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Targeting CXCR1/CXCR2 receptor antagonism in malignant melanoma

Bhawna Sharma[1], **Seema Singh**[2], **Michelle L Varney**[1], and **Rakesh K Singh**[1,†]

[1]University of Nebraska Medical Center, Department of Pathology and Microbiology, 985900 Nebraska Medical Center, Omaha, NE 68198-5900, USA

[2]University of South Alabama, Mitchell Cancer Institute, Department of Oncologic Sciences, Mobile, AL, USA

Abstract

Importance of the field—The incidence of malignant melanoma is increasing throughout the world and is currently rising faster than any other cancer in men and second only to lung cancer in women. Current strategies focused on systemic therapy for treatment of have shown no effect on survival. Therefore there is a pressing need for developing novel targeted therapeutics.

Areas covered in this review—Our goal is to provide an overview regarding targeting CXCR1/2 in malignant melanoma, the rationale behind these approaches and the future perspective.

What the reader will gain—This review illustrates our current understanding of CXCR1/2 receptor in melanoma progression and metastasis. We describe approaches that are being developed to block CXCR1/2 activation, including low-molecular-weight antagonists, modified chemokines and antibodies directed against ligands and receptors.

Take home message—The chemokine receptors CXCR1 and CXCR2 and their ligands play an important role in the pathogenesis of malignant melanoma. Recent reports demonstrated that CXCR1 is constitutively expressed in all melanoma cases irrespective of stage and grade, however, CXCR2 expression was restricted to aggressive melanoma tumors,. Furthermore, modulation of CXCR1/2 expression and/or activity has been shown to regulate malignant melanoma growth, angiogenesis and metastasis, suggesting CXCR1/2 targeting as a novel therapeutic approach for malignant melanoma.

Keywords

chemokine receptors; CXCR1; CXCR2; melanoma; targeted therapeutics

[†]Author for correspondence. University of Nebraska Medical Center, Department of Pathology and Microbiology, 985900 Nebraska Medical Center, Omaha, NE 68198-5900, USA, Tel: +1 402 559 9949; Fax: +1 402 559 5900; rsingh@unmc.edu.

1. Introduction

Chemokines are a family of small proteins (8 – 11 kDa) that are divided into four groups according to the number and spacing of the first two cysteine residue in their amino-terminal end (C, CC, CXC, CX_3C) [1,2]. They represent a large family of polypeptide signaling molecules, originally characterized by their ability to promote the directed chemotaxis of leukocytes, and are known to play important roles in inflammation and cancer [3]. Out of these chemokines, CXC chemokines can be further sub divided into two groups on the basis of presence or absence of an ELR motif (glutamic acid, leucine and arginine) which precedes the first cysteine residues in the protein. These CXC chemokines have been implicated in the initiation and amplification of inflammatory diseases [4–7]. CXC chemokines are known to bind to G-protein-coupled receptors (GPCR) mainly CXCR1 and CXCR2 which plays an important role in cancer progression and metastasis [8–10]. There are 15 human CXC chemokines (CXCL1 – 16), but their function extends beyond leukocyte chemotaxis as the cognate receptors CXCR1 and CXCR2 are expressed on many different cell types. Over the last decade, the understanding of the function of these receptors has increased exponentially [3,8,11], leading to the discovery of potent and selective antagonists [11,12], neutralizing monoclonal antibodies to these receptors and their ligands [4,5,13], the availability of CXCR2 knockout mice [6,14–16] and the identification of polymorphisms and genetic mutations [17–20]. Recent reports provide compelling evidence that CXCR1/2 play an important role in tumor progression and metastasis and several pharmaceutical companies have identified potent CXCR1/2 antagonists, and neutralizing antibodies that are now being tested in clinical trials for inflammatory disease. In this review, we will provide an overview and future implications regarding targeting CXCR1/2 in malignant melanoma.

2. CXCR1/2 and its ligands in malignant melanoma

Although chemokines were first known as chemoattractants for leucocytes, it has been recognized that many cell types express chemokines and chemokine receptors. Interactions between chemokines and their receptors play an important part in regulating various steps of tumor development, including tumor growth, progression, and metastasis (Figure 1). In the case of melanoma, several reports strongly support the proposition that tumor cells take advantage of this chemokine– chemokine receptor interaction either to stimulate the immune response, or to induce tumor angiogenesis and tumor growth, which alters the tumor microenvironment and facilitates metastasis to secondary site [8,10,21].

Melanoma arises from melanocytes and manifests mainly on the skin and is the sixth most common cancer in the United States. According to the American Cancer Society there will be about 68,720 new cases and 8650 deaths due to melanoma during 2009 [22]. The chance of developing melanoma increases with age, but it affects all age groups and is one of the most common cancers in young adults. Most often, melanomas progress through an initial radial growth phase, or *in situ* melanoma, to a more aggressive vertical growth phase that exhibits growth in the mesenchyme and in the epithelium [23]. Melanoma tissues and cell lines derived from them have been shown to express a variety of chemokines, including CXCL8 and its receptors CXCR1 and CXCR2 [23,24]. CXCL8 alone and with its receptors can induce angiogenesis and influence migration and invasion of tumor cells along with

metastasis in melanoma [23–29]. In this review, we provide an update on targeting CXCL8 and its receptors in melanoma progression and metastasis.

3. CXCR1/2 and their ligands in melanoma tumor progression and metastasis

Tumor progression is a chain of cellular and molecular events that occur gradually during the development of neoplasia. CXCL8 was the first chemokine reported to induce melanoma cell chemotactic migration [30] and can act in an autocrine/paracrine fashion to influence the process of melanoma progression by activating CXCR1 and CXCR2 (Figure 1) [26,30]. The expression of CXCL8 along with its receptors CXCR1 and CXCR2 have been shown to correlate positively with melanoma progression [31,32]. The overexpression of CXCR1 and CXCR2 in melanoma cells is associated with aggressive phenotypes of melanoma cells based on their enhanced proliferation, migration and tumor growth in mice [23,25,26]. Knockdown of the receptors or the use of antagonists or neutralizing antibodies against them affects melanoma cell proliferation migration and tumor growth, strongly indicating the involvement of these receptors in melanoma progression [33]. CXCR2 knockout mice exhibited significant inhibition of human melanoma tumor growth [25]. Furthermore, UVB which stimulates the production of CXCL8 in turn enhances the migration of metastatic melanoma cells *in vitro* [34,35]. Altogether, these data suggest an important role for CXCL8 and its receptors in melanoma progression.

CXCL8 and its receptors can affect tumor growth not only directly but also indirectly by promoting angiogenesis and the ability of CXCL8 to elicit angiogenic activity depends on the expression of its receptors by endothelial cells. Recent studies indicate that CXCR1 is highly and CXCR2 is moderately expressed on human microvascular endothelial cells (HMEC), whereas HUVEC show low levels of CXCR1 and CXCR2 expression [36]. Neutralizing antibodies to CXCR1 and CXCR2 abrogated CXCL8-induced migration of endothelial cells, indicating that these two receptors are critical for the CXCL8 angiogenic response (Figure 2) [37,38]. Of these two high-affinity receptors for CXCL8, the importance of CXCR2 in mediating chemokine-induced angiogenesis was demonstrated to be fundamental to CXCL8-induced neovascularization [13,38,39]. CXCL8 stimulates both endothelial proliferation and capillary tube formation *in vitro* in a dose-dependent manner, and both of these effects can be blocked by monoclonal antibodies to CXCL8 [40,41]. Recent studies have also highlighted the importance of CXCR1 and CXCR2 in angiogenesis (Figure 2) [23,25–27]. In addition, it has been reported that there is a direct correlation between high levels of CXCL8 and tumor angiogenesis, progression and metastasis in xenograft models of human melanoma [42,43].

CXCL8 exerts its angiogenic activity by upregulating MMP-2 and MMP-9 in tumor and endothelial cells [37,42,44]. Degradation of the extracellular matrix by MMPs is required for endothelial cell migration, organization, and, hence, angiogenesis [45]. It has been demonstrated that CXCL8 directly enhances endothelial cell proliferation, survival and MMP expression in CXCR1- and CXCR2-expressing endothelial cells, indicating that CXCL8 is an important player in the process of angiogenesis [40].

Cell proliferation, angiogenesis and migration (invasion) are important components of the metastatic process and CXCL8 and its receptors have been implicated inmelanoma progression through several mechanisms, including the promotion of tumor cell growth and migration [30,46]. Our previous study has demonstrated a correlation between CXCL8 expression and metastatic behavior in human melanoma cells in nude mice. Additionally, in a nude mouse model, induction of UV-induced melanoma cell tumorigenesis and metastasis correlated with CXCL8 mRNA and protein expression [47]. It has also been shown that the metastatic variant of melanoma cells expressed higher levels of CXCL8 protein as compared with the non-metastatic variant [47,48]. Elevated serum levels of CXCL8 in patients with metastatic melanoma and hepatocellular carcinoma have also been reported to correlate with tumor burden and poor prognosis [49,50]. Expression of CXCL8 inmetastatic and invasive lesions may result in an increase in the serum CXCL8 concentration and may be of prognostic use and serve as a determinant of melanoma growth and metastasis [33,49,50]. *In vivo* murine studies showed that CXCR2 plays a major role in melanoma metastasis to the lung and a recent study from our laboratory suggested that human melanoma xenografts onto CXCR2 knockout nude mice exhibited inhibition of lung metastasis. This was accompanied by a reduction in tumor cell proliferation, angiogenesis and reduced inflammation [25]. CXCL8 in tumor specimens from different stages of melanoma is differentially expressed in radial growth phase (RGP; melanoma-*in-situ*) and vertical growth phase (VGP; invasive) primary malignant melanoma and subcutaneous, muscle and lymph node metastases. While the RGP tumors did not show any staining for CXCL8, 50% of the VGP tumors were positive and showed a heterogeneous pattern of staining. Interestingly, an intense CXCL8 immunoreactivity was observed in the metastatic lesions from skin, muscle and lymph node [23]. These data suggest an association between the expression of CXCL8 and metastasis in human cutaneous melanoma. Additionally, a concomitant upregulation of one of two putative CXCL8 receptors has been reported in human melanoma specimens [23]. Analysis of CXCR1 in human melanoma specimens from different Clark levels demonstrated that it is expressed ubiquitously in all Clark levels. In contrast, CXCR2 is expressed predominantly by higher grade melanoma tumors and metastases, suggesting an association between expression of CXCL8 and CXCR2 with vessel density in advanced lesions and metastases [23]. More specifically, the effect of CXCL8 can be mediated by CXCR1 and CXCR2, with CXCR1 being a selective receptor for CXCL8 [24]. Overall, the aberrant expression of CXCL8 and its receptors may be a common feature of melanoma. From the functional significance of its receptors, we can contemplate that the expression of CXCL8 and its receptors (CXCR1/CXCR2) play a key role in deciding the fate of developing melanoma tumors and their ability to metastasize to certain preferred organ sites. Given their important role, they are potential targets for therapy against human melanoma.

4. Putative signaling pathways involved in CXCR1 and CXCR2-dependent modulation of cellular phenotypes

Most of the studies with neutrophils and transfected cell lines have demonstrated that CXCR1 and CXCR2 undergo receptor phosphorylation, internalization, calcium mobilization, actin polymerization, enzyme release, chemotaxis and a weak respiratory burst upon activation by CXCL8 [51–57]. Mechanisms regulating CXCR1 and CXCR2 activation

and downstream signaling events following activation with CXCL8 in malignant melanoma are not known. Both CXCR1 and CXCR2 show a similar preference for G protein family members [58]. However, recent reports suggest that the two receptors not only possess distinct ligand binding properties but also could transduce different post-receptor signals [56,59]. In spite of the apparent redundancy, CXCR1 and CXCR2markedly differ in their capacity to activate signal transduction pathways. CXCR1 stimulates phospholipase D activation and the formation of superoxide by NADPH oxidase, whereas CXCR2 does not trigger either response [60–62]. Since CXCR1 and CXCR2 have a similar affinity for CXCL8 and bind with the same selectivity to G proteins, additional receptor-specific signal transducing mechanism(s) are assumed. Despite similar affinities for CXCL8 and similar receptor numbers of CXCR1 and CXCR2, neutrophil chemotaxis is primarily mediated by CXCR1 [63,64] suggesting diverse roles for CXCR1 and CXCR2. Previous reports using CXCL8 have shown that CXCR2, compared with CXCR1, internalizes more rapidly and recovers more slowly [55,56,59]. These differences in receptor trafficking which is mediated by β-arrestins, appear to regulate CXCR1 and CXCR2 activation during neutrophil recruitment and activation [55,56,59]. Nevertheless the molecular basis of such receptor-specific signal transduction has not yet been determined in malignant melanoma. The initial events in chemokine- induced signal transduction determine the outcome of the response and must take place in proximity of the receptor. The scheme, which is shown in Figure 3 and discussed in this paragraph, is not meant to be complete, but to present the most evident effectors in chemokine receptor signaling. Activation of the receptor by a chemokine ligand induces the exchange in the Gα-subunit from the GDP- to the GTP-bound state dissociating the α-subunit from the β and γ from G-protein subunits. These subunits activate phospholipase (PL) Cβ1 and Cβ2, followed by hydrolysis of PIP2 which leads to formation of inositol triphosphate (IP3) and diacylglycerol (DAG) with a subsequent increase in intracellular Ca^{2+} mobilization [61]. Although chemokine receptors lack tyrosine kinase activity, they can stimulate the phosphorylation of cytoskeleton proteins, p130 Cas and paxillin [65] and induce activation of the related adhesion focal tyrosine kinases (FAK) (also known as Pyk2 and CAKβ) [66], MAPK (ERK1/2, p38 and c-jun kinase) [66], PI3K [66] and Janus kinase 2 [67,68]. p44/42 kinases, also termed extracellular signal-regulated kinases (ERK1 and ERK2) are important mediators of growth and other signals [69,70]. Because most of the G protein coupled receptors can activate a variety of effector pathways via various G protein subunits, considerable heterogeneity exists in signaling pathways leading to ERK1/2 phosphorylation and subsequent activation of transcription factors [61]. Recent data suggests that signals dependent on G proteins are mediated through *Rho* and *Rac* pathways which result in actin polymerization, reconstitution of adhesion molecules and other cellular components leading to cell migration [52,71,72]. CXCL8-mediated signal transduction is more complex especially if one takes into account the cross-regulatory mechanism(s) of the integrated network [61,73]. The analysis of signaling events further downstream from receptor activation is more complicated because of the potential contributions from various pathways since many signaling pathways are shared by different receptor systems.

5. Modulation of CXCR1/2 expression and/or activity for therapeutic intervention in malignant melanoma

Various strategies have been employed to modulate the expression of CXCR1/2 which includes low-molecular-weight antagonists, antibodies, siRNA and inhibitory peptides. Here we describe some of these approaches and the data obtained using preclinical models and discuss future perspectives. It has been shown by various groups that CXCL8 is constitutively expressed in malignant melanoma where it functions in an autocrine/paracrine fashion and acts as an invasive and angiogenic factor [31,33,74,75]. The multiple functions that are attributed to CXCR1/2 and their ligand emphasize the possibility of targeting them for cancer therapy.

Antibodies against CXCL8 and other chemokines have shown promising effects against melanoma. Humanized antibodies to CXCL8 have also been shown to inhibit tumor growth, angiogenesis and metastasis in case of melanoma [76,77]. But the positive response of neutralizing antibodies against chemokines other than CXCL8 suggests that melanoma may utilize different chemokine ligand to support its growth. It has also been reported that 17 beta-estradiol, progesterone and dihydrotestosterone suppresses the growth of melanoma by inhibiting CXCL8 production in a receptor dependent manner [79]. Earlier studies have demonstrated that neutralizing antibodies to CXCR1 and CXCR2 inhibit melanoma cell proliferation and its invasive potential. It has also been reported that 17 beta-estradiol, progesterone, and dihydrotestosterone suppress the growth of melanoma by inhibiting CXCL8 production in a receptor dependent manner [79]. All these above evidence emphasizes targeting CXCL8 receptors rather than CXCL8 alone.

Several antagonists for CXCR1/CXCR2 receptors are also under consideration for melanoma therapy. Low-molecular-weight inhibitors with affinity for CXCR1 such as repertaxin or with affinity for CXCR2 such as SB-225002 or SB-332235 have been used against inflammatory diseases [12,80,81]. A recent study, have shown potential of the CXCR1/2 specific inhibitors, SCH-479833 and SCH-527123 in inhibiting human melanoma growth by decreasing tumor cell proliferation, survival and invasion [27]. Histological and histochemical analyses showed significant ($p < 0.05$) decreases in tumor cell proliferation and microvessel density in tumors. A significant increase in melanoma cell apoptosis was also in SCH-479833 or SCH-527123-treated animals as compared to controls [27]. Similarly, SCH-527123 has also been shown to inhibit neutrophil recruitment and inflammatory responses in an animal model [82].

6. CXCR1/2 targeting and chemotherapy

Current strategies focused on systemic therapy for treatment of metastatic melanoma have shown no effect on survival. Different therapeutic approaches have been evaluated including chemotherapy and biological therapy, either as single agents or in combination. Systemic chemotherapy is still considered the mainstay of treatment for stage IV melanoma and is used largely with palliative intent [83]. Systemic chemotherapy with dacarbazine (DTIC) is the standard clinical treatment for malignant melanoma but response rates are very low (10 – 20%) [83,84] with only limited effect on survival [83,85]. Recent reports suggest that

expression of CXCR2 ligands and activation of CXCR2-dependent pathways might provide survival signals for therapy-resistant tumor cells [86–88]. An increase in the expression of CXCR1 and CXCR2 and their ligands in response to chemotherapy in various cancers have been observed [84,86,87,89,90]. An increase in the level of CXCL8, and CXCL1 after chemotherapy suggests that this pathway may be used as an escape mechanism leading to drug resistance. Treatment of malignant melanoma cells with Dacarbazine transcriptionally upregulates CXCL8 expression, which might render them resistant to the cytotoxic effect of drugs [84]. These reports suggest that inhibition of CXCR1/CXCR2 signaling might improve the efficacy of systemic chemotherapy against malignant melanoma progression and metastasis.

7. Expert opinion

The accumulated evidence from the experimental studies points toward a critical role for CXCR1 and CXCR2 and their ligands in melanoma progression and metastasis. The expression of these receptors in melanoma indicates the potential use as a biomarker of relative tumor aggressiveness. Despite decades of research, therapy for early-stage melanoma is surgery with a minor benefit noted with adjuvant therapy; however, there is no effective treatment for advanced disease. This clearly indicates the pressing need for novel and effective therapeutic measures for restricting melanoma tumor growth and metastasis. Blocking CXCR1/CXCR2 signaling using novel therapeutic strategies such as low-molecular-weight antagonists or neutralizing antibodies can inhibit malignant melanoma growth, progression and metastasis. In addition, inhibition of CXCR1/CXCR2 signaling can be targeted to improve the efficacy of systemic chemotherapy against malignant melanoma.

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Article highlights

- The expression of CXCR1 and CXCR2 and its ligands in melanoma correlate positively with disease progression.
- CXCR1 and CXCR2 receptors and their ligands modulate melanoma growth, angiogenesis and metastasis.
- Targeting CXCR1 and CXCR2 using specific low-molecular-weight inhibitors decreased human melanoma growth and invasion, which gives us hope for utilizing these antagonists for future melanoma therapy.
- The aberrant expression and proven role of CXCR1 and CXCR2 receptors and their ligands in melanoma progression and metastasis demonstrates their potential as biomarkers of tumor aggressiveness.

This box summarises key points contained in the article.

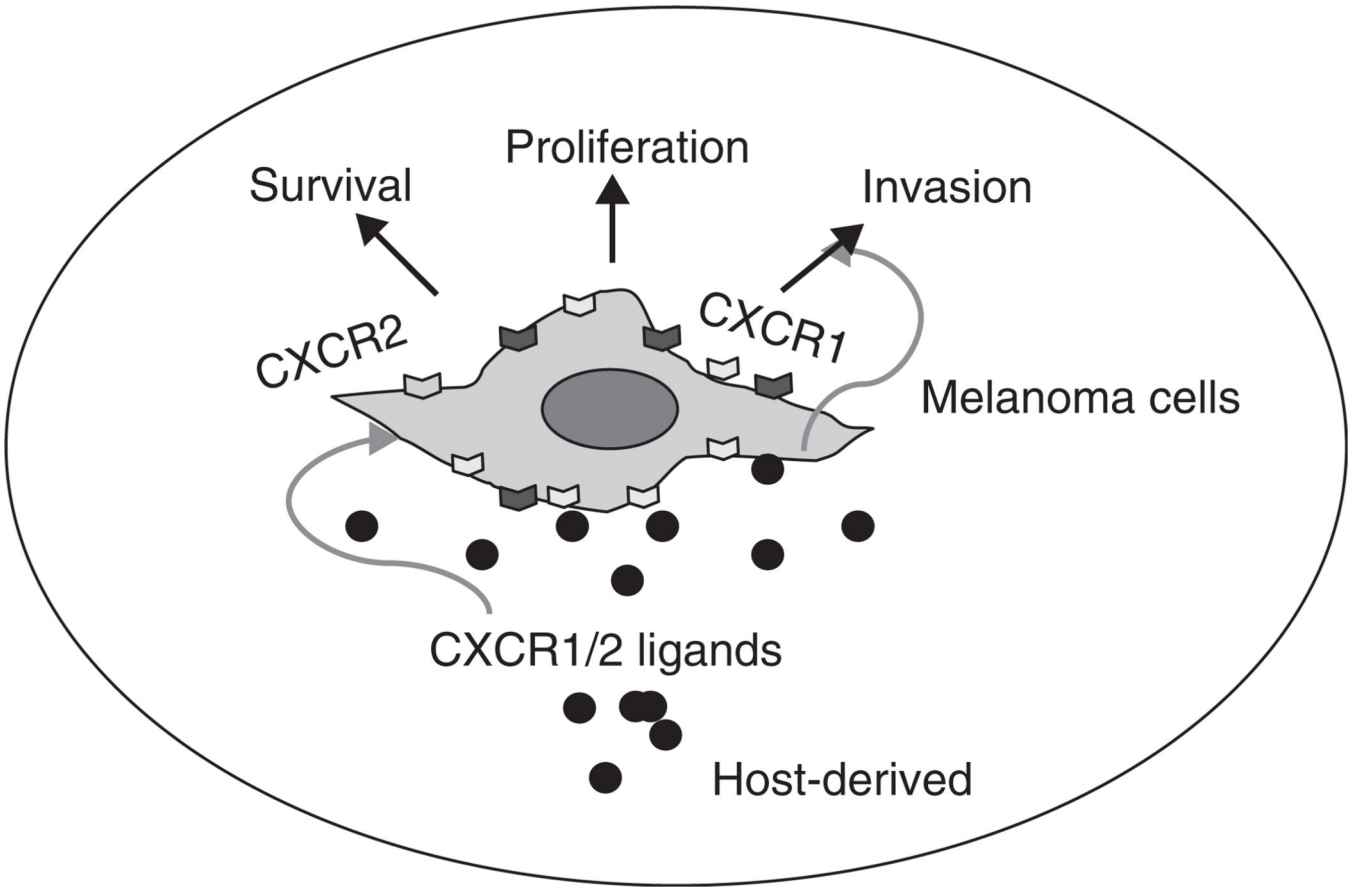

Figure 1.
CXCR1- and CXCR2-dependent regulation of phenotypes associated with malignant melanoma progression and metastasis.

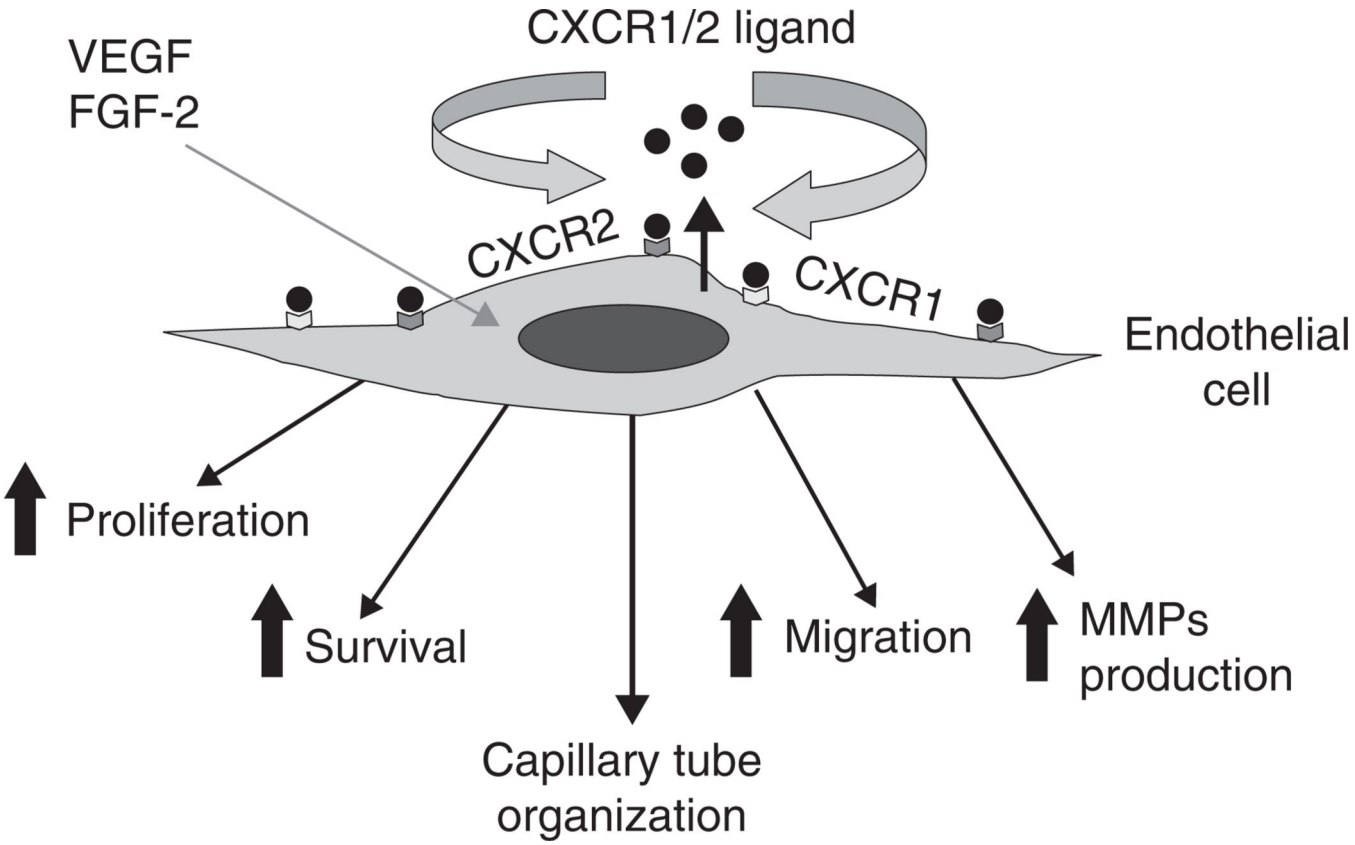

Figure 2.

Autocrine and paracrine signaling and role of CXCR1 and CXCR2-dependent signaling in regulation of angiogenic phenotype.

FGF: Fibroblast growth factor.

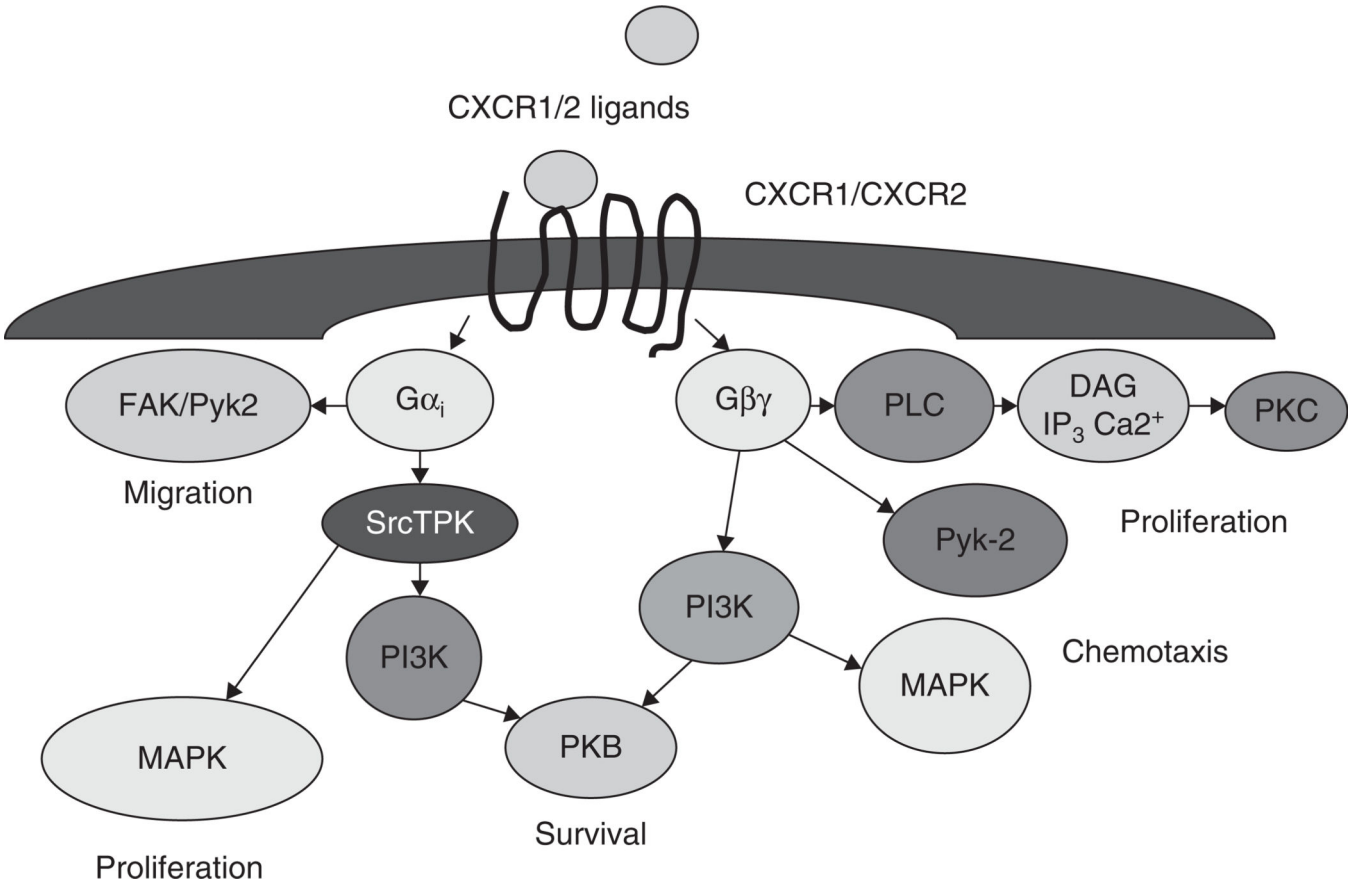

Figure 3.

CXCR1/2 receptor signaling in regulation of malignant cell phenotypes.

DAG: Diacylglycerol; FAK: Focal adhesion kinase; IP3: Inositol triphosphate; PKB: Protein kinase B; PLC: Phospholipase C; Pyk-2: Proline-rich tyrosine kinase 2; srcTPK: Src family tyrosine protein kinase.