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Exposure to radiation and its health effects on the cardiovascular system

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Abstract

Worldwide, people are being exposed to natural and man-made sources of radiation. Epidemiological studies have shown an increased risk of vascular diseases in populations that have been exposed to ionizing radiation. Vascular endothelium is implicated as one of the targets for radiation leading to the development of cardiovascular diseases. However, the molecular mechanisms behind the development of radiation-induced cardiovascular disease in acute or chronic exposed people are not fully elucidated. The hypothesis that chronic low dose rate ionizing radiation accelerates the onset of senescence of primary human umbilical vein endothelial cells has been tested . Therefore, the study aimed to find out the relationship between radiation, heart disease, the devices used for diagnosis, and their relationship to increasing the risk of diseases from various aspects.

Keywords: Radiation; Cardiovascular; Epidemiology; Endothelial

1. Introduction

People are being chronically exposed to natural radiation as well as to man-made sources of radiation[1]. High levels of natural background radiation are found in some regions of the globe such as the southwest coast of Kerala in India, Yangjiang province in China, Ramsar in Iran and Gaurapari in Brazil[2, 3]. Residents living in these high background radiation areas receive a high life time dose due to chronic low-level dose of radiation from environmental radioactive elements[4]. In addition to terrestrial sources, cosmic radiation adds to natural radiation in our environment. Moreover, accidents in nuclear power industries including scenarios of Fukushima Daiichi (Japan), Chernobyl (Ukraine) and atomic bomb explosions (Hiroshima and Nagasaki) disperse radioactive materials into the environment. Man-made sources of ionizing radiation are widely used as diagnostic tools and therapeutic agents in treatment of diseases. The cumulative exposure to ionizing radiation has the potential to cause harmful health effects leading to chronic diseases[5]. Radiation therapy demonstrates a clear survival benefit in the treatment of several malignancies. However, cancer survivors can develop a wide array of cardiotoxic complications related to radiation[6]. This pathology is often underrecognized by clinicians and there is little known on how to manage this population. Radiation causes fibrosis of all components of the heart and significantly increases the risk of coronary artery disease, cardiomyopathy, valvulopathy, arrhythmias, and pericardial disease. Physicians should treat other cardiovascular risk factors aggressively in this population and guidelines suggest obtaining regular imaging once symptomatology is established. Patients with radiation-induced cardiovascular disease tend to do worse than their traditional counterparts for the same interventions[7]. However, there is a trend toward fewer complications and lower mortality with catheter-based rather than surgical approaches, likely because radiation makes these patients poor surgical candidates. When appropriate, these patients should be referred for percutaneous management of valvulopathy and coronary disease[8]. Therefore, the aim of the study was to investigate the relationship of radiation and its effect on cardiovascular diseases within the study area, according to the data obtained.

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2. Ionizing radiation

2.1. General aspects of ionizing radiation

Radiation is defined as the physical process where particles or electromagnetic waves pass through a medium or space. Ionizing radiation consists of either photon-radiation (gamma rays and x-rays) or fast moving sub-atomic particles (beta particles, neutrons, etc.). Gamma rays consist of electromagnetic energy in the form of photons emitted by radioactive nuclides such as caesium-137[9]. Also cosmic radiation is one of the sources of gamma radiation. Gamma rays can penetrate biological tissues and cause ionization of atoms and molecules. Gamma rays as well as x-rays are commonly used for medical and technological purposes[10].

The quantity of energy deposited by ionizing radiation in a defined mass of material is termed the absorbed dose and is measured in J/kg and the unit name is Gray (Gy)[11]. The deposition of energy through ionization of atoms and molecules causes chemical changes[12]. Linear Energy Transfer (LET) is defined as the energy per unit length transferred to material when an ionizing particle/wave travels through it[13]. It is measured in keV μm^{-1} and the value varies with different types of radiation from a few keV μm^{-1} (diagnostic X-rays) to >1000 keV for heavy ions[14].

A radiation track is characterised by energy depositions occurring in clusters along the trajectories of charged particles. The penetration of gamma-rays into the tissue is much deeper than that of alpha particles[15]. The deposition of energy and the subsequent damage induced by gamma-rays is spread throughout the tissue, whereas alpha particles deposit more energy along its track causing high local damage[16].

2.2. Effects of ionizing radiation

The energy deposition releases ionization products along the track in a random manner. These interact with other molecules to cause damage/modification to all molecular components such as deoxy-ribonucleic acid (DNA), proteins and lipids[17]. Direct radiation damage is caused by direct ionizations of the DNA when the track crosses close to DNA strand, which in this case may lead to single or double strand breaks (DSB)[18]. Indirect damage to DNA is mediated by radiation produced free radicals in the medium that diffuse to DNA and react locally[19].

Ionizing radiation can induce several types of DNA lesions including single strand breaks and DSB, base damage, base loss and more complex combinations (also called locally multiple damaged sites)[20]. Severity of lesions depends on the energy deposition in time and space of radiation. The majority of low LET radiation effects arise indirectly by production of free radicals whereas high LET radiation induces a higher density of ionizations and excitations (direct effect) along the track, causing multiple lesions at the sites of DNA[21]. DNA lesions are repaired by specific repair mechanisms including base excision repair, mismatch repair, nucleotide excision repair and DSB repair[22].

Among DNA lesions, DSB are considered as most biologically important as they could be lethal[23], and two distinct double-strand break repair mechanisms are present in the cell: homologous recombination (HR) and non-homologous end-joining (NHEJ)[24]. HR is considered as a precise repair mechanism due to copying information from the undamaged homologous double strand of DNA. In contrast, NHEJ uses no sequence homology and is prone to error. Damage to bases and sugars also results in the breakage of strands, all of which disrupt structural integrity of the DNA. These modified bases and single strand breaks are recognized and restored by base excision repair process[25]. Erroneous DNA repair may lead to the occurrence of mutations, neoplastic transformation, premature senescence and cell death[26].

Additionally, a broad range of molecular mechanisms are also providing evidence to understand the radiation induced effects. At the level of the organism, radiation induced long term consequences may at least in part be systemic due to the action of cytokines, chemokines, continuous generation of free radicals[27].

However, the complete cellular/molecular mechanism behind radiation induced cellular or tissue effects are not fully understood.

3. Epidemiology of radiation-induced non-cancerous health effects

The evidence from epidemiological studies highlights cancer as one of the major health hazards of ionizing radiation in the low and medium dose range. Recently, data are accruing showing that the risk of non-cancerous diseases such as cardiovascular disease (CVD), cataracts, respiratory and digestive diseases etc. are also significantly increased by radiation[28].

The life span studies on survivors of the atomic bomb explosions in Hiroshima and Nagasaki show that these populations have developed an excess risk of non-cancer diseases[29].The dose-response relationship for the risk of solid cancers seems to be linear down to at least 100 mGy[30], but much less is known about the shape of the dose-response curve for non- cancer effects. It has been suggested that radiation-induced non-cancerous diseases can take many decades to develop after radiation exposure[31]. Cardiovascular diseases, especially heart disease and stroke, are the major types of non-cancer effects among Japanese atomic- bomb survivors with a significantly elevated risk at dose levels higher than 0.5 Gy[32].

Due to the increased use of radiation in diagnostic or occupational situations, the number of people exposed to radiation is increasing. In the context of radiotherapy, increased risk of non-cancer effects were observed after radiotherapy for breast cancer[33] .

In addition, cohort studies on occupationally exposed radiation workers show increased risk of mortality from circulatory disease[34] as was shown for the Workers of the Mayak Production Association that were exposed to chronic radiation[35]. However, the studies on long-term chronic low dose radiation-induced circulatory disease still remain elusive. More data on biological effects of chronic doses and different dose rates are also needed for risk estimations of adverse health effects during space travel.

4. Cardiovascular system

The cardiovascular system comprises the heart and blood vessels. Endothelial cells form a unique and single-layered lining of the luminal side of the blood and lymphatic vessels. The endothelium forms an interface between the circulating blood, lymph system and underlying tissues. This disseminated organ possesses several vital functions including formation of new blood vessels in a process called angiogenesis, regulation of perfusion, fluid and solute exchange between tissue and blood, haemostasis. coagulation and inflammatory response , these versatile, multifunctional properties make a proper functioning of the endothelium crucial for health; endothelial damage or senescence leads to multiple vascular diseases. Thus, endothelium plays a key role in physiological as well as pathological processes[36].

4.1. Cardiovascular disease

CVD is one of the major causes of the mortality, accounting for one-third of deaths worldwide and has also become a global economic problem in developed and developing countries. The major risk factors include behavioural factors such as consumption of tobacco, alcohol, and fatty nutrients; metabolic (raised lipid levels, obesity) and other risk factors such as hypertension, advanced age, gender and family history. The major forms of vascular disease are coronary heart disease and stroke[37].

Atherosclerosis- a disease of the arteries- is characterised by development of plaques, thickenings of artery wall as a result of the accumulation of fatty materials such as cholesterol and triglyceride. Rupturing of plaques leads to the formation of a thrombus that rapidly reduces or stops the blood flow and results in death of the local tissue fed by the artery. Thus, atherosclerosis may lead to heart attacks and stroke. Coronary heart disease is a late manifestation of atherosclerotic changes[38]. Factors inducing atherosclerotic plaque formation represent the principal cause of CVD mortality and morbidity.

4.2. Radiation-induced cardiovascular damage

Radiation-induced CVD is seen as a long-term effect of radiation. Cardiovascular pathologies associated with radiation include myocardial infarct, congestive heart disease, pericarditis, vascular abnormalities, atherosclerosis, valvular heart disease, arrhythmias etc[39]. The incidence of cardiovascular disease among radiation exposed populations is primarily influenced by general cardiovascular risk factors - environmental, life style, genetic and other risk factors[40].

The cohort study in Canada on industrial, medical and dental workers exposed to radiation showed a trend of increased mortality due to CVD. An increased risk of CVD was observed in occupational studies on nuclear workers and chronically exposed plutonium plant workers . Increase of circulatory and arteriosclerotic heart diseases have been observed among US nuclear power industry workers exposed to chronic low dose ionizing radiation[41] .

Radiation-related excess of CVD mortality and morbidity was observed in life span studies among Japanese atomic bomb survivors. Epidemiological evidence has established a link between cardiovascular disease and exposure of the heart and major vessels to radiation doses above 0.5 Gy. For lower doses the evidences for a detrimental effect are not conclusive. One of the suggested mechanisms triggered by a low- dose exposure could be endothelial dysfunction[42].

Radiation-induced CVD is of concern for radiotherapy patients. A substantial risk of CVD mortality by myocardial infarctions and ischemic heart disease was observed after radiotherapy for Hodgkin disease . High doses of ionizing radiation ranging from 3 to 17 Gy that were used to treat left sided breast cancer patients have been associated with long- term risk of cardiac pathology such as diffused fibrotic injury to the pericardium and myocardium . Exposure of heart to a mean dose of 4.9 Gy during radiotherapy for breast cancer showed an increased risk of coronary heart disease within a few years in a population-based case-control study in Sweden and Denmark[43]. Long term follow up of cancer survivors have confirmed the association between coronary heart disease and high local doses (5-18 Gy) of ionizing radiation applied to treat peptic ulcers (28) and childhood cancer[44].

Studies using mouse models have indicated that ionizing radiation (14 Gy) may be an independent factor able to induce heart pathologies. Seemann et al. showed the changes in the cardiac function, structural damage to myocardium and functional changes of micro vascular endothelial cells in the dose (2, 8 and 16 Gy) and time dependent manners[45]. Experimental studies using a local heart dose of 2 Gy showed persistent changes after 40 weeks in the mitochondrial metabolism and cardiac cytoskeletal structure . Proteomic studies at 5 and 24 hour after total body irradiation (3 Gy) indicated an early biological response resulting from oxidative stress in the heart[46], thus indicating an increased risk of cardiovascular effects after radiation exposure. In spite of epidemiological and biological evidence demonstrating the damaging effect on the cardiovascular system, the mechanisms still remain elusive.

5. Radiation and endothelial dysfunction

Epidemiological studies have suggested that vascular damage may be involved in radiation- induced CVD at doses from 2 Gy . The delayed injury in several tissues after radiotherapy has been considered to be a consequence of vascular damage, most often affecting the microvessels[47].Using an ApoE-deficient mouse model, Hoving et al. demonstrated by histopathological methods that radiation (> 5 Gy) caused damage to the vasculature of the heart. Endothelial dysfunction is one of the contributors to vascular diseases and adverse cardiovascular events[48].

Consequently, endothelium is being considered as one of the targets for radiation-induced CVD damage. Endothelial damage was observed in human coronary arteries and cardiac microvasculature after high doses[49]. Proteomic studies after gamma irradiation ranging from 200 mGy to 10 Gy have revealed radiation-induced oxidative stress in endothelial cell lines affecting metabolic pathways , cytoskeletal structure and pro-inflammatory processes, Furthermore, angiogenesis has been shown to be inhibited by radiation (15 Gy); a process requiring endothelial cell proliferation. Experimental findings in rats identified the significant loss of the enzyme alkaline phosphatase activity in endothelial cells. These functional and structural changes in endothelial cells could contribute to the development of radiation-induced CVD[50] .

Dysfunction of endothelial cells is involved in inflammatory processes, emphasized by increased adhesiveness of leukocytes and platelets. Further alterations in the permeability of endothelium could result in transmigration and activation of leukocytes which is associated with chronic events of atherosclerotic plaque formation as shown in figure 1. Recognition of chronic events such as trans endothelial migration of leukocytes was observed in endothelium after radiation ,It has been shown that endothelial cell senescence plays an important role in the inflammatory response and also in the initiation and development of atherosclerotic plaques.

Atherosclerotic plaque formation can lead to complications such as myocardial infarction and stroke . Significantly increased risk for arteriosclerotic diseases was observed among

U.S. nuclear power industry workers exposed to chronic low dose radiation . As endothelial senescence can lead to progression of radiation-induced CVD, it is important to investigate the effect of chronic low dose rates and the underlying mechanisms behind radiation-induced premature senescence in endothelial cells[51].

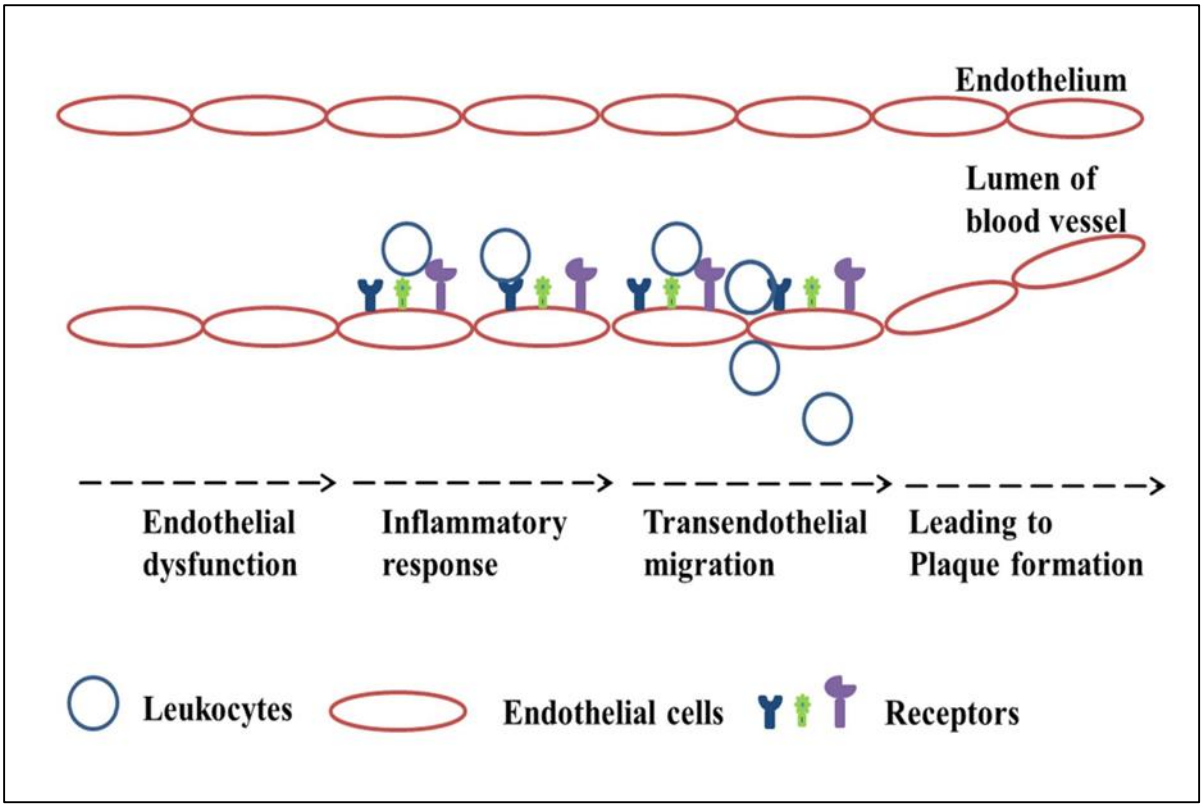

Figure 1 Initial cellular events in the progression of atherosclerosis

Endothelial dysfunction is associated with the increased expression of adhesion molecules such as integrin. Further, inflammatory events follow adhesion and transmigration of leukocytes leading to atherosclerotic plaque formation in the blood vessel[36].

6. Senescence

6.1. Replicative senescence

Replicative senescence was first described in cultured fibroblasts by Leonard Hayflick and Paul Moorhead in 1961.The limited ability of mammalian cells to proliferate is dependent on the type of cells and the maximum number of cell divisions *in vitro is* called the Hayflick limit. Senescence is a complex biological process observed both under *in vitro* and *in vivo* conditions. Senescence is considered to play a major role in aging and age-related diseases. Endothelial senescence is associated with cardiovascular pathologies, cerebrovascular diseases and atherosclerotic lesions[52] .

6.2. Oxidative stress and radiation-induced senescence

Endogenous reactive oxygen species (ROS) originates mainly from mitochondria as a normal by-product of cellular respiration and is rapidly removed. Excess ROS react with intracellular targets leading to peroxidation of lipids, hydroxylation of proteins and DNA base damage.

ROS can also react with 7, 8-dihydro-2'-deoxyguanosine triphosphate in the nucleotide pool and give rise to 8-oxo-7, 8-dihydro-2'-deoxyguanosine triphosphate (8-oxo-dGTP). The human MutT homologue 1 (hMTH1) enzyme prevents incorporation of 8-oxo-dGTP into the DNA during DNA synthesis by hydrolysing it to 8-oxo-dGMP. 8-oxo-dGMP will be further dephosphorylated to 8-Oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxo-dG) and then excreted from the cells to extracellular fluids such as blood and urine *in vivo* or cell culture medium *in vitro* as shown in figure 4. Thus, extracellular 8-oxo-dG is being considered as a sensitive biomarker for oxidative stress[53]

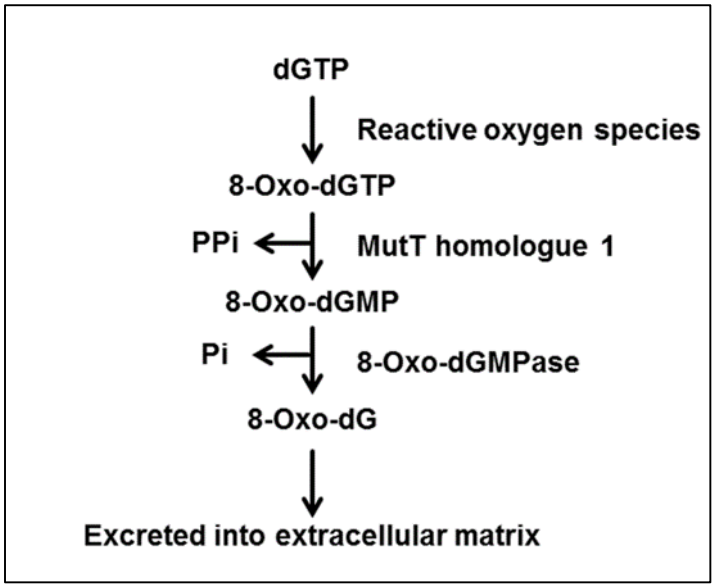

Figure 2 Formation and excretion of 8-oxo-dG

8-oxo-dGTP will be formed in the nucleotide pool from dGTP due to oxidative stress. It is converted into 8-oxo-dG as a result of the action of the enzymes hMTH1 and 8-oxo-dGMPase and is then excreted into the extracellular medium. Modified from Michaels et al[54].

A number of antioxidant defence mechanisms are acting to neutralise the ROS and to protect cells from damage . However, if the production of ROS exceeds the levels of the available antioxidants, oxidative stress is induced which may result in oxidized base damage and increased risk of genotoxicity. In endothelial cell oxidative stress and the levels of free radicals have been shown to correlate with senescence. Accumulated levels of 8- hydroxydeoxyguanosine in the DNA was reported in cellular senescence due to increased oxidative stress. It has been suggested that oxidative stress can cause accumulation of single stranded breaks in DNA (122) which may trigger senescence. Oxidative stress coupled to mitochondrial dysfunction is considered as a major stimulus for senescence.

Ionizing radiation itself induces oxidative stress, DNA damage and mitochondrial dysfunction ,and these are associated with premature senescence. Indeed, exposure to high doses of ionizing radiation 5 or 15 Gy inhibits cell proliferation and induces premature senescence in endothelial cells.Similarly, 5 days after exposure to acute radiation dose of 2, 4 and 8 Gy, a dose dependent increase of SA-β-gal activity was observed in vascular endothelial cells. Endothelial senescence has been observed in vascular lesions of radiotherapy patients exposed to acute doses[55].

So far, induction of senescence-like phenotype was studied as a function of radiation dose but studies on the effect of the dose rate have been scarce. Mitchel et al. investigated the importance of the dose-rate (1 mGy/min and 150 mGy/min) of irradiation on the development and progression of atherosclerotic plaques in ApoE-deficient mice. They reported that many parameters such as dose, dose rate, and age of mice influenced the progression of atherosclerosis[36]. The higher dose rate given at young ages could be both protective and detrimental. However, the role of low dose rate ionizing radiation on induction of endothelial senescence still remains unclear. Therefore, studies on low-dose-rate radiation- induced premature senescence will be helpful in revealing biological mechanisms of vascular diseases in chronically exposed populations[56].

7. Objectives of the thesis

Radiation protection research is challenged to provide more precise risk estimates for chronic radiation-induced cardiovascular diseases and a better mechanistic understanding the long term effect of ionizing radiation on endothelium and the cardiac tissue.

The aims of the studies presented here were:

- To determine whether chronic low dose rate radiation exposure premature endothelial senescence and if the proteomic analysis could provide a mechanistic understanding of the process.

- To study long term effects of acute doses of radiation on cardiac tissue and through a proteomic approach elucidate the possible molecular mechanism leading to cardiovascular disease.

8. Conclusions

Epidemiological studies show an association between both acute and chronic radiation exposure and long term cardiovascular effects. The present study was designed to better understand the long term effect of ionizing radiation on endothelium (Paper I and II) and the cardiac tissue (Paper III).

Our studies have demonstrated that chronic low dose rate gamma radiation induces premature senescence in primary HUVEC. Senescence was observed when the accumulated dose reached the value of around 4 Gy, with dose rates of either 4.1 or 2.4 mGy/h. In case of the dose rate 1.4 mGy/h, the cumulative population doublings were similar to the control cells before senescence was reached although the cumulative dose at this point was around 4 Gy. Our study (unpublished data) also showed significant increased levels of 8-oxo-dG in the medium with only 4.1 mGy/h dose rate at a cumulative dose 4 Gy. Therefore, the cumulative dose alone cannot be correlated to the induction of SIPS. These finding emphasize that the SIPS for HUVEC is both dose and dose rate dependent.

This study highlights the important role of PI3K/Akt/mTOR pathway inhibition in the induction of senescence. Moreover, the proteomic studies presented show the effect of chronic radiation on multiple signal transduction pathways involved in endothelial dysfunction. These include translation process, cellular adhesion, cell-cell communication and cytoskeletal organisation. The alterations of these processes are previously implicated as characteristic of senescent endothelial cells. Although practical significance of this study remains to be confirmed by *in vivo* research, increased understanding of the mechanisms leading to endothelial senescence may provide a basis for preventive measures for CVD seen in populations chronically exposed to low dose rate radiation.

There is a considerable evidence for increased risk of cardiovascular disease among people exposed to fractionated radiation doses . Further studies are necessary to investigate the effects of clinically relevant fractionated doses associated with vascular endothelial senescence. The induction of endothelial senescence after acute radiation (4 Gy) has been shown by SA-β-gal staining . Whether the identical molecular pathways are shared between acute and chronic dose radiation-induced senescence should be investigated.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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