ट्रांसलेशनल रेडियोजीवविज्ञान

12

कैंसर रेडियोथेरेपी में सुधार के लिए प्रासंगिकता के साथ निम्न एवं उच्च एलईटी विकिरण के गैर-लक्षित प्रभाव

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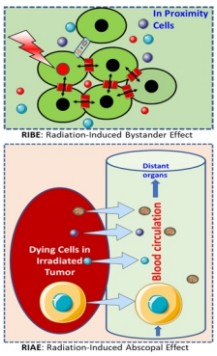

कैंसर रेडियोथेरेपी में गैर-लक्षित विकिरण प्रभाव।

सारांश

गैर-लक्षित विकिरण प्रभाव (NTRE) कोशिकाओं/ऊतकों/अंगों की जैविक अनुक्रिया है, जो किरणित नहीं हुए हैं, लेकिन वे विकिरण स्थल से निकटता/या कुछ दूरी पर हैं। इन घटनाओं को विकिरण प्रेरित बाईस्टैंडर (अति निकटता में) या एब्सकोपल (कुछ दूरी पर) प्रभाव के रूप में जाना जाता है। ट्यूमर/सामान्य ऊतकों की मिश्रित सीमाएँ, आंशिक ट्यूमर विकिरण और मेटास्टैटिक ट्यूमर (विकिरण प्राप्त करने वाले ट्यूमर से दूर) कुछ ऐसी स्थितियाँ हैं, जिनके तहत NTRE कैंसर रेडियोथेरेपी के परिणाम को बेहतर किया जा सकता है, हालाँकि, अभी भी इस पर बहुत अधिक शोध कार्य नहीं किया गया है। कैंसर रेडियोथेरेपी परिदृश्यों का अनुकरण करने वाले हमारे इन-विट्रो और माउस ट्यूमर मॉडल अध्ययनों ने बाईस्टैंडर कैंसर कोशिकाओं/आंशिक रूप से किरणित ट्यूमर और विकिरण स्थल से दूर के ट्यूमर में वृद्धि अवरोधक NTRE दर्शाया है। हमने गामा विकिरण की तुलना में अल्फा कण के संपर्क में आने वाली कोशिकाओं को सीधे किरणित या बाईस्टैंडर कैंसर कोशिकाओं को स्वदेशी रूप से अभिकल्पित और विकसित स्वचालित बेंचटॉप 241 Am अल्फा किरणक (BARC BioAlpha) का उपयोग करके अधिक क्षयित किया। हमारी खोज ने गैप-जंक्शन मध्यस्थता वाले बाईस्टैंडर संचार के माध्यम से फेफड़े के कैंसर कोशिकाओं में साइटोटॉक्सिक प्रभाव के अल्फा कणों के हाई डोज़ पर किन्तु साइटो-प्रोलिफ़ेरेटिव प्रभाव के लो डोज़ को भी प्रमाणित किया। कुल मिलाकर, हमारे परिणाम विकिरण के गैर-लक्षित प्रभावों की नई समझ प्रदान करते हैं, जिसका कैंसर रेडियोथेरेपी के लिए बेहतर प्रोटोकॉल/कार्यनीतियों को अभिकल्पित करने में महत्वपूर्ण उपयोग हो सकता है। इसके अलावा, हमारा शोध बेहतर ट्रांसलेशनल रेडियोजीवविज्ञान अनुसंधान के लिए ट्यूमर माइक्रो-वातावरण परिस्थितियों में NTRE के अन्वेषण के लिए संभावनाओं के नए द्वार खोलता है।

Translational Radiobiology

12

Non-targeted Effects of Low and High LET Radiation with Relevance to Improvement of Cancer Radiotherapy

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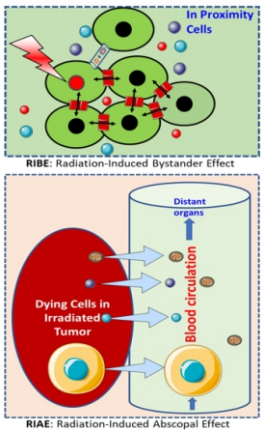

Non-Targeted Radiation Effects in Cancer Radiotherapy

ABSTRACT

Non-targeted radiation effects (NTRE) are the biological response of cells/tissues/organs that didn't receive radiation but are in proximity/ or at a distance from the irradiation site. These phenomena are known as radiation induced bystander (in close proximity) or abscopal (at a distance) effect. The intermixed boundaries of tumor/normal tissues, partial tumor irradiation, and metastatic tumors (distant to the tumor receiving radiation) are a few situations under which NTRE could modulate the outcome of cancer radiotherapy, which however, is still poorly explored. Our in vitro and mouse tumor model studies simulating cancer radiotherapy scenarios showed growth inhibitory NTRE in bystander cancer cells/partially irradiated tumor and the tumors distant from the irradiation site. Using an indigenously designed and developed automated benchtop $_{241}$Am alpha irradiator (BARC BioAlpha), we demonstrated higher killing of cancer cells which are either directly irradiated or bystander to alpha particle exposed cells than gamma radiation. Our finding also established the cyto-proliferative effect of low dose but cytotoxic effect at high dose of alpha particles in lung cancer cells through gap-junction mediated bystander communication. Overall, our results provide novel understanding of non-targeted effects of radiation, which may have significant implication in designing protocols/strategies for improved cancer radiotherapy. Moreover, our research opens new horizons to investigate NTRE in tumor microenvironment conditions for better translational radiobiology research.

KEYWORDS: *Radiation Induced Bystander Effect, Radiation Induced Abscopal Effect, Alpha Particles, Alpha Irradiator, Linear Energy Transfer*

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Introduction

Biological effects of radiation manifest as damage to biomolecules like DNA, proteins, lipids, etc., which subsequently exerted at different tiers ranging from organelle to tissue and organism levels. The deposition of energy (in kilo electron volt; keV) by ionizing radiation along the per unit length (in microns) of the radiation track is referred as linear energy transfer (LET). Gamma and X-rays are considered as low LET radiation, which deposit energy and ionize sparsely in the cells. Consequently, the DNA damage caused mainly consists of single strand breaks, which are easy to repair. Alpha and other charged particles, referred as high LET radiation, deposit their energy very densely resulting in biologically difficult-to-repair complex/clustered DNA damage. While low LET radiation can deeply penetrate and traverse through an organism, the high LET radiation is mainly localized to cells/tissues where such radiation emitting radionuclides reside. This difference also provides the basis for utilization of these radiations for imaging and therapy of cancer. The radiation and radio-isotopes used in diagnosis are low LET X-rays and low energy gamma emitters (such as ^{99m}Tc), while the radiation sources used in teletherapy are high energy gamma emitter like Cobalt-60. Also, high energy beta (^{90}Y, ^{131}I, ^{186}Re, ^{177}Lu) and alpha (^{225}Ac, ^{227}Th, ^{211}At, ^{212}Bi, and ^{213}Bi) emitter radionuclides are used for targeted radionuclide therapy of cancer after conjugating them with various agents and ligands [1]. The pattern of energy loss across the medium for low and high LET radiations is different. When a high LET charged particle passes through matter, its energy decreases, and consequently, the specific ionization increases, resulting in the deposition of energy in a short range as a sharp peak (called Bragg's peak) before the particle stops. This results in minimal energy deposition before or after the peak. This property of high LET radiation is also utilized to kill tumor mass sparing the normal tissue when the peaks of charged particles generated in accelerators are controlled to spread over the tumor region (called spread over Bragg's peak). Since, the radiobiological effects of high LET radiation are almost independent of oxygen presence, they can effectively kill the hypoxic cells in tumors, which otherwise are resistant to gamma and X-rays. Based on these biophysical and radiobiological properties, radiotherapy based on high LET radiation results in higher tumor control with minimal damage to normal tissues and hence emerging as a superior cancer radiotherapy modality compared to the conventional modalities.

Classically, it is believed that damage caused by radiation is limited to the cell that is hit by radiation. Such a notion prevailed due to dominance of DNA-centric dogma without consideration of intercellular communication and tissue microenvironment as contributing factors in the biological effects of radiation. In a landmark paper, Nagasawa and Little observed sister chromatid exchange in ~30 % cells when only <1 % cells in culture were irradiated with low fluence alpha particles. Later on, several studies, including ours, showed that bystander cells which did not receive radiation also showed effects similar to irradiated cells (called Radiation Induced Bystander Effects; RIBE). RIBE is mediated through (a) gap junctions, which connect the cells at the tissue level and mediate the transfer of small molecules (<10 kDa) such as calcium, and (b) secretion of cytokines/chemokines or vesicles such as exosomes from the irradiated cells [2]. More recently, cellular bridges like tunneling nanotubes, which can connect cells even at a few hundred microns away are postulated to play role in RIBE [3]. While RIBE is an intercellular phenomenon between adjacent/neighbouring cells, radiation effects are also observed in the distant tissues/organs, which are kept out of the radiation field. The systemic effect of radiation was first described by R. H. Mole in 1953, who coined the term 'abscopal effects' (*'Ab'* is a prefix with the meaning position away from and 'scopos' Latin meaning a mark or target for shooting). Such effects, known as Radiation Induced Abscopal Effects (RIAE), occur through the release of cytokines and factors in the blood stream from the dying cells which received lethal dose of radiation. In recent years, the scope of these effects has become further complex as it has been established that signals (i) from the irradiated cells/tissues could be damaging as well as protective (or rescue) to the bystander or the distant organs and (ii) the effects can be bidirectional/multi-directional originating from the irradiated cells/tissues as well as vice versa from the bystander/distant tissues. “Non-targeted radiation effects (NTRE)” or “out of the field effects” encompassing RIBE and RIAE have made a paradigm shift in radiation biology, where radiation effects are no more limited only to the irradiated cells/tissues. The emerging evidences supporting NTRE in diverse biological systems and radiation types hold significant implication in radiation risk assessment after environmental, occupational, accidental radiation exposure, and improvement of cancer radiotherapy [2]. The article briefly highlights our research activities to understand radiation biology of NTRE after low and high LET radiation in the framework of cancer radiotherapy.

Non-targeted Radiation Effects in Cancer Radiotherapy

Although RIBE was discovered in the 1970s and RIAE in the 1930s, studies pertaining to cancer radiotherapy are limited in the literature. The NTRE during cancer radiotherapy is highly relevant due to several reasons. (i) In the real scenario, the tumor mass is surrounded by normal tissues and their mixed boundaries provide an excellent platform for bystander interaction when the tumor is targeted to radiation. (ii) In some cases, tumors are located very close to critical organs like lungs and brain, thus to minimize undesired side effects partial tumor irradiation is performed, which provides possibility of bystander interaction between irradiated and non-irradiated regions of the same tumor. (iii) Majority of the cancer patients are diagnosed with metastasis at crucial organs or spread at multiple locations in the body. In such situations, generally radiation oncologists are able to treat only the primary site of tumor, which in turn might affect the growth of distant metastatic/micro-metastatic tumors. Hence, the magnitude, nature (damaging/protective), and direction (unidirectional /bidirectional) of interaction of irradiated and bystander cells/distant tissues and subsequent fate of these cells would govern the clinical outcome of cancer radiotherapy (Fig.1). Our studies employing multiple experimental models/strategies contributed significantly to this research area. In one of the seminal works simulating cancer and normal cell proximity during charged particle therapy, we co-cultured human lung cancer and fibroblast cells together, where nuclei of either cancer or normal cells were selectively irradiated with 500 protons using proton microbeam (3.4 MeV) facility at National Institute of Radiological Sciences, Japan followed by measurement of DNA double strand break in irradiated and bystander cells. The study showed that DNA damaging signal was transmitted from proton irradiated lung cancer to bystander lung cancer cells, however, the magnitude of DNA damage was attenuated in the irradiated lung cancer cells when human normal fibroblasts neighboured these cells. The damaging bystander effect was abrogated when gap-junctions between irradiated and bystander cells were blocked. This study for the first time established the bidirectional and rescuing bystander effect between lung cancer and

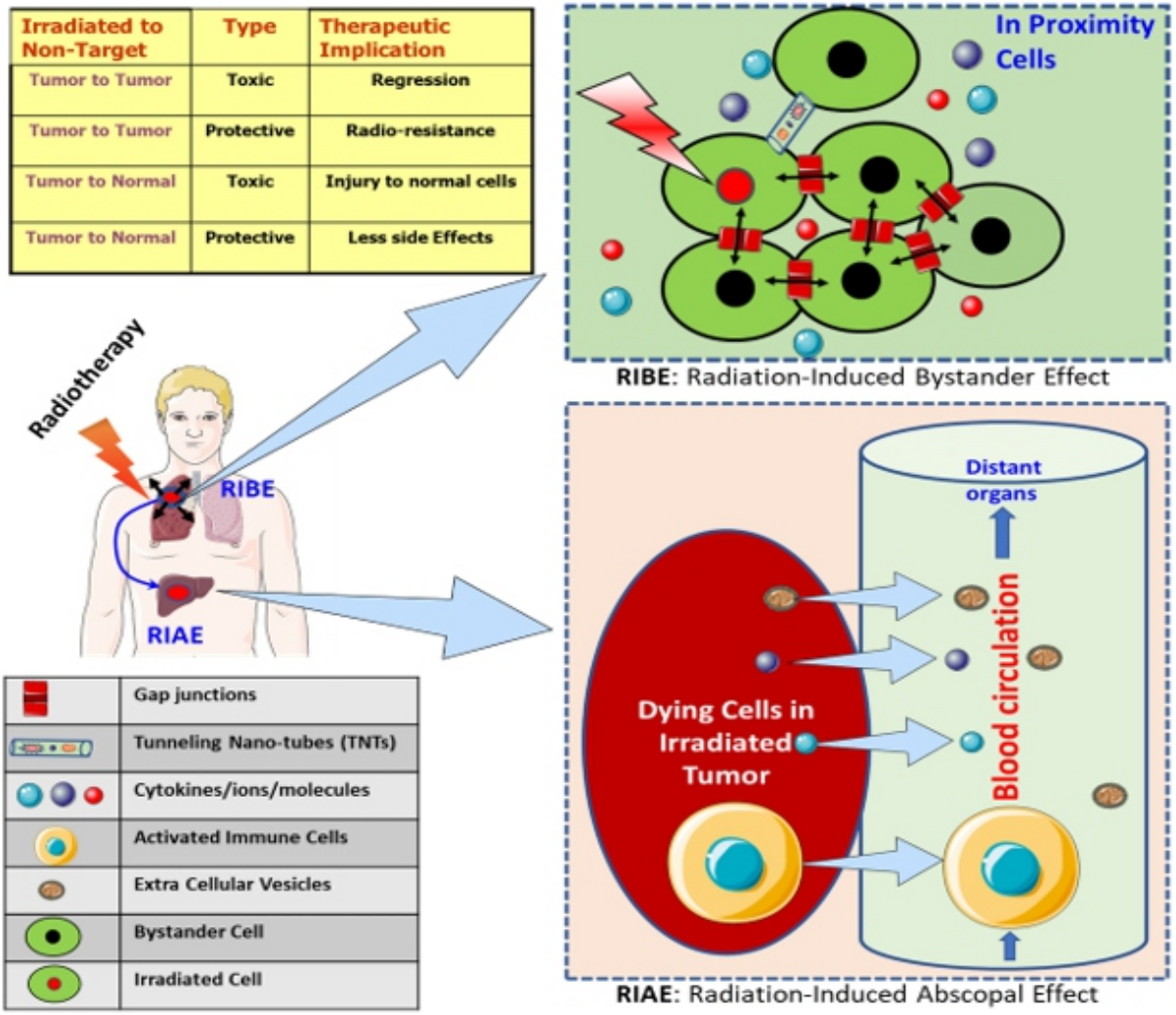

Fig.1: Non-Targeted Radiation Effects in Cancer Radiotherapy. When a tumor mass is irradiated, in addition to directly irradiated cells, the cells in close proximity also show the radiation effects called as Radiation Induced Bystander Effect (RIBE) or effect can be to the distant tissue/organs known as Radiation Induced Abscopal Effect (RIAE). While RIBE is mediated through gap junctions, the RIAE is through release of factors/activated immune cells. Depending on nature and magnitude of NTRE between tumor and normal cells/tissues, the net clinical outcome can affect tumor regression and/or side effects during cancer radiotherapy.

counterpart normal cells after proton microbeam irradiation [4]. The factors/cytokines released from the irradiated cancer cells are also known to contribute to the bystander effect. In this direction, cancer cells of different tissue origins (breast, lung, fibrosarcoma, colon, and brain) showed variation in secretion of cytokine profile when irradiated either with acute (2 Gy) or fractionated (3x2 Gy) doses of gamma radiation. It was interesting to observe that the conditioned medium from the irradiated lung cancer cells showed toxicity to bystander lung cancer cells [5]. Moreover, treatment with macrophage conditioned medium is shown to enhance intercellular communication between breast cancer cells via tunneling nanotube formation and secretion of large extracellular vesicles referred as microplasts [6, 7]. The intercellular communication via tunneling nanotubes modulates chemo-/radio-therapy response and can be important mediator of RIBE. To demonstrate and validate the NTRE results in mouse fibrosarcoma tumor models following strategies were employed.

Co-implantation of lethally irradiated tumor cells with bystander cells

In this approach, only a fraction of tumor cells was irradiated with lethal high doses of gamma radiation (15 Gy), mixed with bystander cells, followed by the implantation of the cell mixture in mice and subsequent measurement of the tumor growth. It was interesting to observe that only a fraction of high dose irradiated tumor cells inhibited the growth of bystander tumor cells, resulting in smaller tumors. The inhibition of tumor growth was found to be associated with secretion of anti-tumor proteins/factors from the irradiated cells, resulting in cell death of bystander cancer cells as well as decrease in angiogenesis during tumor growth [8].

Partial tumor irradiation

Using a cone irradiator designed for Cobalt-60 teletherapy, only a part of mouse tumor was irradiated. Compared to control, significant tumor control was observed when only ~10 % volume of tumor was irradiated. These results showed cytotoxic bystander effect when only a fraction or part of tumor was irradiated.

Non-targeted radiation effects at distant tumors

In this study, we investigated the possibility of controlling the growth of distant tumors when only primary tumor was irradiated. Such studies have gained attention of researchers as well as clinicians as they can be exploited to enhance radio-immunotherapy of metastatic tumors and prevent post-irradiation tumor recurrence. To simulate NTRE at distant tumors, mouse fibrosarcoma tumors were developed in both of hind legs. While one of the tumor was irradiated with gamma radiation, the other tumor and rest animal body parts were

kept shielded. A decrease in tumor growth in radiation shielded tumor was observed when tumor in another leg was irradiated, which was more prominent at higher doses (5 Gy) than at lower doses (2 Gy). The directly irradiated tumors showed expression of immunogenic cell death markers. To enhance the NTRE in distant tumors, radiation in combination with CpG-ODN (cytidine phosphate guanosine-oligonucleotides), an immunomodulatory oligo, was administered in the irradiated tumor. CpG-ODN in conjunction with radiation resulted in better tumor control. These tumor growth inhibitory effects were found to be mediated through an increase in immune-modulatory markers and induction of apoptosis in the shielded tumors. To evaluate whether such combinatorial effects could be exploited to control tumor recurrence, the animals that showed complete tumor regression after CpG-ODN and radiation treatment were implanted with unirradiated tumor cells. It was interesting to observe that in these animals freshly transplanted tumor cells did not produce tumors, suggesting long lasting non-targeted radiation effects.

Cancer stem cells (CSCs) are one of the key factors contributing to recurrence and poor prognosis in cancer radiotherapy [9]. Depending upon the types and stages of tumors, although CSCs constitute only a small fraction (0.5-20%) of the tumor mass, they play a pivotal role in cancer progression, metastasis, recurrence, and resistance to treatment [10, 11]. Our understanding about the magnitude of bystander communication and role of gap junction proteins in the context of CSCs and tumor radio-resistance remains limited [12] and is one of our ongoing research activities.

High LET Radiobiology in Cancer Radiotherapy

Charged particle therapy and targeted alpha therapy are emerging modes of cancer therapy owing to their effectiveness to kill tumor cells while sparing the surrounding normal tissues. However, in addition to technical challenges, such therapies are also limited to a few cancer types and have poor prognosis in some cases. The radiobiology of charged particles is not well studied mainly due to two reasons: (i) the charged particle irradiation facilities are limited all over world owing to high cost and highly sophisticated instrumentation, (ii) the very short range [order of cm in air to few (20-100) µm in water for ~4-10 MeV energy] of alpha particles [13] making it challenging to conduct in vitro radiobiology experiments with accuracy in dose and energy. These limitations have resulted in inadequate optimization of radiobiological parameters and a poor understanding of radiation effects of charged particles, especially in the setting of cancer radiotherapy. Joining the club of few laboratories around the world, for in vitro radiobiological experiments of normal/cancer cells, we have indigenously designed and developed first ^{241}Am alpha particle irradiator, which is a benchtop model automated with several user-friendly features[14]. In human cancer cells, alpha particles were found to induce more damage than gamma radiation measured in terms of DNA double break, chromosomal aberrations, and clonogenic survival. To study the bystander effect, alpha particles irradiated and unirradiated (bystander) cells were cultured in such a way that they share the medium but were physically separated through thin, porous membrane (inserts). In this arrangement, the effect of factors/cytokines released from the irradiated cells on bystander cells could be studied while keeping both cell populations separated. Our results showed that the magnitude of bystander effect from the alpha particle irradiated cells was higher in magnitude than that from the gamma irradiated cells [15,16].

The effect of gamma radiation is known to be governed by several biological factors like DNA repair efficiency, cell cycle, oxygen level. However, these factors are less likely to affect the cellular response to alpha particles. In a typical dose survival curve, the shoulder at lower doses of low LET radiation is known to be associated with capacity of cells to repair the damage. Such shoulder region at the lower doses are absent in a classical dose-survival curve of alpha particles due to poor repair ability of clustered DNA damages. Hence, based on classical understanding in the literature, the cellular response of alpha particles to cancer cells of different origin and dose response at lower doses is not well understood. These questions are very pertinent, especially in the application of charged particle/targeted alpha therapy to different cancer types and how cancer cells would respond if dose delivered to cancer cells is low and sub-lethal. While performing survival curve analysis of lung cancer cells to alpha particles, we unexpectedly encountered a higher proliferation and survival

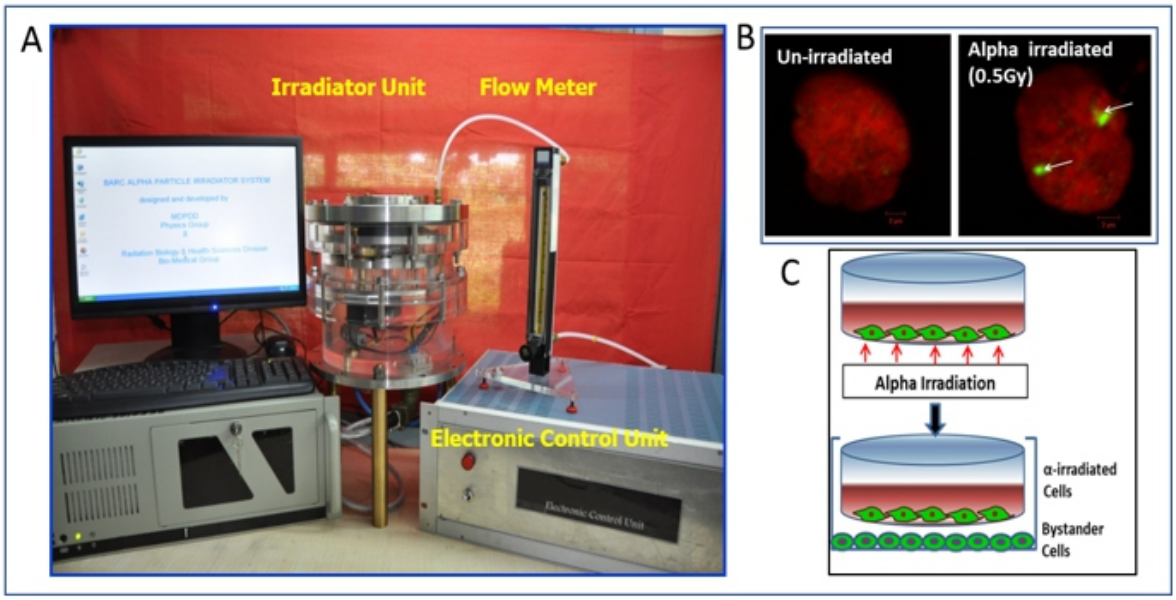

Fig.2: High LET radiobiology studies using automated benchtop alpha irradiator. A. Photograph of indigenously developed $_{241}$Am alpha irradiator and its major components; B. DNA damage in cancer cells after alpha particle irradiation. Green foci (arrows) show the expression of gamma H2AX as marker of DNA double strand break; C. Set up for bystander studies after alpha particle irradiation. Irradiated and bystander cells are cultured on porous membrane so that they share common medium being remained physically separated.

at low doses of radiation (1.36 and 6.8 cGy) contrary to well-known cell killing effect at higher doses (>13 cGy). The cyto-proliferative response of alpha particles to cancer cells was found to be associated with decrease in gap junction communication and Caveolin-1/Survivin signalling pathway. When these low-dose alpha-irradiated cancer cells were transplanted into SCID mice, they showed higher tumor growth [17]. These results suggest that if a lower dose is received to a fraction of tumor cells during charged/targeted alpha therapy, it might make them to survive more and possibly be one of the reasons behind recurrence/poor response in some patients. Hence, there is a need to optimize the dose during charged/targeted alpha therapy for better clinical outcome.

Our further studies determining the radio-sensitivity in cancer cells of different tissue origins also showed differential radio-response, with breast cancer cells showing higher cell killing by alpha particles than glioblastoma cells. This may be governed by cellular factors like status of oxidative stress and gap-junctions. These finding suggest that while selecting the cancer patients for charged particle/targeted alpha therapy, radiation oncologists need to also consider cellular and molecular features promoting non-targeted radiation effects for enhanced tumor radio-sensitivity.

Conclusion

NTRE after low and high LET radiation in the reference of cancer radiotherapy is rather an emerging research area which requires more studies for deeper mechanistic insights. The agents and strategies modulating NTRE for better tumor control would be of great interest to exploit the knowledge in cancer radiotherapy. The knowledge gained from in vitro and pre-clinical models provide further scope to evaluate the findings at the clinical level. The alpha particle radiation biology for cancer radiotherapy is in a nascent stage and requires exploration of the bystander interaction in the real tumor microenvironment conditions like hypoxia.

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