[Frontiers in Bioscience 14, 3962-3973, January 1, 2009]

Tumor angiogenesis and molecular targets for therapy

Yihai Cao

Laboratory of Angiogenesis Research, Department of Microbiology, Tumor and Cell Biology, Karolinska Institute, 171 77 Stockholm, Sweden

TABLE OF CONTENTS

1. ABSTRACT

Tumors produce multiple angiogenic factors to induce neovascularization by angiogenesis, vasculogenesis and vascular remodeling. Although tumors utilize similar mechanisms as normal growing tissues, tumor blood vessels usually appear as malformed vasculatures that have several distinctive features including a high degree of disorganization, lack of clear separation between arterioles and venules, lack of appropriate coating with mural cells, high permeability, and composition of mosaic cell types, which might express specific markers. These unusual features of tumor blood vessels offer a great opportunity for therapeutic intervention and might paradoxically restrict cytotoxic drug delivery. Following an initial clinical success of bevacizumab in combination with chemotherapy for the treatment of human colorectal cancer, several other anti-angiogenesis agents are now available in the clinic. Understanding basic mechanisms of tumor angiogenesis, defining novel and accurate molecular targets, designing optimal clinical trials, and minimizing side effects are crucial issues for a further successful development of anti-angiogenic compounds for the treatment of various human cancers.

2. TUMOR ANGIOGENESIS

2.1. Angiogenic switch by genetic and epigenetic factors

Genetic mutations of oncogenes and tumor suppressor genes characterize the transformation of a normal somatic cell into a malignant cell (1). However, the malignant cells in most cases, will not grow into a clinically detectable mass if they do not switch on an angiogenic phenotype (2) (Figure 1). A tiny malignant cell population, which could consist of a few hundred tumor cells, can remain dormant in the body for months or years feeding on nutrients and oxygen from neighboring blood vessels (3-5). Such cells can be alive and actively dividing, but tumor growth is not evident due to cell loss. A constant renewal and adaptation to the host environment may, however, occur which eventually lead to tumor cell clones that trigger angiogenesis. (6) (Figure 1).

Recent observations indicate that both mutations of oncogenes and tumor suppressor genes could lead to the switch into an angiogenic tumor (1, 7). For instance, in mouse tumor models, mutations of H-ras and amplification of myc oncogenes may contribute to the angiogenic switch by up-regulating vascular endothelial growth factor

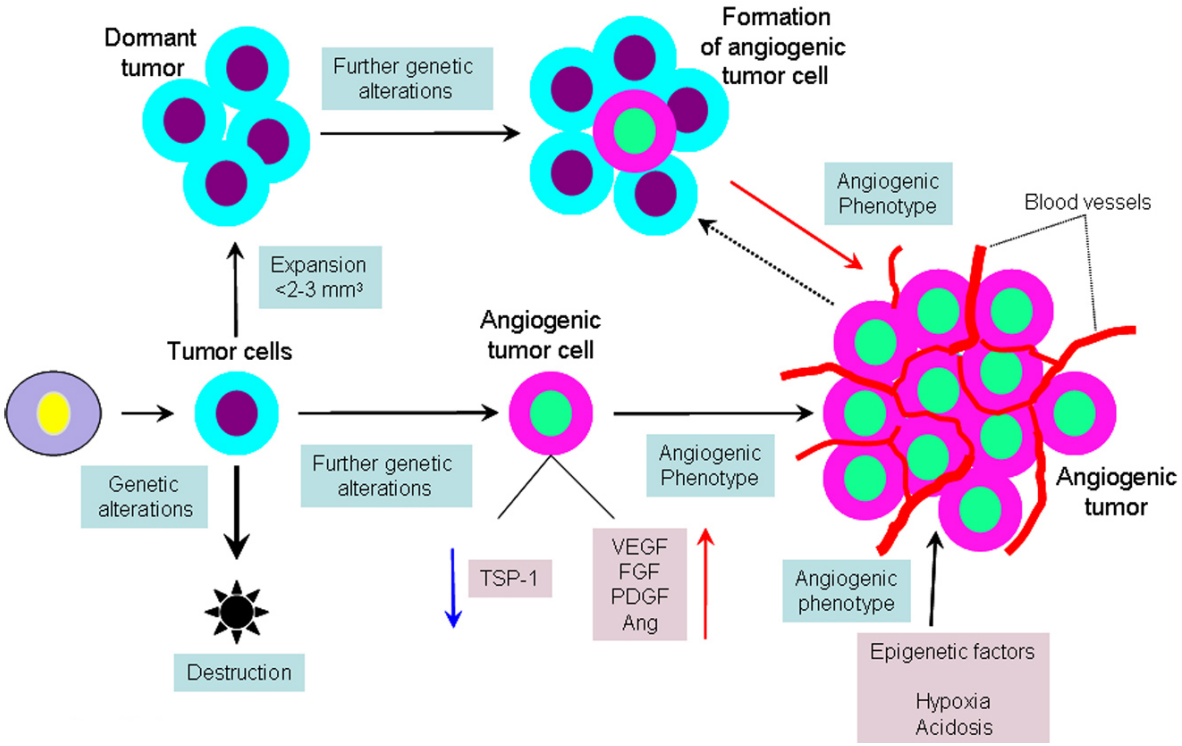

Figure 1. Mechanisms of switching on an angiogenic tumor phenotype. Mutations of oncogenes and tumor suppressor genes lead to transformation of a normal cell into a malignant cell, which in most cases is destroyed in the body by immune surveillance and other mechanisms (dark cells). Some malignant cells might escape from the immune system and expand to a microscopic mass consisting of a few hundreds of cells (green cells). These cell populations cannot no longer grow beyond the sizes of 2-3 mm3 without recruitment of new blood vessels and they remain in the body for months or years. However, tumor cells might still actively divide in the microscopic dormant tumor until they become angiogenic tumor cells (red cells). Only in rare cases, a malignant cell directly gains an angiogenic phenotype from the very beginning. Once an angiogenic phenotype is switched on, tumor growth and progression is exponential.

(VEGF) (3, 8, 9). The von Hippel Lindau VHL) protein, tumor suppressor gene product, targets hypoxia inducible factor-1alpha (HIF-1alpha) for degradation, which results in reduced levels of VEGF expression (10, 11). Mutations of VHL lead to accumulation of HIF-1alpha and its target gene product, VEGF. Loss of p53 function results not only in elevated levels of proangiogenic factors such as VEGF, but also to a reduction of the endogenous angiogenesis inhibitor thrombospondin-1 (TSP-1) (12, 13). Thus p53 may tip the balance of proangiogenic and anti-angiogenic factors toward neovascularization (Figure 2). Once an angiogenic phenotype is initiated, the tumor growth is exponential. A rapid expansion of the tumor mass demands endothelial cells to grow coordinately at the same pace to build up enough vessels for sufficient blood supply. Even though endothelial cells become activated, they frequently can not grow at the same high rate as tumor cells do. The consequence is unsynchronized growth rates manifested by the formation of a primitive, disorganized, and unevenly distributed nascent vessels. Such vessels show poor blood perfusion which may lead to tissue hypoxia and necrosis. Hypoxia and acidosis activates compensatory mechanism of angiogenesis by up-regulating VEGF (11, 14). At present it is well documented that high levels of VEGF are present in hypoxic regions of both human and mouse tumors (15).

2.2. Tumor vasculature and function

Most tumors are not able to grow without recruiting new blood vessels where they use similar mechanisms as growing embryonic tissues (16-20). The neovascularization processes include angiogenesis, vasculogenesis, and intussusception (vascular remodeling) (21). However unlike blood vessels in healthy tissues, the tumor vasculature appears as disorganized tubular structures, which often are interconnected, tortuous, highly leaky, resembling premature sinusoidal vasculatures (22, 23). These abnormal vessels usually lack a clear separation between arterioles and venules and the reqruitment of pericytes and vascular smooth muscle cells (1) (Figure 3). The malformed vasculature leads to a slow sluggish blood flow. In addition, high interstitial fluid pressure (IFP) exists within the tumor tissue due to the high permeability nature of these vessels, sluggish blood flow, lack of mural cell, and incomplete basement membrane (1, 24). In general, a fast growing tumor almost always creates a hypoxic environment due to: 1) *Unsynchronized growth rates of tumor cells and endothelial cells.* Malignant cells contain an aberrant genome and divide at a high rate (25) whereas endothelial cells are genetically stable maintaining a more normal growth rate (26). Thus, in a growing tumor, malignant cells and endothelial cells grow

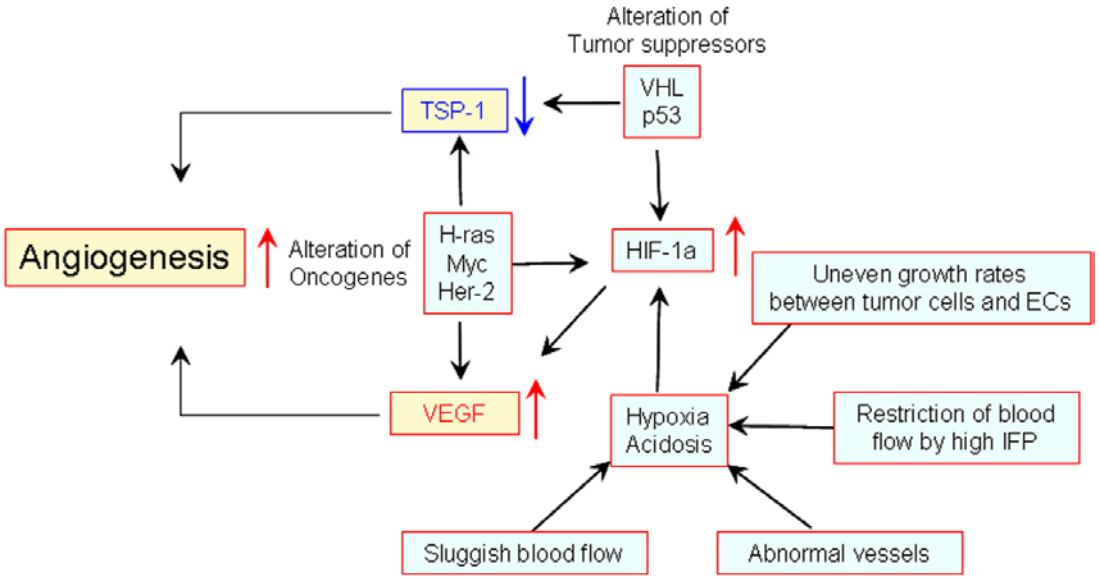

Figure 2. Genetic and epigenetic factors contributing to the angiogenic switch. Both genetic and epigenetic factors contribute to the high expression levels of HIF-1alpha, which directly controls VEGF expression at the transcriptional level. Loss of function of p53 could also lead to down-regulation of angiogenesis inhibitors such as TSP-1. Tipping balance between angiogenic factors and inhibitors leads to the switch of an angiogenic phenotype.

at non-synchronized rates, resulting in hypoxia and a rapid expansion of the tumor population. 2) *A disorganized vascular architecture* that lacks defined arterioles and venules.The blood traveling in this vasculature contains relatively low levels of oxygen; 3) *Sluggish blood flow*. Owing to the abnormal nature of the tumor vasculature, blood flow within tumor vessels are sluggish and the slow flow leads to hypoxia; and 4) *High interstitial fluid pressure* (IFP). The leaky nature of tumor vessels leads to high IFP, which may interfere with premature nascent vessels restricting blood flow inducing hypoxia (Figure 2).

Hypoxia leads to increased levels of hypoxia inducible factor-1alpha (HIF-1alpha) by inhibiting proline hydroxylase activity and stabilizing HIF-1alpha, which increases VEGF expression by activating its promoter (26). Under physiological conditions, this hypoxia-triggered positive feedback loop acts as a compensatory mechanism for improving blood flow in an ischemic tissue by making more vessels *via* VEGF. However in tumors, increased levels of VEGF could further increase vascular disorganization, permeability, and IFP, leading to severe hypoxia (Figure 2). As a consequence, tumor blood vessels are highly leaky and poorly perfused.

2.3. Angiogenic factors and their signaling pathways

The cellular heterogeneity of malignant cell populations contributes to the complex expression of multiple angiogenic factors (16). As indicated above, VEGF is a key tumor-derived angiogenic factor that exerts multiple functions including stimulation of angiogenesis, vasculogenesis, inflammation and vascular permeability (21, 27). VEGF is the prototype of a family of structurally related proteins, which consists of four other members; VEGF-B, placental growth factor (PlGF), VEGF-C and VEGF-D (28-32). These growth factors bind to three tyrosine kinase receptors, VEGFR-1, VEGFR-2 and VEGFR-3 predominantly expressed by endothelial cells (33, 34). According to biological functions and receptor binding patterns, the VEGF family can be divided into three subgroups (1): 1) VEGF-A binds to VEGFR-1 and VEGFR-2 and it stimulates angiogenesis, vasculogenesis and vascular permeability via VEGFR-2 ; 2) PlGF and VEGF-B which bind only to VEGFR-1 but their angiogenic activity remains controversial. While most studies show that PlGF and VEGF-B lack angiogenic activity, a recent study demonstrates that PlGF exhibits potent angiogenic activity in pathological settings such as tumor angiogenesis (93); and 3) VEGF-C and VEGF-D which bind to VEGFR-3, expressed on lymphatic endothelial cells where they mediate lymphangiogenesis. In addition, VEGF-C and VEGF-D can bind to VEGFR-2 inducing angiogenesis (6, 29, 35). The classification, receptor binding patterns and biological functions of the VEGF family are illustrated in Figure 4. However, VEGF is not the only angiogenic factor produced by tumors. Fibroblast growth factor-2 (FGF-2), platelet-derived growth factors (PDGFs), angiopoietins (Ang), hepatocyte growth factor (HGF), and insulin-like growth factors (IGFs) are all frequently produced by malignant cells (1). It seems that tumor-produced angiogenic factors not only individually induce angiogenesis or vasculogenesis *via* their own receptors but also cross-communicate with each other to synergistically induce tumor neovascularization. It is known that FGF-2 and VEGF-A or VEGF-A and Ang-1 could synergistically induce angiogenesis (36, 37). Recent studies in our group have shown that PDGF-BB and FGF-2 can synergistically induce tumor angiogenesis and metastasis (38-40). The underlying mechanisms by which FGF-2 and PDGF-BB synergistically induce tumor vascularization involve up-

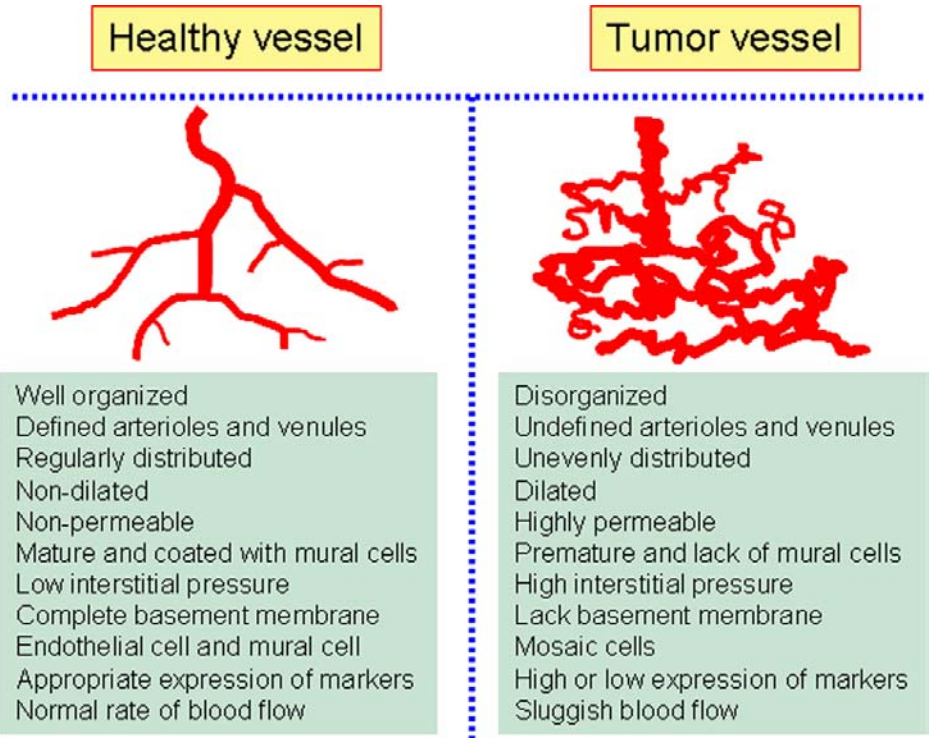

Figure 3. Features of tumor blood vessels. Unlike healthy blood vessels, tumor vessels consist of disorganized, leaky, and primitive vascular networks, which display abnormal functions.

regulation of PDGFRs in endothelial cells by FGF-2 and increased expression of FGFRs in mural cells by PDGF-BB. This reciprocal interaction between two angiogenic factors plays a crucial role in promoting tumor growth and metastasis.

In addition to a positive interplay between various angiogenic factors, some factors negative interaction. For instance, angiopoietin-2 (Ang-2) is a natural antagonist for angiopoietin-1, although both factors bind to the same Tie-2 receptor, primarily expressed on vascular endothelial cells (41). While Ang-1 promotes recruitment of mural cells including pericytes and vascular smooth muscle cells to the newly formed nascent vasculature, Ang-2 can repel mural cells from mature blood vessels, leading to leakiness and the formation of a primitive vasculature (42). Thus, angiopoietins are important regulators for vascular remodeling, permeability and maturation. Another example is the interaction between PlGF and VEGF-A. Although PlGF only binds to VEGFR-1 and does not significantly induce angiogenesis or vascular permeability, it positively and negatively modulates VEGF-A function. When PlGF and VEGF-A are expressed in different cell populations, the homodimeric form of PlGF can compete with VEGF-A for binding to VEGFR-1, allowing more VEGF-A to interact with its functional receptor, VEGFR-2 (30). However when PlGF and VEGF are synthesized in the same cell population, PlGF and VEGF can preferentially form biologically inactive heterodimers, which makes less VEGF-A homodimers available. These early findings have recently been validated by two independent studies (43, 44). Thus, PlGF both positively and negatively modulate VEGF-A function depending upon its temporal and special spatial relation to VEGF-A expression.

New vascular functions of an old class of vascular remodeling factors and their receptor signaling molecules, Notch ligands and their receptor, have recently been reported to play crucial roles in tumor angiogenesis and growth (45-48). Notch ligands and their receptors are involved in arteriogenesis, vascular remodeling, and maturation. Paradoxically, inhibition of Notch signaling evokes suppression of tumor growth accompanied by increased levels of tumor neovascularization (49). These new findings challenge the classical thinking of tumor angiogenesis and tumor growth where more tumor blood vessels would make a tumor growing faster (50). The findings also indicates that vascular functions but not numbers are essential for promoting tumor growth.

In summary, mouse genetic studies have provided important clues for defining new therapeutic targets towards tumor angiogenesis and for the development of anti-angiogenic drugs. Haploid insufficiency of both VEGF-A and Notch ligand, DLL-4, leads to severe vascular defects and lethality during early mouse embryonic development (51-53). Among all genetic deletion studies in mice, VEGF-A and DLL-4 might represent a unique class of genes since the expression must be at critical levels during embryonic development. Similarly, deregulation of their expression levels in tumors

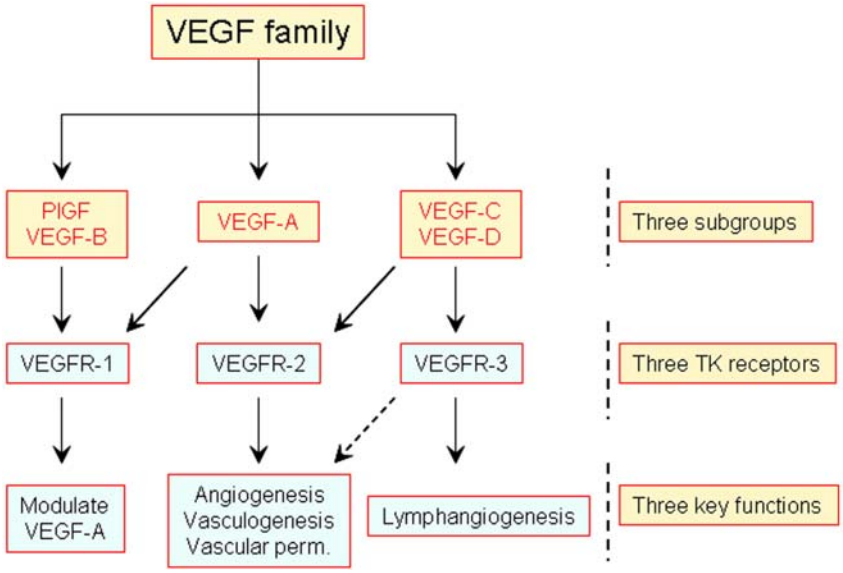

Figure 4. The families of VEGF and VEGFR. According to their receptor binding patterns and angiogenic functions, the VEGF family can be divided into three subgroups. The three VEGFRs are distributed on different cell types and transduce different biological signals. Among many other functions, stimulation of angiogenesis, vascular permeability, and lymphangiogenesis are tree major functions of the VEGF family.

Table 1. Endogenous inhibitors

Proteolytic fragments		**Intact proteins**	
Inhibitor	Ref	Inhibitor	Ref
Angiostatin	5	TSP-1	57
Endostatin	62	Platelet factor-4	85
Kringle 5	60	Gro-beta	86
Kringle 1-5	63	IL-12	87
Tumstatin	65	IP-10	88
Canstatin	79	IL-18	89
Restin	80	Interferon-2α	90
Arrestin	81	Interferon-γ	91
PEX	82	PEDF	91
Prolactin	83	Troponin-1	92
Fibronectin	84		

could lead to malformation of tumor vessels and impaired functions. Indeed, tumors often express VEGF and DLL-4 at high levels, leading to the formation of a disorganized, leaky, and tortuous primitive vasculature (54).

3. ANGIOGENESIS INHIBITION

3.1. Endogenous angiogenesis inhibitors

The original assumption of the existence of endogenous angiogenesis inhibitors in the organism was based on the observation that most adult tissues lack active angiogenesis and that several tissues such as the cornea and cartilage lack vascularization (19, 50, 55). It was hypothesized that tissues produce angiogenesis inhibitors to inhibit vessel growth. Thrombospondin-1 (TSP-1) was the first endogenous angiogenesis inhibitor discovered and it is widely distributed in many tissues and organs (56, 57). Surprisingly, several potent angiogenesis inhibitors have been identified in association with tumor growth (55). For example, angiostatin and endostatin, two potent and specific endogenous angiogenesis inhibitors were discovered in a mouse tumor model and they both reprtesent proteolytic fragments of known proteins in the body (58-62). Following these initial discoveries, several proteolytic fragments exhibiting anti-angiogenic activity have been described, in contrast to the parental protein molecules that lack angiostatic activity (Table 1). Examples of such inhibitors include endostatin, angiostatin, Kringle 5, Kringle 1-5, tumstatin, and vasostatin (59, 61-65). As expected, these inhibitors display potent antitumor activity *in vivo* by blocking tumor angiogenesis. These findings have raised two interesting questions: 1) Why do tumors produce angiogenesis inhibitors as the actively growing tumor tissue recruits new blood vessels?; and 2) Why do proteolytic fragments but not their parental molecules inhibit angiogenesis? Although there are no direct answers to these questions, it is speculated that malignant tissues keep some of the original features of their healthy counterparts which is reflected in the production of angiogenesis inhibitors. Generation of anti-angiogenic proteolytic fragments in tumors probably also reflects the fact that hyper-proteolytic activity exists in malignant tissues and proteolytic degradation is one of the key processes of angiogenesis regulation. Consistent with this notion, matrix metalloproteinases (MMPs) plays crucial roles in regulation of angiogenesis during embryonic development and in pathological settings (66, 67). MMPs can both positively and negatively modulate angiogenesis. For example, while MMP-2 and MMP-9 can cleave circulating large molecules into angiostatic fragments, they can also mobilize a release of angiogenic factors such as VEGF from the matrix (66, 67). , Proteolytic processes are required for basement membrane turnover during neovascularization. The breakdown and reorganization of the endothelial basement membrane occurs, simultaneously

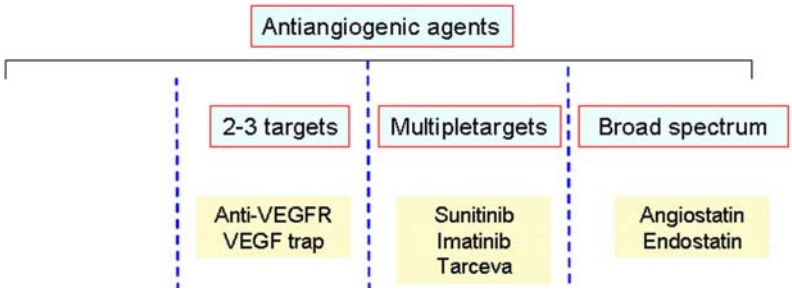

Figure 5. Targets of anti-angiogenic agents. According to their molecular targets, anti-angiogenic agents can be divided into 4 classes: 1) monospecific; 2) 2-3 targeted agents; 3) multitargeted agents; and 4) broad spectrum inhibitors.

at a particular location, in a precisely controlled manner.. This process involves the generation of angiogenesis inhibitors that are required to reduce an overgrowth and sprouting of endothelial cells. In summary, the net balance between pro-angiogenic and anti-angiogenic factors determines the ultimate outcome of neovascularization.

As endogenous angiogenesis inhibitors directly act on endothelial cells, they usually block common pathways of angiogenic signaling (55, 68). For example, endostatin exhibits a broad-spectrum of inhibition of angiogenic pathways triggered by multiple angiogenic factors (69). The molecular mechanisms underlying endothelial inhibition by endogenous angiogenesis inhibitors remain elusive. Unlike pro-angiogenic factors, endogenous angiogenesis inhibitors usually lack specific cell surface receptors although several endothelial cell surface molecules including integrins have been suggested as potential receptors for endogenous angiogenesis inhibitors (69, 70). Perhaps these inhibitors do bind to multiple receptor-like molecules distributed on endothelial cells in order to block multiple signaling pathways triggered by various angiogenic factors. Indeed, gene array analyses have shown that more than 70% of the endothelial cell gene expression is affected by endostatin, suggesting that the molecule has multiple targets on endothelial cells (71).

3.2. Therapeutic approaches targeting the tumor vasculature

Defining the molecular players and their signaling pathways in the regulation of angiogenesis offers outstanding opportunities for therapeutic intervention. The initial success of clinical trials with bevacizumab for the treatment of colorectal cancer patients has set up a milestone in the area of anti-angiogenic cancer therapy (72). Current therapeutic approaches targeting angiogenic pathways are focused on development of anti-VEGF agents, which include VEGF neutralizing antibodies, soluble VEGF receptors, anti-VEGF receptor neutralizing antibodies, tyrosine kinases inhibitors, and anti-intracellular signaling components (1, 18). As expected, almost all these agents are designed towards targeting different levels in the VEGF signaling pathway. Some of the compounds have shown encouraging results in combination with chemotyherapy resulting in prolonged survival. However, preclinical evaluation of anti-VEGF agents is primarily based on their ability to inhibit tumor growth which not necessarily is reflected in prolonged animal survival. There are indications that tumor size not always correlate with survival parameters. Indeed, translation of mouse data into the clinic often fails due to inappropriate animal models that not necessarily reflects the human disease in question.

As discussed above, VEGF is not the only angiogenic factor produced by tumors. At least in mouse tumor models, it has been shown that anti-VEGF agents can cause drug resistance triggering other angiogenic factors (73). Similarly, new anti-angiogenic agents including tyrosine kinase inhibitors are under development for blockage of multiple signaling pathways (74). These inhibitors should repress several signaling systems triggered by different factors. Generally, these multi-targeted anti-angiogenic agents could be more potent than those targeting specifically a single pathway. According to their therapeutic targets, anti-angiogenic agents can be divided into four categories (Figure 5): 1) Monospecific inhibitors. Angiogenesis inhibitors such as bevacizumab that specifically neutralizes only one ligand.; 2) Inhibitors of 2-3 targets. Soluble receptors such as VEGF traps neutralize two or three ligands interacting with the same receptor. In addition, an anti-VEGFR-2 neutralizing antibody would block ligands such as VEGF-A and VEGF-C that interact with the receptor (6); 3) Multi-targeted blockers. Small chemical compounds targeting several receptors and intracellular tyrosine kinases; and 4) Broad-spectrum of inhibitors. Endogenous and exogenous inhibitors such as TNP-470, thalidomide, angiostatin, and endostatin that block common pathways regulating endothelial cell growth (55, 68, 69). The multi-targeted drugs might be more potent and less drug resistant, However, they may produce more side effects because since many of the growth factor signaling pathways affected also play crucial roles in normal cell function. In contrast to kinase inhibitors, endogenous angiogenesis inhibitors such as angiostatin and endostatin are naturally occurring in the body and are less toxic than chemical compounds designed towards specific receptors.

Other therapeutic targets of angiogenesis include mammalian target of rapamycin (mTOR), MMP inhibitors, copper chelators, uPA inhibitors, TSP-1 receptor activators, TNF-alphạinhibitors, neuropilin inhibitors, and angiostatic interleukins or cytokines (Figure 5) (74). These anti-angiogenic agents may, together with growth factor

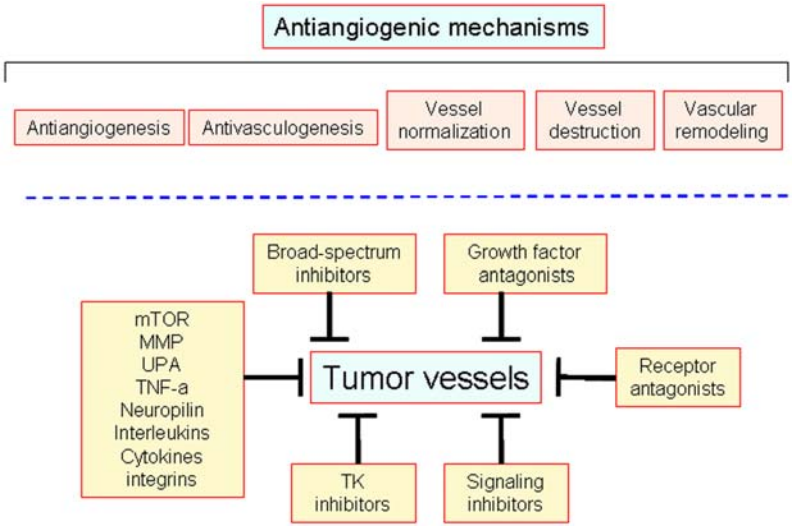

Figure 6. Mechanisms of anti-angiogenic agents. Antiangiogenesis, antivasculogenesis, vessel normalization, vascular destruction, and vascular remodeling are five common mechanisms of anti-angiogenic agents for cancer therapy.

antagonists, lead to synergistic or additive effects affecting different targets.

3.3. Anti-angiogenic mechanisms

According to the original hypothesis, angiogenesis is essential for tumor growth and thus a block of neovascularization should inhibit tumor growth (50). After nearly 40 years, this hypothesis remains nearly as an undisputed dogma as indicated by numerous preclinical and clinical studies. However, as new molecular players and signaling pathways emerge, the complexity of the molecular mechanisms underlying the effects of anti-angiogenic agents increase. There are also considerable differences between animal tumor models and human tumors. Some anti-angiogenic agents exhibiting potent anti-tumor efficacy in animals, do not work to the same extent in humans. For example, an anti-VEGF antibody may display remarkable potency by suppressing a broad-spectrum of tumors in animals (72, 75), yet a similar antibody, as for instance humanized, bevacizumab, show only limited anti-tumor activity when administrated as monotherapy to cancer patients (76). However, bavacizmab in combination with chemotherapeutic drugs may significantly improve patient survival suggesting that also other mechanisms are important to suppress tumor growth. According to current knowledge, there are five possible mechanisms by which anti-angiogenic agents produce beneficial efficacies in cancer patients: 1) Antiangiogenesis. The most straightforward mechanism of anti-angiogenic agents is to simply decrease nutrients and oxygen supply. 2) Antivasculogenesis. Circulating endothelial cells, mainly derived from bone marrow, may contribute to tumor neovascularization and an inhibition of this process should lead to reduced tumor growth (20); 3) Normalization of tumor vessels. Highly permeable and leaky tumor vessels lead to increased IFP, which may restrict blood flow and chemotherapeutic drug delivery (22). Anti-VEGF agents should, when given together with chemotherapeutic drugs, reduce vascular leakage and IFP and thereby increase drug delivery (77). Thus, simultaneous administration of anti-angiogenic agents and cytotoxic drugs could improve the anticancer efficacy of chemotherapy; 4) Vascular destruction. Several angiogenic factors such as VEGF and IGF are also survival factors for the tumor endothelium. Abrogation of their functions by anti-angiogenic agents can lead to tumor vessel regression which has been observed by anti-VEGF agents (78); 5) Vascular remodeling. Recent studies suggest that anti-DLL4 agents can further increase the disorganized tumor vascularizton causing reduced tumor growth. Thus, the Notch signaling system is important in vascular remodeling. Thus the classically used microvascular density as a parameter for monitoring tumor angiogenesis may not necessarily be the best method to assess tumor growth and progression..

4. FUTURE PERSPECTIVES

Tumors produce multiple angiogenic factors and blockage of signaling pathways associated with these stimuli have been shown to have some efficacy in the treatment of human cancers. Although the role of individual factors in regulation of tumor angiogenesis is relatively well characterized, the interplay between these tumor-derived factors remains elusive. Recent studies suggest that the reciprocal interplay between tumor angiogenic factors are far more complex than expected. Thus, inhibition of multiple signaling systems would be more effective and would encounter less probabilities of drug resistance. In addition to growth factor antagonists, endogenous angiogenesis inhibitors are very attractive in therapeutic development. As we still know little about the molecular mechanisms of endogenous angiogenesis inhibitors, it is extremely important to understand how these inhibitors work in the organism. Besides further studies on endogenous angiogenesis inhibitors, it would also be interesting to assess therapeutic efficacies of other angiogenesis inhibitors such as integrin antagonists, MMP

inhibitors, and copper chelators. We are experiencing a truly exciting period of development of potent anti-angiogenic agents that are designed to hit multiple targets of the tumor vasculature. Development of these important therapeutic agents would inevitably bring better therapeutic benefits for a number of human cancers.

5. ACKNOWLEDGEMENTS

Research grants of Yihai Cao´s laboratory are received from the Swedish Research Council, the Swedish Heart and Lung Foundation, the Swedish Cancer Foundation, the Karolinska Institute Foundation, the Karolinska gender research foundation, and the Torsten and Ragnar Söderberg's Foundation, and by European Union Integrated Projects of Angiotargeting Contract 504743 (to Y.C.) and VascuPlug Contract STRP 013811 (to Y.C.).

6. REFERENCES

1. Cao, Y. & Q. Liu: Therapeutic targets of multiple angiogenic factors for the treatment of cancer and metastasis. *Adv Cancer Res*, 97, 203-24 (2007)

2. Brem, S., H. Brem, J. Folkman, D. Finkelstein & A. Patz: Prolonged tumor dormancy by prevention of neovascularization in the vitreous. *Cancer Res*, 36, 2807-12 (1976)

3. Arbiser, J. L., M. A. Moses, C. A. Fernandez, N. Ghiso, Y. Cao, N. Klauber, D. Frank, M. Brownlee, E. Flynn, S. Parangi, H. R. Byers & J. Folkman: Oncogenic H-ras stimulates tumor angiogenesis by two distinct pathways. *Proc Natl Acad Sci U S A*, 94, 861-6 (1997)

4. Indraccolo, S., L. Stievano, S. Minuzzo, V. Tosello, G. Esposito, E. Piovan, R. Zamarchi, L. Chieco-Bianchi & A. Amadori: Interruption of tumor dormancy by a transient angiogenic burst within the tumor microenvironment. *Proc Natl Acad Sci U S A*, 103, 4216-21 (2006)

5. Cao, Y., M. S. O'Reilly, B. Marshall, E. Flynn, R. W. Ji & J. Folkman: Expression of angiostatin cDNA in a murine fibrosarcoma suppresses primary tumor growth and produces long-term dormancy of metastases. *J Clin Invest*, 101, 1055-63 (1998)

6. Cao, Y., P. Linden, J. Farnebo, R. Cao, A. Eriksson, V. Kumar, J. H. Qi, L. Claesson-Welsh & K. Alitalo: Vascular endothelial growth factor C induces angiogenesis *in vivo*. *Proc Natl Acad Sci U S A*, 95, 14389-94 (1998)

7. Hanahan, D. & J. Folkman: Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. *Cell*, 86, 353-64 (1996)

8. Giuriato, S., S. Ryeom, A. C. Fan, P. Bachireddy, R. C. Lynch, M. J. Rioth, J. van Riggelen, A. M. Kopelman, E. Passegue, F. Tang, J. Folkman & D. W. Felsher: Sustained regression of tumors upon MYC inactivation requires p53 or thrombospondin-1 to reverse the angiogenic switch. *Proc Natl Acad Sci U S A*, 103, 16266-71 (2006)

9. Su, W. C., S. C. Shiesh, H. S. Liu, C. Y. Chen, N. H. Chow & X. Z. Lin: Expression of oncogene products HER2/Neu and Ras and fibrosis-related growth factors bFGF, TGF-beta, and PDGF in bile from biliary malignancies and inflammatory disorders. *Dig Dis Sci*, 46, 1387-92 (2001)

10. Cramer, T., Y. Yamanishi, B. E. Clausen, I. Forster, R. Pawlinski, N. Mackman, V. H. Haase, R. Jaenisch, M. Corr, V. Nizet, G. S. Firestein, H. P. Gerber, N. Ferrara & R. S. Johnson: HIF-1alpha is essential for myeloid cell-mediated inflammation. *Cell*, 112, 645-57 (2003)

11. Makino, Y., R. Cao, K. Svensson, G. Bertilsson, M. Asman, H. Tanaka, Y. Cao, A. Berkenstam & L. Poellinger: Inhibitory PAS domain protein is a negative regulator of hypoxia-inducible gene expression. *Nature*, 414, 550-4 (2001)

12. Carmeliet, P., Y. Dor, J. M. Herbert, D. Fukumura, K. Brusselmans, M. Dewerchin, M. Neeman, F. Bono, R. Abramovitch, P. Maxwell, C. J. Koch, P. Ratcliffe, L. Moons, R. K. Jain, D. Collen & E. Keshert: Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. *Nature*, 394, 485-90 (1998)

13. Dameron, K. M., O. V. Volpert, M. A. Tainsky & N. Bouck: Control of angiogenesis in fibroblasts by p53 regulation of thrombospondin-1. *Science*, 265, 1582-4 (1994)

14. Mandriota, S. J., K. J. Turner, D. R. Davies, P. G. Murray, N. V. Morgan, H. M. Sowter, C. C. Wykoff, E. R. Maher, A. L. Harris, P. J. Ratcliffe & P. H. Maxwell: HIF activation identifies early lesions in VHL kidneys: evidence for site-specific tumor suppressor function in the nephron. *Cancer Cell*, 1, 459-68 (2002)

15. Shweiki, D., A. Itin, D. Soffer & E. Keshet: Vascular endothelial growth factor induced by hypoxia may mediate hypoxia-initiated angiogenesis. *Nature*, 359, 843-5 (1992)

16. Cao, Y.: Opinion: emerging mechanisms of tumour lymphangiogenesis and lymphatic metastasis. *Nat Rev Cancer*, 5, 735-43 (2005)

17. Carmeliet, P.: Angiogenesis in life, disease and medicine. *Nature*, 438, 932-6 (2005)

18. Ferrara, N. & R. S. Kerbel: Angiogenesis as a therapeutic target. *Nature*, 438, 967-74 (2005)

19. Langer, R., H. Brem, K. Falterman, M. Klein & J. Folkman: Isolations of a cartilage factor that inhibits tumor neovascularization. *Science*, 193, 70-2 (1976)

20. Lyden, D., K. Hattori, S. Dias, C. Costa, P. Blaikie, L. Butros, A. Chadburn, B. Heissig, W. Marks, L. Witte, Y. Wu, D. Hicklin, Z. Zhu, N. R. Hackett, R. G. Crystal, M. A. Moore, K. A. Hajjar, K. Manova, R. Benezra & S. Rafii: Impaired recruitment of bone-marrow-derived endothelial and hematopoietic precursor cells blocks tumor angiogenesis and growth. *Nat Med*, 7, 1194-201 (2001)

21. Dvorak, H. F.: VPF/VEGF and the angiogenic response. *Semin Perinatol*, 24, 75-8 (2000)

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

23. Mancuso, M. R., R. Davis, S. M. Norberg, S. O'Brien, B. Sennino, T. Nakahara, V. J. Yao, T. Inai, P. Brooks, B. Freimark, D. R. Shalinsky, D. D. Hu-Lowe & D. M. McDonald: Rapid vascular regrowth in tumors after reversal of VEGF inhibition. *J Clin Invest*, 116, 2610-21 (2006)

24. Heldin, C. H., K. Rubin, K. Pietras & A. Ostman: High interstitial fluid pressure - an obstacle in cancer therapy. *Nat Rev Cancer*, 4, 806-13 (2004)

25. Hanahan, D. & R. A. Weinberg: The hallmarks of cancer. *Cell*, 100, 57-70 (2000)

26. Folkman, J.: Looking for a good endothelial address. *Cancer Cell*, 1, 113-5 (2002)

27. Ferrara, N.: The role of VEGF in the regulation of physiological and pathological angiogenesis. *Exs*209-31 (2005)

28. Aase, K., G. von Euler, X. Li, A. Ponten, P. Thoren, R. Cao, Y. Cao, B. Olofsson, S. Gebre-Medhin, M. Pekny, K. Alitalo, C. Betsholtz & U. Eriksson: Vascular endothelial growth factor-B-deficient mice display an atrial conduction defect. *Circulation*, 104, 358-64 (2001)

29. Achen, M. G., M. Jeltsch, E. Kukk, T. Makinen, A. Vitali, A. F. Wilks, K. Alitalo & S. A. Stacker: Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4). *Proc Natl Acad Sci U S A*, 95, 548-53 (1998)

30. Eriksson, A., R. Cao, R. Pawliuk, S. M. Berg, M. Tsang, D. Zhou, C. Fleet, K. Tritsaris, S. Dissing, P. Leboulch & Y. Cao: Placenta growth factor-1 antagonizes VEGF-induced angiogenesis and tumor growth by the formation of functionally inactive PlGF-1/VEGF heterodimers. *Cancer Cell*, 1, 99-108 (2002)

31. Joukov, V., T. Sorsa, V. Kumar, M. Jeltsch, L. Claesson-Welsh, Y. Cao, O. Saksela, N. Kalkkinen & K. Alitalo: Proteolytic processing regulates receptor specificity and activity of VEGF-C. *Embo J*, 16, 3898-911 (1997)

32. Olofsson, B., M. Jeltsch, U. Eriksson & K. Alitalo: Current biology of VEGF-B and VEGF-C. *Curr Opin Biotechnol*, 10, 528-35 (1999)

33. Kanno, S., N. Oda, M. Abe, Y. Terai, M. Ito, K. Shitara, K. Tabayashi, M. Shibuya & Y. Sato: Roles of two VEGF receptors, Flt-1 and KDR, in the signal transduction of VEGF effects in human vascular endothelial cells. *Oncogene*, 19, 2138-46 (2000)

34. Kubo, H., R. Cao, E. Brakenhielm, T. Makinen, Y. Cao & K. Alitalo: Blockade of vascular endothelial growth factor receptor-3 signaling inhibits fibroblast growth factor-2-induced lymphangiogenesis in mouse cornea. *Proc Natl Acad Sci U S A*, 99, 8868-73 (2002)

35. Oh, S. J., M. M. Jeltsch, R. Birkenhager, J. E. McCarthy, H. A. Weich, B. Christ, K. Alitalo & J. Wilting: VEGF and VEGF-C: specific induction of angiogenesis and lymphangiogenesis in the differentiated avian chorioallantoic membrane. *Dev Biol*, 188, 96-109 (1997)

36. Kano, M. R., Y. Morishita, C. Iwata, S. Iwasaka, T. Watabe, Y. Ouchi, K. Miyazono & K. Miyazawa: VEGF-A and FGF-2 synergistically promote neoangiogenesis through enhancement of endogenous PDGF-B-PDGFRbeta signaling. *J Cell Sci*, 118, 3759-68 (2005)

37. Shyu, K. G., H. Chang & J. M. Isner: Synergistic effect of angiopoietin-1 and vascular endothelial growth factor on neoangiogenesis in hypercholesterolemic rabbit model with acute hindlimb ischemia. *Life Sci*, 73, 563-79 (2003)

38. Cao, R., E. Brakenhielm, R. Pawliuk, D. Wariaro, M. J. Post, E. Wahlberg, P. Leboulch & Y. Cao: Angiogenic synergism, vascular stability and improvement of hind-limb ischemia by a combination of PDGF-BB and FGF-2. *Nat Med*, 9, 604-13 (2003)

39. Lu, H., X. Xu, M. Zhang, R. Cao, E. Brakenhielm, C. Li, H. Lin, G. Yao, H. Sun, L. Qi, M. Tang, H. Dai, Y. Zhang, R. Su, Y. Bi, Y. Zhang & Y. Cao: Combinatorial protein therapy of angiogenic and arteriogenic factors remarkably improves collaterogenesis and cardiac function in pigs. *Proc Natl Acad Sci U S A*, 104, 12140-5 (2007)

40. Nissen, L. J., R. Cao, E. M. Hedlund, Z. Wang, X. Zhao, D. Wetterskog, K. Funa, E. Brakenhielm & Y. Cao: Angiogenic factors FGF2 and PDGF-BB synergistically promote murine tumor neovascularization and metastasis. *J Clin Invest*, 117, 2766-77 (2007)

41. Maisonpierre, P. C., 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 & G. D. Yancopoulos: Angiopoietin-2, a natural antagonist for Tie2 that disrupts *in vivo* angiogenesis. *Science*, 277, 55-60 (1997)

42. Thurston, G., C. Suri, K. Smith, J. McClain, T. N. Sato, G. D. Yancopoulos & D. M. McDonald: Leakage-resistant blood vessels in mice transgenically overexpressing angiopoietin-1. *Science*, 286, 2511-4 (1999)

43. Schomber, T., L. Kopfstein, V. Djonov, I. Albrecht, V. Baeriswyl, K. Strittmatter & G. Christofori: Placental growth factor-1 attenuates vascular endothelial growth factor-A-dependent tumor angiogenesis during beta cell carcinogenesis. *Cancer Res*, 67, 10840-8 (2007)

44. Xu, L., D. M. Cochran, R. T. Tong, F. Winkler, S. Kashiwagi, R. K. Jain & D. Fukumura: Placenta growth

factor overexpression inhibits tumor growth, angiogenesis, and metastasis by depleting vascular endothelial growth factor homodimers in orthotopic mouse models. *Cancer Res*, 66, 3971-7 (2006)

45. Hellstrom, M., 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 & C. Betsholtz: Dll4 signalling through Notch1 regulates formation of tip cells during angiogenesis. *Nature*, 445, 776-80 (2007)

46. Noguera-Troise, I., C. Daly, N. J. Papadopoulos, S. Coetzee, P. Boland, N. W. Gale, H. C. Lin, G. D. Yancopoulos & G. Thurston: Blockade of Dll4 inhibits tumour growth by promoting non-productive angiogenesis. *Nature*, 444, 1032-7 (2006)

47. Ridgway, J., 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, F. de Sauvage, G. Plowman & M. Yan: Inhibition of Dll4 signalling inhibits tumour growth by deregulating angiogenesis. *Nature*, 444, 1083-7 (2006)

48. Siekmann, A. F. & N. D. Lawson: Notch signalling limits angiogenic cell behaviour in developing zebrafish arteries. *Nature*, 445, 781-4 (2007)

49. Thurston, G., I. Noguera-Troise & G. D. Yancopoulos: The Delta paradox: DLL4 blockade leads to more tumour vessels but less tumour growth. *Nat Rev Cancer*, 7, 327-31 (2007)

50. Folkman, J.: Tumor angiogenesis: therapeutic implications. *N Engl J Med*, 285, 1182-6 (1971)

51. Carmeliet, P., V. Ferreira, G. Breier, S. Pollefeyt, L. Kieckens, M. Gertsenstein, M. Fahrig, A. Vandenhoeck, K. Harpal, C. Eberhardt, C. Declercq, J. Pawling, L. Moons, D. Collen, W. Risau & A. Nagy: Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. *Nature*, 380, 435-9 (1996)

52. Ferrara, N., K. Carver-Moore, H. Chen, M. Dowd, L. Lu, K. S. O'Shea, L. Powell-Braxton, K. J. Hillan & M. W. Moore: Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. *Nature*, 380, 439-42 (1996)

53. Gale, N. W., M. G. Dominguez, I. Noguera, L. Pan, V. Hughes, D. M. Valenzuela, A. J. Murphy, N. C. Adams, H. C. Lin, J. Holash, G. Thurston & G. D. Yancopoulos: Haploinsufficiency of delta-like 4 ligand results in embryonic lethality due to major defects in arterial and vascular development. *Proc Natl Acad Sci U S A*, 101, 15949-54 (2004)

54. Li, J. L., R. C. Sainson, W. Shi, R. Leek, L. S. Harrington, M. Preusser, S. Biswas, H. Turley, E. Heikamp, J. A. Hainfellner & A. L. Harris: Delta-like 4 Notch ligand regulates tumor angiogenesis, improves tumor vascular function, and promotes tumor growth *in vivo*. *Cancer Res*, 67, 11244-53 (2007)

55. Cao, Y.: Endogenous angiogenesis inhibitors and their therapeutic implications. *Int J Biochem Cell Biol*, 33, 357-69 (2001)

56. Good, D. J., P. J. Polverini, F. Rastinejad, M. M. Le Beau, R. S. Lemons, W. A. Frazier & N. P. Bouck: A tumor suppressor-dependent inhibitor of angiogenesis is immunologically and functionally indistinguishable from a fragment of thrombospondin. *Proc Natl Acad Sci U S A*, 87, 6624-8 (1990)

57. Holland, J. W., D. J. Good, N. P. Bouck & P. J. Polverini: Effect of a naturally occurring inhibitor of angiogenesis on neovascularization *in vivo*. *Northwest Dent Res*, 2, 6-8 (1990)

58. Cao, Y., R. Cao & N. Veitonmaki: Kringle structures and antiangiogenesis. *Curr Med Chem Anticancer Agents*, 2, 667-81 (2002)

59. Cao, Y., A. Chen, S. S. An, R. W. Ji, D. Davidson & M. Llinas: Kringle 5 of plasminogen is a novel inhibitor of endothelial cell growth. *J Biol Chem*, 272, 22924-8 (1997)

60. Cao, Y. & L. Xue: Angiostatin. *Semin Thromb Hemost*, 30, 83-93 (2004)

61. O'Reilly, M. S., T. Boehm, Y. Shing, N. Fukai, G. Vasios, W. S. Lane, E. Flynn, J. R. Birkhead, B. R. Olsen & J. Folkman: Endostatin: an endogenous inhibitor of angiogenesis and tumor growth. *Cell*, 88, 277-85 (1997)

62. O'Reilly, M. S., L. Holmgren, Y. Shing, C. Chen, R. A. Rosenthal, M. Moses, W. S. Lane, Y. Cao, E. H. Sage & J. Folkman: Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. *Cell*, 79, 315-28 (1994)

63. Cao, R., H. L. Wu, N. Veitonmaki, P. Linden, J. Farnebo, G. Y. Shi & Y. Cao: Suppression of angiogenesis and tumor growth by the inhibitor K1-5 generated by plasmin-mediated proteolysis. *Proc Natl Acad Sci U S A*, 96, 5728-33 (1999)

64. Liang, F., L. Dillen, X. Y. Zhang, E. P. Coen, R. Hogue-Angeletti, M. Claeys & W. P. De Potter: Vasostatins, N-terminal products of chromogranin A, are released from the stimulated calf spleen *in vitro*. *Acta Physiol Scand*, 155, 23-30 (1995)

65. Maeshima, Y., A. Sudhakar, J. C. Lively, K. Ueki, S. Kharbanda, C. R. Kahn, N. Sonenberg, R. O. Hynes & R. Kalluri: Tumstatin, an endothelial cell-specific inhibitor of protein synthesis. *Science*, 295, 140-3 (2002)

66. Bergers, G., R. Brekken, G. McMahon, T. H. Vu, T. Itoh, K. Tamaki, K. Tanzawa, P. Thorpe, S. Itohara, Z. Werb & D. Hanahan: Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol*, 2, 737-44 (2000)

67. Zhou, Z., S. S. Apte, R. Soininen, R. Cao, G. Y. Baaklini, R. W. Rauser, J. Wang, Y. Cao & K. Tryggvason: Impaired endochondral ossification and angiogenesis in mice deficient in membrane-type matrix metalloproteinase I. *Proc Natl Acad Sci U S A*, 97, 4052-7 (2000)

68. Nyberg, P., L. Xie & R. Kalluri: Endogenous inhibitors of angiogenesis. *Cancer Res*, 65, 3967-79 (2005)

69. Folkman, J.: Endogenous angiogenesis inhibitors. *Apmis*, 112, 496-507 (2004)

70. Veitonmaki, N., R. Cao, L. H. Wu, T. L. Moser, B. Li, S. V. Pizzo, B. Zhivotovsky & Y. Cao: Endothelial cell surface ATP synthase-triggered caspase-apoptotic pathway is essential for k1-5-induced antiangiogenesis. *Cancer Res*, 64, 3679-86 (2004)

71. Abdollahi, A., P. Hahnfeldt, C. Maercker, H. J. Grone, J. Debus, W. Ansorge, J. Folkman, L. Hlatky & P. E. Huber: Endostatin's anti-angiogenic signaling network. *Mol Cell*, 13, 649-63 (2004)

72. Hurwitz, H., L. Fehrenbacher, W. Novotny, T. Cartwright, J. Hainsworth, W. Heim, J. Berlin, A. Baron, S. Griffing, E. Holmgren, N. Ferrara, G. Fyfe, B. Rogers, R. Ross & F. Kabbinavar: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*, 350, 2335-42 (2004)

73. Casanovas, O., D. J. Hicklin, G. Bergers & D. Hanahan: Drug resistance by evasion of anti-angiogenic targeting of VEGF signaling in late-stage pancreatic islet tumors. *Cancer Cell*, 8, 299-309 (2005)

74. Folkman, J.: Angiogenesis: an organizing principle for drug discovery? *Nat Rev Drug Discov*, 6, 273-86 (2007)

75. Sandler, A., R. Gray, M. C. Perry, J. Brahmer, J. H. Schiller, A. Dowlati, R. Lilenbaum & D. H. Johnson: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*, 355, 2542-50 (2006)

76. Glade-Bender, J., J. J. Kandel & D. J. Yamashiro: VEGF blocking therapy in the treatment of cancer. *Expert Opin Biol Ther*, 3, 263-76 (2003)

77. Winkler, F., S. V. Kozin, R. T. Tong, S. S. Chae, M. F. Booth, I. Garkavtsev, L. Xu, D. J. Hicklin, D. Fukumura, E. di Tomaso, L. L. Munn & R. K. Jain: Kinetics of vascular normalization by VEGFR2 blockade governs brain tumor response to radiation: role of oxygenation, angiopoietin-1, and matrix metalloproteinases. *Cancer Cell*, 6, 553-63 (2004)

78. Polverino, A., A. Coxon, C. Starnes, Z. Diaz, T. DeMelfi, L. Wang, J. Bready, J. Estrada, R. Cattley, S. Kaufman, D. Chen, Y. Gan, G. Kumar, J. Meyer, S. Neervannan, G. Alva, J. Talvenheimo, S. Montestruque, A. Tasker, V. Patel, R. Radinsky & R. Kendall: AMG 706, an oral, multikinase inhibitor that selectively targets vascular endothelial growth factor, platelet-derived growth factor, and kit receptors, potently inhibits angiogenesis and induces regression in tumor xenografts. *Cancer Res*, 66, 8715-21 (2006)

79. Kamphaus, G. D., P. C. Colorado, D. J. Panka, H. Hopfer, R. Ramchandran, A. Torre, Y. Maeshima, J. W. Mier, V. P. Sukhatme & R. Kalluri: Canstatin, a novel matrix-derived inhibitor of angiogenesis and tumor growth. *J Biol Chem*, 275, 1209-15 (2000)

80. Bilbe, G., J. Delabie, J. Bruggen, H. Richener, F. A. Asselbergs, N. Cerletti, C. Sorg, K. Odink, L. Tarcsay, W. Wiesendanger & *et al.*: Restin: a novel intermediate filament-associated protein highly expressed in the Reed-Sternberg cells of Hodgkin's disease. *Embo J*, 11, 2103-13 (1992)

81. Colorado, P. C., A. Torre, G. Kamphaus, Y. Maeshima, H. Hopfer, K. Takahashi, R. Volk, E. D. Zamborsky, S. Herman, P. K. Sarkar, M. B. Ericksen, M. Dhanabal, M. Simons, M. Post, D. W. Kufe, R. R. Weichselbaum, V. P. Sukhatme & R. Kalluri: Anti-angiogenic cues from vascular basement membrane collagen. *Cancer Res*, 60, 2520-6 (2000)

82. Brooks, P. C., S. Silletti, T. L. von Schalscha, M. Friedlander & D. A. Cheresh: Disruption of angiogenesis by PEX, a noncatalytic metalloproteinase fragment with integrin binding activity. *Cell*, 92, 391-400 (1998)

83. Clapp, C., J. A. Martial, R. C. Guzman, F. Rentier-Delure & R. I. Weiner: The 16-kilodalton N-terminal fragment of human prolactin is a potent inhibitor of angiogenesis. *Endocrinology*, 133, 1292-9 (1993)

84. Grant, M. B., S. Caballero, D. M. Bush & P. E. Spoerri: Fibronectin fragments modulate human retinal capillary cell proliferation and migration. *Diabetes*, 47, 1335-40 (1998)

85. Tobelem, G.: Tumor angiogenesis. *Nouv Rev Fr Hematol*, 32, 405-6 (1990)

86. Cao, Y., C. Chen, J. A. Weatherbee, M. Tsang & J. Folkman: gro-beta, a -C-X-C- chemokine, is an angiogenesis inhibitor that suppresses the growth of Lewis lung carcinoma in mice. *J Exp Med*, 182, 2069-77 (1995)

87. Voest, E. E., B. M. Kenyon, M. S. O'Reilly, G. Truitt, R. J. D'Amato & J. Folkman: Inhibition of angiogenesis *in vivo* by interleukin 12. *J Natl Cancer Inst*, 87, 581-6 (1995)

88. Strieter, R. M., P. J. Polverini, S. L. Kunkel, D. A. Arenberg, M. D. Burdick, J. Kasper, J. Dzuiba, J. Van Damme, A. Walz, D. Marriott & *et al.*: The functional role of the ELR motif in CXC chemokine-mediated angiogenesis. *J Biol Chem*, 270, 27348-57 (1995)

89. Bjorndahl, M. A., R. Cao, J. B. Burton, E. Brakenhielm, P. Religa, D. Galter, L. Wu & Y. Cao: Vascular endothelial

growth factor-a promotes peritumoral lymphangiogenesis and lymphatic metastasis. *Cancer Res*, 65, 9261-8 (2005)

90. Hiromatsu, Y., M. Sato, K. Yamada & K. Nonaka: Inhibitory effects of nicotinamide on recombinant human interferon-gamma-induced intercellular adhesion molecule-1 (ICAM-1) and HLA-DR antigen expression on cultured human endothelial cells. *Immunol Lett*, 31, 35-9 (1992)

91. Dawson, D. W., O. V. Volpert, P. Gillis, S. E. Crawford, H. Xu, W. Benedict & N. P. Bouck: Pigment epithelium-derived factor: a potent inhibitor of angiogenesis. *Science*, 285, 245-8 (1999)

92. Moses, M. A., D. Wiederschain, I. Wu, C. A. Fernandez, V. Ghazizadeh, W. S. Lane, E. Flynn, A. Sytkowski, T. Tao & R. Langer: Troponin I is present in human cartilage and inhibits angiogenesis. *Proc Natl Acad Sci U S A*, 96, 2645-50 (1999)

93 Fischer, C., B.Jonckx, M. Mazzone, S. Zacchigna, S.Loges, L.Pattarini, E.Chorianopoulos, L. Liesenborghs, M.Koch, D M.e Mol, M. Autiero, S. Wyns, S.Plaisance, L. Moons, N.van Rooijen, M.Giacca, JM.Stassen, M. Dewerchin, D. Collen, & P. Carmeliet P. Anti-PlGF inhibits growth of VEGF (R)-inhibitor-resistant tumors without affecting healthy vessels. Cell. 131, 463-75 (2007)

Key Words: Angiogenesis, Cancer, Metastasis, Growth Factor, Inhibitor, Review

Send correspondence to: Yihai Cao, Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, 171 77 Stockholm, Sweden, Tel: 46-8-5248 7596, Fax: 46-8-31 94 70, E-mail: yihai.cao@ki.se

http://www.bioscience.org/current/vol14.htm