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Mini-review

Modulation of inflammation by low and high doses of ionizing radiation: Implications for benign and malign diseases

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ABSTRACT

Inflammation is a homeostatic mechanism aiming to maintain tissue integrity. The underlying immunological mechanisms and the interrelationship between ionizing radiation and inflammation are complex and multifactorial on cellular and chemical levels. On the one hand, radiation with single doses exceeding 1 Gy might initiate inflammatory reactions and thereby impact on tumor development. On the other hand, radiation is capable of attenuating an established inflammatory process, which is clinically used for the treatment of inflammatory and degenerative diseases with low-dose radiotherapy (single dose <1 Gy). At higher doses, ionizing radiation, especially in combination with additional immune stimulation, fosters the induction of immunogenic forms of tumor cell death and shifts the tumor microenvironment as well as the infiltration of immune cells from an anti- to a pro-inflammatory state. Distinct tumor infiltrating immune cells predict the response to radiochemotherapy in a multitude of tumor entities. While a high tumor infiltration of these adaptive immune cells mostly predicts a favorable disease outcome, a high infiltration of tumor-associated macrophages predicts an unfavorable response. Pro-inflammatory events should dominate over anti-inflammatory ones in this scenario. This review focuses on how ionizing radiation modulates inflammatory events in benign inflammatory and in malign diseases. A special focus is set on the role of tumor infiltrating lymphocytes and macrophages as biomarkers to predict treatment response and anti-tumor immunity and on mechanisms implicated in the anti-inflammatory effects of low-dose radiation therapy.

Inflammation

The human body is steadily charged by various pathogens. The outer barriers, namely the skin, the mucosal epithelia within the airways and the gut, are effective defense fortifications. However, these barriers can have small or microscopic traumata which enable pathogens to pass. To avoid potential severe diseases, the immune system permanently fights against these invading pathogens and also against damage occurring by endogenous noxae. The immunological response is a multifactorial cellular and chemical process, aiming to reconstitute a healthy environment. It is mostly characterized by the term “inflammation” [1–3].

To understand how inflammation can be modulated by ionizing radiation, one has to consider how the inflammatory process is initiated, maintained, and finally shut down. This is mainly facilitated by the innate immune system, since its components form the first line of defense against invading pathogens. At the site of local inflammation, tissue resident immune cells such as macrophages or dendritic cells, produce and secrete a cluster of different soluble substances, mostly chemokines and cytokines which attract additional immune cells from the peripheral blood into the affected tissue [1,2]. In concert with tissue resident cells, the attracted members of the innate and adaptive immune system display an effective defense system. Finally, these immune cells have to resolve the local inflammatory process and produce soluble signals to shut down the systemic response [2]. The inflammatory process is a self-limiting one. If this regulation is disturbed, however, inflammation might shift from an acute to a chronic stage [1].

The hallmarks of inflammation, first described by the roman Aulus Cornelius Celsus in the first century A.D., comprise *Calor*, *Dolor*, *Rubor*, and *Tumor*. They characterize the ‘fundamentals of inflammation’ heat, pain, redness, and swelling, respectively [4,5]. In many instances inflammation within the body is not detectable by the visible hallmarks, since the first guardians (e.g. tissue resident macrophages) of the immune system are fighting the invaders without creating visible signs. Inflammation is linked to different diseases like atherosclerosis, rheumatoid arthritis, or other disorders with the suffix ‘-itis’, as defined by Virchow in the middle of the 19th century [6]. However, during the past few decades different inflammatory responses have been characterized at the molecular level.

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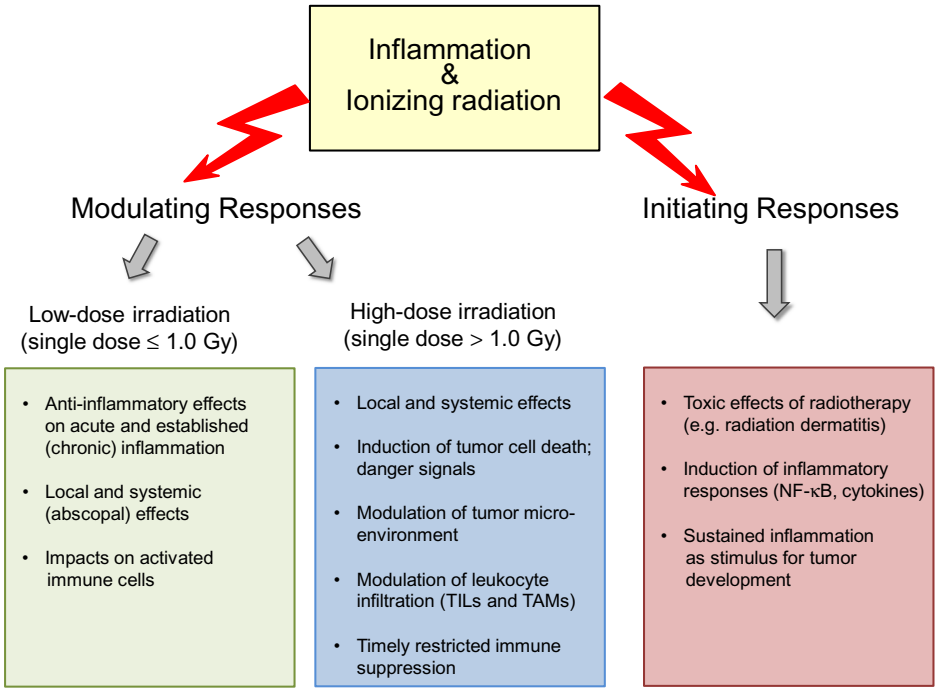

Fig. 1. The impact of ionizing radiation on inflammatory processes. Inflammation is guided by a plethora of initiators, regulators and gatekeepers. Ionizing radiation initiates and modulates inflammation. Low dose radiation attenuates a pre-existing inflammation while higher doses applied in tumor therapy are capable of inducing local and systemic anti-tumor immune reactions. This is initiated by induction of immunogenic tumor cell death characterized by the release of danger signals and by shifting an immune suppressive tumor microenvironment to an activating one.

Chemokines and cytokines for example comprise local and systemic components of the inflammatory process and have overlapping and pleiotropic functions [7]. They further display characteristic activation clusters linked to a specific inflammatory disease [8]. But what do radiation oncologists mean by the term "inflammation" and "immune modulation"?

Despite recent developments in multimodal treatment, which involves radiation therapy (RT) in approximately 50% of the cases, cancer still figures among the leading causes of morbidity and mortality worldwide [9]. If any radiation oncologist becomes aware of visible signs of inflammation in the course of therapy, a dose reduction will normally be the appropriate response [10]. Induction of signs of *radiation dermatitis*, for example, is considered as a toxic side effect of RT [11]. However, by the advent of innovative treatment algorithms and novel radiation treatment techniques such as intensity modulated RT (IMRT), the skin toxicity is decreased [12]. A delicate balance of maximal dose application to the tumor (tumor control probability) and minimal dose exposure to healthy tissue (normal tissue complication probability) has always to be taken into account when applying radiation techniques and dose fractionating schemes [13].

During the past few years, however, it has become evident that RT not only induces inflammatory reactions such as dermatitis and unwanted, temporary immune suppression like leukopenia but is also capable of inducing specific anti-tumor immune responses, especially when applied in multimodal settings [14]. The first hints in that context were published in 1979, when Stone and colleagues reported on effects of ionizing radiation on an immune response against a graft [15]. A comprehensive overview on how radiation fosters anti-tumor responses was published recently by Formenti [16].

In the present review, we will focus on the modulation of inflammatory processes by ionizing radiation. On the one hand, irradiation with doses <1 Gy attenuates established inflammatory diseases. On the other hand, radiation with doses exceeding 1 Gy may act as an initiator of inflammatory processes. This can be beneficial for the induction of anti-tumor immunity and disadvantageous when resulting in promotion of carcinogenesis (depicted in Fig. 1). Cancer often arises when repeated tissue injury or chronic inflammatory conditions exist [17]. The concept of the cancer niche implies that cancer is as much a function of the successful construction of the niche as it is of mutations that enable cancer cell survival and proliferation. Hereby, cytokines such as TGFβ1 can be produced by bone-marrow-derived cells that are recruited to the niche side as well as of cancer-associated fibroblasts or the tumor cells themselves, supporting the cancer niche expansion and maturation [17]. Besides mutagenic consequences of radiation-induced DNA damage, ionizing radiation activates transforming growth factor β1 (TGFβ1) [18] and as a consequence contributes to the assembling and modifying of the tumor microenvironment. This is one example how radiation interconnects DNA damage responses and shaping of the tumor microenvironment.

Radiation as a modulator of inflammation – the role of tumor infiltrating lymphocytes as biomarkers for cancer therapy success and anti-tumor immunity

Fractionated radiotherapy with single doses ≥1.8 Gy modulates the inflammatory reaction within the tumor as well as in the tumor micro- and macro-environments [19]. Moreover, ionizing radiation impacts on the phenotype of the tumor cells and induces a bystander and abscopal response. The latter is strongly driven by the immune system [20,21]. The induction of an immunological response may thus form the basis for combining radiation therapy with immunotherapies to cure cancer not only locally but also systemically [22,23]. Changes in the immune contexture can be used to monitor and/or predict cancer therapy outcome [24]. Especially the extent of tumor infiltrating lymphocytes (TIL) may give clear hints on how inflammation is modulated within the tumor tissue by RT.

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