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Editorial

Effects of ionizing radiation in biomolecules, cells and tissue/organs: basic mechanisms and applications for cancer therapy, medical imaging and radiation protection

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1. Basic mechanisms

Soon after the discovery of X-rays in 1895, ionizing radiation started being used in medicine, both as a diagnostic tool and as a therapeutic agent. However, it was only after some decades that the mechanisms underlying the action of ionizing radiation in cells and tissues/organs started being investigated and, at least partially, understood. Ionizing radiation is also used in some industrial activities that, in addition to some environmental exposure scenarios (e.g., radon), raise radiation protection issues. It is therefore of crucial importance that the scientific community continuously updates and improves the knowledge about the action mechanisms of ionizing radiation and its effects, as well as its applications in different fields including medicine and industry.

It is well known that radiation damage to the DNA double helix plays a pivotal role in the subsequent production of damage at different levels, including chromosomes, cells, tissue/organs and even the whole organism [1]. The initial DNA damage, mainly consisting of single-strand breaks (SSBs), double-strand breaks (DSBs) and base damage, can be induced either by direct energy deposition in the DNA constituents or indirectly, by production of free radicals that diffuse and chemically interact with the double helix. While base damage and SSBs in general do not imply important consequences for the fate of the cell, DSBs, especially the complex ones (that is, associated to other damage types) can lead to the production of chromosome aberrations, consisting in large-scale genome

rearrangements mainly occurring following "Non-Homologous End Joining" (NHEJ) [e.g. 2]. The latter is a repair pathway that plays an important role in the G0/G1 phase of the cell cycle, and is known to be rapid but error-prone, leading to the rejoining of chromatin fragments belonging to different chromosomes, or different regions of a given chromosome. Some aberration types (typically, dicentric chromosomes) have a high probability of leading to cell death [e.g. 3]; on the contrary others, such as reciprocal translocations, do not prevent cell replication thus allowing the transmission of altered DNA sequences to the cell progeny, which in turn can lead to cell neoplastic transformation and, after several years of latency, even cancer. Indeed, several tumour types are associated to aberrations involving specific genes located in specific chromosomes; for instance, most Chronic Myeloid Leukemia cells carry a translocation involving the ABL1 gene in chromosome #9 and the BCR gene in chromosome #22, leading to the production of a fusion gene that encodes for an oncogene [e.g. 4,5].

Although the DNA double helix is widely recognized as the main radiation target, other targets do exist, which are involved e.g. in the so-called bystander effects, consisting of the induction of damage in cells that are not traversed by radiation, but are located close to traversed cells [e.g. 6]. The mechanisms underlying these effects, which may play a non-negligible role at low doses, have not been clarified yet; however, it is widely recognized that cellular communication via molecular signalling does play a role.

2. Medical applications and radiation protection

Concerning medical applications, ionizing radiation is widely used for imaging, including conventional radiography, computed tomography, PET (positron emission tomography) and SPECT (single-photon emission tomography). Furthermore, high-energy X-rays are routinely used for cancer treatment, either alone, or in association with surgery and/or chemotherapy.

More recently, also charged particles started being used for hadrontherapy cancer treatments. Currently, about 300,000 patients have been treated worldwide, and more than 100 hadrontherapy centres are operating [7]. Most treatments have been performed with protons, for which the dose falls to zero beyond the Bragg peak. This makes such particles particularly suitable for treating those tumours that are located just before organs at risk, or, more generally, for all those cases where particular attention must be devoted to spare the healthy tissues, as is the case of paediatric tumours.

A number of patients have been treated with Carbon ions, which are characterized by a higher Relative Biological Effectiveness (RBE) with respect to both photons and protons and thus represent a good strategy for the so-called radio-resistant tumours, which do not respond well to treatment with photons or even protons, for which a constant RBE of 1.1 is assumed in clinical practice. On this subject, it is worth mentioning that, when using heavy ions like Carbon, the RBE variation along the beam must be evaluated as accurately as possible, ideally at the single-voxel level, especially when active beam scanning is used. For this reason, *in vitro* and *in vivo* experiments must be integrated by biophysical models and simulation codes. At the moment, only two models are used in clinics, that is the Local Effect Model (LEM) [e.g. 8] in Europe and Shanghai, and the Microdosimetric Kinetic Model [e.g. 9] in Japan. However, other models are available including BIANCA [10], which, interfaced to the FLUKA radiation transport code [e.g. 11] has shown to be suitable for modelling cell death and chromosome aberrations along hadrontherapy beams of protons, C-ions and He-ions [12–17].

Hadrontherapy is evolving quite rapidly; the most recent applications imply the use of particle therapy together with immunotherapy [18], as well as its possible application according to the so-called FLASH modality, that is at ultra-high dose-rate [19].

Humans are exposed to ionizing radiation for different reasons, including medical exposure for diagnostics or therapy, occupational exposure and environmental exposure. Unless in case of accidents, the involved doses are generally very low: to get an idea, the annual effective dose limits are 1 mSv/year for the public, and 20 mSv/year for exposed workers. The radiation environment on Earth implies an average annual effective dose of about 3 mSv/year, also depending on the characteristics of the considered region. In space, astronauts are exposed to higher doses due to the lack of the protection provided by the atmosphere and the Geomagnetic field. For instance, the effective dose on the International Space Station is about 0.5 mSv/day, which becomes more that 1 mSv/day in case of a mission to the Moon or even to Mars [e.g. 20,21]. On this subject, it is worth mentioning that in these scenarios the physical dose is not sufficient to estimate the effects, since it is delivered by mixed radiation fields that can also contain high-LET components including heavy ions like Iron [22]. In these cases, it is useful that physical dosimetry is integrated by biological dosimetry; one of the most reliable techniques consists of counting dicentric chromosomes in peripheral blood lymphocytes, since lymphocyte dicentrics are considered as indicators of normal tissue damage [e.g. 23–25]. Lymphocyte dicentrics are also useful to estimate the dose in case of accidents or, more generally, when the physical dose is not known or is affected by large uncertainties. The frequency of CAs in peripheral blood lymphocytes was used to evaluate the radiation exposure in survivors of the Hiroshima and Nagasaki A-bombs [26,27] and in victims of radiation accidents including Chernobyl [28], as well as for astronauts involved in space missions [e.g. 29] and cancer patients following radiotherapy [30].

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