# ANGIOGENESIS AND TISSUE REMODELING: SOME PHYSIOLOGICAL AND PATHOLOGICAL CONSIDERATIONS

**C. A. Meza-Herrera[1], R. Castro-Franco[1], R. Bañuelos V.[2], and C. F. Aréchiga-F.[2]**

[1] **Unidad Regional Universitaria de Zonas Aridas. Universidad Autónoma Chapingo. A.P. 8, Bermejillo, Durango, México. 35230. e-mail: cmeza2000@hotmail.com**

[2] **Facultad de Medicina Veterinaria y Zootecnia. Universidad Autónoma de Zacatecas. A.P. 11. Calera de Victor Rosales, Zacatecas. 98500.**

## SUMMARY

Angiogenesis, the process by which new blood vessels are formed, is essential during embryogenesis, organogenesis, as well as for tissue remodeling of reproductive organs, wound repair and oncogenesis. Under normal conditions, angiogenesis occurs during embryogenesis and is a down-regulated process in the healthy adult that is almost exclusively linked to pathological conditions such as tumor growth, wound repair and(or) inflammation. Physiological angiogenesis processes in the adult are restricted to the female reproductive system where they occur cyclically during the ovarian and uterine cycle as well as during pregnancy and lactation. By analyzing the phenotypic changes of endothelial cells during corpus luteum (CL) formation and regression, it has been established a physiological model of blood vessel growth and regression where quantity of vessel density, and percentage of vessels with lumen were established as parameters of angiogenesis. With respect to luteogenesis, sprouting endothelial cells invade the growing CL and continue to grow throughout the first third of the ovarian cycle. Thereafter, a dense network of vessels with gradually decreasing vessel density characterizes the mature CL. During luteolysis all newly formed vessels regress, depicting a gradual foreshortening cells rounding of endothelial cells and subsequent detachment. Based on histochemical detection of nucleosomal fragmentation products, physiological blood vessel regression in the cyclic CL does not appear to involve endothelial cell apoptosis. Studies developed during the past two decades have established that development of new capillaries from an existing network is an essential component of tumor growth. In fact, unless tumors are able to stimulate new vessels formation and thus provide pathways for increased outflow of waste products and inflow of nutrients and oxygen, they do not grow. Tumor angiogenesis also provides essential exit routes for tumor cells to migrate into the blood stream for systemic metastasis. This review provides an up-to-date, comprehensive analysis of the main processes involved in both physiological and pathological angiogenesis and their role in tissue remodeling. Besides a brief description of the molecular controls that regulate steps in activation, assembly, and maturation during vasculogenesis, morphogenic processes regulating those biological steps will be emphasized .

***Key words:*** *Angiogenesis, vasculogenesis, endothelial targeting, cell differentiation.*

## RESUMEN

Angiogénesis, el proceso mediante el cual se forman nuevos vasos sanguíneos, es esencial durante embriogénesis, organogénesis, así como para la remodelación de tejidos en los órganos reproductivos, reparación de heridas y oncogénesis. Bajo condiciones normales, la angiogénesis ocurre durante la embriogénesis y en adultos sanos es un proceso de regulación disminuida el cual solamente está ligado a condiciones patológicas como desarrollo de neoplasias, reparación de heridas y durante procesos de inflamación. En el adulto, los procesos de angiogénesis fisiológica están restringidos al sistema reproductor femenino en donde ocurre de manera periódica durante los ciclos estrales y endometriales, así como durante la preñez y la lactancia. Al analizar los cambios fenotípicos de las células endoteliales durante la formación y regresión del cuerpo lúteo (CL), se ha definido un modelo fisiológico en el desarrollo y regresión de los vasos sanguíneos en el cual tanto la densidad vascular como el porcentaje de vasos con formación de lumen fueron definidos como parámetros de angiogénesis. Con respecto al proceso de luteogénesis, las células endoteliales recién formadas invaden al CL en desarrollo y continúan su crecimiento durante el primer tercio del ciclo estral. Posteriormente, una densa red de vasos sanguíneos con una decrecida densidad vascular van a caracterizar al CL maduro. Durante la luteólisis, todos los vasos sanguíneos recién formados sufren una regresión mostrando encogimiento gradual de las células que rodean a las células endoteliales observándose su posterior desprendimiento. Basados en la detección histoquímica de los productos de fragmentación nucleosomal, la regresión fisiológica de los vasos sanguíneos en el CL cíclico pareciera no involucrar la apoptosis de las células endoteliales. Estudios realizados durante las últimas dos décadas han establecido que el desarrollo de nuevos capilares provenientes de una red preexistente es un componente esencial para el desarrollo de tumores. En efecto, la única posibilidad para que se dé el desarrollo de neoplasias considera el que éstas sean capaces de estimular la formación de nuevos vasos sanguíneos, y proveer rutas que permitan incrementar la salida de productos de desecho, así como la entrada de nutrientes y oxígeno. En el mismo sentido, la angiogénesis neoplásica también debe proveer rutas de diseminación las cuales son esenciales para que las células tumorales puedan migrar hacia el torrente sanguíneo y producir una metástasis sistémica. El presente trabajo provee un análisis detallado de los principales procesos involucrados en el proceso de angiogénesis, tanto desde un punto de vista fisiológico como patológico, y aborda el rol que juega durante el proceso de remodelación de tejidos. Paralelo a una breve descripción de los controles moleculares que regulan la activación, ensamble y maduración durante el proceso de vasculogénesis, se enfatizan los procesos morfogénicos que regulan la biología de la formación de nuevos vasos sanguíneos.

***Palabras claves****: Angiogénesis, vasculogénesis, células endoteliales, diferenciación celular.*

## INTRODUCTION

One of the main characteristics observed in reproductive tissues is their continuous state of change. Reproductive organs have cycles of tissue activity as a characteristic of their mature, functional state and may operate over long or short periods of time. The mammary gland, for instance, may have a period of secretory activity lasting several years, preceded or followed by states of extended but reversible quiescence (Coleman-Krnacik, and Rosen, 1994). In the same way, the ovary may shows cycles of follicular growth, maturation, rupture and ovulation over short periods of time (Reynolds *et al*., 1992). With respect to males, maurine testes regression, which is accompanied not only by decreases in both seminiferous tubule diameter and spermatogenic activity but also by reduced testis mass, occurs because loss of blood vessel maintenance (Young and Nelson, 2000).

In order to accomplish tissue remodeling, cells need to be plastic. In most cases, the cells of mature reproductive tissues can be considered as reversibly differentiated. This means that they can respond to the local environment, often in very dramatic ways. The consequences for the tissue can be even more dramatic, involving destruction, reconstruction and(or) invasion (Daniel and Abrahamson, 2000). Angiogenesis, the process by which new blood vessels are formed, is essential in structural tissue remodeling of reproductive organs, during embryogenesis, wound repair and oncogenesis (Luck and Zhao, 1995). This review provides an up-to-date, comprehensive review of the main molecular processes involved in both physiological and pathological angiogenesis and their role in tissue remodeling.

### Angiogenesis and angiogenic factors: An overview

Angiogenesis occurs mainly during embryonic development but is almost absent in adult tissues. In fact, transient and tightly controlled physiological angiogenesis in adult tissues occurs during the female reproductive cycle as well as during wound healing (Fairchild *et al.,* 1993; Goodger and Rogers, 1993; Wheeler *et al*., 1995; Daniel and Abrahamson, 2000). In contrast, pathological angiogenesis is characterized by persistent and uncontrolled proliferation of endothelial cells, and is a prominent feature of diseases such as diabetic proliferative retinopathy, rheumatoid arthritis, hemangiomas, and psoriasis (Fregene *et al*., 1993; Risau, 1994; Fan et al., 1995). During angiogenesis, formerly differentiated vascular endothelial cells (VEC) return to a proliferative growth state and invade neighboring tissues. Many angiogenic factors acting through autocrine and paracrine mechanisms promote activation of intracellular signaling pathways (Sandberg *et al*., 1998). In turn, these pathways induce VEC migration and modulate intracellular associations involved in microtubule formation as well as neovascularization (Mallery *et al*., 1993; Daniel and Abrahamson, 2000).

Angiogenic factors are potent growth factors promoting proliferation and differentiation of VEC. The major group is the fibroblast growth factor (FGF's) family, which is also involved in granulopoiesis and megakaryocytopoiesis (Kandel *et al*., 1991; Bikfalvi and Han, 1994). Vascular endothelial growth factor (VEGF) and platelet-derived growth factors (PDGF) have also been identified as key regulatory paracrine growth factors for VEC (Ferrara *et al*., 1992; Plate *et al.,* 1994). The VEGF is a homodimeric glycoprotein that promotes angiogenesis and vascular hyperpermeability by interacting with two tyrosine kinase receptors: VEGF-R1 (Flt-1) and VEGF-R2, which contains a kinase domain region (Flk-1/KDR) (Athanassiades *et al.,* 1998), as well as to the auxiliary receptor neuropilin (Keshet and Ben-Sasson, 1999). According to Hagemann *et al*. (1994), the uteroplacental renin-angiotensin system plays an important angiogenic role during implantation and placentation. The hematopoietic granulocyte-macrophage colony stimulating factor (GM-CSF) or erythropoietin, has recently been defined as an angiogenic factor (Bikfalvi and Han, 1994).

### Angiogenesis and cell signaling systems

Korhonen *et al*. (1994) studied the expression of the endothelial tie receptor tyrosine kinase gene during the earliest stages of vascular development. After complementary DNA (cDNA) isolation and sequencing, early postimplantation mouse tissues were analyzed for tie expression by *in situ* hybridization. In 8.5 day embryos, tie expression was observed in differentiating angioblasts as well as in migrating endothelial cells of the developing heart. Tie mRNA was prominent in the endocardium of the embryo and in the VEC of the lung; interestingly, tie gene expression persisted in adult lung capillaries. Endothelial receptor tyrosine kinases are likely to play key roles in the intracellular signaling controlling angiogenesis and (or) maintenance of endothelial cell functions.

The role of Ca-mediated signal transduction upon angiogenesis was evaluated by Kohn *et al*. (1995). They evaluated Ca-dependency of VEC proliferation and invasion by using an inhibitor of ligand-stimulated Ca-influx, CAI (carboxyamidotriazole). Incubation with CAI inhibited VEC-proliferation in response to either serum or basic FGF2. Inhibition of VEC adhesion and motility to basement membrane protein laminin, fibronectin, and type-4 collagen was observed. Endothelial tube formation and *in vivo* angiogenesis were inhibited by CAI. Ca-regulated events were important in FGF2-stimulated VEC-proliferation and invasion, perhaps through regulation of FGF2-induced phosphorylation reaction events, indicating a Ca-regulatory role during *in vivo* angiogenesis.

Hyperlipidemic states have been associated to VEC dysfunction. Accumulation of toxic lipoprotein degradation products in artery walls has been related to transmembrane signaling impairment. Endothelial cell replication associated with vascular growth is markedly decreased under hypercholesterolemic conditions. This defect could play an important role in the pathophysiology of occlusive atherosclerotic disease (Henry, 1993).

**Angiogenesis and extracellular matrix modification**

During angiogenesis, VEC react to stimulation with finely tuned signaling responses, resulting in major morphological changes in their extracellular matrix (ECM). Angiogenesis is thought to proceed by two regulatory pathways. The proliferative pathway depends on various cytokines and other factors that both stimulate and inhibit VEC proliferation. One of these components, the secreted protein acidic and rich in cysteine (SPARC), might function at several levels to control neovessel progression (Sage and Vernon, 1994). Proteolysis of these proteins (e.g., by plasmin) results in release of peptides containing the amino acid sequence Gly-His-Lys, which are angiogenic both *in vitro* and *in vivo*. At later stages of angiogenesis, when VEC proliferation ceases, the intact protein exerts its known inhibitory effect on cell cycle progression.

The morphogenic pathway depends on synthesis and assembly of fibrilar type-1 collagen, which can be used as a template for VEC-migration and lumen formation. The interaction of VEC with substrates of type-1 collagen forms networks based on the establishment of traction centers. These planar cellular networks, in some respects, resemble developing vasculature *in vivo* (Sage and Vernon, 1994). Paracrine signaling cascades regulated by hipoxia initiate sequentially coordinated series of endothelial responses, including matrix degradation, migration, proliferation, and morphogenetic remodeling. Surface receptors on committed endothelial lineage progenitors transduces cues from extracellular-matrix associated proteins and cell-to-cell contact to direct migration, matrix attachment, proliferation, targeting, cell-to-cell assembly, and vessel maturation. (Daniel and Abrahamson, 2000). In fact, through their capacity to spatially segregate and temporarily integrate a diverse range of extracellular signals, endothelial cells determine their migratory paths, cellular partners, and life-or-death responses to local cues.

**Angiogenesis and the female reproductive organs**

The female reproductive organs contain some of the few tissues that exhibit periodic growth and regression. The ruptured ovulatory follicle in cows, which represents less than 200 mg of tissue, forms a mature corpus luteum (CL) weighing about 5 to 6 g within a period of about 10 days. Similar rapid growth is observed in uterine and placental tissues. Fully functional ovarian, uterine, and placental tissues receive some of the greatest rates of blood flow, on a weight-specific basis, of any tissues in the body (Reynolds *et al.,* 1992; Augustin *et al*., 1995).

**Angiogenesis and ovarian tissue**

McClure *et al*. (1994) determined the proliferation percentage of VEC (cell proliferation index, CPI), and the area of tissue occupied by VEC (areal fraction) for both granulosa and theca cell layers. The granulosa layer was avascular until the LH surge subsided. Maximum vascularization was achieved by the mid-luteal phase. The theca endothelial CPI was constant from pre-LH surge to mid-luteal phases. From first appearance in the granulosa layer, VEC had the same CPI as the theca cells. The CPI decreased significantly in both layers after the mid-luteal phase. Proliferation of VEC did not change during the follicular, early or mid-luteal phases, followed by a decrease in the late luteal phase. Invasion of the membrane granulosa by VEC occurred after the LH surge, presumably in response to a chemotactic stimulus.

Upon analysis of VEC-phenotypic changes during bovine CL formation, Augustin *et al.* (1995) reported that sprouting VEC invaded the growing CL

and continued to grow during the first third of the ovarian cycle. Thereafter, a dense network of vessels with gradually decreasing vessel density characterized the mature CL. During the period of luteolysis and for several weeks thereafter, regressing and residual CL did not appeared to involve VEC apoptosis.

Angiogenesis in the preovulatory follicle is confined to the theca cell layers, and penetration of capillaries through the basement membrane into the granulosa layers does not occur until after ovulation. However, elevated expression of the angiogenic growth factor or VEGF has been reported in cumulus cells surrounding the oocyte, which are expelled from the follicle during ovulation, suggesting a spatial and temporal discrepancy between VEGF expression and angiogenesis. According to Tempel *et al.* (2000), besides secretion of VEGF to the follicular fluid, the cumulus cells release molecules with antiangiogenic activity that blocks endothelial cell proliferation, migration and capillary formation *in vitro*; hyaluronic acid produced by the cumulus cells can account for this antiangiogenic factor. In fact, it has been postulated that hyaluronic acid may play a role as a high-molecular-weight angiogenic factor that works as a shield that prevents premature vascularization of the preovulatory follicle by blocking endothelial cell migration and proliferation.

Barboni *et al*. (2000) studied VEGF's production in ovarian follicles as a potential mechanism of ovarian activity regulation and mentioned that VEGF markadly rose in medium and large follicles after equine chorionic gonadotropin (eCG) administration. The increasing levels, essentially atributable to granulosa cells, were likely to be involved in blood vessel development in the wall of the growing follicles, and could play a local key role in gonadotropin-induced follicle development. Once ovulation approaches, under the effect of human chorionic gonadotropin, production of VEGF was switched off, probably creating the safest conditions for the rupture of the follicle wall, while theca cells maintained unaltered angiogenic activity, which is probably required for luteogenesis.

**Angiogenesis and early pregnancy.**

The trophoblast is the most highly invasive of all non-pathological tissues and its actions have often been compared to those of tumors, and there are indeed many mechanistic similarities. The trophoblast secrete two collagenases, MMP2 and MMP9, which facilitate penetration of basement membranes, and a newly characterized member of the metalloproteinase inhibitor family (TIMP3). Regulation of these components may depend on their differential expression at different stages of pregnancy. This regulation appears to involve both paracrine and autocrine control of cytokines and growth factors (Luck and Zhao, 1995).

Using immunohistochemistry techniques, Goodger and Rogers (1993) studied VEC in the rat endometrium during the implantation period. The main findings were (1) endometrial angiogenesis may be occurring before implantation, (2) endometrial endothelial and stromal cell proliferation occurs concomitantly and, (3) during early pregnancy, two main mechanisms appear to control uterine endothelial cell proliferation. The first mechanism is maternally controlled and operates throughout the entire endometrium. The second mechanism functions in the vicinity of the embryo once implantation occurs, and appears to be under both maternal and embryonic control.

*In situ* localization in the pregnant uterus revealed that VEGF mRNA is expressed primarily by the decidua, whereas the receptor Flt-1 is expressed primarily by chorionic vascular endothelium and trophoblast cells, in particular the extravillous trophoblast (EVT). Athanassiades et al. (1998) examined whether the mRNA and protein of VEGF and its receptors are expressed by invasive human first-trimester EVT cells and whether VEGF influences EVT cell proliferation, migration and invasiveness; results indicated that while VEGF had a proliferative effect on EVT cells, it did not promote EVT cell migration or invasiveness.

With respect to placental growth, vascularization of this tissue is a characteristic of early pregnancy, and it is accomplished in an unusually hypoxic environment. Both VEGF mRNA and VEGF protein were found in higher concentrations in placental fibroblast culture media under aerobic conditions. According to Wheeler *et al*. (1995), hypoxia should increase transcription and translation of vascular endothelial growth factors (VEGF) in placental fibroblasts, providing one mechanism linking placental development with its environment.

**Angiogenesis and neoplasias**

Studies over the past 20 years have established that development of new capillaries from an existing network is an essential component of

tumor growth; once a tumor becomes vascularized, the expression of tumor mass is rapid (Fregene *et al.,* 1993). To become vascularized, tumors requires both up-regulation of angiogenic stimulators such as VEGF and FGF's, while in other form of tumors expression of angiogenesis inhibitors, such as angiostatin and endostatin, must be down-regulated (Cao *et al.,* 1998). In fact, according to Risau (1994), unless tumors are able to stimulate the formation of new vessels and thus provide pathways for increased outflow of waste products and inflow of nutrients and oxygen, they do not grow larger than 2-3 $mm^3$. In addition, tumor angiogenesis provides essential exit routes for tumor cells to migrate into the blood stream for systemic metastasis. In several forms of human cancer, however, extensive neovascularization of tumor sites is considered a poor prognostic element (Fan *et al.,* 1995).

As mentioned, angiogenesis is a complex, multistep process driven by many autocrine or local signals within the tumor. These steps involve (1) degradation of the extra cellular matrix around a local venule after the release of collagenases and proteases, (2) invasion of the surrounding stroma, proliferation and directional migration of vascular endothelial cells, and (3) differentiation of these cells into functioning capillaries. The last includes capillary tube morphogenesis, coalescence of capillaries into larger vessels, vascular pruning, and acquisition of periendothelial cell coating (Keshet and Ben-Sasson, 1999). Cytokines, produced by various cell types present within the microenvironment of solid tumors, form complex, dynamic chemical interactions with resulting multiple effects on tumor progression. However, as mentioned by Cao *et al*. (1998), spontaneously arising human and animal tumors during their first stages of tumorigenesis are not often vascularized; these *in situ* microcanceres may exist for months or even years without further expansion of tumor mass. In the prevascular stage, inhibition of tumor angiogenesis from host tissues or tumor cells themselves may be prominent. However, once the expression of angiogenesis inhibitors is down-regulated, dormant tumors become vascularized and the growth of tumor mass is expeditious. Therefore, according to this scenario, the endothelial cell compartment acts as a "gate-controller" during tumorigenesis.

The genetic changes that occur in association with development of human brain neoplasias and their contribution to the neoplastic states have been extensively examined during the last decade. Oncogenes and tumor suppressor genes have been identified. Many powerful molecular genetic techniques and applications have emerged. In astrocytomes, for instance, losses of genetic material on chromosomes 10 and 17, and amplification of the epidermal growth factor-receptor gene is important in pathogenesis associated with glioblastoma multiforme. Brain tumors also express growth factors and growth factor-receptors that may be important in promoting tumor growth and angiogenesis (Leon *et al*., 1994). According to Lewis *et al.* (1995), VEGF, basic-FGF, and tumor necrosis factor (TNF- ) were the main cytokines released by either macrophages found in the stromal compartment of tumors or malignant epithelial cells. In addition, tumor necrosis- receptors were found expressed in leukocytes, malignant cells, and endothelial blood vessels.

**Fighting cancer: Following the angiogenesis antagonist approach**

Cancer therapy, during the last 50 years, has established a direct approach in that the tumor itself has been designed the main target. In this way, any cytotoxic drug able to kill tumor cells *in vitro* was, by definition, a candidate for *in vivo* chemotherapy. The main problem generated with this approach, however, is that normal tissue could also be susceptible to the same spectrum of the pharmacological agent. According to Keshet and Ben-Sasson (1999), a second indirect strategy that considers an antiangiogenic therapy to fight cancer, provides a promising alternative that uses the evolving vasculature that nourishes the tumor, as the prime target; with this approach, tumors can potentially be starved to death by inhibiting their vascularization.

Due to the inherent genetic inestability of neoplastic cells, exposure to chemotherapy eventually may promote selection of drug-resistant clones. Therefore, targeting the tumor vasculature rather than addressing tumor cells has two remarkable advantages. Firstly, because all solid tumors and probably some leukemias are angiogenic-dependent, this approach circumvents the need to fit a specific therapy to the unique genetic make-up of an individual tumor. Secondly, since the targeted vascular endothelial cells are normal and genetically stable, they are less likely than tumor cells to become drug-resistant (Cao *et al.,* 1998; Keshet and Ben-Sasson, 1999). There are some considerations with respect to this antiangiogenic approach. First, it must be endothelial cell-specific and must distinguish

between normal and tumor vasculatures. Second, it must take into consideration the time-scale of action: will it necessarily be chronic, only keeping the tumor from growing bigger, or could be possible to induce tumor regression? These questions must be answered prior definition of any strategy to fight cancer.

Two promising molecules to control tumorigenesis through the antiangiogenic approach are the proteins angiostatin and endostatin, which were isolated by the researching team of Dr. Folkman (Cao *et al*., 1998). The first antiangiogenic protein, angiostatin, is a 38-kDa protein that is an internal fragment of the serum protein plasminogen, which itself lacks any antiangiogenic activity by specifically inhibited endothelial cell proliferation *in vitro* without affecting other cell types. The second antiangiogenic peptide factor, endostatin, is a 20-kDa COOH-terminal fragment of collagen XVIII, a component of the blood vessel wall. This molecule was shown to inhibit VEGF-induced endothelial cell migration *in vitro* and to have anti-tumor activity *in vivo*, without any apparent signs of toxicity. Each of these angiogenesis inhibitors almost completely suppresses the growth of a variety of tumors, with endostatin being more potent. When administrated in combination, these antiangiogenic factors act synergistically and cause partial regression of tumors (Keshet and Ben-Sasson, 1999).

Metastatic growth depends upon neovascularization at two levels. First, malignant cells must exit from a primary tumor into the blood circulation once the tumor becomes vascularized. Secondly, after arrival at distant organs, metastatic cells must, again, induce angiogenesis in order to promote tumor expansion. In an elegant study, Cao *et al.* (1998) evaluated if angiostatin produced by tumor cells affected metastatic tumor growth by examining lung metastases of mice after removal of primary tumors. Angiostatin induced a long-term dormancy of lung metastases which was equivalent to 14 to 15 human year, considering that one mouse day is equivalent to 35 human days. Results indicated that tumor cells in dormant metastases lack new vessels, but replicate as rapidly as those cells in expanding and vascularized tumors, although in this case, proliferation reaches an equilibrium with a high rate of programmed cell death or apoptosis. Even though the mechanisms of induction of tumor cell apoptosis in dormant tumors are unclear, inhibition of neovascularization by angiostatin may restrict the supply of tumor cells survival factors provided either by the endothelial cells or by the circulation. These data demonstrate a diminished growth rate of lung metastases after removal of the primary tumor, and suggest that metastases are self-inhibitory by halting angiogenesis. These findings provide a novel approach for cancer therapy by antiangiogenic gene therapy with a specific angiogenesis inhibitor.

## CONCLUDING REMARKS

Both physiological and pathological angiogenesis requires a constitutive activation of vascular endothelial cells which dissolve their surrounding extracellular matrix and migrate toward certain areas such as the endometrium and(or) neighboring areas. Upon proliferation, they form a new vascular network, which supplies the embryo and(or) tumor with nutrients and oxygen, and removes waste products. The onset of both physiological and pathological angiogenesis is characterized by both (1) the expression of genes encoding angiogenic growth factors such as FGF, VEGF, PDGF, which act in a paracrine fashion, and (2) by a coordinated induction of genes in vascular endothelial cells which encode the respective growth factor receptors. Treatment of neoplasias with angiogenic inhibitors has emerged as a promising strategy to inhibit tumor growth. The identification of receptors for the newly discovered antiangiogenic proteins, angiostatin and endostatin, might open the way for the discovery of small molecules with therapeutic value. A deeper understanding of how proliferation and morphogenesis are controlled during vascular growth is likely to reconcile several current models with respect to the factors that modulate dynamics of vascular endothelial cells during angiogenesis.

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