Radiobiological effects of pulsed, high dose-rate particle beams generated by high-power lasers

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(Received 6 September, 2018; accepted 31 October 2018)

Abstract

As intense laser sources are constructed around the world, various applications are developed. In the medical field it is foreseen to use laser-driven radiation for cancer diagnostic and radiotherapy. High-power lasers can generate pulsed high dose-rate radiation beams (protons, electrons, X-rays and gamma rays) *via* laser interactions with primary targets. Experiments have been carried out at various high-power laser research facilities in order to demonstrate the radiobiological effectiveness of laser-driven radiation. In this article, we review the results of a selection of cell irradiation experiments conducted using laser-generated radiation beams.

Keywords: particle radiotherapy, high-power lasers, radiobiological effectiveness, biomarkers, high dose-rate radiation

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INTRODUCTION

Intense and pulsed laser sources have been developed in the last several decades using chirped pulsed amplification (CPA) (1). At the same time, through laser-matter interactions, the acceleration of radiation beams with novel features was enabled, for example the fs- and ps-long particle bunches or broadband energy spectrum. These features have the potential to allow the development of more efficient solutions in cancer radiotherapy, and possibly in other applications like materials science and space applications. Many high-power laser systems are currently developed around the world, and the Extreme Light Infrastructure (ELI) network is among the most important facilities. The high-power laser system at ELI-NP (Extreme Light Infrastructure – Nuclear Physics) is scheduled to deliver beam lines with laser power in the range of 0.1-10 PW. These lasers generate high-intensity radiation, and their output can be focused on primary solid, liquid or gaseous targets to obtain pulsed, high-dose rate beams (protons, electrons, X-rays and gamma rays) *via* laser-matter interactions. Highly monoenergetic, controllable and stable proton and carbon ion beams have to be obtained in order to be used in medical physics research and further translated to the clinic. Moreover, coherent high-intensity X-ray sources would allow high-resolution imaging for cancer diagnostics (2). The high dose-rate beams obtained by high-power lasers have the potential to be used in radiotherapy, and recent studies show that the delivery of high dose-rates in radiotherapy has a sparing effect on healthy tissue (3, 4) although the variations in the energy output will have to be minimized for a well-defined and controlled treatment.

High-power lasers could also generate radiation fields similar to those within the solar system, including the characteristic broadband energy spectra, through the interaction with solid or gaseous targets (5). Radiobiology experiments involving cells and tissues reveal potential biologic effects of ionizing radiation using dedicated tests at cellular (viability, proliferation, oxidative stress) and molecular level (gene expression) through specific biomarkers (small molecules like glutathione correlate with the level of free radicals, enzymes like superoxide dismutase and catalase are elicited to quench reactive molecules). While the total dose delivered to the sample can be adjusted to a desired value, relevant for space radiation, there is a significant difference between the dose rate of space radiation (mGy/day) (6) and the dose rate of radiation obtained in a ground-based laboratory with high-power lasers (mGy/ps). Thus, high-power lasers can accelerate ultrashort, pulsed ion beams with broadband energy spectrum, which

is a better reproduction of space radiation in laboratory than classically accelerated particle beams at a fixed energy value, but their high dose-rate effects have to be accounted for and quantified, for a better understanding of the biologic impact of ionizing radiation in various settings, aiming at improving radioprotection tools in deep space flights. As these applications of high power lasers are emerging, we review in this article a selection of relevant cell irradiation experiments using laser-driven radiation.

LASER-DRIVEN RADIATION AND RADIOBIOLOGICAL STUDIES

Several research groups reported in the literature cell irradiation experiments using conventional and laser-generated radiation (particularly proton beams) in pulsed beams. In one of the seminal studies, the J-KAREN laser at the Kansai Photon Science (7) delivered protons in a 0.8–2.4 MeV energy range. In cell irradiation experiments an integrated proton dose of 20 Gy was delivered using up to 200 proton bunches (15 ns per proton bunch per laser pulse). At the cell site, the proton irradiation level was estimated to be about 10^3 ns^{-1} mm^{-1}.

The relative biological effectiveness (RBE) was studied, with RBE = D_{10}(x-rays)/D_{10}(p), where D_{10} is the dose necessary for cell damage up to 10% survival. Laser-driven protons from a 20 TW source, yielding bunches of 20 ns (8) with a maximum energy up to 4.3 MeV, all protons bellow 1 MeV being removed from the beam, were shown to have an RBE of 1.47 ± 0.48 at a dose of 1 Gy. On the other hand protons of similar energy (1-3.7 MeV) generated by a conventional accelerator with similar dose rates applied in this case continuously (9) delivered an RBE between 1.25 and 1.91 depending on the incident energy. This shows that the effect on directly impacted cells is similar for laser-driven and classically accelerated protons. However, the toxicity mediated by reactive oxygen species (ROS) to neighbouring cells and tissue can be different.

Generally, in most radiobiology studies comparing the effects of laser-driven radiation with classical radiation, the RBE was found to be fairly independent of the dose rates (8), (10). Various biological endpoints were evaluated for the irradiated cells, and molecular markers indicate an increase in reactive molecular species with classical irradiation when compared to laser-based cell irradiation (11). The reactive molecule concentration has consequences in terms of toxicity to the irradiated cell and also to neighbouring cells. Enhanced radiation efficiency for killing cancer cells whilst sparing surrounding healthy tissue can be attained by real-time

observation of radiation effects using molecular metabolic biomarkers in-cells and *in vivo* (see Fig. 1), as shown by hyperpolarised MRI imaging studies (12).

Kraft *et al*. demonstrated, using laser-accelerated protons in Dresden at the 100 TW Draco source featuring 100 fs laser pulses, that the biological damage is dose-dependent (13). In this experiment only protons with energies larger than 6 MeV were allowed to reach the irradiation site in order to exclude the protons that are absorbed in the cell monolayer and measure the absolute irradiation doses. The irradiations were performed on the radiosensitive squamous cell carcinoma (SCC) cell line SKX, grown on a thin biofilm (50 μm thick) at doses of 1.5 Gy, 2.7 Gy and 4.1 Gy. Double-strand breaks (DBS) were counted using fluorescence microscopy, which showed an increase in the number of DBS with an increase in the delivered doses.

On the other hand, DNA double-strand breaks in cells irradiated by conventionally-accelerated protons using a TANDEM source were assessed by Zlobinskaya *et al.* at the Technical University of Munich (14). The protons were transmitted through a vacuum sealing window, 7.5-μm made of polyimide foil (Kapton foil), then through an air gap of approximately 30 μm and the cell carrier, a 6 μm Mylar foil. Cells (HeLa type) were irradiated with doses of 1 Gy or 5 Gy using a proton beam (of an energy of 20 MeV), either in a continuous mode (100 ms) or with a single pulse of 1 ns. The cumulative energy loss of 20 MeV protons until they reached the target cells was 0.11 MeV. Irradiation effects were measured after 1 h for a 1 Gy exposure and after 24 hrs for a 5 Gy exposure. RBE values for 1 Gy exposures were 0.97 ± 0.19 for pulsed and 1.13 ± 0.21 for continuous irradiations in a first experiment, and 1.13 ± 0.09 and 1.16 ± 0.09 respectively in the second experiment. In the case of 5 Gy exposures, the RBE values were 0.99 ± 0.29 for pulsed and 0.91 ± 0.23 for continuous irradiations. The doses found to be effective using protons, either in a continuous mode or a single pulse irradiation, are therefore similar within experimental errors.

At the 28 TW TARANIS laser at the Queen's University Belfast (15) the effect of proton irradiation at MeV-range energies on cells has been investigated at doses in the range of 0.8 -5 Gy per shot, with delivered dose rates exceeding 10^9 Gy/s at a single exposure. The protons were emitted at energies between 1-3 MeV. However, due to the absorption in the Mylar window (50 μm thickness) the protons exiting the vacuum chamber had energies higher than 2 MeV. The experimental setup also included an aperture slit (500 μm wide), located 10 mm behind the 10

μm Al target on which the laser was focused, and a dipole magnet (100 mm long) of a maximum field strength of 0.9 T was placed behind the slit (10 mm away) such to disperse the protons according to their energies, prior to the cell irradiation. Customised Gafchromic EBT2 films were used for an experimental characterization of the proton spectrum at the cell location (1 cm from the Mylar window) (15). The linear energy transfer value of the laser-accelerated protons (with energy larger than 2 MeV) was between 10 and 30 keV/μm while the relative biological effectiveness of protons accelerated using laser pulses (of 700 nm wavelength) at these energies was found to be in the range of that obtained for conventionally-accelerated protons (9]) Therefore, this indicates that the ultrashort pulses can be used in fast radiotherapy of moving organs (16, 17).

Ions heavier than protons are known to have a stronger biological effect and their acceleration with high power lasers adds the high dose rate feature. However, considerable ion energy is required to make the beams suitable for radiotherapy. Thus, C^{6+} ions were accelerated at the Los Alamos National Laboratory Trident laser facility (18) which produces a 550 fs, 80 J pulse at 1.053 μm. The ion fluxes were measured using a dedicated spectrometer (iWASP) (19). Thin, free-standing, artificially grown diamond foils with thicknesses from 30 nm to 5 μm were used to generate ion beams and CR39 films were used to detect carbon ions above 33 MeV. A standard BAS-TR image plate (IP) was used for ions with energies higher than 200 MeV.

Using accelerated electrons in sub-ns bunches, produced using the Jena titanium:sapphire laser system (JETI), with 10 TW power and 80 fs repetition rates, Beyreuther and collaborators (10) have obtained doses of up to 4 Gy for irradiating cells with multiple pulses, using up to 2000 pulses. The electrons travelled through air over an optimized distance between the vacuum chamber and the cell sample of 220 mm. The detection of radiation doses was performed using a Roos ionization chamber, a Faraday cup, and EBT-1dosimetry films. Oppelt and colleagues (20) also compared the effectiveness of laser-accelerated electrons at the 10-TW laser system JETI, with that of conventionally-accelerated electrons. It was found that there was no significant difference in the radiation-induced tumour growth delay in human squamous cell carcinoma (FaDu) cells for the two investigated electron beams. Thus, the study showed that the ultra-high dose rates generated by laser acceleration of particle beams did not impact their biological effectiveness.

CONCLUDING REMARKS

The field of radiobiology using high-power laser-driven radiation is developing. Such studies will be fully relevant for radiotherapy and other biomedical applications once high-energy beams including proton bunches are created, as it is expected at ELI-NP, where protons with energies $E_p > 200$ MeV are presumed to be produced. The radiation dose rates of laser-driven protons can be nine orders of magnitude higher than those obtained with classical accelerators. The radiobiological effectiveness of the laser-driven radiation sources is currently investigated in several laboratories on cells and in animal models. Biomolecular markers are under investigation for identifying those which can correctly reveal the effects of radiation on biologic structures. For instance, functional imaging *via* magnetic resonance of endogenous molecules that sense the presence of free radicals is a promising approach (12) for real-time monitoring of radiation effects both in-cells and *in vivo.*

Acknowledgements: The authors acknowledge support from the core project of the Romanian Ministry of Research, project PN 18 09 01 05/2018 and the Ministry of Research/UEFISCDI project number PN-III-P4-ID-PCE-2016-0887. This work has been supported by the Extreme Light Infrastructure Nuclear Physics (ELI-NP) Phase II, a project co-financed by the Romanian Government and the European Union through the European Regional Development Fund and the Competitiveness Operational Programme (1/07.07.2016, ID 1334).

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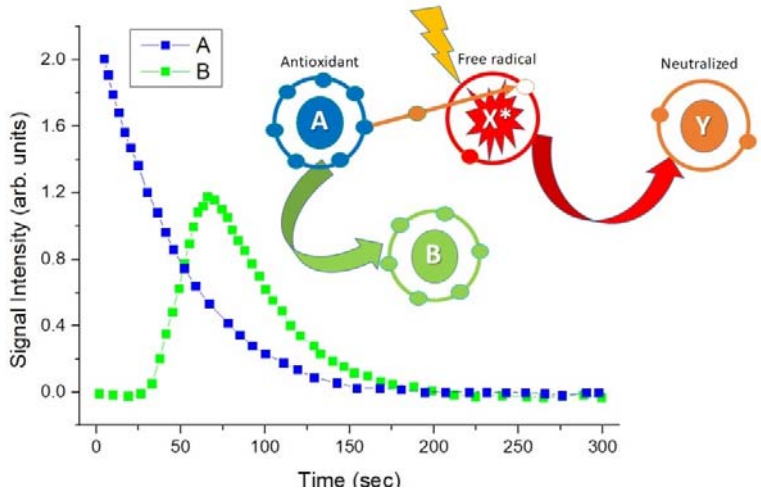

Fig. 1. Free radicals, reactive oxygen and nitrogen species (ROS, RNS) produced directly by radiation or generated by irradiated cells on a timescale of several hours can be detected by molecular imaging with biomarkers *in vivo* or in cells. The free-radical dependent enzymatic transformation of generic molecular markers (noted A and B) is exemplified in the figure. The optimal timing for applying radiation pulses corresponds to maximum levels of the emerging biomarker (B in this case) which offers improved detection sensitivity to kinetics compared to the disappearing biomarker (A in this case).