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Review

Irradiation induces diverse changes in invasive potential in cancer cell lines

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ABSTRACT

Cancer patients without metastasis are generally considered as candidates for curative localized radiation therapy. However, while the benefits of localized radiation have been demonstrated by many clinical studies, recurrences or distant metastases that develop after local treatment remain a major therapeutic challenge. Several *in vitro* and *in vivo* studies have reported that irradiation may subsequently alter tumor aggression by reducing or promoting the invasiveness of the remaining cancer cells after radiation, which appears to differ depending on the form of radiation, as well as the investigated cell lines. Cell lines recapitulate cancer heterogeneity based on the characteristics reflected in their genetic abnormalities, and thus can be used as a tool to investigate the genetic basis of cancer aggression. Importantly, molecular insights into this process would allow us to tailor drug treatments for use in combination with local radiation treatment. This review summarizes the diverse responses of cancer cell invasiveness induced by radiation, and discusses the possible molecular pathways and the genetic variations that may affect radiation-altered invasion.

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1. Introduction

Tumor metastasis is the primary cause of cancer-related death and accounts for more than 90% of mortalities [1,2]. Clarifying the mechanisms of metastasis remains difficult because of the diverse effects associated with the cumulative mutations acquired by metastatic cells and the heterogeneity of mutated genes across metastatic cancer types. Although cell lines may exhibit a narrow range of genetic variations induced by adaptation to the culture environment [3], cell line-derived gene signatures can be used to classify the tumor from which they were derived [3–5]. Cell lines that maintain many of the molecular and genetic characteristics of the parent tumor have long been used as a tool to study the biological characteristics found in primary human tumors [6–9]. Thus, collections of cell lines can provide valuable information of multiple tumor types and serve as a model of tumor heterogeneity.

Radiation therapy is an effective form of cancer treatment [10,11]. In addition to conventional photon radiation, particle radiation therapy has been used worldwide as a novel therapeutic method since the first proposed use of protons and heavy ions in 1946. Photon radiation deposits energy within the first few centimeters from the irradiated body surface, which decreases exponentially with increasing depth [12]. In contrast, particle radiation shows a unique energy deposition with a sharp increase at the end of the particle range, which acutely diminishes beyond the target point, thereby enabling a more accurate dose distribution for tumor therapy compared with photon irradiation [12]. In addition, heavier particles, such as carbon ions (C-ions), exhibit higher ionization density within individual particle tracks, which induces significant DNA damage and cytotoxicity in tumor cells, thereby conferring an advantage over photon or proton irradiation in terms of tumor-killing ability [12,13]. Several clinical studies have shown that C-ion radiotherapy provides high local tumor control and confers a great overall survival benefit in many cancer types [13].

However, overcoming local recurrences or metastases that can occur after radiotherapy remains a therapeutic challenge. While such recurrences or metastases may originate from micrometastases present before radiation therapy, several *in vitro* and *in vivo* studies demonstrate that therapeutic radiation can elicit cellular changes that alter the invasiveness of cancer cells [14]. Generally, evidence indicates that photon radiation may subsequently enhance the migration and/or invasiveness of the cancer cells

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surviving after radiotherapy, whereas C-ion irradiation diminishes this in several cell lines [14]. However, it should be noted that not all cell lines exhibit these migratory responses following irradiation, as some cell lines showed reduced invasiveness after photon radiation, or enhanced invasion after C-ion irradiation [14–16].

In order to elucidate the effects of local radiotherapy on the characteristics of metastatic tumors, it is fundamental to understand the nature of motility utilized by the remaining cancer cells after radiation. Cancer cells invade either as single cells, or by moving collectively as epithelial sheets or detached clusters [17]. The mechanisms of single cell invasion are well-studied and include two modes of motility, mesenchymal and amoeboid (also known as protease-dependent and protease-independent invasion, respectively) [17]. Rho GTPases serve as the master regulators of these two modes of motility. In addition, tumor cells alter the expression of proteases or adhesion molecules and move through the extracellular matrix (ECM) [17]. Thus, investigating the effects of irradiation on the molecules regulating tumor cell invasiveness will further increase our understanding on the mechanisms of radiation-induced cancer cell migration or invasion, and may provide a more detailed view of the complex molecular pathways or key genetic variations to help tailor individual treatments for use in combination with local radiotherapy.

In this review, we will initially summarize the general knowledge on the molecules regulating cancer cell invasion. We will then report on the diversity of cancer cell invasiveness affected by photon or particle beam radiation and discuss the possible molecular pathways and genetic variations that may affect radiation-altered invasion.

2. Molecular principles of cancer cell invasion

2.1. Mesenchymal and amoeboid modes of motility

In the first step of metastasis, cancer cells invade into the ECM by dynamically remodeling their intracellular cytoskeleton through either mesenchymal or amoeboid motility, or a combination of both [17–19]. Cells moving in a mesenchymal mode exhibit an elongated morphology and require the activity of proteases, such as aspartic, cysteine, metallo, serine, and threonine proteases, to remodel the ECM and create a path for cell migration [20–22]. The elongated cells then move through this path by forming a leading edge that extends actin-rich protrusions, such as lamellipodia, in a Ras-related C3 botulinum toxin substrate 1 (RAC1) signaling-dependent manner [19,23,24]. In contrast, cells using amoeboid motility have a rounded morphology with bleb-like protrusions and are able to squeeze through gaps between matrix proteins [19,24]. This process is mediated by actomyosin contractions, which are dependent on Rho/Rho-associated protein kinase (ROCK) signaling, and occurs independently of protease activity [18,19]. However, some tumor-derived cell lines utilize both modes depending on the environmental conditions [15,16,24], making it difficult to suppress invasion using a single class of reagent [15,16].

2.2. Rho GTPases

The Rho GTPases RAC1 and Ras homolog gene family member A (RHOA) are recognized as the masters of cell motilities and essential for the mesenchymal and amoeboid modes of motility, respectively [25]. Active signaling through RAC1 and RHOA has a fundamental role in regulating cellular architecture, and is required for the formation of actin-rich or bleb-like protrusions, as well as the actomyosin contractions contributing to tail retraction [25,26]. The activities of RAC1 or RHOA are tightly regulated by guanine nucleotide exchange factors (GEF) that activate Rho GTPases by allowing them to bind GTP, whereas GTPase-activating proteins (GAP) inactivate Rho GTPases by enhancing GTP hydrolysis [26]. Some GEFs and GAPs show their activity toward several Rho GTPases, whereas others have a more restricted specificity [26]. The molecular switch between the GTP-bound and GDP-bound forms is observed with the cell membrane association; thus, the cytosolic localization of Rho GTPases is necessary to keep them in an inactive state. As such, Rho-specific guanine nucleotide dissociation inhibitors (GDIs) sequester Rho GTPases within the cytosol to prevent their aberrant activation [26,27]. Moreover, recent studies have shown that RAC1 and RHOA activity can also be governed by their ubiquitin (Ub)-mediated proteasomal degradation, which subsequently modulates the plasticity of cell migration [28,29].

2.3. Cell adhesion

Cells express variety of cell surface adhesion receptors, such as integrins, syndecans, proteoglycans, and cadherins. Among these, integrins are the most studied and recognized as important factors that modulate cell migration [30]. Integrins are a family of heterodimeric transmembrane glycoproteins comprised of α and β subunits. Each heterodimer consists of a large extracellular domain capable of binding specific sequence motifs present in ECM proteins, such as fibronectin and collagen [30]. The binding of integrins to their extracellular ligands promotes the formation of an intracellular linkage between the integrin cytoplasmic tail and the actin cytoskeleton through multiprotein complexes [31]. Among the integrins, α2β1, α3β1, α5β1, α6β4 αvβ3, and αvβ6 are known to play a role in cancer invasion and/or metastasis [30,32,33].

2.4. Proteases

Cells migrating via the mesenchymal mode of motility utilize the activity of proteases to penetrate the ECM. Five human protease classes have been classified according to catalytic mechanism: aspartic, cysteine, metallo, serine, and threonine proteases [20–22]. These proteases interact coordinately, by activating or inhibiting reactions, to facilitate the remodeling of the ECM [20]. For instance, an aspartic cathepsin, cathepsin D, activates cysteine proteases such as cathepsin B and cathepsin L. Cathepsin B proteolytically activates other metalloproteases, such as matrix metalloproteases (MMPs), and serine proteases [20].

Growing evidence suggests that MMPs play clear role in tumor metastasis and is associated with a poor prognosis [34,35]. MMPs are a family of zinc-containing proteolytic enzymes comprised of 23 recognized members in humans [36]. Among those, MMP-1, MMP-8, and MMP-13 are collagenases, MMP-2 and MMP-9 act as gelatin-cleaving enzymes, and MMP-3, MMP-7, and MMP-10 degrade a broad range of ECM proteins [36]. In addition, membrane-anchored MT1-MMP (MMP-14) can proteolytically activate MMP-2 or MMP-13, as well as directly degrade ECM proteins – such as type-I, -II, and -III collagen [37] – and some cell-surface proteins, including CD44, αv integrin, and syndecan 1 [38]. In addition to the ECM degradation, some MMPs – such as MMP-7 and MMP-28 – are capable of triggering epithelial-to-mesenchymal transition (EMT) [39,40], a process in which epithelial cells acquire a mesenchymal phenotype to increase their migratory capacity [41]. Accordingly, MMP inhibitors (MMPI) were developed as anticancer agents; however, clinical trials have revealed little benefit for cancer patients in comparison to other chemotherapies, with patients experiencing unexpected side effects of musculoskeletal pain and inflammation. [42,43].

Apart from MMPs, serine proteases are also prominent factors that modulate cell invasion. Among serine proteases, plasmin promotes cellular invasion by degrading several ECM components, such as fibronectin, laminin, vitronectin, type IV collagen,

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