CELL TRAFFICKING OF ENDOTHELIAL PROGENITOR CELLS IN TUMOR PROGRESSION

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ABSTRACT

Blood vessel formation plays an essential role in many physiological and pathological processes, including normal tissue growth and healing, as well as tumor progression. Endothelial progenitor cells (EPCs) are a subtype of stem cells with high proliferative potential which are capable of differentiating into mature endothelial cells; thus, contributing to neovascularization in tumors. In response to tumor-secreted cytokines, EPCs mobilize from the bone marrow to the peripheral blood, home to the tumor site, and differentiate to mature endothelial cells and secrete pro-angiogenic factors to facilitate vascularization of tumors.

In this review, we summarized the expression of surface markers, cytokines, receptors, adhesion molecules, proteases and cell signaling mechanisms involved in the different steps (mobilization, homing and differentiation) of EPC trafficking from the bone marrow to the tumor site. Understanding the biological mechanisms of EPC cell trafficking opens a window for new therapeutic targets in cancer.
1. INTRODUCTION

Blood vessel formation plays an essential role in many physiological and pathological processes, including normal tissue growth and healing, as well as tumor progression. Vasculogenesis is the process by which blood vessels are formed de novo, and angiogenesis is the expansion and remodeling of existing blood vessel network. Both vasculogenesis and angiogenesis occur during embryonic development. In adult life, revascularization is essential for the survival of growing, injured and ischemic tissue (1). For many years, it was believed that the sole mechanism responsible for the development of new vascular networks was angiogenesis (2). The process of angiogenesis is regulated by a balance between multiple endogenous pro-angiogenic and anti-angiogenic factors. This includes members of the fibroblast growth factor and vascular endothelial growth factor families. Modifications in these factors and in their balance, can lead to cancer progression; the imbalance of pro- and anti-angiogenic factors activates an “angiogenic switch” (3). Various cell types were identified to participate in the “angiogenic switch” including endothelial cells, vascular smooth muscle cells, stromal cells, and parenchymal cells (4).

In 1971, Folkman et al hypothesized that tumor growth was angiogenesis-dependent, and emphasized the future possibility of inhibition of angiogenesis could be useful as therapy against cancer (5). Cancer progression is largely dependent on tumor vascularity, and new vessel formation ensures adequate supply of nutrients, oxygen, and growth factors to the growing tumor and facilitates tumor dissemination (6). The three patterns of blood supply to tumors has been proposed including: vasculogenic mimicry, mosaic vessels, and endothelium-dependent vessels (7). One important way of which angiogenesis facilitates tumor metastasis is
by providing a route of exit for tumor cells to leave the primary site and enter the bloodstream during metastasis (8). Besides sprouting from preexisting endothelial cells, tumors utilize other methods of vessel growth, where neoangiogenesis is facilitated through recruitment of endothelial cells to the tumor vascular bed (9). Vasculogenesis occurs when circulating endothelial precursors are recruited in response to factors secreted by tumor cells, resulting in the generation of new vessels in the tumor (7).

Endothelial progenitor’s mobilization can occur in response to low oxygenation in tissues to promote angiogenesis, such as in response to tumor growth and hypoxia and in response to tissue ischemia after myocardial infarction. While the first is considered a negative phenomenon, the second is considered a positive one. In this review, we will focus on the role EPC trafficking in tumor progression.

2. DEFINITION OF ENDOTHELIAL PROGENITOR CELLS

Endothelial progenitor cells (EPCs) are a subtype of stem cells with high proliferative potential, capable of differentiating into mature endothelial cells (ECs) and contributing to neovascularization (10). EPCs are found mainly in the bone marrow (BM) in adults but they are also detected in the peripheral blood (PB); moreover they are detected in fetal liver and in umbilical cord blood (10). The first description of isolation of putative progenitor endothelial cells for angiogenesis was published in 1997 (11). Further studies demonstrated that tumors neovascularization occurs through BM-derived endothelial progenitor cells (12). Essentially, there are two types of cells that compromise the putative circulating EPC definition: proangiogenic hematopoietic cells (early-EPCs) and outgrowth endothelial cells (late-EPCs) (13,
14). With conflicting results reported in the field, the definition, identification, and characterization of EPCs is still not clear. Figure 1 summarizes the expression of the different markers during the trafficking and differentiation of the EPCs to ECs. EPCs are generally identified by expression of several surface markers which characterize the functionality of the EPCs including: CD133 (an early hematopoietic stem cell marker), CD34 (a progenitor marker), and the vascular endothelial growth factor receptor-2 (VEGFR-2) (an endothelial marker, also termed kinase insert domain receptor or Flk-1) (10, 11). EPCs from different sources express different markers. BM-derived EPCs are immature cells expressing CD133+/CD34+/VEGFR-2+/VE-cadherin⁻ (vascular endothelial cadherin); while EPCs isolated from PB are more mature expressing a variety of markers that are typical for the endothelial lineage, including platelet endothelial cell adhesion molecule-1 (CD31), melanoma cell adhesion molecule (CD146), VE-cadherin (CD144), endothelial nitric oxide synthase (eNOS), and von Willebrand factor (vWF) (15, 16). While early PB-derived EPCs express CD133+/CD34+/VEGFR-2+/CD31+/CD146+/VE-cadherin⁻/eNOS⁻/vWF⁻, late PB-derived EPCs express CD133⁻/CD34⁻/VEGFR-2⁺/CD31⁺/CD146⁺/VE-cadherin⁻/eNOS⁺/vWF⁺ (16). Mature endothelial cells (ECs) are terminally differentiated cells with a low proliferative potential expressing CD133⁻/CD34⁻/VEGFR-2⁺/CD31⁺/CD146⁺/VE-cadherin⁻/eNOS⁺/vWF⁺ (15, 17).

3. ROLE OF EPCs IN TUMOR ANGIOGENESIS

Physiological and pathological conditions and mediators have been described to affect the number of EPCs and their functions. Estrogens, erythropoietin, vascular endothelial growth
factor (VEGF), stromal cell-derived factor-1 (SDF-1) and physical training were shown to increase the number of circulating EPCs; diabetes, smoking habit and vascular diseases decrease number of circulating EPCs (15, 17). In addition, physical exercise was shown to enhance circulating EPC levels. Although the mechanism is not fully understood, it has been shown that up-regulation of EPCs by exercise is dependent at least in part on endothelial NO and VEGF (18).

Increased numbers of circulating EPCs was observed in several cancers, including gliomas, non-small lung cancer, myeloid leukemia, hepatocellular carcinoma, colorectal cancer, lymphoma, and breast cancer, and in atherosclerosis (15, 17). EPCs play an important role in the growth and angiogenesis of tumors at both early and late stages (19). Different subpopulations of EPCs play different roles in the angiogenesis process in which early EPCs augment angiogenesis, while late EPCs directly participate in tubulogenesis (20).

EPCs participate in different functions in tumor angiogenesis and vasculogenesis, as well as in the maintenance of vascular homeostasis (1, 21). It is hypothesized that once recruited to tumor sites, EPCs have a dual role in tumor angiogenesis: to regulate the angiogenic process via paracrine secretion of pro-angiogenic growth factors (21), and to provide structural function and direct luminal incorporation into sprouting nascent vessels (22, 23). The generation of a lethal tumor mass requires both tumor cell proliferation and angiogenesis (24); tumor cell proliferation alone, in the absence of angiogenesis can give rise to dormant microscopic tumors, but remain harmless to the host (6). Figure 2 summarizes the dual role of EPCs in tumor angiogenesis. There is evidence suggesting that a hypoxic microenvironment within a tumor
may promote the development of tumor-derived endothelial cells in glioblastoma. These tumor-derived endothelial cells are distinguishable from conventional endothelial cells due to expression of some tumor-specific markers (25).

DNA-binding protein inhibitors (Id proteins) in EPCs were shown to be critical for tumor angiogenesis; these proteins interact with basic helix-loop-helix transcription factors to regulate differentiation and cell cycle progression (26). Knocking out two members of the Id family co-expressed in the development embryonic vasculature (Id1 and Id3) caused embryonic lethality (27). Id3-deficient mice with one functional copy of Id1 did not die in development, but they were not able to support tumor growth and metastasis. Transplantation of BM of the wild-type mice restores their ability to support tumor angiogenesis, growth and metastasis (28).

4. TRAFFICKING OF EPCs IN CANCER

Tumor-derived paracrine signals activate the BM compartment, resulting in the mobilization and recruitment of EPCs to the tumor bed. EPCs have to accomplish three distinct but interrelated steps during vasculogenesis: mobilize from the BM to the PB; home and invasion of tumor site; and differentiate into mature ECs and/or regulate preexisting ECs via paracrine or juxtacrine signals (22). During these steps, EPCs interact with different physiological compartments including BM, PB, blood vessels and cancer tissues. The success of each step depends on the ability of EPCs to interact, adapt and respond to other cells in these compartments (29).
4.1 Mobilization of EPCs from bone marrow to peripheral blood

In normal conditions, EPCs reside within a stem cell niche in the BM, where fibroblasts, osteoblasts, and endothelial cells regulate the maintenance and mobilization of the BM stem cells (30). The release of EPCs from the BM is regulated by a variety of growth factors, enzymes, ligands and surface receptors. Figure 3 summarizes the cytokines, proteases and integrins involved in the mobilization of EPCs from BM to PB.

4.1.1. Cytokines

Cytokines inducing mobilization interfere with the interactions between EPCs and BM stromal cells (BMSCs), which allow EPCs to disengage the BM and to pass through the sinusoidal endothelium to enter the bloodstream (31). EPCs mobilize into the PB in response to tumor cytokines and move to the tumor bed where they incorporate into sprouting neovessels (23).

Tissue injury and hypoxia cause the production and release of factors responsible for mobilization of EPCs from the BM (32). EPC mobilizing factors are released from tumors in a high concentration greater than that in the BM, and the most described are VEGF, granulocyte colony stimulating factor (G-CSF), basic fibroblast growth factor (bFGF), placental growth factor (PIGF), erythropoietin (Epo) and SDF-1 (22, 31, 33). Drugs, such as statins, can induce mobilization of EPCs (34) in a mechanism that requires endothelial nitric oxide synthase (eNOS) (35). Estrogen did not increase EPC mobilization in eNOS-deficient mice (33),
Although estrogen increased the number of circulating EPCs in wild type mice. This data suggests that eNOS play a fundamental role in the regulation of EPC mobilization from the BM (36).

One of the most important regulators of the mobilization of EPCs is VEGF. Its expression is markedly increased in hypoxic tissues and tumors, largely because of the effects of hypoxia-inducible factor-1 (HIF-1) on VEGF transcription (37). VEGF binds to its receptor VEGFR-2 and mediates the further maturation of the hemangioblast/angioblast cascade and early/late EPCs (15). VEGF also activates matrix metalloproteinase-9 (MMP-9) which confirms its key role in the process of cell invasion (38). In the stem cell niche, cells are exposed to high levels of stromal cell-derived factor-1 (a chemoattractant for EPCs that binds via the CXC4 that maintains the cells in the niche (39).

**4.1.2 Proteases**

EPC mobilization is mediated by proteases such as elastase, cathepsin G, and matrix metalloproteinases (MMPs) (40). G-CSF releases these proteases from neutrophils, and these proteases cleave the cytokine SDF-1 (41). The proteases elastase and cathepsin G induce cleavage of adhesive bonds on stromal cells, which interact with integrins on hematopoietic stem cells (42). The EPC-mobilization activity of VEGF and SDF-1 was shown to be MMP9-dependent (38). Stromal cells are stimulated by EPC-mobilizing factors, which activate phosphoinositide 3-kinase/protein kinase (PI3K/AKT) pathway and nitric oxide.
synthase (eNOS), leading to an increased production of nitric oxide that stimulates and maintains MMP-9 activity (36, 38). In particular, the initial step in the mobilization of EPCs from the BM begins with the activation of MMP-9, which cleaves the membrane-bound Kit ligand (mKit-Lig) to a soluble Kit ligand (sKit-Lig) (36, 38, 43). The sKit-Lig binds to EPC receptor c-Kit and facilitates the intravasation of EPCs from the vascular zone of the BM to the PB (38, 43).

### 4.1.3 Integrins

Integrins also regulate different steps of EPC mobilization from the BM (29); the integrin α4β1 mediates cell adhesion to vascular cell adhesion molecule-1 (VCAM-1) and cellular fibronectin, and is a key regulator of EPC retention and mobilization from the BM (44). Down-regulation or functional blockade of α4β1 integrin-mediated EPC lodgment in the BM causes mobilization of EPCs (45). Similarly, VEGF-induced mobilization of EPCs involves downregulation of β3-integrin in BM(46).

### 4.2. Homing of EPCs to tumor bed

Once in the PB, EPCs home to tumor tissues in response to chemokine gradients that are formed in ischemic or hypoxic tumor tissues(29) where they can participate in neovascularization (12). Figure 4 summarizes the cytokines, receptors, adhesion molecules (integrins and selectins) and proteases involved in the homing of EPCs to the tumor bed.
4.2.1 Chemotaxis

The major chemokines and their respective receptors that regulate EPC activation and homing are: VEGF/VEGFR-2 (47), SDF-1/CXCR4 (48), interleukin-8/CXCR2 (49), GRO-α/CXCR1 (50), CCR2/CCL2 and CCR5/CCL5 (51). VEGF was shown to up-regulate SDF-1 and CXCR4 (52); with low VEGF, SDF-1 was insufficient for homing of EPCs to tumor sites (53), demonstrating possible synergistic effect between the two cytokines.

Under hypoxic conditions transcription factors like HIF-1 were activated and led to increased transcription of VEGF and SDF-1α (47). HIF-1α, SDF-1 and VEGF were shown to be important regulators of EPCs homing to hepatocellular carcinoma (54). By binding to the receptors CXCR1 and CXCR2, IL-8 enhanced endothelial cell survival and proliferation, increased MMPs production and increased capillary tube formation (55). CCR2 and CCR5 are chemokine receptors expressed on the surface of EPCs and bind the ligands CCL2 and CCL5, respectively. These chemokines and their receptors are involved in EPC migration and differentiation, and play an important role in vascular remodeling and angiogenesis (56).

4.2.2 Extravasation

EPC homing is an active process involving direct interaction between molecular targets expressed in by EPCs and by tissues that they home to (57). After chemotaxis, EPCs become activated and start selectin-initiated and integrin-
mediated adhesion to endothelial vascular cells resulting in transendothelial migration into sites where vascular remodeling is needed (29). P-selectin glycoprotein ligand-1 (PSGL-1) is expressed on the surface of EPCs interacts with P-selectin and E-selectin expressed on ECs, resulting in EPC rolling to the blood vessel wall (58). After the initial interaction with selectins, the β1 and β2 integrins mediate intercellular adhesion and facilitate EPC transendothelial migration (59, 60). β2 integrins mediate adhesion of EPCs to pre-activated ECs through interaction with intercellular adhesion molecule (ICAM-1) and fibrinogen (FG), resulting in homing of EPCs to active angiogenic sites (59). EPC homing requires other integrins, such as β1 integrins, to facilitate transendothelial migration (29). In particular, α5β1 integrin is a fibronectin (FN) receptor highly expressed on EPCs and participates in homing to vascular injury sites and promotes re-endothelialization (60). α6β1 integrin is a laminin-binding integrin regulated by VEGF and bFGF and necessary for EPC homing and adhesion to the basement membrane (61). Integrin αv is expressed on almost all the cells originating from the mesenchyme and play a significant role in EPC homing. More specifically, αvβ3 and αvβ5 integrins bind to arginine-glycine-aspartic acid (RGD) motif regions of different ligands, including vitronectin, FN, osteopontin, FG and vWF (58). Once adhered at specific homing sites, EPCs need to migrate through the endothelial monolayer, a step mediated by β2 integrins and dependant upon VEGF and increased expression of ICAM-1 in ECs (62).
4.2.3 Tissue invasion

EPCs need to migrate through the blood vessel basement membrane and through the extracellular matrix (ECM) in order to home to sites where they need to exert their functions (29). These processes require interactions with cells and ECM, wherein integrins and extracellular proteases are essential to modulate EPC invasion (63). The major extracellular proteases involved in EPC invasion are members of MMP family (MMP-9) (64), cathepsin family (cathepsin L) (65), and the serine protease family (urokinase-type and tissue-type plasminogen activators) (66). EPCs up-regulate the production of extracellular proteases that allow both matrix degradation and EPC migration (63). In addition, up-regulation of integrins α5β1 and α6β1 mediate EPC invasion and migration towards VEGF gradients within the ECM by PI3K/AKT pathway (67).

4.3 In situ differentiation and paracrine/juxtacrine factors production

EPC differentiation can be divided in three sequential stages: integrin-mediated adhesion to specific ECM components, growth factor-induced proliferation and survival, maturation and functional acquisition of ECs properties (68). Figure 5 summarizes the cytokines and integrins implicated in the differentiation into mature ECs and regulate pre-existing ECs via paracrine or juxtacrine signals.

EPC adhesion to the ECM is an essential step during differentiation, and direct interaction between integrins and ECM can regulate EPCs paracrine/juxtacrine factor production (29). All the integrins implicated are FN-binding integrins, therefore the
interaction of EPCs with FN is essential during endothelial differentiation (11, 29). FN is described as a major regulator of EPC differentiation since it promotes VEGF-induced differentiation of EPCs into ECs via specific binding to integrin α5β1 (69). FN down-regulate the expression of integrins α5β1 and αvβ5 during EPC differentiation (70). Paracrine/juxtacrine factor production by EPCs is also regulated by the integrin/ECM interactions (71). Activation of integrin β5 in EPCs induced expression of pro-angiogenic factors such as IL-8 and CCL2 (67, 72). EPCs contribute to new vessel formation and remodeling by differentiation into mature ECs and regulation of pre-existing ECs and other cell types with production of paracrine and/or juxtacrine signals, such as VEGF, SDF-1, platelet derived growth factor-1 (PDGF-1), CCL2, and insulin-like growth factor 1 (IGF-1) (73).

The maturation and acquisition of an endothelial phenotype depends mainly on the regulation of the transcription factor HoxA (74). HoxA regulates the expression of the endothelial genes for eNOS, VEGFR-2, and VE-cadherin by transcriptional regulation of histone deacetylases (HDAC) (74). These steps lead to an overall response that promotes differentiation and are highly regulated by processes involved in tumor angiogenesis.

5. SUMMARY

EPCs are essential for tumor progression and metastasis; they promote both angiogenic signals and structural support for existing ECs to promote vasculogenesis. EPCs migrate from the BM to
the tumor site, during that process they express different markers and highly regulate process involved in chemotaxis, adhesion and invasion. Hypoxic tumors secrete cytokines that activate the BM (EPCs and BMSCs) to promote deadhesion and intravasation of EPCs to the circulation through downregulation of adhesion signals and activation of proteases. While in the circulation, EPCs respond to tumor-secreted cytokines for homing by activation of chemotaxis through chemokines receptors, extravasation through selectins and integrins and invasion through integrins and proteases. After homing, EPCs differentiate to mature ECs and promote vasculogenesis. This review summarizes the expression and the function of the various surface markers, cytokines, receptors, adhesion molecules, proteases and cell signaling mechanisms involved in the different steps (mobilization, homing and differentiation) of EPC trafficking from the BM to the tumor site. Understanding the biological mechanisms of EPC cell trafficking opens a window for new therapeutic targets in cancer.
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FIGURE LEGENDS

Figure 1. Expression of markers during the trafficking and differentiation of the EPCs to ECs.
Bone marrow endothelial progenitor Cells (BM EPCs) are generally identified by expression of CD133 (early hematopoietic stem cell marker), CD34 (progenitor marker) and VEGFR-2 (endothelial marker). Circulating EPCs are more mature cells and characterized by high expression of VEGFR-2 and CD34 but decreased expression of CD133. In addition, they express CD31 and CD146. Mature endothelial cells (ECs) are terminally differentiated cells characterized by negative expression of CD34 and CD133, and positive expression of VEGFR-2, CD31, CD146, VE-cadherin, eNOS, and vWF.

Figure 2. The role of ECPs in tumor angiogenesis.
Tumor-secreted cytokines activate the bone marrow compartment, resulting in the mobilization of subsets of bone-marrow derived cells and homing to the tumor bed. EPCs play an important role in the growth and angiogenesis of tumor; they regulate the angiogenic process via paracrine secretion of pro-angiogenic factors (angiogenic switch), and by providing structural function (vessel incorporation and stabilization).

Figure 3. Mobilization of EPCs from bone marrow to peripheral blood.
Tumor-secreted cytokines (VEGF, G-CSF, bFGF, Epo) induce the release of EPCs from the bone marrow through downregulation of the interactions between EPCS and bone marrow.
microenvironment. Upon stimulation by cytokines, BMSCs activate eNOS (through the PI3K/AKT pathway), leading to an increase production of NO, which stimulates MMP-9. MMP-9 is a protease that cleaves the membranal Kit ligand (mKit-Lig) to a soluble form (sKit-Lig), which binds to c-Kit receptor on EPCs, and activates the detachment between EPCs and BMSCs, and the intravasation of EPCs from the vascular zone of the BM to the P. The proteases elastase and cathepsin G induce cleavage of adhesive bonds on BMSCs, which interacts with integrins in EPC retention such as α4β1 and β3. G-CSF releases proteases from neutrophils which cleave the cytokine SDF-1 in the bone marrow, which results in decreased adhesion of EPCs.

**Figure 4. Homing of EPCs to tumor bed.**

EPCs migrate to tumor in a chemotaxis response to tumor-secreted cytokines (VEGF, SDF-1, IL-8, GRO-α, CCL5 and CCL2) which interact with their respective receptors (VEGFR-2, CXCR4, CXCR2, CXCR1, CCR5 and CCR2) on EPC surface. After chemotaxis, PSGL-1 interacts with P-selectin and E-selectin expressed on endothelial cells and facilitates the initial interaction of EPCs with the blood vessel wall; this activates integrins mediate intercellular adhesion to facilitate EPC transendothelial migration. β2, α5β1, and α6β1 integrins mediate the adhesion of EPCs to endothelium molecules such as ICAM-1, FG, FN and laminin. Also αvβ3 and αvβ5, integrins expressed on mesenchyme cells, play a role in EPC homing, due to the binding to RGD motif regions of different ligands. Finally, integrins and proteases are essential to facilitate the EPC tissue invasion. Up-regulation of integrins α5β1 and α6β1 mediate EPC invasion and migration towards VEGF gradients within the ECM, in a PI3K/AKT pathway dependent way; and
also extracellular proteases are involved in EPC invasion such as MMP-9, cathepsin L or urokinase-type and tissue-type plasminogen activators.

Figure 5. Differentiation of EPCs to ECs and paracrine/juxtacrine factor production.

EPCs (CD34+/VEGFR-2+/VE-Cadherin-/eNOS-/vWF-) differentiate to mature ECs (CD34-/VEGFR-2+/VE-Cadherin+/eNOS+/vWF+) due to a three-steps process, including: 1) integrin-mediated adhesion to ECM, 2) paracrine/juxtacrine factor production, and 3) expression genes regulated to endothelial maturation by transcriptional regulation of HDAC regulated and factor HoxA.
Figure 2

EPCs in bone marrow

- Activation
- Mobilization
- EPCs in circulation

Cytokines secreted from tumor

Mobilization

Initial tumor

Homing

EPCs at the tumor site

Differentiation and proliferation
- Structural role
- Paracrine role

Proangiogenic factors secretion (Angiogenic switch)

Lethal tumor

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Figure 3

Bone marrow

Activated EPC

Cytokine receptor

↓α4β1
β3

c-Kit

sKit-Lig

Tumor cytokines involved in mobilization
VEGF, G-CSF, bFGF, Epo

Nonactivated EPC

Cytokine receptor

↑α4β1
β3

c-Kit

Detachment

Bone marrow

Activitated BMSC

Cytokine receptor

PI3K

AKT

eNOS

NO

↑MMP-9

sKit-Lig

SDF1↓

α4β1
β3

↓α4β1
β3

↑Elastase

Cathepsin G

Blood vessel

Intravasation

Chemotaxis to tumor

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Blood vessel

Tumor cytokines involved in homing
VEGF, SDF-1, IL-8, GRO-\(\alpha\), CCL5, CCL2

Circulating EPC

Cytokine receptors
VEGFR-2, CXCR4, CXCR2, CXCR1, CCR5, CCR2

PSGL-1

\(\uparrow\beta2\), \(\alpha5\beta1\), \(\alpha6\beta1\)

Tumor site

Chemotaxis to tumor

Extravasation

Homing EPC

Cytokine receptors
VEGFR-2

ICAM1, FG, FN, Laminin

\(\alpha\nu\beta3\), Selectins (E and P)

Endothelium

ECM

Invasion

\(\uparrow\alpha5\beta1\), \(\alpha6\beta1\)

\(\uparrow\text{MMP-9}\), Cathepsin L, Plasminogen activators

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CCR Reviews
Figure 5

(1) Integrin-Mediated Adhesion
Activation with VEGF
Interaction with FN
Downregulation of α5β1 and αvβ5

(2) Paracrine/Juxtacrine Factor Production
Secretion and activation by VEGF,
SDF-1, IL-8, PDGF-1, CCL2, and IGF-1

(3) Maturation and Differentiation
Overexpression of HoxA and HDAC
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