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AT THE PHYSICS–BIOLOGY INTERFACE: THE NEUTRON AFFAIR

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We present predictions of neutron relative biological effectiveness (RBE) for cell irradiations with neutron beams at PTB-Braunschweig. A neutron RBE model is adopted to evaluate initial DNA damage induction given the neutron-induced charged particle field. RBE values are predicted for cell exposures to quasi-monoenergetic beams (0.56 MeV, 1.2 MeV) and to a broad energy distribution neutron field with dose-averaged energy of 5.75 MeV. Results are compared to what obtained with our RBE predictions for neutrons at similar energies, when a 30-cm sphere is irradiated in an isotropic neutron field. RBE values for experimental conditions are higher for the lowest neutron energies, because, as expected, target geometry determines the weight of the low-effectiveness photon component of the neutron dose. These results highlight the importance of characterizing neutron fields in terms of physical interactions, to fully understand neutron-induced biological effects, contributing to risk estimation and to the improvement of radiation protection standards.

INTRODUCTION

Biological effects induced by ionizing radiation can be ultimately traced back to energy depositions at the cellular and sub-cellular scale. This is obviously the case also when the biological target is exposed to uncharged particles such as photons or neutrons. Photons (below nucleon separation energies) cause only ionizations in the target molecules, liberating electrons which are responsible for subsequent interactions and energy depositions. On the other hand, neutrons can undergo a wealth of nuclear reactions in the target, giving rise to a rich mixed field of secondary charged species. The general framework of this work is the promotion of a clearer understanding of neutron biological effectiveness depending on the characteristics of the neutron-induced secondary particle field. It is important to bear in mind that no conclusive understanding of radiobiological results, as well as no reliable information for radiation protection or risk estimate purposes, can be achieved if such fields are not fully characterized at the point of interest. To this aim, the model presented by Baiocco *et al.*[1] for deriving neutron relative biological effectiveness (RBE) combining radiation transport and track structure approaches is applied in this work to experimental neutron fields used for stem cell irradiations. This was the focus of the EU FP7 project ANDANTE[2], which investigated neutrons as a by-product in particle therapy and their possible role in increasing the risk of second primary cancers occurring in low dose regions outside the target volume, especially for pediatric patients. In the following, a brief description of the adopted neutron RBE model is given, the characteristics of three different neutron fields used for irradiations in the framework of the project are summarized, and corresponding predictions for neutron effectiveness based on initial DNA damage induction are presented and discussed.

MATERIAL AND METHODS

The neutron RBE model

The neutron RBE model adopted in this work is discussed in detail in Baiocco *et al.*[1]. The model consists of the following steps:

(a) Transport calculations with the code PHITS[3] are used to characterize the secondary charged-particle field induced by neutron interactions in the region of interest. Two main pieces of information are extracted for each of the species accelerated or produced by neutron reactions, namely: (1) the relative contribution to the total neutron dose and (2) an average indicator of energy deposition pattern and its clustering properties, as the dose-averaged linear energy transfer (LET) or the dose-mean lineal energy, $\overline{y}_D$[4].
(b) The code PARTRAC[5] is used to calculate chosen DNA damage endpoints per Gy per cell induced by different charged particles as a function of their linear energy transfer, averaged in

the nuclear compartment of the cellular model implemented in the code.

(c) Based on results obtained in (b), a DNA damage yield per unit dose is associated with each of the secondary species produced by neutrons, at an LET averaged over the cell nucleus being equal to the dose-averaged LET derived in (a) from transport calculations. The damage induced by secondary species is then weighted by their relative contribution to the total neutron dose, as also derived in (a). The weighted sum of damages induced by all species in the neutron-induced charged-particle field gives the neutron-induced DNA damage.

(d) The expected DNA damage yield per cell per Gy following irradiation with a reference photon field is obtained directly from PARTRAC calculations.

(e) The neutron RBE is finally given by the ratio of neutron- (c) to photon- (d) induced yields of DNA damage, assuming that the chosen damage endpoint is proportional to the absorbed dose.

In Baiocco *et al.*[1], neutron RBE values based on the induction of DSB clusters (i.e. DNA damage sites with a minimum of two double strand breaks within a genomic distance shorter than 25 bp) were calculated as a function of neutron energies in the range 10 eV–1 GeV. Different locations were considered in a 'human-sized receptor', a 30 cm diameter tissue sphere, positioned in an isotropic monoenergetic neutron field. Results for the outer scoring region (at 1.5 cm depth in the phantom) are found to depend on neutron energy in a way consistent with radiobiological datasets used to establish radiation protection standards. In particular, the derived neutron RBE values are in good qualitative agreement with radiation weighting factors w_R given in ICRP103[6] and with quality factors given by U.S. NRC[7]. The *ab-initio* derivation explains the reported dependence on neutron energy by tracing it back to initial physical interactions.

Neutron fields at PTB

In this work, the neutron RBE model is applied to well-characterized neutron fields used for cell irradiations in the framework of ANDANTE[2]. Selected neutron fields were produced at PTB—Physikalisch-Technische Bundesanstalt (Braunschweig, Germany), by:

- (p,n) reactions on thin metallic ^{nat}Li targets, providing quasi-monoenergetic neutrons of 0.56 MeV, with a dose-averaged energy in the cell volume of $<E_n>$ = 0.52 MeV;
- (p,n) reactions on a thin (T)Ti target, yielding quasi-monoenergetic neutrons of 1.2 MeV, with a dose-averaged energy in the cell volume of $<E_n>$ = 1.13 MeV; and
- (d,n) reactions of a 13 MeV d beam on a thick ^{9}Be target, producing neutrons with a broad energy spectrum (up to 18.5 MeV) and a dose-averaged energy in the cell volume of $<E_n>$ = 5.75 MeV.

For all irradiations, cells were irradiated in suspension, in cylindrical PMMA containers (1 ml volume, 3 mm thick, 20 mm diameter). Containers were positioned to ensure a homogeneous exposure of the cell volume depending on the width of the neutron field, and they were kept rotating during the irradiations, thanks to different *ad-hoc* designed motor-driven systems, to avoid deposition of cells on the bottom. Full details of the experimental setup, including information on dosimetry, is given elsewhere[8, 9]. A software replica of each setup was obtained with PHITS[3], including beamline geometry, cell containers and their support system with realistic material compositions. For all neutron sources, known energy and angular distributions[10, 11] were directly implemented in the calculations. Parameters needed as input to the previously introduced neutron RBE model were calculated from the simulations, as discussed in the following. As a reference photon field, the spectrum of X-rays generated by a Xstrahl-200 machine has been used (220 kV field, 2 mm Cu filter)[2].

The neutron RBE model applied to experimental neutron fields

In each setup, the region of interest was defined as the cellular volume in a cell container; liquid water was used as surrogate for biological material. For electrons, protons, deuterons, alpha particles and carbon, nitrogen and oxygen ions delivering dose to the samples, we calculated with PHITS the relative contribution to the total neutron dose and the dose-averaged LET. It is important to recall that the photon component of the neutron dose (i.e. photons generated by neutron interactions) is scored in terms of dose delivered by charged particles (electrons) liberated by photons. As the neutron source is directly implemented in the simulations, the photon component generated by primary beam interactions on target is not included. However, this does not significantly impact RBE predictions with our model, as this latter photon component of the total dose is small (2.5% for the $<E_n>$ = 5.75 MeV, and lower for the quasi-monoenergetic beams), and has a low biological effectiveness. Once relative dose contributions and dose-averaged LET are calculated for all species (step (a) in the RBE model description), we resort to PARTRAC predictions for the yield of DSB clusters associated to charged particles of the same LET (step (b)) and then we go through steps (c)–(e) for the calculation of RBE.

RESULTS AND DISCUSSION

In Figure 1 we show the yield of neutron-induced DSB clusters per Gy per cell as calculated with our RBE model for the three neutron fields. In the histogram, also the contributions to the damage yield from diverse secondary charged species are shown. For the two quasi-monoenergetic neutron fields, neutrons deliver dose to the samples only via recoil protons and O ions: neutrons do not have enough energy to induce any reaction producing other charged products, and the amount of material on their path is too low to moderate them to lower energies, for which capture reactions (e.g. on hydrogen) would become important. As a consequence, only proton- and oxygen-induced DNA damages contribute to the total damage yield. For neutrons with higher energy, more reaction channels on ^{16}O targets open, and alpha particles and carbon fragments can be produced. Also in this latter case, the photon component of the neutron dose is negligible. Besides protons, also alpha particles and O, C ions contribute to the neutron-induced damage.

In Figure 2 we show RBE values obtained with our model as a function of dose-averaged neutron energy in cell irradiation setups. The present results are compared with energy-dependent neutron RBE values from Baiocco *et al.*[1] and current radiation protection standards from ICRP103[6] and U.S. NRC[7]. Error bars on RBE values come from propagation of statistical uncertainties on DSB cluster yields entering RBE calculation, which in turn come from, e.g. statistical uncertainties on doses of neutron-induced secondary species, given by PHITS; deviations among different PARTRAC runs for damage yield and dose to the nucleus. When comparing new RBE results for cell irradiation setups to RBE predictions from Baiocco *et al.*[1] for "human-sized" 30 cm sphere, it is important to underline that a higher effectiveness is found for experimental setups with the lowest neutron energies. This is mainly due to the differences in the geometry of the irradiated target, which plays a fundamental role in determining neutron biological impact: RBE values were obtained in Baiocco *et al.*[1] for exposing a spherical phantom of 30 cm diameter to an isotropic neutron field. Due to the large size of the receptor, the dominant contribution to the total neutron dose is given by photons for neutron energies up to ~1.5 MeV (rapidly decreasing from ~90 to 30% in the range E_n = 0.1–2 MeV). Neutrons are either directly captured for the lowest energies or have the chance to be first moderated and then undergo (n,γ) reactions. In cell irradiation conditions for the two selected energies for quasi-monoenergetic beams, the photon component of the total neutron dose is basically absent, as the amount of material placed before the cells and the volume of the samples themselves are too small to allow for neutron moderation. On the contrary, RBE

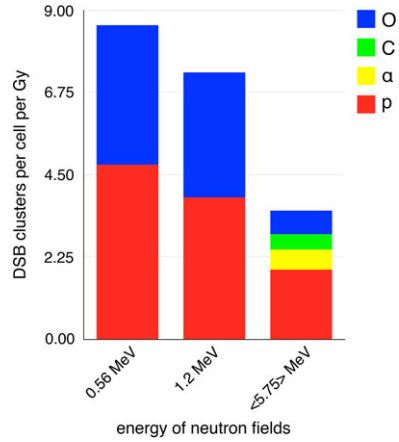

Figure 1. Yield of neutron-induced DSB clusters per Gy per cell as predicted by the neutron RBE model adopted in this work for the three experimental neutron fields. For each case, also the contribution of different secondary species to the total damage is shown.

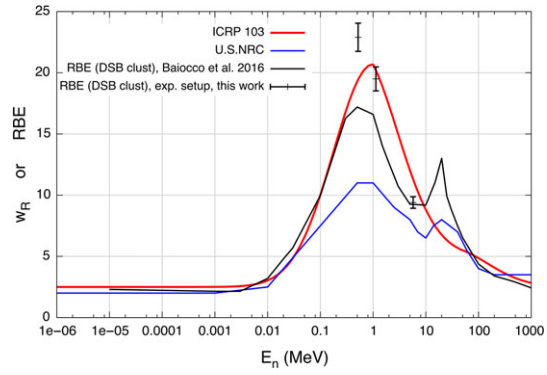

Figure 2. Predicted neutron RBE values (points) in experimental conditions as a function of the average neutron energy of the three neutron fields. RBE values obtained with the same model for a 30-cm-sized receptor in Baiocco *et al.*[1] are also shown (black line), together with current radiation protection standards given in ICRP103 (red) and U.S. NRC (blue). Details of the comparison are provided in the text.

predictions for the broader spectrum with $<E_n>$ = 5.75 MeV do not differ from RBE values for the 30 cm receptor exposed to neutrons of similar energies, as at higher energies the photon component of the neutron dose is much lower and does not contribute significantly to neutron effectiveness.

CONCLUSIONS

In this work, we report on predictions of neutron RBE for cell irradiations in three neutron fields of

different energies at PTB, performed in the framework of the ANDANTE[2] project. Predictions are obtained by applying a recently developed *ab-initio* neutron RBE model based on complex DNA damage induction[1]. Experimental neutron fields are: two quasi-monoenergetic neutron beams with energies of 0.56 and 1.2 MeV, and a neutron field with a broad energy distribution with a dose-averaged energy in the cell volume of $<E_n> = 5.75$ MeV. In particular, the two quasi-monoenergetic neutron fields were chosen to explore the region of maximal neutron effectiveness, as expected from RBE data in the literature and as reflected in radiation protection standards[6, 7]. For the purpose of this work, a complete software replica of the experimental cell irradiation setups is obtained with the code PHITS[3], and parameters characterizing the neutron-induced secondary charged-particle fields needed as input for the neutron RBE model are extracted. For each setup, we report the expected yield of initial DNA DSB clusters per cell per Gy and we discuss which secondary species are contributing to the damage, mainly depending on neutron energy and on the interplay of different neutron-induced nuclear reactions. We then present RBE predictions for experimental cell irradiations, and compare them with RBE values obtained with the same model, but for irradiations of a "human-sized receptor" (a 30 cm diameter spherical tissue phantom) in an isotropic field of neutrons with similar energies. At equal energy, RBE values are found to be higher for the quasi-monoenergetic beamlines in cell irradiation conditions, and this can be attributed to the role played by the target geometry in determining the importance of the photon component of the neutron dose for lower-energy neutrons. The small amount of material in the cell experiments and the small size of irradiated samples result in a photon component of the neutron dose which is practically negligible, hence, the dose is entirely delivered by recoiling charged particles such as protons and oxygen ions, with a higher biological effectiveness. On the contrary, when a large receptor is exposed, neutrons are moderated down to energies for which ^{1}H(n,γ) capture reactions become dominant. Considerations of this kind have already been at the basis of the reevaluation of neutron w_R from ICRP Publication 60[12] to Publication 92[13]. RBE values obtained with the same model for the large receptor have been shown to be in qualitative agreement with radiation protection standards in terms of their dependence on neutron energy[1], even though differing in absolute values both from w_R factors given in ICRP103[6] and quality factors given in U.S.NRC[7]. Our findings confirm that extreme caution is needed when measuring new data on neutron relative radiobiological effectiveness for the purpose of improving knowledge on risk estimation and better establishing radiation protection standards. Experimental constraints in the choice of the neutron fields and the use of setups dedicated to the specific purpose of the study might render the interpretation of old and new results very difficult, if not accompanied by a full characterization of the neutron-induced secondary particle field at the point of interest. Experimental results from radiobiological measurements for the same setups are reported elsewhere[8, 9], and the analysis for benchmarking of model predictions is in progress.

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