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Radiation Therapy and Myeloid-Derived Suppressor Cells: Breaking Down Their Cancerous Partnership

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Abstract

Radiation therapy (RT) has been a primary treatment modality in cancer for decades. Increasing evidence suggests that RT can induce an immunosuppressive shift via upregulation of cells such as tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). MDSCs inhibit antitumor immunity through potent immunosuppressive mechanisms and have the potential to be crucial tools for cancer prognosis and treatment. MDSCs interact with many different pathways, desensitizing tumor tissue and interacting with tumor cells to promote therapeutic resistance. Vascular damage induced by RT triggers an inflammatory signaling cascade and potentiates hypoxia in the tumor microenvironment (TME). RT can also drastically modify cytokine and chemokine signaling in the TME to promote the accumulation of MDSCs. RT activation of the cGAS-STING cytosolic DNA sensing pathway recruits MDSCs through a CCR2-mediated mechanism, inhibiting the production of type 1 interferons and hampering

antitumor activity and immune surveillance in the TME. The upregulation of hypoxia-inducible factor-1 and vascular endothelial growth factor mobilizes MDSCs to the TME. After recruitment, MDSCs promote immunosuppression by releasing reactive oxygen species and upregulating nitric oxide production through inducible nitric oxide synthase expression to inhibit cytotoxic activity. Overexpression of arginase-1 on subsets of MDSCs degrades L-arginine and downregulates CD3z, inhibiting T-cell receptor reactivity. This review explains how radiation promotes tumor resistance through activation of immunosuppressive MDSCs in the TME and discusses current research targeting MDSCs, which could serve as a promising clinical treatment strategy in the future.

Radiation and Systemic Immunity

Radiation therapy (RT) is a highly effective tool that has played a pivotal role in the treatment of cancer for decades.[1,2] Enhanced understanding of the effect of RT on the antineoplastic immune response can support design of treatment approaches with improved efficacy. Although RT is regarded primarily as immune stimulating, it can act as a double-edged sword, compromising immune responses by depleting cytotoxic cells and activating immunosuppressive cell activity.[2] Thus, RT has the potential to be used as an immunomodulatory treatment when used appropriately.

Lymphocytes play a key role in antitumor immunity.[3] Associated with worse outcomes in various types of cancer,[4,5] lymphopenia may be present at diagnosis secondary to tumor-associated immunosuppression and can occur consequent to antineoplastic therapies. Grossman et al found that 2 months after starting chemoradiotherapy (CRT), 43% of patients with newly diagnosed tumors, including malignant glioma, pancreatic cancer, and non-small cell lung cancer (NSCLC), developed severe lymphopenia.[4] A study of patients with NSCLC highlighted that, contrary to chemotherapy treatment alone, lymphocyte counts decreased sharply after commencement of CRT, providing evidence that RT contributes to the induction and severity of lymphopenia.[6] In patients with cervical cancer treated with definitive CRT, the incidence of lymphopenia has been reported to be as high as 95.2% and independently predicted poor survival.[5,7] Similar findings have been reported in nasopharyngeal and lung cancer.[8,9]

Of clinical relevance, high-dose corticosteroids contribute to the development of lymphopenia and may affect the outcomes of RT.[10] Nakamura et al proposed that $CD4^+$ and $CD8^+$ lymphocytes are exquisitely radiosensitive and susceptible to cytotoxic degradation in the presence of low-dose RT.[11] Interleukin (IL) 7 is a cytokine important for lymphocyte homeostasis, and low IL-7 before RT may be an independent predictor of severe RT-induced lymphopenia.[12] Lowered CD4 counts can increase the likelihood of hospitalization among patients, highlighting the importance of evaluating RT-immune interactions in clinical practice.[10]

Tumor-associated macrophages (TAMs) are a crucial population of myeloid cells that modulate RT-induced immunosuppression.[13] Macrophages are generally categorized as classically activated macrophages, M1 macrophages, or alternatively activated (immune suppressive) M2 macrophages.[14] TAMs are M2-like and function to promote an immunosuppressive TME.[14] TAMs produce inflammatory mediators and growth factors

associated with cancer progression, tumor angiogenesis, chemoresistance, and metastasis.[15] High densities of TAMs are associated with worse overall survival in gastric, urogenital, and head and neck cancers.[16] Importantly, TAMs are more radioresistant than lymphocyte populations, and RT may promote the activation of immunosuppressive TAMs.[17]

Although Wunderlich et al showed that low doses of radiation (0.01–2 Gy) can increase macrophage chemotaxis into the TME, the extent of TAM activation may depend on many variables unique to the RT protocol.[18] Fractionation likely plays a key role in TAM activation and recruitment to irradiated sites. Chen et al determined that 2 distinct RT regimens (multifractionated RT consisting of 60 Gy administered in 15 fractions and single-dose RT administered in one 25 Gy fraction) both promote aggregation of TAMs near hypoxic tumor regions in tumor-bearing mice but that the effect is more pronounced for single-fraction RT.[19] In lung epithelial cell lines, RT increases transforming growth factor β (TGF-β)–secreting M2 macrophage migration and promotes the release of tumor-supporting, proinflammatory cytokines.[20]

Although the effect of RT on lymphocytes and TAMs has been increasingly documented in recent years, less is known about its effect on myeloid-derived suppressor cell (MDSC) populations. MDSCs are critical perpetrators of TME-induced immunosuppression that protect cancer cells from immune system attack.[21] Elevated MDSC counts have been associated with poor clinical outcomes, such as shortened overall survival and recurrence-free survival in patients with hepatocellular, rectal, lymphoma, lung, melanoma, esophageal, breast, gastric, brain, and pancreatic cancers, compared with patients with lower MDSC counts.[22–24] Murine models suggest that the accumulation of MDSCs in the TME promotes radioresistance through altered enzymatic activity associated with this cell type.[25,26] Therapeutic elimination of MDSCs may therefore be an effective future approach to improve radiosensitivity without undue adverse effects. This review discusses the current knowledge of mechanisms underlying RT-induced MDSC accumulation in the TME and strategies that MDSCs use to attenuate immune surveillance and contribute to radioresistance.

MDSCs Act as Immunosuppressive Agents in Cancer

MDSCs are a heterogeneous population of immature myeloid cells that acquire immunosuppressive qualities when exposed to host-derived factors.[27,28] Myeloid cells develop from maturation of multipotent hematopoietic stem cells.[29] Myeloid progenitor cells can differentiate into specialized cell types such as suppressive macrophages and immune-stimulating dendritic cells (DCs) that play unique roles in maintaining immune homeostasis.[30,31] Cancer skews the differentiation of myeloid cells toward cancer-supportive phenotypes, such as MDSCs.[29] MDSC counts are elevated in patients with cancer compared with healthy individuals and correlate with cancer stage and disease recurrence status.[32] Diverse tumor cell lines, including those derived from cervical, ovarian, colorectal, renal cell, and head and neck carcinomas, induce MDSC production in coculture with peripheral blood mononuclear cells.[33]

MDSCs are traditionally distinguished from classical monocytes and neutrophils by their ability to inhibit T-cell activity, but both TAMs and tumor-associated neutrophils (TANs)

can also exert immunosuppressive activity.[34–37] MDSCs are neutrophils and monocytes that have been programmed to support cancers.[35] Classical activation of neutrophils and monocytes is short lived and occurs in response to invading pathogens and tissue injury.[38] This activation is characterized by high phagocytosis, respiratory burst, and secretion of proinflammatory (anticancer) cytokines.[35]

In cancer, MDSC pathologic activation occurs when tumor-secreted growth factors and inflammatory signals, such as macrophage colony-stimulating factor (M-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), IL-6, and IL-1β, stimulate myelopoiesis in the bone marrow and spleen, generating a population of immature myeloid cells.[30,35,39] Under healthy conditions, immature myeloid cells migrate to peripheral tissue and differentiate into mature granulocytes, macrophages, and dendritic cells. Pathologic stimulation, however, prevents this maturation, resulting in the accumulation of immature myeloid cells at the tumor site.[30] T cells and tumor stroma cells then activate immature myeloid cells into MDSCs through factors such as interferon γ (IFN-γ), IL-4, IL-13, and TGF-β.[30,39] This pathologic activation produces myeloid cells with poor phagocytic activity that secrete high levels of reactive oxygen species (ROS), nitric oxide (NO), and anti-inflammatory (procancer) cytokines.[35]

In humans, MDSCs are generally defined as CD11b$^+$CD33$^+$HLA-DR$^-$ and subdivided into CD11b$^+$ CD33$^+$HLA-DR$^-$CD15$^+$ granulocytic/polymorphonuclear MDSCs (G-MDSCs), CD11b$^+$CD33$^+$HLA-DR$^-$CD14$^+$ monocytic MDSCs (M-MDSCs), and CD11b$^+$CD33$^+$HLA-DR$^-$CD14$^-$CD15$^-$ early MDSCs (eMDSCs).[28] Although M-MDSCs have a monocytic origin, they exhibit less MHC class II expression compared with monocytes.[39] It is hypothesized that monocytes, M-MDSCs, and TAMs exist in different differentiation states, driven by tumor-secreted factors.[35] During myelopoiesis, expression of retinoic acid–related orphan receptor (RORC1/RORg) is required for M-MDSC and TAM expansion and induced by IL-1β, G-CSF, GM-CSF, and M-CSF.[40] G-MDSCs and neutrophils share characteristic cell surface markers and morphologic similarities, making them difficult to distinguish. However, key differences in G-MDSC and neutrophil maturity, surface and gene expression, and secretion aid in their distinction. G-MDSCs resemble an immature neutrophil phenotype in breast cancer, displaying downregulated expression of the neutrophil maturity markers CD10, CD13, and CD45.[41] In peripheral blood of patients with NSCLC, lectin-type oxidized LDL receptor 1 (LOX-1) encoded by the OLR1 gene is overexpressed in G-MDSCs but undetectable in neutrophils, illustrating their distinct gene profiles related to endoplasmic reticulum (ER) stress.[42] Specifically in renal cell carcinoma, arginase mRNA is elevated in G-MDSCs compared with neutrophils.[43]

Clinical Evidence of the Effects of RT on MDSCs

Conventional RT regimens generally consist of 1.5 to 3 Gy administered daily for 3 to 7 weeks.[44] Hypofractionated regimens deliver RT at a higher dose per fraction and can be employed to shorten the total duration of treatment.[44] Stereotactic body radiation therapy (SBRT) or SABR is carried out in 1 to 5 sessions and uses specialized planning techniques to deliver focused RT to the tumor site with limited dose to the surrounding tissue.[44,45] Emerging research suggests that non-conventional ablative RT promotes different biological

responses than conventionally fractionated RT.[45,46] In murine pancreatic cancer models, 40 Gy administered in 4 fractions induces greater MDSC infiltration to the TME than a single fraction of 25 Gy.[46] Furthermore, ablative RT promotes a greater increase in CD8$^+$ T-cell infiltration, suggesting fractionation may be an important predictor of tumor response to therapy.[46] In murine colon tumors, MDSC quantity in tumors increases a mean of 5% 35 days after a single dose of 30 Gy compared with 20% 10 days after 30 Gy in 10 fractions.[47] Transient but marked temporal MDSC changes after RT are an important consideration, as demonstrated by a study that observed an initial 50% MDSC increase into the TME 3 days post-RT before decreasing to 5% at 35 days.[47] These findings highlight the need for further studies to evaluate the effects of dose, timing, and fractionation on TME remodeling that include consideration of MDSC influx and signaling.

Clinical studies of RT-MDSC interactions in humans remain limited and have yielded varying results (Table 1). However, several have reported increases in peripheral MDSC counts after RT. Studies of patients with NSCLC and with head and neck squamous cell carcinoma have reported elevated general MDSC counts after RT,[48,49] whereas other studies have reported MDSC subtype-specific increases after RT. In one study of head and neck squamous cell carcinoma, G-MDSC counts increased during RT and had detectable signal transducer and activator of transcription 3 (STAT3) and programmed death ligand 1 (PD-L1) activity, underscoring their suppressive activation,[50] but M-MDSC levels did not change in response to RT.[50]

Comparatively, other studies of head and neck cancer have reported elevations in M-MDSC levels after CRT.[51,52] Among these, Parikh et al[51] notably found that M-MDSC frequency increased nearly 3-fold within weeks of receiving RT for oropharyngeal cancer, and Boustani et al[52] reported significantly increased M-MDSC counts in 40% of patients with lung or head and neck cancer, but the overall mean change of M-MDSC levels in the latter study was not significant. In a study of patients with cervical cancer, M-MDSC counts increased significantly and displayed clear temporal changes in 9 out of 10 patients.[53] Peripheral MDSC counts were highest 3 weeks post-RT, and MDSC counts remained elevated for 9 weeks and prominently affected M-MDSC populations.[53] Significant increases in M-MDSC frequencies after RT have also been observed in lung cancer.[54]

In contrast, several studies have reported no change in peripheral or tumor MDSC counts during or after RT. In a cohort of patients with rectal cancer who received conventionally fractionated neoadjuvant RT, Teng et al found that pre-RT MDSC counts in biopsy specimens did not differ from post-RT values.[55] A study evaluating the effect of 20 Gy delivered via intraoperative RT in low-risk breast cancer at the time of surgical resection found no significant changes from baseline in MDSC percentage.[56] This finding in breast carcinoma accords with a prior study that demonstrated MDSC production is not induced in healthy human donor peripheral blood mononuclear cells when cocultured with several breast carcinoma cell lines.[33] One study evaluating MDSC changes in patients with glioblastoma reported no significant changes in MDSC composition in pre- and post-RT blood samples.[57] Of note, this study quantified MDSCs in a distinct way, integrating percentage frequency from flow cytometry data and clinical complete blood counts of

monocyte populations. The fact that monocytes do not include all MDSCs may account in part for discrepancies with similar investigations.

Other studies have reported decreases in MDSC frequencies after RT. In a pilot study of patients with locally advanced rectal cancer receiving 25-Gy short-course RT, both G-MDSC and M-MDSC counts decreased after RT.[58] In a study of patients with lung cancer receiving 50- to 60-Gy SBRT, M-MDSC counts steadily decreased for months while G-MDSC counts transiently increased 72 hours after RT but declined thereafter for 6 months.[59] Finally, M-MDSC counts have been observed to decrease in patients with hepatocellular carcinoma after RT.[60] Interestingly, the average RT dose fractionation was higher than that of conventional RT, ranging from 5 to 20 Gy in most studies that reported no change or decrease in MDSC levels after RT.[56,58,59] This supports that conventional fractionation elicits a greater suppressive response when quantified by MDSC frequency alterations. However, other factors, such as RT volume, can play a role in MDSC accumulation.[48] Collectively, these clinical findings suggest that MDSC subtype concentration changes are likely secondary to multiple underlying factors, including histology, RT dose and fractionation, and timing after completion of treatment.

Because MDSC counts change with treatment, MDSC concentrations may act as predictive and prognostic indicators of response. In a study of patients with locally advanced rectal cancer, a decrease in M-MDSC concentration was associated with poor response to multimodality treatment.[58] Relative changes in peripheral MDSC concentrations to baseline values may therefore offer a noninvasive, indirect measure of clinical response.[58] In patients with esophageal squamous cell carcinoma, increased peripheral MDSC concentration has been correlated with increased recurrence and reduced overall survival.[61] Similarly, Wang et al found that high pretreatment and posttreatment MDSC frequency were associated with a worse prognosis.[60] As a predictive measure, higher pre-RT lymphocyte-to-monocyte ratios in patients with esophageal cancer have been associated with increased progression-free survival and overall survival.[62] These findings are based on the assumption that many MDSCs are included in the monocyte portion.

Radiation Alters the Tumor Microenvironment

The TME is a complex, heterogeneous environment that includes proliferating tumor cells, stromal cells, blood vessels, infiltrating inflammatory cells, and tumor-induced interactions.[63] TME composition is linked to the progression, survival, local invasion, and metastatic dissemination of cancer cells.[64] RT promotes direct and indirect cell damage, inflammation, vascular depletion or endothelial cell death, fibrotic changes through increased TGF-β1 signaling, and vascular changes that alter vessel architecture to promote hypoxia in irradiated tissues.[65] RT can drastically alter the cellular composition and signaling of the TME.[17] In one study, tumors from patients with rectal cancer receiving 25 to 28 fractions of 40- to 45-Gy neoadjuvant CRT had increased CD8$^+$ and CD4$^+$ T cells after treatment compared with baseline tumor sample evaluation.[55] However, this proliferation was insufficient to combat the immune tolerance established by immunosuppressive factors such as MDSC, FOX3$^+$ tumor-infiltrating lymphocytes, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), and PD-L1.[55]

After RT, dying tumor cells secrete cytokines, chemokines, tumor-associated antigens, and general inflammatory mediators attracting immune cells to the TME.[66] RT damage to radiosensitive endothelial cells triggers an inflammatory cascade in which several proinflammatory molecules, including IL-1, IL-6, tumor necrosis factor α (TNF-α), IFN-γ, and GM-CSF, promote the recruitment of MDSCs.[17,67] RT induces the secretion of CC chemokines such as CCL2, CCL3, CCL5, CCL8, CCL11, CCL20, and CCL22,[66] of which CCL2 and CCL5 have been implicated in M-MDSC and G-MDSC mobilization, respectively.[68] In murine breast cancer models, CCL2 promotes $CD14^+CD16^-$ inflammatory monocyte and $CD14^{low}CD16^+$ resident monocyte mobilization, promoting tumor extravasation.[69] In mouse melanoma models, CCR5 overexpression on MDSCs promotes migration to the primary tumor and potentiates their suppressive behavior.[70] In vitro murine studies have demonstrated that the migration of suppressive myeloid cells to the tumor can be prevented by neutralizing CCL2 and blocking CCR2.[71] Ultimately, the post-RT TME favors MDSC production through soluble factor concentration, cellular composition, and other cellular factors.

cGAS-STING Pathway Mediates Antitumor Immunity

The cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway is involved in cytosolic DNA sensing and is a critical mediator of inflammatory responses (Fig. 1).[72] It has emerged as an important target in cancer immunotherapy due to its role in T-cell priming.[72,73] In tumor cells, the cGAS-STING pathway is suppressed by the inhibition of IL-6 and downstream JAK2/STAT3 signaling, preventing the induction of $CD8^+$ T-cell function.[74,75] Although STING activity is traditionally underactive in tumor cells, RT-mediated DNA damage acts as a danger signal, catalyzing cGAS-STING pathway activation and subsequent inflammatory gene production.[76] RT-induced STING activation is a powerful adjuvant tool, promoting the release of type I IFNs and subsequent $CD8^+$ effector T-cell activity.[77,78]

Interestingly, Liang et al found that RT-induced activation of the STING/IFN pathway in tumor cells enhanced suppressive activity in tumors secondary to MDSC recruitment via CCR2, a chemokine overexpressed on the surface of subsets of M-MDSCs.[79,80] Their study demonstrated that the recruitment of MDSCs through STING activation within tumor cells increases future radioresistance.[79] In classical monocytes, STING activates inflammasomes, triggering the release inflammatory cytokines IL-1β and IL-18 and activating the cell death program.[81,82] Unlike other myeloid cells, MDSCs possess unique, intrinsic resistance mechanisms to STING activation (Fig. 1). Traditionally, type 1 IFNs, including IFNα and IFNβ, bind the IFNa receptor (IFNAR), activating JAK1 and tyrosine kinase 2 (TYK2) and phosphorylating the STAT1/STAT2 heterodimer.[83] IFNAR1 is downregulated on subsets of MDSCs, resulting in significant inhibition of the IFN 1 pathway and reduced production of type 1 IFNs.[84]

In MDSCs, upregulated PKR-like endoplasmic reticulum (ER) kinase (PERK) signaling promotes the downregulation IFNAR1.[85,86] When RT induces STING activation, a direct physical association between STING and PERK induces phosphorylation of eukaryotic initiation factor 2α (eIF2α), decreasing the rate of protein synthesis, and subsequent

production of type 1 IFNs in MDSCs.[87–89] Deletion of PERK in mice increases MDSC differentiation into myeloid cells that prime antitumor CD8^{+} T-cell immunity.[86] These previous findings highlight the usefulness of targeting STING-down-regulation in MDSCs to increase radiosensitivity.

MDSC Recruitment by the Hypoxic Tumor Environment

In response to RT damage, tumors secrete hypoxia-inducible factors, potentiating tumor revascularization, promoting MDSC accumulation, and upregulating MDSC immunosuppressive activity (Fig. 2).[90–92] Hypoxia is a major barrier to the efficacy of RT and immunotherapy and is linked to MDSC accumulation, infiltration, and maintenance.[91,93] Hypoxic stress in tumors triggers endothelial cell signaling and secretion of soluble molecules such as vascular endothelial growth factor (VEGF), which mobilizes MDSCs to the TME.[92,94]

Hypoxia inducible factor 1 (HIF-1) is a heterodimeric protein responsible for activating the transcription of genes associated with cancerous progression.[95] In response to RT, tumors protect endothelial cells by secreting cytokines capable of inhibiting apoptosis through a HIF-1–mediated mechanism.[90] Moeller et al reported that radiation-induced tumor reoxygenation increased HIF-1 levels after two 5-Gy fractions in mice, suggesting that the upregulation of ROS after RT contributes to HIF-1 accumulation.[90] In hepatocellular carcinoma mouse models, HIF-1 induces large amounts of ectoenzyme and ectonucleoside triphosphate diphosphohydrolase 2 (ENTPD2/CD39L1), which promote the accumulation of MDSCs in the TME.[96]

HIF-1 promotes MDSC accumulation through several factors, including VEGF, CCL26, and stromal-derived factor 1a (SDF1a/CXCL12).[91,97,98] HIF-1 activation stimulates VEGF production, promoting tumor angiogenesis and tumor immune escape.[92,99] RT has been shown to increase VEGF expression.[100,101] In vivo and in vitro analyses have shown that VEGF stimulates the mobilization of MDSCs from bone marrow to peripheral blood, and in high-grade ovarian cancer models VEGF expression has been positively correlated with MDSC mobilization and infiltration at the tumor site.[102,103] HIF-1 transactivates the enzymatic attachment of phenyl groups to matrix metalloproteinase (MMP)-9, promoting the soluble release of cytokines that bind to VEGFR on MDSCs, such as VEGF.[104,105]

MMPs promote the invasion and spread of tumor cells by actively degrading surrounding basement membranes and extracellular matrices.[104,106] The absence of HIF-1 and subsequent reduction of MMP-9 expression has been observed to abrogate angiogenesis and tumor invasion in humans with glioblastoma, and MMP-9 expressing MDSCs have been shown to decrease in the absence of HIF-1a in glioblastoma mouse models.[98] In a mouse model of head and neck squamous cell carcinoma, inhibition of JAK2/STAT3 decreased VEGF and HIF-1a, which effectively prevented angiogenesis and reduced MDSC accumulation in the TME through reduced VEGF and casein kinase 2 (CK2).[107] Noman et al deduced that hypoxia induces STAT3 phosphorylation in NSCLC cell lines, promoting the secretion of VEGF and impairing the cytotoxic T lymphocyte–mediated killing of tumor cells.[108] These findings indicate that hypoxia is a prominent driver of MDSCs into the TME.

Hypoxic Activation of MDSC Suppressive Activity

As RT modulates the hypoxic tumor milieu, HIF-1α enables MDSC immunosuppression through a variety of mechanisms.[92] Induction of HIF-1 after RT may play an important role in maintaining the suppressive phenotype of MDSCs. In one study, MDSCs isolated from spleens of tumor-bearing mice cultured in hypoxic conditions directed their differentiation toward TAMs, a mechanism mediated by HIF-1α.[109] Another study found that HIF-1 promotes the conversion of extracellular ATP to 5'AMP, preventing MDSC differentiation into immune-stimulating DCs.[96]

HIF-1α is also implicated in the release of arginase-1 (Arg-1) from MDSCs.[110,111] High Arg-1 expression from subsets of MDSC degrades L-arginine (L-Arg).[43,112] When L-Arg is degraded, CD3z is downregulated and the responsiveness and proliferation of T-cell receptor decreases, as well as the production of IFN-γ, IL-5, and IL-10.[113,114] Arg-1-expressing MDSCs also promote the upregulation of ROS, inducible nitric oxide synthase (iNOS), and NO.[30,115] Murine models suggest that HIF-1α is bound to a hypoxia-response element in the miR-20 promoter, resulting in increased Arg-1 and NO production.[110]

Other factors, such as TGF-β, IL-6, IL-3, platelet-derived growth factor (PDGF), and GM-CSF, can stimulate MDSC production of ROS.[30] Corzo et al reported that tumor MDSCs from tumor-bearing mice expressed high levels of Arg-1 and iNOS and were prone to differentiate into TAMs.[109] Nagaraj et al found that the reaction of peroxynitrite, a product of NO and ROS, with MDSC-derived ROS prevents CD8$^+$ T cells from binding phosphorylated MHC and inducing antigen-specific tolerance, suggesting that it is the upregulation of ROS rather than NO that is responsible for suppressing CD8$^+$ T-cell activity.[116]

MDSC-mediated T-cell suppression also occurs via upregulated PD-L1 signaling.[117] In tumor-bearing mice, hypoxia prompts the rapid upregulation of PD-L1 on MDSCs resulting from the direct binding of HIF-1α to the hypoxia-response element in the PD-L1 proximal promoter. In contrast, PD-L1 blockade enhances T-cell activation and down-regulates IL-10 and IL-6.[117] PD-L1 is highly expressed in activated tumor-infiltrating MDSCs.[118] One study found that PD-L1 blockade significantly enhanced immune function in patients with NSCLC, melanoma, and renal cell cancer.[119] Essentially, hypoxia not only recruits more MDSCs to the TME but also enhances their activity.

Mediation of MDSC Expansion in the TME by Several Factors

IL-10 signaling pathways mediate immunosuppressive responses such as the reduction of effector CD4$^+$ and CD8$^+$ T cells and have been strongly associated with cancer progression.[120,121] After RT, IL-10 production is upregulated and antagonizes IFN-γ and toll-like receptor signaling pathways, suppressing macrophage and DC-mediated proliferation of antigen-specific CD4$^+$ T cells.[122–124] IL-10 also inhibits DC maturation, promoting the maintenance of immature MDSCs by inhibiting IFN-γ-induced production of IL-6, IL-1, IL-4, and TNF-α.[125,126] IL-10 inhibits the production of several proinflammatory or Th2 cytokines, leading to the suppression of immune surveillance in

the TME.[127] IL-10 also activates STAT3 signaling, upregulating DNA methyltransferase 3b expression, leading to the hypermethylation of the IRF8 promoter, effectively silencing IRF8 expression in epithelial cells.[128] This IL-10$^+$ MDSC-induced IRF8 abrogation decreases CD8$^+$ T-cell infiltration and effective therapeutic responses.[129] In a murine viral infection model, researchers demonstrated a crucial role for IRF8 in the induction of type 1 IFNs, finding that IRF8$^{-/-}$ DCs inhibited type 1 IFN production, while the reintroduction of IRF8 reinstated type 1 IFN induction.[129] Furthermore, in mouse colon cancer models, IRF8 silencing has been associated with increased tumorigenesis.[128]

TGF-β1 has been extensively implicated in tumor progression, invasion, and resistance to traditional modalities of treatment.[130] TGF-β1 derives antiproliferative abilities through cyclin kinase activities, such as by inducing inhibitors of p15, p21, and p27 cyclin-dependent kinases and preventing the formation of active cyclin E-cdk2 complexes.[131–133] TGF-β1 is bound to a latency-associated peptide, forming a small latent TGF-β complex that can then bind to several latent binding proteins and form a large latent complex.[134] TGF-β1 and MDSC interplay creates a procancerous partnership and contributes to widespread tumor progression.[135]

TGF-β1 mediates the accumulation and induction of MDSCs within the stroma and impairs natural killer cells and regulatory B lymphocyte education/recognition of MDSCs, propagating immunosuppression.[136] Hematopoietic progenitors and monocytes cultured with GM-CSF and TGF-β1 induce M-MDSC accumulation.[137] Furthermore, TGF-β1-enriched tumor exosomes influence myeloid cells toward an MDSC-like phenotype, contributing to the development and accumulation of protumor MDSCs in the TME.[138] MDSCs generated in the presence of TGF-β1 are more effective at suppressing T-cell proliferation and promoting Treg accumulation.[139] Murine models have demonstrated that the accumulation and induction of MDSCs are mediated by TGF-β1-induced microRNA (miR) expression.[136]

TGF-β1 is the primary mediator of miR-494, which aids in recruitment of MDSCs to the TME and contributes to the functional enhancement of CXCR4-mediated MDSC chemotaxis.[140] TGF-β also promotes the upregulation of miR-155 and miR-21 during MDSC induction.[141] Upon depletion of miR-155 and miR-21, the frequency of cytokine-induced MDSCs decreases.[141] Together, these findings elucidate important mechanisms by which RT- and tumor-induced inflammatory signaling stimulate an environment suitable for MDSC induction and recruitment, effectively dampening antitumor immune responses.

Current Clinical Interventions and Future Directions

There is tremendous rationale to combine RT with immunotherapy to minimize RT-induced immunosuppressive effects. Indeed, emerging immunotherapies have shown promise in improving treatment response rates in primary tumors and metastases when combined with RT.[142] Yang et al found that both blocking tumor production of lactate and deleting HIF-1α in MDSCs inhibited tumor growth and decreased tumor resistance to RT in mice.[143] Oweida et al found that neither radiation nor STAT3 inhibition alone delayed tumor growth in mice but that STAT3 inhibition in combination with a single fraction of

10 Gy decreased quantities of MDSCs, Tregs, and suppressive macrophages and enhanced effector T-cell function.[144] Other preclinical animal studies have successfully used agonists such as liver-X nuclear receptors to target MDSC accumulation, in turn decreasing acquired radioresistance.[145]

Despite these promising results in murine models, clinical studies combining immunotherapy and RT in human populations remain limited and have yielded ambiguous results. In patients with oligometastases, Chen et al found that sunitinib, a tyrosine kinase inhibitor of VEGFR1, VEGFR2, and VEGFR3, in combination with 50 Gy SBRT in 1 fraction decreased M-MDSC accumulation, STAT3 phosphorylation, and arginase expression in M-MDSC.[146] Importantly, MDSC response to treatment is a predictor of progression-free survival and treatment-related death, highlighting the potential relevance of MDSC quantification in clinical prognosis.[146] In a study using bevacizumab, a monoclonal antibody, to target VEGF in combination with RT and temozolomide, Treg counts decreased but MDSC counts were unaffected.[147] Finkelstein et al found that intra-tumorally injected DCs in combination with fractionated RT to a total dose of 50.4 Gy in patients with soft tissue sarcoma induced a tumor-specific immune response in individuals with low MDSC counts but no change in the absolute number of MDSCs.[148] These clinical data further highlight that the systemic immune composition can affect the efficacy of treatment and is a target for future manipulation to optimize radio-response. Additional research efforts focusing on clinical applications are needed to target RT-induced immunosuppression.

Conclusion: Tackling Procancerous MDSCs With RT

RT is an effective but complex tool for treating cancers.[1] Increasing evidence suggests that RT can promote immunosuppression by depleting radiosensitive lymphocytes and enhance the tumor supportive activity of TAMs and MDSCs.[2] MDSCs reprogram the TME toward a suppressive environment by hampering T-cell response and decreasing immune surveillance.[30,149] The secretion of soluble factors such as Arg-1, ROS, IL-10, and TGF-β from MDSCs promotes the development of a procancerous niche in the TME.[113,116,124,130] Clinically, MDSCs are important as biological response factors to RT, as they provide crucial prognostic indicators of treatment outcomes. Several studies have identified notable increases in MDSC counts after RT.[48–54] Several other studies have observed that high MDSC frequency is associated with worse treatment outcomes.[58,60–62]

Although dose fractionation may play a role in MDSC response, more research is needed to understand the nuances between RT dose and MDSC induction. Given the accumulating evidence that RT increases MDSC accumulation and activation, targeting RT-mediated MDSC expansion is important to maximize the therapeutic effect of RT. There is additional opportunity to advance our understanding of how MDSCs respond to currently available clinical interventions and to identify avenues for future targeted immunotherapies that maximize RT efficacy.

Acknowledgments—

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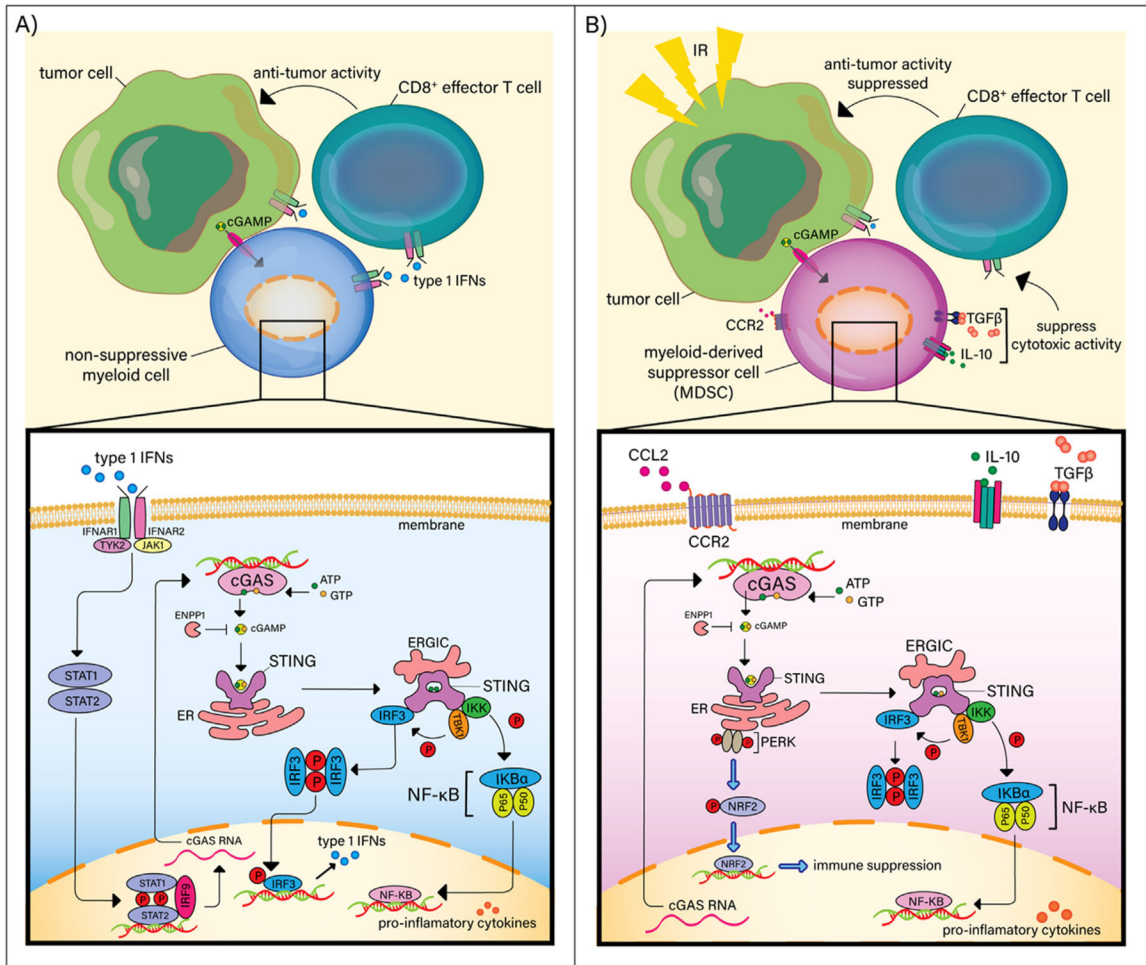
Fig. 1.
Radiation promotes myeloid-derived suppressor cell (MDSC) accumulation and immunosuppression via STING. (A) In non-suppressive myeloid cells, STING activation results in the recruitment and phosphorylation of tank binding kinase 1 (TBK1) and IκB kinase (IKK), which recruit and phosphorylate interferon regulatory factor 3 (IRF3) and nuclear factor kappa B (NF-κB), resulting in IRF3 and NF-κB translocation into the nucleus and inducing type 1 interferons (IFNs) and immune-stimulating cytokines. (B) Radiation-induced activation of the STING/IFN pathway in MDSCs enhances tumor suppressive activity due to the subsequent CCL2/CCR2-mediated recruitment of MDSCs. In MDSCs, type 1 IFN production is inhibited by PERK-dependent IFNAR1 downregulation and production of NRF-2, which negatively regulate STING, inhibiting subsequent production of type 1 IFNs.
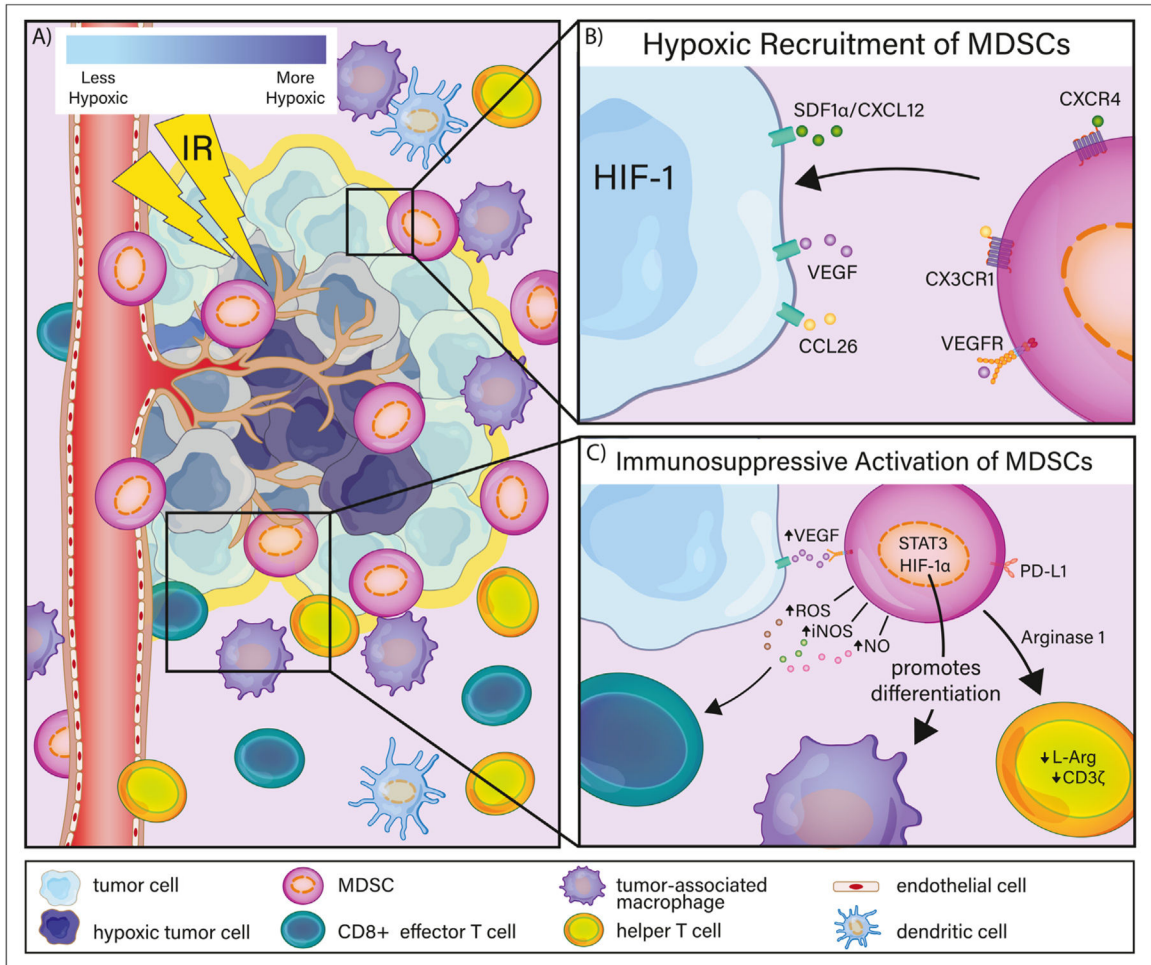
Fig. 2.
Hypoxic recruitment and activation of myeloid-derived suppressor cells (MDSCs). (A) Radiation therapy induces vascular damage, potentiating tumor hypoxia and releasing hypoxia-inducible factor-1 (HIF-1). (B) After radiation therapy, hypoxic tumor cells secrete soluble factors such as CCL26, SDF1a/CXCL12, and vascular endothelial growth factor (VEGF), mobilizing MDSCs to the tumor microenvironment. (C) After recruitment to the tumor microenvironment, MDSCs interact with several cell types to facilitate immunosuppressive activity. Although hypoxic conditions prevent MDSC differentiation into immune-stimulating dendritic cells, MDSCs are preferentially differentiated into tumor-associated macrophages. The upregulation of arginase-1 on subsets of MDSCs degrades T-cell receptor activity, whereas MDSC production of reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS), and nitric oxide (NO) hamper the antitumor cytotoxic activity of CD8^{+} T cells.

Table 1

Clinical outcomes of radiation therapy on MDSC counts in peripheral blood

Total dose	Fractionation	Disease	Clinical outcome	PBMC preparation	Reference number
2 Gy	2 Gy	Non-small cell lung cancer	RT resulted in an increase in peripheral MDSC counts (CD33$^+$CD11b$^+$HLA-DR$^-$). During RT, MDSC counts increased in patients with non-small cell lung cancer adenocarcinoma.	Frozen	48
70 Gy	<3 Gy/fraction over 5–7 wk	Head and neck squamous cell carcinoma	MDSC (CD14$^-$APC$^+$, HLA-DR PC7$^-$) counts increased in most patients after RT.	Frozen	49
66–70 Gy	2- to 2.2-Gy fractions	Stage III-IV head and neck squamous cell carcinoma	RT was correlated with accumulation of G-MDSCs (CD14$^-$CD15$^+$CD33$^+$) with high STAT3 and PD-L1 activity.	Frozen	50
70 Gy	35 fractions of 2 Gy over 7 wk	Stage III-IV oropharyngeal squamous cell cancer	M-MDSC (CD33$^+$CD11b$^+$ HLA-DR$^-$CD14$^+$) counts increased by nearly 3-fold 3 wk after RT. Absolute CD8$^+$ T-cell and CD8$^+$ counts and MDSC effector/suppressor ratios decreased for 6 mo after RT.	Frozen	51
34–70 Gy	Unspecified	Lung or head and neck cancer	M-MDSC (HLA-DR$^{low/-}$CD33$^+$CD14$^+$CD11b$^+$) counts increased significantly in 8 of 20 patients.	Frozen	52
46–50 Gy	23 fractions of 2 Gy or an equivalent dose of 1.8 Gy/ fraction	Stage 1B1-IV cervical cancer	M-MDSC (CD11b$^+$CD3$^-$CD19$^-$CD1a$^-$HLA-DR$^-$CD14$^+$CD15$^-$) counts increased after RT in 9 of 10 patients.	Frozen	53
66 Gy	24 fractions of 2.75 Gy for 5 wk	Non-small cell lung cancer	CD14$^+$CD33$^+$HLA-DR^{low} M-MDSC counts increased after RT.	Frozen	54
20 Gy	Single-fraction IORT	Low-risk breast cancer	No statistically significant change in MDSC (CD45$^+$CD33$^+$CD11b$^+$) counts was found.	Fresh	56
25 Gy	5 fractions of 5 Gy	Locally advanced rectal cancer	M-MDSC (CD14$^+$HLA-DR$^{-/low}$CD11b$^+$CD33$^+$) counts decreased 5 wk from RT and then remained stable. G-MDSC (LIN$^-$HLA-DR$^-$CD11b$^+$CD14$^-$CD15$^+$CD33$^+$) counts decreased 5 wk from RT and continued to decrease before surgery at week 8. Poor responders had lower M-MDSC counts.	Fresh	58
50–60 Gy	4 patients received 8 fractions of 7.5 Gy and 3 received 4 fractions of 12.5 Gy	Lung cancer	M-MDSC (CD33$^+$CD11b$^+$CD14$^+$HLA-DR$^{-/low}$) counts decreased throughout the study. G-MDSC (CD33$^+$CD11b$^+$CD14$^+$) counts increased 72 h after RT and then progressively declined 6 mo after RT.	Fresh	59
60 Gy	2 Gy/fraction and 5 fractions/wk	Hepatocellular carcinoma	M-MDSC (CD14$^+$HLA-DR$^{-/low}$) frequency decreased after RT. Higher frequencies of M-MDSC correlated with shorter overall survival. Pre- and post-RT MDSC (CD14$^+$HLA-DR$^{-/low}$) frequencies >14.6% were associated with a worse prognosis.	Fresh	60
40–66 Gy	Unspecified	Esophageal squamous cell carcinoma	MDSC (CD11b$^+$CD33$^+$HLA-DR$^-$) counts were elevated after RT in patients who developed disease failure and had a higher risk of death.	Frozen	61
50–64 Gy	1.8–2 Gy per fraction for 25–32 fractions	Esophageal squamous cell carcinoma	A high lymphocyte-to-monocyte ratio pre-RT was a predictor of good clinical tumor response to RT, a lower risk of recurrence, and a decreased risk of death.	Fresh	62

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Abbreviations: G-MDSC = granulocytic/polymorphonuclear myeloid-derived suppressor cell; IORT = intraoperative radiation therapy; MDSC = myeloid-derived suppressor cell; M-MDSC = monocytic myeloid-derived suppressor cell; PBMC = peripheral blood mononuclear cell; RT = radiation therapy.