Molecular Pathways:

Emerging Pathways Mediating Growth, Invasion And Metastasis Of Tumors
Progressing In An Irradiated Microenvironment

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Abstract

Radiotherapy is a well-established therapeutic modality in oncology. It provides survival benefits in several different cancer types. However, cancers relapsing after radiotherapy often develop into more aggressive conditions, which are difficult to treat and are associated with poor prognosis. Cumulating experimental evidence indicates that the irradiated tumor bed contributes to such aggressive behavior. The involved mechanisms have long remained elusive. Recent progress in the field revealed previously unrecognized cellular and molecular events promoting growth, invasion and metastasis of tumors progressing in an irradiated microenvironment. Cellular mechanisms include inhibition of sprouting angiogenesis, formation of hypoxia, activation and differentiation of stromal cells and recruitment of bone marrow-derived cells with vasculogenic and pro-metastatic activities. Identified pathways include TGFβ/ALK5, CXCL12/CXCR4, KITL/KIT and CYR61/αVβ5 integrin. The availability of pharmacological inhibitors impinging on these pathways opens novel opportunities for translational and clinical studies. These experimental results and ongoing work highlight the importance of the irradiated microenvironment in modulating the tumor response to radiotherapy and open new opportunities for the development of novel therapeutic strategies for cancer patients relapsing after radiotherapy. Here we review and discuss recent advances in the field and their translational and therapeutic implications to human cancer treatment.
Background

Radiotherapy plays a prominent role in the treatment of various tumor types and provides significant survival benefits in many cancers, including the breast, prostate, rectum, brain, lung, and head and neck cancers (1). In breast cancer, radiotherapy, alone or in combination with chemotherapy, is widely used as adjuvant treatment after breast-saving surgery to reduce the incidence of loco-regional and distant recurrences (2). The therapeutic effects of radiotherapy are traditionally considered as due to the induction of double strand DNA breaks in cancer cells causing cell-cycle arrest, senescence or apoptosis (3). Consistent with this view, efforts aimed at understanding and improving the therapeutic efficacy of radiotherapy largely concentrated on the study of mechanisms of DNA damage and repair (4). It is now becoming increasingly evident that ionizing radiation also induces modifications of the tumor microenvironment, which profoundly impact tumor biology (5). This is particularly relevant to cancers relapsing after radiotherapy, which tend to develop into invasive and metastatic conditions with poor prognosis (6). Cumulating experimental evidence indicates that the irradiated tumor microenvironment actively contributes to such aggressive behavior. Here we review and discuss recent advances in unraveling cellular events and molecular pathways of the tumor microenvironment modulated by ionizing radiation and affecting tumor growth, invasion and metastasis.

The tumor bed effect. Experimental tumors implanted in a pre-irradiated bed grow with slower kinetics, an effect originally referred to as the tumor bed effect (TBE) (7, 8). The TBE is dose dependent between 5 and 20 Gy single doses (9), occurs with
fractionated therapy (e.g. daily doses of 2Gy) (10) and within broad time intervals (0-90 days) between irradiation and tumor implantation (11) and is cell line dependent (10). A second element of the TBE is enhanced invasion and metastasis, which might seem paradoxical considering the reduced primary tumor growth (6, 12). Enhanced metastasis was observed regardless of whether the analysis was metachronic (i.e. equivalent tumor sizes at different time points) (12) or synchronic (i.e. different tumor sizes at the same time point) (13, 14). The TBE is a local effect, as it is only observed for tumors injected inside of the irradiated bed (14). These observations are of clinical relevance, since adjuvant radiotherapy improves local tumor control but tumor recurrences within a pre-irradiated field are often associated with an elevated risk of metastasis and poor prognosis (2, 15-17).

Inhibition of sprouting angiogenesis. Several microenvironmental events have been linked to the TBE, most notably the decrease in tumor vascularity (18-20). We know today that radiotherapy-induced modifications of tumor vasculature are due to direct effects of ionizing radiations on endothelial cells. Garcia-Barros et al., showed that high-dose ionizing radiation induces ceramide-mediated apoptosis of tumor-associated endothelial cells, causing tumor vessel disruption and delayed tumor growth. Preventing ceramide-mediated endothelial cell apoptosis attenuated these effects, indicating that endothelial cells are a therapeutically-relevant target of radiotherapy (21). We showed that ionizing radiation suppresses de novo angiogenesis by inhibiting endothelial cell proliferation, migration and sprouting and by causing premature senescence, in part mediated by the TGFβ/ALK5 pathway (22). ALK5 inhibition rescued radiation-induced cell sprouting and migration defects in vitro and restored angiogenesis in vivo (22). In spite of inhibited sprouting angiogenesis,
vessels can still form, to a certain extent, in irradiated tumors. Hlushchuk et al., demonstrated intussusceptive angiogenesis replaces sprouting angiogenesis in irradiated tumors to support growth of surviving tumor cells (23). The resulting microvascular density is, however, reduced by 30% to 40% compared to non-irradiated tumors. The molecular mechanisms of intussusceptive angiogenesis remain largely unknown.

**Hypoxia, vasculogenesis, invasion and metastasis.** Hypoxia consequent to impaired angiogenesis is considered as a major cause of the TBE (13, 14, 24). Indeed, tumor hypoxia is associated with a shorter disease-free survival in many human cancers (25). Many molecular mechanisms induced by hypoxia and promoting cancer progression have been unraveled (26), including in tumor growing in irradiated beds. The Brown laboratory reported that hypoxia-mediated activation of hypoxia inducible factor (HIF) -1 in glioblastoma cells after radiotherapy leads to increased expression of the chemokine CXCL12 (27). CXCL12 stimulates the recruitment of CXCR4⁺CD11b⁺ BMDC into irradiated tumors to promote MMP-9-dependent blood vessel formation by vasculogenesis, sufficient to support the growth of recurring tumors (27, 28). Using an orthotopic TBE model of breast cancer, we observed HIF-dependent induction of KitL in hypoxic tumors, causing the recruitment of bone marrow-derived pro-metastatic Kit⁺CD11b⁺ BMDC to primary tumors and pre-metastatic lungs (Kuonen et al., in revision). Using a subcutaneous model of TBE we observed that recovered tumor cells expanded *in vitro* and re-injected in non-irradiated mice retained enhanced metastatic capacity (14). The cysteine-rich protein 61 (CYR61), a matricellular protein that regulates cell growth, differentiation, survival, and migration (29), and the adhesion receptor integrin αVβ5 emerged as two
molecules cooperating to enhance metastasis. Importantly, CYR61 and $\alpha V\beta 5$ promoted resistance to hypoxia, although they were not induced by hypoxia (14). These results support the notion that besides HIF-depended adaptive reactions to hypoxia, selection hypoxia-resistant cancer cells with superior metastatic capacities also contributes to the TBE (30).

**Hypoxia-independent mechanisms.** Ionizing radiation induces the generation of reactive oxygen/nitrogen species (ROS/RNS). When exceeding the cellular antioxidants defense, ROS/RNS induce damages to DNA, proteins and lipids resulting in cell cycle arrest, apoptosis, cell activation or differentiation (31). ROS/RNS also regulate cellular functions by acting as messenger molecules in signaling pathways and by direct effects on transcription (32). ROS/RNS also modify production and activation of transforming growth factor (TGF) $\beta 1$ (33, 34). Since ROS/RNS are rapidly induced, and persist over time by self-amplification, they are considered as main mediators of sustained radiation-modifications of the microenvironment, in particular fibrosis (desmoplastic reaction) (35). Ionizing radiation induces expression of growth and inflammatory factors and matrix proteins (5). For example, ionizing radiation induces endothelial cell activation resulting in the activation of the pro-inflammatory pathways NF-κB (36), the expression of pro-coagulant proteins (e.g. thrombomodulin, von Willebrand factor), and leukocyte endothelial-cell adhesion molecules (e.g. intercellular adhesion molecule-1, vascular endothelial cell adhesion molecule-1) (37) (6). Irradiated fibroblasts differentiate into myofibroblasts (38) producing tissue-specific collagens, growth factors and cytokines, such as platelet derived growth factor (PDGF), interleukin (IL) 1$\beta$, tumor necrosis factor (TNF) and TGF$\beta$ (5, 6, 39). Irradiated fibroblasts enhance the invasive capacity of co-cultured
pancreatic cancer cells (40). This effect was attributed to fibroblast-induced activation of MET, a receptor tyrosine kinase promoting cell growth and invasiveness through the Ras/mitogen activated protein kinase (MAPK) pathway (41). While further experiments are needed to confirm the role of MET in the TBE, recent evidence indicates that ionizing radiations induces MET expression in cancer cells, via a ataxia telangiectasia mutated (ATM) and nuclear factor (NF)-κB signaling pathway, resulting in ligand-independent MET activation and enhanced invasiveness (42).

Among all radiation-induced cytokines, TGFβ activation is of particular relevance, since it elicits strong and long-lasting microenvironmental changes (e.g. suppressed angiogenesis, inhibited immune response, fibrosis) and tumor reactions (e.g. invasiveness, epithelial-to-mesenchymal transition) concurring to promote carcinogenesis and accelerating the development of highly malignant phenotypes (43, 44).

**Induction of angiogenesis by low dose radiotherapy.** While high doses of ionizing radiation inhibit sprouting angiogenesis, low doses stimulate it. Sonveaux et al., originally reported that low doses ionizing radiation stimulates endothelial cell migration and tubologenesis *in vitro* and angiogenesis *in vivo* of by activating the nitric oxide pathway (45). More recently, Sofia Vala et al., observed that doses lower or equal to 0.8 Gy cause ligand-independent activation of vascular endothelial growth factor receptor (VEGFR) -2, resulting in enhanced endothelial cell migration, survival and angiogenesis (46). Low-dose ionizing radiation promotes cancer cell dissemination and metastasis of leukemia and breast cancer cells, which are prevented by blocking VEGFR-2 activation (46). These observations might be relevant to human cancer therapy, especially in hyper-fractionation protocols, since
the tissue and the border of the irradiated field is exposed to lower doses compared to the bulk of the tumor (47).

Clinical-translational advances

The fact that tumor bed irradiation promotes metastasis in experimental models is well established. In contrast whether this also occurs in patients treated with radiotherapy is still matter of debate (6). Increased risk of developing distant metastases upon local recurrences after radiotherapy has been reported in some (15-17) but not all (48) studies. Since these analyses were retrospective and non-randomized, it will be necessary to perform prospective randomized studies in order to obtain conclusive results. Translational studies will be necessary to validate or invalidate whether cellular and molecular events observed in preclinical models also apply to human cancer. The fact that different and complementary mechanisms are at play in the TBE, that some of them may be tumor specific or dominant over others, and that tumors are highly heterogeneous tissues may complicate the interpretation of the results issued from these translational studies. Nevertheless, it is important to start considering which of the pathways emerging from pre-clinical studies may be a relevant target for future therapeutic approaches to blunt invasion and metastasis of cancers relapsing after radiotherapy (See Figure 1 and Table 1).

**HIF-1 pathway.** Preclinical models of the TBE point to HIF-1 activation as an important event in promoting tumor invasion and metastasis, suggesting that HIF-1 inhibition might provide therapeutic benefits. Blocking HIF-1 transcriptional activity
would prevent the release of CXCL12 and attraction of CXCR4+ myelomonocytic cells promoting the formation of novel vessels by vasculogenesis, the mobilization of pro-metastatic cKit+CD11b+ cells, and the expression of HIF1-dependent pro-metastatic genes, including the urokinase-type of plasminogen activator receptor (uPAR), lysyl oxidase (LOX), plasminogen activator inhibitor (PAI) 1, matrix metalloproteinase (MMP) 2, snail or fibronectin (26). However, recent preclinical studies warrant caution in the use of HIF inhibitors in cancer as different HIF isoforms (e.g. HIF-1, -2, -3) have pleiotropic and sometimes opposing effects (49). For example, in contrast to its well-known tumor-promoting activity, HIF-1 has growth inhibitory and pro-apoptotic effects in some cancers (50, 51). At this point it might be judicious to target pro-metastatic pathways downstream of HIF-1 rather than HIF-1 itself.

**CXCL12/CXCR4 pathway.** Inhibition of CXCR4 activation using a small molecule (AMD3100) or neutralizing antibodies to CXCR4, prevented the recruitment of vasculogenic CD11b+ cells to glioblastoma relapsing after radiotherapy and inhibited tumor regrowth (27). These pre-clinical results are corroborated by the increased accumulation of CD11b+ cells observed in recurrent human glioblastoma compared to untreated tumors. Thus, targeting the CXCL12/CXCR4 axis might add potential benefits to standard radiotherapy. This hypothesis could be rapidly tested in patients, as CXCR4 inhibitors are available for clinical use (52). It should be noted, however, that CXCR4 inhibition leads to a rapid mobilization of hematopoietic stem cells into the peripheral circulation, some of which may have pro-tumoral activities.

**KITL/KIT pathway.** In our orthotopic breast cancer model of TBE, KitL silencing in tumor cells and systemic Kit inhibition with a blocking antibody or the tyrosine kinase
inhibitor nilotinib (53), reduced the mobilization of Kit⁺CD11b⁺ cells, and their recruitment to primary tumors and lungs and attenuated lung metastasis (Kuonen et al., in revision). Whether mobilized KIT⁺CD11b⁺ cells are present in the blood of breast cancer patients treated with radiotherapy and their relationship to CD11b⁺ cells infiltrating the primary tumor and metastases is currently under investigation. Of interest, increased expression of KITL was reported in peri-necrotic regions of glioblastoma and breast cancer tissues in association with poor prognosis (54).

Several small molecular tyrosine kinase inhibitors targeting KIT are already approved for clinical use (55) thereby facilitating the development prospective clinical studies aimed at inhibiting KIT in patients with post-radiation recurrences.

**CD11b⁺ cells.** Zoledronic acid and liposomal clodronate were successfully used in post-irradiation settings to target MMP-9-expressing tumor-recruited CD11b⁺ monocytes/macrophages and to deplete tumor-mobilized Kit⁺CD11b⁺ populations resulting in reduced tumor growth and metastasis, respectively (28) (Kuonen et al., in revision). Whether bisphosphonates may also be used in cancer patients for the same purpose remains to be demonstrated. Carrageenan, a sulfated polysaccharides extracted from red seaweeds, was also used to deplete monocytes/macrophages with similar inhibitory effects on tumor regrowth after radiotherapy (27). Inhibition of the CD11b/CD18 complex using function-blocking antibodies effectively inhibited the recruitment of CD11b⁺ myeloid cells into irradiated tumors and prevented their growth (56). Humanized antibodies to the CD11b/CD18 complex (β2 integrin subfamily) have been developed for human use (57) and could be tested in patients with post-radiotherapy recurrences. In contrast, humanized, CD11b-selective antibodies, do not exist yet. Considering their essential role in mediating leukocyte recruitment to...
sites of infection, broad and sustained inhibition of β2 integrins bears the risk of increased infections.

**HGF/MET pathway.** A specific antagonist of hepatocyte growth factor (HGF), the MET ligand, suppressed growth, invasion and metastasis of pancreatic cancer cells co-cultured with irradiated fibroblasts (40). MET kinase inhibitors enhanced the efficacy of radiotherapy to halt tumor growth and prevent radiation-induced invasiveness (42). Considering the well-established role of the HGF/MET pathway in mediating invasive tumor growth (41) and the clinical development of novel MET inhibitors (58), MET should be considered as an attractive target to prevent or treat invasive growth of post-radiation tumor relapses.

**TGFβ pathway.** Because of its multiple tumor-promoting effects, the TGFβ pathway has been long considered as an appealing target in cancer (43). For example, genetic and pharmacological targeting of the TGFβ receptor activin receptor-like kinase (ALK) 1, impaired tumor growth and angiogenesis in the Rip1Tag2 model (59), and TGFβ neutralizing antibody enhanced efficacy of radiotherapy in a breast cancer model (60). Since TGFβ signaling is induced by ionizing radiation (61), and TGFβ receptors inhibitors are in clinical development, it may be reasonable to consider this pathway as a valid therapeutic target to prevent invasion and metastasis in post-radiotherapy recurrences. In view of the complexity, and sometimes opposing effects of TGFβ in cancer and its role in healthy tissue homeostasis, however, it may be prudent to focus on the inhibition of molecules up or downstream of TGFβ, such as AKT (62).
αV integrins. The function-blocking anti-αV mAb 17E6 and the αVβ3/αVβ5-specific peptidic antagonist cilengitide (EMD12197) prevented metastasis induced by tumor bed irradiation or CYR61 overexpression (14). Since cilengitide is currently in advanced clinical testing in glioblastoma patients in combination with radio- and chemotherapies (63), it seems reasonable to assess the effect of cilengitide in patients at high risk for post radiation relapses in other cancers. Of note, cilengitide, alone or in combination with radio- and chemotherapy, has shown high tolerability and low toxicity making it an ideal drug for combination therapies (64).

Conclusion

In recent time we have gained insights in some of the cellular events and molecular pathways responsible for the TBE. These results represent a conceptual advance to the understanding of the TBE and provide some rationales to the development of new therapeutic approaches to prevent invasion and metastasis of tumors locally relapsing after radiotherapy. However, they may only represent the tip of the iceberg of the radiation-induced microenvironmental modifications modulating cancer progression, and many more mechanisms are likely to be discovered. Drugs targeting some of the uncovered pathways are already available for human use. We need now to move on and perform innovative translational studies and combination trials to validate or invalidate in patients the molecular pathways uncovered in preclinical models. In addition, we need to determine predictive biomarkers, such as gene expression signatures in primary tumors, circulating molecules or cell populations, in order to identify patients at risk for relapse and progression after
radiotherapy. Such patients would be the ones to benefit most from a concomitant therapy blunting tumor escape and evasive growth. The TBE may also serve as a model relevant to unravel pathways mediating evasive resistance to anti-angiogenic therapies. Indeed, hypoxia and metabolic starvation caused by anti-angiogenic treatments (65), much alike hypoxia caused by radiotherapy, may initiate microenvironmental modifications eliciting adaptive tumor responses or the selection of highly aggressive tumor cell populations. This would be an unexpected but welcome contribution to research in anti-angiogenesis for an effect originally described nearly 100 years ago!

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed

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Legend

Figure 1. Emerging pathways mediating growth, invasion and metastasis of tumors progressing after radiotherapy. High dose ionizing radiation (IR) kills tumor–associated endothelial cells and inhibits sprouting angiogenesis. Tumor cells growing within this angiogenesis-suppressed microenvironment cause tissue hypoxia, which elicits HIF-dependent and HIF-independent responses. Hypoxia induces HIF-dependent expression of CXCl12 and KITL promoting the mobilization from the bone marrow and the recruitment to tumors or metastatic sites of cells promoting vasculogenesis (CXCR4+CD11b+ cells) or metastasis (KIT+CD11b+ cells). Hypoxia selects for invasive and metastatic tumor cells expressing high levels of αV integrins and CYR61. Hypoxia also stimulates the expression of additional pro-metastatic factors, such as uPAR, LOX, PAI-1, MMP-2. Ionizing radiation also induces the expression of tumor-promoting cytokine and growth factor by stromal cells (TGFβ, PDGF, IL1β) directly or indirectly (e.g. thought ROS/NOS). Irradiated tumor cells increase expression of the pro-invasive receptor MET, through the ATM/NF-κB pathway. Together, these events concur to promote growth, invasion and metastasis of tumors progressing in a pre-irradiated microenvironment. The “stop” signs indicate candidate target molecules that can be blocked with available inhibitors in order to suppress growth and metastasis of tumors growing in an irradiated bed. See table 1 for a selection of inhibitory molecules. The pro-angiogenic effects of low dose IR are not depicted here.

Table 1. Synopsis of molecules promoting tumor growth and metastasis in a pre-irradiated bed and selected inhibitory drugs. This table lists candidate
therapeutic targets and a selection of inhibitory molecules to consider in preclinical and clinical studies to impinge on pro-metastatic pathways activated by ionizing radiation.
Table 1. Synopsis of molecules promoting tumor growth and metastasis in a pre-irradiated bed and selected inhibitory drugs.

<table>
<thead>
<tr>
<th>Molecule</th>
<th>Target Class</th>
<th>Molecule</th>
<th>Inhibitor Class</th>
<th>Targeted event</th>
</tr>
</thead>
<tbody>
<tr>
<td>αVβ3 integrin</td>
<td>Adhesion receptor</td>
<td>Celengitide;</td>
<td>Peptide (αVβ3/αVβ5)</td>
<td>Tumor cell adhesion, migration, invasion, metastasis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17E6 Antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β2 integrins</td>
<td>Adhesion receptor</td>
<td>Rovelizumab</td>
<td>Antibody</td>
<td>Recruitment of CD11/18+ monocytes</td>
</tr>
<tr>
<td>(CD11/18 complex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KIT</td>
<td>Receptor tyrosine kinase</td>
<td>Imatinib; Nilotinib</td>
<td>Tyrosine kinase inhibitors</td>
<td>Recruitment of KIT+CD11b+ BMDC</td>
</tr>
<tr>
<td>MET</td>
<td>Receptor tyrosine kinase</td>
<td>PHA665752; JNJ-38877605; SU11274; PF-02341066; XL880;</td>
<td>Tyrosine kinase inhibitors</td>
<td>Tumor cell growth, survival and invasion</td>
</tr>
<tr>
<td>CXCR4</td>
<td>Chemokine receptor</td>
<td>BKT140; ALX40-4C; Plerixafor</td>
<td>Small molecular inhibitors</td>
<td>Recruitment of CD11b+ BMDC</td>
</tr>
<tr>
<td>ALK5 ALK1</td>
<td>TGFβ receptors</td>
<td>EW-7195; SB-431542; PF-03446962</td>
<td>Kinase inhibitors</td>
<td>Inhibition of angiogenesis, invasion, epithelial-to-mesenchymal transition</td>
</tr>
<tr>
<td>HIF-1</td>
<td>Transcription factor</td>
<td>NSC-134754; PX-478; PX-12; YC-1; Topotecan; Camptothecin analogue</td>
<td>Small molecular inhibitors</td>
<td>Metabolism, migration, invasion, angiogenesis, survival</td>
</tr>
</tbody>
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