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Mini-review

Radiation triggering immune response and inflammation

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ABSTRACT

Radiation therapy (RT) is a well-established but still under optimization branch of Cancer Therapy (CT). RT uses electromagnetic waves or charged particles in order to kill malignant cells, by accumulating the energy onto these cells. The issue at stake for RT, as well as for any other Cancer Therapy technique, is always to kill only cancer cells, without affecting the surrounding healthy ones. This perspective of CT is usually described under the terms "specificity" and "selectivity". Specificity and selectivity are the ideal goal, but the ideal is never entirely achieved. Thus, in addition to killing healthy cells, changes and effects are observed in the immune system after irradiation. In this review, we mainly focus on the effects of ionizing radiation on the immune system and its components like bone marrow. Additionally, we are interested in the effects and benefits of low-dose ionizing radiation on the hematopoiesis and immune response. Low dose radiation has been shown to induce biological responses like inflammatory responses, innate immune system activation and DNA repair (adaptive response). This review reveals the fact that there are many unanswered questions regarding the role of radiation as either an immune-activating (low dose) or immunosuppressive (high dose) agent.

Introduction

The use of ionizing radiation in cancer treatment is constantly being improved during the last century [1]. Currently, Radiation Therapy is considered as one of the main strategies in the fight against cancer. Several recent investigations have shown that low-dose radiation (LDR) is even more effective in cancer treatment than the daily doses of 1–2 Gy administrated in the frame of conventional RT. The fact that low dose radiation could stimulate the immune system – in contrast to high doses that usually suppress it – justifies the newly arisen interest in LDR. Therefore, here we discuss how a varied scale of doses could impact a plethora of biological effects in tumor as well as in immune system cells. As can be seen in multiple genome studies, varying the dose of ionizing radiation may lead to quite different effects on several cell types [2–5].

Low dose radiation has been shown to enhance biological responses, involving the immune system, enzymatic repair, physiological functions, and the repair of cellular DNA and protein damage. Experiments based on immunobiology methodologies and omics such as metabolomics, genomics and proteomics can give significant and robust data as well as a higher degree of repeatability [6,7].

The great scale radioactive contamination caused by the atomic bombing of Hiroshima and Nagasaki led to several undesirable outcomes, such as bone marrow suppression and cancer, in humans. This first observation, that radiation is able to suppress the immune system, gave the idea of utilizing IR on purpose, in case for example of bone marrow transplantation. Taking the advantage of IR to suppress immune response, this method is followed up to now in order to inactivate recipients' bone marrow stem cells, enhancing the possibility of graft acceptance [6,8,9].

Since then IR has become an important component of cancer treatment. The use of IR is so common in cancer therapy that it is estimated that almost one out of two patients has undergone RT during his or her treatment regimen [1]. RT is frequently used to achieve local or regional control of malignancies either alone or in combination with other methods such as chemotherapy or surgery [10].

Comprehensive studies conducted on dogs demonstrated the impact of radiation dose on the immune system [11–14]. In these experiments, whole-body gamma-irradiation (from a ^{60}Co source) continuously throughout the life span of the dogs with relatively low dose rates was utilized. At high-dose-rates (from 262.5 mGy/day up to 640 mGy/day) all animals died within 100 days. This was the largest systematic hematological chronic irradiation study known. Dogs were continuously irradiated for their entire lifetime until they

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die. According to the specific study reports, death was always due to anemia and immune deficiencies or septicemia, myeloproliferative disorder, pancytopenia and cancer if they survived enough. As a result of continuous radiation exposure, hematopoietic stem cells didn't have enough time to repair themselves and consequently diminish the likelihood of an effective adaptation of dogs' hematopoietic system. Dogs exposed to moderate radiation doses (from 127.5 mGy/day down to 37.5 mGy/day) may survive up to 1000 days. The causes of death in these cases were severe hematopoietic deficiencies, myeloproliferative disorders aplasia, septicemia or fatal tumors. Animals exposed to the radiation dose-rate of 18.8 mGy/day died from myeloproliferative disorders. However for lower dose-rates, the relative numbers of deaths from fatal tumors were surprisingly comparable with the control group. In the group of animals that were exposed to the radiation dose of 3 mGy/day, no hematopoietic deficiencies, myeloproliferative disorder aplasia or septicemia were observed. This group showed the same incidence of fatal tumors as the control group [11,13,14]. Although a great amount of important data have been and still are being produced from these studies many ethical questions arise due to the use of large number of animals and the unsuitable conditions of irradiation i.e. continuously.

Effect of radiation on the immune system

Low dose effects

The degree of the influence of ionizing radiation on human body cells depends on their rate of proliferation. Thus, bone marrow cells, germ cells and hair follicles as well as tumorigenic cells, since they are rapidly proliferative, are sensitive to IR [9].

Bone marrow cells and hematopoiesis can be severely affected with high-dose radiotherapy. Identification of cell cycle checkpoint processes resulted in important advances in this area. Ionizing radiation (IR) is the main reason for the perturbation of the cell cycle. It is well known that using radiation in cancer treatment results in apoptosis of the cells that are actively dividing and have functioning apoptotic pathways. Moreover, radiation does not affect that much cells which are in the resting stage (G0) or cells that are dividing less often. Ionizing radiation activates cell cycle checkpoints that arrest cell cycle at the G1/S, S, and G2/M phases [9]. The amount and type of radiation affect the speed of cell growth and cell viability. The term tissue *radiosensitivity* describes the relative susceptibility of cells and tissues to irreversible toxic damage by RT, chromosomal instability and cell death, which usually prevents mitosis or completion of normal metabolic pathways [10,11]. In this review, our main goal is to discuss the effects of low and high dose ionizing radiation on the immune system. We are interested in the effects and benefits of LDR on the hematopoiesis and immune system.

Recently, a great number of studies have shown that low-dose radiation (LDR) is even more effective in cancer therapy than the conventional daily doses of 1–2 Gy. While high doses of the radiation therapy are known to suppress the immune system, low doses have been shown to increase the immune response [2,6–9], thus reducing systemic toxicity, as well as increasing anti-tumor response.

In order to understand the radiosensitivity of hematopoietic cell renewal systems, it is necessary to discuss experiments done on rodents, that were subjected to chronic whole-body radiation [15–18]. Lamerton began to perform studies on rats exposed to chronic irradiation in the 1950s. When animals were exposed to radiation (1.76 Gy/day), first their immune system responded positively and peripheral blood count increased. However within 20 days, their bone marrow failed to produce platelets and leukocytes, leading to animal death. Even in an exposure with a radiation dose of 0.84 Gy/day, the first response was always the stimulation of the bone marrow, followed by the failure of the bone marrow. The bone marrow of the rats exposed to radiation (0.16–0.50 Gy/day) repaired itself within 20 days. After homeocytostasis occurred, the body compensated for the cell loss and the rats survived [19].

In some cases, LDR during the first days post-irradiation can have an effect on the bone marrow similar to that of high-dose radiation [20]. The only difference is that the low-dose irradiated bone marrow quickly repairs itself. A potential peripheral-blood cell count would have rather misleading suggestions, since the proliferative capacity of bone marrow is more important than blood count. There are many studies to determine the proliferation capacity of lymphocytes, such as Concanavalin A induced lymphocyte proliferation. Since 1982, many scientists have proved the stimulatory effect of low-dose and suppressive effect of a high-dose whole-body X-irradiation with this study. There are many possible mechanisms behind the proliferative effect of low-dose irradiation including the decrease in Corticosteroid secretion, down-regulation of the number of Cortisol receptors and removal of the anti-inflammatory suppression etc. [21–25].

According to Liu the hypothalamic–pituitary–adrenocortical axis directly relates to the stimulation of immune responses by low-dose radiation [26]. In this study the authors emphasize the fact that radiation which stimulates the bone marrow at the same time causes inflammation [26].The induction of inflammation and bone marrow cell proliferation via LDR are explained in the next section.

Inflammatory responses

Whether or not the cause of inflammation is an infection, the bone marrow is always stimulated. The damage in animals exposed to radiation begins at the skin and goes toward tissues in the inner body. The majority of irradiated cells try to repair DNA and protein damage while some of them die by necrosis or at later stages of apoptosis. Consequently, there are many reasons for bone marrow stimulation in the beginning of radiation exposure. If tumor degradation initiates inflammation, it means that many immune response cells will flow to this region. Inflammation triggers phagocytosis of degraded tumor cells by dendritic cells (DC) and macrophages [27]. As seen above, bone marrow is always stimulated after irradiation [28]. This comes as a result of inflammatory response to tissue damage.

An indirect but unavoidable result of ionizing radiation in tissues is the chemical toxicity, initiated by water radiolysis. Water molecules under the effect of ionizing radiation are being decomposed into ·H and ·OH radicals. Then, these radicals are converted into hydrogen peroxide (H_2O_2) molecules. Increased intracellular hydrogen peroxide is one of the reasons for severe oxygen stress in many cells, but not for lymphocytes. According to Reth H_2O_2 triggers lymphocyte activation by inhibiting protein tyrosine phosphatases [29]. Protein tyrosine phosphatases inhibit stimulation of lymphocytes. They are a kind of negative regulatory control of immune system cells. H_2O_2 plays an important role as a secondary messenger and regulates lymphocyte activation. It is responsible of the initiation and amplification of signaling at the antigen receptor level. This means that H_2O_2 can mimic the effect of antigen molecules. More recent data show that antigen receptors are working as H_2O_2-generating enzymes. In other words, the "oxidative burst" in macrophages seems to play a role not only in killing pathogens but also in the activation of lymphocytes [29].

Consequently, reactive oxygen species (ROS) not only stimulate lymphocytes but also stimulate proliferation of bone marrow cells. Leukocytes are not directly responsible for initiating inflammation. The first response to tissue damage is the activation of coagulation factors, a complementing cascade and activation of proteases. One of the well-known inflammation initiation factors is the Kallikrein–kinin system (KKS). KKS has long been recognized as a