# MCP-1 targeting: Shutting off an engine for tumor development (Review)

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**Abstract.** A large amount of research has proven that monocyte chemotactic protein-1 (MCP-1) is associated with different types of disease, including autoimmune, metabolic and cardiovascular diseases. In addition, several studies have found that MCP-1 is associated with tumor development. MCP-1 expression level in the tumor microenvironment is associated with tumor development, including in tumor invasion and metastasis, angiogenesis, and immune cell infiltration. However, the precise mechanism involved is currently being investigated. MCP-1 exerts its effects mainly via the MCP-1/C-C motif chemokine receptor 2 axis and leads to the activation of classical signaling pathways, such as PI3K/Akt/mTOR, ERK/GSK-3β/Snail, c-Raf/MEK/ERK and MAPK in different cells. The specific mechanism is still under debate; however, target therapy utilizing MCP-1 as a neutralizing antibody has been found to have a detrimental effect on tumor development. The aim of the present review was to examine the effect of MCP-1 on tumor development from several aspects, including its structure, its involvement in signaling pathways, the participating cells, and the therapeutic agents targeting MCP-1. The improved understanding into the structure of MCP-1 and the mechanism of action may facilitate new and practical therapeutic agents to achieve maximum performance in the treatment of patients with cancer.

## Contents



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## 1. Introduction

Approximately 10 million patients succumb to various types of cancer annually, despite a wide variety of available cancer therapies. Malignant cancers demonstrate a poor prognosis, which is evidenced by a reduced expected lifespan and a greater difficulty in treatment. The advent of target therapies that suppress tumor growth, invasion and metastasis, has revolutionized cancer treatment and given optimism to numerous patients with cancer. In this regard, target therapy elicits both a specific and precise action on cancer cells, thereby reducing unpleasant side effects by contrast to traditional cancer treatment. Target therapy directed against lung cancer with the EGFR mutation has already demonstrated encouraging results (1,2). Consequently, the enthusiasm for target therapy remains high since almost all types of cancer possess a key cellular factor that promotes its pathological biochemical metabolism.

The chemokine, monocyte chemoattractant protein-1 (MCP-1), also known as C-C motif chemokine ligand 2 (CCL2), belongs to the C-C chemokine superfamily, which is comprised of at least 4 members (MCP-1, -2, -3 and -4). MCP-1 binds to a G-protein coupled receptor and plays a major role in the promotion of inflammation by modulating monocyte and basophil activity, but not neutrophil or eosinophil activity (3). Regardless of the affinities, MCP-1 has an ability to interact with a number of receptors [e.g., ACKR1, C-C motif chemokine receptor (CCR)-2, CCR5, CCR10 and CCR11] (4-8); however, previous findings suggested that CCR2 is the primary MCP-1 receptor. MCP-1 was initially identified in 1989 and termed glioma-derived chemotactic factor-2 (GDCF-2) (9). Later, GDCF-2 was found in the tissue culture media of phytohemagglutinin-stimulated human mononuclear leukocytes. With amino acid sequencing and cloning, GDCF-2 was finally renamed MCP-1 (10,11). MCP-1 is also known as tumor-derived chemotactic factor, as a wide variety of tumor cells can produce it (12). In addition, MCP-1 is secreted by a range of cell types in the tumor microenvironment (TME), such as fibroblasts, tumor-infiltrating monocytes, endothelial cells and tumor-associated adipocytes (13,14).

The MCP-1 gene (*SCYA2*) is located on human chromosome 17q11.2-q21.1 (15). The precursor MCP-1 comprises 99 amino acids, with 23 amino acids at the N-terminal, as the hydrophobic signal peptide, whereas the mature protein is comprised of

76 amino acids, after cleavage of the signal peptide (Fig. 1A). There are two forms of the MCP-1 structure, known as I and P (Fig. 1B and C) (16). For all the MCPs, the N-terminal residues, 1-6, are essential for chemoattractant activity, and the first amino acid is necessary for direct receptor binding (17). Handel and Domaille (18) reported that the secondary structure of MCP-1 consists of one α-helix and four β-sheets (the grey label), including residues 9-11 (β0), 27-31 (β1), 40-45 (β2) and 51-54 (β3), which are different from the data in the Protein Data Bank (18). The latter shows that MCP-1 has three α-helices. Residue 14 can be glycosylated, which can slightly decrease the potency of its chemotactic activity (19).

MCP-1 has been associated with several diseases, such as HIV-1 pathogenesis, cardiovascular disease and cancer. In the present review, the role and mechanism of MCP-1 in cancer are to be discussed.

## 2. MCP-1 is a key protein in tumor development

Cancer cell heterogeneity within a tumor is well-established due to the acquired mutations, as a result of the selective pressure caused by cell proliferation. Some of these acquired mutations result in the synthesis of cytokines that either activate or deactivate signaling pathways, allowing the cancer cell to escape leukocyte attack or to proliferate faster, leading to a higher survival probability for cancer cells. Consequently, MCP-1, secreted by the cancer cells, results in an advantage for the tumor but a disadvantage for the host, despite the specific signaling pathway involved. For example, MCP-1 expression is induced by IL-1β and regulated by NF-κB and activator protein-1 (AP-1) in renal cell carcinoma and glioblastoma (20,21). MCP-1 is also a downstream molecule of IL-33, which increases tumor metastasis and invasion in esophageal carcinoma cells (22). MCP-1 can also be mediated by the mTOR complex 1 signaling pathway or sushi domain containing 2 in tumor cells (23). A long non-coding RNA LINC01296, termed lymph node metastasis associated transcript 1, activates MCP-1 expression by interacting with hnRNPL and mediating H3K4 trimethylation (24). MCP-1 expression is also mediated by PA28γ, which promotes tumor migration, invasion and angiogenesis (25). In addition, MCP-1 expression is mediated by angiotensin II binding to the angiotensin type 2 receptor and IL-4 in endothelial cells (26,27). Furthermore, TGF-β signaling has been associated with MCP-1 expression in fibroblast cells (28). The aforementioned findings indicate that MCP-1 could be activated by different signaling pathways and contribute to tumor progression (Fig. 2).

MCP-1 and CCR2 are expressed in numerous types of cancer cells (29,30). However, MCP-1 expression may vary in different cancer cell lines that originate from the same organ. For example, MCP-1 has a higher expression level in invasive breast cancer cell lines (e.g., BT594, Hs578T and MDA-MB-231) compared to non-invasive breast cancer cell lines (e.g., MCF7 and T47D) (31).

MCP-1 secretion by cancer cells portends to a poor clinical outcome, due to the induction of both tumor-associated macrophage infiltration and tumor metastasis in several solid tumors [e.g., non-small cell lung cancer (NSCLC), prostate cancer, breast cancer, ovarian cancer, and hepatocellular carcinoma] (32-36). MCP-1 secretion by Schwann cells also portends to a poor clinical outcome, due to the induction of perineural invasion (i.e., the local extension of cancer along nerves) (37). The abnormal stimulation of MCP-1 can be treated with drugs (e.g., minocycline, telmisartan and zoledronic acid), which have been reported to affect glioblastoma stromal cells (38).

Previous findings have demonstrated that the TME has been associated with tumorigenesis due to direct or indirect interaction between surrounding cells (i.e., stromal cells, fibroblasts, endothelial cells, and innate and adaptive immune cells) and tumor cells. The indirect interaction could build a two-way bridge via various cytokines, chemokines, and other factors, including MCP-1 (13,14).

MCP-1 has been associated with tumor development in various manners. For example, i) MCP-1 recognizes and binds directly to CCR2-expressing cancer cells, which encourages tumor growth and invasiveness; ii) MCP-1 recruits monocytes into the tumor, which then differentiate into tumor-associated macrophages (TAMs) encouraging tumor development and angiogenesis; iii) MCP-1 acts directly on endothelial cells to produce endothelial growth factors, which encourages angiogenesis (39); and iv) MCP-1 recruits fibrocytes into the TME and enhances the formation of stroma (40) (Fig. 3). In summary, MCP-1 stimulates activation of various signaling pathways, which promotes tumor growth on the one hand. On the other hand, MCP-1 causes immune-suppression, which encourages tumor growth indirectly. Furthermore, MCP-1 enhances resistance to tumor drugs. MCP-1 expression increases resistance to an antiangiogenic agent, while the MCP-1 inhibitor (mNOX-E36), a L-RAN oligonucleotide chain, restores the sensitivity to the antiangiogenic agent (41).

MCP-1 has been studied mainly in cancer with a high incidence rate (e.g., breast, prostate and lung cancers). In this regard, 24.5% of all new cancer cases in women are due to breast cancer, while 14.1% of all new cancer cases in men are due to prostate cancer, and 11.4% of all new cancer cases in both men and women are due to lung cancer according to the International Agency for Research on Cancer (42). MCP-1 is associated with tumor development in a multi-faceted process and we hypothesized that this multi-faceted process may be analogous in various types of cancer with a high incidence rate. The multi-faceted process of MCP-1 association with tumor development will be subsequently discussed.

*MCP-1 acts on cancer cells directly*. The MCP-1/CCR2 signaling pathway may operate in an autocrine manner to promote tumor development, as some cancer cells secrete MCP-1 and express CCR2 simultaneously. Previous studies (39-41) have addressed specific mechanisms by which MCP-1 has been associated with tumor development.

MCP-1 elevates IL-6 and TNF-α, whose downstream oncogenic signaling pathways involve STAT3 and NF-κB in a hepatocellular carcinoma mouse model. Furthermore, treatment with an MCP-1 specific antibody (Ab) blocks the oncogene, c-MYC, which is downstream of STAT3 and thereby reduces tumor proliferation in a hepatocellular carcinoma mouse model (36). The aforementioned findings suggest that MCP-1 plays a key role in the activation of oncogenes and promotion of tumorigenesis.

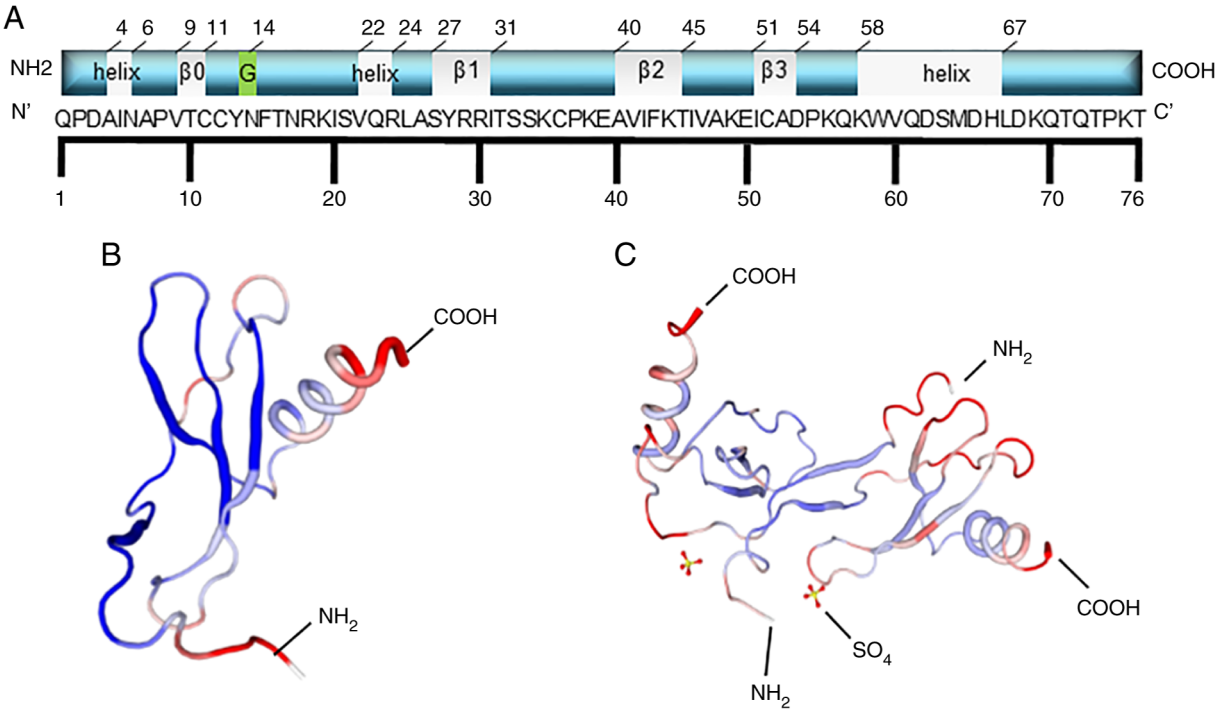


Figure 1. Schematic structural illustration of MCP1. (A) The schematic structural illustration. For all MCPs, N-terminal residues 1-6 are essential for chemoattractant activity, and the first amino acid is necessary for direct receptor binding. MCP-1 is composed of 76 amino acids, and the secondary structure of MCP-1 consisted of one α-helix and four regions of β-sheet (the grey label), including residues 9-11 (β0), residues 27-31 (β1), residues 40-45 (β2), residues 51-54 (β3), which is little different from the data in PDB protein bank. The last one shows that MCP-1 has three α-helix (the grey sections). Residue 14 can be glycosylated (the green section), which can slightly decrease the potency of the chemotactic activity of MCP-1. (B and C) The two forms of secondary structures of MCP-1: (B) is form I and (C) is form P. The former is the single MCP-1 molecule, while the latter is the dimer.

In addition, adipocyte secretion of MCP-1, in the TME, binds to CCR2 on cancer cells and activates the PI3K/Akt/mTOR signaling pathway. The activation of the PI3K/Akt/mTOR signaling pathway induces hypoxia inducible factor-1α, which mediates vascular endothelial growth factor (VEGF)-A expression and thereby stimulates tumor angiogenesis (35,43). The activation of the PI3K/Akt/mTOR signaling pathway by MCP-1 also inhibits autophagy and stimulates tumor proliferation in prostate cancer cells and osteosarcoma cells (30,44,45). MCP-1 also induces Akt activation in a dose-dependent manner (46). In addition to the activation of the PI3K/Akt/mTOR signaling pathway, the c-Raf/MEK/ERK and MAPK signaling pathways play a role in MCP-1-induced tumor migration (47). Furthermore, the IP3-dependent Akt/PKB signaling pathway is associated with MCP-1-induced tumor proliferation and migration (48).

MCP-1 can also induce MMP production in cancer cells and thereby promotes tumor progression (49). MCP-1 enhances the aggressiveness of NSCLC cells by increasing the level of MMP-9 expression *in vitro* (50). MCP-1 induces MMP production by activating the ERK1/2 and p38 MAPK signaling pathways, and upregulates MMP by activating c-Raf/Raf-1, MEK, ERK, MAPK, c-Jun, NF-κB and AP-1 (47,51,52). MMP cleaves cell-to-cell and cell-extracellular matrix adhesion components, which promotes cell detachment and leads to epithelial-mesenchymal transition (EMT) and enhances metastasis (53). In addition, MCP-1 can directly induce EMT by activating the ERK/GSK-3β/Snail signaling pathway (54). Overall, MCP-1 stimulates tumor proliferation and metastasis by activating the MAPK/ERK and ERK1/2-MMP2/9 signaling pathways, respectively (48,55).

In addition, previous studies (30,35,44-46) have found that MCP-1 specifically recognizes the CCR2 receptor and induces a series of signaling pathways that alter cancer cell metabolism. The mechanism involved shows consistency among various tumor types in which MCP1 activates classic signaling pathways, even though the exact mechanism involved remains unclear. Thus, the aforementioned findings suggest that MCP-1 may be a novel target for cancer therapy.

*MCP-1 facilitates endothelial cell angiogenesis*. Excessive angiogenesis is a salient feature of various tumors, which produces a highly unorganized and permeable tumor vasculature compared with that in normal cells. The leaky neo-capillaries within the tumor, not only provide less oxygen/nutrients to the tumor, but also form an abnormal TME promoting tumor development. The endothelial cells are the protagonist during the multi-step process of angiogenesis, and previous studies indicate that MCP-1 interacts with endothelial cells and may therefore be associated with angiogenesis in tumor development (56,57).

MCP-1 downregulates the expression level of TNF superfamily-15 (TNFSF15), which is an inhibitor of neovascularization (58). In addition, elevated MCP-1 expression levels were positively correlated with VEGF expression levels, a potent angiogenic factor (39). MCP-1 also regulates the interaction between cancer cells and endothelial cells *in vitro*, and promotes endothelial cell migration, thereby promoting angiogenesis (57). The binding of MCP-1 to CCR2 activates

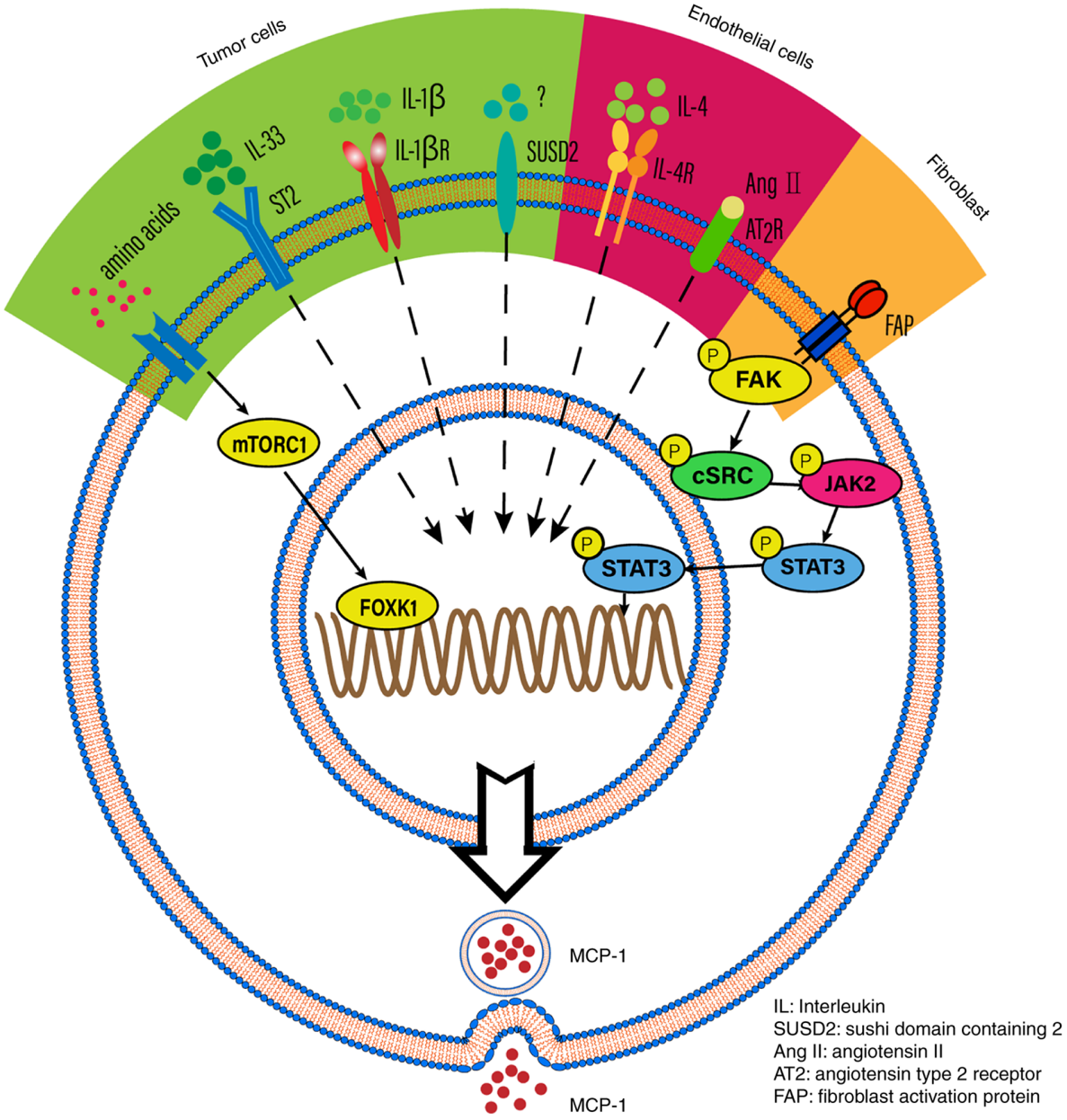


Figure 2. The potential mechanisms that regulate MCP-1 expression. MCP-1 expression is induced by IL-1β in specific tumor cells. MCP-1 is downstream of IL-33, thus IL-33 which binds to its receptor (ST2) may impact on MCP-1 secretion. MCP-1 is also mediated by mTORC1, which is stimulated by amino acids. IN addition, MCP-1 expression is also promoted by SUSD2 in tumor cells. Concerning endothelial cells, angiotensin II and IL-4 can mediate the expression of MCP-1. Fibroblast activation protein can promote MCP-1 expression in cancer-associated fibroblasts. FAP, fibroblast activation protein; IL, interleukin; SUSD2, sushi domain containing 2; AngII, angiotensin II; AT2, angiotensin type 2 receptor; FAP, fibroblast activation protein.

the PI3K/Akt signaling pathway and induces phosphorylation of p38, ERK1/2, Src in endothelial cells *in vitro* (59).

*MCP-1 promotes monocyte/macrophage recruitment in the TME*. In addition to endothelial cells, MCP-1 is also associated with regulating the immune microenvironment in the tumor. Myeloid-derived suppressor cells (MDSCs), as a major regulator of immune responses in cancer, bearing the markers CD11b (CR3A or integrin αM) and Gr-1 [anti-Gr-1 monoclonal (m)Abs recognize epitopes common to Ly6C and Ly6G] (60), infiltrate the tumor tissue under hypoxia, oxidative agents, pro-inflammatory cytokines or nutrient scarcity (39,61). Monocytic MDSCs are derived from circulating Ly6C$^{hi}$ monocytes, originate from either a myeloid or splenic reservoir in a CCR2-dependent manner, and acquire a pro-inflammatory signature that affects lymphocyte activity, proliferation and survival (62,63). In addition, fibroblast activation protein-induced cancer-associated fibroblasts promote the recruitment of MDSCs via the production of MCP-1 (64). Furthermore, MDSC differentiation into TAMs represents one of the major immune cells in the TME in most types of cancer. Blocking the MCP-1/CCR2 axis leads to a notable decrease in TAM abundance (65). TAMs remodel the TME, which promotes EMT and angiogenesis (65), and are divided into two categories, the antitumor M1-like and pro-tumor M2-like TAMs. MCP-1 increases the number of M2 TAMs but decreases the number of M1 TAMs. This also promotes TAM-dependent lymphangiogenesis in bladder cancer (24),

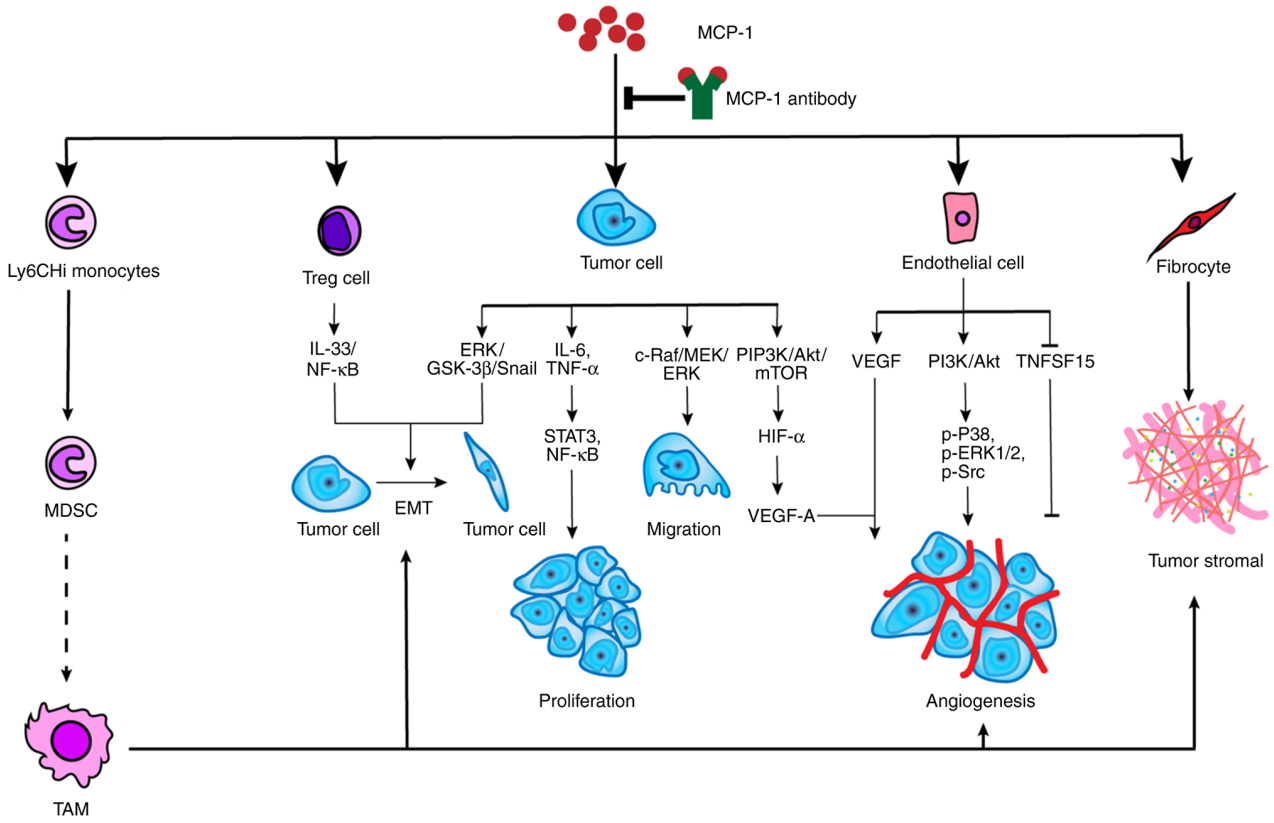


Figure 3. The potential mechanism of MCP-1-promoted tumor development. MCP-1 can not only utilize monocytes, Treg cells, endothelial cells and fibrocytes but also act on tumor directly to affect tumor development. The precise mechanism of MDSC transforming into TAM is not clear. TAM advances tumor development in many respects, including EMT, angiogenesis and tumor stromal formation. Treg cells and tumor cells can induce the process of EMT through IL-33/NF-κB and ERK/GSK-3α/Snail, respectively. MCP-1 facilitates tumor proliferation, migration and angiogenesis through specific pathways, such as ERK/GSK-3β/Snail for migration, and PI3K/Akt/mTOR for angiogenesis. In addition, MCP-1 also promotes tumor angiogenesis by acting on endothelial cells via the PI3K/Akt signaling pathway and suppressing TNFSF15. MCP-1 is also a promoter for fibrocytes that synthesize tumor stromal. Notably, MCP-1 is the engine for tumor development and shutting off the engine will inhibit this process. TNFS15, tumor necrosis factor superfamily-15; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; MCP-1, monocyte chemotactic protein-1; EMT, epithelial-mesenchymal transition; Treg, regulatory T lymphocyte.

which results in the immune escape of tumor cells, initiation of blood vessel growth, and finally the metastasis of tumor cells. A CCR2 antagonist reduces the number of M2 TAMs and production of cytokines (i.e., IL-6, CCL2, KC, G-CSF, MIP-1 and MIP-2), which enhances the efficacy of tumor therapies (66).

Notably, MCP-1 assists in the recruitment of monocytes and their differentiation into macrophages, which suggests that MCP-1 is a key target molecule in tumor development. Furthermore, MCP-1 modulates the progression of mammary tumorigenesis, primarily due to its ability to recruit macrophages to the TME. The loss of MCP-1 expression results in a decline of macrophage markers, and reduces primary tumor volume and delays tumor progression in a triple negative breast cancer model (67).

MCP-1 expression and TAM recruitment demonstrate a positive correlation, while inhibition of MCP-1 activity reduces monocyte infiltration, TAM accumulation and tumor incidence (61). Activation of the MCP-1/CCR2 axis promotes the recruitment of monocytes and TAMs into the TME in several tumor types, including sarcoma and breast cancer (68). Monocyte recruitment into the tumor metastatic site occurs in an MCP-1-dependent manner, and their transformation into macrophages promotes tumor proliferation, metastatic tumor survival/growth, and a poor prognosis in various types of cancer [e.g., breast, prostate, bladder, kidney and NSCLC) (34,41,69). Knockdown of 5'-nucleotidase domain containing 2 notably reduces TAM recruitment via suppression of the MCP-1/CCR2 signaling pathway in colorectal carcinoma (70). Furthermore, as aforementioned, $Tgfbr2^{FspKO}$ improves the level of MCP-1 secretion and enhances tumor progression associated with TAM recruitment, which indicates the MCP-1-dependent attraction of macrophages into the TME depends upon the effects of the surrounding cytokines. By contrast, recent findings showed that MCP-1 recruits and activates macrophages to kill cancer cells in various types of cancer (e.g., gastric and colorectal cancer, and melanoma), and MCP-1 expression was decreased in small cell lung cancer (69).

MCP-1 regulates monocyte attraction and infiltration by the induction of adhesive molecules and cytokines, along with binding to the CCR2 receptor on monocytes. The signaling pathway of MCP-1-induced monocyte/TAM recruitment is not clear, but it has been reported that the JAK/STAT and p42/44 MAPK/c-Jun pathways may be involved in the activation of macrophages (71,72). Furthermore, macrophage infiltration promotes angiogenesis with MCP-1 expression. Elevated MCP-1 expression levels promote both macrophage infiltration and angiogenesis (73). The number of newly formed vascular tubes significantly increases when MCP-1-expressing cancer cells interact with macrophages compared with

Table I. MCP-1 neutralizing antibodies currently available.

| Name | Type | Company name | Time | Application (Refs.) | Remarks (Refs.) |
|---|---|---|---|---|---|
| 2H5 | Mouse MCP-1 antibody | eBioscience/ BD Biosciences | 1994 | Umbilical cord Mesenchymal stem cells (84) | Cross-reacted with human MCP-1 (85) |
| 5D3-F7 | Recombinant human MCP-1 antibody | BD Biosciences | 1994 | Human sarcoma (86) | |
| AF-479-NA | Mouse MCP-1 antibody | R&D systems | 2000 | Human gastric cancer (87); breast cancer (88) | Cross-reacted with human MCP-1 (87) |
| MAB479 | Mouse MCP-1 antibody | R&D systems | 2003 | Mouse lung cancer (89) | |
| MAB679 | Human MCP-1 antibody | R&D systems | 2004 | Human clear cell renal cell carcinoma (90) | |
| MAB279 | Human MCP-1 biotinylated antibody | R&D systems | 2004 | Human glioblastoma multiforme (91); human breast cancer cell line MCF10CA1d (CA1d) (78) | |
| AF-279-NA | Human MCP-1 antibody | R&D systems | 2004 | Human lung cancer (92) | |
| CNTO888/ carlumab | Human MCP-1 antibody | Centocor Inc. | 2007 | Human prostate cancer (33) | |
| C1142 | Mouse MCP-1 antibody | Centocor Inc. | 2007 | Prostate cancer (93) | |

MCP-1-expressing cancer cells only (41), indicating that MCP-1 promotes angiogenesis via macrophage attraction.

*MCP-1 recruits regulatory T lymphocytes (Tregs) into the TME.* In addition to monocytes/macrophages in the TME, MCP-1 also affects the activity of Tregs. MCP-1 recruits Treg lymphocytes into the TME via the IL-33/NF-κB signaling pathway, which promotes tumor development, whereas, Treg lymphocyte recruitment into the TME fails to occur in the absence of MCP-1 (22,74). MCP-1 also recruits Treg lymphocytes into the TME via the downregulation of TNFSF15, whereby TNFSF15 levels are inversely correlated with the degree of $CD4^+CD25^+FOXP3^+$ Treg lymphocyte infiltration (58). In this regard, there is a reduction of $CD4^+$ $FOXP3^+$ Treg lymphocytes and induction of $CD8^+$ T-lymphocyte cytotoxicity, which restricts tumor growth in a CCR2 knockout mouse lung adenocarcinoma model (75). Similarly, blocking of the MCP-1/CCR4 signaling pathway using a CCR4 antagonist inhibits tumor growth and prolongs survival time in patients with head and neck squamous cell carcinoma (HNSCC) (76). The aforementioned findings indicate that MCP-1 recruits Treg lymphocytes into the TME and reduces the antitumor responses of effector T lymphocytes by binding to MCP-1 receptors (Fig. 3).

## 3. MCP-1 is a potential target for tumor therapy

MCP-1 directly or indirectly mediates changes in the tumor, which promotes tumor progression and metastasis. This suggests that blocking the effects of MCP-1 may serve as a novel anticancer therapeutic strategy. MCP-1 target therapy is divided into two categories, MCP-1 inhibitor and MCP-1 neutralizing Ab. The latter is described, as it has a prospective clinical application (Table I).

Previous studies have indicated that MCP-1 overexpression occurs in various cancer cells (34,66). The blocking of the MCP-1/CCR2 signaling pathway inhibits tumor progression (29,46) and weakens recruitment of M2 macrophages and Tregs, which activates antitumor $CD8^+$ T lymphocytes (32,66). MCP-1 neutralizing Ab (CNTO888) treatment delays tumor growth in an *in vivo* xenograft mouse model of prostate cancer (33) and inhibits the dissemination of estrogen-dependent breast cancer induced by macrophages in a zebrafish model (77). MCP-1 target therapy inhibits the development of hepatocellular carcinoma by blocking the oncogenic IL-6 and TNF-α signaling pathways and activating NK cells in the TME (36). Treatment with anti-MCP-1 mAb does not change the total leukocyte recruitment, but does change neutrophil and M2 macrophage recruitment (32). However, MCP-1 neutralizing Ab treatment inhibits cancer cell proliferation *in vitro,* but not *in vivo* (78). The reason for this difference may be due to the fact that the MCP-1 neutralizing mAbs cannot be delivered to the TME *in vivo* at an effective concentration for drug efficacy.

In addition, MCP-1 target therapy and other antitumor therapy can play a synergistic effect. Anti-MCP-1 administration enhances the effect of cisplatin by suppressing colony formation in HNSCC *in vitro* (79), and MCP-1 inhibitor (mNOX-E36) therapy enhances bevacizumab inhibition in tumor progression (41).

Furthermore, since the N-terminal but not C-terminal is essential for all MCP signaling and chemotactic activity, this domain may be a potential target. As early as 1999, Van Coillie identified the N-terminal truncated MCP-2 (the 6th amino acid serine to 76th amino acid proline) can block the activity of intact MCP-1 (80), as the homology sequences between MCP-1 and MCP-2 is 62% (17,80).

## 4. Conclusion

MCP-1 acts as an engine that drives tumor progression and therefore may serve as an effective therapeutic target. In this

regard, the CCR2 blockade (i.e., the MCP-1 receptor) shows promise due to the antitumor effects it exerts (29,36,66,75). However, MCP-1 is secreted not only by tumor cells, but also by stromal cells surrounding the tumor parenchyma (81). MCP-1 neutralizing Ab treatment may be more advantageous as a clinical strategy than CCR2 blockade for three main reasons as indicated below.

First, MCP-1 binds to other CC-chemokine receptors (besides CCR2), which promote tumorigenesis. Therefore, MCP-1 neutralizing Ab treatment may block not only the tumorigenic effects of CCR2 binding, but also the tumorigenic effects of the other CC-chemokine receptor binding. Second, MCP-1 neutralizing Ab treatment reduces MCP-1 serum levels, which decreases systemic inflammation and contributes to a favorable prognosis (82). Third, drug development based on MCP-1 neutralizing Ab treatment appears to have more promise in delivering a highly efficient therapeutic treatment.

However, the use of MCP-1 neutralizing Ab requires further research. Traditionally, it has been argued that cessation of anti-MCP-1 treatment led to a rebound of MCP-1 and a notable increase in metastases (83). It points out the issue of utilizing the MCP-1 neutralizing Ab correctly, which will improve the side effects. Antitumor drugs may be selected according to tumor types, and observe the principle of concomitant drugs and full course of treatment. Certainly, it is on the premise of the development of an ideal antibody of MCP-1.

In conclusion, further research is required to reveal the role of MCP-1 in cancer progression in order to identify the most beneficial target and design the most effective therapeutic strategy.

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**Availability of data and materials**

Not applicable.

**Authors' contributions**

LW was the major person in charge of the organizing and writing of the revised manuscript during the peer review process. JL searched the associated papers, interpreted the information and wrote the draft. JT searched the associated papers, interpreted the information and wrote the outline of the draft. NL was in charge of writing, interpreting and overseeing the manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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