CCL2/CCR2 signaling pathway in tumorigenesis and metastasis (Review)

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Abstract. C-C motif chemokine ligand 2 (CCL2) is associated with tumorigenesis and cancer progression. C-C motif chemokine receptor 2 (CCR2) is the main receptor of CCL2. The present review aimed to summarize the role of the CCL2/CCR2 signaling axis in tumorigenesis and metastasis. The CCL2/CCR2 signaling axis exerts antitumor activities by activating the immune response and immunosurveillance, recruiting neutrophils to destroy cancer cells, inducing tumor-infiltrating lymphocytes to infiltrate tumor tissue, and interfering with the function of T lymphocytes and dendritic cells. In addition, it promotes tumor progression by enhancing cell proliferation, migration and invasion, inducing epithelial-mesenchymal transition, stimulating the production of vascular endothelial growth factor and tumor angiogenesis, recruiting tumor-related cells to the tumor niche and remodeling the tumor microenvironment to render it immunosuppressive. The dual effect of the CCL2/CCR2 signaling axis depends on the specific conditions and stage of tumor metastasis.

Contents

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1. Introduction

C-C motif chemokine ligand 2 (CCL2), is a key member of the CC subfamily of chemokines, which was purified and identified in 1989 by Yoshimura *et al* (1). CCL2 exerts chemotactic effects on monocytes, macrophages and T lymphocytes (2), and is secreted by activated cells through autocrine or paracrine methods. Cytokines in the tumor microenvironment (TME), including TNFα, lipopolysaccharide, IL-1, IL-6 and transforming growth factor-β (TGF-β), stimulate tumor cells to produce CCL2 (2). C-C motif chemokine receptor 2 (CCR2), the main receptor of CCL2, is a G protein-coupled receptor expressed in both immune and tumor cells (2-4). It plays an essential role in different aspects of tumor cell biology, including the regulation of proliferation, angiogenesis, immune response and migration of cells in inflammatory environments (5). CCL2 exerts its biological effects mainly by combining with CCR2 (2,6).

Studies have found that numerous types of tumor cells, including myeloma, breast cancer, prostate cancer and melanoma cells, express CCR2 and secrete high levels of CCL2 (7-9). CCL2 thus promotes tumor cell proliferation and survival through autocrine or paracrine pathways, participating in the regulation of tumor immune tolerance, inducing tumor angiogenesis, and promoting tumor invasion and metastasis (10).

CCL2 signaling is closely associated with tumor growth and progression (11,12). The CCL2/CCR2 signaling axis serves diverse roles in the initiation and progression of cancer by regulating tumor-associated angiogenesis, recruiting tumor-associated immune cells to promote tumor growth, activating tumor-specific immune responses and stimulating tumor cell proliferation (13-15).

The 'seed and soil' hypothesis posited that, during metastasis, tumor cells not only adapt to the recipient microenvironment but also actively remodel it to facilitate

colonization (16,17). The chemokine-receptor crosstalk represents a pivotal research frontier in tumor metastasis biology. Its multifaceted roles include tumor cell proliferation, chemoresistance, migratory/invasive capacity and organotropic metastasis, alongside regulatory effects on angiogenesis and lymphangiogenesis. Growth factors, circulatory hypoxia, antitumor drugs and radiation therapy stimulate tumor cells to secrete more CCL2, induce the establishment of an immunosuppressive TME through the CCL2/CCR2 signaling axis, and promote tumor progression and metastasis. de Visser reviewed the importance of the TME in every stage of cancer progression, including tumor initiation, progression, invasion, infiltration, metastasis, diffusion and growth (18). TME represents a highly complex and dynamic ecosystem, primarily composed of three major cellular components: myeloid cells (including tumor-associated macrophages [TAMs], myeloid-derived suppressor cells [MDSCs], dendritic cells [DCs], and tumor-associated neutrophils [TANs]), lymphoid cells (such as T cells, B cells, natural killer [NK] cells, and innate lymphoid cells [ILCs]), and stromal components (cancer-associated fibroblasts [CAFs] and endothelial cells) (18). While these host-derived cells were historically dismissed as passive bystanders in tumorigenesis, emerging evidence highlights their key roles in driving cancer pathogenesis (18). The cellular architecture and functional phenotype of the TME exhibit pronounced heterogeneity dictated by primary tumor location, cancer cell-intrinsic properties, disease stage and patient-specific factors (18). Deciphering the crosstalk among tumor cell-autonomous signals, microenvironmental cues and systemic regulatory networks is key for the rationale-driven design of next-generation cancer therapeutics. The present study summarized the role of the CCL2/CCR2 signaling axis in tumor progression and metastasis.

2. Antitumor effect of the CCL2/CCR2 signaling axis

CCL2/CCR2 signaling axis activates the immune response and immunosurveillance of tumor cells. CCL2 orchestrates antitumor immune responses by promoting immune cell recruitment and surveillance. *In vitro* studies have shown that diverse tumor cell lines chemoattract $CD8^+$ and $CD4^+$ T lymphocytes through CCL2 secretion (19,20). For example, in a previous study of nude mice, ovarian cancer cells engineered to express CCL2 induced robust monocyte infiltration at the injection site, resulting in localized tumor growth inhibition (20) Clinically, plasma CCL2 levels in patients with pancreatic cancer have been shown to be negatively correlated with tumor proliferation markers (21). In addition, in colorectal cancer preclinical models (22-24), the targeted modulation of tumor-derived chemokines enhances immune cell infiltration and suppresses tumor progression.

CCL2/CCR2 signaling axis recruits neutrophils and has a destructive effect on cancer cells. CCL2 serves a pivotal role in the metastatic cascade, particularly during epithelial-mesenchymal transition (EMT). Preclinical studies have shown EMT-induced cancer cells upregulate CCL2 expression (22-25), which in turn attracts neutrophils to the TME. While neutrophils are traditionally associated with tumor-promoting inflammation, evidence has highlighted their potential to exert cytotoxic effects against cancer cells in specific contexts (26-28). Tumor-associated neutrophils (TANs) have two phenotypes. 'N2' is known as a pro-tumorigenic phenotype, as it exerts a pro-tumorigenic effect at the primary site by secreting oncogenic factors, promoting primary tumor growth and angiogenesis, increasing extracellular matrix degradation and suppressing immune responses (29-33). 'N1' is an antitumorigenic phenotype. These neutrophil phenotype switches are contingent on TGF-β signaling, as the neutralization of TGF-β has been shown to induce a shift from 'N2' pro-tumorigenic to 'N1' antitumorigenic neutrophil states (31). Tumor-entrained neutrophils suppress lung metastatic seeding via H_2O_2-dependent cytotoxic mechanisms, with tumor-derived CCL2 serving as a key mediator of granulocyte colony-stimulating factor-stimulated neutrophil recruitment for optimal anti-metastatic function (28). A preclinical study of mouse breast cancer models further demonstrated that neutrophils accumulate in the lungs prior to the arrival of metastatic cells, establishing a pre-metastatic surveillance niche (28).

TANs exhibit dual roles in cancer progression, with N1-polarized TANs exerting antitumor effects and N2-polarized TANs promoting tumorigenesis. In hepatocellular carcinoma (HCC), cancer-associated fibroblasts (CAFs) secrete cardiotrophin-like cytokine factor 1 (CLCF1), which drives tumor stemness via C-X-C motif chemokine ligand 6/TGF-β and recruits immunosuppressive N2 TANs, forming a pro-tumorigenic feedback loop. Conversely, in lung cancer, C-X-C chemokine receptor type 2 (CXCR2) inhibition shifts TANs toward an N1 phenotype, decreasing immunosuppressive factors (arginase 1, TGF-β) and enhancing $CD8^+$ T-cell activity, thereby improving antitumor immunity and chemotherapy response (34,35). These findings highlight TAN polarization as a critical determinant of tumor fate, suggesting therapeutic strategies targeting N2 TANs (such asCLCF1/ERK inhibition in HCC) or promoting N1 TANs (for example via CXCR2 blockade in lung cancer) may modulate the TME.

CCL2/CCR2 signaling induces tumor-infiltrating lymphocytes (TILs) to infiltrate tumor tissue, and interfere with the function of T lymphocytes and dendritic cells with anti-cancer effects. TILs serve as both prognostic biomarkers in cancer progression and key effectors in immunotherapeutic responses (26). The CCL2/CCR2 signaling axis orchestrates TIL recruitment to the TME, while CCL2 modulates the anti-cancer functions of T lymphocytes and dendritic cells, thereby potentiating antitumor immunity (26).

A previous *in vitro* study has demonstrated that CCL2 triggers γδ T-cell chemotaxis toward tumor-derived extracts, a process abolished by CCL2-neutralizing antibodies (36). Mechanistic investigation using T-cell receptor Δ chain knockout and $CCR2^{-/-}$ murine models have revealed that the loss of γδ TILs accelerates tumor progression *in vivo*, implicating a protective role for the CCR2/CCL2 axis in recruiting antitumor γδ T cells (36). Human tissue analyses (37-39) have further shown that $V\delta1^+$ (but not $V\delta2^+$) γδ T cells selectively express CCR2 and exhibit CCL2-dependent migration, with CCR2 expression dysregulated across various types of malignancies, including lung, prostate, liver and breast cancer. These findings highlight the tumor-suppressive function of CCL2/CCR2 signaling in orchestrating γδ1 T-cell infiltration,

suggesting potential therapeutic strategies targeting Vδ1$^+$ subsets in cancer immunotherapy. The natural killer (NK) group 2D receptor is critical for immune surveillance against malignancy (40). In a murine model of metastatic liver cancer, p53 reactivation has been shown to induce CCL2 expression in tumor cells, which is key for robust NK cell recruitment to the TME (41). Mechanistically, p53-mediated CCL2 secretion establishes a chemotactic gradient that enhances NK cell infiltration, thereby facilitating tumor elimination in an NK cell-dependent manner (42). Restoring p53 function in tumor cells also upregulates chemokines with NK cell-recruiting potential, although the antibody-based neutralization of CCL2 abrogates NK cell accumulation in senescent tumors and impairs their clearance, highlighting the role of CCL2 in anti-cancer immunosurveillance (42-45).

3. Pro-tumor effect of the CCL2/CCR2 signaling axis

CCL2/CCR2 signaling affects tumor cell proliferation, migration and invasion. Enhanced cell motility and survival are hallmarks of metastatic tumor cells (46). The CCL2/CCR2 signaling pathway governs tumor cell chemotaxis, migratory capacity, survival and proliferation, thereby facilitating oncogenic progression in both hematological malignancies and solid tumors (47-49). The CCL2/CCR2 signaling axis can activate downstream pathways, including the PI3K/AKT, SMAD family member 3, P42/44 MAPK and ERK1/2-MMP2/9 pathways, as well as the protein kinase C-dependent protein tyrosine phosphorylation pathway to affect the proliferation, invasion and infiltration of tumor cells (50-52).

CCL2 promotes chondrosarcoma cell migration by upregulating MMP9 expression and engaging CCR2, thereby inhibiting Ras/Raf-1/MEK/ERK and NFκB signaling cascades (53). In HCC cell model, CCL2/CCR2 engagement triggers focal adhesion kinase tyrosine phosphorylation at Y397, promoting the recruitment of Src family kinases and activation of MMP2/9 through the ERK1/2 signaling cascade (54). Concurrently, calcium ion flux mediated by CCR2 activates the calcineurin-nuclear factor of activated T cells pathway, upregulating MMP9 transcription and enhancing extracellular matrix degradation (55). Sustained CCL2 secretion also polarizes tumor-associated macrophages (TAMs) toward the M2 phenotype, fostering a pro-inflammatory milieu rich in IL-6 and TNF-α that supports cancer cell clonal expansion (56-59). This multifaceted signaling network has been implicated in metastatic progression in multiple types of cancer, including cervical and breast malignancy (56,58). In breast cancer, the CCL2/CCR2 axis regulates cellular motility and survival, thereby driving metastatic dissemination (60,61). Similarly, in prostate cancer, CCL2/CCR2 signaling governs proliferation, apoptosis resistance and invasive potential (62). In bladder cancer, the activation of this axis enhances migration and invasion via protein kinase C activation and tyrosine phosphorylation, independent of its effects on cell proliferation (63). Blockade of CCL2/CCR2 signaling markedly impairs the bone marrow homing of multiple myeloma cells, underscoring its role in hematological malignancy metastasis (64). In nasopharyngeal carcinoma (NPC), CCL2/CCR2 signaling promotes metastasis via ERK1/2-MMP2/9 pathway activation (65). In colorectal cancer, alcohol exposure upregulates CCL2/CCR2 signaling via the glycogen synthase kinase 3β/β-catenin pathway, facilitating metastatic progression (66). Epithelial ovarian cancer exploits CCL2/CCR2 signaling to promote peritoneal dissemination, as demonstrated by the enhanced migration and adhesion of ovarian cancer cells following CCL2 stimulation, a process mediated by the P38 MAPK pathway (67,68).

The CCL2/CCR2 signaling pathway drives the proliferation and migration of acute myeloid leukemia cells, as demonstrated by *in vitro* and *in vivo* studies (69). In glioblastoma, tumor-secreted CCL2 orchestrates monocyte recruitment, establishing a pro-tumorigenic microenvironment that fosters neoplastic growth (70). Leveraging this mechanistic insight, preclinical investigation have explored CCR2 antagonists as novel antitumor agents. For example, the pharmacological blockade of CCR2 in lung adenocarcinoma A549 cells attenuates their migratory and invasive capabilities (Fig. 1; Table I) (71).

CCL2/CCR2 signaling axis induces EMT. EMT is the initial step of tumor metastasis, and is involved in the progression and metastasis of various types of cancer (72,73). The CCL2/CCR2 signaling axis promotes EMT in liver cancer through MMP2 (74). There is a growing body of data describing a direct stimulatory effect of CCL2 on tumor epithelial cells (8,75). Notably, interruption of the CCL2/CCR2/STAT3 pathway can inhibit the EMT and migration of prostate cancer cells, inhibiting the progression and metastasis of prostate cancer (75). Furthermore, the TME enhances bladder cancer metastasis by modulating estrogen receptor (ER)β/CCL2/CCR2 EMT/MMP9 signaling following mast cell recruitment (76). The CCL2/CCR2 pathway induces the invasion and EMT of HCC *in vitro* by activating the Hedgehog pathway (Fig. 2) (77).

CCL2/CCR2 signaling stimulates the production of vascular endothelial growth factor (VEGF), and promotes tumor angiogenesis and metastasis. Tumor angiogenesis requires the production of angiogenic factors by tumor cells and stromal components. CCL2 directly promotes angiogenesis via the activation of CCR2-expressing vascular endothelial cells (78-80). Concurrently, the CCL2/CCR2 signaling axis enhances vascular permeability, facilitating efficient extravasation of tumor cells and metastatic niche formation (81). Human endothelial cells express CCR2, which promotes tumor angiogenesis and progression after binding to CCL2. Several clinical studies have shown that CCL2 may be a biomarker of tumor angiogenesis (82-84). The activation of the CCL2/CCR2 signaling axis in the TME promotes tumor angiogenesis (83). CCL2 directly interacts with CCR2 on the surface of endothelial cells, resulting in increased vessel sprouting and angiogenesis (84). As a chemokine produced in abundance by certain types of tumor, such as hepatocellular carcinoma (HCC), glioblastoma, and Small Cell Lung Cancer (SCLC) (85), it can also directly promote tumor progression. Therefore, therapy using MCP-1 antagonists in combination with other angiogenesis inhibitors may suppress tumor growth (86).

In contrast to earlier assumptions, emerging evidence has indicated that tumor vascular endothelial cells lack

Table I. C-C motif chemokine ligand 2/C-C motif chemokine receptor 2 axis affects the proliferation, migration and invasion of tumor cells.

Cell type	Function	Regulatory factors	(Refs.)
Chondrosarcoma	Enhances migration	Increases MMP9 expression, inhibits Ras, Raf-1, MEK, ERK and NFκB signaling pathways	(12)
Hepatocellular carcinoma	Induces migration and invasion	Activated by tyrosine phosphorylation of focal adhesion components, and dependent on MMP2 and MMP9	(6)
Breast cancer	Regulates motility and survival	Increases phosphorylation of Smad3 and P42/44 MAPK proteins; activates SRC and PKC	(14,15)
Prostate cancer	Regulates cell proliferation, apoptosis, migration and invasion	Activates JAK2/STAT3, PI3K/AKT and MAPK	(46)
Bladder cancer	Mediates cell migration and invasion	PKC activation and tyrosine phosphorylation	(48)
Multiple myeloma	Increases bone marrow homing	N/A	(47)
Nasopharyngeal carcinoma	Promotes metastasis	Activates ERK1/2-MMP2/9 pathway	(49)
Colorectal cancer	Promotes metastasis	Causes an initial cytosolic accumulation of β-catenin and subsequent nuclear translocation	(50)
Epithelial ovarian cancer	Promotes peritoneal metastasis	Induces the P38 MAPK pathway	(51)
Acute myeloid leukemia	Promotes proliferation and migration	Activates the GPCR-PKC-PLC signalling cascade and downstream p38 MAPK/NF-κB pathways to drive cellular proliferation and migration	(52)
Glioblastoma	Promotes tumor growth	Polarizes toward an M2 immunosuppressive, pro-angiogenic phenotype	(53)
Lung adenocarcinoma (A549)	Promotes motility and invasiveness	Upregulates MMP9 expression	(54)

PKC, protein kinase C; GCPR, G protein-coupled receptor; PLC, phospholipase C; N/A, not available.

CCR2 expression (87,88). Instead, CCL2 drives angiogenesis indirectly by recruiting TAMs and increasing VEGF-A production in these cells (89-92). In addition, CCL2 enhances cancer cell autonomous VEGF secretion, further contributing to neovascularization. In melanoma, this axis is amplified by autocrine/paracrine loops, wherein CCL2 and its receptor CCR2 are co-expressed (93,94). AM-derived TNFα and IL-1α synergize with VEGF to promote endothelial cell activation, thereby accelerating early-stage tumor angiogenesis and growth (9).

CCL2/CCR2 pathway recruits various tumor-related cells to the tumor niche and remodels the TME to create an immunosuppressive TME. The TME is a dynamically complex ecosystem, where inflammatory networks composed of immune cells and their secretory products influence cancer biology and progression (95). Chemokine-chemokine receptor interactions are key to recruiting inflammatory cells into the TME, with CCL2 serving as a key driver of inflammatory monocyte accumulation (96). Inflammatory monocytes exhibit high expression of CCR2 (26), while other CCR2-expressing leukocytes, including $CD8^+$ effector T cells and $CD4^+$ regulatory T cells (Tregs) (19,97) and myeloid-derived suppressor cells (MDSCs) (98), are enriched in inflamed tumor tissues. The CCL2/CCR2 pathway orchestrates metastatic microenvironment formation, exerting pro-tumorigenic and pro-metastatic functions in numerous types of cancer (99,100).

In sarcoma and breast cancer, the CCL2/CCR2 axis mediates the recruitment of TAMs and MDSCs to the TME (89). T cells infiltrate tumors in an antigen-specific manner, with IFN-γ secreted by early-invading T cells inducing tissue macrophages to increase CCL2 expression (101,102). This creates a positive feedback loop wherein CCL2 recruits additional T cells and macrophages via CCR2 signaling, enhancing immune cell infiltration. CCR2 expression is detectable in tumor-infiltrating immune cells, supporting the role of active chemotactic recruitment (101,102). In NPC, this mechanism is exemplified by T cell-derived IFN-γ activating macrophages to secrete CCL2, thereby amplifying T-cell and macrophage accumulation via the CCL2/CCR2 pathway (103).

CAFs, as a key component of the TME, represent activated fibroblast populations that impact stromal compartment remodeling within the TME via collagen deposition and MMP secretion (104). CAFs constitute one of the most prevalent cell types in the tumor stroma (105), and evidence has highlighted their tumor-promoting functions, including accelerating tumor proliferation, facilitating metastatic progression and shielding tumors from therapeutic agent penetration (106-108).

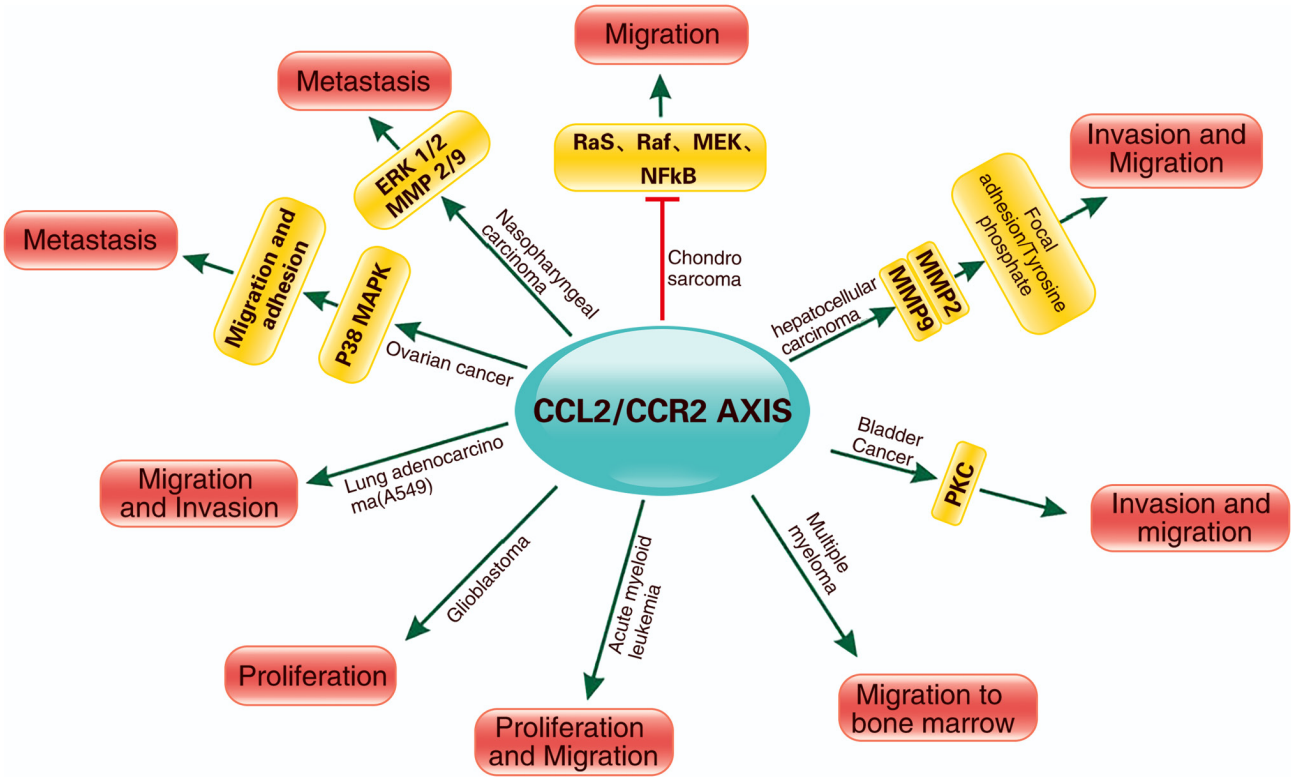

Figure 1. Role of CCL2/CCR2 axis in tumor cells. CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; PKC, protein kinase C.

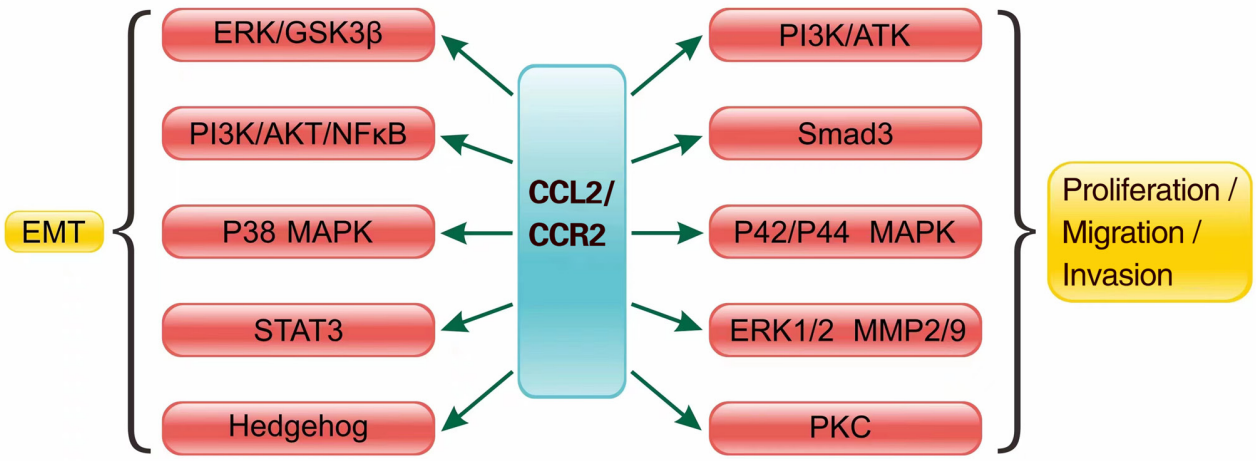

Figure 2. Signaling pathways associated with CCL2/CCR2. CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; PKC, protein kinase C; EMT, epithelial-mesenchymal transition.

Accumulating evidence has highlighted the crosstalk between CAFs and immunosuppressive cell lineages, which is primarily due to the immune-modulatory functions of CAFs (109-111). CAFs secreting CCL2 facilitate the recruitment of $CCR2^+$ monocytes from the bloodstream into the TME, where direct cell-cell interactions drive monocyte differentiation into MDSCs. CAF-educated MDSCs suppress T-cell proliferation via upregulation of NADPH oxidase 2 and indoleamine 2,3-dioxygenase 1, leading to excessive reactive oxygen species production that inhibits immune effector function (Fig. 3) (112).

Crosstalk with cancer cells drives CCL2 upregulation in CAFs, which contributes to metastatic niche establishment during early tumor progression and modulates broader tumor functionality (113-118). In a murine liver tumor model, fibroblast STAT3/CCL2 signaling has been shown to enhance MDSC recruitment, thereby promoting tumor growth (119). In addition, the CCL2/CCR2 signaling pathway facilitates early breast cancer survival and invasion via a fibroblast-mediated mechanism (120).

A previous study demonstrated that discoidin domain receptor 1 (DDR1) orchestrates an immunosuppressive TME by activating CAFs to secrete CCL2 and IL-6. This signaling axis exhibits dual regulatory effects by recruiting immunosuppressive cells, including MDSCs and TAMs, and facilitating

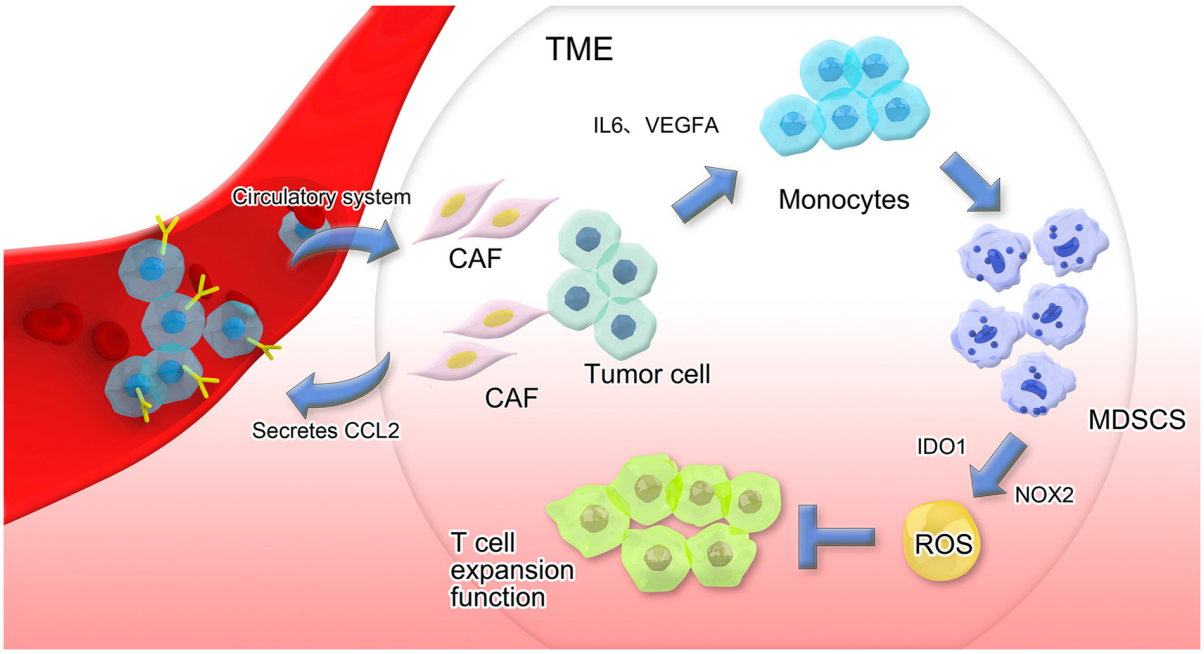

Figure 3. Interaction between the CCL2/CCR2 signaling axis and CAFs in the TME. CAFs secreting CCL2 promote the migration of CCR2-expressing monocytes from the blood circulation to the TME and directly interact with them to promote their differentiation into MDSCs. CAF-induced MDSCs inhibit T-cell proliferation by upregulating NOX2 and IDO1 to generate excess ROS. CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CAF, cancer-associated fibroblast; TME, tumor microenvironment; MDSC, myeloid-derived suppressor cell; NOX2, NADPH oxidase 2; IDO1, indoleamine 2,3-dioxygenase 1; ROS, reactive oxygen species.

extracellular matrix remodeling through enhanced collagen deposition and MMP9 activation. These findings demonstrate the key role of the DDR1/CCL2/IL-6 pathway in CAF-mediated immunosuppression, providing a potential therapeutic strategy to target tumor fibrosis and immune evasion (121,122).

CCL2/CCR2 pathway recruits TAMs and promotes the M2 polarization of macrophages. CCL2 primarily regulates the directional migration and invasive infiltration of reticuloendothelial system cells, with a focus on monocyte/macrophage phenotypes (123). CCL2 induces monocytes to exit the bloodstream and extravasate into peripheral tissue (71), where they differentiate into tissue-resident macrophages. The CCL2/CCR2 signaling pathway has been implicated in recruiting macrophages in various types of human cancer, including those originating in the bladder, cervix, ovary, lung and breast (124-127). TAMs, a major component of infiltrating inflammatory cells, are regulated by the CCL2/CCR2 pathway through a macrophage-dependent mechanism sustained by positive feedback loops (61,128). As a key chemokine system mediating blood cell recruitment, particularly macrophages, into tissues (11,128-130), CCL2/CCR2 signaling drives tumor progression. M2-polarized TAMs influence tumor progression and metastasis (131), and CCL2 secretion recruits TAMs that mediate metastatic phenotypes in ER-negative breast cancer (64).

TAMs drive prostate cancer metastasis via activation of the CCL2/CCR2 signaling pathway (132). Phenotypically, tumor-infiltrating macrophages can be tumor-supportive (M2) or function in tumor immune surveillance (M1). TAMs of the M1 type lead to a better prognosis, whereas TAMs of the M2 type lead to a poorer prognosis. Tumors associated with M2-type TAMs include breast, ovarian and prostate cancer (133-135). TAM recruitment is dependent on the CCL2/CCR2 signaling axis and the formation of a tumor-supportive microenvironment depends on altered cellular dynamics following the interaction of CCL2, T cells and monocytes (136).

TAMs serve a pivotal role in driving hormone resistance in prostate cancer cells (137). Within the prostate TME, M2-polarized TAMs exert pro-tumorigenic effects. Previous studies (78,138) employed a PC3 cell xenograft model to show that CCL2 increases *in vivo* prostate tumor growth and metastasis by enhancing TAM recruitment and angiogenesis. Investigations (139,140) have also revealed that M2-phenotype TAMs influence cancer progression and metastasis; in human lung cancer, CCL2/CCR2 signaling promotes tumor cell proliferation, migration and M2 polarization of TAMs (131). In pancreatic ductal adenocarcinoma, the CCL2/CCR2 axis recruits TAMs to establish an immunosuppressive TME (141). Conversely, anti-CCL2 antibody treatment in breast cancer xenograft models has been shown to diminish macrophage infiltration and tumor growth (142,143).

The CCL2/CCR2 pathway is indispensable for monocyte/macrophage recruitment. The therapeutic interruption of this pathway suppresses inflammatory monocyte recruitment, TAM infiltration and M2 polarization, thereby reversing the immunosuppressive state of the TME and activating antitumor $CD8^+$ T-cell responses (39). Platelet-derived growth factor-BB-mediated autocrine signaling drives CCL2 secretion, which recruits macrophages via the CCL2/CCR2 axis to facilitate lung cancer cell invasion (144). Targeting CCL2/CCR2 signaling in tumor-infiltrating macrophages has emerged as a promising therapeutic strategy for HCC (145).

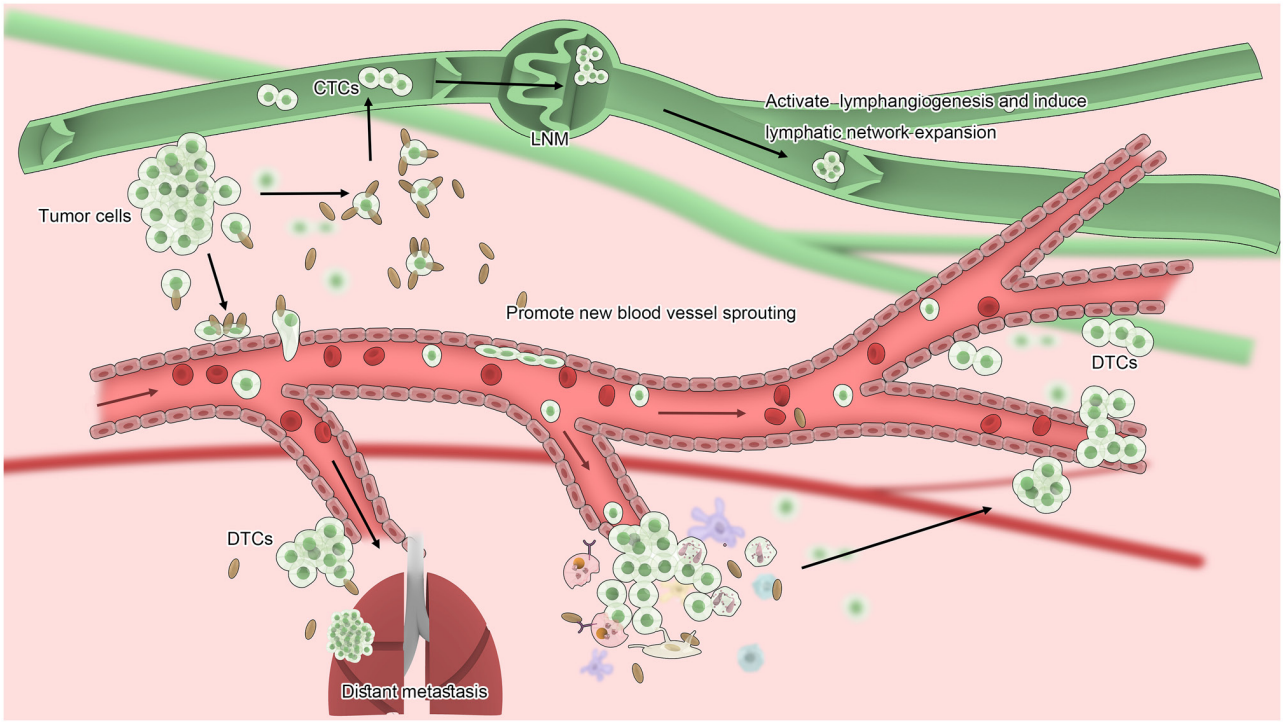

Figure 4. Role of CCL2/CCR2 signaling pathway in the dynamic process of tumor metastasis. In the primary tumor site, the CCL2/CCR2 signaling axis promotes tumor cell survival, proliferation, invasion and migration. The CCL2/CCR2 signaling pathway is involved in constructing the pre-metastatic niche, which mainly involves inflammation, immune suppression, angiogenesis/vascular permeability, lymphangiogenesis, organ tropism and reprogramming. In the circulatory system, the CCL2/CCR2 signaling axis increases vascular permeability and enhances the permeability of CTCs. In addition, this pathway can stimulate lymphangiogenesis, induce lymphatic network expansion and promote lymphatic metastasis. The CCL2/CCR2 signaling pathway can promote EMT. The CCL2/CCR2 signaling pathway is involved in organ-specific metastasis. After reaching the distant metastatic site, CTCs become DTCs. The CCL2/CCR2 axis participates in host immune defense response and exerts antitumor effects. The surviving DTCs enter dormancy. Once a favorable post-metastatic microenvironment is established, DTCs enter a proliferative state, forming metastasis-initiating cells and subsequently developing into metastasis through a series of complex processes. CCL2/CCR2 signaling recruits immune-related CAFs, TAMs, Tregs and MDSCs to construct an immunosuppressive microenvironment, which serves a role in promoting metastasis. CCL2, C-C motif chemokine ligand 2; CCR2, C-C motif chemokine receptor 2; CTC, circulating tumor cell; EMT, epithelial-mesenchymal transition; DTC, disseminated tumor cell; TAM, tumor-associated macrophage; MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell; CAF, cancer-associated fibroblast; LNM, lymph node metastasis.

Preclinical studies (26,93,146,147) have also shown that genetic knockout of CCR2 or pharmacological blockade with CCR2 antagonists inhibits malignant growth and metastasis, decreases postoperative recurrence and improves survival rates. In pancreatic adenocarcinoma, cancer cells exploit chemokine pathways, particularly CCL2/CCR2, to establish an immunosuppressive niche (146). Blocking TAM recruitment inhibits murine breast cancer growth (148). In addition, the JAK2/STAT3 signaling pathway promotes M2-like macrophage polarization, which drives gastric cancer metastasis via EMT (149).

Recruitment of Tregs. Tregs, a specialized subset of T cells, are key for maintaining peripheral self-tolerance and preventing immunopathological responses (150). Tumors exploit immune evasion mechanisms to sustain uncontrolled growth, with high intratumoral Treg abundance contributing to the establishment of immunosuppressive microenvironments. Tregs exert suppressive effects on T-cell proliferation and cytotoxic function (151,152). The infiltration of Tregs in tumors is influenced by both *in situ* generation (mediated by cytokine secretion) and peripheral recruitment (driven by chemokine signaling) (153). Tumor-derived CCL2 has been implicated in inducing Treg migration into the TME. For example, in glioma local immunosuppression is enhanced by selectively recruiting CCL2/CCR2-dependent Tregs (129), while colorectal cancer cells secrete CCL2 that binds to CCR2 on cytotoxic T lymphocytes (CTLs), paradoxically promoting CTL migration to tumors (44).

Recruitment of MDSCs. Tumors employ diverse evasion strategies to circumvent immune recognition and elimination. Intratumoral immunosuppressive MDSCs represent a heterogeneous population of immature myeloid cells originating from bone marrow progenitors (154-156). MDSCs exert multifaceted tumor-promoting activities (157). The CCL2/CCR2 signaling pathway governs the recruitment of myelosuppressive cells to tumor sites. Studies have demonstrated that CCR2 is universally expressed on MDSCs, the primary drivers of tumor immune evasion, and blocking CCL2/CCR2 signaling inhibits MDSC migration and tumor growth facilitated by these cells (31,112,158-160). Collectively, these data demonstrate a key role for the CCL2/CCR2 pathway in regulating MDSC trafficking. CCL2/CCR2 interactions also recruit other immunosuppressive cells, including monocytes, to form a pro-metastatic microenvironment (26,98).

The immunosuppressive Treg-MDSC network drives immune exclusion and immune checkpoint inhibitor (ICI)

resistance. In head and neck squamous cell carcinoma, semaphorin (SEMA)4D blockade using pepinemab disrupts MDSC recruitment while enhancing T-cell infiltration (KEYNOTE-B84 trial) (161). In bladder cancer, gemcitabine/BCG decreases IL-6-mediated MDSC suppression. Prostate cancer subtyping has revealed TGF-β-enriched, immune-excluded tumors (stage I) with a poor ICI response vs. inflamed subtypes (S-IV). Targeting this axis (via SEMA4D inhibition or myeloid modulation) represents a promising therapeutic strategy (162).

4. Discussion

The CCL2/CCR2 signaling pathway serves a central role in shaping the TME by regulating both tumor progression and antitumor immunity (2). Through the activation of the PI3K/AKT, MAPK and EMT pathways (Fig. 2), the CCL2/CCR2 signaling pathway promotes tumor cell proliferation, invasion and metastasis. Paradoxically, it also mediates antitumor effects by recruiting immune cells and activating immunosurveillance mechanisms (143). This dual functionality stems from its ability to recruit diverse immune populations. While MDSCs, TAMs and Tregs establish an immunosuppressive TME that facilitates metastasis, the CCL2/CCR2 pathway simultaneously promotes TIL infiltration and enhances antitumor lymphocyte function (Fig. 4) (163). In melanoma, CCL2/CCR2 signaling drives resistance to BRAF/MEK inhibitors by expanding MDSCs and suppressing $CD8^+$ T cells (164-168). The TNF-related apoptosis-inducing ligand-CCL2 axis further reinforces this resistance by polarizing monocytes toward MDSCs and M2-like macrophages, facilitating tumor progression (169,170).

Melanoma immunogenicity (171) highlights the complex interplay between tumors and immune evasion mechanisms (172). The CCL2/CCR2 axis represents a critical node in this interaction, making its inhibition a potential therapeutic strategy. Preclinical studies (173-175) have demonstrated that targeting this axis, particularly in combination with immunotherapy, may overcome resistance mechanisms and restore antitumor immunity.

The therapeutic targeting of the CCL2/CCR2 axis involves multiple strategies with distinct mechanisms and clinical implications. Small-molecule CCR2 antagonists (such as PF-04136309 and BMS-813160) block immunosuppressive MDSC/TAM recruitment and restore antitumor immunity in preclinical models (164,165,169,176), with ongoing clinical trials (177,178) evaluating their efficacy in combination with chemotherapy or immunotherapy (trial no. NCT03184870). While anti-CCL2 antibodies (carlumab/CNTO-888) have demonstrated partial responses in early trials, compensatory CCL2 upregulation limits their efficacy, prompting the exploration of combination strategies with programmed cell death-1 (PD-1)/CTLA-4 inhibitors to overcome resistance (172). Dual targeting approaches simultaneously inhibiting CCL2 and CCR2 (CCL2-trapping agents and CCR2 antagonists) may prevent microenvironmental bypass mechanisms, particularly in BRAF inhibitor-resistant melanoma (166-168). Furthermore, elevated CCL2/MDSC signatures could serve as predictive biomarkers for patient selection, with studies (179-181) investigating liquid biopsy-based monitoring ($CCR2^+$ exosomes) (170).

The net biological effect of the CCL2/CCR2 axis is fundamentally context-dependent, governed by four intersecting factors: i) Temporal dynamics, where early-phase immune surveillance progressively shifts to late-stage TME remodeling; ii) spatial heterogeneity across distinct tumor niches; iii) immune cell composition ratios, particularly the M1/M2 macrophage equilibrium; and iv) host genetic background, including CCR2 isoform expression patterns. This necessitates identification of the biological threshold where pro-tumor effects supersede antitumor mechanisms. This may be regulated by three factors: i) CCL2 concentration thresholds, ii) specific immune cell infiltration ratio and iii) hypoxia-induced pathway activation states. These mechanistic insight may inform clinical strategies, as evidenced by Phase II trial (182) (trial no. NCT03184870) combining anti-CCL2 agents with PD-1 inhibitors in non-small cell lung cancer, which aim to therapeutically manipulate this balance.

While preclinical findings have provided mechanistic insights into the CCL2/CCR2 pathway in cancer progression, direct clinical validation in human malignancies remains limited. Although studies (183,184) have investigated CCR2 antagonists (PF-04136309) or CCL2 inhibitors (CNTO-888), most therapeutic strategies have focused on an individual target blockade rather than coordinated modulation of the CCL2/CCR2 interaction. Future studies should prioritize the following: i) Comprehensive CCL2/CCR2 co-expression profiling in patient-derived samples, ii) longitudinal assessment of axis activation during CCR2-targeted therapy and iii) development of novel dual-targeting approaches to elucidate the clinical relevance of this chemokine axis in human cancer.

5. Conclusion

The present study provides a rationale for the clinical evaluation of CCL2/CCR2 axis inhibitors in combination with existing immunotherapies, offering potential for treatment-resistant malignancies, including melanoma. Future studies should focus on optimizing combination strategies and identifying predictive biomarkers for patient stratification.

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Availability of data and materials

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Authors' contributions

YZ, BF, HY and ZY conceived and designed the study. YZ wrote the manuscript. HY constructed figures. GC and ZH

designed and implemented the comprehensive literature search strategy, established rigorous eligibility criteria for study inclusion, synthesized key findings to construct the theoretical framework, made substantial contributions to both the Introduction and Discussion sections and actively participated in critical revision of the manuscript with particular focus on ensuring the accuracy and optimal presentation of figures. Specifically, GC conceived the core visual framework for all figures, which was instrumental in interpreting the study's conceptual approach and ZH established the comparative logic and data hierarchy in figures, ensuring perfect alignment with the manuscript's analytical narrative. YiL and XM acquired full-text articles and independently screened literature (resolving discrepancies through consensus), organized references (using EndNote), revised the Discussion section for clarity and clinical relevance, and oordinated revision feedback among all co-authors to ensure consistency. TW conducted supplementary literature searches to validate results, provided visualization support (including figure and table design), revised the Discussion section with critical intellectual input and helped coordinate final revisions. WW, LC, LH, YaL, DL, XC and YY reviewed the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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