Individual radiosensitivity: a key issue in radiation protection

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Individual hypersensitivity to radiation is a key cellular phenomenon at the crossroads of DNA lesions repair and signaling and cell cycle checkpoint. It is a real issue in public health since it concerns low as much as high doses of ionizing radiations and 5-15% of the population. Among these:

- **thousands of patients who benefit from radiation therapy but also suffer from long term side effects. This raises the question of defining the proper dose for any given patient to cure its cancer and to avoid significant side effects;**
- **patients who benefit from medical exposures, especially children and young adults and women as part of breast cancer screening by mammography.**

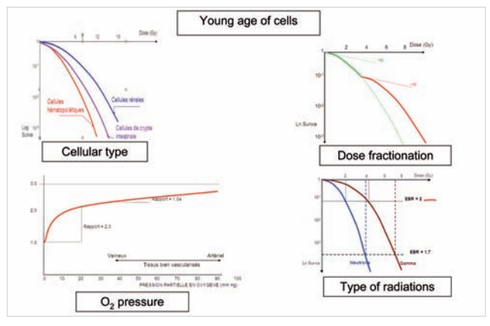
Factors of sensibility to ionizing radiation

5 main factors of sensitivity to ionizing radiation (IR) have long been identified. *Fig. 1* These factors have been taken into account to design and optimize radiation therapy for cancer *(Hall and Giaccia, 2012)*.

The individual response to ionizing radiation is another factor known for a long time, so far difficult to be diagnosed and quantified in routine prior to radiation therapy.

Recent immunofluorescence techniques which permit the detection of nuclear targets specific of DNA lesions repair and signaling (e.g. γH2AX foci reflecting DNA double-strand breaks-DSB-Rothkamm and Löbrich, 2003), have completely renewed the assessment of individual radiosensitivity. *Fig. 2*

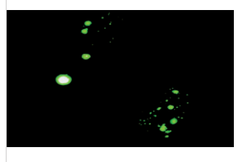
***Factors of radiosensitivity** - Fig. 1*



***New investigation techniques** - Fig. 2*

Demonstration of DNA double strand breaks with fluorescent antibodies anti-histones gH2-AX *(Rothkamm & Löbrich 2003)*:

- increase sensitivity : a factor 100
- threshold : 1 mGy
- the effects of one single examination can be seen !



Foci pH2AX (green) of non transformed human fibroblasts

N. Foray, 2011

Hypersensitivity to high doses of ionizing radiation

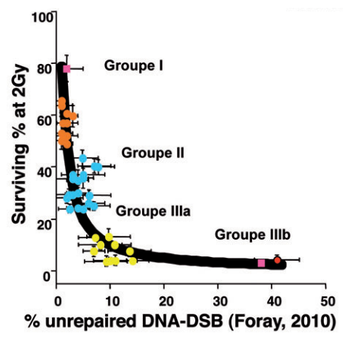
Radiation oncologists have observed that some patients display hypersensitivity to IR and develop adverse side-effects in normal tissues after radiation therapy, although correct delivery of the dose *(Twardella and Chang-Claude, 2002)*. The 5 to 15% estimated rate of side-effects *(Jung et al., 2001; Dörr and Hendry, 2001)* justify to consider the impact of the individual factor in hypersensitivity to IR.

Hypersensitivity to IR is linked to genetic disorders regarding DNA lesions repair and signaling and cell cycle checkpoint control *(Bourguignon et al., 2005)*. Radiation oncologists have been very cautious not to miss the diagnosis of homozygous patients who are very sensitive to radiations.

Patients with heterozygous mutations for the same genes present a lower degree of radiosensitivity *(Angele et al., 2003)* and account for about 10% of the population *(Swift, 1981)*.

Joubert et al. (2008) proposed a classification of individual radiosensitivity on the basis of the results obtained from cell lines of different genetic syndromes and cutaneous fibroblasts of patients. They have notably investigated DSB with γH2AX foci and genomic instability with MRE11 foci. It represents a new insight regarding both individual radiosensitivity and side-effects following radiation therapy. *Fig. 3*

***Groups of radiosensitivity** - Fig. 3*



Definition of 3 groups de radiosensitivity:

- I radioresistance and low genomic instability,
- II intermediate radiosensitivity and genomic instability,
- III hyperadiosensitivity and genomic instability.

Hypersensitivity to low doses of ionizing radiation

The phenomenon of hyper-radiosensitivity to low doses (HRS) in comparison to higher doses has been first described by Joiner et al. in 1996. *Fig. 4*

HRS has also been demonstrated by Slonina et al. (2008), Vaganay-Juéry (2000), Grudzenski et al. (2010) and Krueger et al. (2010) who looked for its mechanisms.

Colin et al (2011) irradiated human mammary epithelial from patients with low risk and high familial risk of breast cancer and quantified the number of γH2AX foci in conditions of mammography irradiation: 2 mGy mimicking one view, repetition of 2 mGy with 3 min interval mimicking a standard mammographic protocol with 2 views, and 4 mGy.

They observed four statistically significant effects:

1. a dose effect with an increase of the DSB yield with increasing dose,
2. a supra-additive dose effect with repeated doses, i.e., more unrepaired DSB with 2+2 mGy than with 4 mGy in one single exposure,
3. a late effect of induction of DSB between 10 min and 24h, suggesting a DSB inducing process during repair,
4. all the 3 previous effects were greater in high family risk patients than in low risk patients. *Fig. 5 & 5 bis*

→ These results suggest modifying guidelines for breast screening in high family risk patients taking into account magnetic resonance imaging advances in breast cancer screening *(Colin and Foray, 2012)*.

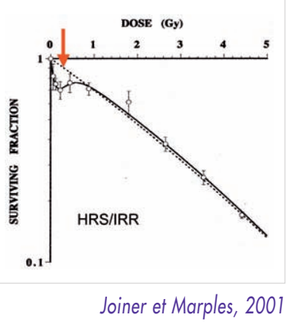
Although they have been obtained *ex vivo*, the results of Colin et al. are in favor of a link between cancer proneness and radiosensitivity.

→ It should be considered that individuals sensitive to radiation have higher cancer risk than the rest of the population when they are exposed to ionizing radiations.

***Hyper radiosensitivity at low doses** - Fig. 4*

Cellular survival and hyper radiosensitivity

- Human glial cells T98G,
- X Rays 240 kV
- peak effect, between 100 and 300 mGy.



Joiner et Marples, 2001

Study on human mammary epithelium exposed to ionizing radiations in the conditions of mammography. Patients with low risk of cancer / high familial risk (C.Colin 2011). Results H2AX.

Fig. 5

Induction of DNA-DSB between 10 min and 24 h

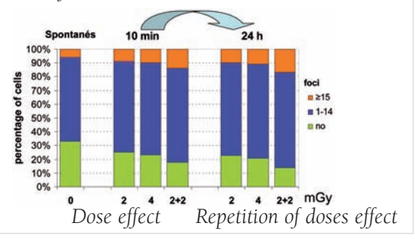
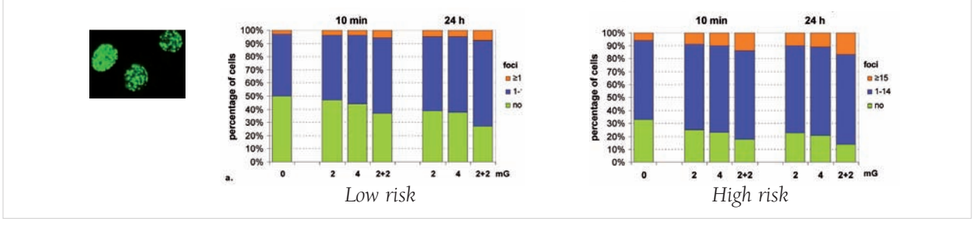


Fig. 5 bis

3 effects increased in HR patients



The French Nuclear Safety Authority (ASN) recommends to address the phenomenon of individual radiosensitivity in the radiation protection system in order to properly protect individuals who are sensitive to ionizing radiation. Besides fundamental research needed to better understand the mechanisms involved in radiosensitivity, a test able to predict the response to radiation is desirable to document this phenomenon on a large scale. It should be easy to perform, manage and interpret, and should produce reliable results within a short time and at a reasonable cost.

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