



# Role of CC Chemokines Subfamily in the Platinum Drugs Resistance Promotion in Cancer

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Cancer is a significant medical issue, being one of the main causes of mortality around the world. The therapies for this pathology depend on the stage in which the cancer is found, but it is usually diagnosed at an advanced stage in which the treatment is chemotherapy. Platinum drugs are among the most commonly used in therapy, unfortunately, one of the main obstacles to this treatment is the development of chemoresistance, which is the ability of cancer cells to evade the effects of drugs. Although some molecular mechanisms involved in resistance to platinum drugs are described, elucidation is still required of others. Secretion of inflammatory mediators such as cytokines and chemokines, by tumor microenvironment components or tumor cells, show direct influence on proliferation, metastasis and progression of cancer and are related to chemoresistance and poor prognosis. In this review, the general mechanisms associated with resistance to platinum drugs, inflammation on cancer development and chemoresistance in various types of cancer will be approached with special emphasis on the current history of CC chemokines subfamily-mediated chemoresistance.

**Keywords:** inflammation, cancer, CC chemokine subfamily, platinum drugs, chemoresistance

## INTRODUCTION

Cancer is a major public health problem, one of the leading causes of death around the world (1). Therapies depend on the stage in which the cancer is found, but usually, diagnosis is at an advanced stage, in which treatment choice is chemotherapy. However, cancer cells develop chemoresistance through a combination of cellular and molecular mechanisms, and are consequently related to poor prognosis and lower patient's survival (2). Inflammation mediated by cytokines and chemokines has been linked to cancer initiation, promotion, and chemoresistance (3), all associated with the tumor microenvironment (TME) composed of stem cells, cancer cells, endothelial cells, immune cells, as well as fibroblasts and the extracellular matrix (ECM) (4). As part of the TME, cancer-associated fibroblasts (CAF) are involved in tumor progression, metastasis and drug resistance. CAFs are activated fibroblasts triggering signals involved in growth, differentiation and therapy evasion, and also secrete growth factors (epidermal growth factor, EGF) and IL-6 cytokine (4). Also, cytokines and chemokines are secreted by the TME and cancer cells through paracrine/autocrine mechanisms associated with chemoresistance (5). In the present review, the general mechanisms

associated with inflammation in cancer development and platinum drug chemoresistance, and in particular, the role of CC chemokines subfamily in chemoresistance will be discussed.

## CANCER AND PLATINUM DRUGS

Cancer is a major cause of mortality worldwide (1), with cancer therapy depending on the tumor stage, which unfortunately, as with most cancers is diagnosed in stages in which the tumor is spread, with low survival rates (6). When chemotherapy is needed in advanced cases of cancer, one of the most used drugs is the platinum-based (6), although a major problem in cancer treatment, in addition to late diagnosis, is chemoresistance.

Platinum drugs are widely used in the treatment of different tumors, three of these compounds are approved by the United States Food and Drug Administration: cisplatin, carboplatin and oxaliplatin (7). Platinum drugs enter the cell through diffusion or by plasma membrane-mediated transporters (CTR1), usually allowing copper influx (8), by binding to methionine, histidine or cysteine CTR1 residues (9) to act as enzyme cofactor (10). Once inside the cell, platinum drugs bind to proteins, reduced Glutathione (GSH), and DNA N-7 site of purines (11). Adduct blocks DNA transcription and synthesis, and DNA repair mechanisms, triggering cell cycle arrest and apoptosis (12). Carboplatin forms a greater amount of intra-strand adducts compared to cisplatin, but the formation rate is 10 times slower, related to a lower toxicity (13). Compared to cisplatin, oxaliplatin induces potentially more lethal functional lesions, with greater cytotoxicity in human tumor cell lines, requiring less DNA lesions than cisplatin to inhibit cell growth (13).

Platinum drugs are an effective way to treat cancer, however, drug resistance may hinder therapy (14). Resistance to platinum drugs could develop through several mechanisms: decreased drug entry into the cell, increased expulsion (8, 11), increased detoxification (15, 16), increased DNA repair pathways (12, 17), upregulation of anti-apoptotic proteins such as Bcl-2, Bcl-XL, MCL-1(11), among others. Alternatively, epithelial mesenchymal transition (EMT) accompanies the development of drug resistance, with several molecules associated with EMT, such as transcription factors (Snail, Twist) and miRNAs (miRNA-200 family, miR-15, miR-186, etc.), being recognized as important for drug resistance (18) with effect in diverse signaling pathways associated with epithelial-mesenchymal transition such as STAT3, Notch, SMAD (19). In addition, DNA methylation of tumor suppressor genes and histone modifications are important resistance mechanisms (20). Finally, recent investigations associate epigenetic regulations as potential resistance mechanisms (21), with cisplatin resistance regulated by microRNAs and methylation/demethylation of genes such as FANCF in ovarian cancer, and related to cytokines/chemokines (axis CXCL12-CXCR4) (8) to be studied in detail later in the review. Examples of reported tumors developing resistance to cisplatin are ovarian cancer (22, 23) usually developed during treatment (acquired resistance) (24), cervical (25, 26), lung (27, 28), and gastric cancer (29, 30); the last two can also develop

intrinsic resistance, occurring when the drug is ineffective from the beginning of treatment (14, 31).

## INFLAMMATION AND CANCER

Inflammation is a physiological response to cell damage by injury or infection (32), with pathogens not only related to chronic inflammation, but also immune system deregulation or autoimmunity, such as inflammatory bowel diseases, which increases colon cancer risk (33). Currently, about 20% of malignant tumors are related to chronic inflammation, including colon, gastric, liver, breast and lung cancer (34), with this phenomenon first observed in 1863 by Rudolph Virchow describing tumor leukocytes (35). Subsequently, the role of inflammatory cells described “chemical mediators” in the development of an inflammatory condition (36), currently known as cytokines and chemokines. Cytokines are low molecular weight polypeptide/glycoproteins synthesized by immune cells, stromal cells (fibroblasts and endothelial cells) (37) and tumor cells. Cytokines are responsible of proliferation, cell survival, differentiation, immune cell activation, cell migration, and death. Chemokines are a group of secreted proteins within the cytokine family of early induction (20), being a group of small proteins (8–12 kDa) stimulating lymphocyte migration from blood to tissues (chemotaxis), inducing integrin expression (38, 39). Cytokines and chemokines act in an autocrine manner, being endogenously synthesized by cells, and when they are secreted act on the same producing cell through specific receptors. In paracrine regulation, chemokines are produced and secreted by a cell acting in adjacent cells, sensed through specific receptors (40). The most studied cytokines in cancer are: tumor necrosis factor (TNF- $\alpha$ ), involved in angiogenesis and invasion; Interleukin-1 (IL-1), associated with metastasis, and IL-8-associated proliferation and migration (41). Therefore, inflammation is involved at various stages of tumor development: in initiation favoring mutation development and increasing reactive oxygen and nitrogen species causing DNA damage (3). Meanwhile, immune cells infiltrating the tumor produce cytokines, activating key transcription factors (NF- $\kappa$ B, STAT3, and AP-1), and participate in tumor progression and angiogenesis. In summation, the main signaling pathways involved in the relationship of inflammation and cancer are NF- $\kappa$ B, STAT3, PI3K/Akt, and MAPK (35).

## CELLULAR COMPONENTS FROM THE TUMOR MICROENVIRONMENT (TME)

In recent years, the concept of TME has been introduced, consisting of various cells including cancer, mesenchymal, endothelial, immune, together with ECM, and fibroblasts contributing to tumor progression (4). Tumors are more complex than just a set of malignant cancer cells, since tumor cells efficiently recruit immune and vascular cells through secretion of growth factors, chemokines and cytokines. These recruited cells release growth-promoting signals and intermediate metabolites, allowing tissue structure remodeling,

and reciprocal communication between cancer cells and TME eventually leads to increased proliferation and metastatic capacity (42).

## CANCER ASSOCIATED FIBROBLASTS (CAF)

The fibroblasts present in the TME “activated” through TGF- $\beta$  (released from tumor cells) generate CAF, with particular characteristics differentiating it from non-activated fibroblasts: star shape, expression of alpha smooth muscle actin ( $\alpha$ -SMA) and fibroblast activation protein (FAP) markers (43). In addition to secretory phenotype, CAFs reshape the ECM and autocrine/dynamic activation in immune signaling functions, allowing persistent stimulus for tumor development favoring growth of tumor cells and metastasis (44). CAFs remodel tumor vasculature through secretion of VEGF, FGF and IL-6, and ECM, through secretion of matrix metalloproteinases (MMPs) and ECM proteins. Furthermore, they modulate pro-tumorigenic inflammation through secretion of IL-1, IL-6, TNF- $\alpha$ , TGF- $\beta$ , and CCL2, favoring tumor growth, angiogenesis, invasion and metastasis (44, 45). In gastric cancer, CAFs also influence carcinogenesis through IL-6 induction in metastasis and invasion through factor overexpression increasing the epithelial-mesenchymal transition (EMT), finally activating the JAK2/STAT3 pathway (46). Additionally, the fibroblast growth factor-9 (FGF-9) secreted by CAFs trigger EMT and metastasis, together with CXCL12 and interleukin-11 inducing migration and invasion (46). In the case of inflammation associated with *Helicobacter pylori* infection, CAFs contribute to neoplastic transformation through activating a positive feedback mechanism of STX3-dependent COX-2, influencing STAT3 regulation via IL-6. Finally, induction of NF- $\kappa$ B increases cytidine deaminase expression leading to multiple mutations in the host genome such as those found in TP53 (47).

## TUMOR-ASSOCIATED MACROPHAGES (TAMs)

TAMs refer to macrophages infiltrating the tumor and are not a homogenous cell population, but rather highly heterogenic cells participating in carcinogenesis (48). Usually, two extreme states of differentiation in macrophages are recognized: the classic phenotype (M1), associated to antitumor and pro-inflammatory activity [mediated by the secretion of cytokines IL-1 $\beta$ , TNF- $\alpha$ , and IL-6 (49)] and the alternative phenotype (M2), with pro-tumor and anti-inflammatory activity. M2 acts directly on the tumor cells and indirectly on the TME (50) by producing growth factors (Fibroblast Growth Factors, FGF; Vascular Endothelial Growth Factor, VEGF, and IL-6), matrix degrading enzymes and cytokines, thus inducing the neo-angiogenesis switch, tumor progression (37), tissue invasion and repair (51–54).

In colorectal cancer (CRC), TAMs show a greater infiltration in patients with better prognosis, or in those with less recurrence or complications (55–58), and are associated with a higher survival (59). Alternatively, M2-type macrophages are associated

with a worse prognosis, less survival and later stages of disease (60, 61). TAMs with M2 profile produce enzymes and inhibitors regulating digestion of the ECM, metastasis and angiogenesis (62, 63) and additionally, control ECM composition directly or through the activation of fibroblasts, thus promoting tumor progression (64).

## MESENCHYMAL STROMAL CELL (MSC)

MSC are adult multipotent stem cells located as pericytes in organs and tissues differentiating into specialized cells. Actually, MSC promote tumorigenic processes, such as angiogenesis, malignant cell, metastasis and chemoresistance (65). TME can be influenced by MSC through cytokine secretion and TGF- $\beta$  involved in the EMT of carcinoma cells, necessary in favoring cancer progression (66). Alternatively, TNF- $\alpha$ -activated MSC promotes metastasis in lung cancer, through CCL5 and CCR2 ligands. Moreover, CXCR2 ligands (CXCL1, 2, and 5) induced by TNF- $\alpha$ -activated MSC recruit CXCR2<sup>+</sup> neutrophils into tumor, responsible for the pro-metastatic effect of MSC (67).

## CYTOKINES AND CHEMORESISTANCE

Cytokines have direct influence on cancer progression (5), secreted by both the TME and cancer cells, with TME cytokines inducing chemoresistance through paracrine regulation on tumor cells, promoting apoptosis inhibition, increased cell proliferation or drug efflux (5). In breast cancer, IL-6 and IL-8 are increased in resistant cells compared to parental cells sensitive to tamoxifen (5). Additionally, cisplatin-treated CAF increases IL-11 secretion, promoting drug resistance of lung adenocarcinoma through IL-11R/STAT3 pathway activation and subsequently upregulation of anti-apoptotic proteins (68). CAFs also secrete IL-11 promoting chemoresistance in gastric cancer through JAK/STAT3/Bcl-2 signaling pathway activation (69). Alternatively, cytokine three signaling suppressor (SOCS3), a negative cytokine regulator inhibiting the JAK/STAT pathway, is decreased in cisplatin-resistant lung tumor cells (70). Autocrine IL-6 or IL-8 secretion by ovarian cancer cells induces resistance to paclitaxel and cisplatin, due to decreased proteolytic caspase 3 activation, increased Bcl-2 expression, and MAPK and PI3K/Akt pathway activation (71, 72). In colon cancer, IL-17 and IL-6-mediated chemoresistance regulates Akt and STAT3 signaling pathways, respectively (73, 74). Lastly, in gastric cancer, CAFs secrete IL-6 inducing resistance to 5-fluorouracil or cisplatin, with inhibition of its receptor (IL-6R), suppressing drug resistance (46).

## CC CHEMOKINES SUBFAMILY AND CHEMORESISTANCE

Chemokines coordinate leukocyte recruitment to tissues in physiological and pathological conditions, also mediating cell differentiation, proliferation and survival (75). Chemokines are a large subfamily of cytokines subdivided into 4 main classes (depending on location of the first two cysteine residues,

C, in the protein sequence), such as: CC (first 2 adjacent cysteines), CXC (cysteines separated by another amino acid), C (cysteine in the amino terminal region), and CX3C (with three intermediate residues separating the cysteine). There is redundancy in this superfamily, with several ligands binding to the same receptors and vice versa (76). Chemokines act through G-protein coupled receptors, having 7 transmembrane regions, interacting with proteoglycan glycosamino-glycans, with a nomenclature associated with the binding-chemokine type: receptors for CC (CCR), CXC (CXCR), C (XCR1), and for CX3C (CX3CR1) (77). Chemokine binding triggers phosphorylation of serine/threonine residues in the receptor, this activation involves GTP binding to the Ga subunit of the Gb dissociation complex and initiating signaling pathways (PI3K, MAPK, and Rho) involved in proliferation, motility, and expression of MMPs and cytokines. Chemokine receptors also activate independent G protein pathways such as JAK/STAT regulating migration and gene transcription (78). The relationship of chemokines with tumor development can be indirect or direct. Indirect action acknowledges that tumors secrete chemokines attracting leukocytes producing growth factors, as CCL2 secretion increases M2-type TAM in breast cancer (79). Additionally, the tumor stroma may deliver inflammatory chemokines affecting tumor development, stroma-derived CXCL12 binds CXCR4 receptor possibly promoting tumor progression by stimulating angiogenesis (80). Direct chemokine action has been related to functional receptor expression by the tumor cells, with receptors associated with increased proliferation and survival. For example, CXCR4 receptor is expressed in tumors such as ovary, glioma, melanoma and renal, CXCR6 in prostate cancer, CXCR2 in melanoma and CCR6 in colorectal and pancreatic cancer (75). Moreover, CCL2 induces a pro-tumorigenic mechanism based on autocrine secretion and activation of CCR2, thus inhibiting apoptosis (80). CXC chemokine receptors have prognostic value in gastric cancer, with CXCR2 (81) and CXCR4 (82) related to poor prognosis, while CXCR3 has good prognosis (83). Regarding CC chemokines, CCL7 and CCL21 overexpression is associated with poor prognosis (84), CCR7 and CCR5 receptors associate with invasion and metastasis in gastric cancer, and lastly CCR7 is associated with EMT (85).

CC subfamily chemokines have been implicated in chemoresistance (Table 1). CCL5 activates STAT3 through an autocrine loop inhibiting caspase-9/PARP and modulates Bcl-2 (5). Autocrine regulation evades drug response, where tumor-derived cytokines activate signaling pathways involved in survival and proliferation, counteracting the effects of chemotherapy. In lung cancer, CCL2 is linked to Docetaxel resistance through PI3K/Akt pathway activation, inhibiting caspase 3-dependent apoptosis (101); this review is focused in platinum drugs, but chemokines also affect other cancer drugs such as Docetaxel (101) or Tamoxifen (102). Additionally in gastric cancer, CCL2 initiates chemoresistance to platinum drugs through PI3K/Akt/mTOR signaling pathway activation by inhibiting pro-apoptotic autophagy and increasing SQSTM1 (receptor member for autophagy) expression (86). In ovarian cancer, cisplatin induces CAF-derived CCL5 secretion, promoting drug resistance,

mediated by PI3K and STAT3 signaling pathway regulation, inhibiting apoptosis and promoting proliferation (92). Also, stroma-derived CCL2/CCL5 induces IL-6 release from the tumor cell generating carboplatin resistance through PYK2 pathway activation (positioned upstream of the JAK1/STAT3 pathway), a critical mediator of survival pathway activation (91). Likewise, CCL20 is associated with doxorubicin resistance through MDR1 membrane transporter expression regulation (103). Finally, CCR9 receptor is associated with cisplatin resistance in ovarian (100) and breast cancer (99) through the PI3K pathway activation.

## TME AND CC CHEMOKINE MECHANISM TO INDUCE CHEMORESISTANCE

Chemokines of the CC subfamily responsible for chemoresistance have different origins according to TME and tumor heterogeneity. In fact, chemokines are secreted in a paracrine manner from the TME mainly by macrophages, CAFs, or MSC (5) (Figure 1).

Monocytes/macrophages are recruited to the tumor area by cancer cell derived-CCL2 (104). Once connected the tumor, TAMs respond to external signals involving innate and adaptive immune processes (105). TAMs polarized to M2 in lung cancer through CCL22 (98), produce an immune suppressive effect, decreasing antitumor activity, spreading tumor cells and chemoresistance (106).

We previously demonstrated that CCL4 tumor levels have a positive correlation with the M2 marker (CD163) (107) associated with a poor clinical outcome of colorectal cancer and lower cumulative survival than patients with low CD163 expression (58).

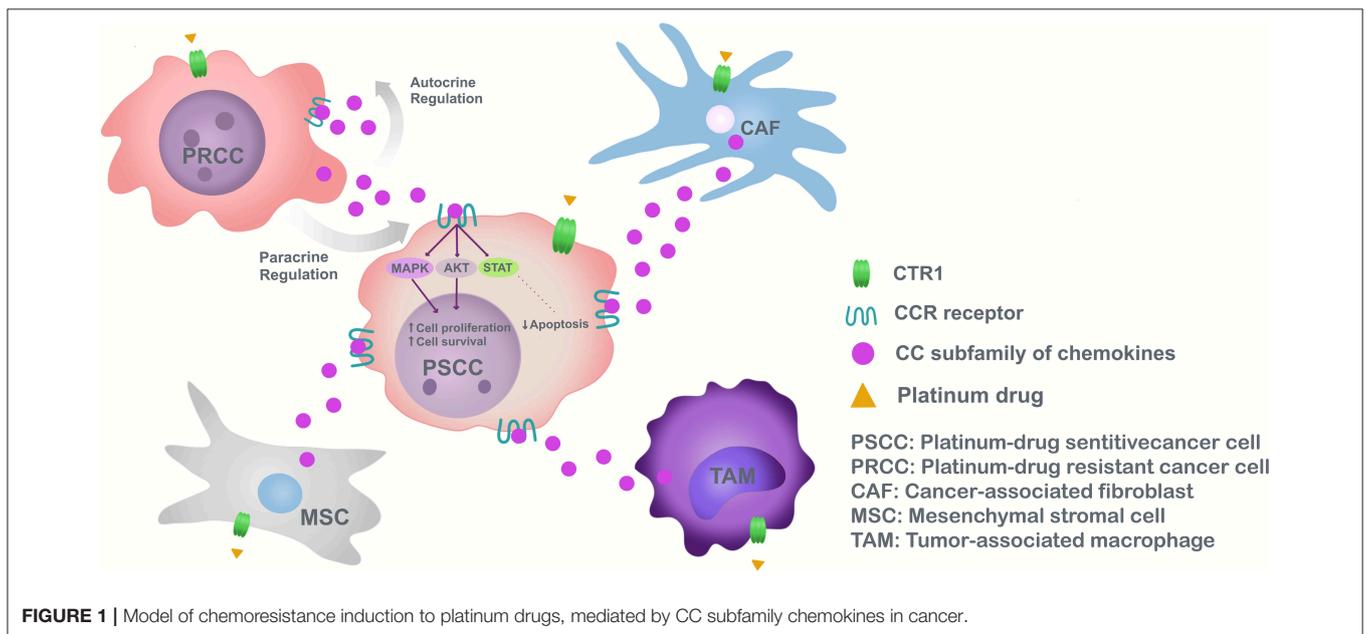
In the case of CAFs, stimulation with cisplatin increases CCL5 secretion contributing to chemoresistance in ovarian cancer (92). CAF constitute a heterogeneous cell population, express a wide range of molecular markers ( $\alpha$ -SMA, FAP), not necessarily exclusive to fibroblasts (108, 109), and may be related to cells undergoing EMT (110). The complexity of CAFs has been underestimated, with subsets tending to promote carcinogenesis (determined by type and location of tumor), have different markers from those generally used, and separating them according to origin: vCAF of perivascular cells, mCAF of resident fibroblasts and dCAF of tumor cells performing EMT (108).

Another TME component is MSC which protect ovarian cancer cells from carboplatin-induced apoptosis through inhibition of caspase activation, however, secrete high levels of IL-6 and IL-8 contributing to chemoresistance in breast cancer (105). MSC pre-treated with cisplatin increased CCL5 expression and phosphorylation of tyrosine kinases (PLC, WNK1, c-Jun, STAT3), possibly playing roles in tumor cell changes, as witnessed in breast cancer cells (111).

Due to the TME as a paracrine secretor of CC type chemokines in response to platinum drugs, chemokine production by tumor cells is studied. In this particular case, because of tumor heterogeneity and CAF origins, possibly resistant cells originating in the tumor secrete CC chemokines and induce

**TABLE 1** | Summary of chemokines of the CC sub-family in chemo resistance to platinum drugs.

CC chemokine	Tumor	Pathway	Model	Mechanism	References
CCL2	Gastric	PI3K	Resistant and sensitive co-culture	Decreases pro-apoptotic autophagy and increases SQSTM1	(86)
CCL2	Ovarian	–	<i>In vitro</i> and <i>in vivo</i>	EMT characteristic	(87)
CCL2	Lung	P38	Resistant v/s sensitive	P53 mediated apoptosis regulation	(88)
CCL2	Lung	NF-κB	<i>In vivo</i> tumor	LUBAC activation	(89)
CCL2/CCL4	Leukemia	NF-κB	Stromal mesenchymal cells	ARC (apoptosis repressor with caspase recruitment domain) /IL1β/ Mesenchymal	(90)
CCL2/CCL5	Ovarian	PYK2	Ascites (mesenchymal) and sensitive	Increase survival	(91)
CCL5	Ovarian	STAT3-PI3K	CAF	Decrease apoptosis and increase anti-apoptotic protein (bcl2)	(92)
CCL11	Ovarian	STAT3 y MAPK	Normal epithelium/tumor cell	Apoptosis control	(93)
CCL14/CCL15	Liver	PKC	Primary culture of human hepatocyte and human hepatoma cell line Alexander	The nuclear receptor (FXR) is involved in the regulation of CCL14 and CCL15. Loss of pro-apoptotic balance/survival.	(94)
CCL18	Lung	GPR30	Cell line A549	Regulation by epithelial-mesenchymal transition	(95)
CCL21	Ovarian	–	Bioinformatic analysis	–	(96)
CCL21	Lung	ERK	Cell lines A549 and H460	Overexpression of anti-apoptotic bcl-2 protein and decrease in pro-apoptotic proteins such as bax and caspase-3	(97)
CCL22	Lung	Src/CD155/ MIF	Co-culture Macrophages with cell line	M2 polarization of TAM through MIF secretion	(98)
CCL25	Breast	PI3K	Two breast cancer cell lines	Activates cell survival signals and inhibits apoptosis	(99)
CCL25	Ovarian	PI3K	Cell lines OVCAR-3 y SKOV-3	Increased survival by phosphorylating and inactivating pro-apoptotic factors, such as FKHR and GSK-3β	(100)



**FIGURE 1** | Model of chemoresistance induction to platinum drugs, mediated by CC subfamily chemokines in cancer.

chemoresistance in adjacent tumor cells (102). Resistant cells found in the heterogeneous population of cancer cells (due to aberrant DNA repair mechanisms and cell death pathway

deregulation) have stem cell properties, forming tumors in distant organs contributing to pathology reappearance after a successful therapy (112). Cancer stem-like cells have received

increasing attention, their existence observed in various tumor types, renewing themselves and differentiating into other cells. Also, cancer stem-like cells influence macrophage polarization (113), in addition to EMT, hindering development of better therapies to reduce cancer relapse (114). Tumor cells release autocrine chemokines aiding cisplatin chemoresistance by inactivating pro-apoptotic autophagy, as demonstrated by CCL2 in gastric cancer cell lines (86). This suggests that CCL2 not only maintain chemoresistance in drug-resistant tumoral cells but also confer drug resistance to drug-sensitive cancer cells (86) (Figure 1).

## CC CHEMOKINE AS THERAPEUTIC TARGET

A current cancer treatment is the immunotherapy, and its principle based in the mechanism of T-cell-mediated immunity is a complicated succession of occasions, with continuous exchange among stimulatory and inhibitory signals, when T cells are active, dynamic dealt to explicit destinations by following a chemokine gradient and advancing cytotoxicity and tumor cell killing (115).

The main targets in cancer immunotherapy are the immune checkpoint receptor called programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte Antigen 4 (CTLA-4) (116) two negative regulators of T-cell function. Inhibition of these targets resulting in increased activation of the immune system anti-tumor, has led to immunotherapies applied to treatment of melanoma, non-small cell lung cancer, and other cancers (117). Chemokines help with T cell trafficking, but some CC chemokine with pro-tumorigenic and drug-resistant function limit immunotherapy treatment.

Due to the above, the chemokines and chemokine receptors are a potential target to therapy and could reverse chemoresistance or synergizing with monotherapy

of immune-treatment (116). Direct CC chemokine antibodies targeting is an option but the main target are CC chemokine receptor such as CCR1, CCR2, CCR4, CCR5, and CCR7 by monoclonal antibodies inhibitors or antagonism molecules (118) for example, Maraviroc is a CCR5 receptor antagonism that decrease metastasis in breast (119) and gastric cancer (120) and provoke remission in pancreatic and liver cancer by apoptosis induction (20). Receptor inhibition could influence in cancer pathway signaling (121) and interfere with autocrine chemokine synthesis (5, 91).

## CONCLUSION

TME cellular components (CAF, TAM, MSC) influence the secretion of CC subfamily chemokines in a paracrine manner inducing tumor progression, metastasis and platinum drug chemoresistance. Additionally, drug-resistant cancer cells can also secrete chemokines to the adjacent environment. Therefore, tumor cellular heterogeneity, cancer-resistant cells (cancer stem-like cells or cells in EMT), and particularly the TME components, are capable of producing and secreting CC chemokines inducing a resistant phenotype in adjacent cancer-sensitive cell.

## AUTHOR CONTRIBUTIONS

MR wrote the first draft of the manuscript. MR, MF, and CI wrote sections of the manuscript. PB and MH made substantial contributions and discussed the content. All authors reviewed and/or edited the manuscript prior submission.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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