



Radioprotective properties of myeloid-derived suppressor cells

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Myeloid derived suppressor cells (MDSCs) are a heterogeneous group of bone marrow derived immature myeloid cells that are expanded in patients with cancer, infection, trauma, or autoimmune diseases (1). MDSC originate from a common myeloid progenitor cell and develop along two separate lineages, monocytic MDSC (M-MDSC) and granulocytic MDSC (G-MDSC), but never develop the characteristics of mature monocytes, macrophages, or neutrophils (1). M-MDSCs are characterized as CD11b⁺Ly6G⁻Ly6C^{hi} in mice and as CD11b⁺CD115⁺CD14⁺HLA DR^{low} cells in humans, whereas G-MDSC are typically CD11b⁺Ly6G⁺Ly6C^{low} in mice and CD11b⁺CD14⁻CD15⁺CD66⁺ in humans. The tumor co-opts physiologic chemokine signaling used in inflammation to recruit the immature myeloid cells from the bone marrow to the tumor microenvironment (2). At the tumor site, M-MDSC and G-MDSC give rise to tumor-associated macrophages (TAM) and tumor-associated granulocytes (TAN), respectively (1). These cells have been shown to have a negative impact on survival in multiple cancer types including but not limited to breast, colon, and pancreatic cancers (2,3). This pro-tumor effect is mediated by the suppression of T-cell function, modulation of macrophage cytokine production, and promotion of angiogenesis and metastasis (4). An additional property of MDSC is their ability to protect tumor cells from radiation.

Jiang *et al.* in previous works have described the role of classically activated macrophages (M1) in radiosensitizing bystander colorectal cancer cells via production of nitric oxide (NO) from L-arginine by inducible NO synthase (iNOS) (5,6). Under hypoxic conditions NO inhibits

mitochondrial respiration with the net effect of increasing oxygen content within cancer cells thus improving radiosensitivity. It is believed that the presence of molecular oxygen during radiation produces oxygen free radicals leading to DNA damage which is lethal to malignant cells (7). More recent work by Leonard *et al.* describes how both M2-macrophages and G-MDSC decrease radiation sensitivity by upregulating arginase expression. This increased arginase expression leads to conversion of L-arginine into ornithine instead of iNOS mediated conversion into NO (8). The immunosuppressive effect of MDSC arginase on T-cells has been well established (4). Depletion of L-arginine by arginase leads to decreased expression of the CD3 zeta chain and subsequent decreased T-cell proliferation (9). Additionally, low L-arginine conditions leads to cell cycle arrest of T-cells at the G0-G1 phase due to an inability to upregulate cyclin D3 and cyclin-dependent kinase 4 (10). The clinical relevance is eluded to in patients with rectal cancer in which an increased neutrophil to lymphocyte ratio and correlating decreased circulating L-arginine in the plasma is associated with poor outcomes (8).

In patients receiving radiation, hypoxic conditions may be frequently encountered due to significant anemia. Harrison *et al.* described these conditions with a retrospective review identifying the prevalence of anemia in cancer patients undergoing radiation therapy. In their study of 574 patients of multiple cancer types, 41% were found to have anemia with hemoglobin <12 g/dL. Malignancies of the uterine-cervix had the highest rate of anemia with a 75% prevalence (11). Not only is this a frequent problem, but it

portends poor response to radiation therapy with increased recurrence and diminished overall survival. Several reviews have demonstrated decreased overall survival for patients with anemia undergoing radiation therapy for carcinoma of the cervix. The 5-year survival was 74% for patients with hemoglobin >12, 52% for patients with Hgb 11.0–11.9, and 45% for patients with Hgb <11. However, patients whose hemoglobin was increased via blood transfusion had survival similar to those patients with a higher baseline hemoglobin independent of transfusion (12). Similar findings have been noted in other cancers and highlight the importance of treating anemia in patients receiving radiation (13).

As the study by Leonard *et al.* suggests depletion of L-arginine may limit NO production in hypoxic conditions, potentially increasing the circulating L-arginine concentration may improve tumor radiosensitization and patient outcomes in this setting. Future directions to validate L-arginine as a predictive biomarker to radiation therapy and or supplementation to negate the effects of G-MDSC arginase-1 may yield promising results. Caution should be taken, however, with deciding which therapeutic strategy to pursue. While NO was found to radiosensitize tumor cells, only when M1-macrophages produce iNOS for the conversion of L-arginine to NO is this likely associated with immunostimulation. As MDSC in the tumor can also produce iNOS, increasing the availability of L-arginine would likely be associated with increased immune suppression (14). Alternatively, MDSC can be directly targeted. For example, human pancreatic cancer is characterized by an increased prevalence of both G-MDSC and M-MDSC (15). Expression of CCL2 in the pancreas tumor environment leads to recruitment of CCR2-expressing M-MDSC to the tumor (2). By disrupting this recruitment through CCR2 blockade, tumor growth was significantly reduced in both a preclinical model (2) and patients with pancreas cancer (16). Importantly, blockade of M-MDSC recruitment was associated with an altered gene expression in the tumor microenvironment from a type-2 immune profile to a type-1 profile. Similarly, G-MDSC that typically express the chemokine receptor, CXCR2 are primarily recruited to pancreas and other tumors through CXCL2 chemokine production in the tumor environment. Disruption of this pathway through genetic or pharmacologic strategies promotes antitumor immunity (17,18). Multiple other strategies are under consideration and we refer to a recent overview by De Sanctis and colleagues for more details (19).

One important aspect to consider in designing

therapeutic strategies aimed at M1-polarization is the plasticity of the tumor microenvironment and its ability to adapt to changes. Since MDSCs are heterogeneous but overlap in functional traits, it may be necessary to inhibit multiple myeloid subsets to see a therapeutic effect. Several investigators have observed that blocking one MDSC subset led to an increase in another. For example, Pahler *et al.* showed that CCR2 knockout mice had reduced M-MDSC, but an increased level of G-MDSC in the tumor while Stromnes *et al.* demonstrated the converse where depleting G-MDSC led to increase in M-MDSC and TAM (18,20). While these therapies are still being assessed in clinical trials, combining radiation with a therapy that targets M1-polarization might hold clinical promise.

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Footnote

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