New cell nucleus geometry for modelling the radiation-induced DNA damage topology

Yann Thibaut, Carmen Villagrasa, S. Incerti, Yann Perrot

New cell nucleus geometry for modelling the radiation-induced DNA damage topology.

THIBAUT Y.*[1], VILLAGRASA C.[1], INCERTI S.[2] and PERROT Y.[1]

[1]*Institut de Radioprotection et de Sûreté Nucléaire (IRSN), PSE-SANTÉ, SDOS, LDRI, Fontenay-aux-Roses, 92262, France.*
[2]*Centre National de la Recherche Scientifique (CNRS), IN2P3, CENBG, UMR 5797, F-33170 Gradignan, France.*

Introduction

Research dealing with a better understanding of the origin and mechanisms behind deleterious effects of radiation therapies on healthy tissues is a crucial topic in radiation protection. For a large part, these side effects result from damage to the nucleus DNA molecule of healthy cells exposed to ionizing radiation during treatment [1]. In order to better describe the molecular mechanisms underlying these undesirable effects, our laboratory is developing a simulation chain to calculate early radiation-induced damage to DNA for different beam qualities [2]. Studies at this scale require a nanodosimetric description of energy deposits, enabled by the Geant4-DNA Monte-Carlo toolkit [3,4,5,6], coupled to DNA geometrical models with molecular resolution. The current version of this simulation chain allows a realistic modeling of the topology of DNA damage (number of DSBs, their complexity, their spatial distribution) at the cellular level for different beam qualities [7,8,9]. Up to now, the geometries of the cell genome used in the simulation take into account chromatin compaction by implementing 52% euchromatin and 48% heterochromatin, distributed randomly along the genome which makes it possible to account for experimental observations [9]. In order to improve the quality of these DNA damage results, we present a more realistic nucleus geometric model. The DNA damage results obtained for a cell using the new geometric isochore model are compared with those obtained previously with a random distribution of chromatin compaction respecting the same overall heterochromatin/euchromatin ratio.

Materials & Methods

The new geometric model is based on the isochore biological model [10,11,12] carrying out a mapping of the genome, by segmenting it into portions of 1 Mbp in our application. Each of these segments is then classified into one of five isochore families (L1, L2, H1, H2, and H3) based on the ratio of CG base pairs it contains and related to different degrees of chromatin fiber compaction [13]. The families that constitute the genome core are the most decondensed, specifically H2 and H3. Therefore, L1, L2 and H1 families compose the genomic desert. To evaluate the influence of these new geometric models on the topology of radiation-induced DNA damage, simulations are performed for perpendicular irradiations of protons ranging from 500 keV to 10 MeV, i.e. for LET ranging from 4.3 keV.μm^{-1} to 43.2 keV.μm^{-1}.

Results

The comparison of nanodosimetric calculation on both geometries indicates that the mean number of DSBs/event/Gbp is increased of 3-10% in the isochore nucleus. The location of the damages, as shown in Figure 1, allows to understand the different mechanisms responsible for this increase.

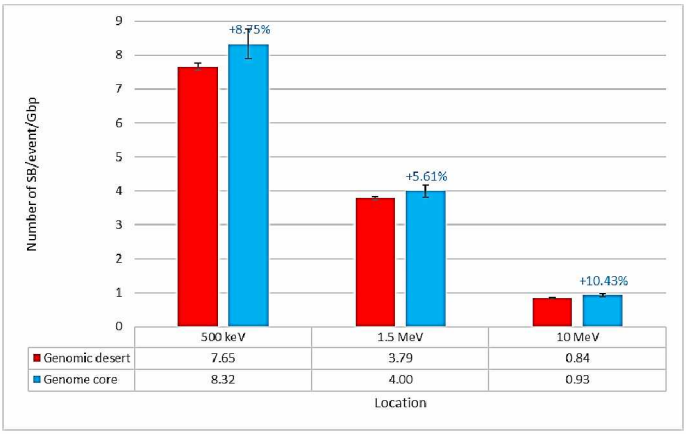

Figure 1: *Strand Break yield in the isochore nucleus respecting their location: genomic desert or genome core.*

Discussion & Conclusions

As a conclusion, chromatin compaction distribution of DNA fiber based on the theory of the isochores increases the mean number of DSB/event calculated, but remains in agreement with previous geometries already validated. This increase is particularly observed in the highly decondensed regions (genome core), more sensitive to indirect damage. However, a moderate increase in damage is also observed in the most condensed regions (genomic desert), due to the higher reaction rate of the excess adenine base present in these regions. From a biological point of view, this model also allows to simulate the higher radiation sensitivity of the genome core in comparison with the genomic desert. This information is fundamental because the genome core is transcriptionally active.

References

[1] Dasu A. and Toma-Dasu I. *Phys. Med.* (2017), DOI: 10.1016/j.ejmp.2017.02.015.
[2] Meylan S. et al. *Comput. Phys. Commun.* (2016), DOI: 10.1016/j.cpc.2016.02.019.
[3] Incerti S. et al. *Med. Phys.* (2018), DOI: 10.1002/mp.13048.
[4] Bernal M.A. et al. Phys. Med. (2015), DOI: 10.1016/j.ejmp.2015.10.087.
[5] Incerti S. et al. Med. Phys. (2010), DOI: 10.1118/1.3476457.
[6] Incerti S. et al. Int. J. Model. Simul. Sci. Comput. (2010), DOI: 10.1142/S1793962310000122.
[7] Meylan S. et al. Sci. Rep. (2017), DOI: 10.1038/s41598-017-11851-4.
[8] Tang N. et al. Med. Phys. (2019), DOI: 10.1002/mp.13405.
[9] Tang N. et al. Int. J. Mol. Sci. (2019), DOI: 10.3390/ijms20246204.
[10] Pačes J. et al. Gene (2004), DOI: 10.1016/j.gene.2004.02.041.
[11] Costantini M., et al. Genome Res. (2006), DOI: 10.1101/gr.4910606.
[12] Costantini M., Musto H. J. Mol. Evol. (2017), DOI: 10.1007/s00239-017-9785-9.
[13] Friedland W. and Kundrát P. Mutat. Res. Genet. Toxicol. Environ. Mutagen. (2013), DOI: 10.1016/j.mrgentox.2013.06.013.

*Corresponding Author: yann.thibaut@irsn.fr