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Potential application of SSRF in radiation oncology: The aspects of radiobiology

FU Shen[1] JIANG Guoliang[2,*]

[1] *Shanghai No.6 People's Hospital Affiliated to Shanghai Jiaotong University, Shanghai 200233, China*

[2] *Shanghai Cancer Hospital of Fudan University, Shanghai 200032, China*

Abstract Conventional radiotherapy remains to be one of the most useful treatments for cancer, but it is not the best strategy to maximize the effects on the tumors and minimize the damage to the surrounding tissues because of its physical and radiobiological characteristics. Synchrotrons represent a unique method for an innovative anti-cancer treatment due to the physical features (i.e. high fluence, tunable and collimated) of X-ray induced by synchrotron, so photon activation therapy and microbeam radiation treatment have been developed, but it is very imperative to understand the radiobiological mechanism of synchrotron radiation before we could transfer the strategy into the clinic. This paper is to summary the results of *in vitro* and *in vivo* experiments with synchrotron radiation, and review the advances of molecular and cellular radiobiological mechanism involved in synchrotron radiation. Since Shanghai Synchrotron Radiation Facility (SSRF) has produced the first synchrotron, it will provide the unique opportunity for the study of radiobiological effects of synchrotron radiation.

Key words Synchrotron radiation, Radiobiology, Photoactivated radiotherapy, Microbeam radiation therapy

1 Introduction

Synchrotron radiations (SR) are emitted by beam bunches of charged particles moving in constant, relativistic speed on a circular orbit. SR was discovered on a 70 MeV synchrotron in 1947 at General Electric Co.[1], hence the name of synchrotron radiation or synchrotron light. Since then, SR facilities have been in developments of the 1st generation to the 3rd generation, and extensively utilized in variety of areas including medicine, particularly in cancer medicine. With outstanding performance of synchrotron radiations, innovative diagnostic imaging tools, such as transvenous angiography, multiple-energy computed tomography, mammography etc. have been developed. A new frontier being explored is to treat cancer utilizing SR.

So far, surgery, chemotherapy and radiotherapy remain the main strategy for cancer treatment. In radiotherapy, although conventional high-energy photons can treat deep-seated tumors and total dose can be limited by the tolerance dose of surrounding normal tissues, outcomes of the radiotherapy are still not desirable for many patients, as X-rays from a standard medical linac do not necessarily produce optimal biological effects.

Modern SR facilities have opened a new option in terms of radiotherapy strategies. Fluence of X-rays from a synchrotron is so high that it enables the production of X-ray beams tunable in energy (monochromatic beams) and in size (microbeams). The possibility of obtaining a beam of monochromatic light, focused down to microns, offers a good opportunity for the radiation oncologist to investigate the therapeutic gain, with maximum effects on the tumors but minimized damage to the surrounding tissues. *In vitro* and *in vivo* studies using synchrotron radiations have been done for treatment of cancers, especially brain tumor, and the results were very encouraging, though data about the clinical benefit of synchrotron radiotherapy to the human are not available at present.

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* Corresponding author. *E-mail address:* jianggl47@hotmail.com

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On the other hand, for innovative technologies developed based on SR, such as stereotactic radiosurgery[2], grid therapy[3,4] and parallel opposed spatially fractionated radiation therapy[5], it is necessary to understand and evaluate the radiobiological response of synchrotron radiation before it could be transferred to the clinic.

Shanghai Synchrotron Radiation Facility (SSRF), a 3.5 GeV 3rd generation facility that began construction in December 2004 and its first synchrotron light was seen in December 2007[6], has been providing beam time for users working on seven beamlines built in Phase I of the SSRF project. And it is expected that the number of beamlines shall exceed 30 in five years. Encouraged by all these developments, teams of oncologists in Shanghai are enthusiastic in doing researches on SSRF. In this paper, we give a review on radiobiology with SRs.

2 Photon activation therapy (PAT)

Contrast agent such as iodine has been extensively used in diagnosis of cancers. Iodinated contrast agents (ICAs) were used to enhance X-ray photoabsorption in radiodiagnostic session, in which a dose of 4 cGy was delivered by a standard polychromatic X-ray tube (65–75 kVp, 1.3mA). This dose is similar to 20–30 cGy delivered by a standard polychromatic X-ray tube without ICAs, causing a significant increase in the frequency of micronuclei in peripheral blood lymphocytes. This was confirmed with Norman's meta-analysis of ten clinical studies using ICAs during angiography or excretory urography[7]. This principle helped the development of a new form of radiation therapy, where a conventional CT scanner is used to deliver an optimized dose distribution on metastatic brain tumors[8,9].

The basic method of beam delivery is now being adapted to the use of SR. Adam *et al*[10] did a study at the European Synchrotron Radiation Facility to stereotactically irradiate rat F98 brain gliomas with 50-keV monochromatic X-rays. Prior to the irradiation, the tumors were loaded with 1% iodine by either intracarotid or intravenous injection with mannitol. For the rats irradiated with 15 Gy, the intracarotid infusion of iodine improved the survival rate compared with either intravenous injection or irradiation alone. The percentage-increased life spans (ILS) were 91%, 116%, and 169% for intracarotid, intravenous injection of iodine and irradiation alone, respectively. At 25 Gy, the rats irradiated without iodine had the longest survival (ILS=607%), but no additional benefit was seen over controls without iodine, presumably due to the excessive damage to normal tissue (i.e. necrosis induced by high doses to normal brain;)[10]. Since the X-ray energy used was 50 keV, corresponding to the maximal relative X-ray absorption of an iodine solution in water, whereas the K-edge of iodine is 33.17 keV, the strategy could be further optimized since the penetration of Auger electrons induced by the low energy X-ray is limited. On the other hand, ICAs do not enter into cells and remain bound to the external cell membrane so the biological response of tumor could be comprised, but this idea opened another area of radiotherapy, i.e. PAT.

PAT is a process in which a high LET radiation in the form of Auger electron distributions is used. A high-Z-containing compound, such as platinum-containing drugs (cisplatin, carboplatin and oxaliplatin), can be specifically photoactivated at 78.4 keV of the Pt K-edge induced by X-ray of about 80 keV, and the Auger electrons are in larger numbers[11]. On the other hand, the drugs are selectively incorporated in tumor cells, which divide more rapidly than normal cells and target proliferating cancer cells in S-G2/M[12,13], so Auger electrons can deposit their energy near the atom where photoabsorption takes place through photoelectric effect and produce lethal damage to the tumor cell nucleus. Therefore, the SR destroys the malignant cells in a selective way.

Ionized molecules, which are highly reactive and undergo a rapid cascade of chemical changes, can cause breaking of chemical bonds. This disrupts the structure of macromolecules such as DNA and cam result in severe consequences if not repaired adequately or in time. Double-strand DNA breaks (DSBs) is an important form of DNA damage induced by irradiation, but DSBs is reparable through relevant genes that play a vital role in the sensors of DSBs, transducer of signal and effector pathways. DSBs are detected by special proteins, which signal to the cell that damage has occurred, thereby initiating the DNA damage response. There are two main repair pathways,

homologous recombination (HR) and non-homologous end-joining (NHEJ)[14,15]. These are quite different in terms of the genes involved, the position in the cell cycle and the kinetics of repair. DSBs produced by X-rays are generally repaired by the NHEJ process. The first event in NHEJ is binding of a Ku heterodimer (two different but related proteins: Ku70 and Ku80) to the DNA ends. This occurs within seconds of the break being formed because of high abundance of the Ku dimmer and its high affinity for ends.

The high-Z-containing compound like cisplatinum bind to DNA and form DNA adducts that prevents the Ku translocation and significantly inhibits NHEJ. Consequently, association between ionizing radiation and cisplatin results in irreparable DSBs, as long as the concentration of DNA adducts is sufficient, and as long as radiation and cisplatin are used concomitantly[16,17]. It has been noticed that alternative form of NHEJ that operated as a backup to the DNA-PK-dependent pathway[18]. The subtype of NHEJ may associate with some particular proteins like BRCA1, Rad50, etc[19], so more *in vitro* experiments with cell cultures and small animal studies are still necessary to propose a molecular model of the mechanisms involved in the PAT-Plat approach in order to secure its clinical transfer. A disadvantage of the strategy is that the secondary radiation and ejected electrons like Auger electrons induced by SR has very small range, just a few tens of nanometers, so the optimized biological effects will be achieve if the high Z-element compounds, perhaps bound to monoclonal antibodies, can be specifically incorporated into the DNA or to the location very close to DNA of tumor cells. This can target the tumors, and with the tunable beams one will be able to select and kill malignant cells, while sparing normal tissue.

3 Microbeam radiation therapy (MRT)

The denomination of microbeam came from Howard J. Curtis[20], a biophysicist, and Charles P. Baker[20], an atomic physicist. Collaborating at the Brookhaven National Laboratory (BNL), they were studying the mouse brain with 22 MeV deuterons in either a Φ25 μm circular beam spot (a cylindrical beam hereinafter) or a narrow rectangular beam spot (a planar beam hereinafter) of 25 μm in width[20,21]. The unprecedented normal tissue spare like the cerebrum and cerebellum was discovered until permanent damage occurred after 150–300 Gy was delivered.

A synchrotron X-ray beam is featured by very small divergence[20,21] (hence the potential of sharply defined beam edges deep in the body) and very high brightness. These provide basis for potential use of microbeam radiation therapy (MRT). Sharply defined microbeam margins like secondary electrons from 50–150 keV X rays are made possible by the microscopically short ranges in tissue. These make it possible to crossfire an isocentric target effectively using a bundle of many closely spaced microbeams. Absorbed doses to nontargeted tissue like the proximal and distal to the isocentric area situated between the microbeams, where the non-overlapping beams will be kept below the threshold for radiation damage.

Fig.1 shows that the brain and spinal cord of a rat irradiated by an array of collimated microplanar beams (MBs). The spatial dose distribution has high and low dose areas that repeat alternately. The minimum dose in the central region between two microbeams is called the "valley dose", the highest dose level called as "peak dose" is in the overlap area of MBs, the peak and valley dose ratio (PVDR, Fig.2) in the irradiation field are believed to be of importance for the therapeutic effect. PVDR strongly depends on the distance between the peaks: a smaller PVDR with narrower spacing[22,23]. The PVDR, as a critical parameter, has to be optimized in MRT[14]. When the tumor is irradiated by either unidirectional or bidirectional microbeams that interact in tissue, the lethal high dose applied will be delivered to cells lying directly in their path (i.e. peak regions). Cells lying in the fraction of a millimeter spacing between adjacent microbeams (i.e. valley regions), receive a superposition of dose contributions from laterally scattered photons and any secondary radiation produced from interactions in tissue. This valley dose is substantially less than the peak dose. It has been reported that the most effective spacing between the micro-beams appears to be around 100–200 mm[24].

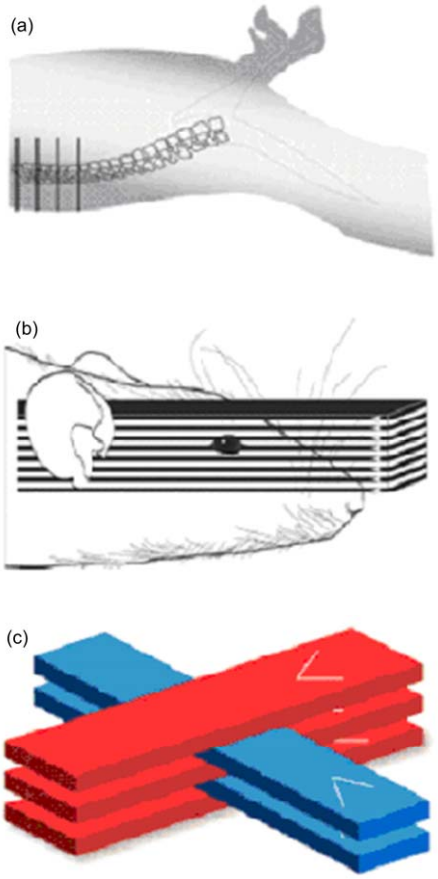

Fig.1 Schematic demonstration of irradiations with MB arrays. (a) Rat spinal cord irradiations with four MBs; (b) Rat brain irradiation with a large array of MBs; (c) Interlaced MBs.

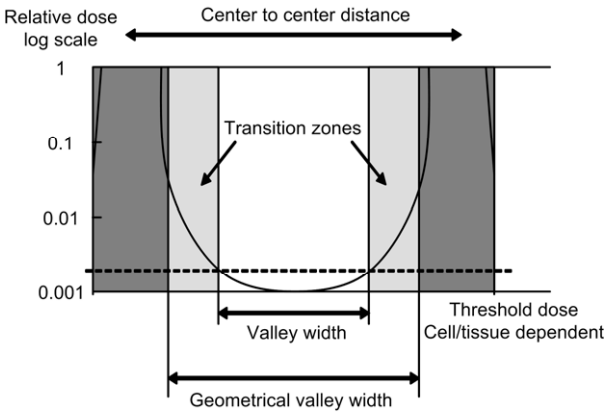

Fig.2 Schematic dose profile between two microbeams, with the different characteristic areas of the peak, the transition zone and the valley.

Previous MRT experiments were essentially applied to the brain of adult rats[25], mice[26], duck embryos[27] and piglets[28]. The results highlight a sparing effect on normal tissues. Physiopathology and histology observations indicate that rat skin could tolerate a 23-fold higher dose delivered in MRT sessions than in conventional beams. For duck embryos, 160 Gy MRT appeared to be equivalent to the biological effect of an 18 Gy broad beam for skin in Ref.[27]. With regard to piglets, the animals was irradiated with microbeams up to 600 Gy and no late tissue effect has been reported[28]. Therefore, the mechanism of different responses of normal and tumor tissues to the microbeams is one of the most key issues,

The sparing effect of microbeams in normal tissues is a combination of the volume effect and the biological repair effect. The volume effect refers to the principle that the threshold dose for radiation damage to the tissue increases with dicreasing volume of the irradiated tissue[29]. On the other hand, although the radiobiological principle of MRT is not well understood, there are strong indications that normal tissue sparing is mediated in part by the tissue's microvasculature that regenerate apparently from the angiogenic cells surviving between the beams[30-32]. Recent studies also indicate the regeneration of the glial system following high dose microbeam irradiation[32,33].

It is thought that the effectiveness is attributed to the difference in regeneration of the radiation-damaged vasculature in the path of microbeams from the contiguous, minimally irradiated vasculature in the valley regions between microbeams[34]. In normal tissue, the well-preserved vasculature in the valley regions ensures the rapid regeneration of directly irradiated blood vessels. In tumor tissue, however, the irreparable damage to the blood vessels starves the surviving tumor cells of oxygenated blood, resulting in their death[35-37]. It is therefore essential that the valley dose is kept to a minimum to ensure the preservation of normal tissue architecture and the survival of sufficient endothelial cells needed for healthy tissue repair.

Another radiobiological issue for MRT is radiation-induced bystander effects (RIBEs). This has been broadly defined as the occurrence of biological effects in non-irradiated cells resulting from exposure of other cells to radiation[38]. Bystander cells in exposed cell populations can be described as the non-irradiated cells that received signals from neighboring or distant irradiated cells[39,40]. The molecular radiobiological mechanism is yet to be fully

understood. According to a few reports about the role of RIBEs in MRT, RIBEs (as DSB formation and micronuclei) in non-target normal cells like human fibroblasts could be observed after MRT[41], but it is still too early to conclude that RIBEs may be a source of additional stress for normal tissues in MRT modality. The impact of RIBEs is expected to diminish gradually as far as the distance from the targeted cells increases[42], But it is not clear whether RIBEs can be an explanation for the necrosis and hypervascularity phenomena observed in the area (i.e. valley zone) close to tumor during MRT treatments[43].

Because of this high resistance of normal brain tissues to very high radiation doses, MRT may represent a feasible and realistic possibility in radiotherapy. It is very important that the dose should be delivered in a timescale short enough before the subject moves a considerable distance, so as to eliminate the valleys between the peaks in the clinical setting during an MRT treatment. Therefore, it is only a synchrotron that can produce such high dose within a short time and has potential use as MRT.

4 Conclusion

Synchrotron radiotherapy represents a great potential radiation source to be applied in the treatment of cancer, but It is crucial to consider the impact of SR radiobiological feature. Although there were some *in vitro* and *in vivo* studies that the synchrotron radiation could spare normal tissue more efficiently throughout either activating high Z-element compound like Platinum-containing drug through photoelectric effect and produce lethal damage to the tumor cell nucleus for PAT or mediating tissue's microvasculature that regenerate from the angiogenic cells between microbeams, there are no better knowledge of the molecular, cellular and tissular mechanisms about PAT and MRT. Further studies is needed before the biological analysis of SR has been clarified, it will be more practical that SR will be begun to apply for the treatment of cancer in the clinic.

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