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REVIEW

Crosstalk between cancer cells and endothelial cells: implications for tumor progression and intervention

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Abstract Communication between tumor cells and stromal cells is crucial to tumor development and progression. Fibroblasts and macrophages are the most common stromal cells in the tumor microenvironment. Endothelial cells are another type of stromal cell in the tumor microenvironment required for angiogenesis via interaction with tumor cells. Tumor angiogenesis provides not only oxygen and nutrients for tumor cells but also the necessary anchorage to facilitate tumor metastasis. The present review summarizes studies on the crosstalk between cancer cells and endothelial cells with a focus on implications for tumor progression. The following four categories are discussed in this review: (1) cell–cell communication in tumor microenvironment; (2) induction of metastasis by interaction between cancer cells and endothelial cells; (3) angiogenesis induced by tumor cells; (4) therapeutic strategies targeting adhesion and signaling molecules as well as chemokines. This review provides useful information highlighting the process of cancer aggressiveness affected by the crosstalk between cancer cells and endothelial cells, and suggests therapeutic strategies against tumor progression.

Keywords Tumor microenvironment · Endothelial cell · Cancer cell · Angiogenesis

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Introduction

The tumor microenvironment is complex, consisting of many cell types and factors (O'Malley et al. 2016). Tumor progression is induced by the activation of adjacent stromal cells in the tumor microenvironment (Li et al. 2007; Egeblad et al. 2010). Endothelial cells are a type of stromal cell present in the tumor microenvironment. Tumor cells penetrate the normal epithelium and interact with the surrounding endothelial cells to produce cytokines and growth factors that affect cells in the microenvironment (Brenner et al. 2010).

Metastasis is the main cause of mortality in cancer patients. A major challenge for cancer therapy is defining an appropriate strategy to control or inhibit metastasis. Adhesion to the endothelium of tumor cells affects the formation of metastases in which many adhesion molecules and chemokines are involved (Iiizumi et al. 2007). Cancer cell invasion is crucial for the metastatic spread of locally proliferating tumors and is a step towards the development of a life-threatening disease (Chambers et al. 2002; Keleg et al. 2003).

The metastatic potential of a tumor is determined not only by the cells in the tumor microenvironment but also by the changes in these cancer cells (Gómez-Cuadrado et al. 2017). Cancer cells can invade blood or lymph vessels through the basal membrane in a process called intravasation, a carcinogenic event in which cancer cells begin to move from primary sites (Soon 2007). Epithelial-mesenchymal transition (EMT) cells with migratory phenotypes can degrade the extracellular matrix (ECM) and enable intravasation into tissues and blood or lymphatic vessels (Tsuji et al. 2008). Many cell adhesion molecules and proteinases are involved in the intravasation process of the primary tumor into the blood vessels (Farahani et al.

2014). Using a cell line derived from rat mammary adenocarcinoma, the correlation between intravasation and lung metastasis was revealed (Wyckoff et al. 2000).

Metastasis begins when tumor cells penetrate normal tissues. Transcoelomic metastasis spreads through the peritoneal cavity that connects the organ surface (Tan et al. 2006). In hematogenous metastasis, cancer cells penetrate the blood vessels and extend their reach through blood vessels that are widely spread throughout the body (Sunami et al. 2000). A lymphatic metastasis penetrates the lymph nodes through the lymphatic system and subsequently spreads to other parts of the body (Karaman and Detmar 2014). When cancer cells arrive at a new location, they multiply again, creating a small tumor called a micrometastasis (Rampaul et al. 2001). The process of metastasis ends when the micrometastasis is fully grown.

Cancer cells stimulate endothelial cells to promote tube formation, which leads angiogenesis. Tumor cells induce vascular growth by secreting various growth factors such as basic fibroblast growth factors (bFGF) or vascular endothelial growth factors (VEGF) (Ferrara 2002; Naoyo et al. 2006). Interrupting this crosstalk reduces angiogenesis and the tumor size within the tumor (Vasudev and Reynolds 2014). Therefore, it is important to understand the surrounding microenvironment of cancer and identify biomarkers that may influence cancer progression for the diagnosis and treatment of cancer. The present review summarizes the current collective understanding of the interaction between cancer cells and endothelial cells in the tumor microenvironment. We focus on the key molecules involved in this crosstalk in the tumor microenvironment and on therapeutic strategies targeting these molecules.

Cell–cell communication in tumor microenvironment

The microenvironment includes extracellular matrix as well as components surrounding the tumor cells and vascular endothelial, fibroblast, and bone marrow-derived cells (Tahmasebi and Carloni 2017). The mechanism of cancer development is highly dependent on the interaction between tumors with the components secreted by tumor microenvironment (Witz 2009; Korneev et al. 2017). Cancer cells are surrounded by tumor microenvironment, consisting of fibroblasts, immune and inflammatory cells, blood vascular networks, ECM, and so on (Hanahan and Coussens 2012; Gkretsi et al. 2015). The physiological condition of the tumor microenvironment is related at every stage of tumorigenesis (Wang et al. 2017). A microenvironment in an unhealthy state may cause tumor growth and invasion (Goubran et al. 2014).

The interaction between cancer cells and stromal cells in the microenvironment surrounding tumors plays an important role in the formation and progression of cancer (Bremnes et al. 2011). Major stromal cells include vascular endothelial cells, cancer-associated fibroblasts (CAFs), and tumor-associated macrophages (TAMs) in tumor microenvironment (Junttila and de Sauvage 2013). Endothelial cells are also important determinants of the tumor microenvironment (Chouaib et al. 2010).

CAFs have heterogeneous origins, phenotypes, and functions within the tumor microenvironment (Ishii et al. 2016). CAFs are a heterogeneous group of fibroblasts that are redirected by cancer cells to carcinomas (Lim and Moon 2016). CAFs are fibroblasts similar to activated fibroblasts with stimulation of inflammatory conditions (Augsten 2014). CAFs secrete signaling factors such as VEGF, FGF, and platelet-derived growth factor (PDGF) to support tumor growth (Xing et al. 2010). CAFs also secrete transforming growth factor (TGF)-β associated with EMT (Yu et al. 2014).

TAMs play a major role in tumor progression by producing cytokines and matrix metalloproteinases (MMPs) (Baay et al. 2011; Quatromoni and Eruslanov 2012). MMPs are involved in ECM composition, and cancer cells play an important role in cell migration during invasion and metastasis (Bodey et al. 2001; Nabeshima et al. 2002). Circulating monocytes in blood are differentiated into M1 macrophages and M2 macrophages which are also called as TAMs (Chanmee et al. 2014; Almatroodi et al. 2016). Infiltrating M1 macrophages present in the early stages of tumorigenesis secrete pro-inflammatory cytokines and inhibit tumor growth (Mantovani et al. 2002). M2 macrophages secrete proteases such as cathepsin, cytokines, and an epidermal growth factor in the later stages of tumorigenesis (Ham and Moon 2013; Rhee 2016; Choi et al. 2017). TAMs secrete cytokines, chemokines, MMPs, and a variety of growth factors, which are associated with angiogenesis, tumor growth, invasion, and metastasis (Baay et al. 2011). TAMs promote the migration and invasion of cancer cells through the cell-ECM (Finkernagel et al. 2016). TAMs can produce proteases such as MMP-2 and MMP-9 which digest the ECM (Yang and Zhang 2017). In addition, an increase in TAM-derived interleukin (IL)-6 has been shown to promote the development of hepatocellular carcinoma (Kong et al. 2016). These results suggest that TAMs play an important role in the occurrence of cancer. Crosstalk between the cancer cells and the endothelial cells (Upreti et al. 2013; Lim and Moon 2016) in the tumor microenvironment was depicted in Fig. 1.

Tumor endothelial cells proliferate and migrate more rapidly than normal endothelial cells (Hida et al. 2010). Cancer cells induce changes in endothelial cells by targeting cells through adhesion receptors, gap junctions, and

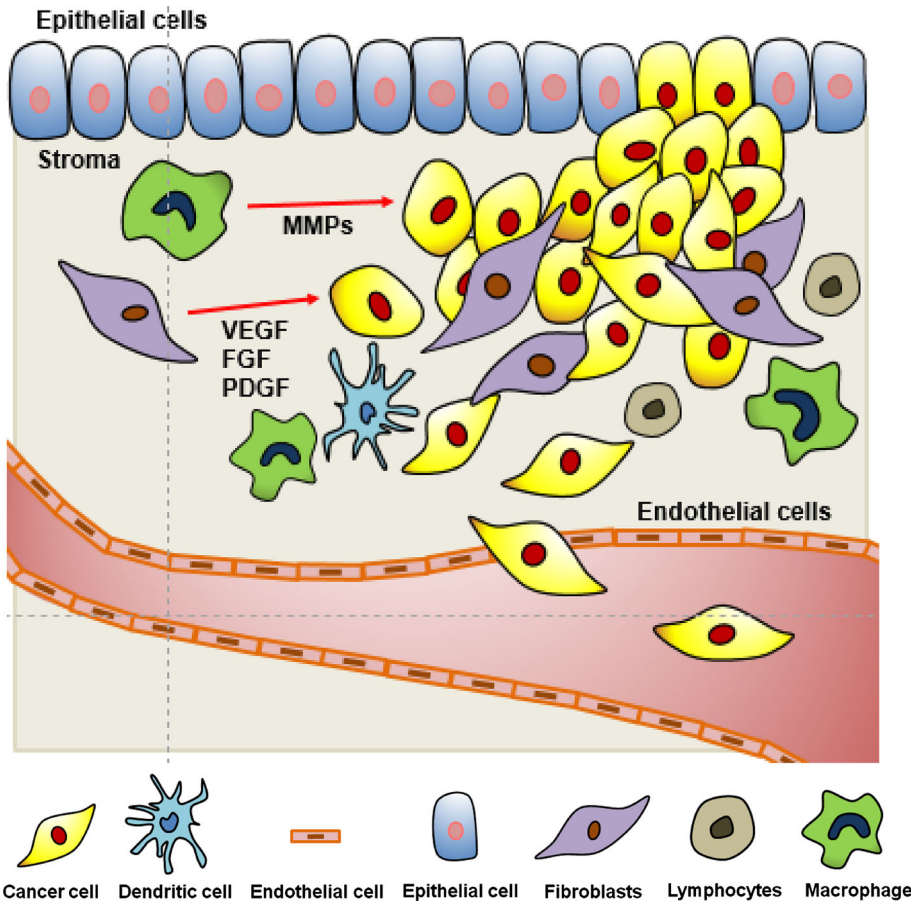

Fig. 1 Crosstalk between cancer cells and endothelial cells in tumor microenvironment

vesicles (Lopes-Bastos et al. 2016). Cancer cells stimulate signaling pathways by activating stromal cells, secreting proteases into the extracellular space, or changing the pH and temperature (Lopes-Bastos et al. 2016). Breast cancer cells regulate lymphatic endothelial cells to promote metastasis (Lee et al. 2014a). Tumor cell-secreted IL-6 induces the phosphorylation of signal transducer and activator of transcription (STAT)-3 in lymphatic endothelial cells (Nilsson et al. 2005). The phosphorylation of STAT3 induces hypoxia-inducible factor (HIF)-1α and VEGF, which activates chemokine (C–C motif) ligand (CCL)-5 expressions in lymphatic endothelial cells (Lee et al. 2014a).

Induction of metastasis via interaction with endothelial cells

Adhesion molecules mediating the interaction between cancer cells and endothelial cells

The initial contact between cancer cells and the endothelium is mild or transient and is mediated via recognition of carbohydrate–carbohydrate interactions (Dube and Bertozzi 2005; Nakahara and Raz 2008). This contact initiates activation of endothelial and cancer cells via cytokines, free radicals, physiologically active lipids, and growth factors (Orr et al. 2000). These mediators induce the expression of adhesion molecules by endothelial and cancer cells, thereby enhancing or fixing initial adhesion bonds (Tang and Honn 1994; Kannagi 1997). Selectins, integrins, cadherins, immunoglobulins, tetraspanins, and thrombospondin (TSP) are known to regulate the adhesion between cancer cells and the endothelium (Nicolson 1988; Pauli et al. 1990). Adhesion and intravasation of cancer cells by various cytokines and proteins are depicted in Fig. 2.

Selectin is a vascular cell adhesion molecule (VCAM) mediating the interaction between endothelium and leukocytes and platelets in the blood circulation (Ala et al. 2003). E-selectin expressed in activated endothelial cells has been detected in the liver metastatic colonies (Soto et al. 2014). Down-regulation of E-selectin expression has been shown to result in experimental liver metastasis (Brodt et al. 1997; Khatib et al. 1999; Bendas and Borsig 2012). Selectin binds to a variety of molecules, most of which function in vivo (Rinko et al. 2004). The selectin family includes P-, E-, and L-selectin. According to other

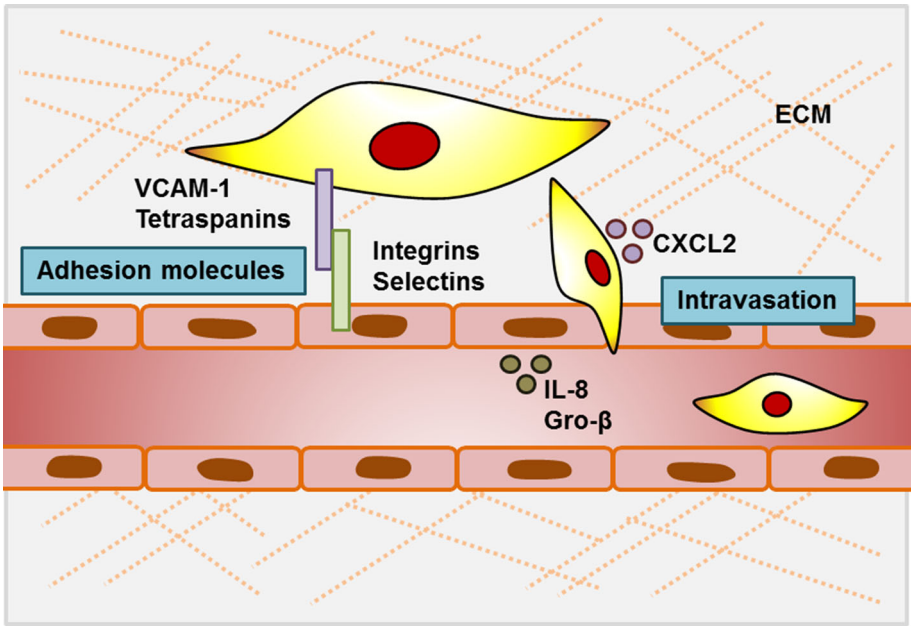

Fig. 2 Adhesion and intravasation of cancer cells by various cytokines and proteins

studies, at least one selectin binds to all human carcinomas that have been tested so far, and selectin mediates contact with the tumor (Faryammanesh et al. 2014).

Expression of P-selectin on the cell surfaces of endothelial cells and platelets contributes to metastasis by inducing nuclear factor-kappa B (NF-κB) activation and further expression of P-selectin (Foreman et al. 1994). The expression of P-selectin on the cell surfaces of endothelial cells and platelets also contributes to metastasis (Reyes–Reyes et al. 2006). The absence of L-selectin induces a significant reduction in metastasis, indicating that L-selectin contributes positively to leukocyte recruitment and metastatic crevice formation (Läubli and Borsig 2010).

E-selectin binds to its receptors and mediates the adhesion of tumor cells (Zen et al. 2008). Inhibition or down-regulation of E-selectin has been shown to attenuate experimental liver metastasis, which was induced by the overexpression of E-selectin (Kang et al. 2016). The cytokines secreted by breast cancer cells stimulate macrophages in order to produce tumor necrosis factor (TNF)-α, the regulatory factor of E-selectin expression, resulting in increased adhesion of endothelial cells (Eichbaum et al. 2011; Reymond et al. 2013). In colorectal cancer cells, in vitro studies using sialyl-Lewis X (an E-selectin ligand)-related carbohydrate determinants showed adhesion of cultured vascular endothelial cells to TNF-α-induced E-selectin (Takada et al. 1991). E-selectin levels were significantly increased in the serum and tissues of breast cancer patients compared to those of the control group (Ragab et al. 2017). The E-selectin gene was found more often in malignant tissues than in control tissues (Ragab et al. 2017), suggesting that E-selectin may be associated with aggressive tumors.

Integrin is a transmembrane receptor that promotes ECM attachment and activates signal transduction pathways that mediate cellular signals such as cancer progression and metastasis (Seguin et al. 2015). Integrin is composed of two chains, that is, α- and β-subunits (Campbell and Humphries 2011). Binding of vascular integrins to ECM components contributes to the invasion of endothelial cells. Tumor-associated blood vessels express αvβ3 and αvβ5 integrins, and the targeting of these vessels has been studied with a promising anti-angiogenic approach. (Brooks et al. 1994; Bendas and Borsig 2012). Antagonists of integrin such as cilengitide, an inhibitor of αvβ3 and αvβ5, have been shown to be promising anti-cancer agents (Desgrosellier and Cheresh 2010).

Tetraspanins, cell surface proteins, are associated with adhesion receptors in the integrin family (Hemler 2005). The expression of tetraspanins correlates with the tumor stage and type (Lazo 2007; Vences-Catalán et al. 2015). Cell surface proteins of the tetraspanin family are present in almost all cell and tissue types and regulate integrin-dependent cell migration (Berditchevski 2001). Several members of the tetraspanin superfamily, including CD9, CD81, and CD151, are located in the tumor cell-endothelial cell contact area (Longo et al. 2001). The interaction between CD9 and TGF-α was decreased through ectodomain shedding to release soluble TGF-α (Imhof et al. 2008). CD9 can interact with transmembrane TGF-α to activate epidermal growth factor receptor (EGFR) (Imhof et al. 2008). Increased TGF-α-EGFR signaling is known to induce cancer progression (Lee et al. 1995; Kenny and

Bissell 2007). Expression of CD9 is often markedly reduced in a variety of metastatic cancers, including lung, colon, and pancreatic cancers (Parkes and Jewell 2001). CD81 directly interacts with integrin α4β1 and CD151 directly binds with integrin α3β1 and α6β1 (Serru et al. 1999). Tetraspanin CD151 mediates cell adhesion with integrins (α3β1, α6β1, α6β4, and α7β1) on different types of laminin (Boucheix and Rubinstein 2001). Platelets increase cancer cell adhesion to endothelial cells, which enhances angiogenesis of endothelial colony-forming cells in platelets with integrin α6β1 (Reymond et al. 2013; Huang et al. 2016). The regulation of tetraspanin in tumor cell lines significantly increases cell growth, morphology, invasion, tumor growth, and metastasis (Detchokul et al. 2014; Hemler 2014). Among VCAMs and TSPs, VCAM-1 and thrombospondin (TSP)-1 have been extensively studied in cancer progression and metastasis (Sargiannidou et al. 2001; Lin et al. 2007a).

TSPs, a family of ECM proteins, are involved in cell proliferation and differentiation (Bornstein 2009; Huang et al. 2017). TSP-1 plays an important role in the microenvironment of the tumor and also affects tumor cell adhesion, proliferation, invasion, migration, apoptosis, and tumor immunity (Baenziger et al. 1971; Jeanne et al. 2015). TSP-1 controls inflammation by regulating the activity of other secreted factors (Varma et al. 2008; Lopez-Dee et al. 2011; Stenina-Adognravi 2014). TSP-1 regulates the production and activation of pro-inflammatory cytokine IL-1β by macrophages (Stein et al. 2016). TSP-1 has been shown to exert its CD47-dependent inflammatory effect on the IL-1β pathway (Stein et al. 2016). Other studies have confirmed that CD47 is an important regulator of lymphocyte function-associated antigen (LFA)-1 and very late antigen (VLA)-4 integrin-adherence in the proliferation and recruitment of T cells (Azcutia et al. 2017).

VCAM-1 is involved in this process (Schlesinger and Bendas 2015). VCAM-1 is abnormally expressed in breast cancer cells and has been shown to bind to the natural ligand α4β1 integrin (also known as VLA-4) (Sharma et al. 2017). This binding triggers metastasis of breast cancer cells to the lungs, bones, and brain (Sharma et al. 2017). Intercellular adhesion molecule (ICAM)-1 and VCAM-1 are involved in tumor progression and metastasis (Regidor et al. 1998). Up-regulation of these adhesion molecules promotes endothelial cell adhesion and angiogenesis, and also contributes to changes in the invasive phenotype (Regidor et al. 1998).

Invasion and migration in the interaction between cancer cells and endothelial cells

The ability of malignant tumor cells to induce cell migration and the invasion of cancer has been investigated for years (Clark and Vignjevic 2015; Krakhmal et al. 2015). Metastasis occurs when cancer cells penetrate the basement membrane and wall of the endothelium and travel to distant organs (Valastyan and Weinberg 2011; van Zijl et al. 2011). Stroma and tumor cells exchange signals to modify the ECM and stimulate cell migration (Lomberk 2010). It is known that tumor cells overcome the ECM barrier and spread to surrounding tissues (Krakhmal et al. 2015).

Cells are polarized during this migration process (Friedl and Wolf 2003). This polarity can be reflected through specific regions and molecules on the cell surface (Ridley et al. 2003). Upon polarization, phosphatidylinositol-3, 4, 5-trisphosphate (PIP_3), activated Rac, and Cdc42 are found in the same direction (Ridley et al. 2003). In the opposite direction, Rho GTPase and phosphatase and tensin homolog (PTEN) are observed (Parent and Devreotes 1999). After establishment of polarity, actin filament polymerization at the leading edge stimulates lamellipodium (Atilgan et al. 2005). Next, translocation of the cell body occurs due to the formation of adhesive contact (Shieh et al. 2011). The depolymerization of the actin network completes the cell migration assembly process (Carlsson 2010).

Tumor cells attach to endothelial cells and invade connective tissue (Mierke et al. 2008). Vascular endothelial cells promote cancer invasion and metastasis, mostly via Akt and NF-κB pathways (Wang et al. 2013). The integrin-induced signal pathway is involved in cell migration, and the integrins-focal adhesion kinases -Rho GTPases are activated in both endothelial and cancer cells (Feng et al. 2017). Cancer cells secrete growth factors, which significantly increase endothelial cell proliferation, migration, and tube formation (Hwang et al. 2016).

The invasiveness of cancer cells plays an important role in the cytokines secreted following the interaction with endothelial cells (Kamińska et al. 2015). TGF-β can induce EMT and enhance intravasation (Tsuji et al. 2008). Also, activation of EGFR family members stimulates invadopodia through phosphoinositide 3-kinase (PI3K), neural Wiskott–Aldrich syndrome protein (N-WASP), RhoA, and WASP (Keklikoglou et al. 2012; Chiang et al. 2016). Intratavation and invasion are associated with urokinase-type plasminogen activator (uPA)/uPAR in relation to proteinases, and the role of MMPs is important (Ossowski 1988; Ploug et al. 2001; Shin et al. 2011). Endothelial cells co-cultured with invasive hepatocellular carcinoma cells have been shown to increase the levels of IL-8 as well as growth-regulated oncogene (Gro)-β expression in intravasation (Fig. 2) (Loukinova et al. 2000; Mierke et al. 2008). Expression of two chemokine receptors, chemokine (C-X-C motif) receptor (CXCR) 2, has been shown to be up-regulated in invasive cancer cells (Murdoch et al. 1999; Salcedo et al. 2000). Invasive cancer cells, along with

CXCR2 expression, contribute to the destruction of the endothelial barrier (Mierke et al. 2008). Metastasis chips have been developed in which endothelial cells and stromal cells are patterned close to tumor cells (Caballero et al. 2017). These metastasis chips have made it possible to imitate the production of microvascular blood vessels, allowing for the identification of angiogenesis, intravasation, and extravasation (Lee et al. 2014b).

The chemokines that are most important for endothelial progenitor cell migration include CCL2 (MCP-1) and CCL5 (RANTES) (Yu et al. 2016; Phi et al. 2017). Cancer cells secrete chemokines such as CCL2, which secrete inflammatory stimuli that activate endothelial cells and induce the expression of VCAM1 and vascular adhesion protein 1 (VAP1) (Reymond et al. 2013). CCL5 is produced by several tumor cells (Azenshtein et al. 2002). High plasma CCL5 levels are associated with advanced breast cancer, and breast cancer cell-derived CCL5 promotes the progression and invasion of breast cancer (Niwa et al. 2001; Azenshtein et al. 2002). Expression of CCL2 and CCL5 is also increased in prostate cancer (Zhang et al. 2010). CCL2, CCL3, CCL4, and CCL5 are expressed by inflammatory stimuli (Laurence 2006; Bobanga et al. 2013). In mouse models of liver cancer, tumor-associated endothelial cells have been shown to up-regulate the expression of CCL2, CCL3, CCL4, CCL7, and CCL8 (Spring et al. 2005; Ryschich et al. 2006). CCL1 and CCL3 promote the progression of tumor metastasis in leukemia (Ridiandries et al. 2016). Chemokine (C-X-C motif) ligand (CXCL) 1, CXCL2, and CXCL3 are important in the growth of pancreatic cancer, melanoma, lung cancer, and gastric cancer (Bendall 2005). CXCL4 was shown to be involved in the proliferation of cancer as well as overexpressed in many cancers including prostate, breast, ovarian, and lung cancers, as well as melanoma (Müller et al. 2001; Kijima et al. 2002; Darash-Yahana et al. 2004; Sarvaiya et al. 2013).

Angiogenesis induced by tumor cells

Heterologous interaction between tumor cells and endothelial cells plays an important role in the vascularization of neoplastic cells and the pathological angiogenesis of tumors (Longo et al. 2001). Tumor angiogenesis is a complex process in which new blood vessels are formed in response to the interaction between tumor cells and endothelial cells, growth factors, and ECM components (Jung et al. 2002; Khodarev et al. 2003). Angiogenesis is characterized by mitosis of the ECM and endothelial cells (Dudley 2012).

Since endothelial cells form a capillary-like tube structure, they proliferate and migrate in the presence of these growth factors (Prior et al. 2004). Tumors induce vascular growth by secreting various growth factors such as bFGF or VEGF (Ferrara 2002; Naoyo et al. 2006). VEGF, a potent stimulator of angiogenesis, plays an important role in angiogenesis (Bloor 2005; Carmeliet 2005). The secreted VEGF binds to receptors on the surface of vascular endothelial cells, creating new blood vessels that supply oxygen and nutrients to the tumor (Sounni and Noel 2013). VEGF induces a large amount of signal transduction in endothelial cells (Hofer and Schweighofer 2007). VEGF receptors (VEGFRs) are associated with endothelial cell-dependent tumor angiogenesis (Meng et al. 2017). uPA inhibits the uPA dependence of VEGFR1 and VEGFR2 gene transcription by binding to the hematopoietically expressed homeodomain protein or proline-rich homeodomain protein (HHEX/PRH), mediating the angiogenic effect of VEGF and the control of pathological angiogenesis (Stepanova et al. 2016; Song et al. 2018).

PDGF induces mitogenesis with angiogenesis, fibroblasts, osteoblasts, stromal cells, vascular smooth muscle cells, and mesenchymal stem cells (Hollinger et al. 2008). PDGF is one of the many growth factors that regulate cell growth and differentiation (De Donatis et al. 2008). The important roles of PDGF-B and PDGFR-β in angiogenesis have been demonstrated by gene targeting experiments, and their expression has been found to be associated with endothelial vascularization and maturation (Raica and Cimpean 2010). PDGF-B directly induces endothelial cell proliferation, migration, and tube formation, whereas PDGF-A shows no such effect (Gacche and Meshram 2014). PDGF-D regulates VEGF signaling and promotes tumor cell growth in a variety of cancer cell types (Li et al. 2003).

Notch signaling plays an important role in the development and differentiation of various hematopoietic systems (Artavanis-Tsakonas et al. 1999; Milner and Bigas 1999). Notch receptors promote the growth and survival of tumor cells through the interaction between tumor cells and Notch ligands (Jundt et al. 2004). One of the Notch ligands, Jagged (JAG) 1, is overexpressed in many cancer types (Grochowski et al. 2016). JAG1 can indirectly affect tumor microenvironmental components such as the vasculature of the tumor (Li et al. 2014). Blocking the Notch in the tumor vasculature has been shown to inhibit tumor growth (Wu et al. 2010). Tumor vessels use Notch signaling for vascular stability while controlling vascular wall cell function (Kofler et al. 2011). JAG1 expression is induced by TGF-β which induces EMT phenotype in vitro (Camenisch et al. 2002; Zavadil et al. 2004).

Semaphorin (SEMA)-4D, also known as CD100, is a protein belonging to class IV semaphorin that is strongly implicated in tumor progression via interaction with the high affinity receptor Plexin-B1 (Lin et al. 2007b; Okuno

Table 1 Drugs that target key molecules in the crosstalk between cancer cells and endothelial cells

Drug	Target molecule	Clinical trial	References
Bevacizumab	VEGF-A	Phase III	Los et al. (2007)
Brivanib alaninate	FGFR	Phase II	Finn et al. (2012)
	VEGFR		Park et al. (2011)
Cediranib	VEGF	Phase III	Batchelor et al. (2013)
Imatinib	PDGFR	Phase II	McGary et al. (2004)
	c-kit		Hantschel et al. (2008)
Sunitinib	PDGFR	Phase III	Demetri et al. (2006)
	VEGFR2		
Sorafenib	PDGFR	Phase III	Keating and Santoro (2009)
	VEGFR		Smalley et al. (2009)
	Raf kinase		Wilhelm et al. (2008)
Pazopanib	FGFR	Phase III	Pick and Nystrom (2012)
	PDGFR		Sternberg et al. (2013)
	VEGFR		Verweij and Sleijfer (2013)
	c-kit		Zivi et al. (2012)
Vandetanib	EGFR	Phase III	Yoshikawa et al. (2009)
	VEGFR		Zhang et al. (2011)

et al. 2010). SEMA4D-Plexin-B1 signaling pathway in angiogenesis occurs as SEMA4D binds to Plexin-B1 and induces tumor angiogenesis via two independent downstream pathways (Ch'ng and Kumanogoh 2010). SEMA4D-Plexin-B1 signaling pathway in angiogenesis occurs as SEMA4D binds to Plexin-B1 and induces tumor angiogenesis via two independent downstream pathways (Ch'ng and Kumanogoh 2010). When SEMA4D interacts with Plexin-B1, a Plexin-B1-Met interaction on its binding is possible, resulting in Met activation and tyrosine phosphorylation (Conrotto et al. 2005). Another mechanism involves Plexin-B1 and PDZ-binding motifs in order to activate RhoA (Basile et al. 2007). In addition, cancer cells activate the PI3K/Akt signaling pathway and increase endothelial tube formation as well as survival (Lauring et al. 2013; Massihnia et al. 2016; Zhou et al. 2016). Cancer cells also partially activate the PI3K/Akt signaling pathway and promote endothelial tube formation and survival (Cheng et al. 2017).

Strategies targeting the crosstalk between cancer cells and endothelial cells

Targeted cancer therapy should cause minimal collateral damage to normal cells while targeting cancer cells. Drugs used in chemotherapy work in multiple ways to stop the growth of cancer cells by killing, stopping the division of, or preventing the spread of cells (Shewach and Kuchta 2009). Molecular targets include adhesion molecules, signaling molecules, and chemokines mediating the interaction of cancer cells with endothelial cells (Agemy et al. 2013; Kummar and Doroshow 2013; Farahani et al. 2014). Molecules associated with angiogenesis and regulators of invasion can also be effective targets for anti-cancer strategies (Ferrara and Kerbel 2005; Zhao and Adjei 2015).

The most widely known approach inhibiting tumor angiogenesis involves blockade of the VEGF pathway (Kuhnert et al. 2011). VEGF-targeted therapy was initially designed to inhibit neoangiogenesis and starve the tumor of needed oxygen and nutrients (Ellis and Hicklin 2008). In clinical trials, the anti-VEGF approach increased survival rates in metastatic cancer patients (Gyanchandani and Kim 2013). Bevacizumab was the first VEGF inhibitor approved as a cancer treatment (Meadows and Hurwitz 2012). Adding a VEGF-specific antibody, bevacizumab, to chemotherapy improves the overall survival in patients with colorectal cancer and lung cancer (Jain et al. 2006). Sunitinib is a targeted therapy that is a receptor protein-tyrosine kinase inhibitor (Demetri et al. 2006). Multikinase inhibitors that inhibit VEGFR1, 2, 3, PDGFR, and c-Kit include sunitinib, sorafenib, and pazopanib (Keating and Santoro 2009; Sternberg et al. 2013). A number of VEGF inhibitors, including brivanib alaninate, cediranib, and vandetanib, are currently in phase 3 clinical trials or in clinical development (Meadows and Hurwitz 2012). These drugs and their target molecules are summarized in Table 1.

Kangai-1 (KAI1), also known as CD82, is a typical tumor metastasis suppressor (Singh et al. 2016). Inhibition of KAI1 has been shown to negatively regulate VEGF-induced angiogenesis (Nomura et al. 2016). KAI1 is known to block the metastatic process without affecting primary tumor growth (Park et al. 2012; Lee et al. 2017). Imatinib

mesylate inhibits the growth of cancer cells by blocking a few of the enzymes needed for cell growth (Table 1) (Dewar et al. 2003; Danchev et al. 2008). Imatinib mesylate regulates metastasis by up-regulating KAI1 gene expression in human breast cancer MCF-7 cell line (Shandiz et al. 2016).

TSP-1 serves as an angiogenesis inhibitor by regulating the bioavailability and activity of VEGF (Lawler 2000). TSP-1 is a multifunctional glycoprotein involved in various biological processes including angiogenesis, apoptosis, and activation of TGF-β1 (Crawford et al. 1998; Murphy-Ullrich and Poczatek 2000). Tumors overexpressing TSP-1 show decreased growth, metastases, and angiogenesis, suggesting TSP-1 as a therapeutic target for cancer (Kazerounian et al. 2008). Both ABT-510 and ABT-898, TSP-1 synthetic analogs mimicking anti-angiogenic activity, have been shown to inhibit the growth of prolactinoma (Recouvreux et al. 2012).

Notch signaling is important in tumor angiogenesis through VEGF-A (Funahashi et al. 2008). Inhibition of Notch signaling in endothelial cells limited VEGF-A-induced tumor growth and caused endothelial dysfunction (Patenaude et al. 2014). Using co-culture and tumor growth assays, Notch-mediated nitric oxide (NO) production in endothelial cells demonstrates the need for VEGF-A signaling (Fukumura et al. 2006). NO, mainly produced by endothelial NO synthase (eNOS), acts as a cardiovascular signal molecule. The eNOS activated by the phosphorylation of the Ser1177 residue was reduced through Notch inhibition, which caused tumor growth and diminished vascular function (Miller et al. 2009). BAY41-2272, a soluble guanylate cyclase activator and vasodilator, can inhibit tumor growth and the vascular function of eNOS (Patenaude et al. 2014).

Conclusions

The tumor microenvironment is composed of complex and diverse elements such as extracellular matrix, growth factors, signaling substances, and cells surrounding cancer cells. Cancer-endothelial cell interactions in the tumor microenvironment secrete adhesion molecules and chemokines, which are critical to tumor growth and metastasis (Buess et al. 2009). Drug resistance and cancer recurrence may be overcome through control of this tumor microenvironment. Studies investigating the anti-cancer mechanisms targeting cytokine secretion by cancer-derived stromal cells or stromal cells in particular provide a new breakthrough in the development of selective chemotherapeutic agents. In the present study, we summarize the current perspective on the interaction between cancer cells and endothelial cells and also suggested anti-cancer strategies based on these interactions.

Intercellular interactions between cancer and other cells in the surrounding tumor microenvironment are critical for tumorigenesis and tumor progression. Understanding the mechanisms of these interactions can lead to the development of new therapies that block tumor progression and metastasis. This review provides useful information underlying cancer aggressiveness affected by the crosstalk between cancer cells and endothelial cells, and suggests therapeutic strategies against tumor progression.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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