Human Radiosensitivity, Radiosusceptibility and Radiodegeneration

Subjects: Radiology, Nuclear Medicine & Medical Imaging

Contributor: Nicolas Foray

The individual response to ionizing radiation may show several clinical features such as skin burns, cancers or cataracts, according the tissue type, the genetic status or the dose. To avoid any confusion with a non-univocal way of using the term “radiosensitivity”, we have proposed the following definitions :

- “Radiosensitivity is the proneness to the radiation-induced adverse tissue events generally attributable to cell death that is correlated with unrepaired DNA damage.

-“Radiosusceptibilty” is the proneness to the radiation-induced cancers generally attributable to cell transformation that is correlated with misrepaired DNA damage.

-"Radiodegeneration" is the proneness to radiation-induced non-cancer effects attributable to mechanisms related to accelerated aging that is correlated with the accumulation of tolerated unrepaired DNA damage.

Keywords: radiosensitivity ; radiosusceptibility ; radiodegeneration ; ATM ; ionizing radiation

1. Introduction

The individual response to ionizing radiation (IR) raises a number of medical, scientific, and societal issues. While the term “radiosensitivity” was used by the pioneers at the beginning of the 20st century to describe only the radiation-induced adverse tissue reactions related to cell death, a confusion emerged in the literature from the 1930s, as “radiosensitivity” was indifferently used to describe the toxic, cancerous, or aging effect of IR. In parallel, the predisposition to radiation-induced adverse tissue reactions (radiosensitivity), notably observed after radiotherapy appears to be caused by different mechanisms than those linked to predisposition to radiation-induced cancer (radiosusceptibility).

The individual response to ionizing radiation has been the subject of a plethora of studies in the last decades, notably to evaluate the related risks, not only for exposed humans, but also for ecosystems. In particular, the International Commission of Radiation Protection (ICRP) set up in 2018 a dedicated group (TG111) to address the corresponding issues. Unfortunately, while the individual response to radiation is more and more documented, some of its various features are described with non-univocal terms, which does not facilitate their understanding and the elucidation of their intrinsic mechanisms.

This review aims to document these differences in order to better estimate the different radiation-induced risks. It reveals that there are very few syndromes associated with the loss of biological functions involved directly in DNA damage recognition and repair as their role is absolutely necessary for cell viability. By contrast, some cytoplasmic proteins whose functions are independent of genome surveillance may also act as phosphorylation substrates of the ATM protein to regulate the molecular response to IR. Hence, the role of the ATM protein may help classify the genetic syndromes associated with radiosensitivity and/or radiosusceptibility.

2. Historical context

The term ’radiosensitivity’ is one of the most extensively used words in radiation biology, oncology, and protection. The first occurrence of the “radiosensitivity” term was found in the French “radiosensibilité” and German “Strahlenempfindlichkeit” in 1907 [1]. The French “radiosensibilité” likely originates from “radioactivité” (radioactivity) that was proposed by Curie to replace the term “hyper-phosphorescence” initially chosen by Becquerel after his discovery of natural radioactivity [2]. Although the exact origin of this term is still unclear, “radiosensitivity” was systematically used to

describe radiation-induced tissue reactions, such as skin burns, with the widely accepted hypothesis that these tissue events were associated with cellular death and that there was a causal link between clinical and cellular features [3]. This was notably the case of the reactions reported by Albers-Schönberg in 1898 in patients treated for lupus [4] and by Bouchacourt in patients treated for hypertrichosis [5].

By contrast, to describe the first radiation-induced cancers, notably that reported by Frieben in 1902 [6], and those from the over-exposed dial painters (the “radium girls”) between 1917 and 1926, the term “radiosensitivity” was not used but was simply replaced by “radiation-induced cancers” [7].

From the 1930s, English became the official language during the first International Congresses of Radiology, the term “radiosensitivity” was used indifferently whether for describing radiation-induced tissue reactions or cancers [8]. As a consequence, confusion has emerged [1].
Since the 1930s, in the ICRP publications, the term “radiosensitivity” was used as a synonym of:

- radiation-induced cancers, e.g., “Children are more radiosensitive than adults” [9] or “thyroid is a radiosensitive organ” [10];
- radiation-induced cataracts, e.g., “eyes are radiosensitive” [11];
- radiation-induced toxicity as adverse tissues reactions in “ataxia telangiectasia, caused by *ATM* mutations, is the most radiosensitive syndrome” [12].

A practical consequence of such confusion is to allow the belief that a “radiosensitive” patient may have the same quantitative risk of radiation-induced cancers, radiation-induced cataracts, and post-radiotherapy adverse tissue reactions. Additionally, such confusion may raise obvious legal issues, as radiation-induced cancers, cataracts, or skin burns do not obey the same incidence laws and do not correspond to the same level of clinical injuries and repairability [13].

To date, while the term “radiosensitivity” is still used indifferently, there is increasing evidence that the molecular and cellular bases that lead to radiation-induced cellular death and tissue reactions are different from those that lead to radiation-induced and spontaneous cancer proneness. A typical example is given by three genetic syndromes:

- the Li Fraumeni’s syndrome (LFS), caused by the heterozygous mutations of *p53* [14] is associated with cancer proneness but not with significant post-radiotherapy adverse tissue reactions [14];
- the ataxia telangiectasia (AT) caused by the homozygous mutations of *ATM* [15] is associated with post-radiotherapy fatal reactions and AT patients are at high risk of leukemia [15][16];
- the Cockayne’s syndrome (CS) caused by the homozygous mutations of the *CS* genes [17] is associated with a significant tissue radiosensitivity but no cancer proneness [17][18].

Altogether, these observations strongly suggest that radiation-induced tissue reactions are not necessarily linked to spontaneous and radiation-induced cancer proneness. Practically, such a conclusion is important for radiation oncologists who should, in the first case (tissue radiosensitivity but not radiation-induced cancer proneness), decrease the total dose in the planned treatment, or even forbid any radiotherapy [16] while, in the second case (radiation-induced cancer proneness but not tissue radiosensitivity), they can treat their patient by considering his age: if the patient is young, they should reduce drastically the dose on healthy tissues surrounding the tumors, maybe by using new-generation radiotherapy modality, while if the patient is old, they may consider that the transformation of cells into a radiation-induced malignancy may be longer than the general life span of the patient.

Similar conclusions can be reached with radiation-induced cataracts vs. tissue reactions and/or cancer proneness. For example, some genetic syndromes may be associated with both juvenile cataracts and tissue radiosensitivity like in the case of the Rothmund–Thomson syndrome [19], or else both juvenile cataracts and cancer proneness like in the case of the neurofibromatosis type 2 [20].

3. Univocal Definitions

To avoid all these confusions with the use of the term “radiosensitivity”, two approaches, at least, were possible:

- the “genomic approach” which consists of inventorying all the genes involved by their expression or polymorphisms in the high throughput studies of radiosensitivity, in order to establish causal links with clinical features [21]. The major advantage of this approach is to get a large number of candidate genes. The major inconvenience is to consider gene expression as a major feature of the response to radiation, while some cases of radiosensitivity are not necessarily linked to a higher or lower gene expression but to protein dysfunction [8];

- the “clinical approach” which consists of defining the major clinical features of the response to radiation, and thereafter to identify genes in each category. The major advantage of this approach is to gather all the different types of radiation-induced events observed by clinicians. The major inconvenience is to omit some genes that may be involved in the response to radiation while their mutations lead to non-viability and therefore are not associated with any described syndrome [8].

In the present review, we have considered only this second approach, arguing that it permits to alleviate the major confusions caused by non-univocal definitions of the terms used. In addition, this approach permits us to indifferently apply the following terms to the individual, tissue, cellular, or molecular scales. The following definitions have therefore been proposed in the literature:

- The radiosensitivity is the proneness to the adverse tissue events that are considered as non-cancer radiation-induced effects and attributable to cell death. Radiosensitivity is generally correlated with unrepaired DNA damage [12];

- The radiosusceptibility is the proneness to the radiation-induced cancers that are non-toxic radiation-induced effects attributable to cell transformation and genomic instability. Radiosusceptibility is generally correlated with misrepaired DNA damage [22]. As IR is considered as a carcinogenic agent, radiosusceptibility is strongly linked to susceptibility to spontaneous cancers. The term “radiosusceptibility” was proposed through its similarities with “cancer susceptibility”, extensively used in the ICRP reports, and as it introduces the notions of stochastic events [8];

- The radiodegeneration responses are non-cancer effects attributable to mechanisms related to accelerated aging. Radiodegeneration should be correlated with unrepaired DNA damage that is tolerated by and can cumulate in cells [8]. Radiodegeneration responses cannot be considered similar to radiosensitivity responses as defined above, as their incidence rates, the types of cellular death, and the genes involved are different.

4. Conclusions

The notions of radiosensitivity, radiosusceptibility, and radiodegeneration appear to be necessary to better describe the different types of individual radiation responses, and permit an evaluation of the specific radiation-induced risks in agreement with clinical observations. This review reveals that there are very few syndromes associated with the loss of biological functions involved directly in DNA damage recognition and repair bas their role is absolutely necessary for cell viability. Interestingly, some cytoplasmic proteins, whose functions are clearly different from genome surveillance, may also act as ATM phosphorylation substrates to regulate the DSB recognition and repair. The radiation-induced ATM nucleoshuttling model may therefore provide a novel approach to classify the genetic syndromes associated with abnormal individual response to radiation, whether linked to toxicity, cancer, or aging.

References

1. Britel, M.; Bourguignon, M.; Foray, N. Radiosensitivity: A term with various meanings at the origin of numerous confusions. A semantic analysis. Int. J. Radiat. Biol. 2018, 94, 503–512.
2. Becquerel, H. Sur les radiations émises par phosphorescence. C. R. Acad. Sci. 1896, 122, 420–421.
3. Regaud, C. Notice Sur les Travaux Scientifiques Publiés de 1893 à 1935; Presses Universitaires de France: Paris, France, 1935.
4. Albers-Schönberg, H. Über die Benadlung des Lupus und des chronischen Ekzems mit Röntgenstrahlen. Fortschr. Rôntgenstr. 1898, 2, 20–29.
5. Bouchacourt, L. Sur la différence de sensibilité aux rayons de Roentgen de la peau des différents sujets, et, sur le même sujet des différents régions du corps. In Proceedings of the Comptes-Rendus des Sessions de l’Association Française pour l’Avancement des Sciences, 40ème Congrès, Dijon, France, 1911; pp. 942–947.
6. Frieben, A. Cancroid des rechten Handrückens. Dtsch. Med. Wochenschr. 1902, 28, 335.
7. Gunderman, R.B.; Gonda, A.S. Radium Girls. Radiology 2015, 274, 314–318.

8. Foray, N.; Bourguignon, M.; Hamada, N. Individual response to ionizing radiation. Mutat. Res. Mutat. Res. 2016, 770, 369–386.
9. ICRP. Radiation and Your Patient—A Guide for Medical Practitioners; Supporting Guidance Annals of ICRP; ICRP: Stockholm, Sweden, 2001; p. 31.
10. Sinnott, B.; Ron, E.; Schneider, A.B. Exposing the Thyroid to Radiation: A Review of Its Current Extent, Risks, and Implications. Endocr. Rev. 2010, 31, 756–773.
11. Brown, N.P. The lens is more sensitive to radiation than we had believed. Br. J. Ophthalmol. 1997, 81, 257.
12. Granzotto, A.; Benadjaoud, M.A.; Vogin, G.; Devic, C.; Ferlazzo, M.L.; Bodgi, L.; Pereira, S.; Sonzogni, L.; Forcheron, F.; Viau, M.; et al. Influence of Nucleoshuttling of the ATM Protein in the Healthy Tissues Response to Radiation Therapy: Toward a Molecular Classification of Human Radiosensitivity. Int. J. Radiat. Oncol. 2016, 94, 450–460.
13. Foray, N.; Bourguignon, M. Comment on ‘Considerations on the use of the terms radiosensitivity and radiosusceptibility’ by Wojcik et al. J. Radiol. Prot. 2019, 39, 309–313.
14. Le, A.N.; Harton, J.; Desai, H.; Powers, J.; Zelley, K.; Bradbury, A.R.; Nathanson, K.L.; Shah, P.D.; Doucette, A.; Freedman, G.M.; et al. Frequency of radiation-induced malignancies post-adjuvant radiotherapy for breast cancer in patients with Li-Fraumeni syndrome. Breast Cancer Res. Treat. 2020, 181, 181–188.
15. Amirifar, P.; Ranjouri, M.R.; Lavin, M.; Abolhassani, H.; Yazdani, R.; Aghamohammadi, A. Ataxia-telangiectasia: Epidemiology, Pathogenesis, Clinical Phenotype, Diagnosis, Prognosis and Management. Expert Rev. Clin. Immunol. 2020, 16, 859–871.
16. Schoenaker, M.; Suarez, F.; Szczepanski, T.; Mahlaoui, N.; Loeffen, J. Treatment of acute leukemia in children with ataxia telangiectasia (A–T). Eur. J. Med. Genet. 2016, 59, 641–646.
17. Vessoni, A.T.; Guerra, C.C.C.; Kajitani, G.S.; Nascimento, L.L.S.; Garcia, C.C.M. Cockayne Syndrome: The many challenges and approaches to understand a multifaceted disease. Genet. Mol. Biol. 2020, 43 (Suppl. S1), e20190085.
18. Lehmann, A.R. DNA repair-deficient diseases, xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy. Biochimie 2003, 85, 1101–1111.
19. Larizza, L.; Roversi, G.; Volpi, L. Rothmund-Thomson syndrome. Orphanet J. Rare Dis. 2010, 5, 1–16.
20. Halliday, D.; Parry, A.; Evans, D.G. Neurofibromatosis type 2 and related disorders. Curr. Opin. Oncol. 2019, 31, 562–567.
21. Pavlopoulou, A.; Bagos, P.G.; Koutsandrea, V.; Georgakilas, A.G. Molecular determinants of radiosensitivity in normal and tumor tissue: A bioinformatic approach. Cancer Lett. 2017, 403, 37–47.
22. Joubert, A.; Zimmerman, K.M.; Bencokova, Z.; Gastaldo, J.; Rénier, W.; Chavaudra, N.; Favaudon, V.; Arlett, C.F.; Foray, N. DNA double-strand break repair defects in syndromes associated with acute radiation response: At least two different assays to predict intrinsic radiosensitivity? Int. J. Radiat. Biol. 2008, 84, 107–125.