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Representing Tumor-Associated Macrophages as the Angiogenesis and Tumor Microenvironment Regulator

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ABSTRACT

Over the recent years, studies in the area of cancer microenvironment and the cellular groups existing in this environment have indicated the significant role of them in progression of cancer studies. Among the mentioned cellular groups, as the main inflammatory components of stroma, Tumor associate macrophage (TAM) cells have the capacity of affecting the cancer tissue in different aspects. With their plasticity capacity, macrophages can change into M1 (classic) or M2 (alternative) macrophage reacting to different signals. In the tumor environment, they usually change into the M2 phenotype, and this phenotype can create a precancerous role in the macrophage and facilitate the invasion of tumor cells and metastasis, angiogenesis, remodeling of the extracellular matrix, and suppression of the immune system. The various roles of these cells and their reversibility have made the TAMs a potential target of the cancer treatment. This process takes place by different mechanisms such as Interference with TAMs survival, Inhibition of macrophage recruitment, repolarization of M2-like TAMs towards an M1-like phenotype, nano particle and liposome-based drug delivery system. This review study investigates the markers and the function of M1, M2, and tumor-associated macrophages, and finally, it proposes the latest clinical and laboratory approach for targeting the TAMs.

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Abbreviations

TAM, tumor associated macrophages; IL, Interleukin; IL-1Ra, Interleukin-1 Receptor Antagonist; CCL, chemokine (C-C motif) ligand; CXCL, chemokine (C-X-C motif) ligand; TGF-β, Transforming growth factor beta; EGF, Epidermal growth factor; MMP, Matrix metalloproteinase; VEGF, Vascular endothelial growth factor; PDGF, Platelet-derived growth factor; FGF, Fibroblast growth factor; CD, cluster of differentiation; HLA-DR, Human Leukocyte Antigen – DR isotype; STAT-3, Signal transducer and activator of transcription 3; TNF-a, Tumor necrosis factor alfa; SOCS3, Suppressor of Cytokine Signaling 3; IFN-γ, Interferon gamma; NOS, nitric oxide synthase; MR 206, Mannose receptor 206; LPS, Lippopoly saccharide; GM-CSF, Granulocyte-macrophage colony-stimulating factor; HCC, hepatocellular carcinoma; HSC, hematopoietic stem cells; CSF-1, colony stimulating factor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; ROS, Reactive oxygen species; P53, Tumor protein P53; TLR, Toll Like Receptor; HSC, hematopoietic stem cells; MCSF-R, Macrophage colony-stimulating factor; PITPNM3, Phosphatidylinositol Transfer Protein, Membrane-Associated 3; bFGF, Basic fibroblast growth factor; CTL, Cytotoxic T lymphocytes; uPA, plasminogen activator; PGE2, Prostaglandin E2; DC, Dendritic cells; NK, natural Killer cells; Siglec-15, Sialic acid binding ig-like lectin 15; PD-L1, Programmed cell death ligand

Introduction

Leukocytes are considered as one of the main immune system barriers against the invasion of pathological agents and they aggregate in the target tissue at the time of tumor formation (1). In tumor microenvironment that is first detected as a foreign agent by the body, in addition to tumor cells, there are other cells such as fibroblasts, endothelial cells, and leukocytes; one of the most important leukocyte cells is macrophage (2). In the early stage of tumor establishment, macrophages play an anti-tumor role and they induce immunity in the environment by supplying antigens and producing the different factors of specialized immune cells, and in the later stages of tumor development, they can get into a protumor state (3). The macrophages penetrating the tumor tissue are considered as TAM that are involved in the process of tumorogenesis (4). TAMs are considered as one of the main inflammation-cancer mediators and can play an anti-tumor or protumor role in tumor microenvironment. This flexibility causes these cells to get different phenotypes in response to different environmental signals. They play a protective role against infection and after the infection discharge, they help the tissue restoration; they are considered as the cells of monocyte-macrophage cell line (5). As already stated, TAMs are involved in all the processes of tumor progression. However, they do not depend on only a phenotype. In the early stages of tumorogenesis, TAMs have a M1-LIKE phenotype and then, they change into the M2-LIKE phenotype. It should be mentioned that the macrophages with a M2-LIKE phenotype are classified in four categories a, b, c, and d (6). These categories are different from each other in terms of the markers and some of their functions. TAMs have a M2-LIKE phenotype due to the high expression of anti-inflammatory markers such as Interlukin-10 (IL-10) and Interleukin-1 Receptor Antagonist (IL-1Ra). In addition, primary TAMs induce the expression of chemotactic factors such as chemokine (C-C motif) ligand-2(CCL2), CCL5, CCL7, chemokine (C-X-C motif) ligand (CXCL8), and CXCL12 and so, they cause the entrance of monocytes into the tumor environment. These monocytes can become polarized into M2-LIKE phenotype induced by IL-4, IL-6, IL-10, IL-13, and Transforming growth factor beta (TGF-β). Also, production of tumor-promoting growth factors such as epidermal growth factor (EGF) by TAMs leads to immune system regulation and angiogenesis. In this process, MMP synthesis that has a major effect on angiogenesis is regulated by vascular endothelial growth factor (VEGF), Platelet-derived growth factor (PDGF), Fibroblast growth factor (FGF), and TGF-β (7). Also, it should be mentioned that the large number of TAMs is related to prognosis of most of the human cancers (8). This review article investigates the markers and the function of M1, M2, and tumor-associated macrophages, and finally, it proposes the latest clinical and laboratory approach for targeting the TAMs.

Characteristics of M1 and M2 macrophages

Macrophages are classified based on the expression of CD68, CD14, Human Leukocyte Antigen– DR isotype (HLA-DR), CD204; and other proteins such as MMP2L9, B7/H4, Signal transducer and activator of transcription 3 (STAT-3), CD163, CD206 are specifically used for classification of TAM (6).

However, each of the M1 and M2 macrophages are classified based on different markers; the specified markers used to classify the M1-Like macrophages include CD80+ , CD86+ , TNF-a , VEGF, Suppressor of Cytokine Signaling 3(SOCS3), and CCR7 (9) (10), and the specific markers of all the subtypes of M2-like macrophages include CD163, IL-10, SOSC1/2, CD206 , CCL-18 , PDGF-BB , and MMP (10) (11) (12). M1 macrophages secrete pro-inflammatory cytokines such as IL-12, Tumor necrosis factor alfa(TNF-α), CXCL-10, and Interferon gamma (IFN-γ), and they produce a high level of nitric oxide synthase (NOS, an enzyme metabolizing arginine to the "killer" molecule nitric oxide); whereas, M2 macrophages secrete anti-inflammatory cytokines such as IL-10, IL-13, and IL-4, and they express a high level of arginase-1, mannose receptor (MR 206), and scavenger receptor (figure 1) (3) (13). However, the noteworthy point is that classification of TAMs should be done based on their functions such as metastasis, angiogenesis, and immune response regulation.

Monocytes are called and polarized by different factors. For example, studies have shown that IFN-γ can induce active M1 macrophages only by bacterial Lipopolysaccharide (LPS) or cytokines such as TNF and Granulocyte-macrophage colony-stimulating factor (GM-CSF) (14). On the other hand, infection immune complex, IL-4, IL-6, IL-10, IL-13, IL-21, IL-33, and NOTCH can activate and induce M2 macrophages (14-17). Also, various factors such as VEGF, chemokines such as CCL2 and CSF-1 are used for calling the monocytes and using them in tumor environments (18).

VEGF-A is a powerful protumor factor (19) with pre-agniogenic effects. This factor that induces the penetration of TAMs and polarization of M2 macrophages in the presence of IL-4 and IL-10 develops the cancerous tissues (20). M2-like macrophages that are induced by IL-4, IL-13, and glucocorticoids are involved in biological angiogenic processes, tissue remodeling, wound healing, and anti-inflammatory processes.

Also, M2-like macrophages can increase angiogenesis by carrying nutrients and foods; it is accompanied by tumor growth, metastasis, tissue remodeling, and immunesuppression in tumor environments. This process results in increased secretion of VEGF and FGF by TAMs and cancer cells, increased angiogenic potential of tumor cells by production and high expression of cyclooxygenase-2 (21). The other factor i.e. endothelial growth factor and the signaling created by its bond to EGFR receptor not only increases the invasion and proliferation of tumor cells, but also regulates the macrophage calling and M2-like polarization (22, 23). Also, chemokines such as CCL7, CCL8, CCL9, CCL18, and CXCL12 are highly expressed in the tumor microenvironment and cause the attraction and polarization of TAMs (24, 25).

According to the recent studies, inflammation can induce tomorogenesis. With regard to the fact that macrophages exist in almost all the tissues and are involved in induction of inflammation they can be considered as effective cells in tumor microenvironment due to their ability to regulate inflammation. M1-like macrophages that are induced by TNF-α, GM-CSF, and IFN-γ are considered as pro-inflammatory cells due to their special characteristics and their release is involved in tumor growth. M1-like macrophages kill the viruses and the bacteria existing in the cells by secreting inflammatory factors such as IL-12 and Il-23; whereas in cancer microenvironment, this process increases the metastasis potential by activating NF-Kb signaling (26). So, it is believed that carcinogenesis can be induced by many cytokines such as pro-inflammatory M1-like macrophages. For example, M1-like macrophages called by TNF-α can increase the accumulation of Reactive oxygen species (ROS) in latent tumor cell, and so, they can damage the proto-oncogens and anti-oncogens such as Tumor protein P53 (p53) (27, 28). In addition, EGF and IL-6 induce the activation of STAT3 and consequently, tumorogenesis (29). In contrast, other studies have shown that high levels of pro-inflammatory factors released by M1-like macrophage can be detrimental to cancer cells (30). In spite of the variety of theories, it is quite obvious that TAMs have M14-like properties in the early stages of tumor development. However, M2-like macrophage phenotype is created in the advanced stages of tumor development, and it is effective in tumor growth by improving angiogenesis, matrix remodeling, and secretion of anti-inflammatory cytokines (30, 31).

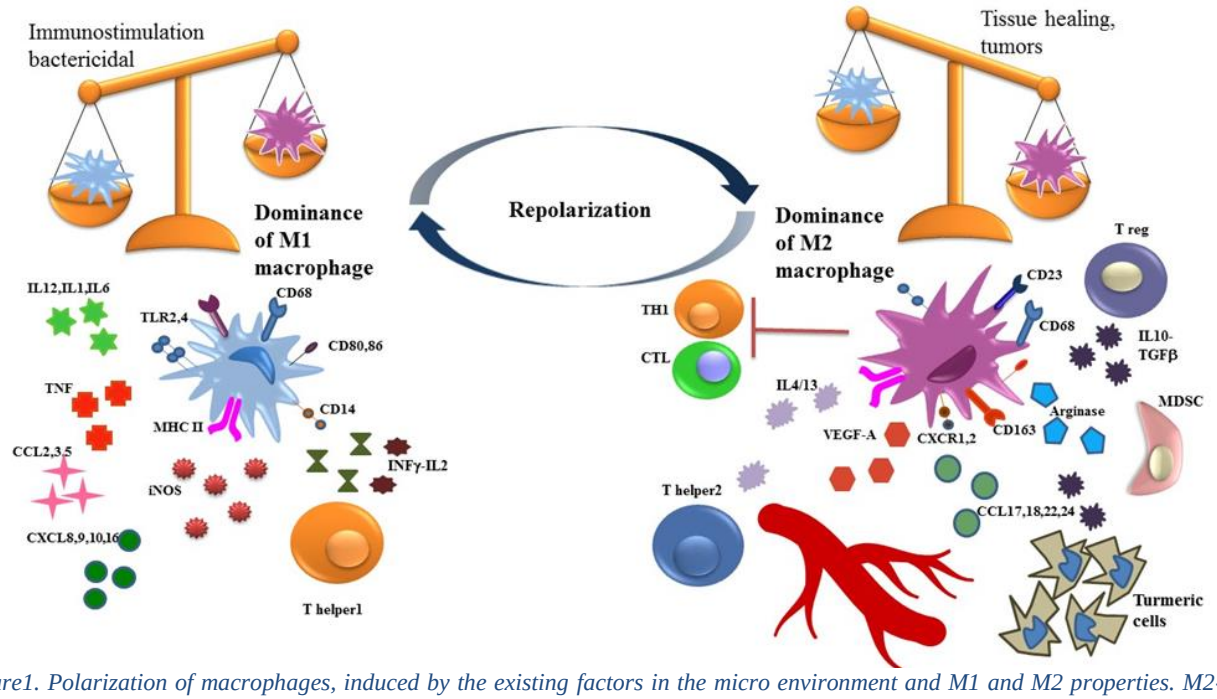

Figure1. Polarization of macrophages, induced by the existing factors in the micro environment and M1 and M2 properties. M2-like macrophages can induce suppression to other immune cells through different mechanisms like secreting cytokines like IL10, TGF-β, arginase, VEGF-A, expression of markers like PDL-1/2, as well as cytotoxic T-lymphocyte associated protein 4 (CTLA4), promoting differentiation of T reg cells. While M1-like macrophages can mediate tumoricidal impacts by upregulation of major histocompatibility complex (MHC) type2, secretion of INFγ, TNF-α, IL-12, IL-1, IL-6, NOS. IL, Interleukin; TGF-β, Transforming growth factor beta; VEGF, Vascular endothelial growth factor; PD-L, Programmed cell death ligand; IFN-γ, Interferon gamma; TNF-α , Tumor necrosis factor alfa; NOS, Nitric oxide synthase.

TAMs are involved in production of high levels of IL-10 and TGF-β in TME (32) and they express inflammatory cytokines such as IL-1β, IL-6, IL-12, and TNF-α to a limited extent (33). Also, increased secretion of IL-6 and IL-10 by TAMs in tumor microenvironments is accompanied by immune suppression, angiogenesis, and antiapopotic factors (34-37). Studies performed in this area suggest that increased level of IL-6 derived from TAM exerts a strengthening effect on inflammatory response. Therefore, it promotes the creation and progression of hepatocellular carcinoma (HCC) by STAT3 signaling (38). In addition, excessive presence of cytokines and chemokines in this niche leads to absorption and calling the macrophages and other components of immune cells by the tumor environment; this cellular network produces more cytokines and creates a cycle (39).

M1 macrophages appear under inflammation and invasion of bacterial agents. These macrophages are detected by specific markers such as Toll like receptor (TLR) -2,-4, CD80, CD86, CD14 and CD68. They aslo discharge the infective agents by producing inflammatory factors such as INFγ, IL12, CXCL 8,9,10,16, etc. cooperating with T helper1. With the discharge of the infections and at the time of invasion of the tumor cells, M2 macrophages appear with specific markers such as CD163, CXCR1, CXCR2 and CD23, and they suppress inflammation and inflammatory cells by producing arginase, TGF-β, IL-10 and VEGF-A.

The origin of TAMs

In 1863, Virchow proposed the issue of the presence of inflammatory leukocytes in tumor tissue, and he stated that lymphoreticular penetration in tumor indicates a chronic infection in the tumor environment (40). The main idea is that the primary origins of macrophages are blood monocytes derived from hematopoietic stem cells (HSC) (41-43). The recent findings suggest that most of the macrophages existing in the tissue are proliferated and differentiated in their establishment site and they become differentiated to more specialized macrophages such as alveolar macrophages, brain macrophages (microglia), liver macrophages (kupffer cell) that are originated from yolk sac progenitors (44-48).

During the process of tumoreogenesis, peripheral blood monocytes that are originated from bone marrow are called to the tissue in response to chemokines and growth factors secreted from stromal and cancer cells, and they become differentiated to TAMs. Regardless of originating from bone marrow or yolk sac, colony stimulating factor 1 (CSF1) is considered as the main regulator and chemotactic factor for most of the macrophages (49).

Chemokines (such as monocyte chemotactic protein 1 (CCL2) and complement cascade products are the main determinants of macrophage calling and macrophage location in tumors (50-53). Blocking the CCL52-CCR2 interaction by genetic ablation technique and using antibodies can obviously prevent metastasis and prolong the survival of tumor bearing mice; also, it can decrease the expression of proinflammatory cytokines (54). It has been recently reported that CSF-1 and STAT1 play a major role in different levels of the monocyte differentiation to macrophage in a tumor. It implies the M-CSFR and GM-CSFR in protecting the macrophage phenotypes in tumor (43, 55-57). In a xenograft model, VEGFA calls the monocytes that have been changed into TAM in the presence of IL-4; so that the absence of these TAMs prevents tumor growth, invasion, proliferation, and angiogenesis (20). The human breast cancer models have also shown that CCL18 binding to its receptor Phosphatidylinositol Transfer Protein, Membrane-Associated 3 (PITPNM3) with the aid of CSF2 calls macrophages (58). In other studies on colon cancer model, macrophages have been called by CCL20 binding to its receptor (CCR6) (59).

TAM and angiogenesis

The reaction between tumor growth and angiogenesis is a mutual interaction. Angiogenesis provides the necessary nutrients for tumor growth. On the other hand, in tumor microenvironment, endothelial cells will be quickly proliferated from TAMs and tumor cells for forming vascular buds by stimulation of the growth factors. Consequently, vascular bud will growth in a direction towards the tumor and then, growth factors will be secreted. Vascular bud growth in the tumor can stimulate tumorogenesis by producing the factors initiating the angiogenesis and create a cycle. Also, endothelial cells accelerate the tumor progression by increasing the angiogenesis (60).

In tumor microenvironment, blood vessels are twisted or inflated. Proliferation and differentiation of the silent epithelial cells and stimulation of them to the angiogenic form and activation depend on VEGF and other growth factors (61). TAMs express different molecules for regulating angiogenesis, facilitating the proliferation of endothelial cells, and formation of the blood vessels. These molecules include VEGF, Basic fibroblast growth factor (Bfgf) , TNF-α, IL-1β, CXCL8 , cyclooxygenase 2, plasminogen activator (uPA), PDGF-β, MMP7, MMP9, MMP12 (55, 62-63).

Each of these factors can support and balance the process of angiogenesis in different stages. For example, IL-1β, VEGF, TGF-β,α, and other cytokines stimulate the stromal cells and form an appropriate microenvironment for angiogenesis (64). MMPs and especially MMP-9 that is secreted from TAMs affect the extracellular matrix and facilitate the budding process. This proteolytic process is activated by invasion of endothelial cells and supports the migration of other cells (65).

TAM and inflammation

Under normal conditions, tissue remodeling takes place with tissue damage or at the end of inflammation and infection discharge. However, in the tissues with carcinogenic mutations, tumor growth is started in response to tissue damage repair. So, tissue is activated in response to continuous tissue damage and this vicious cycle results in a sustainable chronic inflammation in the tissue. This chronic inflammation can be also caused by other factors such as excessive obesity, exposure to radiation and infection. In addition, the process of cell aging and accumulation of damaged DNAs in the tissue can also cause a chronic inflammation (tumor promoted chronic inflammation) (66, 67). This chronic inflammation that occurs prior to tumorogensis can increase angiogenesis, induce immunosuppression and carcinogenic mutations. Furthermore, most of the cytokines and growth factors that facilitate the process of angiogenesis, tumor growth, and metastasis will be generated during this chronic inflammation and tissue repair process. IL-6 and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammatory signals will change the micro-RNA in chronic inflammation that results in cancer cells' resistance to apoptosis and increased probability of metastasis (68).

As stated before, the recent studies suggest that inflammation can induce tumorogensis and as one of the effective cells in tumor microenvironment, macrophages that exist in almost all the tissues can regulate the inflammation (60). Also in chronic inflammation, macrophages are considered as the most important inflammatory cells due to producing the cytokines (such as chemokines, growth factors, acid compounds, and specific metabolites).

Regarding the differences between acute and chronic inflammation, chronic inflammation is caused by inflammatory stimulation and angiogenesis, and connective tissue growth take place in the presence of macrophages and monocytes. As a result, the presence of TAMs in tumor microenvironment leads to continuation of chronic inflammation by the release of inflammatory molecules that initiate the process of remodeling (69).

TAM and immunosuppression

TAMs are one of the main immunoregulatory cells in tumors and they can prevent the Cytotoxic T lymphocytes (CTL) response in tumor microenvironment (62, 70). IL-10, TGF-β, and Prostaglandin E2 (PGE2) that move towards M2-like phenotype can increase angiogenesis and tissue remodeling (51, 62). Other cytokines such as M-CSF, MMPs, and EGF are produced by TAMs in tumor microenvironment and they cause the tumor invasion. On the other hand, the chemokines released from the TAMs can call other cells such as Th2 and Treg to the tumor niche and create an immunosuppressive environment. Also, TAMs can suppress the activity of T cells by releasing cytokines, chemokines, and different enzymes. It takes place by calling the natural Tregs and discharging the L-arginine in the tumor microenvironment (71). PGE2, TGF-β and other chemokines existing in the microenvironment can prevent the maturity of Dendritic cells (DCs); disturb the balance between the innate and the adaptive immunity, and it also suppresses the activity of Natural killer (NK) cells and T cells (31, 72-74). In addition, IL-10 that is secreted from the TAMs can induce PD-L1 molecule in monocytes which can finally prevent the CTL response (75). Sialic acid binding Ig-like lectin 15 (Siglec-15) is one of the molecules with a low expression in immune cells and normal tissues, and it is a suppressive molecule produced by macrophages for T cells (76). So, Siglec-15 is proposed as a probable target of cancer immunotherapy (77).

Programmed cell death ligand (PD-L1) is a T cell inhibitory receptor, and PD-1 ligand that has been proposed as another active agent in immunosuppression. Several studies have approved the fact that PD-1 can be involved in suppression of the immune system by the tumor of the host (78).

An in-vivo study investigating the effect of PD-1 ligand mechanism on anti-tumor activity, reported that TAM-derived PD-1s have a more significant role in suppression of anti-tumor activity than the PD-1s isolated from the host. The research also indicated the important role of TAM-derived PD-2 as another ligand for PD-1 in anti-tumor immunosuppression (79).

Biomarkers associated with tumor associated macrophage

The CD markers expressed by this group of cells include the following: CD68 (an adhesion glycoprotein which is expressed in M1+ and M2+), CD14 (LPS co-receptor which is expressed in M1+ and M2+), CD163 (that is known an scavenger receptor hemoglobin which is expressed in M1- and M2++), CD206 (as a mannose receptor that is expressed in M1- and M2++) (6), (and scavenger receptor 1 that is expressed in M1+ and M2+) (80).

The other expressed factors include the following: MMP2/9 (Matrix metalloproteinase that is expressed in M1- and M2+) (81), B7-H4 (inhibiting costimulatory molecule expressed in M1- and M2+) (82, 83), STAT3 (as a transcription factor expressed in M1- and M2+) (29), iNOS (nitric oxide synthase that is expressed in M1+ and M2-) (9, 84, 85), and HLA-DR (as an antigen presenting molecule expressed in M1+ and M2+) (86). Other cytokines include IL-12p70 (expressed in M1++ and M2-) and IL-10 (expressed in M1+ and M2++) (87).

About the importance of TAM biomarkers, a recent study has reported that the markers expressed by these macrophages are involved in determining the prognosis of breast cancer. This study has suggested that high concentration of macrophages is related to CD11c, CD68, and CD163 markers, negative markers of estrogen and progesterone, severe tripathological grades of tumor, larger sizes of tumor, and the higher proliferation index of Ki-67. Also, survival of CD163+ macrophages was decreased in the independent prognosis market of tumor nest and the survival of CD11c+ macrophages was increased in the tumor stroma (88).

Targeting Tumor Associated Macrophages: Effective Therapeutic Approach in Cancer Treatment

Due to the effectiveness of the macrophages existing in the tumor environment in treatment and improvement of invasion, angiogenesis, and metastasis, they can be modified to limit the tumor growth. This group of macrophages play a major role in angiogenesis with their capacity of producing angiogenic factors. So, targeting them can decrease the angiogenesis and it is the importance of their presence. It should be mentioned that the various antibodies developed for targeting angiogenesis including anti-VEGF, anti-EGFT, etc. have had a limited effectiveness and tumor recurrence and metastasis can be observed in most of the patients receiving these antibodies (89-91). One of the mechanisms proposed for anti-angiogenesis resistance is the cooperation of stromal cells and the use of TAM cells as the groups that can significantly produce angiogenic factors (92). So, targeting these cells by eliminating and changing one of the most important angiogenesis supporting factors leads to decreased probability of angiogenesis and tumor invasion. One of the methods used for modifying these group of cells is targeting their survival, preventing their calling, and reprogramming them to M1 macrophage (table 1). Due to the important role of macrophages in angiogenesis, these cells have been targeted in several clinical trials beside the use of monoclonal antibodies for inhibition of angiogenesis. For example, in a study being performed in a phase I clinical trial investigating the repolarization of macrophages by CD40 (R07009879), the effects of this treatment besides bevacizumab (Anti-VEGF) on solid tumors is being studied; the clinical trial is being performed under the no. NCT02665416. Targeting CD47 in tumors increases the phagocytosis capacity of the macrophages. Another study on colorectal cancer is investigating the effect of Hu5F9-G4 antibody with cetuximab targeting EGFR; the study is being performed in stage I under the clinical trial no. NCT02953782.

Among the mentioned methods, some of them were studied in clinical trials. One of these methods is limiting the calling of macrophages to the tumor environment that is considered as one of the appropriate treatment targets. CCL2 that is produced by the macrophages, stromal cells, and tumor cells is effective in calling the other macrophages to the tumor environment. So, blocking its receptor i.e. CCR2 is effective in preventing the tumor progression (135, 136). Based on the laboratory studies, this hypothesis suggests the positive effects and the decrease of calling the suppressive cells to the tumor. Some of the blockers of this receptor are being studied in clinical trials; these blockers include CCX872-B, PF-04136309, MLN1202, and BMS-813160 (137). MLN1202 monoclonal antibody is investigated in the second phase of a clinical trial under no. NCT01015560; this study targets the patients with bone metastasis. In another clinical trial being performed in stage I/II under no. NCT03767582, the effect of the combined treatment by Nivolumab, GVAX, and BMS-813160 of patients with locally advanced pancreatic cancer (LAPC) undergoing chemotherapy or radiotherapy. The other factors are CSF and its receptor that play a major role in polarization of TAMs. According to the studies, inhibition of this factor and blocking its receptor can decrease the polarization of macrophages, target their activation, decrease the tumor invasion, and increase its survival; so, in recent years, this factor has been considered as an appropriate target (110). So far, anti-CSFR1 has been used for different targets including Pexidartinib, BLZ945, ARRY-382،JNJ-40346527, Emactuzumab, IMC-CS4 (anti-CSF1R), and FPA008 (Cabiralizumab, anti-CSF1R) that have been studied along or with other treatments; these factors has been studied in phase I and II clinical trials (137). A stage I clinical trial under no. NCT03153410 is investigating the effects of the combination of cyclophosphamide, GVAX (pancreatic cancer vaccine), Pembrolizumab (an antibody that blocks negative signals to T cells) and also CS4 (LY3022855) on patients with borderline resectable pancreatic cancer. The other phase II clinical trial being performed under no NCT03557970 is investigating the effect of a CSFR1-inhibitor named JNJ-40346527 on patients with acute myeloid leukemia, and this inhibitor is hoped to inhibit the growth of tumor cells.

Table1. The methods used for targeting tumor associated macrophages.

Method	Target	Approach of the Targeting
Interference with TAMs survival	Legumain(93)	legumain-base DNA vaccine
	CD204(94)	anti-204 immunotoxin
	IL4Rα/CD124(95)	RNA aptamer
	CD52(96)	Alemtuzumab
	FRβ(97)	anti-FRβ mAb
	Cytotoxicity in monocytes(98-100)	Trabectedin (ET-743)
		Liposomal clodronate
		M2pep
Inhibition of macrophage recruitment	CCL2/CCR2(101-105)	Neutralizing antibody CNTO 888
		CCL2 inhibitor bindarit
		CCR2 kinase antagonist PF-04136309
		Luteolin
	CSF1/CSF1R(106-109)	Neutralizing antibody RG7155
		CSF-1R inhibitor PLX6136, GW2580 or PLX3397
		Liposomal bisphosphonate
		miR-26a
Repolarization of M2-like TAMs towards an M1-like phenotype	CSF1/CSF1R(110)	CSF-1R inhibitor BLZ945
	Micro environmental stimuli(111-117)	bacteria-mediated tumor therapy
		polyI:C
		IFN-γ
		IL-12
	Vascular normalization(118-121)	Histidine-rich
		Zoledronic acid
		DMXAA
		Hydrazinocurcumin
		Glycoprotein
	NF-κB pathway(122-127)	TLR agonists(polyI:C, CpG-ODN, TLR9 ligand, IL10R mAb
		PA-MSHA
		Flavone glycoside Baicalin
		CD40 mAb
		Natural compound corosolic acid
	MAPK/ERK pathway(128)	CuNG
	Epigenetic regulation (129-132)	Overexpressing miR-155/miR-511-3p
		Deletion of miR-146a
Nano particle and liposome-based drug delivery system(133, 134)	Albumin nanoparticle-based Abraxane	
	Mitoxantrone-loaded SLNs	
	Cisplatin-and cyclodextrin-loaded polymer nanoparticles	
	Liposomal Doxil	

The next strategy of using the macrophages existing in tumors is reprogramming them to M1 phenotype. Various targets have been defined for repolarization of macrophages; one of these factors is PI3Kγ that is expressed by myeloid cells. It has been observed that inhibition of this factor induces the expression of proinflammatory cytokines in TAMs and suppresses the growth of breast, head, neck tumors, etc (138, 139).

Also, it has been found that inhibition of this factor is accompanied with increased migration, infiltration of TCD8 cells, increased production of interferon gama, and finally decreased tumor growth and metastasis in rats (41, 140). In a phase II clinical trial being performed under no. NCT02637531, the effect of monotherapy by PI3Kγ inhibitor named IPI-549 and its combination with nivolumab is investigated to determine the proper dosage; also, the safety and the effectiveness of pharmacokinetics and pharmacodynamics are investigated in different tumors such as non-small cell lung cancer, melanoma, squamous cell cancer of head and neck, triple negative breast cancer, adenocortical carcinoma, mesothelioma, and progressive solid tumors. The other factors are TLR agonists that can stimulate antitumor responses and accompany macrophage repolarization by stimulating the innate immune cells. The agonists TLR 4, 7/8, and TLR9 named GSK1795091, IMO-2125, Imiquimod, NKTR-262, SD101, and CMP-001 are investigated in different phase I to III clinical trials (137). In a phase I clinical trial being performed under no. NCT03447314, TLR4 antagonist named GSK1795091 is investigated to determine its proper dosage to be combined with pembrolizumab for patients with head and neck squamous cell carcinoma and other malignant solid tumor. In a phase III clinical trial under no. NCT03445533, the effectiveness of Ipilimumab and its combination with TLR7/8 antagonist named IMO-2125 is investigated. Also, another clinical trial being performed under no. NCT02521870, the biological effects, tolerability, and safety of TLR9 antagonist named SD101 combined with pembrolizumab is investigated in patients with metastasis melanoma and metastasis head and neck cancer. CD40 is a costimulatory molecule that was originally discovered on B-cells and other antigen presenting cells. On monocytes, CD40 stimulation induces the production of inflammatory cytokines and chemokines. The agonists of anti-CD40 have been accompanied by stimulation of tumor killing macrophages in rat model cell line (141, 142). This marker is another target of macrophage reprogramming. The CD40 recombinant ligand and anti-CD40 antibodies named ADC-1013،SEA-CD40, CP-870,893,APX005M,SGN-40, and RO7009789 are being investigated in the early stages of clinical trials (137).

For example, a clinical trial (NCT02376699) is investigating the effectiveness and safety of SEA-CD40 monotherapy and its combination with pembrolizumab ،gemcitabine and nab-paclitaxel in patients with different tumors such as Carcinoma, Non-Small-Cell Lung،Hematologic Malignancies, Hodgkin Disease, Lymphoma, Large B-Cell, Diffuse, Squamous Cell Neoplasm, etc.

Conclusion

Monocyte cells constitute a 1-10% (143) population of blood leukocytes circulating in blood and different tissues, and they can transform into macrophage and giant cells. As a bridge connecting the innate immune system and the acquired immune cells in the case of invasion of foreign agents and especially cancer cells, they play a major role by different mechanisms and with their plasticity to M2 group, they decrease the inflammation after the improvement of infection. In recent years, several studies in America (144) have investigated tumor microenvironments as the second major death cause. These studies have indicated that invasion of these cells is involved in tumor growth by supporting and stimulating angiogenesis and suppressing the killing cells (31). Due to the mentioned fact, this group of cells is considered as an appropriate target of tumor therapy. So far, several methods have been investigated to target their survival, calling, reprogramming to M1, and their role in drug delivery. The drugs used for targeting the survival and calling of these cells and their repolarization are investigated in clinical trials (137, 145). Regarding the important role of these cells in the process of angiogenesis that is involved in tumor development and metastasis, there should be further studies in this area. Also, it seems that more detailed investigation of the effect of combined treatments targeting angiogenesis and macrophage cells and studying the effect of other variables such as the microbiota can provide promising results.

Declarations

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Authors' Contributions

Conceptualization, project administration, supervision, A.J., A.E.S.; investigation, writing original draft, E.M.S., M.M., H.S.H., A.K., N.B.; writing, review and editing, M.M., All authors have read and agreed to the published version of the manuscript.

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