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Radiation effects on the tumor microenvironment: Implications for nanomedicine delivery☆

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ABSTRACT

The tumor microenvironment has an important influence on cancer biological and clinical behavior and radiation treatment (RT) response. However, RT also influences the tumor microenvironment in a complex and dynamic manner that can either reinforce or inhibit this response and the likelihood of long-term disease control in patients. It is increasingly evident that the interplay between RT and the tumor microenvironment can be exploited to enhance the accumulation and intra-tumoral distribution of nanoparticles, mediated by changes to the vasculature and stroma with secondary effects on hypoxia, interstitial fluid pressure (IFP), solid tissue pressure (STP), and the recruitment and activation of bone marrow-derived myeloid cells (BMDCs). The use of RT to modulate nanoparticle drug delivery offers an exciting opportunity to improve antitumor efficacy. This review explores the interplay between RT and the tumor microenvironment, and the integrated effects on nanoparticle drug delivery and efficacy.

Contents

Abbreviations: Ang2, Angiopoietin 2; BMDCs, Bone marrow-derived myeloid cells; CSF1, Colony stimulating factor 1; CSF1R, Colony stimulating factor 1 receptor; CT, Computed tomography; CXCR4, C-X-C motif receptor 4; CXCR7, C-X-C motif receptor 7; CXCL12, C-X-C motif ligand 12; ECM, Extracellular matrix; EPR, Enhanced permeability and retention; Gy, Gray; HIF1, Hypoxia inducible factor 1; IFP, Interstitial fluid pressure; MVP, Microvascular pressure; RT, Radiotherapy; SDF1, Stromal cell-derived factor 1; STP, Solid tissue pressure; TAMs, Tumor-associated macrophages; VEGF, Vascular endothelial growth factor.

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1. Introduction

Radiotherapy (RT) is used to treat approximately 50% of all cancer patients and contributes to long-term disease control and cure in a substantial proportion [1]. The therapeutic benefit of RT is optimized based on the balance between tumor control and toxicity. Advances in technology, including image-guided and intensity-modulated RT, have substantially improved the ability to precisely deliver high doses of RT to tumors while minimizing dose to neighboring normal tissues and maintaining treatment side effects at acceptable levels. Nevertheless, tumor recurrence after RT remains a significant problem.

There has been extensive interest in combining RT with systemic treatment, either cytotoxic chemotherapy or biologically targeted agents as a means of further enhancing treatment efficacy. Much of this effort has focused on the use of chemotherapy to improve the curative potential of RT by offsetting accelerated tumor cell repopulation during a prolonged treatment course, sensitizing or directly killing radioresistant cells, targeting occult metastases outside of the irradiated volume, or protecting normal tissues from injury [2,3]. Combined treatment with RT and concurrent weekly cisplatin is now the standard of care for head and neck, lung, esophageal, cervical, and bladder cancers among others, based on evidence from phase III trials demonstrating improved primary tumor control and/or patient survival compared to RT alone. However, the potential for further, significant improvements in clinical outcome using currently available cytotoxic chemotherapeutics in combination with RT is limited because of additive toxicity. Instead, the focus of investigation has shifted to better understanding the biological mechanisms that drive tumor recurrence after RT, including the interplay among genetic, microenvironmental, and immunologic effects, to guide more strategic molecular targeting of radioresistance pathways using drugs with non-overlapping toxicities. Abnormal vascular morphology and physiology, hypoxia, high interstitial fluid pressure (IFP), and tumor-infiltrating bone marrow-derived myeloid cells (BMDCs) have all been implicated as important drivers of tumor recurrence after RT and are potential therapeutic targets [4].

Despite past and continuing efforts over many years to use cytotoxic or molecular chemotherapeutics to enhance radiation response, there has been relatively little investigation of the role of RT to modify chemotherapy efficacy. RT is known to have profound, time-dependent effects on tumor, endothelial, and stromal cells that, in turn, would be expected to influence drug delivery to tumors, distribution within tumors, and uptake by cancer cells. This is likely to be even more relevant with new, long-circulating nanotherapeutics, including liposomal drug carriers. The biophysical principles that most strongly influence the transport of these agents are recognized to be different than for conventional, low-molecular-weight chemotherapeutics, resulting in a greater accumulation in tumors than in normal tissues. RT has been shown to enhance this accumulation and improves the intra-tumoral distribution of nanoparticles, leading to even greater therapeutic effect [5,6]. This appears to be mediated by RT-induced changes to the tumor microenvironment including the vasculature and stroma, with secondary effects on hypoxia, IFP, and BMDC recruitment and activation. It has been proposed that nanomedicine-based radio-chemotherapy may leverage synergies between these two therapeutic approaches, with RT improving the tumor accumulation of drug delivery systems harboring payloads designed, in turn, to enhance radiation treatment response and further improve drug delivery [6].

This review explores the dynamic interplay between RT and the tumor microenvironment with a particular focus on RT to enhance nanoparticle transport, as summarized in Fig. 1. The effects of RT on the tumor vasculature and stroma, and the resultant change in hypoxia, IFP, and BMDC recruitment, are discussed in the context of nanoparticle delivery, uptake, and distribution. Perspectives on the current state of the art, potential clinical applicability, and limitations of using RT in combination with nanoparticle-based therapies are highlighted.

2. Pathophysiology of the tumor microenvironment

Solid tumors are composed of cancer cells surrounded by an extracellular matrix (ECM) of cross-linked collagen, hyaluronic acid, and glycoproteins that supports the tumor vasculature and a wide range of host-derived cells, including fibroblasts, lymphocytes, and myeloid cells that coexist in a dynamic and adaptive environment [7–9]. The vasculature in solid tumors is structurally and functionally abnormal

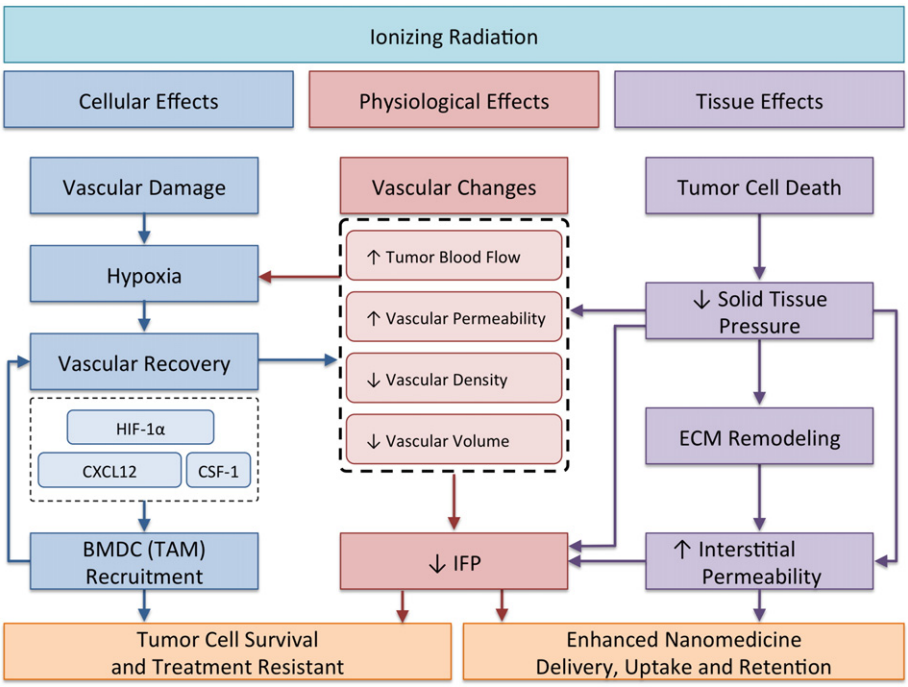

Fig. 1. Summary of the interplay between RT and the tumor microenvironment, including vascular and stromal effects leading to hypoxia, decreased IFP and decreased STP, and the integrated impact on tumor cell survival, treatment resistance, and nanomedicine delivery.