Challenges of Ionizing Radiation in Tumor Treatment and Role of Angiogenesis

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Ionizing radiation is a non-specific, but most widely used therapeutic method for cancer treatment. However, a minor fraction of tumor cell population manages to survive after radiation. Radiation efficacy depends on adequate oxygen supply. Rapid growing tumors cause hypoxia that upregulates many pro-survival pathways. At clinical doses, radiation activates inflammatory pathways and causes oxidative stress that plays a positive role during angiogenesis. Selective targeting of signaling mechanisms may radiosensitize tumors.

Keywords: Angiogenesis, Hypoxia, Ionizing radiation, Signaling mechanism, VEGF

Introduction

Ionizing radiation (IR) is a non-specific, widely applied and highly effective therapeutic modality for the treatment of majority of the solid malignant neoplasms. This might often be the only feasible option for the primary intervention\(^1\). The efficacy of IR is depends mostly on the localization of the tumor and also oxygen tension in the tumor. In addition to IR, cytotoxic drugs also rely on adequate oxygen tension in the tumor\(^2\).

Tumor angiogenesis (Schema 1) is a hallmark of advanced cancers and promotes invasion and metastasis. Rapidly growing tumors can cause hypoxic environment in the tumor, which up-regulates the tumor cell survival factors, such as hypoxia-inducing factor-1α (HIF-1α) and vascular endothelial growth factor (VEGF)\(^3\). VEGF stimulates abnormal vessel formation that is leaky and tortuous, causing irregular blood flow\(^4\). HIF-1 promotes tumor angiogenesis\(^5\). The resulting increase in HIF-1 regulated cytokines enhances endothelial cell (EC) radioreistance\(^6\).

IR is a potent antiangiogenic agent that inhibits endothelial cell survival, proliferation, tube formation and invasion\(^7\). Yet, it is also found that IR has angiogenic potential\(^7,8\). Local, low-dose IR upregulates angiogenic chemokines and results in progenitor cell mobilization to the systemic circulation\(^8\). Thus, IR enhances invasiveness of surviving tumor cells and several proteolytic enzyme molecules, including urokinase plasminogen activator (uPA)\(^9\). uPA and its receptor (uPAR) have been strongly implicated in tumor invasiveness, angiogenesis, proliferation and increased radioreistance\(^3,9\).

Matrix metalloproteinases (MMPs), a wide family of proteases secreted by tumors and microenvironmental cells are also linked with invasion and metastasis through complete extracellular matrix (ECM) breakage. In vitro studies have demonstrated an enhanced migration, invasiveness and angiogenic ability of cancer cells after radiation exposure through an increase in MMP activity\(^10\).

Oxidative stress

During angiogenesis, oxidative stress plays a positive role. The reactive oxygen species (ROS) can be generated either endogenously through mitochondrial electron transport chain reactions and NADPH oxidase or exogenously, resulting from exposure to environmental agents, such as UV or IR. In many conditions, ROS promote angiogenesis; either directly or via generation of reactive oxidation products\(^11\). It has been established that irradiation dose-dependently induces activation of proangiogenic nitric oxide (NO) pathway in ECs through increase in endothelial nitric oxide synthase (eNOS). Production of NO is accounted for EC migration and sprouting that stimulate the capillary-like structures formation\(^12\) (Schema 1).

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Abbreviations: EC, endothelial cell; ECM, extracellular matrix; HIF-1α, hypoxia-inducing factor-1α; IR, ionizing radiation; MMP, Matrix metalloproteinase; NF-κB, nuclear factor kappa B; NO, nitric oxide; ROS, reactive oxygen species; TF, transcription factor; TGF-β1, transforming growth factor-β1; TIMP, tissue inhibitors of metalloproteinases; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator receptor; VEGF, vascular endothelial growth factor.
Inflammation

At clinical doses, radiation activates the cytoplasmic phospholipase A2, leading to increased production of arachidonic acid and lysophosphatidylcholine. The former is the initial step in the generation of eicosanoids, while the later is the initial step in the formation of lysophosphatidic acid, leading to the activation of inflammatory pathways. The radiation-induced activation of pro-inflammatory cytokine network, including interleukin (IL)-1β, IL-6 and TNF-α (Schema 2) has been shown to mediate pain, fatigue and local inflammation in cancer patients. Radiation also induces the increased expression of inflammatory mediator transforming growth factor-β1 (TGF-β1) (Schema 2). TGF-β1 regulates various biological processes, including differentiation, bone remodeling and angiogenesis and is particularly important as a regulator of homeostasis and cell growth in normal tissue. It is reported to induce apoptosis through the induction of specific genes, whereas others suggest that it inhibits the apoptosis and facilitates cell survival. In another study, it is suggested that TGF-β1 protects cells against γ-irradiation by decreasing DNA damage and apoptosis and thereby enhances cell survival.

Signaling mechanisms

Many pro-survival pathways are activated by IR-induced multi-layered signaling response in mammalian cells that converge to transiently activate a few important transcription factors (TFs), including nuclear factor kappa B (NF-κB) and signal transducers and activators of transcription (STATs), the central mediators of inflammatory and carcinogenic signaling. These TFs are dependent on pro-survival genes that regulate inflammation, anti-apoptosis, invasion and angiogenesis pathways, which confer tumor cell radiosensitivity.

The transmission of death signals from stress stimuli, such as IR, inflammation and chemotherapy in normal and malignant cells, is associated with the action of p38MAPK. It shows pleiotropic functions, ranging from cellular proliferation and survival to cell cycle arrest and regulation of the tumor microenvironment. In contrast, p38MAPK is required for the effects of cytotoxic agents in some hematological malignancies.

The integrins and PI3K/Akt are also important mediators of signal transduction pathways involved in tumor angiogenesis and cell survival after exposure to IR. Radiation can up-regulates alpha(v)beta3 expression in ECs and consequently phosphorylates Akt, which may provide a tumor escape mechanism from radiation injury through integrin survival signaling.

Treatment

Though radiotherapy is one of the most widely used cancer treatments, the development of tumor radioresistance is an ongoing problem. Selective targeting of signaling mechanisms, such as either NF-kappa B, p38MAPK or integrins and PI3K/Akt can radiosensitize tumor cells. The biology of irradiated cells is altered, leading to the up-regulation of genes that favor cell survival, invasion and angiogenesis. In addition, hypoxia within the tumor mass limits the cytotoxicity of irradiation, whereas irradiation itself may worsen hypoxic conditions.
which also contribute to the generation of resistant cells\(^1\). Therefore, tumor blood vessels have been recognized as a critical component of radiation response to the point of being independent of tumor oxygenation during radiation. An anti-angiogenic approach for solid tumors destroys tumor vasculature and reduces tumor growth\(^2\), and has been considered less likely to develop drug resistance\(^2\). VEGF and its receptor VEGFR2 represent central molecular targets for antiangiogenic intervention because of their integral involvement in endothelial cell proliferation and migration\(^2\). Protein tyrosine kinase inhibitors (TKIs) have been shown to potentiate radiation-induced destruction of tumor blood vessels. Inhibition of receptor tyrosine kinases (RTKs) attenuates downstream signaling from various angiogenic growth factors, including VEGF, primarily through inhibition of the PI3K/Akt signaling pathway, which results in induction of apoptosis\(^3\). The human anti-VEGF antibody bevacizumab, as well as the VEGFRTK inhibitors sunitinib and sorafenib have been licensed by the US Food and Drug Administration (USFDA) and the European Medicines Agency (EMEA) for the treatment of colorectal, renal and lung cancer\(^4\).

However, tumor recurrence sustained by a minor fraction of surviving tumor cells is a common phenomenon\(^5\). A cell population manages to survive after the exposure either because it receives sub-lethal doses and/or because it successfully utilizes the repair mechanisms\(^5\). Evidence suggests that doses of IR delivered inside the tumor target volume during fractionated radiotherapy can promote tumor invasion and metastasis\(^6\). The original mechanism of antiangiogenesis is to induce ischemia and hypoxia in tumors, thereby "starve" the tumors. However, emerging data suggest that antiangiogenic agents could reduce the proportion of hypoxic cells through normalizing tumor vasculature, decreasing oxygen consumption and other mechanisms\(^6\). Furthermore, the tissues that surround the tumor area are also exposed to low doses of IR\(^7\). The improved accuracy offered by advanced radiotherapy (RT)-technology permits the reduced volume of healthy tissue in the irradiated field\(^8\). The combined treatment modality of IR with inhibitors of angiogenesis is a promising therapeutic option\(^9\).

References


