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Review Article

Macrophage biology plays a central role during ionizing radiation-elicited tumor response

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ABSTRACT

Radiation therapy is one of the major therapeutic modalities for most solid tumors. The anti-tumor effect of radiation therapy consists of the direct tumor cell killing, as well as the modulation of tumor microenvironment and the activation of immune response against tumors. Radiation therapy has been shown to promote immunogenic cells death, activate dendritic cells and enhance tumor antigen presentation and anti-tumor T cell activation. Radiation therapy also programs innate immune cells such as macrophages that leads to either radiosensitization or radioresistance, according to different tumors and different radiation regimen studied. The mechanisms underlying radiation-induced macrophage activation remain largely elusive. Various molecular players such as NF-κB, MAPKs, p53, reactive oxygen species, inflammasomes have been involved in these processes. The skewing to a pro-inflammatory phenotype thus results in the activation of anti-tumor immune response and enhanced radiotherapy effect. Therefore, a comprehensive understanding of the mechanism of radiation-induced macrophage activation and its role in tumor response to radiation therapy is crucial for the development of new therapeutic strategies to enhance radiation therapy efficacy.

Radiation therapy is one of the cornerstones of cancer therapies. By inducing lethal DNA damages (such as DNA single- and double-strand breaks), ionizing radiation (IR) may eliminate irradiated cells, but also non-irradiated neighboring cells (also known as by-stander effect) through distinct death modalities (including apoptosis,

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necrosis and mitotic catastrophe). Several studies recently highlighted that ionizing radiation may also impact the tumoral microenvironment, the associated immune system and modulate tumor response to radiation therapy [1]. For example, accumulating evidence demonstrates that radiation therapy can promote tumor immune response by eliciting immunogenic cell death, tumor antigen release and immune cell activations. In addition, the combination of radiation therapy with a variety of immune modulators also enhanced tumor regression outside the field of irradiation, also know as abscopal effect, confirming that the biological consequences of the ionizing radiation of tumoral microenvironment components (such as immune effectors) are key events in tumor response to radiotherapy that remain to be elucidated [2].

Despite the macrophages play important roles in organ development, in host defense against tissue insults and infections, and in maintaining tissue homeostasis, these myeloid cells also participate in metabolic disorders, immune diseases and cancer development [3]. Characterized by their functional plasticity and heterogeneity, these innate cells can be activated by a plethora of stimuli such as growth factors, cytokines, microbial products, nucleotides and many other modulators. *In vitro* stimulation of macrophages by interferon-γ (IFN-γ) or tumor necrosis factor-α (TNF-α) and/or microbial products such as lipopolysaccharides (LPS) induces classical (M1) macrophage activation, which is characterized by an IL-12^{high}IL-23^{high}IL-10^{low} phenotype with elevated production of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, increased expression of inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS). Classical activated macrophages are proficient effectors in promoting Th-1 type immune response and in fighting against bacterial infections as well as malignant tumors. On the other hand, macrophages stimulated by Th-2 related cytokines (such as IL-4 or IL-13), IL-10, immune complexes, glucocorticoids are grouped as alternative activated (M2) macrophages with an IL-12^{low}IL-23^{low}IL-10^{high}TGF-β^{high} phenotype. Alternative activated macrophages express high level of arginase 1 (Arg1), mannose receptors, scavenger receptors, galactose-type receptors, and participate in the Th-2 type immune response, the resolution of inflammation, the tissue repair, the intracellular parasite clearance, the immune regulation, the angiogenesis and the tumor progression [4].

Macrophages also represent a major cellular component of the tumor stroma. These tumor-associated macrophages (TAMs) derived from blood monocytes that differentiate into macrophages after recruitment to the tumor area by tumor-derived cytokines and chemokines. In the majority of cases, TAMs acquire pro-tumorigenic phenotypes that contribute to tumor growth, tumor invasion, angiogenesis, and tumor metastasis, making them attractive targets for developing new anti-cancer strategies [5]. The interaction of ionizing radiation and macrophage activity is the subject of intensive investigation. This review summarizes recent findings with regard to the regulation of macrophage activities by ionizing radiation (IR) and their roles in tumor responses.

Biological consequences of ionizing radiation on macrophages

In vitro/ex vivo studies

Ionizing radiation is reported in many studies to affect the biological functions of stimulated macrophages. The physic characteristics of IR (such as type, dose and treatment schedules), basal activation states and host genetic factors impact the biological responses of macrophages to ionizing radiation.

Delivered doses dictate biological functions of macrophages

A large body of evidence indicated that low-dose (single dose ≤1.0 Gy) irradiation predominantly induced anti-inflammatory activation of macrophages while high-dose irradiation was more prone to enhance the pro-inflammatory properties of macrophages [6]. For example, earlier studies using murine resident macrophages or macrophage-like cell lines demonstrated that ionizing radiation activated macrophages, increased the production of iNOS and subsequent nitric oxide (NO) as well as the production of O_2^- [7–9], and induced the expression of several pro-inflammatory cytokines such IL-1β, IL-6 and TNF-α [10–13]. However, *ex vivo* irradiation of LPS-activated BALB/c peritoneal macrophages with low dose (0.5 Gy) X-ray led to reduced secretion of pro-inflammatory cytokine IL-1β while increased secretion of anti-inflammatory cytokine TGF-β, indicating that low-dose irradiation promoted anti-inflammatory macrophage phenotype in this particular setting [14]. Low-dose X-ray irradiation at 0.5 or 0.7 Gy reduced the expression of pro-IL-1β and secretion of IL-1β from LPS- and monosodium urate crystals-stimulated THP1-differentiated macrophages without affecting cell viability. This IR-induced anti-inflammatory phenotype was associated with reduced nuclear translocation of RelA and the decreased amount of p38 and Akt kinases [15]. Low-dose but not high dose X-ray irradiation also reduced the oxidative burst in activated macrophages [16]. However, there are also reports showing that low to intermediate dose irradiation of mouse peritoneal macrophages induced an early production of pro-inflammatory IL-1β and IL-6 in a protein kinase C- and phosphatidylinositol 3-kinase-dependent manner [13].

When irradiated at a higher dose (≥1 Gy), macrophages tend to display a pro-inflammatory phenotype. For example, irradiation at 1–5 Gy potentiated the production of iNOS and NO in IFN-γ and LPS-stimulated J774.1 and RAW264.7 macrophages [17]. Interestingly, TNF-α was involved in this boost of pro-inflammatory mediator as TNF-α blocking antibody treatment before irradiation inhibited the induction of NO by IFN-γ [18]. Irradiation of RAW264.7 murine macrophages with gamma-ray at 2.5 Gy up to 20 Gy did not significantly induced the production of NO and IL-1β but strongly enhanced NO production and IL-1β expression in LPS-activated macrophages [19].

Effects of ionizing radiation on human monocytes/macrophages have also been evaluated. A single dose of 2 Gy irradiation significantly increased the production of IL-1α and IL-1β in human alveolar macrophages [20]. Another study failed to detect significant induction of IL-1β or TNF-α after 10 Gy of