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Radiation-enhanced cell migration/invasion process: A review

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Contents

Abstract

Radiation therapy is a keystone treatment in cancer. Photon radiation has proved its benefits in overall survival in many clinical studies. However, some patients present local recurrences or metastases when cancer cells survive to treatment.

Metastasis is a process which includes adhesion of the cell to the extracellular matrix, degradation of the matrix by proteases, cell motility, intravasation in blood or lymphatic vessels, extravasation in distant parenchyma and development of cell colonies.

Several studies demonstrated that ionizing radiation might promote migration and invasion of tumor cells by intricate implications in the micro-environment, cell–cell junctions, extracellular matrix junctions, proteases secretion, and induction of epithelial–mesenchymal transition. This review reports various cellular pathways involved in the photon-enhanced cell invasion process for which potential therapeutic target

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may be employed for enhancing antitumor effectiveness. Understanding these mechanisms could lead to therapeutic strategies to counter the highly invasive cell lines via specific inhibitors or carbon-ion therapy.

Keywords: Radiation-enhanced; Cell invasion; Carbon ion; Epithelial–mesenchymal transition; Stroma

1. Introduction

The multistep process of invasion and metastasis has been schematized as a sequence of distinct steps. Initial local invasion generally includes: adhesion of cell to the extracellular matrix (ECM), degradation of the ECM by cellular proteases and, migration/invasion through the ECM [1]. Subsequently, the intravasation of tumor cells to the lymphatic capillary system or blood flow [2] and the extravasation to the parenchyma of distant tissues led to the formation of micrometastases. One main program by which transformed epithelial cells can acquire the abilities to invade and to disseminate is the epithelial–mesenchymal transition (EMT). EMT is a succession of events during which epithelial cells lose E-cadherin functions. The process is described during specific stages of embryonic development in which epithelial cells migrate and colonize different embryonic tissues [3]. E-cadherin regulates the establishment of the adherens junctions, which leads to a continuous adhesive epithelium. Mesenchymal cells do not have E-cadherin and so do not have stable intercellular junctions. The decrease in intercellular adhesive forces presumably facilitates dispersion of cells. Frixen et al. demonstrated in cancer cell lines that loss of E-cadherin is correlated with a fibroblastoid phenotype and invasiveness, while its re-expression inhibited this phenomenon [4]. Moreover, there is a growing body of evidence that crosstalk between cancer cells and cells of neoplastic stroma is involved in the acquired capability for invasive growth and metastasis. Each of them has the ability to secrete growth factors, cytokines and proteins to remodel the extracellular cell matrix (ECM) [5]. For example, cancerous and stromal cells secrete matrix metalloproteinases (MMPs), which degrade ECM proteins [6]. As a result from this phenomenon, cells lose the interactions with ECM and gain in motility.

Surprisingly, it has been suggested that radiotherapy, a keystone treatment in the cancer armamentarium, may promote invasion and metastatic process. Radiation therapy is an efficient modality to treat malignant tumors, and its benefit on overall survival has been repeatedly demonstrated in numerous types of cancers [7]. However, local recurrences (primary tumor site) or metastases (distant organ) that occur could partially be favorized by the enhanced migratory properties of the surviving cancer cells resisting to ionizing radiation. In 1991, Von Essen first wrote a report describing the occurrence of metastatic cells in both the primary tumor site and in the normal tissues after irradiation [8]. Since then, several studies demonstrated that ionizing radiation might promote migration and invasion abilities of tumoral surviving cells (Table 1). In this review, we will report the various cellular pathways involved in the radiation-enhanced cell invasion process for which potential intracellular target may be employed for enhancing antitumor effectiveness.

2. Molecular mechanisms implicated in the radiation-enhanced cell invasion

2.1. Irradiation promotes EMT

Several authors explored the link between EMT and photon-enhanced cell invasion. Jung et al. [24] observed that irradiated cell changed in morphology and looked like fibroblasts corresponding to mesenchymal phenotype. These cells had an increased actin stress fiber immunostaining, with a reorganized E-cadherin distribution, and displayed more focal contacts, reminiscent of the EMT. Moreover, they realized a scratch motility assay where irradiated cells migrated more than in the control group. Fujita et al. [18] observed that radiation-enhanced cell invasion was correlated with an increase of a mesenchymal phenotype in microscopy. However, it was observed that exogenous transforming growth factor-β (TGFβ) had no effect on irradiated cells [42–44]. TGF-β is one cytokine that plays a significant role in inducing EMT. Jung et al. explored TGFβ secretion while cells changed their phenotype after irradiation, higher concentration was detected in cell medium but was not correlated with migration. Thus radiation-enhanced cell invasion is associated to EMT, but the implication of TGFβ is not well understood. More, TGFβ was explored in an *ex vivo* study. Biswas et al. [12] inoculated breast cancer cells in the abdominal area of mice and delivered irradiation to the thorax. Increased circulating level of TGFβ as well as increased circulating tumor cells and lung metastases were observed. Irradiation to normal tissue may then cause changes in gene expression in the resident fibroblasts and the release of TGFβ, which may be implicated in inflammation pathway and tumorigenesis [45]. In conclusion, the role of TGFβ is not well defined and more studies are needed in order to conclude about is implication in radiation-enhanced cell invasion.

2.2. Interaction with stromal environment

The observation made by Biswas et al. shows the importance of the tumor environment. Most of tumor cells interact with host cells (stromal fibroblasts, adipocytes, endothelial cells, and the extracellular matrix), which support them by secreting growth factors, cytokines. Ohuchida et al. [28] explored the influence of radiation in the microenvironment