Chapter

Immunomodulation of NK Cells under Ionizing Radiation

Chang-Sheng Shao, Xin Yu, Leisheng Zhang, Ya-Hui Wu and Qing Huang

Abstract

Natural killer (NK) cells are the effector lymphocytes of the innate immune system and control many types of tumors and microbial infections. Ionizing radiation (IR) has a pronounced effect on NK cells. However, the role of NK cells in radiotherapy remains elusive. In this chapter, we summarized the direct and indirect effects of ionizing radiation on NK cells. Low doses of ionizing radiation can enhance the toxic effects of NK cells. In contrast, high doses of ionizing radiation will lead to functional impairment of NK cells. In addition, under ionizing radiation, NK cells are also modulated by other immune cells. Overall, combining NK cell therapy and radiation therapy can improve the efficacy of oncology treatment.

Keywords: natural killer cells, ionizing radiation, radiotherapy, immunotherapy, immunomodulation

1. Introduction

Living on Earth, human beings have always been exposed to natural radiation effects from the universe and the subsurface, which naturally trigger radiobiological phenomena. Since the publication of the first research paper on radiation by the German experimental physicist Roentgen in 1895, research on the processes and biological effects of ionizing radiation has attracted increasing research attention [1]. Ionizing radiation is often used to treat tumors due to its effect on killing tumor cells and is one of the top three current cancer treatments [2]. Ionizing radiation has direct effects on DNA, subcellular organelles, and protein macromolecules in cells, and also has indirect effects on cells by oxidative stress, such as re-damaging DNA by free radicals and damage to the electron respiratory chain [3]. In recent decades, there has been a growing awareness of the interactions between ionizing radiation and the immune system. For a long time, high doses of ionizing radiation were considered to be a net immunosuppression, mainly due to the sensitivity of the lymphatic system to radiation. However, in recent years, studies have increasingly shown that irradiation of local tumors can modulate the immunogenicity of tumor cells and the anti-tumor immune response at the topical and systemic levels of the tumor microenvironment, and in particular, low-dose ionizing radiation can stimulate the cytotoxicity of T and NK cells [4]. Natural killer (NK) cells, which are innate lymphocytes, are important

effectors of tumor immune surveillance and play an important role in regulating adaptive immune responses [5]. Ionizing radiation has a significant effect on altering NK cell biology. In addition, we briefly described the importance of ionizing radiation research and summarized its direct and indirect effects on NK cells and the advantages of radiotherapy in combination with immunotherapy.

2. Definition and classification of ionizing radiation

Since Roentgen won the first Nobel Prize in Physics in 1901 for the discovery of X-rays, there has been an exponential increase in the understanding and study of radiation [6, 7]. The discovery of radiation has even driven progress in physics and other scientific fields since the twentieth century. It has had a huge impact on the advancement of science and technology and has become a model research tool and instrument. Radiation is defined in physics as the emission or propagation of energy in the form of particles or waves through space or a medium [8]. Radiation is essentially energy and takes different forms.

Electromagnetic radiation has wave-particle duality, and its nature is an electromagnetic wave. Maxwell used a system of equations to derive electromagnetic waves and predicted that light is an electromagnetic wave [9]. Electromagnetic radiation is distinguished according to frequency or wavelength [10]. All electromagnetic radiation has the same speed, and if the wavelength is shorter and the frequency is higher, the energy is greater, and the energy possessed to pass through the matter is greater. Among them, gamma rays are more energetic than X-rays, which are composed of photons outside the nucleus, while X-rays are composed of photons inside the nucleus.

Particle radiation, also known as particle beams, is the process by which particles that make up matter and move at high speeds, or nucleus made up of elementary particles, transfer energy to other matter by losing their own kinetic energy. Common

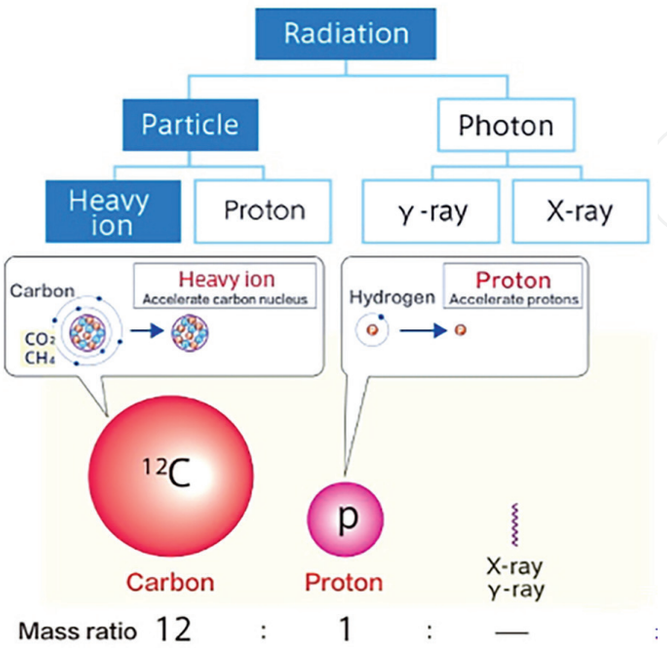

Figure 1.
Commonly used ionizing radiation modalities in clinical practice.

particles are helium nucleus (alpha particles), beta particles, neutrons, protons, heavy ions, etc.

But whether it is particles (α, β, neutrons, protons, charged heavy ions, etc.) or electromagnetic waves (γ-rays, X-rays, etc.), they are ionizing radiation if their energy is sufficient for ionization to occur [11]. As shown in **Figure 1**, the main means of ionizing radiation currently used in clinical practice to treat tumors include photon rays (X-rays, γ-rays) and particle radiation (protons, carbon 12 heavy ions, etc.).

3. Biological effects induced by ionizing radiation

Ionizing radiation can cause direct DNA damage to cells and subcellular organelles (mitochondria, etc.), commonly referred to as target effects.

The direct effects of ionizing radiation on DNA include (1) altering the chemical nature of nucleotides, (2) disrupting the sugar-phosphate backbone, and (3) breaking the hydrogen bonds between bases. Among them, altering the chemical nature of nucleotides is the factor that leads to their mutation [12]. In comparison disruption of the DNA backbone and disruption of hydrogen bonds between bases are physical damages that alter the chemical structure of the DNA molecule [13].

The ionizing radiation-induced DNA damage response is a continuous multilevel response network. The DNA damage signaling process under ionizing radiation is complex. Likewise, it is regulated by a combination of DNA damage signal sensor, apical kinase, damage signal mediator, and downstream kinase [14]. The radiation effects of these early processes further produce beneficial biological effects such as inhibition of cell cycle progression, activation of DNA repair, and maintenance of genomic stability to rescue cells. In contrast, in some cell types or when damage is beyond repair, the reverse effect is initiated, which not only initiates permanent cell cycle arrest (cellular senescence) but also eliminates unrepairable cells by way of programmed cell death [15].

Ionizing radiation also affects DNA indirectly, as mentioned before, ionizing radiation acting on water molecules produces hydrogen (H+) and hydroxyl (OH-) ions. These are called free radicals, as shown in **Figure 2**. Since free radicals are highly reactive, they can easily bind to other ions within the cell. For example, hydroxyl ions (OH-) can react with hydrogen atoms within DNA molecules to form hydrogen peroxide (H_2O_2), which can continue to cause DNA damage, and free radicals can accumulate to cause ongoing damage [16]. Free radical damage is associated with diseases such as aging, cancer, and Alzheimer's disease. Studies have shown that about 65% of cell death caused by ionizing radiation is generated by DNA breakage damage caused by hydroxyl radicals (-OH) [17, 18].

In addition, ionizing radiation can produce bystander effects on cells. As early as 1954, a study reported that plasma from patients treated with local radiation-induced chromosomal aberrations in lymphocytes from patients not treated with radiation, which is one of the most classic cases of bystander effects [19]. In general, paracrine effects are those in which irradiated cells (by alpha particles, X-rays or gamma rays, heavy ions, etc.) can release a certain number of signaling molecules. These signaling molecules are transferred through media or gap junctions, consequently, cytotoxicity or genotoxicity can be observed in non-irradiated cells [20–22].

The mechanism of the paracrine effect may be a signaling pathway, such as the irradiated cell releasing an "attack" signal that is transmitted to distant cells and attacks neighboring cells or diffusion through cellular gap-junction intercellular

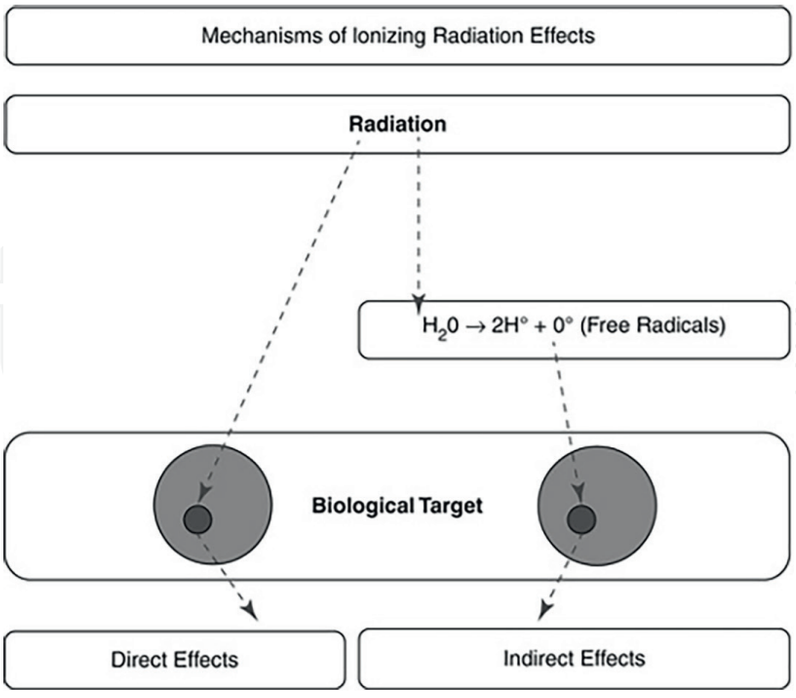

Figure 2.
Direct and indirect effects of ionizing radiation on the cells [13].

communication (Gap-junction) or through certain media. The generation release, and propagation of these signals, such as free radicals and reactive oxygen species generated by ionizing radiation, play a vital role in bystander effects [23, 24]. In addition, some signal transduction pathways may be associated with side effects caused by ionizing radiation, such as MAPK pathway, NO signaling pathway, interleukins (IL-1, IL-8), etc. [25].

Ionizing radiation leads to many forms of cellular processes and effects. These include but are not limited to apoptosis, necrosis, necroptosis, autophagy, and autophagic death. In addition, ionizing radiation can likewise have biological effects on immune cells.

4. The effects of ionizing radiation on NK cells

Ionizing radiation induces immune death of tumor cells, leading to the release of tumor antigens and damage-associated molecular patterns (DAMPs), which in turn stimulate and activate antigen-presenting cells (e.g., dendritic cells and T cells). The above processes can lead to the proliferation of cytotoxic T cells (CTLs), which then migrate into the tumor and initiate an anti-tumor immune response. In addition, ionizing radiation also affects tumor-associated macrophages (TAMs). Ionizing radiation induces macrophage infiltration and differentiation in tumors. Moreover, ionizing radiation promotes the activation of pro-inflammatory macrophages (M2) and enhances their immunostimulatory and tumoricidal activities (**Figure 3**). A growing number of studies now show that ionizing radiation may modulate the function of other innate immune cells, such as myeloid-derived suppressor cells, NK cells, tumor-associated neutrophils, and other cell types [26].

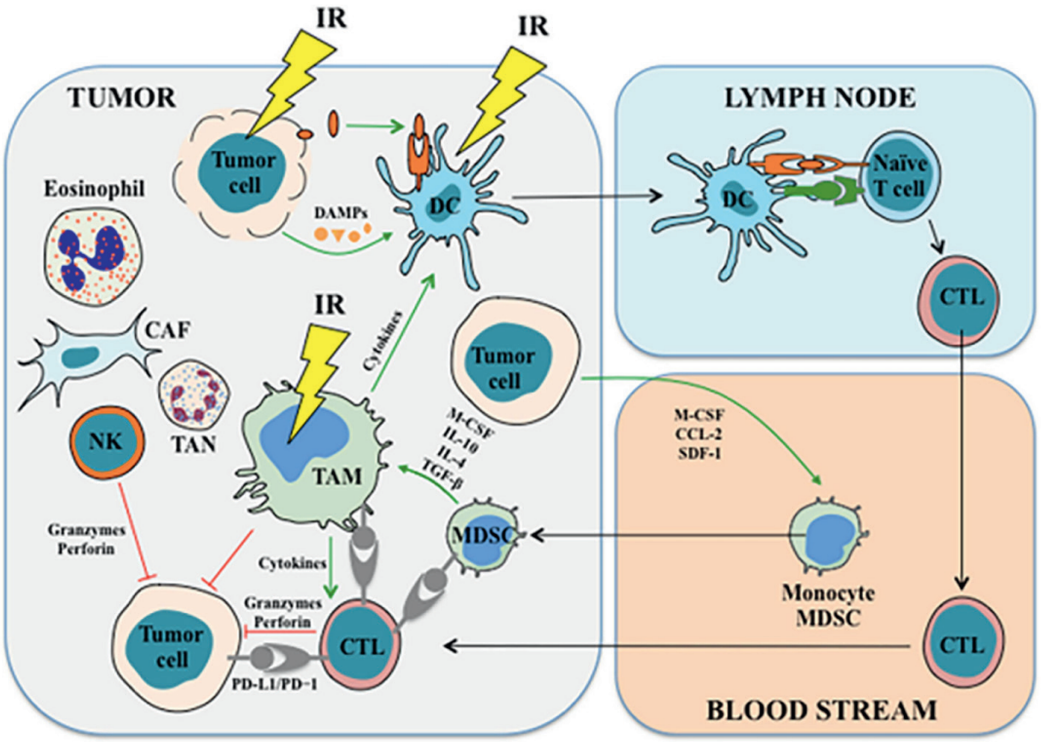

Figure 3.
Schematic diagram of the pathway of the effect of ionizing radiation on immune cells [26].

NK cells play a key role in anti-tumor immunity [27, 28]. NK cells are phenotypically determined by the expression of CD56 and the absence of CD3 and can be classically divided into two populations: CD56bright CD16dim population and CD56dim CD16bright population. Irradiation can directly affect the function of NK cells.

The effect of ionizing irradiation on the function of NK cells was significant. In vitro studies have shown that X-ray irradiation from 5 to 15 Gy doses can temporarily increase the activity of NK cells [29, 30]. The cytotoxic activity of human peripheral blood NK cells was reported to be enhanced at an irradiation dose of 1 Gy, reaching a maximum at 6 Gy. In addition, low-dose gamma irradiation at less than 0.2 Gy induced NK cell expansion and enhanced NK cell cytotoxicity [31]. Low-dose ionizing radiation significantly increased the expression of IFN-γ and TNF-α in NK cells in a p38MAPK-dependent manner [32]. Ionizing irradiation can also affect NK cell function by modulating the interaction between tumor cells and NK cells. For example, ionizing irradiation can upregulate the expression of natural-killer group 2, member D (NKG2D) ligand, and HSP70 in tumor cells, which may increase the sensitivity of tumor cells to NK cell-mediated cytolytic attack [33, 34].

It is still controversial that high and low doses of ionizing radiation have different effects on NK cell function. Rana et al. found that exposure of peripheral blood mononuclear cells to different doses of gamma radiation increased the sensitivity of human NK cell activity (binding and killing). Peripheral blood mononuclear cells were irradiated with low (2–6 Gy) and high (10–30 Gy) doses, and NK cell binding and cytotoxic activity against K562 target cells were studied after 3 and 48 hours of incubation. An overall decrease in cytotoxic activity was observed, but ionizing radiation produced a selected subpopulation of more cytotoxic NK cells and thus may be considered more resistant to radiation damage than the less cytotoxic NK cells [35]. Vokurková et al. identified the secondary CD8+ subpopulation of NK cells as a

radiosensitive lymphocyte population whose disappearance was directly correlated with the dose received. Thus, CD3−/CD8+ NK cell subpopulations can be used as low-dose bioassay markers [36, 37].

4.1 Low-dose ionizing radiation can enhance NK cell activity

Although high doses of ionizing radiation are generally harmful and damaging to organisms, low doses of radiation have been shown to be beneficial in various animal models. Mice exposed to low doses of radiation, both very low and low doses, exhibited normal ranges of body weight and whole blood cell counts. However, increased levels of cytokine release in serum and exhibited inhibition of pro-inflammatory responses [38]. Shin et al. showed that irradiation of mice with low doses (0.1 Gy) of X-rays significantly stimulated NK cell-mediated tumor cell lysis [39].

Since NK cells are early responders to exogenous stress, NK cells may reveal rapid subtle changes in function after exposure to low doses of ionizing radiation. Sonn et al. demonstrated that low doses (dose rate of 4.2 mGy/h, total dose of 0.2 Gy) of ionizing radiation promoted anti-tumor toxicity in NK cells but did not affect cell proliferation or apoptosis [31]. Then what would be the effect on NK cells if they were irradiated at a much lower dose? Lacoste et al. further irradiated 560 mice using a very low dose (10 cGy/year) and found that ultra-low dose irradiation did not impair immune system damage by examining mouse lifespan and immune response effects [40].

However, because the mechanism by which low-dose ionizing radiation enhances NK killing is unclear, a great deal of exploration and research has been conducted. Yoon et al. found that low-dose ionizing radiation not only increased the expression of chemokines in tumor cells, but more importantly, increased the expression of CXCL16 (ligand of CXCR6) in NK cells. The above findings suggest that low-dose ionizing radiation enhances the migration of NK cells to tumor sites and achieves effective tumor treatment [41]. In addition, low-dose irradiation has been reported to increase NKG2D ligand expression and enhance NK toxicity [42]. Several studies have claimed that low-dose ionizing radiation may induce direct expansion and activation of NK cells via the P38-MAPK pathway, providing a potential mechanism for low-dose radiation stimulation of NK cells and a novel but simplified stimulation method for NK cell pericyte therapy [32]. Ionizing radiation also triggers the release of a second mitochondria-derived caspase activator (Smac) that competes with X-linked inhibitory apoptosis proteins to enhance NK cell-mediated apoptosis of tumor cells [43]. Currently, in response to heat shock proteins that increase apoptotic resistance of tumor cells, some studies have found that the combination of quercetin and low-dose irradiation can be used to decrease the expression of heat shock protein HSP70, increase the expression of NKG2D, and improve the killing ability of NK cells [44].

4.2 High-dose radiation impairs NK cell immunity

Many treatments directly and adversely affect NK cell function, but observations obtained through in vitro systems may differ from those obtained using clinical samples. Radiotherapy affects NK cell antitumor immunity from multiple perspectives, and the interactions are complex [45]. Radiotherapy produces non-targeted effects on normal tissues such as bone marrow. Thus, alteration of the microenvironment by ionizing radiation is thought to affect the dynamic host-cancer ecosystem, thus influencing cancer behavior including metastasis. Shin et al. demonstrated that high doses of irradiation in mice result in progressive depletion of total leukocytes

and platelets at a later stage, with the highest number of NK cells in lung tissue. Thus high doses of radiation can cause hematotoxicity and lung metastasis [46]. p53 tumor suppressor gene has been shown to be associated with programmed cell death, apoptosis in immature thymocytes of mice after ionizing radiation treatment, as reported by Seki et al. High-dose ionizing radiation also induces apoptotic cell death in peripheral mature lymphocytes [47].

In addition, it has also been reported that ionizing radiation may produce adverse reactions and promote tumor metastasis. Heo et al. found that ionizing radiation induces the expression of matrix metalloproteinases (MMPs), which play an important role in the invasion and metastasis of cancer cells. While MMPs have been shown to increase the shedding of NKG2DLs, which may decrease the surface expression of NKG2DLs on cancer cells. Therefore, cancer cells may evade NK-mediated anticancer immunity due to ionizing radiation intervention [48].

5. Combination of ionizing radiation and immunotherapy for anti-tumor

Radioresistance is a major challenge in the treatment of NK/T-cell lymphoma. Wu et al. found that miR-150 was significantly reduced in NK/T-cell lymphoma tissues and cell lines by analyzing a large number of clinical samples. Low miR-150 expression was positively correlated with treatment resistance, and overexpression of miR-150 inhibited the PI3K/AKT/mTOR pathway, thereby significantly enhancing the sensitivity of NK/T-cell lymphoma cells to ionizing radiation therapy [49].

Rational combination therapeutic strategies have been shown to be beneficial in the management of cancer. Regulatory T (T reg) cells are densely distributed in solid tumors, which may promote progression by suppressing anti-tumor immune responses. Bos et al. found that short-term ablation of T reg cells in advanced spontaneous tumors leads to extensive apoptotic tumor cell death. This anti-tumor activity was dependent on IFN-γ and CD4+ T cells, but not on NK or CD8+ T cells. Transient regulatory T cell ablation blocks oncogene-driven breast cancer and provides overall survival by increasing tumor killing in combination with ionizing radiation [50]. Jeong et al. showed that ionizing irradiation enhanced the adhesion between NK cells and target cells by upregulating intercellular adhesion molecule-1 (ICAM-1) on target cells. Ionizing irradiation upregulated ICAM-1 expression on the surface of human cancer cells and enhanced activated NK cell-mediated cytotoxicity. Thus, this also provides a basis for the possibility that ionizing irradiation combined with NK cell therapy may enhance the antitumor effects of NK cells [51].

In addition, ionizing radiation can be combined with mild heat therapy for anti-tumor enhancement of NK cell immune response. Recent studies have shown that the application of local thermotherapy in combination with standard oncologic therapies such as radiotherapy and/or chemotherapy may not only improve local tumor control but also lead to systemic and immune-mediated anti-tumor responses. Werthmöller et al. reported that a local irradiation and heating procedure was established in a mouse model of melanoma and found that tumors treated with ionizing irradiation and heat therapy had significantly delayed tumor growth compared to tumors treated with radiotherapy alone. This combined treatment produced a beneficial tumor microenvironment by enhancing infiltration of CD11c+/MHCII+/CD86+ dendritic cells, CD8+ T cells, and NK cells, and reduced regulatory T cells and myeloid-derived suppressor cells [52]. Thus, ionizing radiation combined with heat therapy has the potential to lead to immunostimulation of anti-tumor immunity.

6. Conclusion

As a complement to antitumor T-cell immunity, NK cells are independent of antigen presentation and can kill tumors directly in a major histocompatibility complex (MHC)-independent manner. A large number of engineered modified NK cell therapies are now proposed, with particular emphasis on anti-tumor immunotherapy. This chapter focuses on the functional changes in NK cells caused by different doses of ionizing radiation are essential. Low doses of ionizing radiation can enhance the toxic effects of NK cells. On the contrary, high doses of ionizing radiation will lead to functional impairment of NK cells. In addition, the combined application of radiotherapy and immunotherapy in clinical treatment is also highly promising.

However, the involved mechanisms are still largely unexplored. With the elucidation of the molecular basis of NK cells activated by proper ionizing radiation, radiation therapy may be better applied with the facilitation of the modulation of the immune system.

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Conflict of interest

The authors declare no conflict of interest.

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Author details

Chang-Sheng Shao[1], Xin Yu[2,3], Leisheng Zhang[2,4*], Ya-Hui Wu[2,3] and Qing Huang[2*]

1 CAS High Magnetic Field Laboratory, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, China

2 CAS Key Laboratory of High Magnetic Field and Ion Beam Physical Biology, Institute of Intelligent Machines, Hefei Institutes of Physical Science, Chinese Academy of Sciences, Hefei, China

3 Science Island Branch of Graduate School, University of Science and Technology of China, Hefei, China

4 Key Laboratory of Molecular Diagnostics and Precision Medicine for Surgical Oncology in Gansu Province & NHC Key Laboratory of Diagnosis and Therapy of Gastrointestinal Tumor, Gansu Provincial Hospital, China

*Address all correspondence to: leisheng_zhang@163.com and huangq@ipp.ac.cn

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