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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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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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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

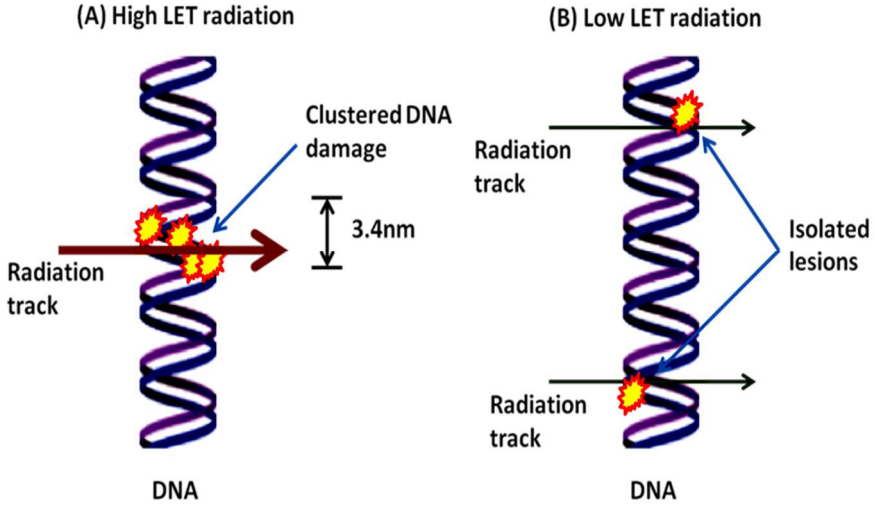


Figure 1. Production of DNA damage by ionizing radiation. (A) High LET radiation (densely ionizing radiation) induces a clustered DNA damage site which is defined as multiple lesions within a region of a few nm. (B) Low LET radiation (sparsely ionizing radiation) induces randomly isolated damage [26,27].

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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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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.

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REFERENCES

1. Townsend LW (2005) Implications of the space radiation environment for human exploration in deep space. *Radiation protection dosimetry*, ***115****: 44-50.*
2. Durante M and Cucinotta FA (2008) Heavy ion car cinogenesis and human space exploration. *Nature reviews. Cancer*, ***8****: 465-472.*
3. Bahadori AA., Van Baalen M, Shavers MR, Dodge C, Semones EJ, Bolch WE (2011) The effect of anatomical modeling on space radiation dose estimates: a comparison of doses for NASA phantoms and the 5th, 50th, and 95th percentile male and female astronauts. *Physics in medicine and biology*, ***56****: 1671-1694.*
4. Cucinotta FA, Wu H, Shavers MR, George K (2003) Radiation dosimetry and biophysical models of space radiation effects. *Gravitational and space biology bulletin: publication of the American Society for Gravitational and Space Biology*, ***16****: 11-18.*
5. Asaithamby A and Chen DJ (2011) Mechanism of cluster DNA damage repair in response to high-atomic number and energy particles radiation. *Mutation research*, ***711****: 87-99.*
6. Hellweg CE and Baumstark-Khan C (2007) Getting ready for the manned mission to Mars: the astronauts' risk from space radiation. *Die Naturwissenschaften*, ***94****: 517-526.*
7. Katz R, Ackerson B, Homayoonfar M, Sharma SC (1971) Inactivation of cells by heavy ion bombardment. *Radiation Research*, ***47****: 402-425.*
8. Curtis SB and Letaw JR (1989) Galactic cosmic rays and cell-hit frequencies outside the magnetosphere. *Adv Space Res*, ***9****: 293-298.*
9. Durante M and Loeffler JS (2010) Charged particles in radiation oncology. *Nature reviews. Clinical Oncology*, ***7****: 37-43.*
10. Tsujii H and Kamada T (2012) A review of update clinical results of carbon ion radiotherapy. *Jpn J Clin Oncol*, ***42****: 670-685.*
11. Cucinotta FA and Durante M (2006) Cancer risk from exposure to galactic cosmic rays: implications for space exploration by human beings. *The lancet oncology*, ***7****: 431-435.*
12. Hamada N, Imaoka T, Masunaga S, Ogata T, Okayasu R, Takahashi A, Kato TA, Kobayashi Y, Ohnishi T, Ono K *et al.* (2010) Recent advances in the biology of heavy-ion cancer therapy. *Journal of Radiation Research*, **51**: 365-383.
13. Okada T, Kamada T, Tsuji H, Mizoe JE, Baba M, Kato S, Yamada S, Sugahara S, Yasuda S, Yamamoto N *et al.* (2010) Carbon ion radiotherapy: clinical experiences at National Institute of Radiological Science (NIRS). *Journal of Radiation Research*, ***51****: 355-364.*
14. Brenner DJ and Ward JF (1992) Constraints on energy deposition and target size of multiply damaged sites associated with DNA double-strand breaks. *International Journal of Radiation Biology*, ***61****: 737-748.*
15. Sutherland BM, Bennett PV, Sidorkina O, Laval J (2000) Clustered DNA damages induced in isolated DNA and in human cells by low doses of ionizing radiation. *Proceedings of the National Academy of Sciences of the United States of America*, ***97****: 103-108.*
16. Blaisdell JO., Harrison L, Wallace SS (2001) Base excision repair processing of radiation-induced clustered DNA lesions. *Radiation Protection Dosimetry*, ***97****: 25-31.*
17. Harrison L, Hatahet Z, Purmal AA, Wallace SS (1998) Multiply damaged sites in DNA: interactions with Escherichia coli endonucleases III and VIII. *Nucleic Acids Research,* ***26****: 932-941.*
18. Kramer M, Weyrather WK, Scholz M (2003) The increased biological effectiveness of heavy charged particles: from radiobiology to treatment planning. *Technology in Cancer Research & Treatment*, ***2****: 427-436.*
19. Rydberg B, Cooper B, Cooper PK, Holley WR, Chatterjee A (2005) Dose-dependent misrejoining of radiation-induced DNA double-strand breaks in human fibroblasts: experimental and theoretical study for high- and low-LET radiation. *Radiation Research*, ***163****: 526-534.*
20. Asaithamby A, Uematsu N, Chatterjee A, Story MD, Burma S, Chen DJ (2008) Repair of HZE-particle-induced DNA double-strand breaks in normal human fibroblasts. *Radiation Research*, ***169****: 437-446.*

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[DOI: 10.18869/acadpub.ijrr.14.1.1]

21. George K, Durante M, Willingham V, Wu H, Yang TC, Cucinotta FA (2003) Biological effectiveness of accelerated particles for the induction of chromosome damage measured in metaphase and interphase human lymphocytes. *Radiation Research*, ***160**: 425-435.*
22. Goodhead DT (1994) Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. *International Journal of Radiation Biology*, ***65**: 7-17.*
23. Pan D, Xue G, Zhu JY, Hu BR (2014) Ionizing radiation induced biological effects in three-dimensional cell cultures. *Rend Lincei-Sci Fis*, ***25**: S81-S86.*
24. Hu BR, Zhu JY, Zhou HN, Hei TK (2013) No significant level of inheritable inter-chromosomal aberrations in the progeny of bystander primary human fibroblasts after alpha particle irradiation. *Advances in Space Research*, ***51**: 450-457.*
25. Hamada N, Imaoka T, Masunaga S, Ogata T, Okayasu R, Takahashi A, Kato TA, Kobayashi Y, Ohnishi T, Ono K *et al.* (2010) Recent Advances in the Biology of Heavy-Ion Cancer Therapy. *Journal of Radiation Research*, ***51**: 365-383.*
26. Urushibara A (2007) Dependence of yield of DNA damage refractory to enzymatic repair on ionization & excitation density of radiation: exploring the induction mechanism of clustered DNA damage. JAEA R&D Review, 2007, 71.
27. Shikazono N (2008) Biological effects of clustered DNA damage: mutation induction by DNA lesions in close proximity. JAEA R&D Review, 2008, 71.
28. David-Cordonnier MH, Cunniffe SM, Hickson ID, O'Neill P (2002) Efficiency of incision of an AP site within clustered DNA damage by the major human AP endonuclease. *Biochemistry*, ***41**: 634-642.*
29. Gulston M, Fulford J, Jenner T, de LaraC, O'Neill P (2002) Clustered DNA damage induced by gamma radiation in human fibroblasts (HF19), hamster (V79-4) cells and plasmid DNA is revealed as Fpg and Nth sensitive sites. *Nucleic Acids Research*, **30**: *3464-3472.*
30. Lomax ME, Salje H, Cunniffe S, O'Neill P (2005) 8-OxoA inhibits the incision of an AP site by the DNA glycosylases Fpg, Nth and the AP endonuclease HAP1. *Radiation Research*, ***163**: 79-84.*
31. Gulston M, de Lara C, Jenner T, Davis E, O'Neill P (2004) Processing of clustered DNA damage generates additional double-strand breaks in mammalian cells post-irradiation. *Nucleic Acids Research*, ***32**: 1602-1609.*
32. Eccles LJ, Lomax ME, O'Neill P (2010) Hierarchy of lesion processing governs the repair, double-strand break formation and mutability of three-lesion clustered DNA damage. *Nucleic Acids Research*, ***38**: 1123-1134.*
33. Fujimoto H, Pinak M, Nemoto T, O'Neill P, Kume E, Saito K, Maekawa H (2005) Molecular dynamics simulation of clustered DNA damage sites containing 8-oxoguanine and abasic site. *Journal of Computational Chemistry*, ***26**: 788-798.*
34. Blaisdell JO and Wallace SS (2001) Abortive base-excision repair of radiation-induced clustered DNA lesions in Escherichia coli. *Proceedings of the National Academy of Sciences, USA,* ***9:** 7426-7430.*
35. D'Souza DI and Harrison L (2003) Repair of clustered uracil DNA damages in Escherichia coli. *Nucleic Acids Research,*, ***31**: 4573-4581.*
36. Harrison L, Brame KL, Geltz LE, Landry AM (2006) Closely opposed apurinic/apyrimidinic sites are converted to double strand breaks in Escherichia coli even in the absence of exonuclease III, endonuclease IV, nucleotide excision repair and AP lyase cleavage. *DNA Repair*, ***5**:324-335.*
37. Malyarchuk S, Castore R, Harrison L (2008) DNA repair of clustered lesions in mammalian cells: involvement of non-homologous end-joining. *Nucleic Acids Research,*, ***36**: 4872-4882.*
38. Sedelnikova OA, Redon CE, Dickey JS, Nakamura AJ, Georgakilas AG, Bonner WM (2010) Role of oxidatively induced DNA lesions in human pathogenesis. *Mutation Research*, ***704**: 152-159.*
39. Shrivastav M, De Haro LP, Nickoloff JA (2008) Regulation of DNA double-strand break repair pathway choice. *Cell Research*, **18**: *134-147.*
40. Asaithamby A, Hu B, Delgado O, Ding LH, Story MD, Minna JD, Shay JW, Chen DJ (2011) Irreparable complex DNA double-strand breaks induce chromosome breakage in organotypic three-dimensional human lung epithelial cell culture. *Nucleic Acids Research*, ***39**: 5474-5488.*
41. Asaithamby A, Hu B, Chen DJ (2011) Unrepaired clustered DNA lesions induce chromosome breakage in human cells. *Proceedings of the National Academy of Sciences, USA,*, ***108**: 8293-8298.*
42. Okayasu R, Okada M, Okabe A, Noguchi M, Takakura K, Takahashi S (2006) Repair of DNA damage induced by accelerated heavy ions in mammalian cells proficient and deficient in the non-homologous end-joining pathway. *Radiation Research*, ***165**: 59-67.*
43. Heilmann J, Rink H, Taucher-Scholz G, Kraft G (1993) DNA strand break induction and rejoining and cellular recovery in mammalian cells after heavy-ion irradiation. *Radiation Research*, ***135**: 46-55.*
44. Goodhead DT (2006) Energy deposition stochastics and track structure: what about the target? *Radiation Protection Dosimetry*, ***122**: 3-15.*
45. Sutherland BM, Bennett PV, Saparbaev M, Sutherland JC, Laval J (2001) Clustered DNA damages as dosemeters for ionising radiation exposure and biological responses. *Radiation Protection Dosimetry*, ***97**: 33-38.*
46. Tamulevicius P, Wang M, Iliakis G (2007) Homology-directed repair is required for the development of radioresistance during S phase: interplay between double-strand break repair and checkpoint response. *Radiation Research*, ***167**: 1-11.*
47. Kass EM and Jasin M (2010) Collaboration and competition between DNA double-strand break repair pathways. *FEBS letters*, ***584**: 3703-3708.*
48. You Z and Bailis JM (2010) DNA damage and decisions: CtIP coordinates DNA repair and cell cycle checkpoints. *Trends in Cell Biology*, ***20**: 402-409.*
49. Nagasawa H, Little JB, Inkret WC, Carpenter S, Raju MR, Chen DJ, Strniste GF (1991) Response of X-ray-sensitive

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CHO mutant cells (xrs-6c) to radiation. II. Relationship between cell survival and the induction of chromosomal damage with low doses of alpha particles. *Radiation Research*, ***126****: 280-288.*

50. Zafar F, Seidler SB, Kronenberg A, Schild D, Wiese C (2010) Homologous recombination contributes to the repair of DNA double-strand breaks induced by high-energy iron ions. *Radiation Research*, ***173****: 27-39.*
51. Gerelchuluun A, Zhu J, Su F, Asaithamby A, Chen DJ, Tsuboi K (2014) Homologous recombination pathway may play a major role in high-LET radiation-induced DNA double-strand break repair. *Journal of Radiation Research*, ***55****: 83-i84.*
52. Zhu JY, Asaithamby A, Chen DJ, Hu BR (2012 *IMP&HIRFL Annual Report*, *pp. 193-194.*
53. Perry JJ, Yannone SM, Holden LG, Hitomi C, Asaithamby A, Han S, Cooper PK, Chen DJ, Tainer JA (2006) WRN exonuclease structure and molecular mechanism imply an editing role in DNA end processing. *Nature Structural & Molecular Biology*, ***13****: 414-422.*
54. Karlsson KH and Stenerlow B (2004) Focus formation of DNA repair proteins in normal and repair-deficient cells irradiated with high-LET ions. *Radiation Research*, ***161****: 517-527.*
55. Wang J, Pluth JM, Cooper PK, Cowan MJ, Che DJ, Yannone SM (2005) Artemis deficiency confers a DNA double-strand break repair defect and Artemis phosphorylation status is altered by DNA damage and cell cycle progression. *DNA Repair*, ***4****: 556-570.*
56. Suit H and Urie M (1992) Proton beams in radiation therapy. *Journal of the National Cancer Institute*, ***84****: 155-164.*
57. Linstadt DE, Castro JR, Phillips TL (1991) Neon ion radiotherapy: results of the phase I/II clinical trial. *Int J Radiat Oncol, Biol Phys* ***20****: 761-769.*
58. Castro JR (1995) Results of Heavy-Ion Radiotherapy. *Radiat Environ Bioph*, ***34****: 45-48.*
59. Combs SE, Jakel O, Haberer T, Debus J (2010) Particle therapy at the Heidelberg Ion Therapy Center (HIT). Integrated research-driven university-hospital-based radiation oncology service in Heidelberg, Germany. *Radiother Oncol*, ***95****: 41-44.*
60. Sawada K, Sawada J, Sakata T, Uno K, Okanishi K, Harada H, Itano A, Higashi A, Akagi T, Yamada S *et al.* (2000) Performance test of electron cyclotron resonance ion sources for the Hyogo Ion Beam Medical Center. *Rev Sci Instrum*, ***71****: 987-989.*
61. Kitagawa A, Fujita T, Muramatsu M, Biri S, Drentje AG (2010) Review on heavy ion radiotherapy facilities and related ion sources (invited). *Rev Sci Instrum*, ***81：*** *02B909.*
62. Hada M and Sutherland BM (2006) Spectrum of complex DNA damages depends on the incident radiation. *Radiation Research*, ***165****: 223-230.*

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