Life Sciences in Space Research 12 (2017) 51–60

Contents lists available at ScienceDirect

Life Sciences in Space Research

journal homepage: www.elsevier.com/locate/lssr

Development and performance evaluation of a three-dimensional clinostat synchronized heavy-ion irradiation system

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ARTICLE INFO

Article history:
Received 4 November 2016
Accepted 21 January 2017

Keywords:
Microgravity
Three-dimensional clinostat
Space radiation
Heavy-ion
Combined effects

ABSTRACT

Outer space is an environment characterized by microgravity and space radiation, including high-energy charged particles. Astronauts are constantly exposed to both microgravity and radiation during long-term stays in space. However, many aspects of the biological effects of combined microgravity and space radiation remain unclear. We developed a new three-dimensional (3D) clinostat synchronized heavy-ion irradiation system for use in ground-based studies of the combined exposures. Our new system uses a particle accelerator and a respiratory gating system from heavy-ion radiotherapy to irradiate samples being rotated in the 3D clinostat with carbon-ion beams only when the samples are in the horizontal position. A Peltier module and special sample holder were loaded on a static stage (standing condition) and the 3D clinostat (rotation condition) to maintain a suitable temperature under atmospheric conditions. The performance of the new device was investigated with normal human fibroblasts 1BR-hTERT in a disposable closed cell culture chamber. Live imaging revealed that cellular adhesion and growth were almost the same for the standing control sample and rotation sample over 48 h. Dose flatness and symmetry were judged according to the relative density of Gafchromic films along the X-axis and Y-axis of the positions of the irradiated sample to confirm irradiation accuracy. Doses calculated using the carbon-ion calibration curve were almost the same for standing and rotation conditions, with the difference being less than 5% at 1 Gy carbon-ion irradiation. Our new device can accurately synchronize carbon-ion irradiation and simulated microgravity while maintaining the temperature under atmospheric conditions at ground level.
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1. Introduction

Astronauts can now stay in space longer than before because of scientific advances, such as the construction of the International Space Station (ISS). The ISS orbits the Earth at an altitude of about 400 km, and astronauts are exposed to high-energy radiation originating from space. Exposure doses in the ISS have been estimated at about 1 mSv/day, which is about 100 times the dose received on the ground. There is thus an urgent need to obtain basic data of the effects of space radiation for the assessment and management of health risks in space. Several space agencies (i.e., the Russian Space Agency, European Space Agency, and Canadian Space Agency) have established their own maximum allowable effective doses for an astronaut's lifetime, which are generally 1 Sv (Zeitlin et al., 2013). Continuous area radiation monitoring has been performed within the Japanese experiment module Kibo on board the ISS (Nagamatsu et al., 2013).

To further human activity in space, it is necessary to study biological effects of combined microgravity and space radiation. In previous space experiments, there was no appreciable difference in results between space and ground samples because the time spent in space was short and samples were thus exposed to space radiation at a low dose (Bender et al., 1968). Although various organisms were pre-irradiated before space flight to test the effect of microgravity on the repair of radiation-induced damage, there was again no appreciable difference in results (Horneck et

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http://dx.doi.org/10.1016/j.lssr.2017.01.003
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al., 1997; Pross and Kiefer., 1999; Takahashi et al., 2001, 2000). Meanwhile, it has been reported that the presence of microgravity enhances the effects of space radiation (Bücker et al., 1986; Gao et al., 2015; Ikenaga et al., 1997), although suppressing effects (i.e., recovery from radiation damage was enhanced under microgravity) have also been observed (Kobayashi et al., 1996). Control experiments performed in space at 1*G* have been limited. Discussions on whether microgravity and radiation have combined effects remain unsettled (Yatagai and Ishioka, 2014). It has been demonstrated that spaceflight preferentially disturbs the expression of cytoskeletal genes, including the expression of mitochondrial anchoring protein (Nikawa et al., 2004). Organelles, which are held in precise positions by the cytoskeleton, and especially mitochondria, are disturbed in spaceflight owing to the low production of chemical energy and leaking of free radical species in microgravity (Nikawa et al., 2004). In addition, there has been an interesting study on the inactivation of survival signaling, such as insulin-like growth factor-1 (IGF-1)/phosphoinositide 3-kinase (PI3K)/v-akt murine thymoma viral oncogene homolog 1 (Akt-1) signaling, in microgravity (Nakao et al., 2009). It is thought that radiobiological effects are affected by these phenomena in microgravity.

In the field of space biology, it is presently difficult to investigate the combined effects of radiation and microgravity because space experiments and replicate experiments are restricted. Independent effects of only microgravity or radiation at ground level have been reported, assuming a space environment. However, there have been few reports on the true combined effects of microgravity and radiation. To address these problems relating to ground experiments, a novel approach that will facilitate evaluation of the combined biological effects of microgravity and radiation.

Well-known methods of simulating microgravity on Earth make use of freefall employing a drop tower or parabolic flight but produce microgravity conditions for only a short time (Pietsch et al., 2011). In the case of parabolic flight, there is an effect of hypergravity in addition to the effect of microgravity. The duration of microgravity obtained employing these methods is too short for plants or cultured cells to exhibit obvious changes in growth and development, whereas the environment created on Earth within a clinostat is often referred to as simulated microgravity and can be used without time restriction (Russomano et al., 2005). In addition to the methods of free-fall flight and the (two-dimensional or three-dimensional (3D)) clinostat, the method of using a rotating wall vessel (RWV) is also well known (Pietsch et al., 2011). The 3D clinostat was thus used in the present study to generate microgravity on the ground. This device can manipulate the effect of gravity through 3D rotation about two orthogonal axes and through continuously changing the direction of gravity. However, problems arise when irradiating cell samples in the 3D clinostat. In previous studies on the effects of simulated microgravity and radiation using the 3D clinostat (Indo et al., 2015) or the RWV (Wang et al., 2015), it was necessary to stop rotation during irradiation. The effects of simulated microgravity are not present during irradiation in that approach. The chronic irradiation of samples on the 3D clinostat in an incubator using neutrons of several MeV from a radioisotope (RI) ^{252}Cf has been reported (Beck et al., 2014; Pani et al., 2016), but radiation effects were not compared with those of non-rotating control samples in the cited studies. The dose rates used for the 1*G* control samples and the 3D clino-rotation samples were different because of partial nonuniformity of the dose in the irradiation area owing to rotation. To solve this issue, a theoretical system that rotates the sample and the RI together in an incubator can be proposed. Using this system, a large machine is needed to eliminate location dependence by reducing the distance between the RI and samples. However, the use of a large machine is not a realistic method of chronic irradiation under simulated microgravity (Ikeda et al., 2016). It has thus been difficult to combine microgravity and irradiation in controlled experiments.

Moreover, heavy-ion particles induce a high density of severe damage to deoxyribonucleic acid (DNA) along particle tracks, unlike the case for photons such as X-rays, which induce DNA damage that is more randomly distributed (Asaithamby et al., 2011). Using a immunocytochemistry of phosphorylation of the Ser-139 residue of the histone variant H2AX (γH2AX), it was also reported that heavy-particle irradiation produces complex DNA double-strand breaks (DSBs), and clustered γH2AX foci at DSBs induced by heavy-particle radiation cause prolonged check point arrest compared with simple γH2AX foci following X-irradiation (Izumi Nakajima et al., 2013). It is thus necessary to investigate the biological effects induced by high-energy charged particles using an accelerator on the ground.

Without being subject to the temporal restriction faced in previous experiments, our new device provides accurate and synchronized irradiation of samples rotating in the 3D clinostat, which simulates microgravity, only when the samples are in the horizontal position. In addition, our system maintains temperature and atmospheric conditions during irradiations using a large accelerator. The present paper describes the development and performance evaluation of the new 3D clinostat synchronized irradiation system.

2. Materials and methods

2.1. System descriptions

The 3D clinostat and irradiation synchronization system comprised four subsystems: (1) the 3D clinostat, (2) sample stages, (3) controllers, and (4) the synchronized carbon-ion irradiation subsystem. Specifications are summarized in Table 1. The subsystems are described in subsequent sections.

2.2. 3D clinostat

The 3D clinostat (Portable Microgravity Simulator PMS-CSTI; Advanced Engineering Services Co. Ltd. (AES), Ibaraki, Japan) is shown in Fig. 1A. The X:Y ratios of clino-rotation were set at 11:13 rpm and = 66°/s:78°/s using a special controller to maintain suitable conditions. The rotation angle between the Z-axis of the 3D clinostat (i.e., the axis of radiation exposure) and the normal line of the sample holder on the 3D clinostat, θ, was kept at less than 12°, assuming an X: Y clino-rotation of 11:13 rpm. This corresponds to an irradiation time of 0.2 s per sample at intervals of 60 s between exposures for each of the two samples in the holder. When the surface of the sample holder was projected on the X-Y surface for the angle $\theta = 12°$, the projected area was at most 98.4% of the projected area for $\theta = 0°$ The build-up time of the 3D clinostat was set at 10 s. A static stage (AES) (Fig. 1B) for control experiments under a standing (non-rotating) condition was used to compare the effects of radiation alone with those of combined radiation and microgravity. Although the X-axis and Y-axis of the static stage were horizontally fixed, the dimensions and temperature control method of the static stage were the same as those of the 3D clinostat.

2.3. Cell culture

Normal human fibroblasts 1BR-hTERT were typically grown in minimum essential medium, alpha modification (MEMα) (Wako, Osaka, Japan) with L-glutamine by adding 10% (v/v) fetal bovine serum (MP, Santa Ana, CA, USA), 1 mM 2-[4-(2-hydroxyethyl)−1-piperazinyl] ethanesulfonic acid (Dojindo, Kumamoto, Japan), and penicillin-streptomycin mixed solution (Nacalai Tesque, Kyoto,

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