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SYSTEMIC EFFECTS OF RADIATION THERAPY-REVIEW ARTICLE

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Systemic Effects of Radiation Therapy
Radiotherapy is one of the cornerstone treatment modalities for cancer. It is also the most commonly used cancer treatment modality, with approximately 60% of patients with solid tumors receiving radiation therapy either with curative or palliative intent as part of their treatment. It remains an important curative treatment modality for uncomplicated loco-regional tumors. It is used in hematological malignancy also, as prophylactic or radical treatment purposes. Thus radiation therapy is a highly effective tool for the cancer treatment and also an important component of cancer management, conferring a survival and palliative benefits.[1,2,3]

Radiation therapy not only kills cancer cells that are dividing, but it also affects dividing cells of normal tissues. This damage to normal cells produces unwanted side effects. Radiation therapy is applied in a course of multiple fractions over several weeks to reduce the normal cell toxicity,[4] with an estimation of about 40% toward the curative treatment.[5] Ionizing radiation (Photon radiation and Particle radiation) use low and high linear energy transfer (LET) radiations to efficiently kill the tumor cells while minimizing dose to normal tissues to prevent toxicity.[6,7] The major effects of ionizing radiation on tissues are the direct cell killing mostly by damaging the DNA, resulting in the depopulation of cells and subsequent functional deficit. It can act indirectly, producing free radicals which are derived from the ionization or excitation of the water molecules of the cells. For ionizing radiations such as low LET X- rays and gamma-rays, 60% of the cellular damage is due to indirect effects. Radiation therapy like the most anticancer treatments achieves its therapeutic effect by inducing DNA damage and thereafter cell death like radiation induced double strand breaks, which is the most lethal types of DNA damage, leading to cell death, if unrepaired.[9] However, DNA damage response mechanisms represent a vital line of defense response against exogenous and endogenous damage caused by radiation and promote two distinct outcomes: survival and the maintenance of genomic stability. P^{53} is a transcription factor and also one of the most commonly mutated genes in cancer.[10] It responds to ionizing radiation by initiating cell cycle arrest, senescence, apoptosis and DNA damage repair.[11] However, whether p53 induces apoptosis or cell cycle arrest; for the DNA damage, repair is a complex process and partly depends on the abundance of the p53 protein. However, various DNA repair mechanisms within the tumor cells interfere with the radiation induced damage and further increase the radio resistance of cancer cells.[12] Furthermore, inhibition of DNA repair proteins such as ATM or DNA-dependent protein kinase (DNA-PK) have been shown to sensitize the cancer cells to radiation treatment.[13,14,15]

Bystander Effect

Radiation biology have demonstrated that the radiation is an effective tool to control the localized tumors. However, in recent years many evidences indicate that the radiation also can damage not only the cells adjacent to the tumor, but also far from the radiation track by the generation of gap-junction or cytokine-mediated cellular toxicity and also through various cellular and micro environmental signaling cascades.[16,17,18,19] Evidence has been mounted for a novel biological phenomenon termed as "bystander effect" (BE). Ionizing radiation induces DNA damage in the form of chromosomal aberrations reported not only in the directly exposed cells but also in their neighboring non-irradiated cells, termed as radiation-induced bystander effect (RIBE).[20] Various biological effects of ionizing radiation are not restricted to only the directly irradiated cells (targeted effects), but are also observed in the progeny of non-irradiated cells (non-targeted effects).[21] RIBE has been demonstrated in numerous *in vitro* and *in vivo* studies using a variety of biological endpoints. These effects include various molecular and genomic instabilities as seen in the targeted cells. Bystander effects has been extensively studied in the past two decades and reported cell death,[22,20] induction of sister chromatid exchanges,[23] formation of micronuclei mutations, delay in cell cycle and transformation and DNA damage response.[24,25]

In the normal and certain cancer cells, mechanisms between cell to cell communications are through the direct gap junction-mediated intercellular communication.[26] Secondly, a range of soluble signaling molecules such as cytokines are involved in the communications between the targeted to distant non-targeted organs or sub-confluent cells.[27] In recent years, number of candidate mediators in bystander effects were identified, among them transforming growth factor-b (TGF-β), tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), interleukin-8 (IL-8) and increase in reactive oxygen species (ROS) were found to be significant factors.

Recently, Jiang et al. showed, that the RIBE is mediated by the TGF-β 1–miR-21–ROS pathway in the lung cancer cells.[28] Further cancer-associated events such as p53 alteration, MMPs (Matrix metalloproteinase activity and epigenetic changes were reported in the RIBE. BE can be mediated through an increase in genomic instability, cell cycle delay, cell death (apoptosis), formation of micronucleus, mutations, changes in proteins (gene) expression, and further by malignant transformation. Recently, Bensimon et al. showed that in breast cancer cells, a cancer stem cell (CSC) marker CD24 is associated with the transmission of genomic instability of the bystander cells.[29] Recently Aravindan et al. reported that the clinical doses of abdominal irradiation (2Gy) in mice showed an increase in the onset of NF-kB signal transduction and subsequent NF-kB activation in the non-targeted distant organ (heart).[30]

Among non-targeted effects, main effect seems to be due to the activation of the immune system via the induction of immunogenic cell death by ionizing radiation. Radiation is able to modify tumor phenotypes and the tumor microenvironment as well. Anti-tumor responses may also be mediated by these nontargeted effects in a specific and systemic manner and have the ability to target both relapsing tumor cells and distant metastases.

Ionizing Radiation and the Immune System

The effects of ionizing radiation are seen not only in the tumor cells but also in the tumor microenvironment. In general, lymphocytes (T cells, B cells and NK) are among the most radiosensitive cells, followed by monocytes, macrophages and antigen-presenting cells (APCs), specifically dendritic cells (DC), which have a higher radio resistance potential. Ionizing radiation also has an effect on the vascular endothelium, with an increase in the production of molecules involved in cellular adhesion, which facilitates the recruitment of antitumor T cells against the corresponding sites. After irradiation, dead and stressed cells release a variety of substances that gives ionizing radiation either immunosuppressive or immune stimulating properties. Nevertheless, a number of experimental studies have clarified some aspects of the immune response after exposure to radiation. Radiation induces distinct tumor cell death forms and, consequently, the release of pro-inflammatory cytokines, chemokine, tumor antigens, and other danger signals. Through this mechanism, radiation may enhance tumor immunogenicity. Radiation may promote a large amount of tumoral neoantigens that are then presented to the T lymphocytes. Therefore, radiation carries the potential to initiate the adaptive and innate immune responses, resulting in systemic ant tumorigenic effects inside and outside of the irradiation field.

Abscopal Effect

The observed regression of metastases or tumors outside the irradiation field is called the abscopal effect, and its relationship with immune events has been known since 1969. The abscopal effect is partially mediated by the immune system, and T cells are the cells elected to mediate distant tumor immune inhibition induced by radiation. More recently, this radiation-induced cell death that causes an immune reaction has also been called ‘‘immunogenic death’’. After cell death, pro-inflammatory mediators are released. They are called damage-associated molecular patterns (DAMPs). Among them, reactive oxygen (ROS) and nitrogen species, cytotoxic cytokines, tumor growth factor b-1 (TGb-1), tumor necrosis factor-alpha (TNF-a), a number of interleukins, heat shock proteins (HSPs), high mobility group box 1 molecules (HMGB1), and nucleotides or uric acid are capable of activating the innate or adaptive immune system. These DAMPs are recognized by the Toll-like receptors (TLR) expressed on the surface of the DCs and are responsible for their activation and maturation. Tumor infiltrating DCs are associated with either good or poor prognosis in different cancer types. Although they seem to be quite radioresistant, radiation may cause a functional impairment of DCs, possibly leading to a change in the DC-mediated balance between T-cell activation and tolerance. Adenosine-5-triphosphate (ATP) is another inflammatory molecule associated with immunological cell death. ATP binds to the DC receptors and can stimulate the release of interleukin-1b (IL-1b), which can promote T cell priming. Moreover, ATP released from tumor cells also modulates the immunosuppressive properties of myeloid-derived suppressor cells (MDSCs) and contributes to tumor growth. The MDSCs together with other cells such as tumor infiltrating macrophages or tumor-associated macrophages (TAMs) can contribute to tumor growth and inhibit antitumor immunity. This paradoxical immunosuppressive effect of radiation is mainly due to the inactivation of NK lymphocytes, with the recruitment of MDSCs and Treg lymphocytes, secretion of TGF-b and the modification of the macrophage phenotype. Understanding the role of these cells in the anticancer immune response is important for the development of anticancer therapies. Cell death causes an intense inflammatory response due to the release of intracellular components.

Effects of ionizing radiation on the tumor microenvironment (TME)

Ionizing radiation effects not only affect cancer cell and cancer cell death but also the complex biological interactions between tumors and stroma in which they grow, known as the tumor microenvironment (TME). It is becoming increasingly evident that responses that are triggered within TME may be critical in determining the success or failure of therapy. Endothelial cells and the tumor vasculature are possibly the best studied components involved in the effect of radiation on the TME. Radiation induces endothelial cell dysfunction, which is characterized by increased permeability, detachment from the underlying basement membrane and apoptosis. Within vessels, irradiation also generates a pro-thrombotic state characterized by platelet aggregation, microthrombus formation and increased adhesion of inflammatory cells to endothelial cells with subsequent diapedesis into the perivascular space. The effects of radiation on the tumor microenvironment and immune system may be modified by the radiation dose and the dose delivery methods used. However, the effects of radiotherapy on the TME and on the antitumoral immune response described in preclinical studies has led to the concept of an existing immunogenic cell death (ICD) and immune-mediated tumor rejection. To date, a variety of hypotheses about the specific impact of different dose/fractionation regimens on the anti-tumoral response are under investigation. In preclinical studies, the use of hypofractionated high doses rather than high single dose schedules showed the best results regarding the proimmunogenic effect of radiation. In addition, larger doses should have more pro-immunogenic effects regarding the induction of ICD in in- vitro studies. However, the relationship of the immune response with dose and fractionation may be more complex.

Currently, a consensus about the optimal dose schedule to stimulate the immune system has not yet been achieved with preclinical data that have been published. Therefore, the radiation and immunotherapy partnership is completely dependent on the radiation dose and fraction involved. Several immunological manipulation treatments have been used, including immune checkpoint blockade, adaptive T cell transfer, cytokine therapy, dendritic cell and peptide vaccines, and monoclonal antibodies. The induction of anti-tumor immunity seems to be regulated by positive and negative signals. Immunotherapies that have been currently approved and those in development act at one or multiple steps of this process. Radiotherapy seems to potentially accentuate each step, including the uptake of tumor antigens by dendritic cells and their activation, as well as migration of the activated effector T cells back to the tumor. Therefore, radiotherapy enhances and complements the action of many different immunotherapy agents, and its synergistic use is the goal of many exploratory studies.

Currently, it is possible to deliver higher doses per fraction with better sparing of the adjacent normal tissue. Techniques such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), stereotactic radiosurgery (SRS), and stereotactic body radiation therapy (SBRT or stereotactic ablative radiotherapy - SABR) have transformed the delivery of radiotherapy, and the trend is the increasing use of hypofractionated schedules. Published papers have suggested that SBRT regimens can promote an immune response, mediating anti-tumorigenic effects. Few studies suggest that carbon ion therapy with the same dose might generate a stronger activation of the immune system than conventional photon radiotherapy.

Currently, there is still a lack of information about the ideal combination of ionizing radiation with immunotherapy, and there are no recommended ‘‘off-protocol’’ approaches already established for routine patient management. The main objective of the current ongoing trials is to evaluate the abscopal effect of the combination of ionizing radiation with immunotherapy, mainly in patients with advanced disease. Different vaccines and immune checkpoint inhibitors are combined with radiotherapy that is delivered to the primary tumor or metastatic sites in oligometastatic disease.

Increasingly, evidences indicate that radiotherapy recruits biological effectors outside the treatment field and has systemic effects. Because the effects of chemotherapy and radiotherapy are sensed by the immune system, their combination with immunotherapy presents a new therapeutic opportunity. Radiotherapy directly interferes with the primary tumour and possibly reverses some immunosuppressive barriers within the tumor microenvironment. Local radiation also triggers systemic effects that can be used in combination with immunotherapy to induce responses outside the radiation field.

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