Macrophage Polarization and Its Role in Cancer

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Abstract

The immune system plays an important role in the development of, and progression of cancer. Macrophages exhibit a variety of responses according to varying stimuli, and express different functions depending upon the microenvironment surrounding them. Macrophages can be pro-inflammatory (M1) or anti-inflammatory (M2). Research studies have shown that infiltration of macrophages can account for >50% of the tumor mass in some cancers, aid in metastasis by inducing angiogenesis, and signify a poor prognosis. Macrophages that migrate to the tumor site, remain there, and aid in angiogenesis and metastasis are termed tumor associated macrophages (TAMs) and are thought to express an M2 phenotype. This review will examine the polarization states of macrophages, their functions and role in cancer, their activation pathways and metabolism, and potential approaches to cancer immunotherapies using macrophages.

Keywords: Macrophage polarization; Inflammation; Cancer

Introduction

Cancer is a group of diseases that involve unregulated cell growth and death, genome instability and mutations, tumor-promoting inflammation, induction of angiogenesis, evasion of the immune system, disregulation of metabolic pathways, immortal cell replication, and activation of metastasis and invasion [1]. Cancer is the second leading cause of death in the United States after heart disease, and more than 1.6 million new cases are expected to be diagnosed each year. More than 580,000 Americans are expected to die yearly from cancer (about 1,600 cancer deaths per day), nearly 1 in 4 of all deaths overall [2,3].

The immune system plays an important role in the development and progression of cancer. In fact, immune cell infiltration to the tumor site can affect malignancy progression and metastasis [4,5]. Infiltration of macrophages to the tumor site has been shown to account for more than 50% of the tumor mass in certain breast cancer cases, suggesting macrophages have a significant role in tumor progression [6-8].

Macrophages are cells derived from the myeloid lineage and belong to the innate immune system. They are derived from blood monocytes that migrate into tissue. One of their main functions is to phagocytose microbes and clear cellular debris. They also play an important role in both the initiation and resolution of inflammation [9,10]. Moreover, macrophages can exhibit different responses depending on the type of stimuli they receive from the surrounding microenvironment, varying from pro-inflammatory to anti-inflammatory [11]. In fact, two major macrophage phenotypes have been proposed: M1 and M2, which correspond to the extreme phenotypes of a spectrum of responses.

The in vivo molecular mechanisms of macrophage polarization are poorly characterized because of the variety of signals macrophages experience in the cellular microenvironment [10,12]. In recent years, progress has been made in identifying in vivo macrophage polarization under physiological conditions, especially during ontogenesis and pregnancy, and during pathological conditions such as allergies, chronic inflammation, and cancer. However, several macrophage populations are observed during specific pre-clinical and clinical conditions, as a result of the complex signaling between the tissue microenvironment and the immune system [11]. We do know, however, that in vitro macrophage polarization is plastic, and macrophages exposed to specific cytokines, can be polarized back and forth to either phenotype [13,14].

This review discusses the characteristics and functions of polarized macrophages, their role in cancer, their activation pathways and metabolic functions, and their use in potential cancer immunotherapy approaches.

M1 Phenotype

M1 macrophages, or classically activated macrophages, are aggressive and highly phagocytic, produce large amounts of reactive oxygen and nitrogen species, and promote a Th1 response [11]. This is a macrophage response usually seen during microbial infections. M1 macrophages secrete high levels of IL-12 and IL-23, two important inflammatory cytokines. IL-12 induces the activation and clonal expansion of Th17 cells, which secrete high amounts of IL-17, and thus contribute to inflammation [15].

In the context of cancer, classically activated macrophages are thought to play an important role in the recognition and destruction of cancer cells, and their presence usually indicates good prognosis. After recognition, malignant cells can be destroyed through several mechanisms, which include contact-dependent phagocytosis and cytotoxicity (i.e. cytokine release such as TNF-α) [16]. Environmental signals such as the tumor microenvironment or tissue-resident cells, however, can polarize M1 macrophages to M2 macrophages. In vivo
studies of murine macrophages have shown that macrophages are plastic in their cytokine and surface marker expression and that re-polarizing macrophages to an M1 phenotype in the presence of cancer can help the immune system reject tumors [17].

For a long time, M1 macrophages were thought to be the only functional macrophages and that anti-inflammatory molecules were inhibitory to their function. Now we understand that anti-inflammatory molecules did not inhibit macrophage function but provided alternative activation of macrophages.

**M2 Phenotype**

M2 macrophages, or alternatively activated macrophages, are anti-inflammatory and aid in the process of angiogenesis and tissue repair. They express scavenger receptors and produce large quantities of IL-10 and other anti-inflammatory cytokines [18,19]. While they upregulate certain MHC-II molecules, M2 macrophages are not capable of efficient antigen presentation. Expression of IL-10 by M2 macrophages promotes a Th2 response, and Th2 cells, in turn, upregulate the production of IL-3 and IL-4. IL-4 is an important cytokine in the healing process because it contributes to the production of the extracellular matrix [15]. M2 macrophages have different subsets, each induced by a different set of molecules and different activation responses.

M2a macrophages or M(IL-4 or IL-13) are usually referred as profibrotic. They mainly induce a Th2 response and promote type II responses in response to IL-4 and IL-13 [20]. M2b or M(IC or TLR/ILL-R ligands) macrophages are also involved in Th2 activation and immune regulation, and they are often referred as regulators. M2c or M(IL-10 or TGF-β), also described as deactivated, are involved in immune suppression, tissue repair and matrix remodeling. M2d or tumor associated macrophages exhibit functions that may help tumor progression by allowing new blood vessel growth, which feeds the malignant mass of cells, thus promoting their growth [21]. The presence of macrophages (thought to be M2d) in the majority of solid tumors negatively correlates with treatment success and longer survival rates [5].

Anti-inflammatory signals present in the tumor microenvironment such as adiponectin and IL-10, can help macrophages maintain an M2 state and enhance an M2 response [15,22,23].

**Macrophage Polarization**

The tumor microenvironment significantly affects macrophage polarization. The process of polarization can be diverse and complicated because of the complex environment of IL-10, glucocorticoid hormones, apoptotic cells, and immune complexes that can interfere with the function of innate immune cells [11,17].

Inflammatory signals such as IFN-γ, TNF-α, IL-18 and LPS can polarize macrophages to the M1 phenotype in vitro [24,25]. LPS or IFN-γ can interact with Toll-like receptor 4 (TLR4) on the surface of macrophages inducing the Trif and MyD88 pathways, inducing the activation of transcription factors IRF3, AP-1, and Nfkb and thus activating TNFs genes, interferon genes, CXCL10, NOS2, IL-12, etc. which are necessary in a pro-inflammatory response [26]. Classically activated macrophages initiate the induction of the STAT1 transcription factor which targets CXCL9, CXCL10 (also known as IP-10), IFN regulatory factor-1 (IRF-1), and suppressor of cytokine signaling-1 [27].
In the tumor microenvironment, Notch signaling plays an important role in the polarization of M1 macrophages, as it allows transcription factor RBP-J to regulate classical activation. Macrophages that are deficient in Notch signaling express an M2 phenotype regardless of other extrinsic inducers [28]. M2 phenotype subsets are polarized by a variety of signals, which is why it is important to include the inducer molecule when referring to these subtypes (Figure 1) [29].

M2a macrophages are induced by IL-4 and IL-13, IL-4 and IL-13 bind to IL-4R and activate the Jak/Stat6 pathway, which regulates the expression of CCL17, ARG1, IFR4, IL-10, SOCS3, etc., which are genes associated with an anti-inflammatory response. M2b macrophages are usually induced by IC (FCR receptors)+TLR/IL-1R ligands. Additionally, these macrophages over express IL-10, CCL1, IL-1 and IL-6 [30]. M2c macrophages polarize in the presence of IL-10+TGF-β. They upregulate IL-10 and TGF-β production and express CD163 and CD206 as well as several scavenger receptors [21,31].

Other transcription factors associated with macrophage polarization either towards an M1 or M2 response are IRF5, IRF4, Krüppel-like factor 4 (KLF4), CCAAT/enhancer-binding protein-β (C/EBPβ), PU.1, pSTAT1, RBP-J, and CMAF [12,32-35].

Additional mechanisms of macrophage polarization include miRNA micromanagement. miRNAs are small non-coding RNAs of 22 nucleotides in length that regulate gene expression post-transcriptionally, as they affect the rate of mRNA degradation. Several miRNAs have been shown to be highly expressed in polarized macrophages, especially miRNA-155, miRNA-125, miRNA-378 (M1 polarization), and miRNA let-7c, miRNA-9, miRNA-21, miRNA-146, miRNA147, miRNA-187 (M2 polarization) [32,36,37]. miRNA-155, is upregulated when macrophages are transitioning from M2 to M1, and M1 macrophages overexpressing miRNA-155 are generally more aggressive and are associated with reduction of tumors [19]. Moreover, miRNA-342-5p has been found to foster a greater inflammatory response in macrophages by targeting Akt1 in mice. This miRNA also promotes the upregulation of Nos2 and IL-6, both of which act as pro-inflammatory signals for macrophages [38]. Other miRNAs such as miRNA-125 and miRNA-378 have also been shown to be involved in the classical activation pathway of macrophages (M1) [37].

Macrophage polarization is a complex process. In the past years, there has been much controversy on the definition/description of macrophage activation and macrophage polarization. A recent paper published by Murray et al. describes a set of standards to be considered for the consensus definition/description of macrophage activation, polarization, activators, and markers. This publication was much needed to clarify the definition and characterization of activated/polarized macrophages [29]. Basically, the new nomenclature requires to specify the activation molecules (i.e. M(IL-4), M(IL-10), M(LPS), etc.).

**Tumor associated macrophages (TAMs)**

Cells exposed to a tumor microenvironment behave differently. For example, tumor associated macrophages found in the periphery of solid tumors are thought to help promote tumor growth and metastasis, and have a M2-like phenotype [39]. Tumor associated macrophages can be either tissue resident macrophages or recruited macrophages derived from the bone marrow (macrophages that differentiate from monocytes to macrophages and migrate into tissue). A study by Cortez-Retamozo found that high numbers of TAM precursors in the spleen migrate to the tumor stroma, suggesting this organ as a TAM reservoir. TAM precursors found in the spleen were found to initiate migration through their CCR2 chemokine receptor [40]. Recent studies have found CSF-1 as the primary factor that attracts macrophages to the tumor periphery, and CSF-1 production by cancer cells predicts lower survival rates and indicates an overall poor prognosis [41-43]. Other cytokines such as TNF-α and IL-6 have also been linked to the accumulation/recruitment of macrophages to the tumor pheriphery [42].

It is thought that macrophages that are recruited around the tumor borders are regulated by an “angiogenic switch” that is activated in the tumor. The angiogenic switch is defined as the process by which the tumor develops a high density network of blood vessels that potentially allow the tumor to become metastatic, and are necessary for malignant transition. In a breast cancer mouse model, it was observed that the presence of macrophages was required for a full angiogenic switch. When macrophage maturation, migration, and accumulation around the tumor was delayed, the angiogenic switch was delayed as well, suggesting that the angiogenic switch does not occur in the absence of macrophages, and that macrophage presence is necessary for malignancy progression [44]. Moreover, the tumor stromal cells produce chemokines such as CSF1, CCL2, CCL3, CCL5, and placental growth factor that will recruit macrophages to the tumor surroundings and provide an environment for macrophages to activate the angiogenic switch, during which macrophages will produce high levels of IL-10, TGF-β, ARG-1 and low levels of IL-12, TNF-α, and IL-6. The level of expression of these cytokines suggests macrophages modulate immune evasion. It is important to point out that in solid tumors, macrophages will be attracted by hypoxic environments and will respond by producing hypoxia-inducible factor-1α (HIF-1α) and HIF-2α, which regulate the transcription of genes associated with angiogenesis. During the angiogenic switch, macrophages can also secrete VEGF (stimulated by the NF-κB pathway), which will promote blood vessel maturation and vascular permeability [45].

Tumor associated macrophages are thought to be able to maintain their M2-like phenotype by receiving polarization signals from malignant cells such as IL-1R and MyD88, which are mediated through the IκB kinase β and NF-κB signaling cascades. In fact, inhibition of NF-κB in TAMs promotes classical activation [46]. Moreover, another study suggested p50 NF-κB as the factor involved in suppression of M1 macrophages, and that the inflammation reduction helped in tumor growth. When they created a p50 NF-κB knock-out mouse, they found out that M1 aggressiveness was restored and that tumor survival was reduced [47].

Because the tumor mass contains a great number of M2-like macrophages, TAMs can be used as a target for cancer treatment. Reducing the number of TAMs or polarizing them towards an M1 phenotype can help destroy cancer cells or impair tumor growth [48-50]. Luo et al. in a study published in 2006, used a vaccine against legumain, a cysteine protease and stress protein upregulated in TAMs, as a potential tumor target. When the vaccine against legumain was administered to mice, the results showed that the angiogenesis genes were down-regulated and tumor growth was halted [49].

**Metabolism and activation pathways**

Metabolic alterations present in tumor cells are controlled by the same mutations that produce cancer [51,52]. As a result of these metabolic alterations, cancer cells are able to produce signals that can
modify the polarization of macrophages and promote tumor growth [53,54].

M1 and M2 macrophages demonstrate distinct metabolic patterns that reflect their dissimilar behaviors [55]. The M1 phenotype is characterized by increased glycolysis and glucose metabolism which is skewed towards the oxidative pentose phosphate pathway, decreased oxygen consumption, and the production of large amounts of radical oxygen and nitrogen species, as well as inflammatory cytokines such as TNF-α, IL-12, and IL-6 [55,56]. The M2 phenotype is marked by increased fatty acid intake and fatty acid oxidation, decreased flux towards the pentose phosphate pathway, increased overall cell redox potential, upregulated scavenger receptors, and immunomodulatory cytokines such as IL-10 and TGF-β [55].

Multiple metabolic pathways play important roles in macrophage polarization. Protein kinases, such as Akt1 and Akt2, alter macrophage polarization by allowing cancer cells to survive, proliferate, and use an intermediary metabolism [57]. Other protein kinases can direct macrophage polarization through glucose metabolism by increasing glycolysis and decreasing oxygen consumption [56,58]. Shu et al. were the first to visualize macrophage metabolism and immune responses in vivo, using a PET scan and a glucose analog [59].

L-arginine metabolism also exhibits discrete shifts important to cytokine expression in macrophages and is exemplary of distinct metabolic pathways altering TAM-tumor cell interactions [60]. Classically activated (M1) macrophages favor inducible nitric oxide synthase (iNOS). The iNOS pathway produces cytotoxic nitric oxide (NO), and cells consequently exhibit anti-tumor behavior. Alternatively activated (M2) macrophages have been shown to favor the arginase pathway, and produce ureum and l-ornithine, which contribute to progressive tumor cell growth [60,61].

Direct manipulation of metabolic pathways can alter macrophage polarization. The carbohydrate kinase-like (CARKL) protein, which plays a role in glucose metabolism, has been used to alter macrophage cytokine signatures [55,56]. When CARKL is knocked down by RNAi, macrophages tend to adopt an M1-like metabolic pathway (metabolism skewed towards glycolysis and decreased oxygen consumption), whereas when CARKL is overexpressed, macrophages adopt an M2-like metabolism (decreased glycolytic flux and more oxygen consumption) [55]. When macrophages adopt an M1-like metabolic state through LPS/TLR4 engagement, CARKL levels decrease and the macrophages activate genes controlled by the NFκB pathway such as TNF-α, IL-12, and IL-6, while also increasing cell redox potential by increasing concentrations of NADH:NAD+ and GSH:GSSG complexes. During an M2-like metabolic state, macrophages upregulate CARKL and genes regulated by STAT6/IL-4 (IL-10 and TGF-β).

Switching the environment to a M1 phenotype bias by targeting metabolic pathways in TAMs may offer an alternative means of reducing tumor growth and metastasis.

Macrophage immunotherapy approaches against cancer

Cancer immunotherapy involves stimulation of the immune system to recognize, reject, and destroy cancer cells. Cancer immunotherapy with macrophages has the goal to polarize macrophages towards a pro-inflammatory response (M1), thus allowing the macrophages and other immune cells to destroy the tumor. Many cytokines and bacterial compounds can achieve this in vitro, although the side effects are usually too severe when replicated in vivo. The key is to find a compound that will have minimal or easily managed side effects in the patient. Immunotherapy using macrophages has been used in the past decades and new approaches are being developed every year [62,63].

Early immunotherapy established a good foundation for better cancer therapies and increased patient survival rates [64].

Some approaches to cancer immunotherapy are the use of cytokines or chemokines to recruit activated macrophages and other immune cells to the tumor site and allow the tumor cells to be recognized as foreign and destroyed [65,66]. IFN-α and IFN-β have been shown to inhibit tumor progression by inducing differentiation and apoptosis [67]. Also, IFN treatments are anti-proliferative and can increase S phase in the cell cycle [68,69]. Zhang et al. performed a study in nude mice in which they used IFN-β gene therapy to target human prostate cancer cells. Their results show that adenovirus-delivered IFN-β gene therapy involves macrophages and helps suppress growth and metastasis [70].

Another cytokine that can be used in cancer immunotherapy is macrophage inhibitory factor (MIF). MIF is usually found in solid tumors and its presence usually means poor prognosis. MIF, as its name describes, inhibits aggressive macrophage function, and therefore causes macrophages to express an M2 response. An M2 response can aid tumor growth and progression. Simpson, Templeton & Cross (2012) found that MIF induces differentiation of myeloid cells, macrophage precursors, into a suppressive population of myeloid cells that express an M2 response. By targeting anti-MIF shRNA, they were able to deplete this suppressive population of macrophages and inhibit their growth and thus control tumor growth and metastasis [71].

The chemokine receptor type 2, CCR2, is crucial to the recruitment of monocytes to inflammatory sites and it has been shown as a target to prevent the recruitment of macrophages to the tumor site, thus preventing angiogenesis and metastasis. Sanford et al. studied a novel CCR2 inhibitor (PF-04136309) in a pancreatic cancer mouse model, showing that the CCR2 inhibitor depleted monocyte/macrophage recruitment to the tumor site and decreased tumor growth, metastasis, and increased antitumor immunity [72]. Another recent study showed that macrophages co-cultured with 10 different human lung cancers upregulated CCR2 expression. Moreover, they showed that using a CCR2 antagonist in a lung cancer mouse model reduced tumor growth and metastasis [73].

Other studies have used liposomes to deliver drugs to deplete M2 macrophages from tumors and to stop angiogenesis. Cancer cells that express high levels of IL-1β grow faster and induce more angiogenesis in vivo. Kimura et al. (2007) found that macrophages exposed to tumor cells expressing IL-1β produced higher levels of angiogenic factors and chemokines such as vascular endothelial growth factor A (VEG-A), IL-8, monocyte chemotactant protein 1, etc. When they used clodronate liposomes to deplete macrophages, they found fewer IL-1β-producing tumor cells. They also found that by inhibiting NF-κB and AP-1 transcription factors in the cancer cells, tumor growth and angiogenesis were reduced, which may suggest that macrophages found near the tumor site may be involved in the stimuli that promote tumor growth and angiogenesis [74].

Compounds such as methionine enkephalin (MENK) have anti-tumor properties in vivo and in vitro. MENK has the ability to polarize M2 macrophages to M1 macrophages by down-regulating CD206 and arginase-1 (M2 markers) while upregulating CD64, MHC-II, and the
production of nitric oxide (M1 markers). MENK can also upregulate TNF-α and down-regulate IL-10 [75].

Recent studies have focused on bisphosphonates as a potential inhibitor of M2 macrophages. Bisphosphonates are commonly used to treat metastatic breast cancer patients to prevent skeletal complications such as bone resorption [76]. While bisphosphonates stay in the body for only short periods of time, they can target osteoclasts, cells in the same family as macrophages, due to high affinity for hydroxyapatite. Once bisphosphonates bind to the bones, the bone matrix internalizes the bisphosphonates by endocytosis and once in the cytoplasm, bisphosphonates can inhibit protein prenylation, an event that prevents integrin signaling and endosomal trafficking, forcing the cell to go apoptotic. Until recently, it was unknown whether bisphosphonates could target tumor associated macrophages, but a recent study by Junankar et al. has shown that macrophages uptake nitrogen-containing bisphosphonate compounds by pinocytosis and phagocytosis, events that do not occur in epithelial cells surrounding the tumor [77]. Forcing TAMs to go apoptotic may reduce angiogenesis and metastasis. Another study using bisphosphonates was performed by Coscia et al. where they used zoledronic acid (ZA) to target mammary tumors in mice. They used female BALB-neuT mice that develop spontaneous metastatic breast tumors and administered ZA intravenously once a week for 4 weeks. Compared to control mice (saline injections), ZA-treated mice were able to survive free of cancer for a longer time, they had decreased tumor rates and had a reduction in tumor multiplicity with no toxicity associated with the ZA dosage. When compared to control, the number of infiltrating TAMs was reduced in ZA-treated mice while other lymphocyte numbers remain the same. The authors concluded that ZA impairs TAM recruitment, angiogenesis and VEGF release at the tumor site [78].

Additional approaches to cancer immunotherapy include the use of biomaterials that may elicit an immune response. Cationic polymers are used in immunotherapy because once dissolved in water they can react with nucleic acids, adjuvants, etc. Chen et al. used cationic polymers including PEI, polylysine, cationic dextran and cationic gelatin to produce a strong Th1 immune response. They were also able to induce proliferation of CD4+ cells and to induce secretion of IL-12 in macrophages, a cytokine produced by M1 macrophages [75]. Huang et al. (2013) also used biomaterials to modulate TAMs to an anti-tumor response by targeting TLR4. This study found that TAMs were able to polarize to an M1 phenotype and express IL-12. They found that these cationic molecules have direct tumoricidal activity. They were also able to show tumor reduction in mice (Table 1) [79].

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Table 1: Summary of cancer immunotherapy approaches.

**Conclusion**

Macrophages play an important role in tumor progression and metastasis because of the plasticity they express during activation, especially in vivo. Depending on the signals present in the tumor microenvironment, macrophages can express pro-inflammatory (M1 phenotype) or anti-inflammatory (M2 phenotype) responses. The tumor microenvironment can polarize macrophages towards an M2 response, an anti-inflammatory response, which can lead to tumor progression, angiogenesis, and metastasis. M2 macrophages resemble tumor associated macrophages (TAMs) which help recruit blood vessels at the tumor site and allow the tumor cells to invade other tissues.

It is obvious that macrophages play a significant role in cancer progression, and immunotherapies involving macrophages should be considered in the treatment of this disease. The polarization of
macrophages towards an M1 response with minimal side effects may prove to be a powerful therapy against solid tumors. Inflammatory signals such as LPS or TNF-α can easily polarize macrophages towards an M1 phenotype in vitro. However, use of substances such as an LPS and TNF-α in vivo exacerbate a whole-body inflammatory response involving cells of both the innate and adaptive immune systems. They can cause fever and inflammation in several tissues including the mucosal surfaces and the lungs. These inflammatory signals are highly cytotoxic as well [80-82]. This can be detrimental to cancer patients and compromise their health.

Current approaches to cancer immunotherapy using macrophages involve cytokines and chemokines and interferons and biomaterials and inorganic molecules that can elicit immune responses. These approaches have been shown to reduce tumor size and angiogenesis, recruit immune cells to the tumor site, and prevent the polarization of macrophages to an M2 phenotype.

Because immunotherapy requires the activation of the immune system, it is difficult to find a cytokine, chemokine, compound, or biomaterial that will not produce some side effects. However, because macrophages belong to the innate immune system and exhibit pro-inflammatory and anti-inflammatory properties, they are ideal immunotherapy candidates.

Further work is needed to identify substances and protocols that can adeptly re-educate the immune system to attack cancer cells, prevent angiogenesis and metastasis, and to protect the host from developing a damaging inflammatory response.

References


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