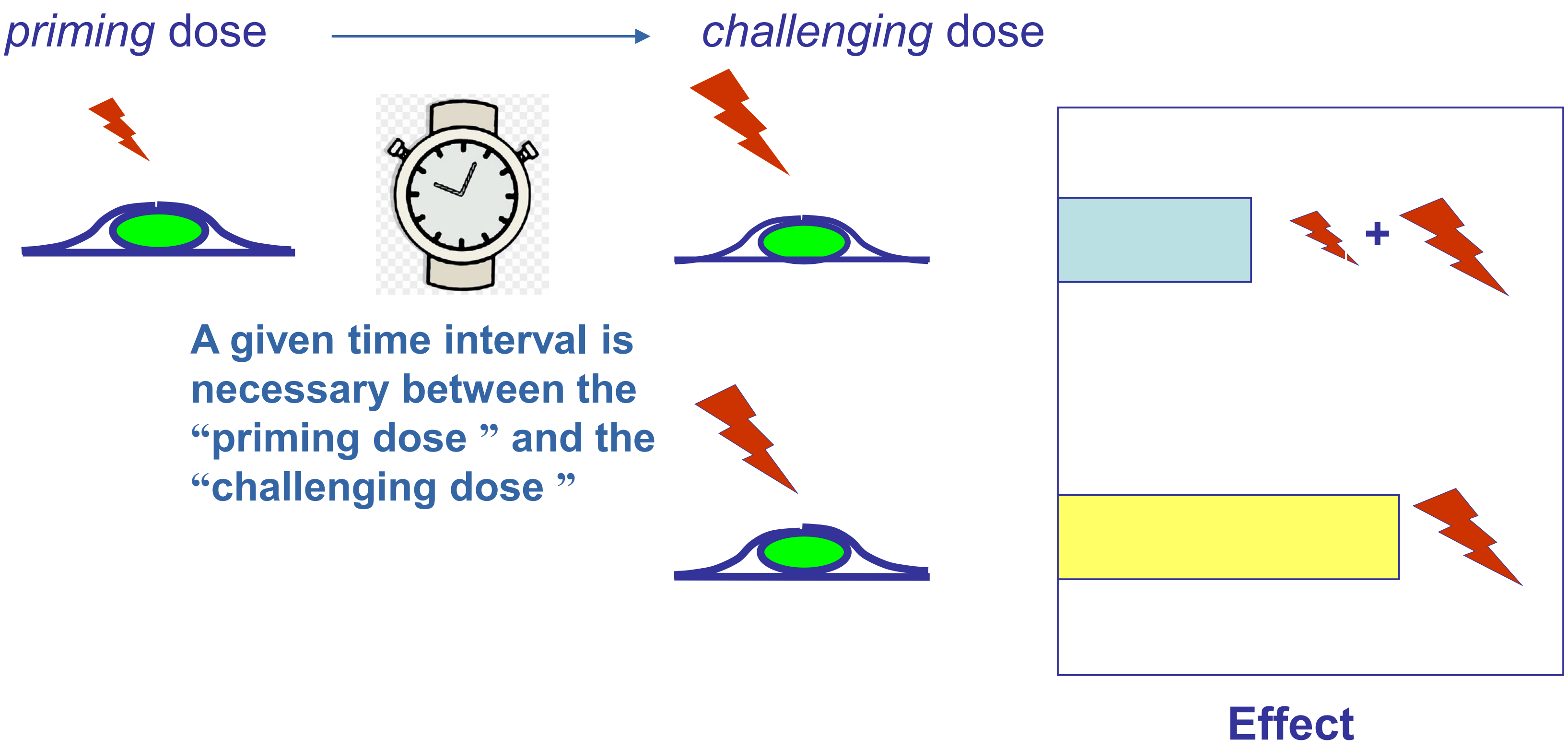
- Bystander effects (effects from hit cells to unhit ones) ⟶
- Adaptive responses (protection by pre-exposure)
- Abscopal (out-of-field) effects
- Radiation-induced genomic instability (raised mutation rate) ⟶ Hallmark of cancer !
- Release of clastogenic factors into the circulating blood of irradiated individuals
- …etc.



- Some of them were already known since many years, but recently they have received more attention in view of their interpretation as manifestation of general phenomena, such as intra- or inter-signalling in cells and epigenetic effects.

Adaptive Response

AR is the induction, in cells pre-exposed to a low “priming” dose, of cellular radioresistance to subsequent, larger “challenging” doses.
(Olivieri, Bodycote and Wolff, *Science*, *1984)*



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NTE are related to epigenetic action of radiation

Most NTE have been observed *in vitro*, but they can also be relevant *in vivo*

There is evidence that

- **these phenomena are inter-related and they may share some common radiation-induced epigenetic mechanisms**
- **even if it is usually thought that ionising radiation acts through DNA damage, it may also cause epigenetic alteration**

Epigenetic changes and mechanisms

The heritable changes in gene function that cannot be explained by changes in DNA sequence (Riggs et al1996)

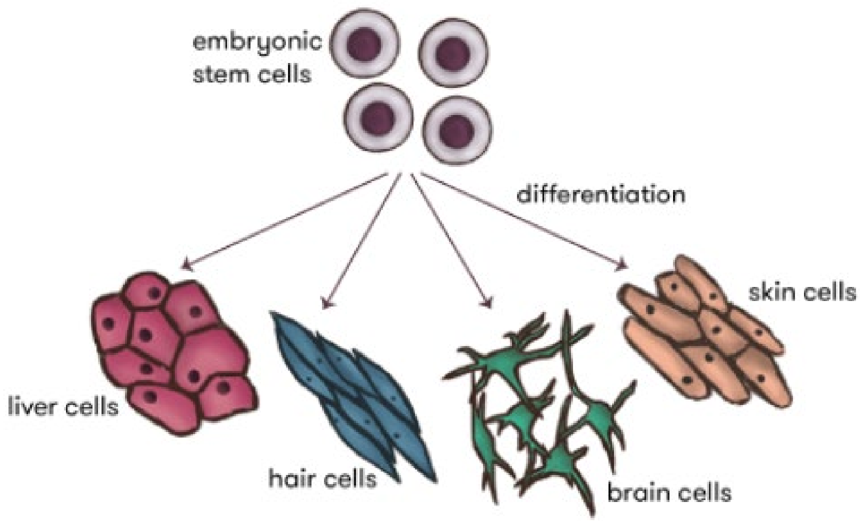
Heritable changes in gene expression
=
epimutations

1. DNA Methylation
2. Histone modifications (chromatin organization)
3. Modulation of non-coding RNAs

Epigenetic mechanisms are involved in adapting the gene expression programme of the cell to the stress situation, often when they are transient.

Development and differentiation are regulated by epigenetic mechanisms

Epigenetic mechanisms regulate the gene expression in our body's cells to create all the different cell types of our body although they have the same genome.



This is obtained by silencing of specific genes by epigenetic factors.

Epigenetic changes determine the phenotype without alteration of the genotype

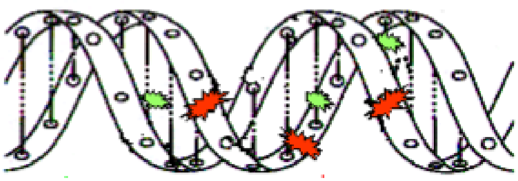
Identical (homozygote) twins = same genotype, but different phenotypes

Twin aspronauts Scott and Mark Kelly

We are Not (only) Our DNA..

Biological response to low doses is more complex than previous thought

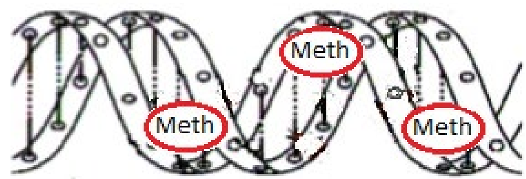
GENETICS



DNA damage, changes in base sequence

mutation, chromosome aberration

EPIGENETICS



DNA methylation, histone modifications, miRNA expression

gene silencing, genomic instability

Altered gene product

Ionizing radiation dualism

….or ionizing radiation as a double-edged sword

Epigenetics and radiation background

Epigenetic events are known to regulate gene activity and expression not only during development and differentiation, but also in response of environmental stimuli, including ionizing radiation.

Is background radiation only a damaging agent or also a stimulatory agent ? What if this background was removed ?

Are epigenetic mechanisms important to radiation background response ?

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Relevance of underground experiments

Controlled long-term experiments with model organisms, conducted in underground laboratories have opened a new avenue to deal with the low dose issue.

- **Protozoan**
Planel et al 1987
- **Bacteria**
Smith et al 2011, Castillo et al.2015
- **Yeast**
Satta et al 1995
- **Rodent cells**
Satta et al 2002, Antonelli et al 2008, Fratini et al 2015
- **Human cells**
Carbone et al 2009, 2010
- **Fruit flies**
Morciano et al 2017, 2018

Results already obtained are consistent with the hypothesis that the natural radiation background is capable to stimulate defence mechanisms that are acquired by epigenetic regulation,

Relevance of underground experiments and perspectives

This kind of investigations can provide basic information for understanding:

- the robustness of the present radiation protection system and, in case, if a more robust one could be developed;

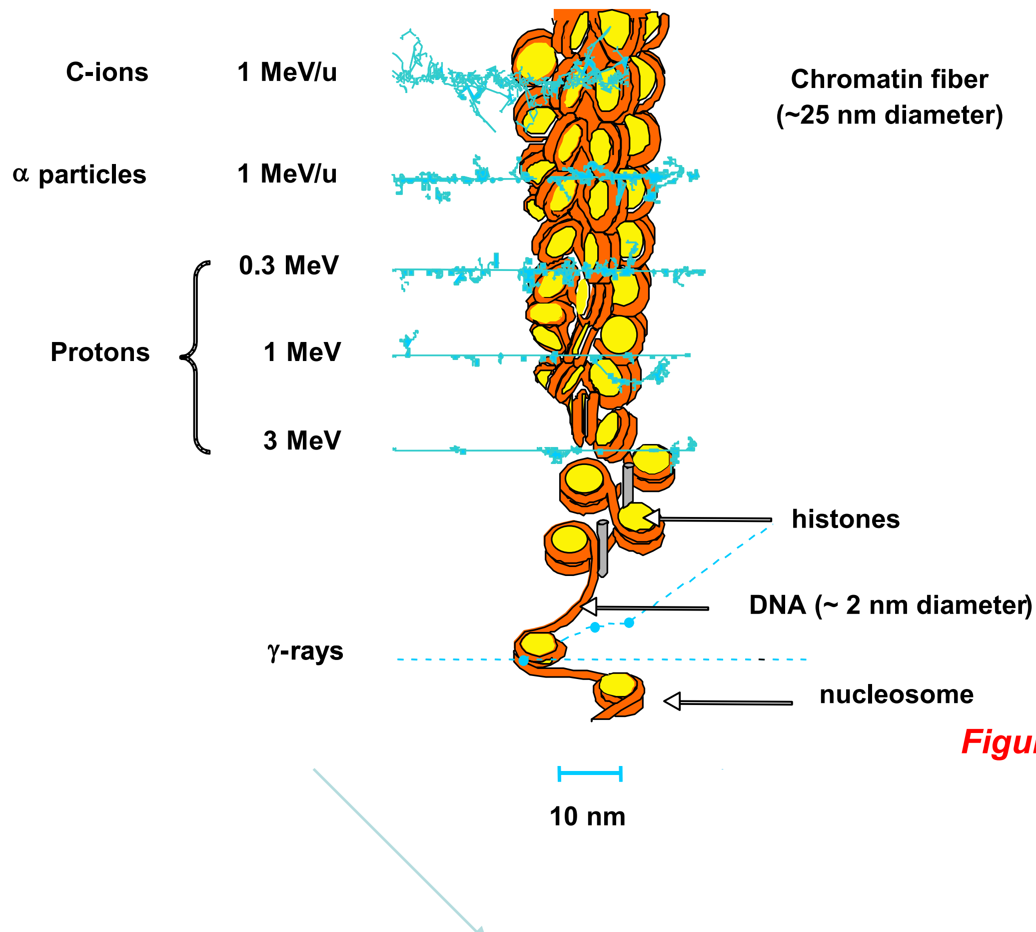
- if and how the natural radiation played a role in life evolution on Earth

An important goal to be considered is the understanding of the role of dose protraction and radiation quality

Thanks for your attention

Spatial distribution of energy events

Which is the role of radiation quality ?



Different radiation qualities (high vs. low LET) ⇒ different qualities for DNA damage.

High LET ⇒ more closely correlated damage, in terms of:
- complex damage;
- small fragments (deletions)(*Loebrich et al 1996*, *Belli et al IJRB 2002*);

Complex damage repaired with decreased efficiency (unrepair, misrepair)

Figure adapted from Belli et al. J.Rad.Res. 2003