Volume 14, No 1 | International Journal of Radiation Research, January 2016

The biological effects induced by high-charged and energy particles and its application in cancer therapy

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► ***Mini review article***

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Revised: April 2015
Accepted: May 2015

Int. J. Radiat. Res., January 2016; 14(1): 1-7

DOI: 10.18869/acadpub.ijrr.14.1.1

ABSTRACT

The radiobiological effects of high atomic number and energy (HZE particles) ion beams are of interest for radioprotection in space and tumor radiotherapy. Space radiation mainly consists of heavy charged particles from protons to iron ions, which is distinct from common terrestrial forms of radiation. HZE particles pose a significant cancer risk to astronauts on prolonged space missions. With high delivered energies and intense ionization, HZE particles can damage not only the biological systems but also the shielding materials. HZE particles are more effective than low-LET radiation like γ- or X-rays to induce genetic mutation and cancer. On Earth, similar ions are being used for targeted cancer therapy due to the advantage of the inverse dose profile, with delivering higher doses to the tumor while keeping lower doses to the surrounding tissues. In this review, we focus on the recent insights into the biological effects caused by HZE particles and the corresponding mechanism. We also discuss the current application of HZE particle in cancer therapy. Understanding the mechanisms underlying the repair of DNA damage induced by HZE particles contribute to accurately estimate the risks to human health associated with HZE particle exposure and to improve the effectiveness of tumor radiotherapy.

Keywords: *HZE particles, space radiation, clustered DNA damage, radiotherapy.*

INTRODUCTION

Space radiation is considered to be one of the major hazards for manned space exploration. It is composed of high-energy protons and heavier charged particles, which is distinct from common terrestrial forms of radiation. Exposure to types of ionizing radiation encountered during space travel may cause a number of health-related problems. There are three major sources of space radiation: galactic cosmic rays (GCR), solar cosmic radiation (SCR) and geomagnetically trapped particles. GCR are mainly composed of 85 % protons, 14 % alpha particles and about 1 % heavier particles, such as iron ions [1-3]. SCR are episodic emissions of high-intensity radiation from the sun with energies much lower than those of GCR [3].

High-linear energy transfer (LET) radiation is composed of high-charge and energy (HZE) particles, which are a critical component of GCR [4-6]. Although HZE particles only account for less than 1% of the GCR particle fluxes, they contribute significantly to the severe biological effects due to their high atomic number, energy and intense ionization [5,7]. For a three-year mission, 3% of the cells of the human body would be traversed on average by one iron ion [8]. Therefore, heavy ions are considered as a major barrier to human space exploration.

Low LET X or γ-ray radiation treatment has been commonly used for radiotherapy due to its effective in tumor cell killing. However, there are issues associated with tumor recurring and lack of specific targeting delivery, thereby resulting in normal tissue damage and side effect. High

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[DOI: 10.18869/acadpub.ijrr.14.1.1]

LET and high-energy particles induced DNA lesions are difficult to repair and therefore are more efficiency in killing of tumor cells. Most important, the physical characterizations of the charged particles allow delivery higher dose and higher energy of particles at targeted tumor region [9]. Therefore, recently, high LET and high -energy particles, such as carbon ion beam has been used for radiotherapy with good efficacy [10].

The limited knowledge about the biological effects of, and the response to, space radiation has been considered the most important factor limiting the prediction of health risks associated with human space exploration[11]. In addition, the information are pertinent to radiotherapy, as particle therapy with energetic protons or heavy ions (e.g. carbon ions) is increasingly being used in cancer treatment [9,12,13]. Therefore, to understand the mechanisms that underlay the biological effects induced by HZE particle radiation is essential for space exploration and for radiotherapy.

The biological effects of HZE particle

The radiobiology of highly charged ions differs from the conventional radiobiology with photons because of the great local ionization density that is produced along a particle track. HZE particle radiation is believed to produce high yields of clustered DNA damage (figure 1A). Unlike the isolated DNA lesions induced by low-LET radiation such as X and γ-rays (figure 1 B) [14,15], the clustered DNA damage is a unique class of DNA lesions that includes two or more individual lesions within one or two helical turns of the DNA [14]. These lesions can be a basic sites, base damage (oxidized purines or pyrimidines), single-strand breaks (SSBs) and double-strand breaks (DSBs) [16,17]. It is well established that HZE particles have a higher (several to many fold greater) relative biological effectiveness (RBE) than X or γ-rays (sparsely ionizing radiation) [2, 18-23]. Cells exposed to high-LET irradiation exhibit increased relative biological effectiveness of death, chromosomal aberrations, mutagenesis and carcinogenesis [5,14,18,24,25].

Many evidence clearly demonstrated that complex DNA lesions are more difficult for the cellular machinery to repair than are individual damage sites [28-33]. With synthetic oligonucleotides containing several types of DNA damage, David-Cordonnier *et al.* demonstrated that the efficiency of incision of an AP site within a region of clustered DNA damage is significantly reduced by the presence of a second AP site or SSB [28]. Several studies also have shown APs or 8 -oxoguanine (8-OxoG) sites within clustered DNA damage sites are poorly handled by mammalian cell extracts or purified repair

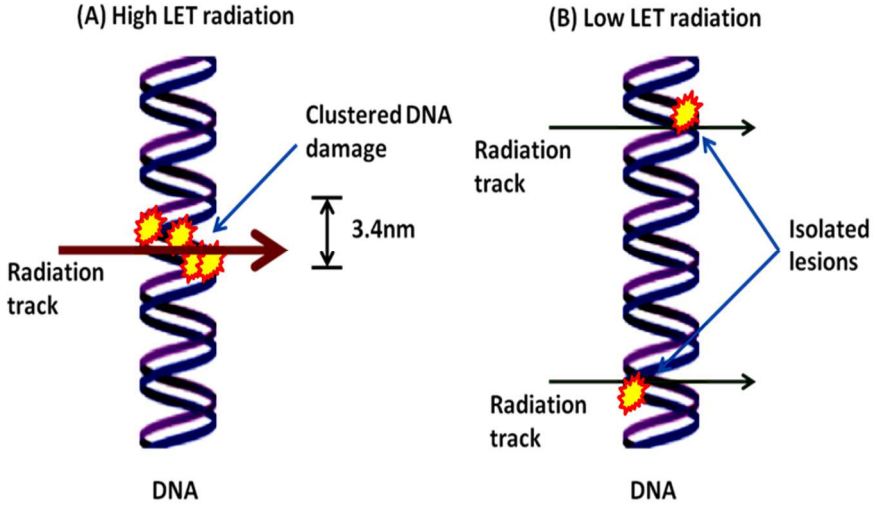

Figure 1. Production of DNA damage by ionizing radiation. (A) High LET radiation (densely ionizing radiation) induces a clustered DNA damage site which is defined as multiple lesions within a region of a few nm. (B) Low LET radiation (sparsely ionizing radiation) induces randomly isolated damage [26,27].

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enzymes [28-30]. Some types of clustered damage sites may lead to a lethal DSB during attempted repair of the site in E. coli and mammalian cells [31,34-37]. The spatial distribution of different types of lesions within the clustered DNA damage and the physical location of damage within nuclear subdomains (euchromatic or heterochromatic) might influence the cellular ability to repair complex DNA damage. Approaches based on molecular dynamics (MD) simulation have been applied to examine conformational changes and energetic properties of DNA molecules containing clustered damage sites with a basic or 8-OxoG, the results showed that DNA molecules containing a clustered damage site develops specific characteristic features: sharp bending at the lesioned site and weakening or complete loss of electrostatic interaction energy between 8-oxoG and bases located on the complementary strand [33]. These conformations may make it difficult for repair enzymes to bind to the region. It is also possible that a tight spatial distribution of various lesions within the clustered DNA damage makes certain lesions inaccessible to repair enzymes, thereby resulting in a reduction of repair capacity [5]. Recently, it has been suggested that non-DSBs clusters, if unrepaired, can lead to the formation of mutations and chromosome abnormalities[38].

The repair pathways of clustered DNA damage induced by HZE particle

The two basic groups of complex DNA damage induced by HZE particle are DSBs and non-DSBs. The correct repair of DSBs is essential for the viability and genomic integrity of a cell [39], however, the repair status of the clustered DSBs cannot be clearly explained by the current understanding of DSB repair pathways. The studies showed that clustered DSBs lesions induced by Fe particles are difficult to be repaired and resulting in elevated chromosome instability and enhanced cellular radiosensitivity [40,41]. The difficulty of repairing the clustered DSBs may due to the nature of the complex DNA damage induced by dense ionizations along the HZE particle track[19,22,42-45]. In mammalian cells, DNA DSBs are repaired mainly by two distinct pathways: nonhomologous end joining (NHEJ) and homologous recombination (HR). These two pathways have diverse substrate requirements, operate with different kinetics, and are used differently throughout the cell cycle [46]. In general, HR and NHEJ are viewed as competing pathways, but more recent evidences indicate that these two pathways collaborate to enhance overall DNA repair and safeguard genomic integrity [39,47,48]. Although evidence clearly indicates that NHEJ is the major repair pathway for low-LET radiation induced DSBs [49], it is not clear which pathways of DSB repair can handle clustered DNA lesions accurately. Recent reports indicated that RAD51-mediated DNA repair (HR) is needed for processing HZE-induced DNA damage [50,51]. Our study showed that Fanconi anemia pathway may coordinate with HR factor and play an important role in the high LET Fe ion radiation induced clustered DNA damage repair [52]. Also several nucleases Mre11, WRN and Artemis which are involved in various DNA repair processes might play crucial roles in processing complex DNA ends generated by HZE particles [53-55]. Although Mre11 and WRN can be recruited to the sites of DNA lesions in response to ion irradiation, the mechanisms underlying repair pathway choice and the precise role of proteins responsible for this process in response to clustered DNA lesions remain largely unclear. Future work is required to identify the multiprotein complexes that are involved in processing of complex DNA lesions.

The application of HZE particle radiation in cancer therapy

Radiotherapy using charged and/or high-LET particles has a long history, performed with proton for nearly 50 years and for nearly 30 years with heavy ions[56,57]. In 1954 particle therapy started at the Lawrence Berkeley National Laboratory (LBNL) with the first proton treatment.

The development for heavy ions treatment facilities is much slower than for protons due to the required accelerators are more expensive to build and the RBE problem had to be explored in its clinical aspects. The major pioneering work for heavy ions was done at LBNL between 1977

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and 1992, in which most patients were treated with helium and neon ions [57,58]. Full-scale clinical studies with carbon ion therapy were started in 1994 at the NIRS (National Institute of Radiological Sciences) in Chiba. In 1997, the GSI (Gesellschaft für Schwerionenforschung) in Darmstadt, Germany, started clinical trials with carbon, which terminated clinical application and was succeeded by Heidelberg Ion-Beam Therapy Center (HIT) in 2009 [59]. In 2001, the Hyogo Ion Beam Medical Center (HIBMC) was established in Japan as the first commercial heavy-ion radiotherapy facility with the support of NIRS [60]. The Institute of Modern Physics (IMP), Chinese Academy of Sciences, with the heavy ion accelerator complex—Heavy Ion Research Facility in Lanzhou, China, started carbon-ion therapy in 2006. The worldwide heavy-ion radiotherapy facilities are summarized in table 1. The number of the patients treated throughout the world is steadily increasing. Until 2011, almost 6000 patients have been treated by NIRS, 450 patients by GSI and more than 100 patients by IMP with extremely good results.

The main reason to use heavy charged particles in therapy instead of conventional photons is the inversed dose profile. The increase of energy deposition with penetration depth up to a sharp maximum at the end of the particle range, the Bragg peak, named after William Bragg, who measured an increase of ionization at the end of the range of alpha particles in air. In tumor therapy, high-energy protons and carbon ions exhibit an inverse dose profile, an increase of energy deposition with penetration depth. The key issue of radiation therapy is to effectively kill tumor cells while protect the normal tissue as far as possible. Heavy ion beam therapy has the potential ability to deliver higher doses to the tumor but less doses to the surrounding tissues. This allows a greater tumor dose for protons and carbon ions than for photons. In addition, for particles heavier than protons, i.e. in the region of carbon, the biological killing efficiency increases at the end of the beam's range while it is low in the entrance channel, thus allowing a better inactivation of otherwise very radio resistant cells of deep-seated tumors. On the other hand, DNA is the main target for cell inactivation by ionizing radiation. As we reviewed in part 2, HZE particles induce more clustered DNA damages than low-LET radiation. At low X-ray doses, mainly isolated damage such as single strand breaks is produced. The cell has a very efficient repair system for this type of damage, even simultaneous damage at both DNA strands, like double strand breaks, can be repaired by the cell with high fidelity. But if the local damage is enhanced by higher local doses, more complex DNA damages (clustered damages) which are less reparable, are produced and the clustered DNA damage has been associated with the increased RBE of densely ionizing radiation [62]. Tumors that are usually very radio resistant become sensitive to heavy ion exposure because of the larger RBE effect.

Perspective

The radiobiology of highly charged ions differs from the conventional radiobiology with photons because of the great local ionization density that is produced along a particle track. In space exploration, a major issue is the cosmic galactic rays that consist of highly charged ions from protons up to iron, these particles have a greater biological efficiency than X-rays to induce genetic mutations and cancer. Up to now, it is not possible to calculate the radiation risk in space with the desired accuracy due to the energy spectrum of the GCR stretches up to very high values and secondary radiation produced by

Table 1. Worldwide heavy ion radiotherapy facilities [10,61].

Institute/ hospital	Name of facility	Location (country)	Start year	Total patients	Ion species	Target diseases
LBNL	Bevalac	Berkeley	1977-1992	433	He, Ne	Whole body
NIRS	HIMAC	Chiba (Japan)	1994-	>9000	C	Whole body
GSI	UNILAC+ SIS	Darmstadt (Germany)	1997-2008	450	C	Head and Neck
HIBMC	HIBMC	Hyogo (Japan)	2002	>2000	C, p	Whole body
IMP	HIRFL-CSR	Lanzhou (China)	2006	203	C	Whole body
HIT	HIT	Heidelberg (Germany)	2009	>3000	C, p, O, He	Whole body

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[DOI: 10.18869/acadpub.ijrr.14.1.1]

the interaction of space radiation with shielding materials. Therefore, more accurate measurements and modeling is necessary to determine the radiation risk in space through the ground basement with heavy ion accelerator facility. Heavy particle therapy by the advantage of the inverse dose profile is predominantly applied to deep-seated tumors, especially for brain tumors where surgery cannot be utilized. A great number of projects for dedicated particle therapy centers are underway all over the world. Future studies on the biological effects caused by HZE particles and the corresponding mechanism (s) would help us better evaluate radiation related risk to astronauts and for the development of the heavy ion radiotherapy.

ACKNOWLEDGMENT

This work was supported by National Natural Science Foundation of China [31170803, U1432121] and National Key Scientific Instrument and Equipment Development Project of China [2012YQ03014210] to BH.

Conflicts of interest: *none to declare.*

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