



Myeloid-Derived Cells in Tumors: Effects of Radiation

Ralph E. Vatner, MD, PhD and Silvia C. Formenti, MD

The discrepancy between the *in vitro* and *in vivo* response to radiation is readily explained by the fact that tumors do not exist independently of the host organism; cancer cells grow in the context of a complex microenvironment composed of stromal cells, vasculature, and elements of the immune system. As the antitumor effect of radiotherapy depends in part on the immune system, and myeloid-derived cells in the tumor microenvironment modulate the immune response to tumors, it follows that understanding the effect of radiation on myeloid cells in the tumor is likely to be essential for comprehending the antitumor effects of radiotherapy. In this review, we describe the phenotype and function of these myeloid-derived cells, and stress the complexity of studying this important cell compartment owing to its intrinsic plasticity. With regard to the response to radiation of myeloid cells in the tumor, evidence has emerged demonstrating that it is both model and dose dependent. Deciphering the effects of myeloid-derived cells in tumors, particularly in irradiated tumors, is key for attempting to pharmacologically modulate their actions in the clinic as part of cancer therapy.

Semin Radiat Oncol 25:18-27 © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/3.0/>).

Introduction

Tumors are not merely a collection of cancer cells, rather they function more like an organ comprising a complex and organized scaffolding of cellular and noncellular stroma and recruited cells.^{1,2} The primary elements of the tumor stroma are fibroblasts and the noncellular collagen-rich extracellular matrix they produce, the endothelial cells and pericytes of the tumor vasculature, and resident leukocytes such as macrophages driving progression. Tumors also recruit inflammatory immune cells, including tumor-infiltrating lymphocytes (TILs, both CD4⁺ and CD8⁺), natural killer (NK) cells, NK T-cells, B cells, and an array of myeloid-derived cells.³ The various components of the microenvironment interact to influence the growth and function of each of the other elements, including the cancer cells themselves, mediated

through direct cell-cell contact and secreted cytokines and chemokines.

Myeloid-derived cells are an important part of the microenvironment, both numerically and functionally, and play a central role in regulating the antitumor immune response.³⁻⁵ Arising from the common myeloid progenitor cell, these include tumor-associated macrophages (TAMs), dendritic cells (DCs), polymorphonuclear neutrophils (PMNs), and myeloid-derived suppressor cells (MDSCs). Although each of these is usually considered distinct populations, the functional distinctions in the tumor microenvironment can be somewhat artificial.⁶ Rather, myeloid cells in tumors exist along a spectrum of maturation and a plastic immunomodulatory phenotype that can be influenced by ionizing radiation and other exogenous agents.⁷⁻¹⁰

Functionally, myeloid cells are both friend and foe to the antitumor immune response. They are essential for facilitating antitumor immunity, but they take on an immunosuppressive phenotype in established tumors, helping to promote immune evasion.¹¹ For example, DCs are necessary for cross-priming of cytotoxic CD8⁺ T lymphocytes against tumor-specific antigens and are required for immune-mediated rejection in murine tumor models.¹²⁻¹⁴ However, tumor-resident DCs often have a regulatory phenotype and express low levels of costimulatory molecules and proinflammatory cytokines, leading to T-cell anergy and tolerance.^{1,2,15-18} Similarly,

Department of Radiation Oncology, New York University School of Medicine, New York, NY.

S.F. is supported by grants from the National Cancer Institute, NIH, USA (R01CA161891-01), Department of Defense Breast Cancer Research Program (BC100481 and W81XWH-11-1-0530), and Breast Cancer Research Foundation, USA (13-A0-00-001870-01).

The authors declare no conflict of interest.

Address reprint requests to Silvia C. Formenti, MD, Department of Radiation Oncology, New York University School of Medicine, New York, NY 10016. E-mail: Silvia.Formenti@nyumc.org

macrophages can promote immune effector function, yet TAMs usually have an immunosuppressive phenotype that promotes tumor growth, invasion, and metastasis.^{3,19-22}

The fact that myeloid-derived cells contribute to an immunosuppressive tumor microenvironment is no accident. Most tumors evolve in the context of a competent immune system that recognizes neoplastic cells by the expression of tumor-specific neoantigens and embryonic antigens normally expressed exclusively during development. Tumors can only grow after selection of immune escape variants by immunoediting, and clinically apparent tumors have undergone this process, developing the means to escape immune recognition.^{3,5,23-25} Myeloid-derived cells are at the center of immune escape. They are actively recruited by tumor-secreted factors and maintained in an immunosuppressive phenotype that allows for tumor growth in the context of an otherwise competent immune system.^{5,6,8}

Phenotype and Function of Myeloid-Derived Cells in the Tumor Microenvironment

Macrophages

Macrophages are large mononuclear phagocytes that ingest cellular debris, promote wound healing, and modify the local

immune response in tissues and tumors.^{7-10,26,27} Most tumor macrophages develop from monocytes recruited from the blood. They have tremendous tissue-specific phenotypic variability, and although there is no single set of macrophage-specific surface markers, useful markers include the general myeloid-lineage marker CD11b and F4/80 (in mice) and CD14 and CD68 (in humans). Functional classification of macrophages as classically activated (M1) vs alternatively activated (M2) is a useful and commonly used paradigm to describe the extremes of a spectrum of macrophage phenotype based on patterns of gene expression and cytokine production.^{8-11,28,29} (Fig. 1). M1 polarization develops in response to inflammatory stimuli, such as interferon (IFN)- γ and lipopolysaccharide, and is characterized by higher surface expression of major histocompatibility complex (MHC) Class II and CD86. These M1 cells generate nitric oxide (NO) catalyzed from arginine by inducible NO synthase (iNOS), signal through STAT3 and STAT1, can kill tumor cells directly, and stimulate antitumor T-cells by secreting the proinflammatory cytokines IL-12 and IL-6. Conversely, in the presence of IL-4 and IL-13 macrophages develop an M2 phenotype, which suppress antitumor immunity by producing arginase and the cytokines transforming growth factor (TGF)- β and IL-10. M2 cells can be further identified by STAT6 phosphorylation and surface expression of mannose receptor (CD206), programmed death ligand 2 (PD-L2), and restin-like molecule-a.

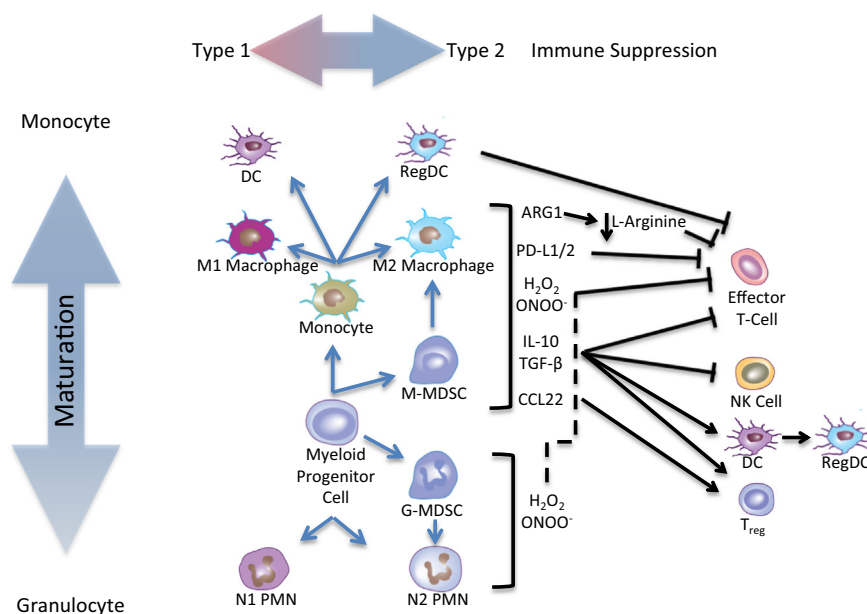


Figure 1 Myeloid-derived cells in tumors and mechanisms of immune suppression. Tumor-associated myeloid cells originate from a myeloid progenitor cell in the bone marrow. These produce the granulocytes (primarily PMNs) and granulocytic MDSCs (g-MDSC), and the monocytic cells including monocytes, macrophages, dendritic cells (DCs), and monocytic MDSCs (m-MDSC). Influenced by their environment, myeloid cells can acquire a phenotype ranging from proinflammatory (type 1) to immunosuppressive (type 2). Type 2 myeloid cells suppress antitumor immunity through the following 4 general mechanisms: (1) They produce arginase (ARG-1), which depletes L-arginine and inhibits T-cell function. (2) They produce reactive oxygen species such as hydrogen peroxide (H_2O_2) and reactive nitrogen intermediates such as peroxynitrite ($ONOO^-$), which modify receptors for antigens and chemokines on T-cells and impairing their function. (3) They produce cytokines such as IL-10 and TGF- β that impair effector T-cells and convert DCs into regulatory DCs, which can further impair T-cell function. (4) They produce chemokines such as CCL22, which selectively attract Tregs, and TGF- β also directly stimulates Tregs to suppress antitumor effector T-cells. (Color version of figure is available online.)

Download English Version:

<https://daneshyari.com/en/article/5881535>

Download Persian Version:

<https://daneshyari.com/article/5881535>

[Daneshyari.com](https://daneshyari.com)