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Blocking HIF-1 α Following Radiotherapy to Prolong and Enhance the Immune Effects of Radiotherapy: A Hypothesis

Cancer Center, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF **Luo Wei**
G **Ge Wei**
G **Song Jing**
G **Chen Cong**
G **Xu Huilin**
G **Ming Pingpo**





Corresponding Author: Ge Wei, e-mail: 1353117665@qq.com
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Tumor local immune escape is one of the “hallmarks” of cancer leading to poor prognosis. The effects of local radiotherapy on tumors are rapidly emerging as opportunities to remodel and enhance immunity against cancer. However, this immunity remodeling and enhancing are not permanent after local radiotherapy. High expression of HIF-1 α following local radiotherapy for tumor cell reoxygenation has been confirmed, and recently accumulating evidence shows the tumor immune suppression effects. These research findings suggest a new direction in the investigation of methods to enhance the efficacy of local radiotherapy. We speculate that by blocking HIF-1 α , the immune effects of radiotherapy might be prolonged and enhanced.

MeSH Keywords: Hypoxia-Inducible Factor 1, alpha Subunit • Immunity, Active • Radiotherapy

Abbreviations: HIF-1 α – hypoxia-inducible factor 1 α ; MDSC – myeloid-derived suppressor cells; Treg – T regulatory cells; TAM – tumor-associated macrophages; HLA-1 – human leukocyte antigen 1; MICA/B – MHC class I chain-related molecule A or B; VEGF – vascular endothelial cell growth factor; IL-10 – interleukin-10; TGF- β – transforming growth factor beta; PGE2 – prostaglandin E2; FAS/FASL – factor-related apoptosis /factor-related apoptosis ligand; ICAM-1 – intercellular adhesion molecule-1; VCAM-1 – vascular cell adhesionmolecule-1; ADAM10 – A disintegrin and metalloproteinase domain 10; NKp46/30/44 – NK cell protein 46/30/44; NKG2D – natural killer group 2, member D; JAK2 – Janus kinase 2; STAT5 – signal transduction and activator of transcription 5

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Background

Each stage in the development and progression of cancer is the result of cross-talk between the tumor and the host's immune system. The constant selective pressure of the immune system promotes the emergence of tumor cells that are highly resistant to immune rejection [1]. Several mechanisms may be involved in the "tumor escape", including cell-mediated immune tolerance, loss of some antigens, defective death receptor signaling, and immunosuppressive cytokines. Various immune cell types (e.g., Tregs, MDSCs, and TAMs) have been shown to contribute to the establishment and maintenance of immune tolerance [2]. Tumor cells frequently downregulate expression of HLA Class I antigens, which play an important role in antigen presentation to CD8+ T cells [3]. NK cells express activating receptors, such as NKG2D, which bind to stress-induced ligands (MICA and MICB) that can be up-regulated in a variety of tumors, making the tumor susceptible to NK cell-mediated cytotoxicity, which means that their paucity in the tumor may prevent NK-cell recruitment to the tumor site. Evidence shows that the expression of MICA and MICB can be suppressed in the hypoxic environment of the tumor [4]. As one of the death receptors, down-regulation or loss of Fas expression in tumors may also contribute to their resistance to tumor immunity [5,6]. Tumor cells also produce a variety of cytokines (e.g., VEGF, IL-10, TGF- β , and PGE2) that can negatively affect maturation and function of immune cells [3]. As a consequence, these negative regulators create a balance between immune activation and immune inhibition, resulting in "tumor escape" and tumor progression.

However, this balance has been proven to be upset by interventions such as radiotherapy that contribute to systemic antitumor immunity [7,8]. Enhanced expression of death receptors, MHC class I molecules, costimulatory molecules, adhesion molecules (ICAM-1 and VCAM-1), and stress-induced ligands on tumor cells after radiation increased their recognition and killing by T cells or NK cells *in vitro* and/or *in vivo* in several cancer models [9]. Interestingly, although many phenotypic changes have been observed and demonstrated to benefit antitumor immunity, some negative regulators have also been reported to be induced in some trails, like TGF- β and Tregs [9,10]. This means that the effects of radiation should not be simply considered as promoting antitumor immunity, but may be a tendency of the tumor to regain the balance. In fact, the phenotypic changes are not persistent, so there is a chance to enhance the immune effects of radiotherapy by prolonging the phenotypic changes. Here, we concentrate on HIF-1 α , a factor which increases after radiation and has recently been shown to suppress antitumor immunity.

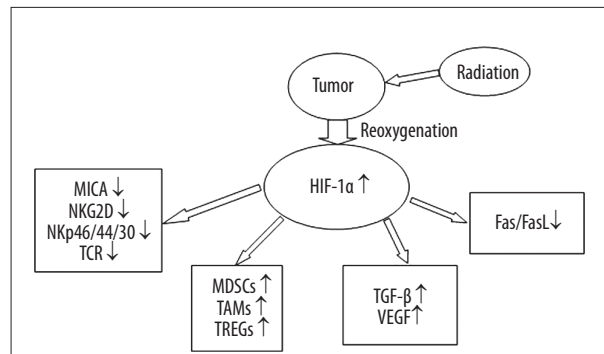


Figure 1. HIF-1 α is elevated following radiation and suppresses the immune effects.

Hypothesis

Although HIF-1 α is mostly known as a transcription factor activated by hypoxia in tumors, it can also elevate in other situations, for example after radiotherapy in cancer treatment. Within hours after irradiation, intratumoral HIF-1 α activity decreases due to von Hippel-Lindau-dependent HIF-1 α degradation under these reoxygenated conditions [11]. However, during reoxygenation, free radical species accumulate in tumor tissue and lead to overexpression of HIF-1 α [12]. As a result, HIF-1 α expression increases in a hypoxia-independent manner 18 to 24 h after radiotherapy. This upregulation endures up to 1 week [13].

In the past several years, accumulating evidence has indicated that HIF-1 α can act as a suppressor of antitumor immunity. Corzo et al. reported that hypoxia dramatically alters the function of MDSC in the tumor microenvironment and redirects their differentiation toward TAMs via HIF-1 α [14]. Ben-Shoshan et al. found that HIF-1 α increases the number and suppressive properties of naturally occurring CD4(+)CD25(+) Treg [15]. Deng et al. suggested that intratumor hypoxia promotes immune tolerance by inducing Tregs via TGF- β 1 in gastric cancer [16]. It has also been shown that TGF- β is a HIF-1 target gene, and introduces the possibility that hypoxia induction of Tregs involves a coordinated response involving HIF-1 α and TGF- β [17,18]. In addition to promoting the generation of Tregs, HIF-1 α can also negatively regulate functions of T cells directly by regulating T cell receptor signal transduction [19,20]. ADAM10 is an enzyme required for the hypoxia-induced shedding of MICA. A study found a mechanistic link between HIF-1 α , increased expression of ADAM10, and decreased surface MICA levels [21]. The expression of HIF-1 α in NK cells also seems impair their ability to upregulate the surface expression of the major activating NK-cell receptors (NKp46, NKp30, NKp44, and NKG2D) [22]. The association of HIF-1 α and FAS expression has been implied in some experiments. Andrew et al. showed that a VEGF/JAK2/STAT5 axis may decrease the apoptosis of endothelial cells by repression of proapoptotic FAS/FASL [23], and VEGF can be induced by HIF-1 α .

In summary, accumulating evidence shows that the immune suppression effects of HIF-1 α and the elevating of HIF-1 α after irradiation could prevent the immune effects of irradiation (Figure 1). Therefore, we speculate that inhibition of HIF-1 α following radiotherapy may prolong and enhance the immune effects of radiotherapy.

Conclusions

In the past decades, the immune effects of radiotherapy in tumors have been investigated extensively. However, tumors

are so “clever” that they can remodel themselves and reverse the immune effects of radiotherapy, which makes the effects temporary. HIF-1 α may be one of factors taking part in the remodeling, and inhibition of HIF-1 α following radiotherapy may prevent the process.

Conflict of interest statement

The authors declare that they have no conflict of interest in any matter related to this work.

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