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The synergistic effect of radiotherapy and immunotherapy: A promising but not simple partnership

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ABSTRACT

Radiotherapy (RT) is one of the main components in the treatment of cancer. The better understanding of the immune mechanisms associated with tumor establishment and how RT affects inflammation and immunity has led to the development of novel treatment strategies. Several preclinical studies support the use of RT in combination with immunotherapy obtaining better local and systemic tumor control. Current ongoing studies will provide information about the optimal RT approach, but the development of reliable predictors of the response from the preclinical and the early phases of clinical studies is necessary to avoid discarding treatment strategies with significant clinical benefit. This review summarize the current concepts of the synergism between RT and immunotherapy, the molecular effects of RT in the tumor microenvironment, their impact on immune activation and its potential clinical applications in trials exploring this important therapeutic opportunity. Finally, the potential predictors of clinical response are discussed.

1. Introduction

Radiotherapy (RT) is one of the main treatment options for cancer, with more than a half of patients diagnosed of solid tumors receiving RT with a curative intent or in a palliative context (Delaney et al., 2005). RT used alone or in combination with surgery, chemotherapy, or target therapies improves local control and prolongs the overall survival of patients with different tumor types.

Traditionally, most importance has been attributed to the double-strand DNA damage induced by RT in tumor cells as the predominant mechanism of action and tumor control, followed by some kind of cell death like apoptosis, necrosis, autophagy, mitotic catastrophe or replicative senescence (Eriksson and Stigbrand, 2010). Even if the role of the degree of immune-competence of the host was first recognized since 1979 as a factor influencing radiation response (Stone et al., 1979), it is only in the last years that scientific evidence clarified some of the mechanisms involved in

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the radiation induced immune activation and its impact in tumor control.

Ionizing radiation is a complex therapeutic agent and the so called in-field effect allowing to the classical forms of cell death seems to be limited in the context of the tumor microenvironment and the host immune status. In the traditional dogma of induced tumor cell death by conventional fractionated RT, mitotic catastrophe is the most frequent form of cell death resulting from DNA damage (Ianzini et al., 2006). Apoptosis, a pre-mitotic cell death that occur rapidly, seems to be less frequently associated with the direct effect of radiation (Dewey et al., 1995). However, an inter-connected and complex sequence of events between these mechanisms leads to other forms of cell death like necrosis, senescence an autophagy with immunogenic potential, in order to stop the mitotic defective cells following DNA damage (Roos et al., 2016). RT is a promising immunological adjuvant and a complex modifier of the tumor microenvironment. For these reasons, a critical analysis of the current literature and its application is proposed in this overview. The molecular effects of RT in the tumor cells and its microenvironment, their impact on immune activation and its potential clinical applications in trials exploring this exiting and important therapeutic opportunity are reviewed. Finally, but not less important, the potential predictors of clinical response will be discussed.

2. Immune effects of RT in the tumor microenvironment

Radiation-induced damage in the tumor and normal tissues is affected by various regulatory immune mechanisms (Schaue and McBride, 2010). The effects of RT in immunologic cells has been studied in vitro and results of these studies show that irradiated tissues interact with the innate immune system in a manner similar to those damaged by pathogens. For instance, within the hours following irradiation, the stimulation of granulocyte-macrophage colony formation promote the myeloid-derived suppressor cells (MDSCs) migration into the circulation and through the inflamed tissues (Gough et al., 2013). Such cells can differentiate into mature granulocytes and macrophages. Macrophages have the ability to produce high levels of pro-inflammatory and anti-inflammatory cytokines, they can differentiate into antigen-presenting cells (APCs), and participate in angiogenesis and wound healing (Sica and Mantovani, 2012). The complex balance of inflammation has been described by Schaue et al. (Schaue et al., 2015). Briefly, two extreme phenotypes can be described as follows: *1*.- the pro-inflammatory phenotype that enhances antigen-specific responses mediated by reactive oxygen species (ROS), IL-12, macrophages of type M1 (killer), toll-like receptors (TLRs), IFN-γ and *2*.- the immunosuppressive phenotype driving angiogenesis, wound healing and fibrosis, generally favoring cancer establishment and progression, mediate by macrophages of type M2 (healer), MHC of class II expression, release of transforming growth factor-β (TGF-β), IL-4, IL-13, IL-10, and vascular endothelial growth factor (VEGF) (Reits et al., 2006; Hauser et al., 1993).

The therapeutic effects of RT have been observed not only in cancer cells, but also in their microenvironment. Nowadays, the role of the host's immune system in the mechanisms of tumor regression by generating a cytotoxic adaptive immune response is well described and is recognized as immunogenic cell death (ICD). In this complex myriad of events, intrinsic characteristics of the tumor cells (tumor type, immunogenic capacity) and the immune status of the host are important factors determining the successful induction of ICD (Panaretakis et al., 2008; Apetoh et al., 2007). RT has the potential to shift this finely tuned process through a pro-inflammatory profile more favorable for ICD, by activating key steps involved in this process. A minimum of molecular conditions seems to be necessary to induce ICD by RT. The major histocompatibility complex (MHC) of class I surface expression, cell surface translocation of calreticulin, extracellular release of high-mobility group protein box 1 (HMGB-1), extracellular release of ATP and other damage-associated molecular patterns (DAMP) seems to be essential molecular steps (Panaretakis et al., 2008; Apetoh et al., 2007; Obeid et al., 2007). In adition, RT can make tumors more immunogenic by the increase of dendritic cells (DCs) antigen uptake and presentation (Garnett et al., 2004; Chakraborty et al., 2004). Mature and activated intratumoral DCs have the potential to secrete chemokines that attract other immune cells like effector CD8+ T-cells into the tumor (Liao et al., 2004; Lee et al., 2009). Moreover, other RT induced immunostimulatory factors can result in changes in the tumor phenotype, like upregulation of MHC class I expression, increase of tumor-associated antigens expression and upregulation of the Fas/Fas ligand pathway, making tumor cells more sensitive to T-cell attack (Lugade et al., 2005; Burnette et al., 2011; Chakraborty et al., 2003). In summary, these data suggests that RT has the capacity to prime an adaptive T-cell mediated immune response by mechanisms that enhance antigen uptake by APCs, activation and migration of DCs, and cross-presentation of tumor-associated antigens.

3. Systemic effects of the immune activation mediated by RT: the abscopal effect

In addition to the potential synergism in terms of local control, the possibility to obtain systemic responses mediated by ICD has aroused great interest. This phenomenon described initially by Mole in 1953 as "the absopal effect" describe the tumor regression of lesions distant from the irradiated volume (Mole, 1953). Unfortunately this phenomenon is rarely observed in the clinic and was mainly described in sporadic case reports (Ehlers and Fridman, 1973; Kingsley, 1975; Antoniades et al., 1977; Fairlamb, 1981; Rees and Ross, 1983; MacManus et al., 1994; Nam et al., 2005; Wersall et al., 2006; Cotter et al., 2011; Okuma et al., 2011; Tubin et al., 2012; Ishiyama et al., 2012; Siva et al., 2013). Renewed interest in the systemic effect of RT has emerged thanks to the work of Formenti and Demaria. The authors demonstrate that T-cells are required to mediate distant tumor inhibition induced by RT. Using the growth factor FIt3-Lignad (FIt3-L) in immunocompetent mice bearing a syngeneic mammary carcinoma (67NR) in both flanks, they showed that irradiation to only one of the 2 tumors results in impaired tumor growth not only of the irradiated tumor but also of the non-irradiated tumor. Using an A20 lymphoma in the same mice containing the treated 67NR tumor and nude mice they also showed that this abscopal effect was tumor specific and that an intact immune system was required to reproduce abscopal responses (Demaria et al., 2004). To achieve this immune-mediated tumor rejection, the priming and effector phase of antitumor immune response are two important conditions which RT has the potential to induce by enhancing the number and function of DCs and by promoting extravasation of effector T cells at the tumor site (Teitz-Tennenbaum et al., 2003; Lugade et al., 2008). These steps results in a critical concentration of activated CD8+ T-cells primed against the tumor favoring ICD and tumor control (Demaria et al., 2005a). Otherwise, established cancer is characterized by a highly suppressive microenvironment dominated by immature DCs and CD4+ T-cells with regulatory function (Treg) (Kusmartsev and Gabrilovich, 2002; Lu et al., 2011; Nishikawa and Sakaguchi, 2010). These data support the capacity of RT to induce the release of tumor antigens by ICD, the activation and migration of DCs and cross presentation of tumor antigens with the consequent T-cell activation. All this steps represents the main downstream by which RT induces systemic antigen specific antitu-