OncoTargets and Therapy

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Tumor-Associated Macrophages (TAMs): A Critical Activator In Ovarian Cancer Metastasis

This article was published in the following Dove Press journal:
OncoTargets and Therapy

Meichen Yin
Jiayu Shen
Shuqian Yu
Jing Fei
Xiaoqing Zhu
Jiayao Zhao
Lingyun Zhai
Annapurna Sadhukhan
Jianwei Zhou

Department of Gynecology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, Zhejiang, People's Republic of China

Abstract: Tumor-associated macrophages (TAMs) that appear in every stage of cancer progression are usually tumor-promoting cells and are present abundantly in the tumor-associated microenvironment. In ovarian cancer, the overall and intratumoral M1/M2 ratio is a relatively efficient TAM parameter for predicting the prognosis of patients, especially for serous tissue type cancer. TAMs exhibit immunological checkpoint modulators, such as the B7 family and programmed death-ligand 1 (PD-L1), and play a key role in the development, metastasis and invasion of ovarian cancer, but the underlying mechanism is barely understood. Ovarian cancer is a severe gynecological malignancy with high mortality. Ovarian cancer-associated death can primarily be attributed to cancer metastasis. The majority of patients are diagnosed with wide dissemination in the peritoneum and omentum, limiting the effectiveness of surgery and chemotherapy. In addition, unlike other well-documented cancers, metastasis through vasculature is not a usual dissemination pathway in ovarian cancer. This review sheds light on TAMs and the main process and mechanism of ovarian cancer metastasis.

Keywords: ovarian cancer, tumor associated macrophages, classical activated macrophage, alternative activated macrophage, transcoelomic metastasis, hematogenous metastasis

Introduction

Ovarian cancer is the most deadly female reproductive system malignancy and the fifth leading cause of death in women with cancer.[1] Ovarian carcinoma cannot be defined as a single disease as they are composed of five histological subtypes including epithelial, serous, endometrioid, clear cell and mucinous cancer.[2–4] The high lethality of ovarian cancer is associated with the lack of warning symptoms at an early stage leading to diagnosis at advanced stages (FIGO stage III or IV)[5] Moreover, screening tests for ovarian cancer are not sensitive. Screening for ovarian cancer possesses several obstacles like shortage of specific detection markers and high false-positive rates for morbidity.[3] The mortality rate of ovarian cancer patients did not differ significantly between screened and unscreened women.[6]

Monocyte–macrophage cell lineage are essential inflammatory components of the ecological tumor niche and strongly influence disease progression.[7–10] In hepatocellular carcinoma, tumor-associated macrophages (TAMs) secrete IL-6 to enhance $CD44^+$ cancer stem cells' activity and benefit tumor progression dependent on Signal Transducer And Activator Of Transcription 3 (STAT3) signaling.[11] TAMs promote tumor progression to varying degrees: by cultivating cancer stem cells, supporting genetic instability, promoting metastasis and domestication of protective

Correspondence: Jianwei Zhou
Department of Gynecology, The Second Affiliated Hospital of Zhejiang University School of Medicine, No 88, Jiefang Road, Shangcheng District, Hangzhou, Zhejiang 310002, People's Republic of China
Email 2195045@zju.edu.cn

submit your manuscript | www.dovepress.com
DovePress
http://doi.org/10.2147/OTT.S216355

adaptive immunity.[12,13] Owing to expression of programmed death 1 (PD-1) ligands PD-L1, cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) ligands B7-1 and B7-H4, TAM-focused therapeutic strategies are pivotal in immunotherapy such as immune checkpoint therapy.[14–19]

TAMs are intimately related to ovarian cancer metastasis.[20,21] Metastasis-associated macrophages (MAM), a distinct phenotype of macrophages, are required for metastatic extravasation.[22] Migrating influx of tumor cells with TAM moves at a higher speed in a more direct way.[23,24] This process is achieved through self-reinforcement paracrine loops, including colony-stimulating factor 1 (CSF1) produced by cancer cells, hepatocyte growth factor (HGF) released from endothelial cells and epidermal growth factor (EGF) produced by TAM.[25,26] TAM is located in the center of the spheroid and secretes EGF, which upregulates intercellular cell adhesion molecule-1 (ICAM-1) on tumor cells and αMβ2 integrin on TAM to promote the binding between tumor cells and TAM, thereby contributing to the formation of spheroids which emerge in the early phase of transcoelomic metastasis.[27]

Origin Of TAMs

As we all know, TAMs, the most abundant immune-related stromal cells in the tumor microenvironment, are vital orchestrators in tumor progression.[28] Meanwhile, they also played an indispensable role in tumor development, metastasis, invasion and angiogenesis.[29,30] So what is the process of TAM transformation?

Transformation From Ly6C$^+$ CCR2$^+$ Monocytes

By using modern pedigree tracking techniques, the recent understanding of the origin of macrophages has undergone profound changes. Accumulating evidence indicates that circulating Ly6C$^+$ CCR2$^+$ monocytes are critical progenitors for macrophages.[31–34] Bead labeling and BrdUrd incorporation experiments indicate that all different TAM subpopulations in TS/A tumors originate from Ly6C^{hi} monocytes. Deficiency of chemokine (C-X3-C motif) receptor 1 (CX3CR1) on monocytes leads to TAM recruitment via accumulation of Ly6C^{hi} inflammatory monocytes.[35] However, TAM can also originate from erythrocyte progenitor cells (EMP) that develop in the yolk sac of embryos in cancers such as gliomas and pancreatic cancer.[36,37]

Recruitment Of Monocytes/Macrophages

Monocytes produced from bone marrow hematopoietic stem cells are recruited into tumor tissue and subsequently polarized into TAM.[38,39] In brain malignancies, brain-dwelling microglia and monocyte-derived macrophages contribute to amplify the TAM pool. In lung cancer, interstitial resident macrophages of embryonic origin together with monocyte-derived (MoD) macrophages contribute to the TAM pool. Interstitial pulmonary macrophages serve as nutritional support for tumor cells, while MoD cells are involved in tumor remodeling and proliferation.[38]

Recruitment of monocytes contributes to the augmentation of TAM population. In response to chemokines and growth factors secreted by tumor cells and stromal cells contained in TME, peripheral blood mononuclear cells originating from the bone marrow are locally aggregated and polarized to TAM.[39] This course is mainly modulated by CSF-1 and chemokines[40,41] (Figure 1).

Intriguingly, growing information indicates that spleen constitutes an extramedullary reservoir of monocytes. During cancer progression, spleen can significantly amplify pro-tumor TAM response.[42] According to this, we can infer that TAMs accumulated in tumor area segment originated from the spleen.

Mechanism Of Monocytes Recruitment

Among the broad spectrum of human neoplasms, recruitment mechanisms of monocytes are multifarious. Integration of C-C chemokine receptor type 2 (CCR2) and chemokine C-C motif ligand 2 (CCL2) elicit monocytes to cluster to primary or secondary tumor loci.[31,43] CCL20, the specific ligand for CCR6, contributes to migration and accumulation of monocytes in vitro and in vivo. So, CCL20-CCR6 can accelerate tumor development via recruitment of monocytes.[44] Vascular endothelial growth factor A (VEGF-A) is a crucial angiogenic factor while it also acts as an indispensable chemoattractant related to monocytes recruitment. Elevated VEGF-A combined with interleukin-4 (IL-4) and interleukin-10 (IL-10) induce skin carcinogenesis by promoting M2-polarized macrophages in cells and angiogenesis. Besides, extracellular matrix(ECM) components[45] and hypoxia[46,47] also promote macrophages to cluster into tumor location.

Properties And Functions Of TAMs

Polarization Of TAMs

Macrophages are crucial components of both innate and adaptive immune system and are involved in pathogen

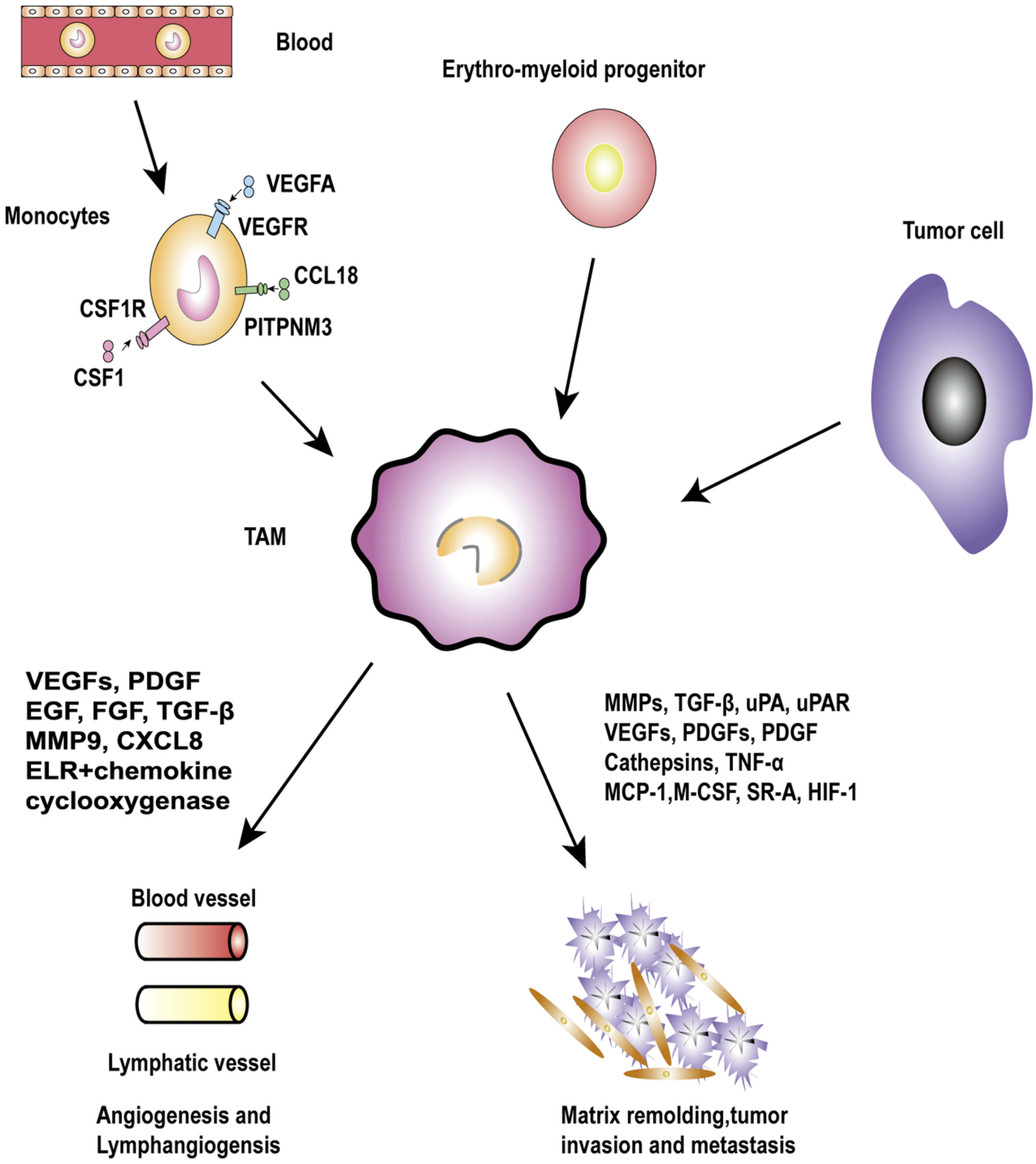

Figure 1 Cytokines and chemokines that influence TAM transformation and function.
Abbreviations: VEGFA, vascular endothelial growth factor A; VEGFR, vascular endothelial growth factor receptor; CCL18, chemokine ligand 18; PITPNM3, Membrane-associated phosphatidylinositol transfer protein; CSF1, colony-stimulating factor; CSF1R, colony-stimulating factor receptor; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; FGF, fibroblast growth factor; TGF-β, transforming growth factor-β; MMP9, matrix metallopeptidase 9; CXCL8, chemokine (C-X-C motif) ligand 8; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator receptor; TNF-α, tumor necrosis factor-α; MCP-1, methylcyclopropene-1; M-CSF, macrophage colony-stimulating factor; SR-A, scavenger receptor A; HIF-1, hypoxia-inducible factor.

response and in-tissue homeostasis.[48] According to the cytokines that macrophages are exposed to, they can be polarized into two mainstreams, classically activated macrophage (M1) and alternatively activated macrophage (M2).[49,50] M1 with IL-12^{high}, IL-23^{high} and IL-10^{low} phenotype is superior in the elimination of microbes and

tumor cells. Conversely, M2 with IL-12^{low}, IL-23^{low}, IL-10^{high} phenotype and mannose receptor and scavenger receptor A are potent effector cells that promote parasite containment, angiogenesis and tissue remodeling, thereby yielding pro-tumoral functions.[51] The notion that the process of M1 polarization is meditated by interferon or lipopolysaccharides (LPS) has been widely recognized during the past several years. IL-4 and IL-13 can directly transform macrophages into M2,[52,53] whereas IL-13, IL-25 and other cytokines promote the formation of M2 indirectly.[53–55] Furthermore, M2 consists of three well-defined forms, including M2a (induced by exposure to IL-4, IL-13), M2b(induced by immune complexes, agonists of Toll-like receptors or IL-1R) and M2c (induced by contacting to IL-10 and glucocorticoid hormones).[56–59]

Macrophages are dynamic cells that can transform into either M1 or M2 with their specific properties. So, polarization does not represent terminal differentiation. When substitution arises in the cytokines contained in the medium, polarized macrophages in a position either revert back to uncommitted M0 or transform into M2.[60] And inhibition of IκB kinase (IKK) beta activity can result in a shift in TAM from M2 to M1, as evidenced by enhanced expression of IL12, MHCII and iNOS and reduction of IL-4Rα, TNF-α and arginase.[61,62]

Repolarization Of TAMs

As mentioned above, macrophages are functionally plastic. Modulated by molecules in the TME, macrophages can be repolarized from an anti-inflammatory to a pro-inflammatory phenotype. In ovarian cancer ascites, macrophages polarized into M1 phenotype producing less VEGF, CCL18 and MMP9.[63] Nowadays, editing macrophage repolarization from M2 to M1 to inhibit cancer progression raises high interest. Bossche et al found that M1-related suppression of mitochondrial oxidative phosphorylation prevents M1 from polarizing into M2. Reducing the production of nitric oxide can inhibit decline of mitochondrial function, thus improving macrophage phenotype repolarization.[64] Certain microRNA are shown to facilitate repolarization of TAMs. MiR-125b is expressed in macrophages at a higher level than other immune cells and responsible for macrophages repolarization. Amplifying expression of miR-125b has been viewed as a bright method of repolarizing TAMs. Hyaluronic acid-based nanoparticles delivery system of miR-125b has been exploited in transforming miR-125b into TAMs in Neha et al test.[65] During the course of M1 to M2 polarization, we can see that the miR-155 levels were strikingly attenuated. On the contrary, the miR-155 levels were elevated in M2 to M1 transformation. Further experiments prove the hypothesis that microRNA-155 did encourage M2 to M1 repolarization.[66] Present studies demonstrated that miR-146a involved as a negative regulator in the acquisition of pro-inflammatory cytokines. It has been proved that tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) can exert cytotoxic effects on tumor cells by re-educated M2 to an M1 phenotype in a miR-146a-depended way.[67] Additionally, activin A is also a key trigger in the macrophage repolarization caused by GM-CSF and impaired the acquisition of M2 phenotype via Smad2-dependent transduction.[68] In the resolution of inflammation, TAMs repolarization partly relies on the dissociation of P2X7R from caspase-1 activation.[69] Aside from the molecules, the pathway transduction is also involved in TAMs repolarization. NF- κ B signaling is essential in mannose-sensitive hemagglutination pilus strain of *Pseudomonas aeruginosa* (PA-MSHA) mediated-repolarization in macrophages.[70] Besides, MAPK/ERK pathway is also indispensable in the course of repolarization.[71]

Functional Properties Of TAMs

They have other specific functional properties. M1 macrophages exhibit proinflammatory properties as they show elevated expression of IL-1β, IL-6, IL-12 and TNF-a and accompanied with Th1-mediated immune responses, whereas M2 macrophages show anti-inflammatory properties via enhanced expression of anti-inflammatory cytokines.[72] M1 is superior in cytotoxic and antitumor activity, whereas M2a and M2c are expert in driving type II response and immunoregulatory function; M2c is also associated with suppression of immune response and tissue remolding.[56] In inflammation response, lipopolysaccharide (LPS) or interferon-γ activates NO Synthase 2, which can mutate arginine into OH-arginine and subsequently into NO when macrophages contact the Th1-type cytokines. M1 can exert disruption via this kind of mechanism. On the contrary, when macrophages interact with Th2 cytokines, such as IL-4, IL-10 and IL-13, arginase I decompose arginine into urea and ornithine and then metabolized into proline and polyamines. Proline regulates the production of collagen, whereas polyamines mediate cell proliferation. So, the damaged extracellular matrix can be reconstructed through this process.[73,74] This metabolic conversion occurs preferentially during activation of the M2a and M2c polarization programs.[56]

TAMs In Ovarian Cancer

TAMs are considered to be one of the most abundant invasive immune cells in ovarian cancer patients' tissues and ascites. Studies on the presence of TAMs in ovarian cancer suggest that macrophages tend to the M2 phenotype and express M2 signature markers like CD204, CD206, CD163 and IL-10.[20] Intra-islet M1/M2 TAM ratio is a critical factor related to ovarian cancer prognosis because increased M1/M2 ratio presented with improved progression-free survival (PFS).[75] In Xia et al's meta-analysis, which involved 9 studies including 794 patients, worse PFS was associated with a high density of CD163+ TAMs and a higher ratio of CD163+/CD68+ TAMs in ovarian cancer.[76] The upregulation genes linked to interferon signaling in TAMs negatively related to ovarian cancer survival and IFN γ-mediated recovery of IL-12 induction in macrophages may be a possible explanation for this phenomenon.[77] Besides, it is reported that CCL22 produced by TAMs generates chemokine gradient that induces Treg cells moving toward local microenvironment of ovarian cancer, thus raising the percentage of Tregs. Accumulation of Tregs may be a pivotal mechanism of immunosuppression.[78] During ovarian cancer stem cells and M2 macrophage interaction procedure, the paracrine WNT can be fired up and constitutes a positive feedback loop. This feedback loop likely enhances the aggressive phenotype of macrophages and cancer cells.[79] Interestingly, compared with other histological subtype, macrophages are more frequently accumulated in serous and mucinous ovarian carcinoma. Meanwhile, low grade serous ovarian cancer was reported to have a lower density of CD68+ macrophages (M1).[80]

Metastasis Of Ovarian Cancer

Ovarian cancer metastasis can proceed through several distinct pathways, including transcoelomic, hematogenous and lymphogenous.[81] However, unlike other well-documented cancers which spread mainly via hematogenous route, transcoelomic pathway is the most predominant route in ovarian cancer.[82] During this process, adipocytes facilitate ovarian cancer metastasis and support tumor growth.[83,84]

Transcoelomic Metastasis Process

Leave Primary Tumor

The first step of transcoelomic metastatic cascade is to leave the primary tumor site. Before cancer cells detach from the primary site and initiate the metastatic journey, they experience an epithelial-to-mesenchymal transition (EMT). During EMT, intercellular adhesion of the cell to cell and attachment between an epithelial cell and basement membrane can be loosened.[85,86] Besides, resistance to anoikis also facilitates the development of activating yes-associated protein 1 (YAP1) pathway which promotes anoikis inhibition and metastasis development. Norepinephrine and epinephrine prevent ovarian cancer cells from anoikis.[87,88] Inhibitor of c-Met and VEGFR-2, Foretinib (GSK1363089), can enhance anoikis and suppress ovarian cancer metastasis.[89]

Dissemination Within The Peritoneal Cavity

Once cancer cells depart from the primary site, they survive in ascites and evade immunological surveillance in the form of a single cell, aggregates or spheroids. Meanwhile, the physiological movement of ascites promotes exfoliated cancer cells to disseminate within the peritoneal cavity.[90] In ovarian cancer, ascites is a symptom of advanced stage and represent poor prognosis. Evidence confirmed that malignant ascites generates a circumstance that promotes transcoelomic metastasis of ovarian cancer. Additionally, ascites also facilitates cancer cell escape from immunological surveillance.[91] Ovarian cancer cells in ascites secrete exosome containing CD95 ligand (CD95L) which can induce CD95 positive immune cell apoptosis.[92] Feki et al identified that cancer cells preferentially colonized in the milk spots located on the subdiaphragmatic surface[93] because tissues in the milk spots exhibit enhanced direct migration capability.[94] It has been widely accepted that VEGF factors contribute to ascites accumulation by increasing vascular peritoneal permeability.[95–97]

Connect To Peritoneal Mesothelium

After transportation through ascites, carcinoma cells set about undergoing peritoneal implantation. It is reported that attachment of disseminated cancer cells to peritoneal mesothelium can be meditated by CXCL12–CCR4 combination.[98] And, once cancer cells adhere to the mesothelium to anchor to the metastatic site, matrix metalloproteinase-2 (MMP-2) transcription level is upregulated. Following this, MMP-2 cleaves fibronectin (FN) and vitronectin (Vn) into smaller sections, so that the junction of cancer cells to the small fragments and their receptors $\alpha_5\beta_1$, $\alpha_v\beta_3$ integrin can be tightened.[99] In addition, cancer cells can exert various methods to enhance the connection with peritoneal mesothelium such as binding to hyaluronan emerging in mesothelial cells via CD44,[100] integrating

with the basement membrane composed of laminin, fibronectin and I, IV collagen[101] by integrins. Interestingly, previously described studies discovered that spheroids disseminate into several single cells when they intrude the mesothelium.[102,103] Additionally, ovarian cancer cells themselves struggle to enhance migration ability by secreting exosomes enriched by CD44. Mesothelial cells absorb these exosomes, inducing upregulation of MMP-9[3,13] level which can enhance ovarian cancer cells invasion.[104,105]

Destroy The Mesothelial Lining And Erode Submesothelial Parenchymal Tissues

When ovarian cancer connects to mesothelial monolayer in order to accomplish implantation, they need to destroy the mesothelial lining and erode submesothelial parenchymal tissues.[106,107] Noticeably, $\alpha_5\beta_1$ integrins combine with myosin contractility within spheroids and destroy mesothelial lining. At an early stage of implantation, adhesion harmoniously collaborates with proteolysis, thus greatly promoting tumor establishment process. As we all know, tumor growth depends on the formation of new blood vessels. When shedding ovarian cancer cells reach a certain size, diffusion alone cannot supply enough nutrients. So, angiogenesis response emerges in metastatic sites.[108] It is now apparent that VEGF is a crucial element involved in the pluripotent activity of angiogenesis.[109] Of note, tumor-associated stromal cells also support shedding cancer cell growth by promoting angiogenesis.[110] For example, angiopoietin receptors TIE2 positive TAMs occur with high microvascular density,[111] neutrophils facilitate VEGFA, BV8 and Mmp9 transcription in order to mediate pro-angiogenic functions by STAT3[112–116] and TAMs produce Semaphorin-4D (Sema4D) to contribute to proper vessel maturation.[117] Besides, the expression of regulated in development and DNA damage response 1 (REDD1) is upregulated in hypoxic TAMs, mammalian target of rapamycin (mTOR) inhibition is mediated by REDD1 leading to suppression of glycolysis in TAMs, thus inducing abnormal vessel formation.[81,82,118–122]

Hematogenous Metastasis

Characteristic Of Hematogenous Metastasis

It is widely accepted that the mechanism of ovarian cancer metastasis is usually by passive transportation through ascites, while hematogenous metastasis associated with distant metastasis is of limited importance.[121] However, emerging evidence indicates that high grade serous ovarian cancer arising from fallopian tube preferentially spread to ovaries by hematogenous pathway.[123] Furthermore, clinical treatment methods such as inferior vena cava filter placement can increase the risk of hematogenous metastasis.[124] This phenomenon can be attributed to IVC filter-mediated activation of platelets and proinflammatory response. Moreover, circulating tumor cells (CTCs), which are exfoliated tumor cells from primary sites that have disseminated into peripheral blood, have long been seen as an effective indicator for hematogenous metastasis in various solid tumors as well as in ovarian cancer.[125–127] So, we should pay sufficient attention to this uncommon pathway of ovarian cancer metastasis.

Mechanism Of Hematogenous Metastasis

The mechanism of hematogenous metastasis is complex. It has been reported that inhibition of CCR4 can suppress EMT transition and decrease CTCs which are related to hematogenous metastasis. This process is associated with downregulated levels of Src and ERKs.[128] Besides, p90RSK is intimately connected to hematogenous metastasis. p90RSK activates YB-1 to sustain a pro-adhesive circuit including α5β1 integrin, fibronectin and TGF-β1. However, silencing RSK1/RSK2 can diminish pro-adhesive circuit components' translation. So, knockdown RSK1/RSK2 can also impair hematogenous metastasis of ovarian cancer.[129] Interestingly, omentum is commonly involved in transcoelomic metastasis, but it has been proved that cancer cells can spread to omentum hematogenously too. Strong expression of ErbB3 in CTCs induces this kind of hematogenous metastasis via ErbB3/NRG1 axis[130] (Figure 2).

TAMs In Cancer Metastasis

In present study, we consider that infiltration of TAMs in the invasive frontier is associated with metastasis and reversing the polarization of TAMs from M2 to M1 can impair metastasis..[131–133] However, the underlying mechanism of affecting tumor metastasis through TAMs is still under investigation.

Signal Transduction In TAMs Contribute To Metastasis

TAMs have a wide variety of signal transduction patterns, and there is evidence that their activity is proportional to TAM's tumor-promoting function. In Qian et al's research, we can see that FLT1 signaling in TAMs is essential for metastasis process. FLT1 regulates a range of inflammatory response genes like CSF-1 and FLT1 loss-of-function experiment reduces tumor metastatic efficiency.[134] In xenograft

cancer mouse models, PDGF-BB-SOX7 axially upregulated IL-33 to promote metastasis by acting on TAMs.[135] Meanwhile, inhibition of SOCS3 (suppressor of STAT3 signaling) by TAMs prevents cancer metastasis by modifying the macrophage phase and inhibition of the NF-kB in TAMs can attenuate tumor metastasis by polarizing TAMs to an anti-tumor phenotype.[136,137] In a mouse model of orthotopic 4T1 mammary cancer, we can conclude that Stat6 pathway in TAMs facilitates metastasis with the aid of protumorigenic and prometastatic function of macrophages.[138]

Molecular Mechanism Of TAMs In Cancer Metastasis

Abundant shreds of evidence reveal that some molecular substances contained in TAMs play a promoting role in the process of tumor metastasis. Cytochrome P450 (CYP) 4A released by TAMs infiltration is positively related to pre-metastatic niche formation accompanied with tendency to M1 polarization.[139] In Nielsen et al's experiment, it is apparent that granulin secretion by TAMs transforms resident hepatic stellate cells (hStCs) into pericyte-secreting myofibroblasts, forming a microenvironment that supports the growth of metastatic tumors;[140] Caveolin-1 (Cav1) has been reported to have dual effects of promoting and inhibiting tumor growth. Deletion of Cav1 in macrophages promotes lung metastasis by increasing angiogenesis;[141] Release of sphingosine-1-phosphate (S1P) by apoptotic tumor cells stimulates TAMs to secrete Lipocalin 2 to promote metastasis.[142] In renal cell carcinoma model treated with IL-2/anti-CD40 immunotherapy, the expression of TAM-dependent NO in the tumor microenvironment is an

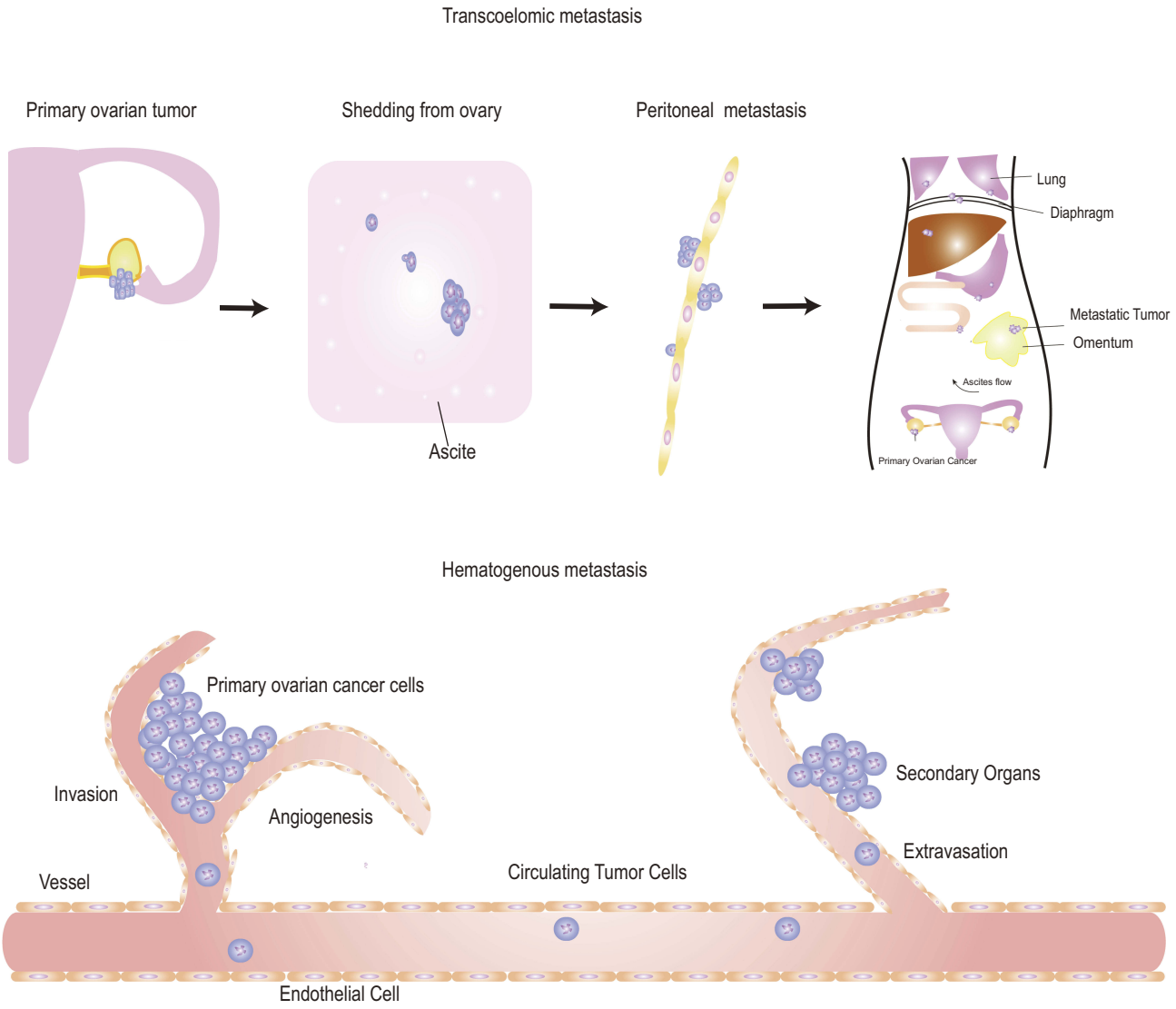

Figure 2 The process of transcoelomic and hematogenous metastasis of ovarian cancer.

important molecular readout, which is essential for regulating MMP activity and adhesion molecule expression, and is the basis for inhibiting the metastatic process;[143] CCL18 from TAMs acts on its receptor, PITPNM3, to promote breast cancer metastasis.[144]

The Underlying Mechanism Of TAMs In Promoting Ovarian Cancer Metastasis

Abundant studies indicate that TAMs are frequently identified in patients with ovarian cancer and progression of ovarian cancer is accompanied by an increase in TAMs in the surrounding ascites. However, the in-depth mechanism of TAMs in promoting ovarian cancer metastasis are under exploring. In a severe combined immunodeficient and a syngeneic immunocompetent mouse model, the prometastatic effect of inflammation can be detected. Deletion of macrophages alone, resulting in decreasing of vascular endothelial growth factor, presenting inhibition of ascites formation and peritoneal metastasis.[145] In Kaitlin et al's research, experimental validation proves that secretomes derived from macrophages promoting MMP-9 mediated spheroid spreading by activating JAK2/STAT3 signaling.[146] Liu et al found that upregulation of lipid leads to decrease in M1/M2 ratio, thus facilitates ovarian cancer adhere to lipid-loaded mesothelial cell.[147] In an M2 co-cultured system, it is obvious to see that ovarian cancer cells present stronger migration ability with increased concentration of epidermal growth factor (EGF). However, these effects can be reversed by inhibitor of EGF and overexpression of lncRNA inhibiting metastasis (LIMT).[148] In the process of ovarian cancer metastasis, we can see that P-selectin is overexpressed in mesothelial cell surface, resulting in an increased rolling under ascites flow and adhesion between cancer cells and mesothelial cell. The overexpression of P-selectin is mediated by macrophage inflammatory protein-1β (MIP-1β) secreted by macrophages via CCR5/PI3K signaling.[149] The characteristics of the peritoneum of ovarian cancer include massive infiltration of macrophages and high expression of coagulation factors FXII. After treatment of FXII, macrophages exhibit strong tendency to M2 phenotype. Matrigel results proved that the metastasis of ovarian cancer cells was strengthened when infiltrated in medium from FXII-stimulated macrophages.[150]

Conclusion

TAMs are involved in various aspects of ovarian cancer treatment like radiotherapy, chemotherapy and immunotherapy.[151–153] Macrophage subpopulations with identifiable markers are attractive therapeutic targets for standard and immune therapy. TAM-targeted approaches consist of TAM depletion, inhibition of TAM recruitment and reprogramming of TAMs.[10,12] Targeting CSF1–CSF1R axis can be an effective method to deplete TAMs.[154–156] Chemokines have long been associated with macrophage accumulation in tumors.[42,56] Antibody-specific inhibition of CCL2 greatly reduces tumor development and inhibit invasion process in different experimental models.[157,158] In conclusion, TAMs significantly influence the pathophysiological process of metastasis.[10,19,21] Editing M2 phenotype repolarize to M1 is a promising strategy for cancer therapy. For instance, intraperitoneal paclitaxel in combination with MicroRNA-125b can consolidate the anti-tumor efficacy of paclitaxel as seen by impeding formation of ascites and cut down VEGF levels.[159] In mouse models of several adenocarcinomas, like colon cancer, breast cancer and sarcoma, CSF-1R antibody antagonists combined with CD40 agonistic antibody drive repolarization from M2 to a tumoricidal phenotype and prolong survival.[160] Similarly, bacteria-mediated macrophage repolarization is also applicable in cancer therapy. It was found that the combination of heat-killed *Mycobacterium indicus pranii* (Mw) and agonistic GITR antibody (DTA-1) is effective for advanced tumor therapy. Mw aims at repolarizing macrophages synergized with DTA-1 aims at impairing the acquisition of intratumor regulatory T cell create antitumor atmosphere.[161] So, identifying the underlying mechanism of TAM in ovarian cancer metastasis is pivotal in inhibiting the spread of ovarian cancer cells into the peritoneum, omentum and vasculature, thus improving the five-year survival rate and reducing mortality. Additionally, it has been elucidated that TAMs play causative role in ovarian cancer metastasis. Removing peritoneal macrophages, rather than other immune cells resident in TME, abrogated tumor progression as shown by peritoneal metastasis.[162] As mentioned earlier, macrophages are involved in various aspects of ovarian cancer progression. Macrophage infiltration is a marker of poor prognosis in ovarian carcinoma, but there is no direct evidence or literature supporting the presence of macrophages as a diagnostic marker for ovarian cancer metastasis. In consequence, we need to explore macrophage-specific biomarker in metastatic ovarian carcinoma. It helps us to clinically screen patients with a strong tendency to metastasize and intervene in advance. It is also of great clinical significance in improving the prognosis of ovarian cancer patients.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin*. 2018;68:7–30. doi:10.3322/caac.21442
2. Pearce CL, Rossing MA, Lee A, et al. Association between endometriosis and risk of histological subtypes of ovarian cancer: a pooled analysis of case-control studies. *Lancet Oncol*. 2012;13(4):385–394. doi:10.1016/S1470-2045(11)70404-1
3. Temkin SM, Miller EA, Samimi G, Berg CD, Pinsky P, Minasian L. Outcomes from ovarian cancer screening in the PLCO trial: histologic heterogeneity impacts detection, overdiagnosis and survival. *Eur J Cancer*. 2017;87:182–188. doi:10.1016/j.ejca.2017.10.015
4. Marquez RT, Baggerly KA, Patterson AP, et al. Patterns of gene expression in different histotypes of epithelial ovarian cancer correlate with those in normal fallopian tube, endometrium, and colon. *Clin Cancer Res*. 2005;11:6116–6126. doi:10.1158/1078-0432.CCR-04-2509
5. Matulonis UA, Sood AK, Fallowfield L, Howitt BE, Sehouli J, Karlan BY. Ovarian cancer. *Nat Rev Dis Primers*. 2016;2:16061. doi:10.1038/nrdp.2016.61
6. Henderson JT, Webber EM, Sawaya GF. Screening for ovarian cancer: updated evidence report and systematic review for the US preventive services task force. *JAMA*. 2018;319:595–606. doi:10.1001/jama.2017.21421
7. Ginhoux F, Schultze JL, Murray PJ, Ochando J, Biswas SK. New insights into the multidimensional concept of macrophage ontogeny, activation and function. *Nat Immunol*. 2016;17:34–40. doi:10.1038/ni.3324
8. Cortes M, Sanchez-Moral L, de Barrios O, et al. Tumor-associated macrophages (TAMs) depend on ZEB1 for their cancer-promoting roles. *Embo J*. 2017;36:3336–3355. doi:10.15252/embj.201797345
9. Kaneda MM, Cappello P, Nguyen AV, et al. Macrophage PI3Kgamma drives pancreatic ductal adenocarcinoma progression. *Cancer Discov*. 2016;6:870–885. doi:10.1158/2159-8290.CD-15-1346
10. Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. *Nat Rev Drug Discov*. 2018;17:887–904. doi:10.1038/nrd.2018.169
11. Wan S, Zhao E, Kryczek I, et al. Tumor-associated macrophages produce interleukin 6 and signal via STAT3 to promote expansion of human hepatocellular carcinoma stem cells. *Gastroenterology*. 2014;147:1393–1404. doi:10.1053/j.gastro.2014.08.039
12. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P. Tumour-associated macrophages as treatment targets in oncology. *Nat Rev Clin Oncol*. 2017;14:399–416. doi:10.1038/nrclinonc.2016.217
13. Saha D, Martuza RL, Rabkin SD. Macrophage polarization contributes to glioblastoma eradication by combination immunovirotherapy and immune checkpoint blockade. *Cancer Cell*. 2017;32:253–267 e255. doi:10.1016/j.ccell.2017.07.006
14. Sharma PAJ. The future of immune checkpoint therapy. *Science*. 2015;03(6230):348.
15. Gordon SR, Maute RL, Dulken BW, et al. PD-1 expression by tumour-associated macrophages inhibits phagocytosis and tumour immunity. *Nature*. 2017;545:495–499. doi:10.1038/nature22396
16. Kryczek I, Zou L, Rodriguez P, et al. B7-H4 expression identifies a novel suppressive macrophage population in human ovarian carcinoma. *J Exp*. 2006;203:871–881. doi:10.1084/jem.20050930
17. Bloch O, Crane CA, Kaur R, Safaee M, Rutkowski MJ, Parsa AT. Gliomas promote immunosuppression through induction of B7-H1 expression in tumor-associated macrophages. *Clin Cancer Res*. 2013;19:3165–3175. doi:10.1158/1078-0432.CCR-12-3314
18. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell*. 2015;27:450–461. doi:10.1016/j.ccell.2015.03.001
19. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell*. 2010;141:39–51. doi:10.1016/j.cell.2010.03.014
20. Colvin EK. Tumor-associated macrophages contribute to tumor progression in ovarian cancer. *Front Oncol*. 2014;4:137. doi:10.3389/fonc.2014.00137
21. Qian B, Deng Y, Im JH, et al. A distinct macrophage population mediates metastatic breast cancer cell extravasation, establishment and growth. *PLoS One*. 2009;4:e6562. doi:10.1371/journal.pone.0006562
22. Leung E, Xue A, Wang Y, et al. Blood vessel endothelium-directed tumor cell streaming in breast tumors requires the HGF/C-Met signaling pathway. *Oncogene*. 2017;36:2680–2692. doi:10.1038/onc.2016.421
23. Patsialou A, Bravo-Cordero JJ, Wang Y, et al. Intravital multiphoton imaging reveals multicellular streaming as a crucial component of in vivo cell migration in human breast tumors. *Intravital*. 2013;2:e25294. doi:10.4161/intv.25294
24. Patsialou A, Wyckoff J, Wang Y, Goswami S, Stanley ER, Condeelis JS. Invasion of human breast cancer cells in vivo requires both paracrine and autocrine loops involving the colony-stimulating factor-1 receptor. *Cancer Res*. 2009;69:9498–9506. doi:10.1158/0008-5472.CAN-09-1868
25. Wyckoff J, Lin EY, Wang Y, et al. A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. *Cancer Res*. 2004;64(19):7022–7029. doi:10.1158/0008-5472.CAN-04-1449
26. Yin M, Li X, Tan S, et al. Tumor-associated macrophages drive spheroid formation during early transcoelomic metastasis of ovarian cancer. *J Clin Invest*. 2016;126:4157–4173. doi:10.1172/JCI87252
27. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *The Lancet*. 2001;357:539–545. doi:10.1016/S0140-6736(00)04046-0
28. Lewis CE, Harney AS, Pollard JW. The multifaceted role of perivascular macrophages in tumors. *Cancer Cell*. 2016;30:18–25. doi:10.1016/j.ccell.2016.05.017
29. Bingle L, Lewis CE. The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. *J Pathol*. 2002;196(3):254–265. doi:10.1002/path.1027
30. Ruiz-Rosado Jde D, Olguin JE, Juarez-Avelar I, et al. MIF promotes classical activation and conversion of inflammatory Ly6C (high) monocytes into TipDCs during murine toxoplasmosis. *Mediators Inflamm*. 2016;9101762.
31. Franklin RA, Liao W, Sarkar A, et al. The cellular and molecular origin of tumor-associated macrophages. *Science*. 2014;344:921–925. doi:10.1126/science.1252510
32. Serbina NV, Pamer EG. Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2. *Nat Immunol*. 2006;7:311–317. doi:10.1038/ni1309
33. Feng X, Szulzewsky F, Yerevanian A, et al. Loss of CX3CR1 increases accumulation of inflammatory monocytes and promotes gliomagenesis. *Oncotarget*. 2015;6(17):15077–15094. doi:10.18632/oncotarget.3730
34. Zhu Y, Herndon JM, Sojka DK, et al. Tissue-resident macrophages in pancreatic ductal adenocarcinoma originate from embryonic hematopoiesis and promote tumor progression. *Immunity*. 2017;47(323–338):e326. doi:10.1016/j.immuni.2017.08.018
35. Chen Z, Feng X, Herting CJ, et al. Cellular and molecular identity of tumor-associated macrophages in glioblastoma. *Cancer Res*. 2017;77(9):2266–2278. doi:10.1158/0008-5472.CAN-16-2310
36. Arwert EN, Harney AS, Entenberg D, et al. A unidirectional transition from migratory to perivascular macrophage is required for tumor cell intravasation. *Cell Rep*. 2018;23:1239–1248. doi:10.1016/j.celrep.2018.04.007

37. Zigmond E, Varol C, Farache J, et al. Ly6C hi monocytes in the inflamed colon give rise to proinflammatory effector cells and migratory antigen-presenting cells. *Immunity*. 2012;37:1076–1090. doi:10.1016/j.immuni.2012.08.026
38. Loyher PL, Hamon P, Laviron M, et al. Macrophages of distinct origins contribute to tumor development in the lung. *J Exp Med*. 2018;215:2536–2553. doi:10.1084/jem.20180534
39. Glass CK, Natoli G. Molecular control of activation and priming in macrophages. *Nat Immunol*. 2016;17:26–33. doi:10.1038/ni.3306
40. Cheng H, Clarkson PW, Gao D, Pacheco M, Wang Y, Nielsen TO. Therapeutic antibodies targeting CSF1 impede macrophage recruitment in a xenograft model of tenosynovial giant cell tumor. *Sarcoma*. 2010;174528.
41. Scholl SM, Bascou CH, Mosseri V, et al. Circulating levels of colony-stimulating factor 1 as a prognostic indicator in 82 patients with epithelial ovarian cancer. *Br J Cancer*. 1994;69:342–346. doi:10.1038/bjc.1994.62
42. Cortez-Retamozo V, Etzrodt M, Newton A, et al. Origins of tumor-associated macrophages and neutrophils. *Proc Natl Acad Sci U S A*. 2012;109:2491–2496. doi:10.1073/pnas.1113744109
43. Qian BZ, Li J, Zhang H, et al. CCL2 recruits inflammatory monocytes to facilitate breast-tumour metastasis. *Nature*. 2011;475:222–225. doi:10.1038/nature10138
44. Nandi B, Shapiro M, Samur MK, et al. Stromal CCR6 drives tumor growth in a murine transplantable colon cancer through recruitment of tumor-promoting macrophages. *Oncoimmunology*. 2016;5:e1189052. doi:10.1080/2162402X.2016.1189052
45. Kobayashi N, Miyoshi S, Mikami T, et al. Hyaluronan deficiency in tumor stroma impairs macrophage trafficking and tumor neovascularization. *Cancer Res*. 2010;70:7073–7083. doi:10.1158/0008-5472.CAN-09-4687
46. Murdoch C, Giannoudis A, Lewis CE. Mechanisms regulating the recruitment of macrophages into hypoxic areas of tumors and other ischemic tissues. *Blood*. 2004;104:2224–2234. doi:10.1182/blood-2004-03-1109
47. Laoui D, Van Overmeire E, Di Conza G, et al. Tumor hypoxia does not drive differentiation of tumor-associated macrophages but rather fine-tunes the M2-like macrophage population. *Cancer Res*. 2014;74:24–30. doi:10.1158/0008-5472.CAN-13-1196
48. Wynn TA, Chawla A, Pollard JW. Macrophage biology in development, homeostasis and disease. *Nature*. 2013;496:445–455. doi:10.1038/nature12034
49. Mantovani A, Locati M, Allavena P, Sica A. Macrophage polarization: tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes. *Trends Immunol*. 2002;23(11):549–555.
50. Kurahara H, Shinchi H, Mataki Y, et al. Significance of M2-polarized tumor-associated macrophage in pancreatic cancer. *J Surg Res*. 2011;167:e211–219. doi:10.1016/j.jss.2009.05.026
51. Sica A, Schioppa T. Mantovani A and Allavena P. Tumour-associated macrophages are a distinct M2 polarised population promoting tumour progression: potential targets of anti-cancer therapy. *Eur J Cancer*. 2006;42:717–727. doi:10.1016/j.ejca.2006.01.003
52. Stein M, Harris N, Gordon S. Interleukin-4 potently enhances murine mannose receptor activity: a marker of alternative immunologic macrophage activation. *J Exp Med*. 1992;176(1):287–292. doi:10.1084/jem.176.1.287
53. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. *Immunity*. 2010;32:593–604. doi:10.1016/j.immuni.2010.05.007
54. Deshmane SL, Kremlev S, Amini S, Sawaya BE. Monocyte chemoattractant protein-1 (MCP-1): an overview. *J Interferon Cytokine Res*. 2009;29:313–326. doi:10.1089/jir.2008.0027
55. Mantovani A, Romero P, Palucka AK, Marincola FM. Tumour immunity: effector response to tumour and role of the microenvironment. *The Lancet*. 2008;371:771–783. doi:10.1016/S0140-6736(08)60241-X
56. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, Locati M. The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol*. 2004;25:677–686. doi:10.1016/j.it.2004.09.015
57. Hume DA. The many alternative faces of macrophage activation. *Front Immunol*. 2015;6:370. doi:10.3389/fimmu.2015.00370
58. Sica A, Mantovani A. Macrophage plasticity and polarization: in vivo veritas. *J Clin Invest*. 2012;122:787–795. doi:10.1172/JCI59643
59. Chanmee T, Ontong P, Konno K, Itano N. Tumor-associated macrophages as major players in the tumor microenvironment. *Cancers (Basel)*. 2014;6:1670–1690. doi:10.3390/cancers6031670
60. Tarique AA, Logan J, Thomas E, Holt PG, Sly PD, Fantino E. Phenotypic, functional, and plasticity features of classical and alternatively activated human macrophages. *Am J Respir Cell Mol Biol*. 2015;53:676–688. doi:10.1165/rcmb.2015-0012OC
61. Hagemann TLT, McNeish I, Charles KA, et al. "Re-educating" tumor-associated macrophages by targeting NF-kappaB. *J Exp Med*. 2008;09(6):205.
62. Fong CH, Bebien M, Didierlaurent A, et al. An antiinflammatory role for IKKbeta through the inhibition of "classical" macrophage activation. *J Exp Med*. 2008;205:1269–1276. doi:10.1084/jem.20080124
63. Duluc D, Corvaisier M, Blanchard S, et al. Interferon-gamma reverses the immunosuppressive and protumoral properties and prevents the generation of human tumor-associated macrophages. *Int J Cancer*. 2009;125(2):367–373. doi:10.1002/ijc.24401
64. Van Den Bossche J, Baardman J, Otto NA, et al. Mitochondrial dysfunction prevents repolarization of inflammatory macrophages. *Cell Rep*. 2016;17(3):684–696. doi:10.1016/j.celrep.2016.09.008
65. Parayath NN, Parikh A, Amiji MM. Repolarization of tumor-associated macrophages in a genetically engineered nonsmall cell lung cancer model by intraperitoneal administration of hyaluronic acid-based nanoparticles encapsulating MicroRNA-125b. *Nano Lett*. 2018;18(6):3571–3579. doi:10.1021/acs.nanolett.8b00689
66. Cai X, Yin Y, Li N, et al. Re-polarization of tumor-associated macrophages to pro-inflammatory M1 macrophages by microRNA-155. *J Mol Cell Biol*. 2012;4(5):341–343. doi:10.1093/jmcb/mjs044
67. Gao J, Wang D, Liu D, et al. Tumor necrosis factor-related apoptosis-inducing ligand induces the expression of proinflammatory cytokines in macrophages and re-educates tumor-associated macrophages to an antitumor phenotype. *Mol Biol Cell*. 2015;26(18):3178–3189. doi:10.1091/mbc.E15-04-0209
68. Sierra-Filardi E, Puig-Kröger A, Blanco FJ, et al. Activin A skews macrophage polarization by promoting a proinflammatory phenotype and inhibiting the acquisition of anti-inflammatory macrophage markers. *Blood*. 2011;117(19):5092–5101. doi:10.1182/blood-2010-09-306993
69. Pelegrin P, Surprenant A. Dynamics of macrophage polarization reveal new mechanism to inhibit IL-1beta release through pyrophosphates. *Embo J*. 2009;28(14):2114–2127. doi:10.1038/emboj.2009.163
70. Wang C, Hu Z, Zhu Z, et al. The MSHA strain of Pseudomonas aeruginosa (PA-MSHA) inhibits gastric carcinoma progression by inducing M1 macrophage polarization. *Tumour Biol*. 2016;37(5):6913–6921. doi:10.1007/s13277-015-4451-6
71. Chakraborty P, Chatterjee S, Ganguly A, et al. Reprogramming of TAM toward proimmunogenic type through regulation of MAP kinases using a redox-active copper chelate. *J Leukoc Biol*. 2012;91(4):609–619. doi:10.1189/jlb.0611287
72. Helm O, Held-Feindt J, Grage-Griebenow E, et al. Tumor-associated macrophages exhibit pro- and anti-inflammatory properties by which they impact on pancreatic tumorigenesis. *Int J Cancer*. 2014;135(4):843–861. doi:10.1002/ijc.28736

73. Classen A, Lloberas J, Celada A. Macrophage activation: classical versus alternative. *Methods Mol Biol*. 2009;531:29–43. doi:10.1007/978-1-59745-396-7_3
74. Yeramian A, Martin L, Arpa L, et al. Macrophages require distinct arginine catabolism and transport systems for proliferation and for activation. *Eur J Immunol*. 2006;36:1516–1526. doi:10.1002/eji.200535694
75. Zhang M, He Y, Sun X, et al. A high M1/M2 ratio of tumor-associated macrophages is associated with extended survival in ovarian cancer patients. *J Ovarian Res*. 2014;7:19. doi:10.1186/1757-2215-7-19
76. Yuan X, Zhang J, Li D, et al. Prognostic significance of tumor-associated macrophages in ovarian cancer: A meta-analysis. *Gynecol Oncol*. 2017;147(1):181–187. doi:10.1016/j.ygyno.2017.07.007
77. Adhikary T, Wortmann A, Finkernagel F, et al. Interferon signaling in ascites-associate macrophages is linked to a favorable clinical outcome in a subgroup of ovarian carcinoma patients. *BMC Genomics*. 2017;18(1):243. doi:10.1186/s12864-016-3396-5
78. Wertel I, Surówka J, Polak G, et al. Macrophage-derived chemokine CCL22 and regulatory T cells in ovarian cancer patients. *Tumour Biol*. 2015;36(6):4811–4817. doi:10.1007/s13277-015-3133-8
79. Raghavan S, Mehta P, Xie Y, Lei YL, Mehta G. Ovarian cancer stem cells and macrophages reciprocally interact through the WNT pathway to promote pro-tumoral and malignant phenotypes in 3D engineered microenvironments. *J Immunother Cancer*. 2019;7(1):190. doi:10.1186/s40425-019-0666-1
80. Kawamura K, Komohara Y, Takaishi K, Katabuchi H, Takeya M. Detection of M2 macrophages and colony-stimulating factor 1 expression in serous and mucinous ovarian epithelial tumors. *Pathol Int*. 2009;59(5):300–305. doi:10.1111/j.1440-1827.2009.02369.x
81. Yeung TL, Leung CS, Yip KP, Au Yeung CL, Wong ST, Mok SC. Cellular and molecular processes in ovarian cancer metastasis. A review in the theme. cell and molecular processes in cancer metastasis. *Am J Physiol Cell Physiol*. 2015;309:C444–456. doi:10.1152/ajpcell.00188.2015
82. Barbolina MV. Molecular mechanisms regulating organ-specific metastases in epithelial ovarian carcinoma. *Cancers (Basel)*. 2018;15(11):10.
83. Nieman KM, Kenny HA, Penicka CV, et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med*. 2011;17:1498–1503. doi:10.1038/nm.2492
84. Miranda F, Mannion D, Liu S, et al. Salt-inducible kinase 2 couples ovarian cancer cell metabolism with survival at the adipocyte-rich metastatic niche. *Cancer Cell*. 2016;30:273–289. doi:10.1016/j.ccell.2016.06.020
85. Davidson B, Trope CG, Reich R. Epithelial-mesenchymal transition in ovarian carcinoma. *Front Oncol*. 2012;2:33. doi:10.3389/fonc.2012.00033
86. Vergara D, Merlot B, Lucot JP, et al. Epithelial-mesenchymal transition in ovarian cancer. *Cancer Lett*. 2010;291:59–66. doi:10.1016/j.canlet.2009.09.017
87. Haemmerle M, Gutschner T, Pradeep S, et al. Platelets reduce anoikis and promote metastasis by activating YAP1 signaling. *Nat Commun*. 2017;08(1):21.
88. Sood AK, Armaiz-Pena GN, Halder J, et al. Adrenergic modulation of focal adhesion kinase protects human ovarian cancer cells from anoikis. *J Clin Invest*. 2010;120:1515–1523. doi:10.1172/JCI40802
89. Zillhardt M, Park SM, Romero IL, et al. Foretinib (GSK1363089), an orally available multikinase inhibitor of c-Met and VEGFR-2, blocks proliferation, induces anoikis, and impairs ovarian cancer metastasis. *Clin Cancer Res*. 2011;17:4042–4051. doi:10.1158/1078-0432.CCR-10-3387
90. Carmignani CP, Sugarbaker T, Bromley CM, Sugarbaker PH. Intraperitoneal cancer dissemination: mechanisms of the patterns of spread. *Cancer Metastasis*. 2003;22(4):465–472. doi:10.1023/A:1023791229361
91. Kipps E, Tan DS, Kaye SB. Meeting the challenge of ascites in ovarian cancer: new avenues for therapy and research. *Nat Rev Cancer*. 2013;13:273–282. doi:10.1038/nrc3432
92. Abrahams VM, Straszewski SL, Kamsteeg M, et al. Epithelial ovarian cancer cells secrete functional Fas ligand. *Cancer Res*. 2003;63(17):5573–5581.
93. Feki A, Berardi P, Bellingan G, et al. Dissemination of intraperitoneal ovarian cancer: discussion of mechanisms and demonstration of lymphatic spreading in ovarian cancer model. *Crit Rev Oncol Hematol*. 2009;72:1–9. doi:10.1016/j.critrevonc.2008.12.003
94. Clark R, Krishnan V, Schoof M, et al. Milky spots promote ovarian cancer metastatic colonization of peritoneal adipose in experimental models. *Am J Pathol*. 2013;183:576–591. doi:10.1016/j.ajpath.2013.04.023
95. Byrne AT, Holash J, Nakanishi M, et al. Vascular endothelial growth factor-trap decreases tumor burden, inhibits ascites, and causes dramatic vascular remodeling in an ovarian cancer model. *Clin Cancer Res*. 2003;9:5721–5728.
96. Bekes I, Köhler T, Möbus V, Janni W, Wöckel A, Wulff C. Does VEGF facilitate local tumor growth and spread into the abdominal cavity by suppressing endothelial cell adhesion, thus increasing vascular peritoneal permeability followed by ascites production in ovarian cancer? *Mol Cancer*. 2016;15:13. doi:10.1186/s12943-016-0497-3
97. Herr D, Sallmann A, Bekes I, et al. VEGF induces ascites in ovarian cancer patients via increasing peritoneal permeability by downregulation of Claudin 5. *Gynecol Oncol*. 2012;127:210–216. doi:10.1016/j.ygyno.2012.05.002
98. Scotton CJ, Wlison JL, Scott K, et al. Multiple actions of the chemokine CXCL12 on epithelial tumor cells in human ovarian cancer. *Cancer Res*. 2002;62(20):5930–5938.
99. Kenny HA, Kaur S, Coussens LM, Lengyel E. The initial steps of ovarian cancer cell metastasis are mediated by MMP-2 cleavage of vitronectin and fibronectin. *J Clin Invest*. 2008;118:1367–1379. doi:10.1172/JCI33775
100. SA KG C, Niloff J, DeFranzo B, Kim Y, Ottensmeier C. Binding of ovarian cancer cells to peritoneal mesothelium in vitro is partly mediated by CD44H. *Cancer Res*. 1993;53(16):3830–3838.
101. Witz CA, Cho S, Centonze VE, Bonewald LF, Schenken RS. Composition of the extracellular matrix of the peritoneum. *J Soc Gynecol Investig*. 2001;8:299–304.
102. Burleson KM, Boente MP, Pambuccian SE, Skubitz AP. Disaggregation and invasion of ovarian carcinoma ascites spheroids. *J Transl Med*. 2006;4:6. doi:10.1186/1479-5876-4-6
103. Burleson KM, Casey RC, Skubitz KM, Pambuccian SE, Oegema TR Jr., Skubitz AP. Ovarian carcinoma ascites spheroids adhere to extracellular matrix components and mesothelial cell monolayers. *Gynecol Oncol*. 2004;93:170–181. doi:10.1016/j.ygyno.2003.12.034
104. Mehner C, Miller E, Ran S, Radisky DC, Radisky ES. Tumor cell-produced matrix metalloproteinase 9 (MMP-9) drives malignant progression and metastasis of basal-like triple negative breast cancer. *Oncotarget*. 2014;5:2736.
105. Nakamura K, Kinose Y, Yoshimura A, et al. Exosomes promote ovarian cancer cell invasion through transfer of CD44 to peritoneal mesothelial cells. *Mol Cancer Res*. 2017;15:78–92.
106. Birbeck MS. An electron microscopic study of the invasion of ascites tumor cells into the abdominal wall. *Cancer Res*. 1965;25:490–497.
107. Iwanicki MP, Davidowitz RA, Ng MR, et al. Ovarian cancer spheroids use myosin-generated force to clear the mesothelium. *Cancer Discov*. 2011;1:144–157. doi:10.1158/2159-8274.CD-11-0010

108. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med*. 1995;1:27–31. doi:10.1038/nm0195-27
109. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005;23:1011–1027. doi:10.1200/JCO.2005.06.081
110. De Palma M, Biziato D, Petrova TV. Microenvironmental regulation of tumour angiogenesis. *Nat Rev Cancer*. 2017;17:457–474. doi:10.1038/nrc.2017.51
111. Matsubara T, Kanto T, Kuroda S, et al. TIE2-expressing monocytes as a diagnostic marker for hepatocellular carcinoma correlates with angiogenesis. *Hepatology*. 2013;57:1416–1425. doi:10.1002/hep.25965
112. Liang W, Ferrara N. The complex role of neutrophils in tumor angiogenesis and metastasis. *Cancer Immunol Res*. 2016;4:83–91. doi:10.1158/2326-6066.CIR-15-0313
113. Kujawski M, Lee H, Herrmann A, Kay H, Yu H. Stat3 mediates myeloid cell-dependent tumor angiogenesis in mice. *J Clin Invest*. 2008;118:3367–3377.
114. Shojaei F, Wu X, Zhong C, et al. Bv8 regulates myeloid-cell-dependent tumour angiogenesis. *Nature*. 2007;450:825–831. doi:10.1038/nature06348
115. G BR B, McMahon G, Vu TH, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol*. 2000;2:737–744. doi:10.1038/35036374
116. Deryugina EI, Zajac E, Juncker-Jensen A, Kupriyanova TA, Welter L, Quigley JP. Tissue-infiltrating neutrophils constitute the major in vivo source of angiogenesis-inducing MMP-9 in the tumor microenvironment. *Neoplasia*. 2014;16:771–788. doi:10.1016/j.neo.2014.08.013
117. Sierra JR, Corso S, Caione L, et al. Tumor angiogenesis and progression are enhanced by Sema4D produced by tumor-associated macrophages. *J Exp Med*. 2008;205:1673–1685. doi:10.1084/jem.20072602
118. Wenes M, Di Matteo M, Goveia J, et al. Macrophage metabolism controls tumor blood vessel morphogenesis and metastasis. *Cell Metab*. 2016;24(5):701–715. doi:10.1016/j.cmet.2016.09.008
119. Naora H, Montell DJ. Ovarian cancer metastasis: integrating insights from disparate model organisms. *Nat Rev Cancer*. 2005;5:355–366. doi:10.1038/nrc1611
120. DS AR T, Kaye SB. Mechanisms of transcoelomic metastasis in ovarian cancer. *Lancet Oncol*. 2006;11:925–934.
121. Lengyel E. Ovarian cancer development and metastasis. *Am J Pathol*. 2010;177:1053–1064. doi:10.2353/ajpath.2010.100105
122. Kenny HA, Dogan S, Zillhardt M, Yamada SD, Krausz T, Lengyel E. Organotypic models of metastasis: A three-dimensional culture mimicking the human peritoneum and omentum for the study of the early steps of ovarian cancer metastasis. *Cancer Treat Res*. 2009;149:335–351. doi:10.1007/978-0-387-98094-2_16
123. Coffman LG, Burgos-Ojeda D, Wu R, Cho K, Bai S, Buckanovich RJ. New models of hematogenous ovarian cancer metastasis demonstrate preferential spread to the ovary and a requirement for the ovary for abdominal dissemination. *Transl Res*. 2016;75:92–102 e102. doi:10.1016/j.trsl.2016.03.016
124. Matsuo K, Carter CM, Ahn EH, et al. Inferior vena cava filter placement and risk of hematogenous distant metastasis in ovarian cancer. *Am J Clin Oncol*. 2013;36:362–367. doi:10.1097/COC.0b013e318248da32
125. Obermayr E, Castillo-Tong DC, Pils D, et al. Molecular characterization of circulating tumor cells in patients with ovarian cancer improves their prognostic significance – a study of the OVCAD consortium. *Gynecol Oncol*. 2013;128:15–21. doi:10.1016/j.ygyno.2012.09.021
126. Allard WJ, Miller MC, Repollet M, et al. Tumor cells circulate in the peripheral blood of all major carcinomas but not in healthy subjects or patients with nonmalignant diseases. *Clin Cancer Res*. 2004;10(20):6897–6904. doi:10.1158/1078-0432.CCR-04-0378
127. Gasparri ML, Savone D, Besharat RA, et al. Circulating tumor cells as trigger to hematogenous spreads and potential biomarkers to predict the prognosis in ovarian cancer. *Tumour Biol*. 2016;37:71–75. doi:10.1007/s13277-015-4299-9
128. Figueras A, Alsina-Sanchis E, Lahiguera A, et al. A role for CXCR4 in peritoneal and hematogenous ovarian cancer dissemination. *Mol Cancer Ther*. 2018;17:532–543. doi:10.1158/1535-7163.MCT-17-0643
129. Torchiaro E, Olivero M, Valdembri D, et al. Peritoneal and hematogenous metastases of ovarian cancer cells are both controlled by the p90RSK through a self-reinforcing cell autonomous mechanism. *Oncotarget*. 2016;7(1):712–728. doi:10.18632/oncotarget.6412
130. Pradeep S, Kim SW, Wu SY, et al. Hematogenous metastasis of ovarian cancer: rethinking mode of spread. *Cancer Cell*. 2014;26:77–91. doi:10.1016/j.ccr.2014.05.002
131. Yuan R, Li S, Geng H, *et al*. Reversing the polarization of tumor-associated macrophages inhibits tumor metastasis. *Int Immunopharmacol*. 2017;49:30–37. doi:10.1016/j.intimp.2017.05.014
132. Zhou Q, Peng RQ, Wu XJ, et al. The density of macrophages in the invasive front is inversely correlated to liver metastasis in colon cancer. *J Transl Med*. 2010;8(8):13. doi:10.1186/1479-5876-8-72
133. Qing W, Fang WY, Ye L, et al. Density of tumor-associated macrophages correlates with lymph node metastasis in papillary thyroid carcinoma. *Thyroid*. 2012;22(9):905–910. doi:10.1089/thy.2011.0452
134. Qian BZ, Zhang H, Li J, et al. FLT1 signaling in metastasis-associated macrophages activates an inflammatory signature that promotes breast cancer metastasis. *J Exp Med*. 2015;212(9):1433–1448. doi:10.1084/jem.20141555
135. Yang Y, Andersson P, Hosaka K, et al. The PDGF-BB-SOX7 axis-modulated IL-33 in pericytes and stromal cells promotes metastasis through tumour-associated macrophages. *Nat Commun*. 2016;6(7):11385. doi:10.1038/ncomms11385
136. Hiwatashi K, Tamiya T, Hasegawa E, et al. Suppression of SOCS3 in macrophages prevents cancer metastasis by modifying macrophage phase and MCP2/CCL8 induction. *Cancer Lett*. 2011;308(2):172–180. doi:10.1016/j.canlet.2011.04.024
137. Ryan AE, Colleran A, O'Gorman A, et al. Targeting colon cancer cell NF-κB promotes an anti tumour M1-like macrophage phenotype and inhibits peritoneal metastasis. *Oncogene*. 2015;34(12):1563–1574. doi:10.1038/onc.2014.86
138. Binnemars-Postma K, Bansal R, Storm G, et al. Targeting the Stat6 pathway in tumor-associated macrophages reduces tumor growth and metastatic niche formation in breast cancer. *Faseb J*. 2018;32(2):969–978. doi:10.1096/fj.201700629R
139. Chen XW, Yu TJ, Zhang J, et al. CYP4A in tumor-associated macrophages promotes pre-metastatic niche formation and metastasis. *Oncogene*. 2017;36(35):5045–5057. doi:10.1038/onc.2017.118
140. Nielsen SR, Quaranta V, Linford A, et al. Macrophage-secreted granulin supports pancreatic cancer metastasis by inducing liver fibrosis. *Nat Cell Biol*. 2016;18(5):549–560. doi:10.1038/ncb3340
141. Celus W, Di Conza G, Oliveira AI, et al. Loss of caveolin-1 in metastasis-associated macrophages drives lung metastatic growth through increased angiogenesis. *Cell Rep*. 2017;21(10):2842–2854. doi:10.1016/j.celrep.2017.11.034
142. Jung M, Ören B, Mora J, et al. Lipocalin 2 from macrophages stimulated by tumor cell-derived sphingosine 1-phosphate promotes lymphangiogenesis and tumor metastasis. *Sci Signal*. 2016;9(434):ra64. doi:10.1126/scisignal.aaf3241
143. Weiss JM, Ridnour LA, Back T, et al. Macrophage-dependent nitric oxide expression regulates tumor cell detachment and metastasis after IL-2/anti-CD40 immunotherapy. *J Exp Med*. 2010;207(11):2455–2467. doi:10.1084/jem.20100670
144. Chen J, Yao Y, Gong C, et al. CCL18 from tumor-associated macrophages promotes breast cancer metastasis via PITPNM3. *Cancer Cell*. 2011;19(4):541–555. doi:10.1016/j.ccr.2011.02.006

145. Robinson-Smith TM, Isaacsohn I, Mercer CA, et al. Mediate inflammation-enhanced metastasis of ovarian tumors in mice. *Cancer Res*. 2007;67(12):5708–5716. doi:10.1158/0008-5472.CAN-06-4375
146. Fogg KC, Olson WR, Miller JN, et al. Alternatively activated macrophage-derived secretome stimulates ovarian cancer spheroid spreading through a JAK2/STAT3 pathway. *Cancer Lett*. 2019;458:92–101. doi:10.1016/j.canlet.2019.05.029
147. Liu Y, Metzinger MN, Lewellen KA, et al. Obesity contributes to ovarian cancer metastatic success through increased lipogenesis, enhanced vascularity, and decreased infiltration of M1 macrophages. *Cancer Res*. 2015;75(23):5046–5057. doi:10.1158/0008-5472.CAN-15-0706
148. Zeng XY, Xie H, Yuan J, et al. M2-like tumor-associated macrophages-secreted EGF promotes epithelial ovarian cancer metastasis via activating EGFR-ERK signaling and suppressing lncRNA LIMT expression. *Cancer Biol Ther*. 2019;20(7):956–966. doi:10.1080/15384047.2018.1564567
149. Carroll MJ, Fogg KC, Patel HA, et al. Alternatively activated macrophages upregulate mesothelial expression of P-selectin to enhance adhesion of ovarian cancer cells. *Cancer Res*. 2018;78(13):3560–3573. doi:10.1158/0008-5472.CAN-17-3341
150. Wang R, Zhang T, Ma Z, et al. The interaction of coagulation factor XII and monocyte/macrophages mediating peritoneal metastasis of epithelial ovarian cancer. *Gynecol Oncol*. 2010;117(3):460–466. doi:10.1016/j.ygyno.2010.02.015
151. SL RB S, DeNardo DG, Faddegon BA, Park CC, Coussens LM. TH2-polarized CD4(+) T cells and macrophages limit efficacy of radiotherapy. *Cancer Immunol Res*. 2015;3(5):518–525. doi:10.1158/2326-6066.CIR-14-0232
152. Song M, Liu T, Shi C, Zhang X, Chen X. Bioconjugated manganese dioxide nanoparticles enhance chemotherapy response by priming tumor-associated macrophages toward m1-like phenotype and attenuating tumor hypoxia. *ACS Nano*. 2016;10:633–647. doi:10.1021/acsnano.5b06779
153. Petty AJ. Tumor-associated macrophages: implications in cancer immunotherapy. *Immunotherapy*. 2017;9(3):289–302. doi:10.2217/imt-2016-0135
154. Dammeijer F, Lievense LA, Kaijen-Lambers ME, et al. Depletion of tumor-associated macrophages with a CSF-1R kinase inhibitor enhances antitumor immunity and survival induced by DC immunotherapy. *Cancer Immunol Res*. 2017;5:535–546. doi:10.1158/2326-6066.CIR-16-0309
155. Zhu Y, Knolhoff BL, Meyer MA, et al. CSF1/CSF1R blockade reprograms tumor-infiltrating macrophages and improves response to T-cell checkpoint immunotherapy in pancreatic cancer models. *Cancer Res*. 2014;74:5057–5069. doi:10.1158/0008-5472.CAN-13-3723
156. Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity*. 2014;41:49–61. doi:10.1016/j.immuni.2014.06.010
157. Li X, Yao W, Yuan Y, et al. Targeting of tumour-infiltrating macrophages via CCL2/CCR2 signalling as a therapeutic strategy against hepatocellular carcinoma. *Gut*. 2015;66:157–167. doi:10.1136/gutjnl-2015-310514
158. Loberg RD, Ying C, Craig M, et al. Targeting CCL2 with systemic delivery of neutralizing antibodies induces prostate cancer tumor regression in vivo. *Cancer Res*. 2007;67:9417–9424. doi:10.1158/0008-5472.CAN-07-1286
159. Parayath NN, Gandham SK, Leslie F, Amiji MM. Improved anti-tumor efficacy of paclitaxel in combination with MicroRNA-125b-based tumor-associated macrophage repolarization in epithelial ovarian cancer. *Cancer Lett*. 2019;461:1–9. doi:10.1016/j.canlet.2019.07.002
160. Wiehagen KR, Girgis NM, Yamada DH, et al. Combination of CD40 Agonism and CSF-1R blockade reconditions tumor-associated macrophages and drives potent antitumor immunity. *Cancer Immunol Res*. 2017;5(12):1109–1121. doi:10.1158/2326-6066.CIR-17-0258
161. Banerjee S, Halder K, Ghosh S, Bose A, Majumdar S. The combination of a novel immunomodulator with a regulatory T cell suppressing antibody (DTA-1) regress advanced stage B16F10 solid tumor by repolarizing tumor-associated macrophages in sit. *Oncoimmunology*. 2015;4(3):e995559. doi:10.1080/2162402X.2015.1008371
162. Robinson-Smith TM, Isaacsohn I, Mercer CA, et al. Macrophages mediate inflammation-enhanced metastasis of ovarian tumors in mice. *Cancer Res*. 2007;67(12):5708–5716. doi:10.1158/0008-5472.CAN-06-4375