Individual radiosensitivity: a key issue in radiation protection

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Abstract: Immunofluorescence that permits the detection of nuclear targets specific to DNA damage signalling and repair have completely renewed the approach of individual radiosensitivity. It is a concern in radiotherapy in which radiosensitivity is responsible for the development of adverse side-effects in normal tissues in absence of any mistake in the dose delivery. Furthermore, individual radiosensitivity at low-dose has been recently demonstrated in human mammary epithelium exposed \textit{ex vivo} in the conditions of mammographic screening. Although these results do not demonstrate directly the existence of mutagenesis, they indicate a possible link between cancer proneness and radiosensitivity. Hence, individual radiosensitivity is a real
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Concern for public health since 5-15% of the population may be concerned and radiosensitive individuals generally show higher cancer risk than the rest of the population. Thus, individual radiosensitivity is a key issue to be addressed in future recommendations of the radioprotection system.

Keywords: ionising radiations; radiosensitivity; cancer proneness.


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1 Introduction

Many factors of sensitivity to ionising radiation (IR) have long been identified: type of cells, type of radiation, oxygen partial pressure, dose fractionation. These factors have been taken into account to design and optimise radiotherapy against cancer (Hall and Giaccia, 2012).

The individual response to ionising radiation is another factor described by Bouchacourt as early as 1911 (Bouchacourt, 1911) and named “radiosensitivity” notably by Regaud (e.g. Regaud, 1927). It was early believed that radiosensitivity is due to some hereditary or acquired predisposition (e.g. Regaud, 1927). This concept has been somehow forgotten mostly because radiosensitivity has been so far difficult to be diagnosed and quantified in routine prior to radiotherapy although Puck and Markus (Puck and Markus, 1957) and Fertil and Malaise (Fertil and Malaise, 1981) suggested that it could be predicted by in vitro clonogenic survival. Recent immunofluorescence
techniques that permit the detection of nuclear targets specific of DNA lesions repair and signalling, (e.g. γH2AX foci) reflecting DNA double-strand breaks (DSB), have completely renewed the assessment of individual radiosensitivity (Rothkamm and Löbrich, 2003). Because it concerns low as much as high doses of IR and 5–15% of the population, individual sensitivity to IR is likely to be a key cellular phenomenon at the crossroads of DNA lesions repair and signalling and cell cycle checkpoint. The purpose of this short paper is to emphasise the importance of individual radiosensitivity for radioprotection.

2 Hypersensitivity to high doses of IR

Since many years, radiation oncologists have observed that some patients display sensitivity to IR and develop adverse side-effects in normal tissues after radiation therapy, although there are no mistakes whatsoever in the dose delivery (Twardella and Chang-Claude, 2002). Since the rate of side-effects was estimated to be about 5–15% (Jung et al., 2001; Dörr and Hendry, 2001), it can be justified to consider the impact of the individual factor in hypersensitivity to IR. The individual radiosensitivity measured \textit{in vitro} has been correlated with \textit{in vivo} curability of cancers in 1981 (Fertil and Malaise, 1981). Thus, the identification of radio-sensitive cancer patients and the quantification of the degree of radiosensitivity should facilitate the choice of an individualised dose, instead of the common standardised dose, in order to avoid side-effects and while increasing the cure rate of tumours (Turreson et al., 1996; Marples et al., 2003; Appleby et al., 1997).

As evoked above, radiosensitivity is linked to genetic disorders regarding DNA lesions repair and signalling and cell cycle checkpoint control (Bourguignon et al., 2005a). A large series of genetic diseases, e.g., ataxia telangiectasia (ATM mutations), ligase IV deficiency (LIG4 mutations) or Nijmegen syndrome (NBS1 mutations), has been identified in which the homozygous status of patients is associated with hyper-radiosensitivity (Bourguignon et al., 2005b). The survival fraction of the patient cells after one single exposure \textit{ex vivo} to 2 Gy IR is usually below 50%. These patients present a high degree of radiosensitivity. Thus, radiation oncologists have been very cautious not to miss the diagnosis of these patients in order not to irradiate them or to limit the irradiation dose in case of cancer radiotherapy.

Patients with heterozygous mutations for the same genes evoked above present a lower degree of radiosensitivity (Angele et al., 2003). The rate of heterozygous patients for these genes is in the range of 10% of the population (ATM heterozygous carriers representing already 1% of the population) (Swift, 1991).

Joubert et al. (2008) have used two different assays to predict intrinsic radiosensitivity in patients with syndromes associated with acute radiation response (Joubert et al., 2008). These assays used immunofluorescence techniques on human cutaneous fibroblasts exposed to 2 Gy IR. They have notably investigated DSB with γH2AX foci and genomic instability with MRE11 foci. Joubert et al. (2008) also proposed a classification of individual radiosensitivity on the basis of their results obtained from 40 cell lines representing 89 different genetic syndromes and a series of 50 patients (Granzotto et al., in preparation). Although the method used is cumbersome, it represents a new insight regarding both individual radiosensitivity and side-effects following radiotherapy.
3 Hypersensitivity to low doses of IR

The phenomenon of hyper-radiosensitivity to low doses (HRS) in comparison to higher doses has been first described by Joiner et al. in 1996 by quantifying survival fraction of human glial cells exposed to 240 kV X-rays (Joiner et al., 1996). HRS phenomenon was also observed by Slonina et al. (2008) in human fibroblasts and keratinocytes exposed to γ-rays by demonstrating a low-dose-induced increase of the fraction of micronuclei in binucleated cells. Grudzenski et al. (2010) showed in mice a default of late repair of DNA lesions (24 to 72 h) after exposure to 10 mGy with low Linear Energy Transfer (LET) radiation throughout the persistence of 53BP1 foci whereas this default did not exist with higher doses (100 mGy and 1 Gy).

Looking for some possible mechanisms for HRS, Vaganay-Juéry et al. (2000) showed a decreased DNA-PK activity in human cancer cells exposed to 200 mGy, suggesting the implication of the DNA-PK repair complex in this phenomenon. Krueger et al. (2010) confirmed that HRS phenomenon in MR4 cells is linked to the early G2/M checkpoint through the damage responses of G2-phase cells. Grudzenski et al. (2010) also showed in human fibroblasts that the absence of repair DNA DSB repair after 2.5 mGy disappear after induction of repair by pre-treatment with H2O2.

While further investigations are needed to document the HRS phenomenon, recent works suggest the significance of the impact of individual factor on HRS phenomenon. Notably, in three human fibroblast cell lines irradiated in the 9–2000 mGy range and subjected to MRE11 and H2AX immunofluorescence, Colin et al. (2011a) have observed specific response in the 9–50 mGy range and quantified the balance between individual radiosensitivity and genomic instability. Furthermore, in a second study, Colin et al. (2011b) have 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 three previous effects were greater in high family risk patients than in low risk patients.

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). Interestingly, these results do not contradict the risk calculations of radiation-induced breast cancer from mammographic screening for young BRCA mutation carriers made by Berrington de Gonzales (2009).

At this stage, one does not know if the general HRS phenomenon described by Joiner et al. and the phenomenon of individual radiosensitivity at low doses described by Colin et al. (2011a) are distinct or have a common feature.
Interestingly, patients with high risk of breast cancer related to a BRCA1 mutation may be also more radiosensitive than normal patients (Foray et al., 1999). Thus, although they have been obtained ex vivo, the data from human mammary epithelium are in favour of a link between cancer proneness and radiosensitivity. The results of Colin et al. (2011b) do not demonstrate the existence of mutagenesis at low-dose since γH2AX marker is not a sensor of genomic instability. However, the systematic presence of poorly repaired DSB in cancer-proned patients as demonstrated by MRE11 immunofluorescence is also a sign of the incomplete recovery of DNA after irradiation (Joubert et al., 2008). Furthermore, it is likely that a few of the much more frequent DNA lesions other than DSB after IR might not be properly repaired. Consequently, one must consider that individuals that are sensitive to radiation have higher cancer risk than the rest of the population when they are exposed to IR.

4 Conclusions

In conclusion, we believe that individual hypersensitivity to radiation is a real concern in public health since 5–15% of the population could be more sensitive to radiation. Among these people, one can identify:

- the 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 cancer and to avoid significant side effects;
- all patients who benefit from medical exposures, especially children and young adults and the women as part of breast cancer screening by mammography.

In order to properly protect individuals that are sensitive to IR, this phenomenon must be addressed in the radiation protection system.

Finally, 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.

References


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