[Frontiers in Bioscience 15, 195-212, January 1, 2010]

Regulation of tumor angiogenesis by the local environment

Kelly Hall, Sophia Ran

Department of Medical Microbiology, Immunology and Cell Biology, Southern Illinois University School of Medicine and SimmonsCooper Cancer Institute, Springfield, IL, 62794-9678, USA

TABLE OF CONTENTS

1. ABSTRACT

Angiogenesis is the process of formation of new blood vessels from pre-existing vessels or endothelial cell progenitors. It plays an essential role in embryogenesis, inflammation, wound healing, tumor growth and metastasis. The tumor microenvironment contains excessive amounts of pro-angiogenic factors derived from neoplastic, stromal, and infiltrating immune cells. The imbalance of pro-angiogenic and anti-angiogenic factors promotes abnormal angiogenesis, creating numerous blood vessels with structural abnormalities and functional defects. These defective vessels often create an inflammatory environment within the tumor that promotes coagulation, thrombosis, and impairs blood supply, causing further complications to the cancer patient. The structural and functional abnormalities of the tumor vessels promote hematogenous metastasis, which is strongly associated with shorter patient survival. Furthermore, tumor blood vessels are poorly perfused, which impedes drug delivery to the tumor, thus reducing the efficacy of anti-cancer agents. Tumor angiogenesis is widely studied as an important target for suppressing tumor growth and metastasis. This review will briefly summarize the current findings related to regulation of angiogenesis by the tumor microenvironment, while highlighting potential targets for inhibiting this process.

2. INTRODUCTION

Blood vasculature is essential for tissue health serving as a highway for the delivery of oxygen and nutrients. Diffusion of oxygen through the tissues is limited to approximately 200 μm (1), thus cells must be located within this distance from a blood capillary to prevent death from hypoxia and nutrient deprivation. The blood vasculature also transports growth factors, cytokines, and hormones throughout the body. Additionally, blood vessels regulate vascular tone essential for controlling both systemic and local blood flow. Blood vasculature also contributes to regulation of the immune response by controlling access of circulating immune cells to the sites of inflammation and immune stress. Blood vessels control the fibrinolytic status of the normal endothelium permitting coagulation upon vascular injury to prevent excessive blood loss. Wound healing relies heavily on all functions of blood vessels, including control of the coagulation cascade, immune cell trafficking, and angiogenesis.

Angiogenesis is defined as the formation of new blood vessels from pre-existing vessels with the possible aid of endothelial cell progenitors. Normal physiological angiogenesis plays an essential role in embryogenesis, inflammation, wound healing and female reproductive functions. The formation, maturation and regression of new

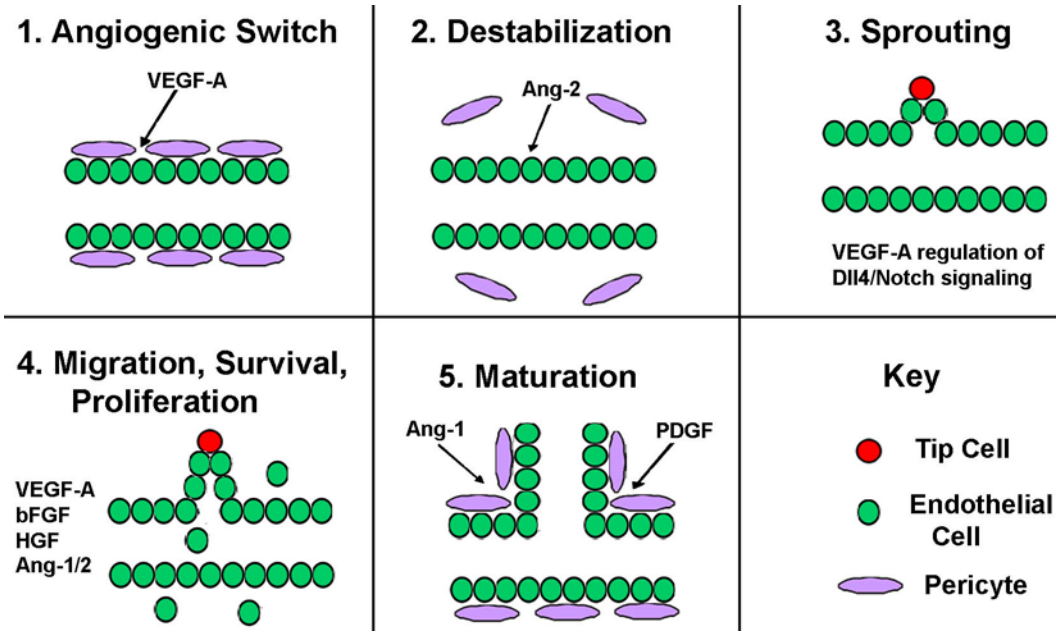

Figure 1. *Steps in generation of new blood vessels*. Five discrete steps in angiogenesis have been highlighted in this review: 1) Angiogenic switch; 2) Destabilization; 3) Sprouting; 4) Migration, Survival, and Proliferation; and 5) Maturation and Stabilization. All stages occur in both normal and tumor angiogenesis, but tumor vessels are defective due to abnormalities of their microenvironment.

vessels induced by normal physiological needs are regulated by the environmental cues that coordinate blood delivery and tissue expansion or remodeling. In contrast, abnormal angiogenesis induced by tumors that typically contain disproportionately high levels of pro-angiogenic factors creates structurally deficient and functionally impaired blood vessels (2). These incorrectly constructed vessels often create an inflammatory environment within the tumor that promotes coagulation and thrombosis, causing further complications to the patient (3,4). The structural and functional abnormalities of the tumor vessels promote hematogenous metastasis, which is linked to decreased patient survival (5). Importantly, tumor blood vessels are poorly perfused, which impedes drug delivery to the tumor, thus reducing the efficacy of anti-cancer agents. It is, therefore, widely accepted that tumor angiogenesis is an important target for suppressing tumor growth and metastasis. This review will briefly summarize the current concepts of angiogenesis in the context of the tumor microenvironment, while highlighting potential targets for inhibiting this process.

3. MECHANISMS OF TUMOR BLOOD VESSEL FORMATION

The process of angiogenesis can be tentatively separated into five main steps regulated by the microenvironment. In reality, no step is clearly separated from another and some steps might occur simultaneously. For the purpose of this review, we will describe five discrete steps in the tumor-inducing angiogenic cascade that are typically required to form a new vessel. As illustrated in Figure 1, these steps include: 1) induction of angiogenesis by tipping the balance of pro- and anti-angiogenic factors; 2) vessel destabilization; 3) vascular sprouting; 4) induction of endothelial cell migration, proliferation, and survival; and 5) vessel maturation and stabilization.

3.1. Step 1: tipping the angiogenic balance

In adulthood, blood vessels generally remain in a state of quiescence in which they are neither growing nor regressing. Maintenance of the quiescent state requires a balance of pro- and anti-angiogenic factors whose expression is regulated by the local environment of the vessel, endothelium-supporting mural cells and the endothelial cells themselves. However, conditions created by solid tumors turn on an angiogenic switch that tips the balance in favor of angiogenesis, resulting in transformation of quiescent vessels to actively sprouting vessels (6). The angiogenic switch is a complex mechanism involving a wide array of factors. Of these, vascular endothelial growth factor (VEGF-A) has been shown to play a particularly important role (7).

3.1.1. Role of VEGF-A in induction of tumor angiogenesis

The vascular endothelial growth factor (VEGF) family includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placental growth factor (PlGF). Each of these proteins participates in angiogenesis, lymphangiogenesis, or both to varying degrees. VEGF-A is a homodimeric glycoprotein that is generated through several alternatively spliced isoforms (8). VEGF-A_{165} is the most abundant of the three main isoforms (i.e., $VEGF_{121}$, $VEGF_{165}$, and $VEGF_{189}$) (8). VEGF-A can be produced by

Table 1. Cell-type expression of VEGF-A and VEGF-A receptors in human cancers

Protein	Tumor Type	Expressed in	Reference
VEGF-A	Breast	Tumor cells	(161,162)
	Gastric	Tumor cells	(163)
	Hepatocellular	Tumor cells	(164)
	Melanoma	Tumor cells	(165)
	Non small cell lung cancer	Tumor cells	(166)
	Melanoma	Endothelial cells	(165)
	Hodgkin lymphoma	Endothelial cells, Dendritic cells	(167)
	Melanoma	Fibroblasts, Macrophages	(165)
VEGFR-1	Breast	Tumor cells	(162)
	Non small cell lung cancer	Tumor cells	(166)
	Ovarian	Tumor cells, Endothelial cells	(168)
	Uterine Sarcoma	Tumor cells	(169)
	Non small cell lung cancer	Pericytes	(170)
	Head and neck squamous cell carcinoma	Macrophages, Fibroblasts	(171)
VEGFR-2	Bladder	Tumor cells	(172)
	Colorectal	Tumor cells	(173)
	Non small cell lung cancer	Tumor cells	(166)
	Ovarian	Tumor cells, Endothelial cells	(168)
	Hepatocellular	Endothelial cells, Macrophages	(174)
	Head and neck squamous cell carcinoma	Macrophages	(171)
NRP-1	Colon	Tumor cells	(175)
	Non small cell lung cancer	Tumor cells	(176)
	Ovarian	Tumor cells	(177)
	Pancreatic	Tumor cells	(178)
	Neuroblastoma	Endothelial cells	(179)
	Pituitary	Endothelial cells	(180)
NRP-2	Non small cell lung cancer	Tumor cells	(176)
	Pancreatic	Tumor cells	(181)
	Neuroblastoma	Endothelial cells	(179)

VEGF-A and its receptors are expressed in a variety of cell types within the tumor including neoplastic cells, endothelial cells, pericytes, infiltrating macrophages, dendritic cells, and fibroblasts. Abbreviations: VEGF-A, VEGFR-1 and VEGFR-2 correspond to vascular endothelial growth factor A, receptor 1 and receptor 2; NRP-1 and NRP-2 correspond to neuropilin-1 and -2.

a variety of cell types present in the tumor microenvironment, including infiltrating macrophages (9,10,11), mast cells (12), neutrophils (13), platelets (14), stromal fibroblasts (15), endothelial cells (16) and neoplastic cells (17) (Table 1). Thus, both the local environment and the tumor contribute to high intratumoral concentrations of VEGF-A.

Members of the VEGF family bind two types of receptors: 1) VEGF receptors (VEGFR) that contain a tyrosine kinase domain; and 2) neuropilins that lack a cytosolic domain. The tyrosine kinase VEGFR family consists of VEGFR-1, -2, and -3. They are primarily expressed on blood and lymphatic endothelium, but have also been detected on monocytes, a subset of hematopoietic cells, and on neoplastic cells of different tumor types (18,19). VEGF-A binds VEGFR-1 and VEGFR-2, but not VEGFR-3 (8). VEGF-A has a higher affinity to VEGFR-1 but the signaling transduction of VEGFR-2 has increased functional impact on endothelial cells (20). One study concluded that VEGFR-2 is the primary signaling receptor, whereas VEGFR-1 is a decoy receptor (21). However, other studies demonstrated a functional role for both receptors on tumor (22,23) and endothelial cells (24). Expression of functional VEGFR-1 and VEGFR-2 receptors was also shown in several human tumors on both endothelial and malignant epithelial cells (Table 1). Based on these studies, both receptors can contribute to tumor progression through autocrine (25) and paracrine (26) loops.

VEGF ligands also have affinity for members of the Neuropilin (NRP) family, including neuropilin-1 (NRP-1) and neuropilin-2 (NRP-2). Originally, NRP-1 and NRP-2 were identified as neuronal receptors involved in axon guidance (8). Subsequently, both neuropilins were found to be expressed on vascular smooth muscle and endothelial cells, and to participate in angiogenesis (27) and lymphangiogenesis (28). Blood vascular endothelial cells primarily express NRP-1 (27), where lymphatic endothelial cells mainly express NRP-2 (29). NRP-1 binds an exon of $VEGF_{165}$ encoding for a heparin-binding domain, which contrasts the binding site known to interact with its cognate tyrosine kinase receptor, VEGFR-2 (28). NRP-1 presumably plays an ancillary role in VEGFR-dependent activation of endothelial cells by cooperating with tyrosine kinase receptors and enhancing their signaling (28,30). Co-expression of NRP-1 with VEGFR-2 on porcine aortic cells mediated a four-fold increase in VEGF-A binding to VEGFR-2 that subsequent increase in chemotaxis response of these cells for VEGF-A (31). Both NRP-1 (32,33) and NRP-2 (32) also form functional complexes with VEGFR-1 that enhance its activity. In addition, VEGF-A can signal through neuropilins in the absence of VEGFRs (34,35). Neuropilins are abundantly expressed on both endothelial (36,37) and malignant epithelial cells (38,37) in a variety of tumors, and contribute to tumor progression through paracrine and autocrine mechanisms.

3.1.2. Regulation of VEGF-A expression and activity

Expression of VEGF-A is elevated in response to hypoxia and inflammation, conditions characteristic of

Table 2. A selected list of inflammatory factors that induce VEGF-A expression in the tumor environment

Factor	The main responder cell type responsible for VEGF-A production	Reference
IL-1 beta	Macrophages	(182,183,10)
IL-6	Tumor cells Macrophages, Macrophages	(48, 11)
IL-8	Tumor cells, Neutrophils, Endothelial cells	(184, 185, 186)
IL-18	Tumor cells, Macrophages, Dendritic cells	(187, 188, 189)
Oncostatin M	Macrophages, T lymphocytes	(190, 191)
TGF-beta1	Tumor cells, Stromal cells	(192, 193)
TNF alpha	Tumor cells, Macrophages	(13,194, 195)

Abbreviations: IL-1, interleukin-1; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; TGF, transforming growth factor; TNF, tumor necrosis factor

most epithelial malignancies (39). All solid tumors contain hypoxic pockets primarily caused by the lack of coordination between growth of the tumor mass and generation of new blood vessels to support tumor cell proliferation (8). Tumor hypoxia promotes expression of VEGF-A through stabilization of a transcription factor, hypoxia inducible factor-1 (HIF-1) alpha that binds the VEGF-A promoter and activates its transcription (40,41). Upregulation of VEGF-A by hypoxia has been demonstrated in many human tumors, including breast (42), colorectal (43), brain (42,44) and gallbladder cancers (45) (see Table 1).

Another parameter that plays a significant role in regulation of VEGF-A expression is tumor-associated inflammation. Many inflammatory cytokines that are present in the tumor environment up-regulate VEGF-A expression (Table 2). For instance, IL-1 beta induces VEGF-A expression in gastric carcinoma cells via extracellular signal regulated kinases 1 and 2 (ERK1/2) and p38-dependent pathways (46). IL-6 dependent upregulation of VEGF-A has been shown in non-small cell lung (47) and gastric cancers (48). VEGF-A transcription is potently enhanced by the binding of the transcription factor nuclear factor kappa B (NF-κB) to the VEGF-A promoter (49,50). Increased production of VEGF-A exacerbates tumor inflammation by recruiting macrophages and neutrophils (51,52,53) that secrete additional angiogenic factors and further promote vascular formation (54).

VEGF-A signal transduction activates pathways that mediate survival, proliferation, migration and invasion of endothelial cells, all of which are essential for induction of angiogenesis. VEGF-A binding to VEGFR-1 induces the activation of phospholipase C gamma and the mitogen-activated protein kinase (MAPK) cascade, promoting migration and proliferation of endothelial cells (55,56). VEGFR-2 signaling induces endothelial cell proliferation, survival and changes in gene expression via activation of the MAPK and phosphatidylinositol 3-kinase (PI3K)/AKT pathways (57,58). Additional downstream gene targets of VEGF-A signaling are nitric oxide (NO) (59,60) and angiopoietin-2 (Ang-2) (61), both of which regulate steps of angiogenesis that immediately follow the induction of the angiogenic switch.

3.2. Step 2: destabilization of pre-existing vessels

New vessels sprout and branch from pre-existing vasculature (62). Normally, tight endothelial cell-to-cell interactions and contacts between endothelial and peri-endothelial mural cells keep the vasculature stable (62). These contacts must destabilize to permit sprouting, division and migration of the endothelial cells in order to initiate the formation of new blood vessels (63). Destabilization of blood vasculature decreases the number and intensity of endothelial cell interactions with mural cells, creating leaky and dilated vessels that are primed for the action of VEGF-A (63). Ang-2 is thought to be primarily responsible for this critical event (64,65).

3.2.1. Role of angiopoietins in stabilization and destabilization of blood vessels

The angiopoietin (Ang) family consists of four secreted glycoproteins: Ang-1, Ang-2, Ang-3, and Ang-4 (64,63). Ang-1 and Ang-2 were the first discovered and are the most well-studied members. Ang-1 is secreted by endothelial cells, pericytes and vascular smooth muscle cells, whereas Ang-2 is primarily produced by endothelial cells, stored in Weibel-Palade bodies, and released upon activation (66). While Ang-1 is expressed in many tissues, Ang-2 expression is localized to areas of vascular remodeling (65). These secreted proteins are the ligands for a tyrosine kinase receptor, Tie-2 (63). A structurally related receptor, Tie-1, does not bind known angiopoietins but might facilitate binding and signal transduction mediated by Tie-2▪angiopoietin interactions (63). Tie receptors are expressed on endothelial cells (67), leukemia cells (63,68) and a sub-set of hematopoietic cells (69,27). Tie-2 is also expressed on smooth muscle cells, neuronal cells and stem cells (70,66). In blood vascular endothelial cells, both Ang-1 and Ang-2 bind Tie-2, but only Ang-1 causes Tie-2 phosphorylation under normal conditions. Based on these observations, Ang-1 has been proposed to stimulate Tie-2 signal transduction in blood vascular endothelial cells, whereas Ang-2 is suggested to antagonize activation of the Tie-2 pathway (65).

The signaling of Tie-2 induced by Ang-1 resulting in stabilization of blood endothelium is mediated through the PI3K pathway (71,72) that induces NOS expression and promotes endothelial cell survival (71,73). Endothelial cell motility is also induced by the PI3K pathway through interaction with signaling components, such as growth factor receptor-bound protein 7 (GRB-7) and src homology 2-containing tyrosine phosphatase protein (SHP2), leading to activation of focal adhesion kinase (FAK) (71). Association of the docking protein, Dok-R, with phosphorylated Tie-2 leads to the phosphorylation of Nck/Pak kinases that are involved in cell migration (71). Induction of Tie-2 signaling by Ang-1 binding mainly results in activation of endothelial cells. However, in some contexts, angiopoietin-dependent Tie-2

Table 3. Clinical significance of angiopoietins in human cancers

Angiopoietin Type	Tumor Type	Comments	Reference
Ang-2	Bladder	Positive expression correlated with histological stage (P=0.0.09), histological grade (P=0.0.26) and decreased survival (P<0.0.5)	(196)
Ang-2	Breast	Immunostaining of 198 human breast cancers showed a significant correlation between Ang-2 and increased MVD (P=0.0.006), VEGF-A (P=0.0.04) and a worse DFS (P=0.0.3)	(197)
Ang-2	Breast	Ang-2 transcript levels correlated with positive lymph nodes (P=0.0.05) and decreased DFS (P<0.0.001) and OS (P<0.0.003)	(82)
Ang-2	Colon	Immunostaining showed Ang-2 expressed in both tumor and normal endothelium while Ang-1 was primarily expressed in normal vessels	(85)
Ang-2	Colorectal	Ang-2 expression significantly correlated with lymphatic metastasis (P=0.0.42), venous invasion (P=0.0.31), high MVD (P<0.0.01) and decreased overall survival	(83)
Ang-2	Gastric	Increased Ang-2 mRNA correlated with advanced disease stage and decreased survival (all P<0.0.5)	(94)
Ang-2	Glioma	Ang-2 was expressed in tumor and microvascular cells. Its expression correlated with increased number of immature vessels	(198)
Ang-2	Glioma	Ang-2 had a similar expression pattern as MMP2 and was detected primarily on the borders of the invading tumor	(95)
Ang-2	Hepatocellular	Ang-2 transcript level correlated with increased MVD (P=0.0.01) and tumor size (P=0.0.3)	(199)
Ang-2	Hepatocellular	Ang-2 expression was associated with increased MVD (P=0.0.4) and decreased DFS (P=0.0.3)	(200)
Ang-2	Pancreatic	Ang-2 expression was increased in tumor cells	(201)
Ang-2	Colorectal	Ang-2 expression correlated with increased MVD (P=0.0.09)	(83)
Ang-1/Ang-2	Esophageal	Transcript expression of both Ang-1 and Ang-2 correlated with increased MVD (P<0.0.001)	(202)
Ang-1/Ang-2	Hepatocellular	High Ang-2/Ang-1 ratio was positively associated with MVD (P=0.0.1)	(201)
Ang-1/Ang-2	Ovarian	High Ang-2/Ang-1 ratio correlated with increased MVD (P=0.0.03) and decreased OS (P=0.0.1)	(203)
Ang-1	Non-small cell lung carcinoma	High Ang-1 expression was associated with poor prognosis (P=0.0.03)	(204)

Abbreviations: Ang-1 and Ang-2, angiopoietin-1 and -2; MVD, microvascular density; DFS, disease-free survival; OS, overall survival.

activation can result in an inhibitory effect through activation of A20-binding inhibitor of NF-kappaB 2 (ABIN2) (72,74).

The destabilizing effect on vasculature is mediated by overexpression of Ang-2 in a variety of human tumors including liver (75,76), gastric (77), renal cell (78) non-small cell lung (79), ovarian (80), prostate (81) and breast (82) cancers (Table 3). In several cancers, overexpression of Ang-2 is associated with increased lymph node metastasis, venous invasion, and high microvascular density (MVD) (83,84). In normal tissues, expression of Ang-2 is restricted to the endothelium (65). In tumors, however, Ang-2 is expressed in both neoplastic epithelial (85,83) and endothelial cells (86). Similarly to VEGF-A, tumor expression of Ang-2 is regulated by hypoxia and inflammatory cytokines (86).

Expression of Ang-2 is regulated by both VEGF-A (61) and fibroblast growth factor-2 (basic FGF or bFGF) (7). Basic FGF has been shown to increase Ang-2 expression up to 2-fold in bovine microvascular endothelial cells (7). The same study reported that hypoxic conditions also promoted Ang-2 expression by 3- to 5-fold (61,87). Hypoxia has been shown to significantly increase Ang-2 (88) and Tie-2 (89) expression in bovine microvascular (88) and human umbilical cord vein endothelial cells (HUVEC) (89). However, it is currently unclear whether hypoxia induces Ang-2 directly, through binding of HIF-1 alpha to the Ang-2 promoter, or indirectly, through upregulation of VEGF-A (41) or bFGF (90,91) that subsequently increases Ang-2 expression.

Ang-2 competes with Ang-1 for the Tie-2 receptor, and can prevent Ang-1-mediated stabilizing effects (92). The destabilization effect of Ang-2 prevents maturation of angiogenic vasculature, which can lead to regression of blood vessels. In a rat glioma model, overexpression of Ang-2 in tumor endothelial cells in the absence of VEGF-A led to vessel regression (93). However, in the presence of both VEGF-A and Ang-2, vasculature growth is renewed (93). The results of this study suggested that in the absence of VEGF-A, Ang-2 destabilizes vasculature leading to vessel regression, but in the presence of VEGF-A, Ang-2 promotes angiogenesis by priming the vessels (93). This showed, for the first time, that Ang-2 plays an important role in vessel dismantling that is mediated, in part, by increased expression of matrix metalloproteinases (MMPs). Another study demonstrated that overexpression of Ang-2 in gastric carcinoma cells up-regulated MMP-1 and MMP-9 expression (94). In human glioma cells, Ang-2 was shown to induce expression of another member of this family, MMP-2 (95). The MMPs promote angiogenesis by degrading the extracellular matrix (ECM) [reviewed in (96)] that allows tumor expansion and dissemination of metastatic cells. Thus, Ang-2 can promote tumor growth through both endothelial-dependent and -independent mechanisms.

3.3. Step 3: blood vessel sprouting

3.3.1. Role of Notch and its ligand Delta-like 4 (Dll4) in regulation of tumor vessel sprouting

The destabilization of the pre-existing capillaries by VEGF-A, Ang-2 and MMPs prepares for endothelial cell sprouting. Tip cells, endothelial cells that guide the developing vessel, develop filopodia-like extensions and sprout from the primary vessel. The quantity and activity of tip cells are regulated by two cell surface proteins, Notch and its ligand, Delta-like 4 (Dll4) (97). Activation of Notch signaling occurs when Notch binds to Dll4 on a neighboring cell, leading to proteolytic cleavage of the Notch intracellular domain followed by downstream signaling (100). An *in vitro* model of angiogenesis demonstrated that suppression of Notch signaling in

HUVEC increased sprouting by 2- to 4-fold (101). Additionally, inhibition of Notch/Dll4 signaling by the inactivation of Dll4 allele, Notch cleavage inhibition, and deletion of Notch all enhance the number of tip cells in the mouse retina (99). Based on these observations, it is hypothesized that Notch signaling induction by Dll4 regulates tip cell numbers and plays a major role in vascular sprouting (99).

Dll4/Notch signaling between tip cells and supporting stalk cells acts as a negative feedback loop limiting endothelial response to VEGF-A. VEGF-A stimulates the activation of tip cells (97) that includes an increase in Dll4 expression (98). Overexpression of Dll4 in HUVEC was shown to increase expression of the angiogenic factors VEGF-A, basic FGF, hepatocyte growth factor (HGF) and VEGFR-1 (102). At the same time, VEGFR-2 and NRP-1 expression decreased and soluble VEGFR-1 increased concomitant with a reduction of proliferation and migratory response to VEGF-A, which was reversed by inhibition of the Notch pathway (98,103).

Tumor angiogenesis is modulated by both increased expression of Dll4 and Notch proteins, and activation of Notch signaling. Upregulation of Dll4 expression has been reported in human bladder and renal cell cancers (98,104). Forced overexpression of Dll4 in murine tumor lines decreased blood vessel density, accompanied by a decrease in tumor size and an increase in hypoxia (105). The blockade of Dll4 in murine lung carcinoma and glioma models initially promoted vascular sprouting and branching, thus increasing vessel density. However, the blockade ultimately increased hypoxia due to incomplete vascular remodeling and poor perfusion, which led to inhibition of tumor growth (106). These studies suggest that the Dll4/Notch signaling pathway is a finely balanced regulatory system designed to control vessel sprouting and maturation. As such, it is a potential target for inhibition of new tumor vasculature.

3.4. Step 4: induction of endothelial cell migration, proliferation and survival

Tip cells lead the migration of endothelial cells, following signals from malignant and other cells within the tumor microenvironment. The main chemotactic signal inducing this step is VEGF-A, which stimulates migration of endothelial cells through binding to VEGFR-1 and activation of PLC gamma and MAPK pathways (55,56). VEGFR-2 can also mediate migration of microvascular endothelial cells via activation of Src homology 2 domain containing adaptor protein B (Shb) and the subsequent activation of the PI3K pathway (107). In addition to recruiting endothelial cells, VEGF-A also attracts hematopoietic stem cells and endothelial progenitor cells (EPC) (108). An increase in endothelial cells at angiogenic regions has two causes: VEGF-A-dependent recruitment of EPC from the blood circulation and emergence of differentiated endothelial cells from pre-existing vessels.

Both Ang-1 and Ang-2 are also implicated in induction of migratory responses in blood vascular endothelial cells. Ang-1 has been shown to induce HUVEC migration, whereas Ang-2 was reported to block this response (109). However, another study showed that Ang-2 stimulates migration of a murine brain capillary endothelial cell line via activation of Tie-2 signaling (110). The question of whether Ang-2 causes phosphorylation of Tie-2 and downstream signaling is still debatable. It appears that a low concentration of Ang-2 does not induce Tie-2 signaling; however, a high dose of Ang-2 (more than 800 ng/ml) was shown to cause Tie-2 phosphorylation in HUVEC (111). A significantly lower concentration of Ang-2 (200 ng/ml) was sufficient for activation of Tie-2 signaling in human cord blood-derived EPCs. This suggests that Ang-2 might contribute to tumor angiogenesis by promoting EPC recruitment (112), in addition to its known role in pre-sensitizing tumor vasculature to VEGF-A's effect.

Migration of endothelial cells can also be induced by HGF and bFGF, both of which are up-regulated in a variety of solid tumors. HGF induces endothelial cell migration through binding and activation of its tyrosine kinase receptor, C-mesenchymal-epithelial transition factor (c-Met), which leads to activation of several pathways (113). c-Met signaling increases cell motility by either direct activation of PI3K or through the indirect mechanism of phosphorylating the effector Gab1 (114). The PI3K pathway is also implicated in chemotaxis of endothelial cells induced by bFGF through activation of fibroblast growth factor receptor 1 (FGFR1) signaling (115). Other prominent stimulators of tumor endothelial cell migration are inflammatory cytokines such as IL-8 and IL-6, which play a role in tumor progression and angiogenesis (116,117).

Some of the factors involved in endothelial cell migration can also signal for proliferation and survival. Preventing apoptosis of migrating endothelial cells is extremely important because, after vessel destabilization, endothelial cells no longer receive pro-survival signals from interactions with the ECM or cell-to-cell contacts with peri-endothelial or adjacent stromal cells (118). Therefore, the survival of migrating endothelial cells intimately depends on the intracellular activation of pro-survival pathways by the tumor's environmental cues. Numerous studies have shown that VEGF-A is one of the most potent pro-survival factors for endothelial cells under adverse conditions (58,119,120). For instance, the survival of serum-starved HUVEC is significantly increased when exogenous VEGF-A activates the pro-survival PI3K/AKT pathway (58). VEGF-A binding to VEGFR-2 also induces proliferation of endothelial cells via activation of PLC gamma pathway (121). Both proliferation and survival traits promoted by VEGF-A signaling are essential for endothelial cells to complete the angiogenic cascade, culminating in creation of new vessels.

Other factors that contribute to endothelial cell survival and proliferation are Ang-1 and bFGF. Ang-1 increases endothelial cell survival by stimulating the AKT pathway and by up-regulating the expression of an apoptotic inhibitor, survivin (71). Blocking or neutralizing Ang-1 diminishes the ability of endothelial cells to survive

under stressful conditions (122,123). For instance, Ang-1 has been shown to suppress endothelial cell death induced by the anticancer drug doxorubicin, demonstrating the potential chemoprotective ability of Ang-1 in the tumor microenvironment (124). Basic FGF also protects HUVEC from cell death, as demonstrated by the reduction of apoptosis induced by the cytotoxic HIV protein, gp120 (125). All known endothelial pro-survival factors activate similar intracellular pathways involving ERK1/2, PI3K, and AKT signaling (125).

3.5. Step 5: vessel stabilization

Stabilization of the new vessels is essential for proper vessel function and is promoted by endothelial cell-to-cell contact or by interactions between endothelial cells and pericytes. Two main factors that promote these interactions are platelet-derived growth factor (PDGF) and Ang-1.

3.5.1. Role of PDGF factors in maturation and stabilization of new vessels

The PDGF family consists of four factors: PDGF-A, -B, -C, and -D. These proteins form either homodimers or a heterodimer PDGF-AB factor (126). PDGF receptors (PDGFR) are dimers consisting of either PDGFR-alpha or -beta chains. PDGF ligands have different affinities to the receptor dimers. PDGF-AA binds only PDGFR-alpha homodimers, PDGF-AB can bind PDGFR-alpha/alpha and PDGFR-alpha/beta, whereas PDGF-BB binds all three receptor dimers (i.e. PDGFR-alpha/alpha, -alpha/beta, and -beta/beta). Differential expression of PDGF ligands and receptors creates a complex interplay. For example, PDGF-BB ligand and PDGFR-beta/beta receptor are expressed on endothelial cells and pericytes, respectively (127). PDGF-BB expressed by endothelial cells stabilizes newly-formed blood vessels by recruiting pericytes. This role of PDGF-B has been shown in retention motif-deficient (pdgf-beta$^{ret/ret}$) mice that had significantly fewer pericytes overall with remaining pericytes detached from the endothelium (128). Exogenous PDGF-B improved recruitment of pericytes but not the abnormal attachment of the pericytes to the endothelium. The role of PDGFR-beta in pericyte recruitment was also shown in a mouse wound-healing model, where inhibition of this receptor correlated with a reduction in pericytes (127). In an *in vivo* angiogenic model, PDGF-AB co-expression with bFGF promoted stabilization of newly-formed blood vessels by pericyte recruitment (129). This effect was significantly blocked by inhibition of PDGFR-beta (129).

Several studies showed that expression of PDGF ligands and receptors is regulated by VEGF-A, FGF-2 and other angiogenic factors commonly found in the tumor environment. For instance, VEGF-A was shown to enhance endothelial PDGF-B expression, whereas FGF-2 enhanced expression of PDGF receptor beta (PDGFR beta) on peri-endothelial mural cells (130). FGF-2 increased expression of PDGF receptors on blood vascular endothelial cells (129). Both VEGF-A and bFGF induced migration of mural cells *in vitro* (130). PDGF expression is up-regulated by hypoxia in a HIF-1 alpha-dependent manner, as demonstrated in studies of glioblastoma cells (131) and human breast cancer (132). The induction of PDGF ligands and receptor expression by mediators of angiogenesis suggests that PDGF plays an important role during formation of new vessels, mainly through recruitment of pericytes and stabilization of the endothelial monolayer.

3.5.2. Role of Ang-1 in regulation of vessel integrity

Ang-1 is another regulator of vessel integrity and a potent inhibitor of vascular permeability (133). Both of these functions stem from the ability of Ang-1 to promote pericyte migration and survival (133,134). This is exemplified by the *in vitro* wound-healing study in which Ang-1 promoted migration and survival of pericytes stressed by TNF alpha or high glucose concentration (134). Antagonistic roles of Ang-1 and Ang-2 in regulation of blood vasculature were also shown in another study, demonstrating that Ang-1 increases expression of endothelial cell-activating HGF, whereas Ang-2 inhibits this effect (135). Neutralization of HGF blocked Ang-1-induced migration of smooth muscle cells, suggesting that the effects of Ang-1 on perivascular cell recruitment might be mediated, in part, by HGF (135). Based on this study, it has been proposed that Ang-1 can stabilize blood vessels directly, on the endothelium via binding to the Tie-2 receptor, and through indirect mechanisms such as upregulation of HGF.

In the tumor microenvironment, Ang-1 and PDGF are expressed by endothelial, stromal, and tumor-infiltrating immune cells. Overexpression of Ang-1 was detected in brain, breast, and lung tumors (64), whereas high expression of PDGF was found in colorectal (136), pancreatic (137) and small cell lung cancers (138). Although both proteins are thought to stabilize vasculature, tumor vessels are notoriously leaky and characterized by abnormal pericyte coverage. This suggests that, in the tumor microenvironment, destabilizing vascular factors are more prevalent or more potent than Ang-1 and PDGF. Overexpression of Ang-1 and PDGF in tumors not only fails to promote maturation of blood vessels but also contributes to resistance to anti-angiogenic therapy and chemotherapy (139). Nevertheless, the presence of these factors ensures survival and functionality of a sufficient number of vessels to sustain the needs of a continuously expanding tumor mass.

4. ABNORMALITIES OF TUMOR VESSELS AND CONSEQUENCES OF THEIR MALFUNCTION FOR TUMOR GROWTH AND ANTI-CANCER THERAPY

Although tumors typically contain increased blood vessel density compared with normal tissues (140), tumor vessels are characterized by diverse abnormalities induced by the aberrant microenvironment. Tumor blood vasculature is chaotically arranged, disorganized, and has atypical branching patterns that lack a normal distinct vessel hierarchy (141,142). The morphological features of tumor vessels are blurred, which prevents their categorization to a specific vascular type. The following structural abnormalities of tumor vessels cause leakiness and dilation, resulting in irregular blood flow (143). First, a defective monolayer of disorganized, overlapping, and

loosely connected endothelial cells contributes to leaking (144). Second, the basement membrane includes redundant layers and extensions that project away from the vessel (2). Third, the plasma membrane of perivascular cells displays cytoplasmic processes extending away from endothelial cells rather than toward blood vessels (5). Collectively, these morphologic abnormalities prevent tight association of endothelial cells with the basement membrane and pericytes, which significantly contributes to hyperpermeability of the tumor vessels (2,5).

Structural abnormalities associated with tumor vessels are attributed, in part, to an imbalance of pro- and anti-angiogenic factors found in the tumor microenvironment. In general, production of pro-angiogenic factors vastly exceeds expression of negative vascular regulators (145). The most prominent angiogenic factors in all solid tumors include VEGF-A (146), Ang-2 (82), basic FGF (136), and TGF beta (147). Notch/Dll4 feedback that controls branching and endothelial tip cell number is also drastically increased in tumors (141). Other angiogenic factors produced in tumors include inflammatory mediators and chemokines that contribute to the lack of directional migration of the growing vessels, leading to heterogeneous and disorganized arrangement of the tumor vasculature.

The prevalence of pro-angiogenic VEGF-A and Ang-2 over anti-angiogenic factors leads to overactive angiogenesis and a reduced number of stabilized and mature blood vessels. The abnormalities in the perivascular cells (5) and basement membrane (2) suggest that the local concentrations of pro-angiogenic factors are overwhelmingly higher than the stabilizing signals. As a result, the newly-formed vessels are unable to mature due to continuous stimulation by promoters of angiogenesis. One example of how pro-angiogenic stimuli may overpower stabilizing factors is in the fine balance between Ang-1 and Ang-2 proteins. Ang-2 is stored in Weibel-Palade bodies within the endothelial cells and, when angiogenic signals are received, it is quickly released in the interstitial space between the endothelial and perivascular cells (66). Ang-2 concentration quickly exceeds Ang-1 levels secreted by the endothelial and perivascular cells. Ang-2 then transiently replaces Ang-1 in the Tie-2 binding site, leading to destabilization of the vasculature. However, unlike Ang-1, Ang-2 does not bind to the extracellular matrix (148) and quickly dissipates, causing Ang-1 local concentration to increase. Once the balance is tilted toward the Ang-1 factor, interactions within the endothelial monolayer are tightened and the vessel becomes less permeable and more stable. This normal interplay maintained by a proper ratio between Ang-1 and Ang-2 is severely skewed in the tumor environment, where both factors are overexpressed (Table 3), thus off-setting the natural balance. Continuous destabilization of the new tumor blood vessels plays a major role in critical events underlying tumor pathology, including vascular hyperpermeability, chronic inflammation and poor tissue perfusion. Additionally, Ang-2 overexpression is likely to promote both hematogenous and lymphatic metastasis because of its potent ability to dismantle vessels, making them accessible to tumor cell penetration.

Structural abnormalities of the tumor vessels result in malfunction of tumor blood vasculature. Insufficient blood perfusion prevents attainment of the necessary amount of oxygen and nutrients to match the continuous expansion of the tumor mass. This leads to perpetual hypoxia and nutrient deprivation within the tumor microenvironment that, in turn, increases the expression of angiogenic factors. Consequently, tumor angiogenesis: a) promotes growth of the primary tumor by increasing the vessel density and blood supply; b) promotes metastasis by increasing the number of easy-to-penetrate vascular channels; and c) generates a chronically inflamed site by creating dilated and leaky vessels that expose numerous adhesion sites for circulating immune cells. Additionally, poor perfusion of the tumor tissue creates a major problem for delivery of anti-cancer drugs to avascular tumor regions. Shielding these regions from cytotoxic drug activity creates reservoirs of tumor cells ready to repopulate necrotic areas accessible to chemotherapy. Thus, the pathology of tumor angiogenesis contributes to tumor progression by two independent mechanisms: functional blood vessels promote tumor expansion, while malfunctioning vessels protect tumor cells from cytotoxic drugs.

5. ANTI-ANGIOGENIC THERAPIES FOR THE TREATMENT OF SOLID TUMORS

Angiogenesis became a major target in cancer treatment because of its important role in tumor growth and metastasis. It was initially hypothesized that preventing or reducing tumor angiogenesis would inhibit tumor growth by decreasing delivery of nutrients and oxygen, which would ultimately lead to tumor death. VEGF-A has become the primary target for such a strategy, as a key mediator of tumor angiogenesis that is almost ubiquitously up-regulated in solid tumors (149). In the past decade, many drugs have been developed that target VEGF-A, including antibodies that neutralize this factor or block its receptors, and small organic compounds that inhibit VEGF-A receptor tyrosine kinase activity. In experimental human cancer xenograft models, the anti-VEGF-A strategy demonstrated a remarkable potency to suppress tumor growth, resulting in as much as a 90% tumor inhibition compared with untreated or saline-treated tumors (150,151). However, this success did not translate in human clinical trials. For instance, in a phase I/II trial of 75 metastatic breast cancer patients, only 17% of patients responded to a humanized anti-VEGF-A monoclonal antibody, bevacizumab, and only four patients remained progression-free for more than one year (152). Many other trials showed no objective responses in the majority of patients and no sustainable benefits for patients with partial response. One of the main differences between experimental tumor models and human patients is the status of angiogenic growth: in animal models, treatment typically begins when the tumors are barely established and angiogenesis is at a vigorous stage, while human patients often have tumors with well-established vasculature that is no longer sensitive to VEGF-A. The attempt to translate anti-VEGF-A therapy as a single treatment

into clinics has proven to be largely ineffective, underscoring the extreme complexity of human cancers as compared to animal models. Recently, however, studies that combine anti-VEGF-A therapy and chemotherapy show more promising results. For instance, in a phase III trial with 462 metastatic breast cancer patients, use of bevacizumab in combination with the chemotherapeutic drug capecitabine had a 19.8% response, compared to 9.1% for capecitabine alone (153).

The relative success of combination therapy may lend support to the theory of vessel normalization (154). The inability to form properly functioning vessels within the tumor and the low perfusion of abnormal tumor blood vessels is believed to decrease the delivery of chemotherapeutic drugs and, therefore, decrease the effectiveness of cancer treatment (154). It has been hypothesized that stabilizing tumor vessels by balancing angiogenic factors might improve cancer treatment by normalizing the vessels and increasing perfusion, thus increasing drug delivery (155). Anti-VEGF-A therapy has shown a vessel-normalization effect, both in experimental models (156) and in human clinical trials (157).

Several other angiogenic factors have been proposed as targets for anti-angiogenic therapy, including the Notch/Dll4 pathway, PDGF receptors, and a combination of either target with anti-VEGF-A drugs. In rodent tumor models, blocking Dll4 increased hypoxia and retarded tumor growth (106,158). In mouse tumor models, combination therapy against VEGF-A and PDGFR reduced tumor vessel density, the number of perivascular cells, and tumor growth (159). In clinical trials for renal cell carcinoma, the addition of anti-PDGFR to anti-VEGF-A increased the response from less than 10% to greater than 40% (160). Undoubtedly, insights gained in the rapidly developing angiogenesis field will continue to uncover new targets for attacking tumor vasculature. Additionally, the recent success of combinations of VEGF-A targeting reagents and chemotherapeutic drugs calls for inclusion of anti-angiogenic drugs as a standard modality for anti-cancer treatment.

6. CONCLUDING REMARKS

Tumor angiogenesis is a multi-step process involving interactions among epithelial, stromal, tumor-infiltrating, endothelial, and endothelium-supporting cells. All components of the tumor microenvironment secrete factors that influence vascular formation. Tumors contain excessive amounts of angiogenic factors unbalanced by negative regulators, which disrupts the regulatory mechanisms of physiological angiogenesis. Consequently, tumor vessels develop abnormally, leading to increased tumor growth and metastasis, and resistance to therapy. Studying the similarities and differences of physiological and tumor angiogenesis will aid in a better understanding of tumor biology, and give rise to potential new anti-cancer targets.

7. ACKNOWLEDGMENTS

Sophia Ran is supported by NIH (#1R15CA125682-01) and Illinois William E. McElroy Foundation.

8. REFERENCES

1. D. Fukumura and R. K. Jain: Tumor microenvironment abnormalities: causes, consequences, and strategies to normalize. *J Cell Biochem* 101, 937-949 (2007)

2. P. Baluk, S. Morikawa, A. Haskell, M. Mancuso, and D. M. McDonald: Abnormalities of basement membrane on blood vessels and endothelial sprouts in tumors. *Am J Pathol* 163, 1801-1815 (2003)

3. D. M. Noonan, Barbaro A. De Lerma, N. Vannini, L. Mortara, and A. Albini: Inflammation, inflammatory cells and angiogenesis: decisions and indecisions. *Cancer Metastasis Rev* 27, 31-40 (2008)

4. I. Gouin-Thibault, A. Achkar, and M. M. Samama: The thrombophilic state in cancer patients. *Acta Haematol* 106, 33-42 (2001)

5. S. Morikawa, P. Baluk, T. Kaidoh, A. Haskell, R. K. Jain, and D. M. McDonald: Abnormalities in pericytes on blood vessels and endothelial sprouts in tumors. *Am J Pathol* 160, 985-1000 (2002)

6. G. Bergers and L. E. Benjamin: Tumorigenesis and the angiogenic switch. *Nat Rev Cancer* 3, 401-410 (2003)

7. M. Inoue, J. H. Hager, N. Ferrara, H. P. Gerber, and D. Hanahan: VEGF-A has a critical, nonredundant role in angiogenic switching and pancreatic beta cell carcinogenesis. *Cancer Cell* 1, 193-202 (2002)

8. A. M. Byrne, D. J. Bouchier-Hayes, and J. H. Harmey: Angiogenic and cell survival functions of vascular endothelial growth factor (VEGF). *J Cell Mol Med* 9, 777-794 (2005)

9. E. Barbera-Guillem, J. K. Nyhus, C. C. Wolford, C. R. Friece, and J. W. Sampsel: Vascular endothelial growth factor secretion by tumor-infiltrating macrophages essentially supports tumor angiogenesis, and IgG immune complexes potentiate the process. *Cancer Res* 62, 7042-7049 (2002)

10. J. H. Harmey, E. Dimitriadis, E. Kay, H. P. Redmond, and D. Bouchier-Hayes: Regulation of macrophage production of vascular endothelial growth factor (VEGF) by hypoxia and transforming growth factor beta-1. *Ann Surg Oncol* 5, 271-278 (1998)

11. R. Evans, M. Fong, J. Fuller, S. Kamdar, J. Meyerhardt, and G. Strassmann: Tumor cell IL-6 gene expression is regulated by IL-1 alpha/beta and TNF alpha: proposed feedback mechanisms induced by the interaction of tumor cells and macrophages. *J Leukoc Biol* 52, 463-468 (1992)

12. R. M. bdel-Majid and J. S. Marshall: Prostaglandin E2 induces degranulation-independent production of vascular endothelial growth factor by human mast cells. *J Immunol* 172, 1227-1236 (2004)

13. M. McCourt, J. H. Wang, S. Sookhai, and H. P. Redmond: Proinflammatory mediators stimulate neutrophil-directed angiogenesis. *Arch Surg* 134, 1325-1331 (1999)

14. N. P. McCabe, S. H. Selman, and J. Jankun: Vascular endothelial growth factor production in human prostate cancer cells is stimulated by overexpression of platelet 12-lipoxygenase. *Prostate* 66, 779-787 (2006)

15. L. Hlatky, C. Tsionou, P. Hahnfeldt, and C. N. Coleman: Mammary fibroblasts may influence breast tumor angiogenesis via hypoxia-induced vascular endothelial growth factor up-regulation and protein expression. *Cancer Res* 54, 6083-6086 (1994)

16. I. Nilsson, M. Shibuya, and S. Wennstrom: Differential activation of vascular genes by hypoxia in primary endothelial cells. *Exp Cell Res* 299, 476-485 (2004)

17. B. Berse, L. F. Brown, Water L. Van de, H. F. Dvorak, and D. R. Senger: Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. *Mol Biol Cell* 3, 211-220 (1992)

18. D. Ribatti: The crucial role of vascular permeability factor/vascular endothelial growth factor in angiogenesis: a historical review. *Br J Haematol* 128, 303-309 (2005)

19. T. Asahara, T. Takahashi, H. Masuda, C. Kalka, D. Chen, H. Iwaguro, Y. Inai, M. Silver, and J. M. Isner: VEGF contributes to postnatal neovascularization by mobilizing bone marrow-derived endothelial progenitor cells. *EMBO J* 18, 3964-3972 (1999)

20. M. Clauss: Functions of the VEGF receptor-1 (FLT-1) in the vasculature. *Trends Cardiovasc Med* 8, 241-245 (1998)

21. R. D. Meyer, M. Mohammadi, and N. Rahimi: A single amino acid substitution in the activation loop defines the decoy characteristic of VEGFR-1/FLT-1. *J Biol Chem* 281, 867-875 (2006)

22. M. Weigand, P. Hantel, R. Kreienberg, and J. Waltenberger: Autocrine vascular endothelial growth factor signalling in breast cancer. Evidence from cell lines and primary breast cancer cultures *in vitro*. *Angiogenesis* 8, 197-204 (2005)

23. Y. Wu, A. T. Hooper, Z. Zhong, L. Witte, P. Bohlen, S. Rafii, and D. J. Hicklin: The vascular endothelial growth factor receptor (VEGFR-1) supports growth and survival of human breast carcinoma. *Int J Cancer* (2006)

24. B. Bussolati, C. Dunk, M. Grohman, C. D. Kontos, J. Mason, and A. Ahmed: Vascular endothelial growth factor receptor-1 modulates vascular endothelial growth factor-mediated angiogenesis via nitric oxide. *Am J Pathol* 159, 993-1008 (2001)

25. I. Sher, S. A. Adham, J. Petrik, and B. L. Coomber: Autocrine VEGF-A/KDR loop protects epithelial ovarian carcinoma cells from anoikis. *Int J Cancer* 124, 553-561 (2008)

26. C. E. Clarkin, R. J. Emery, A. A. Pitsillides, and C. P. Wheeler-Jones: Evaluation of VEGF-mediated signaling in primary human cells reveals a paracrine action for VEGF in osteoblast-mediated crosstalk to endothelial cells. *J Cell Physiol* 214, 537-544 (2008)

27. Y. Herzog, C. Kalcheim, N. Kahane, R. Reshef, and G. Neufeld: Differential expression of neuropilin-1 and neuropilin-2 in arteries and veins. *Mech Dev* 109, 115-119 (2001)

28. L. M. Ellis: The role of neuropilins in cancer. *Mol Cancer Ther* 5, 1099-1107 (2006)

29. L. Yuan, D. Moyon, L. Pardanaud, C. Breant, M. J. Karkkainen, K. Alitalo, and A. Eichmann: Abnormal lymphatic vessel development in neuropilin 2 mutant mice. *Development* 129, 4797-4806 (2002)

30. M. Klagsbrun and A. Eichmann: A role for axon guidance receptors and ligands in blood vessel development and tumor angiogenesis. *Cytokine Growth Factor Rev* 16, 535-548 (2005)

31. M. Murga, O. Fernandez-Capetillo, and G. Tosato: Neuropilin-1 regulates attachment in human endothelial cells independently of vascular endothelial growth factor receptor-2. *Blood* 105, 1992-1999 (2005)

32. Z. Gluzman-Poltorak, T. Cohen, M. Shibuya, and G. Neufeld: Vascular endothelial growth factor receptor-1 and neuropilin-2 form complexes. *J Biol Chem* 276, 18688-18694 (2001)

33. G. Neufeld, O. Kessler, and Y. Herzog: The interaction of Neuropilin-1 and Neuropilin-2 with tyrosine-kinase receptors for VEGF. *Adv Exp Med Biol* 515, 81-90 (2002)

34. M. Cai, H. Zhang, and R. Hui: Single chain Fv antibody against angiopoietin-2 inhibits VEGF-induced endothelial cell proliferation and migration *in vitro*. *Biochem Biophys Res Commun* 309, 946-951 (2003)

35. A. Latil, I. Bieche, S. Pesche, A. Valeri, G. Fournier, O. Cussenot, and R. Lidereau: VEGF overexpression in clinically localized prostate tumors and neuropilin-1 overexpression in metastatic forms. *Int J Cancer* 89, 167-171 (2000)

36. T. Baba, M. Kariya, T. Higuchi, M. Mandai, N. Matsumura, E. Kondoh, M. Miyanishi, K. Fukuhara, K. Takakura, and S. Fujii: Neuropilin-1 promotes unlimited growth of ovarian cancer by evading contact inhibition. *Gynecol Oncol* 105, 703-711 (2007)

37. M. J. Gray, Buren G. Van, N. A. Dallas, L. Xia, X. Wang, A. D. Yang, R. J. Somcio, Y. G. Lin, S. Lim, F. Fan,

L. S. Mangala, T. Arumugam, C. D. Logsdon, G. Lopez-Berestein, A. K. Sood, and L. M. Ellis: Therapeutic targeting of neuropilin-2 on colorectal carcinoma cells implanted in the murine liver. *J Natl Cancer Inst* 100, 109-120 (2008)

38. A. A. Parikh, W. B. Liu, F. Fan, O. Stoeltzing, N. Reinmuth, C. J. Bruns, C. D. Bucana, D. B. Evans, and L. M. Ellis: Expression and regulation of the novel vascular endothelial growth factor receptor neuropilin-1 by epidermal growth factor in human pancreatic carcinoma. *Cancer* 98, 720-729 (2003)

39. S. Frede, U. Berchner-Pfannschmidt, and J. Fandrey: Regulation of hypoxia-inducible factors during inflammation. *Methods Enzymol* 435, 405-419 (2007)

40. E. B. Rankin and A. J. Giaccia: The role of hypoxia-inducible factors in tumorigenesis. *Cell Death Differ* 15, 678-685 (2008)

41. J. A. Forsythe, B. H. Jiang, N. V. Iyer, F. Agani, S. W. Leung, R. D. Koos, and G. L. Semenza: Activation of vascular endothelial growth factor gene transcription by hypoxia-inducible factor 1. *Mol Cell Biol* 16, 4604-4613 (1996)

42. G. L. Semenza: HIF-1: using two hands to flip the angiogenic switch. *Cancer Metastasis Rev* 19, 59-65 (2000)

43. S. Rasheed, P. J. McDonald, J. M. Northover, and T. Guenther: Angiogenesis and hypoxic factors in colorectal cancer. *Pathol Res Pract* 204, 501-510 (2008)

44. D. J. Brat, B. Kaur, and E. G. Van Meir: Genetic modulation of hypoxia induced gene expression and angiogenesis: relevance to brain tumors. *Front Biosci* 8, d100-d116 (2003)

45. A. Giatromanolaki, E. Sivridis, C. Simopoulos, A. Polychronidis, K. C. Gatter, A. L. Harris, and M. I. Koukourakis: Hypoxia inducible factors 1alpha and 2alpha are associated with VEGF expression and angiogenesis in gallbladder carcinomas. *J Surg Oncol* 94, 242-247 (2006)

46. M. Kawaguchi, M. Akagi, M. J. Gray, W. Liu, F. Fan, and L. M. Ellis: Regulation of vascular endothelial growth factor expression in human gastric cancer cells by interleukin-1beta. *Surgery* 136, 686-692 (2004)

47. H. H. Yeh, W. W. Lai, H. H. Chen, H. S. Liu, and W. C. Su: Autocrine IL-6-induced Stat3 activation contributes to the pathogenesis of lung adenocarcinoma and malignant pleural effusion. *Oncogene* 25, 4300-4309 (2006)

48. S. P. Huang, M. S. Wu, C. T. Shun, H. P. Wang, M. T. Lin, M. L. Kuo, and J. T. Lin: Interleukin-6 increases vascular endothelial growth factor and angiogenesis in gastric carcinoma. *J Biomed Sci* 11, 517-527 (2004)

49. S. Huang, J. B. Robinson, A. Deguzman, C. D. Bucana, and I. J. Fidler: Blockade of nuclear factor-kappaB signaling inhibits angiogenesis and tumorigenicity of human ovarian cancer cells by suppressing expression of vascular endothelial growth factor and interleukin 8. *Cancer Res* 60, 5334-5339 (2000)

50. Q. Tong, L. Zheng, L. Lin, B. Li, D. Wang, C. Huang, and D. Li: VEGF is upregulated by hypoxia-induced mitogenic factor via the PI-3K/Akt-NF-kappaB signaling pathway. *Respir Res* 7, 37 (2006)

51. S. I. Zittermann and A. C. Issekutz: Endothelial growth factors VEGF and bFGF differentially enhance monocyte and neutrophil recruitment to inflammation. *J Leukoc Biol* 80, 247-257 (2006)

52. K. Ohtani, K. Egashira, K. Hiasa, Q. Zhao, S. Kitamoto, M. Ishibashi, M. Usui, S. Inoue, Y. Yonemitsu, K. Sueishi, M. Sata, M. Shibuya, and K. Sunagawa: Blockade of vascular endothelial growth factor suppresses experimental restenosis after intraluminal injury by inhibiting recruitment of monocyte lineage cells. *Circulation* 110, 2444-2452 (2004)

53. S. P. Dineen, K. D. Lynn, S. E. Holloway, A. F. Miller, J. P. Sullivan, D. S. Shames, A. W. Beck, C. C. Barnett, J. B. Fleming, and R. A. Brekken: Vascular endothelial growth factor receptor 2 mediates macrophage infiltration into orthotopic pancreatic tumors in mice. *Cancer Res* 68, 4340-4346 (2008)

54. G. Chakraborty, S. Jain, and G. C. Kundu: Osteopontin promotes vascular endothelial growth factor-dependent breast tumor growth and angiogenesis via autocrine and paracrine mechanisms. *Cancer Res* 68, 152-161 (2008)

55. A. Sawano, T. Takahashi, S. Yamaguchi, and M. Shibuya: The phosphorylated 1169-tyrosine containing region of flt-1 kinase (VEGFR-1) is a major binding site for PLCgamma. *Biochem Biophys Res Commun* 238, 487-491 (1997)

56. E. Landgren, P. Schiller, Y. Cao, and L. Claesson-Welsh: Placenta growth factor stimulates MAP kinase and mitogenicity but not phospholipase C-gamma and migration of endothelial cells expressing Flt 1. *Oncogene* 16, 359-367 (1998)

57. J. Kroll and J. Waltenberger: The vascular endothelial growth factor receptor KDR activates multiple signal transduction pathways in porcine aortic endothelial cells. *J Biol Chem* 272, 32521-32527 (1997)

58. H. P. Gerber, A. McMurtrey, J. Kowalski, M. Yan, B. A. Keyt, V. Dixit, and N. Ferrara: Vascular endothelial growth factor regulates endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. Requirement for Flk-1/KDR activation. *J Biol Chem* 273, 30336-30343 (1998)

59. P. Parsons-Wingerter, U. M. Chandrasekharan, T. L. McKay, K. Radhakrishnan, P. E. DiCorleto, B. Albarran, and A. G. Farr: A VEGF165-induced phenotypic switch

from increased vessel density to increased vessel diameter and increased endothelial NOS activity. *Microvasc Res* 72, 91-100 (2006)

60. J. Kroll and J. Waltenberger: VEGF-A induces expression of eNOS and iNOS in endothelial cells via VEGF receptor-2 (KDR). *Biochem Biophys Res Commun* 252, 743-746 (1998)

61. H. Oh, H. Takagi, K. Suzuma, A. Otani, M. Matsumura, and Y. Honda: Hypoxia and vascular endothelial growth factor selectively up-regulate angiopoietin-2 in bovine microvascular endothelial cells. *J Biol Chem* 274, 15732-15739 (1999)

62. P. Carmeliet and R. K. Jain: Angiogenesis in cancer and other diseases. *Nature* 407, 249-257 (2000)

63. F. Bach, F. J. Uddin, and D. Burke: Angiopoietins in malignancy. *Eur J Surg Oncol* 33, 7-15 (2007)

64. C. R. Tait and P. F. Jones: Angiopoietins in tumours: the angiogenic switch. *J Pathol* 204, 1-10 (2004)

65. P. C. Maisonpierre, C. Suri, P. F. Jones, S. Bartunkova, S. J. Wiegand, C. Radziejewski, D. Compton, J. McClain, T. H. Aldrich, N. Papadopoulos, T. J. Daly, S. Davis, T. N. Sato, and G. D. Yancopoulos: Angiopoietin-2, a natural antagonist for Tie2 that disrupts *in vivo* angiogenesis. *Science* 277, 55-60 (1997)

66. L. Eklund and B. R. Olsen: Tie receptors and their angiopoietin ligands are context-dependent regulators of vascular remodeling. *Exp Cell Res* 312, 630-641 (2006)

67. H. Schnurch and W. Risau: Expression of tie-2, a member of a novel family of receptor tyrosine kinases, in the endothelial cell lineage. *Development* 119, 957-968 (1993)

68. C. Schliemann, R. Bieker, T. Padro, T. Kessler, H. Hintelmann, T. Buchner, W. E. Berdel, and R. M. Mesters: Expression of angiopoietins and their receptor Tie2 in the bone marrow of patients with acute myeloid leukemia. *Haematologica* 91, 1203-1211 (2006)

69. M. Yano, A. Iwama, H. Nishio, J. Suda, G. Takada, and T. Suda: Expression and function of murine receptor tyrosine kinases, TIE and TEK, in hematopoietic stem cells. *Blood* 89, 4317-4326 (1997)

70. A. Sato, A. Iwama, N. Takakura, H. Nishio, G. D. Yancopoulos, and T. Suda: Characterization of TEK receptor tyrosine kinase and its ligands, Angiopoietins, in human hematopoietic progenitor cells. *Int Immunol* 10, 1217-1227 (1998)

71. N. Jones, K. Iljin, D. J. Dumont, and K. Alitalo: Tie receptors: new modulators of angiogenic and lymphangiogenic responses. *Nat Rev Mol Cell Biol* 2, 257-267 (2001)

72. E. Hofer and B. Schweighofer: Signal transduction induced in endothelial cells by growth factor receptors involved in angiogenesis. *Thromb Haemost* 97, 355-363 (2007)

73. W. S. Shim, I. A. Ho, and P. E. Wong: Angiopoietin: a TIE(d) balance in tumor angiogenesis. *Mol Cancer Res* 5, 655-665 (2007)

74. U. Fiedler and H. G. Augustin: Angiopoietins: a link between angiogenesis and inflammation. *Trends Immunol* 27, 552-558 (2006)

75. C. Morrissey, L. D. True, M. P. Roudier, I. M. Coleman, S. Hawley, P. S. Nelson, R. Coleman, Y. C. Wang, E. Corey, P. H. Lange, C. S. Higano, and R. L. Vessella: Differential expression of angiogenesis associated genes in prostate cancer bone, liver and lymph node metastases. *Clin Exp Metastasis* (2007)

76. I. Takanami: Overexpression of Ang-2 mRNA in non-small cell lung cancer: association with angiogenesis and poor prognosis. *Oncol Rep* 12, 849-853 (2004)

77. J. Wang, K. Wu, D. Zhang, H. Tang, H. Xie, L. Hong, Y. Pan, M. Lan, S. Hu, X. Ning, and D. Fan: Expressions and clinical significances of angiopoietin-1, -2 and Tie2 in human gastric cancer. *Biochem Biophys Res Commun* 337, 386-393 (2005)

78. M. J. Currie, S. P. Gunningham, K. Turner, C. Han, P. A. Scott, B. A. Robinson, W. Chong, A. L. Harris, and S. B. Fox: Expression of the angiopoietins and their receptor Tie2 in human renal clear cell carcinomas; regulation by the von Hippel-Lindau gene and hypoxia. *J Pathol* 198, 502-510 (2002)

79. J. H. Park, K. J. Park, Y. S. Kim, S. S. Sheen, K. S. Lee, H. N. Lee, Y. J. Oh, and S. C. Hwang: Serum angiopoietin-2 as a clinical marker for lung cancer. *Chest* 132, 200-206 (2007)

80. P. Szlosarek, K. A. Charles, and F. R. Balkwill: Tumour necrosis factor-alpha as a tumour promoter. *Eur J Cancer* 42, 745-750 (2006)

81. G. J. Caine, A. D. Blann, P. S. Stonelake, P. Ryan, and G. Y. Lip: Plasma angiopoietin-1, angiopoietin-2 and Tie-2 in breast and prostate cancer: a comparison with VEGF and Flt-1. *Eur J Clin Invest* 33, 883-890 (2003)

82. C. Sfiligoi, A. de Luca, I. Cascone, V. Sorbello, L. Fuso, R. Ponzone, N. Biglia, E. Audero, R. Arisio, F. Bussolino, P. Sismondi, and M. De Bortoli: Angiopoietin-2 expression in breast cancer correlates with lymph node invasion and short survival. *Int J Cancer* 103, 466-474 (2003)

83. Y. C. Chung, Y. C. Hou, C. N. Chang, and T. H. Hseu: Expression and prognostic significance of angiopoietin in colorectal carcinoma. *J Surg Oncol* 94, 631-638 (2006)

84. T. Nakayama, G. Hatachi, C. Y. Wen, A. Yoshizaki, K. Yamazumi, D. Niino, and I. Sekine: Expression and significance of Tie-1 and Tie-2 receptors, and angiopoietins-1, 2 and 4 in colorectal adenocarcinoma: Immunohistochemical analysis and correlation with clinicopathological factors. *World J Gastroenterol* 11, 964-969 (2005)

85. S. A. Ahmad, W. Liu, Y. D. Jung, F. Fan, N. Reinmuth, C. D. Bucana, and L. M. Ellis: Differential expression of angiopoietin-1 and angiopoietin-2 in colon carcinoma. A possible mechanism for the initiation of angiogenesis. *Cancer* 92, 1138-1143 (2001)

86. C. E. Lewis, Palma M. De, and L. Naldini: Tie2-expressing monocytes and tumor angiogenesis: regulation by hypoxia and angiopoietin-2. *Cancer Res* 67, 8429-8432 (2007)

87. S. J. Mandriota and M. S. Pepper: Regulation of angiopoietin-2 mRNA levels in bovine microvascular endothelial cells by cytokines and hypoxia. *Circ Res* 83, 852-859 (1998)

88. S. J. Mandriota, C. Pyke, Sanza C. Di, P. Quinodoz, B. Pittet, and M. S. Pepper: Hypoxia-inducible angiopoietin-2 expression is mimicked by iodonium compounds and occurs in the rat brain and skin in response to systemic hypoxia and tissue ischemia. *Am J Pathol* 156, 2077-2089 (2000)

89. C. Willam, P. Koehne, J. S. Jurgensen, M. Grafe, K. D. Wagner, S. Bachmann, U. Frei, and K. U. Eckardt: Tie2 receptor expression is stimulated by hypoxia and proinflammatory cytokines in human endothelial cells. *Circ Res* 87, 370-377 (2000)

90. C. Conte, E. Riant, C. Toutain, F. Pujol, J. F. Arnal, F. Lenfant, and A. C. Prats: FGF2 translationally induced by hypoxia is involved in negative and positive feedback loops with HIF-1alpha. *PLoS ONE* 3, e3078 (2008)

91. K. J. Lavine, A. C. White, C. Park, C. S. Smith, K. Choi, F. Long, C. C. Hui, and D. M. Ornitz: Fibroblast growth factor signals regulate a wave of Hedgehog activation that is essential for coronary vascular development. *Genes Dev* 20, 1651-1666 (2006)

92. A. Hegen, S. Koidl, K. Weindel, D. Marme, H. G. Augustin, and U. Fiedler: Expression of angiopoietin-2 in endothelial cells is controlled by positive and negative regulatory promoter elements. *Arterioscler Thromb Vasc Biol* 24, 1803-1809 (2004)

93. J. Holash, P. C. Maisonpierre, D. Compton, P. Boland, C. R. Alexander, D. Zagzag, G. D. Yancopoulos, and S. J. Wiegand: Vessel cooption, regression, and growth in tumors mediated by angiopoietins and VEGF. *Science* 284, 1994-1998 (1999)

94. T. Etoh, H. Inoue, S. Tanaka, G. F. Barnard, S. Kitano, and M. Mori: Angiopoietin-2 is related to tumor angiogenesis in gastric carcinoma: possible *in vivo* regulation via induction of proteases. *Cancer Res* 61, 2145-2153 (2001)

95. B. Hu, P. Guo, Q. Fang, H. Q. Tao, D. Wang, M. Nagane, H. J. Huang, Y. Gunji, R. Nishikawa, K. Alitalo, W. K. Cavenee, and S. Y. Cheng: Angiopoietin-2 induces human glioma invasion through the activation of matrix metalloprotease-2. *Proc Natl Acad Sci U S A* 100, 8904-8909 (2003)

96. A. Noel, M. Jost, and E. Maquoi: Matrix metalloproteinases at cancer tumor-host interface. *Semin Cell Dev Biol* 19, 52-60 (2008)

97. S. Suchting, C. Freitas, Noble F. le, R. Benedito, C. Breant, A. Duarte, and A. Eichmann: The Notch ligand Delta-like 4 negatively regulates endothelial tip cell formation and vessel branching. *Proc Natl Acad Sci U S A* 104, 3225-3230 (2007)

98. N. S. Patel, J. L. Li, D. Generali, R. Poulsom, D. W. Cranston, and A. L. Harris: Up-regulation of delta-like 4 ligand in human tumor vasculature and the role of basal expression in endothelial cell function. *Cancer Res* 65, 8690-8697 (2005)

99. M. Hellstrom, L. K. Phng, J. J. Hofmann, E. Wallgard, L. Coultas, P. Lindblom, J. Alva, A. K. Nilsson, L. Karlsson, N. Gaiano, K. Yoon, J. Rossant, M. L. Iruela-Arispe, M. Kalen, H. Gerhardt, and C. Betsholtz: Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. *Nature* 445, 776-780 (2007)

100. W. R. Gordon, D. Vardar-Ulu, G. Histen, C. Sanchez-Irizarry, J. C. Aster, and S. C. Blacklow: Structural basis for autoinhibition of Notch. *Nat Struct Mol Biol* 14, 295-300 (2007)

101. R. C. Sainson, J. Aoto, M. N. Nakatsu, M. Holderfield, E. Conn, E. Koller, and C. C. Hughes: Cell-autonomous notch signaling regulates endothelial cell branching and proliferation during vascular tubulogenesis. *FASEB J* 19, 1027-1029 (2005)

102. L. S. Harrington, R. C. Sainson, C. K. Williams, J. M. Taylor, W. Shi, J. L. Li, and A. L. Harris: Regulation of multiple angiogenic pathways by Dll4 and Notch in human umbilical vein endothelial cells. *Microvasc Res* 75, 144-154 (2008)

103. C. K. Williams, J. L. Li, M. Murga, A. L. Harris, and G. Tosato: Up-regulation of the Notch ligand Delta-like 4 inhibits VEGF-induced endothelial cell function. *Blood* 107, 931-939 (2006)

104. N. S. Patel, M. S. Dobbie, M. Rochester, G. Steers, R. Poulsom, Monnier K. Le, D. W. Cranston, J. L. Li, and A. L. Harris: Up-regulation of endothelial delta-like 4 expression correlates with vessel maturation in bladder cancer. *Clin Cancer Res* 12, 4836-4844 (2006)

105. M. Segarra, C. K. Williams, Mde L. Sierra, M. Bernardo, P. J. McCormick, D. Maric, C. Regino, P. Choyke, and G. Tosato: Dll4 activation of Notch signaling reduces tumor vascularity and inhibits tumor growth. *Blood* 112, 1904-1911 (2008)

106. I. Noguera-Troise, C. Daly, N. J. Papadopoulos, S. Coetzee, P. Boland, N. W. Gale, H. C. Lin, G. D. Yancopoulos, and G. Thurston: Blockade of Dll4 inhibits tumour growth by promoting non-productive angiogenesis. *Nature* 444, 1032-1037 (2006)

107. K. Holmqvist, M. J. Cross, C. Rolny, R. Hagerkvist, N. Rahimi, T. Matsumoto, L. Claesson-Welsh, and M. Welsh: The adaptor protein shb binds to tyrosine 1175 in vascular endothelial growth factor (VEGF) receptor-2 and regulates VEGF-dependent cellular migration. *J Biol Chem* 279, 22267-22275 (2004)

108. K. Hattori, S. Dias, B. Heissig, N. R. Hackett, D. Lyden, M. Tateno, D. J. Hicklin, Z. Zhu, L. Witte, R. G. Crystal, M. A. Moore, and S. Rafii: Vascular endothelial growth factor and angiopoietin-1 stimulate postnatal hematopoiesis by recruitment of vasculogenic and hematopoietic stem cells. *J Exp Med* 193, 1005-1014 (2001)

109. B. Witzenbichler, P. C. Maisonpierre, P. Jones, G. D. Yancopoulos, and J. M. Isner: Chemotactic properties of angiopoietin-1 and -2, ligands for the endothelial-specific receptor tyrosine kinase Tie2. *J Biol Chem* 273, 18514-18521 (1998)

110. Y. Mochizuki, T. Nakamura, H. Kanetake, and S. Kanda: Angiopoietin 2 stimulates migration and tube-like structure formation of murine brain capillary endothelial cells through c-Fes and c-Fyn. *J Cell Sci* 115, 175-183 (2002)

111. I. Kim, J. H. Kim, S. O. Moon, H. J. Kwak, N. G. Kim, and G. Y. Koh: Angiopoietin-2 at high concentration can enhance endothelial cell survival through the phosphatidylinositol 3'-kinase/Akt signal transduction pathway. *Oncogene* 19, 4549-4552 (2000)

112. K. L. Kim, I. S. Shin, J. M. Kim, J. H. Choi, J. Byun, E. S. Jeon, W. Suh, and D. K. Kim: Interaction between Tie receptors modulates angiogenic activity of angiopoietin2 in endothelial progenitor cells. *Cardiovasc Res* 72, 394-402 (2006)

113. R. Montesano, J. V. Soriano, K. M. Malinda, M. L. Ponce, A. Bafico, H. K. Kleinman, D. P. Bottaro, and S. A. Aaronson: Differential effects of hepatocyte growth factor isoforms on epithelial and endothelial tubulogenesis. *Cell Growth Differ* 9, 355-365 (1998)

114. R. Abounader and J. Laterra: Scatter factor/hepatocyte growth factor in brain tumor growth and angiogenesis. *Neuro Oncol* 7, 436-451 (2005)

115. M. J. Cross and L. Claesson-Welsh: FGF and VEGF function in angiogenesis: signalling pathways, biological responses and therapeutic inhibition. *Trends Pharmacol Sci* 22, 201-207 (2001)

116. C. Charalambous, L. B. Pen, Y. S. Su, J. Milan, T. C. Chen, and F. M. Hofman: Interleukin-8 differentially regulates migration of tumor-associated and normal human brain endothelial cells. *Cancer Res* 65, 10347-10354 (2005)

117. J. S. Yao, W. Zhai, W. L. Young, and G. Y. Yang: Interleukin-6 triggers human cerebral endothelial cells proliferation and migration: the role for KDR and MMP-9. *Biochem Biophys Res Commun* 342, 1396-1404 (2006)

118. G. Rennebeck, M. Martelli, and N. Kyprianou: Anoikis and survival connections in the tumor microenvironment: is there a role in prostate cancer metastasis? *Cancer Res* 65, 11230-11235 (2005)

119. G. Klement, S. Baruchel, J. Rak, S. Man, K. Clark, D. J. Hicklin, P. Bohlen, and R. S. Kerbel: Continuous low-dose therapy with vinblastine and VEGF receptor-2 antibody induces sustained tumor regression without overt toxicity. *J Clin Invest* 105, R15-R24 (2000)

120. C. J. Bruns, W. Liu, D. W. Davis, R. M. Shaheen, D. J. McConkey, M. R. Wilson, C. D. Bucana, D. J. Hicklin, and L. M. Ellis: Vascular endothelial growth factor is an *in vivo* survival factor for tumor endothelium in a murine model of colorectal carcinoma liver metastases. *Cancer* 89, 488-499 (2000)

121. L. W. Wu, L. D. Mayo, J. D. Dunbar, K. M. Kessler, M. R. Baerwald, E. A. Jaffe, D. Wang, R. S. Warren, and D. B. Donner: Utilization of distinct signaling pathways by receptors for vascular endothelial cell growth factor and other mitogens in the induction of endothelial cell proliferation. *J Biol Chem* 275, 5096-5103 (2000)

122. A. Papapetropoulos, D. Fulton, K. Mahboubi, R. G. Kalb, D. S. O'Connor, F. Li, D. C. Altieri, and W. C. Sessa: Angiopoietin-1 inhibits endothelial cell apoptosis via the Akt/survivin pathway. *J Biol Chem* 275, 9102-9105 (2000)

123. A. J. Hayes, W. Q. Huang, J. Mallah, D. Yang, M. E. Lippman, and L. Y. Li: Angiopoietin-1 and its receptor Tie-2 participate in the regulation of capillary-like tubule formation and survival of endothelial cells. *Microvasc Res* 58, 224-237 (1999)

124. D. Yin, C. Li, R. L. Kao, T. Ha, G. Krishnaswamy, M. Fitzgerald, and C. A. Stuart: Angiopoietin-1 inhibits doxorubicin-induced human umbilical vein endothelial cell death by modulating fas expression and via the PI3K/Akt pathway. *Endothelium* 11, 247-252 (2004)

125. D. Langford, R. Hurford, M. Hashimoto, M. Digicaylioglu, and E. Masliah: Signalling crosstalk in FGF2-mediated protection of endothelial cells from HIV-gp120. *BMC Neurosci* 6, 8 (2005)

126. J. Yu, C. Ustach, and H. R. Kim: Platelet-derived growth factor signaling and human cancer. *J Biochem Mol Biol* 36, 49-59 (2003)

127. V. S. Rajkumar, X. Shiwen, M. Bostrom, P. Leoni, J. Muddle, M. Ivarsson, B. Gerdin, C. P. Denton, G. Bou-Gharios, C. M. Black, and D. J. Abraham: Platelet-derived growth factor-beta receptor activation is essential for fibroblast and pericyte recruitment during cutaneous wound healing. *Am J Pathol* 169, 2254-2265 (2006)

128. A. Abramsson, P. Lindblom, and C. Betsholtz: Endothelial and nonendothelial sources of PDGF-B regulate pericyte recruitment and influence vascular pattern formation in tumors. *J Clin Invest* 112, 1142-1151 (2003)

129. J. Zhang, R. Cao, Y. Zhang, T. Jia, Y. Cao, and E. Wahlberg: Differential roles of PDGFR-{alpha} and PDGFR-{beta} in angiogenesis and vessel stability. *FASEB J* (2008)

130. M. R. Kano, Y. Morishita, C. Iwata, S. Iwasaka, T. Watabe, Y. Ouchi, K. Miyazono, and K. Miyazawa: VEGF-A and FGF-2 synergistically promote neoangiogenesis through enhancement of endogenous PDGF-B-PDGFRbeta signaling. *J Cell Sci* 118, 3759-3768 (2005)

131. D. Yoshida, K. Kim, M. Noha, and A. Teramoto: Hypoxia inducible factor 1-alpha regulates of platelet derived growth factor-B in human glioblastoma cells. *J Neurooncol* 76, 13-21 (2006)

132. R. Bos, P. J. van Diest, J. S. de Jong, Groep P. van der, der van, V, and Wall E. van der: Hypoxia-inducible factor-1alpha is associated with angiogenesis, and expression of bFGF, PDGF-BB, and EGFR in invasive breast cancer. *Histopathology* 46, 31-36 (2005)

133. C. S. Milner, T. M. Hansen, H. Singh, and N. P. Brindle: Roles of the receptor tyrosine kinases Tie1 and Tie2 in mediating the effects of angiopoietin-1 on endothelial permeability and apoptosis. *Microvasc Res* (2008)

134. J. Cai, O. Kehoe, G. M. Smith, P. Hykin, and M. E. Boulton: The angiopoietin/Tie-2 system regulates pericyte survival and recruitment in diabetic retinopathy. *Invest Ophthalmol Vis Sci* 49, 2163-2171 (2008)

135. H. Kobayashi, L. M. DeBusk, Y. O. Babichev, D. J. Dumont, and P. C. Lin: Hepatocyte growth factor mediates angiopoietin-induced smooth muscle cell recruitment. *Blood* 108, 1260-1266 (2006)

136. Y. Nakamura, F. Tanaka, Y. Yoshikawa, K. Mimori, H. Inoue, K. Yanaga, and M. Mori: PDGF-BB is a novel prognostic factor in colorectal cancer. *Ann Surg Oncol* 15, 2129-2136 (2008)

137. M. L. Fjallskog, O. Hessman, B. Eriksson, and E. T. Janson: Upregulated expression of PDGF receptor beta in endocrine pancreatic tumors and metastases compared to normal endocrine pancreas. *Acta Oncol* 46, 741-746 (2007)

138. E. T. Shinohara, A. Gonzalez, P. P. Massion, S. J. Olson, J. M. Albert, Y. Shyr, D. P. Carbone, D. H. Johnson, D. E. Hallahan, and B. Lu: PDGFR-beta expression in small cell lung cancer patients. *Int J Radiat Oncol Biol Phys* 67, 431-437 (2007)

139. Bender J. Glade, E. M. Cooney, J. J. Kandel, and D. J. Yamashiro: Vascular remodeling and clinical resistance to antiangiogenic cancer therapy. *Drug Resist Updat* 7, 289-300 (2004)

140. N. Weidner, P. R. Carroll, J. Flax, W. Blumenfeld, and J. Folkman: Tumor angiogenesis correlates with metastasis in invasive prostate carcinoma. *Am J Pathol* 143, 401-409 (1993)

141. D. M. McDonald and P. L. Choyke: Imaging of angiogenesis: from microscope to clinic. *Nat Med* 9, 713-725 (2003)

142. P. Vajkoczy and M. D. Menger: Vascular microenvironment in gliomas. *J Neurooncol* 50, 99-108 (2000)

143. D. Fukumura and R. K. Jain: Imaging angiogenesis and the microenvironment. *APMIS* 116, 695-715 (2008)

144. H. Hashizume, P. Baluk, S. Morikawa, J. W. McLean, G. Thurston, S. Roberge, R. K. Jain, and D. M. McDonald: Openings between defective endothelial cells explain tumor vessel leakiness. *Am J Pathol* 156, 1363-1380 (2000)

145. M. K. Gupta and R. Y. Qin: Mechanism and its regulation of tumor-induced angiogenesis. *World J Gastroenterol* 9, 1144-1155 (2003)

146. B. K. Linderholm, T. Lindahl, L. Holmberg, S. Klaar, J. Lennerstrand, R. Henriksson, and J. Bergh: The expression of vascular endothelial growth factor correlates with mutant p53 and poor prognosis in human breast cancer. *Cancer Res* 61, 2256-2260 (2001)

147. P. Barrett-Lee, M. Travers, Y. Luqmani, and R. C. Coombes: Transcripts for transforming growth factors in human breast cancer: clinical correlates. *Br J Cancer* 61, 612-617 (1990)

148. Y. Xu and Q. Yu: Angiopoietin-1, unlike angiopoietin-2, is incorporated into the extracellular matrix via its linker peptide region. *J Biol Chem* 276, 34990-34998 (2001)

149. N. Ferrara: Vascular endothelial growth factor as a target for anticancer therapy. *Oncologist* 9 Suppl 1, 2-10 (2004)

150. H. P. Gerber and N. Ferrara: Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res* 65, 671-680 (2005)

151. N. Ferrara, K. J. Hillan, and W. Novotny: Bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody for cancer therapy. *Biochem Biophys Res Commun* 333, 328-335 (2005)

152. M. A. Cobleigh, V. K. Langmuir, G. W. Sledge, K. D. Miller, L. Haney, W. F. Novotny, J. D. Reimann, and A. Vassel: A phase I/II dose-escalation trial of bevacizumab in previously treated metastatic breast cancer. *Semin Oncol* 30, 117-124 (2003)

153. K. D. Miller, L. I. Chap, F. A. Holmes, M. A. Cobleigh, P. K. Marcom, L. Fehrenbacher, M. Dickler, B. A. Overmoyer, J. D. Reimann, A. P. Sing, V. Langmuir, and H. S. Rugo: Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. *J Clin Oncol* 23, 792-799 (2005)

154. R. K. Jain: Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. *Science* 307, 58-62 (2005)

155. R. K. Jain: Normalizing tumor vasculature with anti-angiogenic therapy: a new paradigm for combination therapy. *Nat Med* 7, 987-989 (2001)

156. R. T. Tong, Y. Boucher, S. V. Kozin, F. Winkler, D. J. Hicklin, and R. K. Jain: Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. *Cancer Res* 64, 3731-3736 (2004)

157. C. G. Willett, Y. Boucher, Tomaso E. di, D. G. Duda, L. L. Munn, R. T. Tong, D. C. Chung, D. V. Sahani, S. P. Kalva, S. V. Kozin, M. Mino, K. S. Cohen, D. T. Scadden, A. C. Hartford, A. J. Fischman, J. W. Clark, D. P. Ryan, A. X. Zhu, L. S. Blaszkowsky, H. X. Chen, P. C. Shellito, G. Y. Lauwers, and R. K. Jain: Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer. *Nat Med* 10, 145-147 (2004)

158. J. Ridgway, G. Zhang, Y. Wu, S. Stawicki, W. C. Liang, Y. Chanthery, J. Kowalski, R. J. Watts, C. Callahan, I. Kasman, M. Singh, M. Chien, C. Tan, J. A. Hongo, Sauvage F. de, G. Plowman, and M. Yan: Inhibition of Dll4 signalling inhibits tumour growth by deregulating angiogenesis. *Nature* 444, 1083-1087 (2006)

159. Y. Hasumi, A. Klosowska-Wardega, M. Furuhashi, A. Ostman, C. H. Heldin, and C. Hellberg: Identification of a subset of pericytes that respond to combination therapy targeting PDGF and VEGF signaling. *Int J Cancer* 121, 2606-2614 (2007)

160. D. J. George: Phase 2 studies of sunitinib and AG013736 in patients with cytokine-refractory renal cell carcinoma. *Clin Cancer Res* 13, 753s-757s (2007)

161. A. Fontana, S. Filleur, J. Guglielmi, L. Frappart, G. Bruno-Bossio, S. Boissier, F. Cabon, and P. Clezardin: Human breast tumors override the antiangiogenic effect of stromal thrombospondin-1 *in vivo*. *Int J Cancer* 116, 686-691 (2005)

162. E. Mylona, P. Alexandrou, I. Giannopoulou, G. Liapis, M. Sofia, A. Keramopoulos, and L. Nakopoulou: The prognostic value of vascular endothelial growth factors (VEGFs)-A and -B and their receptor, VEGFR-1, in invasive breast carcinoma. *Gynecol Oncol* 104, 557-563 (2007)

163. M. Ohta, Y. Kitadai, S. Tanaka, M. Yoshihara, W. Yasui, N. Mukaida, K. Haruma, and K. Chayama: Monocyte chemoattractant protein-1 expression correlates with macrophage infiltration and tumor vascularity in human gastric carcinomas. *Int J Oncol* 22, 773-778 (2003)

164. J. B. Jia, P. Y. Zhuang, H. C. Sun, J. B. Zhang, W. Zhang, X. D. Zhu, Y. Q. Xiong, H. X. Xu, and Z. Y. Tang: Protein expression profiling of vascular endothelial growth factor and its receptors identifies subclasses of hepatocellular carcinoma and predicts survival. *J Cancer Res Clin Oncol* (2008)

165. S. Brychtova, M. Bezdekova, T. Brychta, and M. Tichy: The role of vascular endothelial growth factors and their receptors in malignant melanomas. *Neoplasma* 55, 273-279 (2008)

166. T. Donnem, S. Al-Saad, K. Al-Shibli, M. P. Delghandi, M. Persson, M. N. Nilsen, L. T. Busund, and R. M. Bremnes: Inverse prognostic impact of angiogenic marker expression in tumor cells versus stromal cells in non small cell lung cancer. *Clin Cancer Res* 13, 6649-6657 (2007)

167. T. Mainou-Fowler, B. Angus, S. Miller, S. J. Proctor, P. R. Taylor, and K. M. Wood: Micro-vessel density and the expression of vascular endothelial growth factor (VEGF) and platelet-derived endothelial cell growth factor (PdEGF) in classical Hodgkin lymphoma (HL). *Leuk Lymphoma* 47, 223-230 (2006)

168. S. Inan, S. Vatansever, C. Celik-Ozenci, M. Sanci, N. Dicle, and R. Demir: Immunolocalizations of VEGF, its receptors flt-1, KDR and TGF-beta's in epithelial ovarian tumors. *Histol Histopathol* 21, 1055-1064 (2006)

169. S. Arita, F. Kikkawa, H. Kajiyama, K. Shibata, M. Kawai, K. Mizuno, T. Nagasaka, K. Ino, and S. Nomura: Prognostic importance of vascular endothelial growth factor and its receptors in the uterine sarcoma. *Int J Gynecol Cancer* 15, 329-336 (2005)

170. R. G. Bagley, C. Rouleau, S. D. Morgenbesser, W. Weber, B. P. Cook, S. Shankara, S. L. Madden, and B. A. Teicher: Pericytes from human non-small cell lung carcinomas: an attractive target for anti-angiogenic therapy. *Microvasc Res* 71, 163-174 (2006)

171. R. V. Lalla, D. S. Boisoneau, J. D. Spiro, and D. L. Kreutzer: Expression of vascular endothelial growth factor receptors on tumor cells in head and neck squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg* 129, 882-888 (2003)

172. G. Xia, S. R. Kumar, D. Hawes, J. Cai, L. Hassanieh, S. Groshen, S. Zhu, R. Masood, D. I. Quinn, D. Broek, J. P. Stein, and P. S. Gill: Expression and significance of vascular endothelial growth factor receptor 2 in bladder cancer. *J Urol* 175, 1245-1252 (2006)

173. A. Giatromanolaki, M. I. Koukourakis, E. Sivridis, G. Chlouverakis, E. Vourvouhaki, H. Turley, A. L. Harris, and K. C. Gatter: Activated VEGFR2/KDR pathway in tumour cells and tumour associated vessels of colorectal cancer. *Eur J Clin Invest* 37, 878-886 (2007)

174. R. Yamaguchi, H. Yano, Y. Nakashima, S. Ogasawara, K. Higaki, J. Akiba, D. J. Hicklin, and M. Kojiro: Expression and localization of vascular endothelial growth factor receptors in human hepatocellular carcinoma and non-HCC tissues. *Oncol Rep* 7, 725-729 (2000)

175. A. A. Parikh, F. Fan, W. B. Liu, S. A. Ahmad, O. Stoeltzing, N. Reinmuth, D. Bielenberg, C. D. Bucana, M. Klagsbrun, and L. M. Ellis: Neuropilin-1 in human colon cancer: expression, regulation, and role in induction of angiogenesis. *Am J Pathol* 164, 2139-2151 (2004)

176. S. Lantuejoul, B. Constantin, H. Drabkin, C. Brambilla, J. Roche, and E. Brambilla: Expression of VEGF, semaphorin SEMA3F, and their common receptors neuropilins NP1 and NP2 in preinvasive bronchial lesions, lung tumours, and cell lines. *J Pathol* 200, 336-347 (2003)

177. G. H. Hall, L. W. Turnbull, K. Bedford, I. Richmond, L. Helboe, and S. L. Atkin: Neuropilin-1 and VEGF correlate with somatostatin expression and microvessel density in ovarian tumours. *Int J Oncol* 27, 1283-1288 (2005)

178. M. Li, H. Yang, H. Chai, W. E. Fisher, X. Wang, F. C. Brunicardi, Q. Yao, and C. Chen: Pancreatic carcinoma cells express neuropilins and vascular endothelial growth factor, but not vascular endothelial growth factor receptors. *Cancer* 101, 2341-2350 (2004)

179. M. Fakhari, D. Pullirsch, D. Abraham, K. Paya, R. Hofbauer, P. Holzfeind, M. Hofmann, and S. Aharinejad: Selective upregulation of vascular endothelial growth factor receptors neuropilin-1 and -2 in human neuroblastoma. *Cancer* 94, 258-263 (2002)

180. C. Onofri, M. Theodoropoulou, M. Losa, E. Uhl, M. Lange, E. Arzt, G. K. Stalla, and U. Renner: Localization of vascular endothelial growth factor (VEGF) receptors in normal and adenomatous pituitaries: detection of a non-endothelial function of VEGF in pituitary tumours. *J Endocrinol* 191, 249-261 (2006)

181. T. Cohen, Y. Herzog, A. Brodzky, J. K. Greenson, S. Eldar, Z. Gluzman-Poltorak, G. Neufeld, and M. B. Resnick: Neuropilin-2 is a novel marker expressed in pancreatic islet cells and endocrine pancreatic tumours. *J Pathol* 198, 77-82 (2002)

182. J. R. Jackson, J. A. Minton, M. L. Ho, N. Wei, and J. D. Winkler: Expression of vascular endothelial growth factor in synovial fibroblasts is induced by hypoxia and interleukin 1beta. *J Rheumatol* 24, 1253-1259 (1997)

183. T. Tanaka, H. Kanai, K. Sekiguchi, Y. Aihara, T. Yokoyama, M. Arai, T. Kanda, R. Nagai, and M. Kurabayashi: Induction of VEGF gene transcription by IL-1 beta is mediated through stress-activated MAP kinases and Sp1 sites in cardiac myocytes. *J Mol Cell Cardiol* 32, 1955-1967 (2000)

184. M. Li, Y. Zhang, L. W. Feurino, H. Wang, W. E. Fisher, F. C. Brunicardi, C. Chen, and Q. Yao: Interleukin-8 increases vascular endothelial growth factor and neuropilin expression and stimulates ERK activation in human pancreatic cancer. *Cancer Sci* 99, 733-737 (2008)

185. A. G. Lowrie, D. M. Salter, and J. A. Ross: Latent effects of fibronectin, alpha5beta1 integrin, alphaVbeta5 integrin and the cytoskeleton regulate pancreatic carcinoma cell IL-8 secretion. *Br J Cancer* 91, 1327-1334 (2004)

186. S. Wei, J. H. Liu, D. K. Blanchard, and J. Y. Djeu: Induction of IL-8 gene expression in human polymorphonuclear neutrophils by recombinant IL-2. *J Immunol* 152, 3630-3636 (1994)

187. M. L. Cho, Y. O. Jung, Y. M. Moon, S. Y. Min, C. H. Yoon, S. H. Lee, S. H. Park, C. S. Cho, D. M. Jue, and H. Y. Kim: Interleukin-18 induces the production of vascular endothelial growth factor (VEGF) in rheumatoid arthritis synovial fibroblasts via AP-1-dependent pathways. *Immunol Lett* 103, 159-166 (2006)

188. S. Lebel-Binay, N. Thiounn, G. De Pinieux, A. Vieillefond, B. Debre, J. Y. Bonnefoy, W. H. Fridman, and F. Pages: IL-18 is produced by prostate cancer cells and secreted in response to interferons. *Int J Cancer* 106, 827-835 (12003)

189. M. N. Manoussakis, S. Boiu, P. Korkolopoulou, E. K. Kapsogeorgou, N. Kavantzas, P. Ziakas, E. Patsouris, and H. M. Moutsopoulos: Rates of infiltration by macrophages and dendritic cells and expression of interleukin-18 and interleukin-12 in the chronic inflammatory lesions of Sjogren's syndrome: correlation with certain features of immune hyperactivity and factors associated with high risk of lymphoma development. *Arthritis Rheum* 56, 3977-3988 (2007)

190. M. M. Queen, R. E. Ryan, R. G. Holzer, C. R. Keller-Peck, and C. L. Jorcyk: Breast cancer cells stimulate neutrophils to produce oncostatin M: potential implications for tumor progression. *Cancer Res* 65, 8896-8904 (2005)

191. M. Burger, A. Glodek, T. Hartmann, A. Schmitt-Graff, L. E. Silberstein, N. Fujii, T. J. Kipps, and J. A. Burger: Functional expression of CXCR4 (CD184) on small-cell lung cancer cells mediates migration, integrin activation, and adhesion to stromal cells. *Oncogene* 22, 8093-8101 (2003)

192. S. Kitamura, Y. Maeshima, T. Sugaya, H. Sugiyama, Y. Yamasaki, and H. Makino: Transforming growth factor-beta 1 induces vascular endothelial growth factor expression in murine proximal tubular epithelial cells. *Nephron Exp Nephrol* 95, e79-e86 (2003)

193. M. Pilichowska, N. Kimura, H. Fujiwara, and H. Nagura: Immunohistochemical study of TGF-alpha, TGF-beta1, EGFR, and IGF-1 expression in human breast carcinoma. *Mod Pathol* 10, 969-975 (1997)

194. M. Niiya, K. Niiya, T. Kiguchi, M. Shibakura, N. Asaumi, K. Shinagawa, F. Ishimaru, K. Kiura, K. Ikeda, H. Ueoka, and M. Tanimoto: Induction of TNF-alpha, uPA, IL-8 and MCP-1 by doxorubicin in human lung carcinoma cells. *Cancer Chemother Pharmacol* 52, 391-398 (2003)

195. J. Nakagawa, M. Saio, N. Tamakawa, T. Suwa, A. B. Frey, K. Nonaka, N. Umemura, H. Imai, G. F. Ouyang, N. Ohe, H. Yano, S. Yoshimura, T. Iwama, and T. Takami: TNF expressed by tumor-associated macrophages, but not microglia, can eliminate glioma. *Int J Oncol* 30, 803-811 (2007)

196. N. Oka, Y. Yamamoto, M. Takahashi, M. Nishitani, H. O. Kanayama, and S. Kagawa: Expression of angiopoietin-1 and -2, and its clinical significance in human bladder cancer. *BJU Int* 95, 660-663 (2005)

197. S. Tsutsui, H. Inoue, K. Yasuda, K. Suzuki, H. Takeuchi, T. Nishizaki, H. Higashi, S. Era, and M. Mori: Angiopoietin 2 expression in invasive ductal carcinoma of the breast: its relationship to the VEGF expression and microvessel density. *Breast Cancer Res Treat* 98, 261-266 (2006)

198. K. Koga, T. Todaka, M. Morioka, J. Hamada, Y. Kai, S. Yano, A. Okamura, N. Takakura, T. Suda, and Y. Ushio: Expression of angiopoietin-2 in human glioma cells and its role for angiogenesis. *Cancer Res* 61, 6248-6254 (2001)

199. W. S. Moon, K. H. Rhyu, M. J. Kang, D. G. Lee, H. C. Yu, J. H. Yeum, G. Y. Koh, and A. S. Tarnawski: Overexpression of VEGF and angiopoietin 2: a key to high vascularity of hepatocellular carcinoma? *Mod Pathol* 16, 552-557 (2003)

200. H. Wada, H. Nagano, H. Yamamoto, Y. Yang, M. Kondo, H. Ota, M. Nakamura, S. Yoshioka, H. Kato, B. Damdinsuren, D. Tang, S. Marubashi, A. Miyamoto, Y. Takeda, K. Umeshita, S. Nakamori, M. Sakon, K. Dono, K. Wakasa, and M. Monden: Expression pattern of angiogenic factors and prognosis after hepatic resection in hepatocellular carcinoma: importance of angiopoietin-2 and hypoxia-induced factor-1 alpha. *Liver Int* 26, 414-423 (2006)

201. Z. L. Zhang, Z. S. Liu, and Q. Sun: Expression of angiopoietins, Tie2 and vascular endothelial growth factor in angiogenesis and progression of hepatocellular carcinoma. *World J Gastroenterol* 12, 4241-4245 (2006)

202. S. Loges, H. Clausen, U. Reichelt, M. Bubenheim, A. Erbersdobler, P. Schurr, E. Yekebas, G. Schuch, J. Izbicki, K. Pantel, C. Bokemeyer, and W. Fiedler: Determination of microvessel density by quantitative real-time PCR in esophageal cancer: correlation with histologic methods, angiogenic growth factor expression, and lymph node metastasis. *Clin Cancer Res* 13, 76-80 (2007)

203. K. Hata, K. Nakayama, R. Fujiwaki, H. Katabuchi, H. Okamura, and K. Miyazaki: Expression of the angopoietin-1, angopoietin-2, Tie2, and vascular endothelial growth factor gene in epithelial ovarian cancer. *Gynecol Oncol* 93, 215-222 (2004)

204. N. Reinmuth, E. Piegelbrock, M. Raedel, N. Fehrmann, H. Hintelmann, R. Wagner, W. E. Berdel, M. Thomas, L. Freitag, and R. M. Mesters: Prognostic significance of vessel architecture and vascular stability in non-small cell lung cancer. *Lung Cancer* 55, 53-60 (2007)

Key Words: Angiogenesis, Tumor Environment, VEGF-A, Angiopoietins, Anti-Angiogenic Targets, Review

Send correspondence to: Sophia Ran, Department of Medical Microbiology, Immunology and Cell Biology, Southern Illinois University School of Medicine and SimmonsCooper Cancer Institute, Springfield, IL, 62794-9678, USA, Tel: 217-545-7026, Fax: 217-545-3227, E-mail: sran@siumed.edu

http://www.bioscience.org/current/vol15.htm