Cellular Immunology 316 (2017) 1–10

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Review article

Tumor promoting role of anti-tumor macrophages in tumor microenvironment

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ARTICLE INFO

Keywords:
M1/M2
Macrophages
Immune response
Tumor
Tumor microenvironment

ABSTRACT

Recent advances in tumor biology demand detailed analysis of the complex interaction of tumor cells with their adjacent microenvironment (tumor stroma) to understand the various mechanisms involved in tumor growth and metastasis. Mononuclear phagocytes or macrophages, a type of innate immune cells, defend the organism against infection and injury. On the otherhand, tumor associated macrophages (TAMs) constitute a significant part of the tumor-infiltrating immune cells, have been linked to the growth, angiogenesis, and metastasis of a variety of cancers, most likely through polarization of TAMs to the M2 (alternative) phenotype. Clinical and experimental evidences have shown that cancer tissues with high infiltration of TAMs are associated with poor patient prognosis and resistance to therapies, thus, targeting of TAMs in tumors is considered as a promising immunotherapeutic strategy. Depletion of M2 TAMs or 're-education' of them as anti-tumor effectors might contribute significantly to the search of new modalities in anti-cancer treatments. Basic questions on the factors responsible for homing of macrophages in tumors, mechanism of conversion of M1 to M2 TAMs, their functionality and, finally, the possible ways to target M2 TAMs are discussed.

1. Introduction

Macrophages exhibit noteworthy plasticity and their physiology can be modified in response to environmental cues, resulting generation of various subpopulations of macrophages having versatile functions. Macrophages in tumors, generally known as tumor-associated macrophages or TAMs, are upregulated in the stromal compartment of various solid tumors and participate in the growth, angiogenesis and metastasis of tumors. Macrophage biology in relation to tumor can be addressed by answering four basic questions:

i. What are the signals attracting macrophages into tumor?
ii. What are the mechanisms of polarization of M1 to M2 TAM phenotype?
iii. What functions do TAMs exhibit in tumor microenvironment (TME)?
iv. How pro-tumor M2 TAMs can be targeted for their elimination?

Élie Metchnikoff won the Nobel Prize in 1908 for explaining 'phagocytosis'. Since then, "stimulation of the phagocytes" was anticipated as a key to immunity [1]. The discovery proposes 'macrophages as immune effector cells that participate in host defense' [2]. Tissue resident macrophages combat infection, resolve acute inflammation and regulate metabolic response to tissue stress. Broad phenotypic heterogeneity and plasticity of macrophages depend on their microenvironment [3].

In malignancy, macrophages represent a prominent component (up to 50% cells) of infiltrated leukocytes [4]. Macrophages, in general, are cytotoxic towards tumor cells *in vitro* by producing cytotoxic molecules (e.g., TNFα, IL-12, nitric oxide (NO) and reactive oxygen intermediates [5]. However, TAMs majorly help in tumor escalation rather than tumor inhibition [6] (see Table 1). Macrophages also present tumor-associated antigens (TAA) to T cells, and express immunostimulatory cytokines for propagation and anti-tumor functions of T cells and NK cells *in vitro* [7]. In bare contrast, macrophages from experimental or human tumors illustrate altered activities, possibly due to exposure of tumor-derived IL-4, IL-10, TGFβ and prostaglandin E2 [3]. Mantovani et al. [8] have proposed that exposure of TAMs to IL-4 and IL-10 may

Abbreviations: CSC, cancer stem cells; CSF-1, colony stimulating factor-1; EGF, epidermal growth factor; HIF, hypoxia inducible factor; IDO, indoleamine-pyrrole 2,3-dioxygenase; NO, nitric oxide; NLGP, neem leaf glycoprotein; PHD2, prolylhydroxylase domain 2; STAT, signal transduction and activator of transcription; TAM, tumor associated macrophages; TME, tumor microenvironment; TNFa, tumor necrotic factor alpha; TAA, tumor associated antigen; TGFb, transforming growth factor beta; Tregs, T regulatory cells; TLR, toll-like receptors; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; MHC, major histocompatibility complex; TDF, tumor derived factor

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http://dx.doi.org/10.1016/j.cellimm.2017.04.005
Received 20 December 2016; Received in revised form 9 April 2017; Accepted 12 April 2017
Available online 13 April 2017
0008-8749/

Table 1
Variable prognostic significance of TAMs in different forms of cancer.

Site of Primary Tumor	TAM status	Prognosis	References
Stomach	High macrophage infiltration	Favorable Survival 87%	Ohno et al. (2003)
Colorectal	Peritumoral macrophage infiltration	Favorable Survival 100%	Funada et al. (2003)
Melanoma	$CD163^+$ macrophage infiltration in tumor stroma $CD68^+$ macrophage infiltration at the invasive front	Poor	Jensen et al. (2009)
Breast	High TAM density	Worse	Tsutsui et al. (2005)
Prostate	Increased TAM profile	Poor	Lissbrant et al. (2000)
Endometrial	Increased hot-spot TAM	Poor Promotes metastasis	Ohno et al. (2004)
Bladder	High TAM count	Poor Promotes distant metastasis	Hanada et al. (2000)
Kidney	Increased TAM	Poor Facilitates cancer growth via angiogenesis	Hamada et al. (2002)
Esophagus	High monocytic count	Poor Worse 5 years survival	Jadus et al. (1996)
Squamous Cell carcinoma	High M2 TAM infiltration	Poor survival and facilitates angiogenesis	Koide et al. (2004)
Uveal Melanoma	A high number of macrophages	Poor Mortality increased	Makitie et al. (2001)

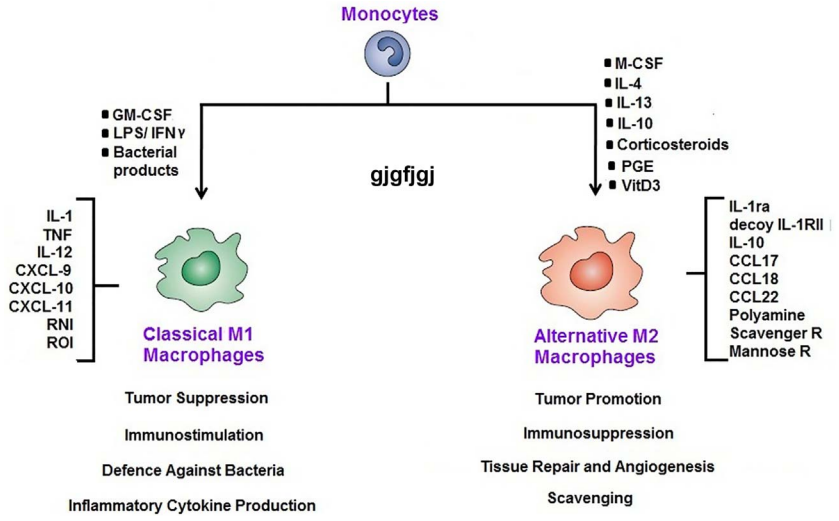

Fig. 1. Polarization of macrophages. Macrophages are heterogeneous population could be divided schematically into two main classes: M1 and M2. Blood monocytes differentiating in the presence of LPS/IFNγ mature to M1/classically-polarized macrophages. They produce high levels of IL-12, IL-1, IL-23, TNFα and CXCL10 and are characterized by the cytotoxic activity against microorganisms and neoplastic cells, expression of high levels of ROI, and proficiency as APCs. On the other hand, when monocytes differentiate in presence of IL-4, IL-13, IL-10, or corticosteroids, they mature into M2 macrophages (alternatively activated, which secrete IL-10, CCL17, CCL22, CCL18, IL-1ra, and IL-1R decoy). M2 cells are active workers of the host, promoting scavenging of debris, angiogenesis, remodeling, and repairing of wounded/damaged tissues. Within the tumor mass, they exert the same functions favoring tumor promotion. M2 macrophages also control the inflammatory response by down-regulating M1-mediated functions and adaptive immunity.

develop alternatively activated M2 macrophages, show more phagocytic activity, elevated expression of scavenging, mannose and galactose receptors, exhibit impaired expression of reactive nitrogen intermediates, produce ornithine and polyamines through the arginase pathway, express IL-1 decoy receptor and exhibits an IL-12^{low}IL-10^{high} phenotype [9]. In contrast to the classically activated type I (M1) macrophages, these cells have poor antigen-presenting potential, suppress T-cell proliferation, dampen inflammation, promote tissue remodeling and tumor progression. In addition to cytokines, macrophages of M1 and M2 type exhibit distinctive chemokine profiles, for example, M1 macrophages are expressing type-1 cell-attracting chemokines (e.g., CXCL9 and CXCL10), whereas, M2 macrophages are expressing the chemokines CCL17, CCL22 and CCL24. Chemokines can also affect macrophage polarization [10] (Fig. 1).

Moreover, macrophage phenotypes are differentially distributed within tumor. For example, in a mammary adenocarcinoma model, $MHCII^{high}$ TAMs can confine to normoxic tumor tissues, express M1 markers and anti-angiogenic chemokines, whereas, $MHCII^{low}$ TAMs were found in hypoxic tumor tissues, preferentially express M2 markers with greater pro-angiogenic functions [11]. Although most of the studies are focused on M2 population in various malignancies, several markers rather typical for type 1 macrophages (M1) were also characterized. Macrophages isolated from RCC tumors were shown to produce proinflammatory cytokines TNFα, IL-1β, IL-6, and CCL2. Kovaleva et al. concluded that RCC is an excellent example of a tumor with hybrid phenotype of TAMs that share both M1 and M2 properties [12].

2. Driving force for monocyte infiltration in tumor

Interaction of tumor cells with their microenvironment affects tumor growth and metastasis. Tumor creates a widespread tolerogenic environment by altering normal hematopoiesis and promoting the expansion of myeloid cells through the release of tumor derived factors (TDFs). This process of reactive myelopoiesis causes the accumulation of myeloid derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs). Tumor-reprogrammed myeloid cells not only blocks T cell functions, but also directly drive tumor growth by