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Review

Consequences of irradiation on bone and marrow phenotypes, and its relation to disruption of hematopoietic precursors

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ABSTRACT

The rising levels of radiation exposure, specifically for medical treatments and accidental exposures, have added great concern for the long term risks of bone fractures. Both the bone marrow and bone architecture are devastated following radiation exposure. Even sub-lethal doses cause a deficit to the bone marrow microenvironment, including a decline in hematopoietic cells, and this deficit occurs in a dose dependent fashion. Certain cell phenotypes though are more susceptible to radiation damage, with mesenchymal stem cells being more resilient than the hematopoietic stem cells. The decline in total bone marrow hematopoietic cells is accompanied with elevated adipocytes into the marrow cavity, thereby inhibiting hematopoiesis and recovery of the bone marrow microenvironment. Poor bone marrow is also associated with a decline in bone architectural quality. Therefore, the ability to maintain the bone marrow microenvironment would hinder much of the trabecular bone loss caused by radiation exposure, ultimately decreasing some comorbidities in patients exposed to radiation.

Contents

Introduction

It has been well established that radiation exposure causes a drastic deficit to bone marrow populations, but the severity of even sub-lethal doses will lead to irreparable tissue damage of the bone tissue. As cancer patients continue to undergo whole body and localized radiation therapy, it becomes imperative to determine a means to rescue their bone marrow population and maintain their bone architecture, to prevent the risk of bone fractures long term. Understanding the relationship between the cell phenotypes within the bone marrow and the bone architecture could lead to new insights on repairing the bone quality and immunological health. We will review the effects of irradiation on bone marrow phenotypic populations and the bone structure, and current treatment methods used to mitigate bone loss.

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Bone marrow failure induced by ionizing radiation

Bone marrow failure and current treatment methods

Bone marrow failure is defined as the inability to produce the proper number of blood cells necessary to control immune function. There are many different causes of bone marrow failure syndromes, of which some are acquired and some are inherited. Those that are acquired are typically due to exposure to chemicals, radiation, viruses, or other toxins. Both acquired and inherited disorders often lead to aplastic anemia [1], which is the failure to produce blood cells in the bone marrow. Acquired bone marrow failure disorders include aplastic anemia, hypoplastic myelodysplastic syndrome, myelodysplastic syndrome, myeloproliferative disorders, acquired pure red cell aplasia, amegakaryocyric thrombocytopenia, and chronic acquired neutropenia [2]. The inherited bone marrow disorders include Fanconi's Anemia, Diamond-Blackfan Anemia, Shwachman-Diamond Syndrome, Dyskeratosis Congenita, Severe Congenital Neutropenia, Thrombocytopenia Absent Radii, Amegakaryocytic Thrombocytopenia, and Pearson's Syndrome [1]. Patients who have these acquired or inherited bone marrow syndromes are at high risk of developing cancer and leukemia during their lifetimes. All types of bone marrow failure syndromes result in the inability to produce or maintain proper blood cell numbers and function in the bone marrow. Treatment options are dependent on the type of bone marrow failure syndrome. Often times patients will undergo hematopoietic stem cell transplantation from a donor who has the matching human leukocyte antigen, in many cases a sibling, and/or pharmacologic treatments including immunosuppressants [2], with the ultimate goal of maintaining a healthy bone marrow population to support a healthy immune response. Prior to transplantation though, ionizing radiation or chemotherapy are used to ablate the cancerous and the immune cells.

Ionizing radiation

Exposure to high doses of ionizing radiation will lead to bone marrow failure and eventually death. Sub-lethal doses of irradiation will cause bone marrow suppression, which is a less severe case of bone marrow failure, and will leave a patient immunosuppressed due to an abnormal number of functional blood cells. One of the more common types of radiation that humans are exposed to is γ-irradiation. Gamma irradiation is a result of nuclear decay and penetrates through tissue in an exponential fashion. The absorbed dose is measured in units of Gray (Gy), which is a measure of 1 joule of energy per kilogram of matter (J/kg). Alternatively, radiation can be measured using "equivalent dose," which is primarily used to describe the dose of radiation to a fixed amount of biological tissue, and uses the Sievert (Sv) unit. To convert from the absorbed dose measured in gray to the equivalent dose measured in Sv, it is necessary to use a radiation weighting factor which is specific to the type of ionizing radiation. For γ-rays and x-rays, this weighting factor is 1, therefore 1 Gy of γ-irradiation is equivalent to 1 Sv to the biological tissue.

Human and mouse exposure to ionizing radiation

Ionizing radiation occupational exposure limits are heavily regulated in the United States by the United States Nuclear Regulatory Commission (U.S.NRC) and are categorized by dose equivalents for eye exposure, organ exposure, and whole body exposure. The annual limit for the total effective dose equivalent to the whole-body is 50 mSv/yr, where 1 Sv is the dose equivalent of a 1 Gy absorbed dose of γ-irradiation. To put this into perspective, a CT scan of the chest is approximately 5 mGy and exposure from a dental X-ray exam is approximately 0.2 mGy. Even if one avoids irradiation from medical imaging techniques, everyone receives minimal doses of radiation from the natural environment which includes radon, cosmic, and terrestrial sources.

In 2006, the average person is the United States was exposed to approximately 6.2 mGy annually [3], which is presumed to be below a harmful dose. The lethal dose of radiation though is species dependent. For instance, the median lethal dose of total body γ-irradiation within 60 days (LD50/60) in humans falls between 2.5 and 5 Gy [4], whereas in C57BL/6 mice, the median lethal dose within 30 days (LD50/30) is approximately 8 Gy [5]. The region surrounding the Fukushima Daiichi reactors sustained radiation levels that could have certainly been harmful to humans, with doses estimated as high as 400 mGy/year [6], and well above the 50 mGy/yr U.S.NRC limit. It is likely that it will take decades to decay without proper cleanup, therefore people who return to settle or work in the evacuated regions receiving 100 mGy/yr could receive a cumulative dose up to 1 Gy over a 10 year period, which could pose a large biological hazard.

While some argue that there are beneficial effects of low doses of radiation, such a platform remains controversial [7,8]. However, high doses of radiation exposure are often beneficial for pursuing medical treatments. Many patients with hematological disorders and cancers of the bone marrow undergo elective radiation therapy, where they are exposed to 12 Gy of total body irradiation in order to ablate the marrow prior to bone marrow transplantation [9]. Patients with tumors can also undergo localized radiotherapy and are often administered doses as high as 66 Gy of γ-irradiation [10]. Many of these patients undergoing radiation therapy are exposed to fractionated doses of radiation [11], allowing the radiation dose to be spread out over a period of time. The purpose of fractionation is to allow for the repopulation and repair of non-cancerous cells while still providing the toxic effect to the cancerous cells. For tumor ablation, the fractionated doses range between 2 Gy/fraction to 20 Gy/fraction, and can be administered daily or even twice a day, up to a few weeks. The fractionated regime is dependent on the type of tumor being ablated.

Patients undergoing radiation therapies though have been shown to suffer from bone loss, and have elevated fracture risk [12–14], which is quite problematic due to the vast number of people undergoing radiation therapy annually and the difficulty in managing radiation associated fractures [15]. According to the 2013 Surveillance, Epidemiology, and End Results Program statistics, there were 12.8 cases of leukemia diagnosed in every 100,000 people in the United States. Furthermore, there are more than 1,129,800 people living with or in remission from leukemia, myeloma, non-Hodgkin's lymphoma, and Hodgkin's lymphoma [16], for all of which whole body irradiation therapy is a common treatment, and often used in combination with chemotherapy. The fracture rate in these patients is believed to be elevated and has been shown in children with acute lymphoblastic leukemia, but data has not been collected quantifying the overall fracture risk of leukemia patients on a mass scale [13,14,17]. In 2006 alone, there were 17,875 people in North America and 50,417 people worldwide who underwent a bone marrow transplant, primarily due to leukemia or another lymphoproliferative disorder, and many of them were exposed to total body irradiation prior to transplantation [18]. Now that there is a 60% survival rate for leukemia patients compared to a 10% survival in the 1950s, a 72% survival for non-Hodgkin's lymphoma compared to 33% in the 1950s, an 89% survival for Hodgkin's lymphoma compared to a 30% survival in the 1950s and a 45% survival for myeloma compared to only a 6% survival in the 1950s [16], these increased survival rates inevitably increase the complications due to radiation exposure, including osteopenia and osteoporosis [12]. Therefore the ability to protect and/or regenerate bone and reduce the risk for bone fractures is of increasing importance, particularly considering patients are now living longer following diagnosis of the disease and radiation associated fractures are difficult to treat [15].

Relationship between mesenchymal stem cells and hematopoietic stem cells within the bone marrow

The bone marrow is situated internal to the skeleton and serves as a principal home for two multipotent stem cell populations, the