Angiogenesis: a curse or cure?

K Gupta, J Zhang

Angiogenesis, the growth of new blood vessels is essential during fetal development, female reproductive cycle, and tissue repair. In contrast, uncontrolled angiogenesis promotes the neoplastic disease and retinopathies, while inadequate angiogenesis can lead to coronary artery disease. A balance between pro-angiogenic and antiangiogenic growth factors and cytokines tightly controls angiogenesis. Considerable progress has been made in identifying these molecular components to develop angiogenesis based treatments. One of the most specific and critical regulators of angiogenesis is vascular endothelial growth factor (VEGF), which regulates endothelial proliferation, permeability, and survival. Several VEGF based treatments including anti-VEGF and anti-VEGF receptor antibodies/agents are in clinical trials along with several other antiangiogenic treatments. While bevacizumab (anti-VEGF antibody) has been approved for clinical use in colorectal cancer, the side effects of antiangiogenic treatment still remain a challenge. The pros and cons of angiogenesis based treatment are discussed.

Angiogenesis fascinated the minds of many for centuries. Leonardo da Vinci speculated that the vasculature developed from the heart, like a tree from the seed and compared the sprouting roots with the capillary meshwork and the tree trunk with the aorta and arteries. However, the term angiogenesis was coined by John Hunter in 1787, to describe the growth of new blood vessels (http://www.angio.org). Despite its discovery centuries ago, angiogenesis research remained underexplored. In 1971 Judah Folkman proposed the hypothesis that tumour vascularization is angiogenesis dependent. Since then publications on angiogenesis have been spiralling in a logarithmic fashion.

ANGIOGENESIS

Development of blood vessels from in situ differentiating endothelial cells (EC) is called vasculogenesis, whereas sprouting of new blood vessels from the pre-existing ones is termed angiogenesis or neovascularisation. All blood vessels are lined with endothelial cells that must proliferate to form new vessels, migrate to reach remote targets, and survive to limit attrition and senescence. On the other hand the host microenvironment must convey signals for cells to multiply and avoid apoptosis. Disruption of endothelial growth constraints, acquisition of a motile phenotype, dynamic modification of the coupling between cells and the extracellular matrix (ECM), tube formation, and resistance to programmed cell death define the complex, multi-step process of angiogenesis. Successful execution of this process depends upon the delicate balance of growth promoting factors and growth inhibitory factors surrounding the endothelium (table 1).

ANGIOGENESIS PROMOTING GROWTH FACTORS

Although a vast variety of growth factors and cytokines act as inducers of angiogenesis, vascular endothelial growth factor (VEGF) is the most specific growth factor for vascular endothelium.

Vascular endothelial growth factor/vascular permeability factor (VEGF/VPF)

The key feature of the VEGF family of growth factors is their specificity for endothelial cells. VEGF is not a single protein, but a small menagerie of several peptide growth factors of different amino acids in length and type. It was first discovered in 1983 as vascular permeability factor. In 1989 it was characterised and sequenced by different groups of investigators as an endothelial cell mitogen and called vascular endothelial growth factor. It differs from the earlier described endothelial mitogen fibroblast growth factor (FGF). VEGF is a secretory protein with a signal peptide, whereas, genes for FGF do not encode for conventional secretory signal peptide and therefore it is believed that FGF remains sequestered in the cells. Because of its diffusibility, VEGF seemed to be a more dynamic regulator of angiogenesis. Since then, several isoforms generated by alternative splicing of a single gene consisting of eight exons and homologs of VEGF have been discovered and ascribed distinct receptors and vascular functions (table 2).

VEGF is required for normal embryonic vasculogenesis and angiogenesis was shown by two separate landmark studies. They found that inactivation of a single allele of VEGF in mice resulted in embryonic lethality. The VEGF+/− embryos experienced growth retardation and other developmental abnormalities that could not be compensated by other VEGF family members.

Abbreviations: EC, endothelial cell; ECM, extracellular matrix; VEGF, vascular endothelial growth factor; VPF, vascular permeability factor; FGF, fibroblast growth factor; PLGF, placenta derived growth factor; TSP, thrombospondin; PEGF, pigment epithelium derived growth factor; MMP, matrix metalloproteinases; COX-2, cyclooxygenase-2; AMD, age related macular degeneration; PTK, protein tyrosine kinase; HIF, hypoxia inducible transcription factor

members. This led to a turning point in angiogenesis research. Thus VEGF and their receptors have been the most "wanted" target for angiogenic/anti-angiogenic therapy in angiogenesis dependent pathological conditions.

VEGF receptors are type III receptor tyrosine kinases, VEGFR1 (Flt-1; fms-like tyrosine kinase) and VEGFR2 (Flk-1/KDR; kinase insert domain containing receptor), are expressed primarily on endothelial cells. Genie targeting studies show that both VEGFR1 and VEGFR2 are essential for development of the embryonic vasculature in mice. Subsequently two other VEGF receptors VEGFR3 (Flt-4), mainly expressed on lymphatic vessels and neuropilin, also expressed on neuronal cells, were also identified (table 2). Flk-1 is considered the most potent mitogenic receptor and neuropilin aids in the binding of VEGF to Flk-1, thus increasing its mitogenic capability. VEGFR3 binds to VEGF-C and VEGF-D to control the growth and maintenance of lymphatic vessels. VEGFR1 is critical in the recruitment of haematopoietic precursors and monocytes to the pathological pro-inflammatory sites and promoting angiogenesis.

**Placenta derived growth factor (PLGF)**

PLGF encodes three isoforms: PLGF-1, PLGF-2, PLGF-3. PLGF can bind both VEGFR1 and VEGFR-2. Flt1 and PLGF have a potent and persistent effect on vessel formation. PLGF stimulates the formation of vessels in ischaemic heart disease, and anti-Flt1, by blocking PLGF effect, can inhibit the neovascularisation in the ischaemic retina and tumours. PLGF and Flt1 also play a critical part in the recruitment and homing of circulating endothelial progenitor cells (CEPs) and support monocyte recruitment for vasculogenesis at the site of ischaemia and in tumours.

**ANGIOGENESIS INHIBITORS**

Table 1 describes several inhibitors of angiogenesis. The first and the most recently discovered naturally occurring anti-angiogenesis inhibitory proteins are described.

Thrombospondin (TSP), a 450 kDa matrix cellular protein was the first antiangiogenic factor discovered in 1990s. We found that TSP prevented VEGF induced angiogenesis by directly binding to it and by interfering with its binding to cell surface heparan sulphates. Because of the large size (450 kDa), poor bioavailability, and proteolytic breakdown, clinical use of TSP is limited. However, ABT-510, a mimetic peptide sequence of TSP possessing antiangiogenic activity is in phase II clinical trials.

Pigment epithelium derived growth factor (PEDF) is a secreted glycoprotein with molecular weight of 50 kDa. It is a member of the serpin superfamily of serine protease inhibitors and is the most recently discovered antiangiogenesis factor. PEDF can promote neuronal cell survival but acts as a potent inhibitor of angiogenesis. Wang et al reported that adenovirus mediated gene transfer of PEDF could significantly reduce tumour neoangiogenesis and tumour growth in animal models with hepatocellular carcinoma and Lewis lung carcinoma.

**ANGIOGENESIS IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS**

While unregulated angiogenesis is seen in several pathological conditions including psoriasis, nephropathy, cancer, and retinopathy, it is essential for embryonic development, menstrual cycle, and wound repair. The dysregulated and excessive vessel growth can have a significant impact on health, and contribute to various diseases, such as rheumatoid arthritis, obesity, infectious diseases, etc. However, it can also be therapeutic in the treatment of some diseases. Some of the important pathological conditions where it acts as a cause or cure are discussed.

**Tumour growth and metastasis**

Progression of tumour growth and metastasis are angiogenesis dependent. After the initial neoplastic transformation, the tumour cells undergo further genetic changes resulting in selection of dominant clones with distinct growth advantage and metastatic potential. There is an active interaction between the tumour and the blood vessels. Classic studies by Folkman et al in the 1970s showed that tumours cannot grow beyond 1 mm or 2 mm without the new blood vessels. This process is now referred to as an angiogenic switch. It is indeed tilting the balance towards pro-angiogenic tumour microenvironment comprised of hypoxia, increased growth promoting factors/cytokines, decreased antiangiogenic factors, secretion of matrix metalloproteinases (MMPs), and increased cyclooxygenase-2 (COX-2). More recently proposed mechanisms suggest that in addition to pre-existing endothelial cells, marrow derived endothelial and haematopoietic precursor cells can be mobilised and incorporated into the newly formed tumour vessels.

**Ocular angiogenesis**

Angiogenesis plays a central part in the visual impairment attributable to retinopathy in diabetes, sickle cell disease, retinopathy of prematurity, retinal vascular occlusion, and in age related macular degeneration (AMD). In diabetes hyperglycaemia results in retinal microvascular occlusion.
and ischaemia, which can promote angiogenesis because of subsequent hypoxia induced increase in angiogenic growth factors. Pathogenesis of AMD is not well understood but involves abnormalities of the extracellular matrix in Bruch’s basement membrane. Choroidal neovascularisation in this context may be the result of hypoxia of overlying retinal pigment epithelial cells, attributable either to the thickening of Bruch’s membrane or to abnormalities of choroidal perfusion, leading to the expression of pro-angiogenic cytokines. Laser pan-retinal photocoagulation is presently the conventional treatment for these conditions. However, it may not be effective in all cases and may have side effects. Newer treatments including recombinant adeno associated virus mediated local gene transfer of VEGF inhibitors, inhibitors of intracellular signalling cascades, and use of endogenous inhibitors such as pigment epithelium derived growth factor (PEDF) seem to be more promising.

THERAPEUTIC ANGIOGENESIS
In tissue remodelling
Recently stem cell derived vascular cells or endothelial progenitor cells (EPCs) have attracted significant attention because of their capability for (re)vascularisation called vasculogenesis. Vascularisation resembles the embryological process where the haematopoietic/endothelial progenitors, “haemangioblasts” differentiate into blood cells as well as blood vessels. These endothelial precursors in an adult are derived primarily from bone marrow but increasing evidence is accumulating regarding their tissue specific origins. These precursors, whether embryonic or adult, may have no or little contribution physiologically in an adult, but seem promising in organ repair and tissue remodelling and promoting tumour growth. It has been shown that liver organogenesis is promoted by endothelial cells before vascular function.

In cardiovascular disease
Angiogenesis is even more critical in cardiovascular disease. Various angiogenic agents are in clinical trials for treating ischaemic heart disease. However, one growth factor may not be sufficient by itself, but may require additional growth promoting cytokines. VEGF and PLGF have been shown to stimulate angiogenesis and collateral growth with comparable efficiency in the ischaemic heart and limb. This and other studies show that additional mechanisms including the recruitment of myeloid progenitors and haematopoietic precursors are also required in addition to angiogenic agents to stimulate the growth of new vessels in the ischaemic tissue. The formation of new vessels by tissue engineering holds promise to regenerate vessels for cardiac collateralisation and in vascular healing.

In wound healing
The formation of new blood vessels provides a route for oxygen and nutrient delivery, as well as a conduit for components of the inflammatory response during the healing of wounds. Pro-angiogenic treatments have shown remarkable promise in the healing of wounds in pathological conditions. Kirchner et al reported that topical use of VEGF had 50% improvement in time for wound healing in diabetic mice. Galeano et al also suggested VEGF gene transfer might be a new approach to treat wound healing disorders associated with diabetes. It is encouraging that recombinant platelet derived growth factor-BB (rPDGF-BB) has been approved to treat diabetic neuropathic foot ulcers. Table 3 shows angiogenesis based experimental/clinical trial treatment for wound healing.

THERAPEUTIC AGENTS IN ANGIOGENESIS
DEPENDENT PATHOLOGICAL DISEASES
Since the 1990s there has been a voluminous rise in antiangiogenic treatments and several angiogenesis inhibitors are in pre-clinical/clinical trials (table 4). Based on their mechanism of action, angiogenesis based treatment is classified into:

Exogenous or endogenous inhibitors of angiogenic growth factors or their receptors
These include proteins, cytokines, and antibodies that directly bind to the growth factor or its receptor. One of the endogenous proteins discussed in this review is TSP. Others are described in table 1. These proteins by themselves may be too large and subject to proteolysis. Therefore, peptide sequences with antiangiogenic activity derived from these proteins are being developed, for example, ABT-510, a peptide sequence from type 1 repeats domain of TSP. Several antibodies of growth factors and their receptors, including a wide array of VEGF and VEGF receptor antibodies, are showing promise in pre-clinical studies and clinical trials (table 4). Bevacizumab, an antibody to VEGF, has been approved for clinical use and is discussed later in this review.

Inhibitors of endothelial cell growth and survival
Angiogenesis depends upon endothelial proliferation and survival. Cancer as a disease is characterised by deregulated proliferation and survival due to dysregulated upregulation of cell cycle protein cyclin D and survival signal Akt. Inhibitors of cell proliferation and/or survival include agents that act

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### Table 2 VEGF family of proteins, receptors, and their function

<table>
<thead>
<tr>
<th>VEGF isoforms/homologues</th>
<th>Receptor(s)</th>
<th>Functionality</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF 121</td>
<td>Flk-1, Flk-1/KDR</td>
<td>Angiogenesis, lower bioactivity as compared with others</td>
</tr>
<tr>
<td>VEGF 165</td>
<td>Flk-1, Flk-1/KDR NRP1, NRP2</td>
<td>Angiogenesis, optimal characteristics of bioavailability and biological potency</td>
</tr>
<tr>
<td>VEGF 189</td>
<td>Flk-1, Flk-1/KDR</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>VEGF 206</td>
<td>Flk-1, Flk-1/KDR</td>
<td>Angiogenesis</td>
</tr>
<tr>
<td>VEGF-B</td>
<td>Flk-1</td>
<td>Main role is in the cardiovascular system</td>
</tr>
<tr>
<td>VEGF-C</td>
<td>Flk-1, Flk-4, NRP2</td>
<td>Lympangiogenesis, metastatic spread</td>
</tr>
<tr>
<td>VEGF</td>
<td>Flk-1, Flk-4</td>
<td>Angiogenesis, lymphangiogenesis, metastatic spread</td>
</tr>
<tr>
<td>VEGF-E (viral homologue)</td>
<td>Flk-1, Flk-4</td>
<td>Mitogen, permeability</td>
</tr>
<tr>
<td>PLGF</td>
<td>Flk-1, Flk-1/KDR NRP1 (activates VEGFR2)</td>
<td>Reconstitution of haematopoiesis, angiogenesis, permeability</td>
</tr>
</tbody>
</table>

The understanding of VEGF family members and their interactions with specific receptors has been used to develop angiogenesis based treatments. PLGF, not from family of proteins but interacts with VEGF receptors. NRP, neurophilin that is also present on neuronal cells. Flk-1/KDR (kinase insert domain containing receptor); Flt (fms-like tyrosine kinase).
Angiogenesis

**Table 3** Angiogenesis based treatments in experimental and clinical trial therapy for wound healing

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Status</th>
<th>Conclusion</th>
<th>Reference or web site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regranex 0.01% (recombinant platelet derived growth factor-BB, hPDGF-BB)</td>
<td>Stimulates migration of cells to the ulcer site</td>
<td>FDA approved</td>
<td>Treatment of diabetic foot ulcers</td>
<td><a href="http://www.angio.org/researcher/library/library.html">http://www.angio.org/researcher/library/library.html</a> Emeryville, CA</td>
</tr>
<tr>
<td>PDGF-B/AdS5</td>
<td>Gene therapy</td>
<td>Phase I trial</td>
<td>The goal of first part of the trial is to determine the maximum tolerated dose. The second part of the trial is to evaluate the safety and biological feasibility in a standard 24 week trial for treatment of a venous leg ulcer.</td>
<td><a href="http://clinicaltrials.gov/ct/show/NCT00000431?order=55">http://clinicaltrials.gov/ct/show/NCT00000431?order=55</a></td>
</tr>
<tr>
<td>Adenoviral vector expressing VEGF-A</td>
<td>Gene therapy</td>
<td>Experimental therapy</td>
<td>VEGF-A gene transfer may cause defective healing in a rodent model</td>
<td>Tarkka et al.60</td>
</tr>
<tr>
<td>Adeno-associated virus expressing the 165-amino acid isoform of VEGF-A</td>
<td>Gene therapy</td>
<td>Experimental therapy</td>
<td>VEGF 165 gene transfer improved wound healing in diabetic mice through the stimulation of angiogenesis and lymphangiogenesis, re-epithelialisation, synthesis and maturation of extracellular matrix</td>
<td>Galiano et al.63</td>
</tr>
<tr>
<td>VEGF 165</td>
<td>Topical use</td>
<td>Experimental therapy</td>
<td>VEGF showed significant healing in wounds in diabetic mice compared with control</td>
<td>Poonawala et al.66</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Topical use</td>
<td>Phase I</td>
<td>Stimulates angiogenesis, cell proliferation, nitric oxide synthase signalling and wound healing in ischemic wounds in rats</td>
<td>Gal et al.67</td>
</tr>
</tbody>
</table>

*All the above treatments are based on growth promoting, angiogenesis promoting factors except for hydromorphone, which is an opioid analgesic.*

directly on these processes in endothelium or indirectly by stimulating the activation or release of another protein. Some of the antiangiogenic agents that act directly are angiotatin, arresten, endostatin, 2-methoxyestradiol, etc (table 3). Indirect antiangiogenic agents, such as herceptin, inhibit the secretion of pro-angiogenic factors VEGF, angiopeptin-1, and TGF-β and upregulate the inhibitory protein TSP-1, which lead to the inhibition of endothelial proliferation and survival.

**Inhibitors targeting the basement membrane and extracellular matrix**

One of the cardinal features for endothelial proliferation, migration, and survival is the EC-matrix interaction. Cell surface integrins αβ3 and other integrins mediate this interaction. Blockers of these integrins and cell-matrix interaction can potentially block angiogenesis. Some of the blockers in clinical trials are constatin, tumstatin, and vitaxin. Other of these are currently under clinical trials and their outcome remains to be known.

**Inhibitors of angiogenic signalling pathway**

Oncogenic participants in the angiogenic signalling pathways include protein tyrosine kinase (PTK), MAPK/ERK, Akt, Bcl-2, p53, and cell cycle proteins that promote cell proliferation and survival. These are reasonably specific targets to inhibit angiogenesis and have led to the development of small molecular size PTK inhibitors for the treatment of cancer. The PTK inhibitor, Gleevac (imatinib mesylate) specifically targets the BCR-Abl and c-kit tyrosine kinases. PTK inhibitors bind to the ATP binding site of the receptor, and thus prevent their subsequent phosphorylating capability. These are low molecular weight compounds and thus non-immunogenic. Other PTK inhibitors that specifically interfere with angiogenesis are VEGF R2 selective, SU5416, PTK 787, and ZD6474. Therefore, these agents have been more successful than others as angiogenic agents.

**RATIONALE FOR ANGIOGENESIS BASED TREATMENTS IN CANCER**

Most of the development in antiangiogenic treatment is targeted towards cancer because of tremendous heterogeneity of different cancers and only one common feature of increased angiogenesis among different cancers. Some of the major advantages of angiogenesis based treatment over others are:

1. A single vessel provides the nutrition for thousands of tumour cells and has to be damaged at only one point to block blood flow upstream and downstream.
2. A change of shape of local initiation of blood coagulation may be sufficient, other than killing the endothelial cells.
3. The endothelial cell is a normal diploid cell, which is unlikely to acquire genetic mutations that render it drug resistant.
4. Blood flow, a surrogate marker for biological activity, is measurable in the clinic.
5. Temporary effects on vascular function may be sufficient to kill the endothelial cells.

**LIMITATIONS OF ANGIOGENESIS BASED TREATMENTS**

Most of the angiogenesis based treatments have worked in experimental rodent models but have not been successful in clinical trials. First of all, angiogenesis treatments target actively proliferating endothelial cells. However, the relative number of proliferating EC is far smaller in human tumours than in rodent tumour models. Mature vessels in human tumour at any given time may not undergo regression with the conventional antiangiogenic agents. Thus, additional markers associated specifically with specific pathological angiogenesis need to be identified. Secondly, multiple growth factors, receptors, and other components of the microenvironment support angiogenesis. Therefore, treatment targeted to a single factor may not be completely effective. Thirdly, vasculature is tissue and/or tumour type specific. Moreover, vascular mimicry—where the tumour vasculature presents genomic and phenotypic similarities with that of the tumour itself—makes the tumour microvasculature more unpredictable than it is perceived to be. Fourthly, the drug delivery to the ischaemic site can be a major limiting factor, specifically without any tools to monitor the site specific drug availability within the tumour. Moreover, it is not yet feasible to monitor the angiogenenic response in the patients. However, with the recent advances in magnetic resonance imaging it may be possible to do vascular imaging in patients.

In addition, angiogenesis based treatment is more effective in small tumours than advanced cancers; however, most of the...
prevailing clinical trials are carried out in the setting of advanced disease. Moreover, there is still concern about the effect on physiological forms of angiogenesis in various situations. Thus, wound healing would be adversely affected in a cancer patient receiving antiangiogenic drugs, as reproductive angiogenesis would be. Antiangiogenic treatment is most effective in small primary tumour and metastasis with a good blood supply. Different kinds of cancers should follow an individual strategy for angiogenesis based treatment. For instance, breast cancer can release more, and different types of pro-angiogenic proteins with passage of time, while high grade giant cell tumours and angioblastomas produce only or mainly β-FGF. Also, endothelium is genetically stable, so the treatment can be repeated. Duration of treatment is presently unclear, but many propose long term maintenance. Several modes of drug delivery including metronomic delivery at spaced intervals alternating with chemotherapeutic combinations are in progress. Most of these treatments hold promise but will have to be clinically tested for different kinds and different stages of tumour growth. Despite these limitations, several angiogenesis based treatments hold promise in clinical trials and two have been approved for clinical use (table 4), which are described below.

FOOD AND DRUG ADMINISTRATION (FDA) APPROVED ANGIOGENESIS BASED TREATMENTS

Avastin

Bevacizumab (commercially called Avastin) is the first approved anticancer agent developed on angiogenesis based treatment. Bevacizumab is a recombinant humanised monoclonal antibody directed against VEGF. It has shown significant activity in the treatment of a number of solid tumours in clinical trials. It was significantly effective when used in combination with fluorouracil based chemotherapy and led to improvement in overall response rates, time to progression, and survival in patients with metastatic colon cancer. Bevacizumab and IFL (irinotecan, fluorouracil, leucovorin) chemotherapy regimen showed an increase in median survival by 4.7 months, in progression free survival by 4.36 months and in overall response rates (complete and partial responses) by 10.2%, as compared with IFL plus placebo. Most frequent adverse effects associated with bevacizumab in both phase II and III clinical trials were hypertension, bleeding episodes, and thrombotic events and proteinuria. Therefore, use of bevacizumab warrants caution while being used in patients with hypertension, thromboembolism, bleeding, or pre-existing proteinuria.

Regranex

Regranex 0.01% (recombinant platelet derived growth factor-BB, rPDGF-BB, becaplermin, Ortho-McNeil Pharmaceuticals product) is approved by FDA for the treatment of diabetic neuropathic foot ulcers. Based on the preclinical/clinical outcome of angiogenesis based treatment, we are cautiously optimistic that targeting angiogenesis combined with chemotherapy or radiotherapy will eventually enter the clinics to treat the cancer.

Table 4  Angiogenesis inhibitors in pre-clinical/clinical trials

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Mechanism</th>
<th>Phase-clinical/clinical trial</th>
<th>Company and reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTK787/ZK225</td>
<td>Black VEGF</td>
<td>Phase I against advanced cancers, glioblastoma and Kaposi’s sarcoma</td>
<td>Novartis, East Hanover, NJ</td>
</tr>
<tr>
<td>Rhu Mab VEGF</td>
<td>Monoclonal antibody against VEGF</td>
<td>Phase II metastatic renal cell cancer, phase II with chemotherapy in untreated advanced colorectal, metastatic breast</td>
<td>Genentech, San Francisco, CA</td>
</tr>
<tr>
<td>SU6668</td>
<td>Blocks VEGF-R, FGF-R</td>
<td>Currently in phase II clinical trial</td>
<td>Sugen, S. San Francisco, CA</td>
</tr>
<tr>
<td>SU11248</td>
<td>Multi-targeted kinase inhibitor</td>
<td>Phase I clinical trial</td>
<td></td>
</tr>
<tr>
<td>IMC-1121b Op-547,632</td>
<td>Black VEGF signalling</td>
<td>Phase I in advanced solid tumours.</td>
<td></td>
</tr>
<tr>
<td>Angiozyme</td>
<td>Targets VEGF-R and -R1</td>
<td>Phase II breast and colorectal cancer</td>
<td>Ribzyme Pharmaceuticals, Boulder, CO</td>
</tr>
<tr>
<td>Endostatin</td>
<td>EC proliferation and migration</td>
<td>Phase II neuroendoctrine tumours and metastatic melanoma</td>
<td>EntreMed, Rockville, MD <a href="http://entremed.com">http://entremed.com</a></td>
</tr>
<tr>
<td>Angiostatin</td>
<td>ATP synthase, inhibits EC proliferation</td>
<td>Ongoing: phase I clinical trials for advanced solid tumours and phase II for multiple myeloma. Completed: phase II - prostate</td>
<td></td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Decrease TNFα, bFGF, VEGF</td>
<td>Phase I malignant glioma, phase II/III for advanced melanoma, phase II ovarian, metastatic prostate, phase II with chemotherapy against solid tumours, adjuvant study in recurrent or untreated colorectal cancer; myeloidiosis with myeloid metaplasia, follicular lymphoma myelodysplastic syndrome, refractory ovarian, phase II gynaecological sarcomas, liver cancer; metastatic melanoma, CLI, multiple myeloma; phase III non-small cell lung, non-metastatic prostate, refractory multiple myeloma, renal cancer.</td>
<td>Celgene Warren, NJ</td>
</tr>
<tr>
<td>CAI</td>
<td>Inhibitor of calcium influx</td>
<td>Phase I studies in combination against solid tumours, phase II ovarian cancer, metastatic renal cell cancer. Phase I/II prostate cancer; phase I/II cervical cancer; phase II basal cell cancer; metastatic breast cancer.</td>
<td>National Cancer Institute, Bethesda, MD</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>COX-2 inhibitor</td>
<td></td>
<td>Pharmacia Peapack, NJ</td>
</tr>
</tbody>
</table>

More complete information on the above clinical trials is available on individual company web sites or on the web sites described above. COX-2, cyclooxygenase 2; EC, endothelial cell.
SUMMARY OF OTHER ANGIOGENESIS BASED CLINICAL TRIALS AND FDA APPROVED DRUGS

Up to the end of February, 2004, there are 171 active anti-angiogenesis clinical trials sponsored by the NCI, university/institutions, and other pharmaceutical companies, among which are 28 phase III or IV clinical trials. Another 178 clinical trials have been closed. Some drugs have been proved to be ineffective and suspended for further clinical trials. For example, SU5416, which showed promise in animal studies as well as early clinical trials, has been shelved because of a lack of efficacy in phase III trials. Marimastat, prirnomastat (AG3340), and BAY 12-9566 are three MMP inhibitors that have proved not to be effective in phase III clinical trials.

OTHER PROMISING ANGIOGENESIS BASED TREATMENTS

Gene therapy

A variety of viral and non-viral methods are being assessed: retroviruses, adenoviruses, cationic liposomes. Delivery of these genes and maintenance of long term gene expression at high levels remains challenging in vivo. In terms of the patients with retinal neovascular disease, the high systemic doses required to achieve therapeutic intraocular levels would be expensive and hazardous, because of the blood-retinal barrier. In contrast, gene treatment provides the possibility of localised, targeted, sustained delivery of therapeutic proteins into an appropriate intraocular site. Brainbril et al showed that inhibition of VEGF by local gene transfer of its soluble receptor sFlt-1 consistently reduces neovascularisation by 78.1 and 79.2%, respectively, in a mouse model of hypoxia induced neovascularisation.52

HIFs

Hypoxia is a strong stimulus for angiogenesis in numerous disorders, and it can switch on the expression of several angiogenic factors including VEGF, nitric oxide synthase, PDGF etc, via activating hypoxia inducible transcription factors (HIFs). HIF-1 is a αβ-heterodimer that was first recognised as a DNA binding factor. Both HIF-α and β subunits exist as a series of isoforms encoded by distinct genetic loci. Among three isoforms of HIF-α, HIF-1α and HIF-2α are more closely related with hypoxia response elements to induce transcriptional activity.53 Several strategies have been carried out in the experimental treatment based on HIF-α. However, the most exciting possibility is the use of small molecule inhibitors of the HIF hydroxylases. For example, favourable response to one such compound, FG0041, in a rat model of myocardial infarction was seen even in the face of little detectable fibrosis in control animals.54

Morphine

Morphine is widely used to treat pain in cancer patients. Although the effects of morphine on central nervous systems have been studied widely, we know little about morphine's activity on non-neuronal systems, including vascular endothelium. It has been shown that endothelial cells express specific opioid receptors, including μ opioid receptor. Our laboratory showed that morphine at medically relevant concentrations stimulates tumour growth by promoting tumour angiogenesis.55 It does so by nitric oxide mediated activation of MAPK/ERK and by stimulating the survival signal PKB/Akt, inhibition of apoptosis, and promotion of cell cycle progression by increasing cyclin D1. Tumour promoting effects of morphine have also been shown in mice model of leukaemia or sarcoma.56 However, the use of morphine and other opioids in wound healing and cardiovascular disease can have therapeutic implications. We are currently testing the topical use of hydromorphine for wound healing in phase I clinical trials. In pre-clinical studies morphine hydromorphine and fentanyl promoted healing of ischaemic wounds in rats.57 We believe that topical use of opioids in wound healing will also provide pain relief without the side effects of systemically administered opioids. Importantly, opioid receptors provide additional promising targets for angiogenesis based treatments.

Combination therapy

Tumours become self reliant, although still nurtured by the blood vessels, and therefore targeting both the vessel as well as the tumour cells may be a reasonable strategy. Administration of recombinant proteins together with chemotherapy yielded a potent anticancer effect in ovarian and pancreatic cancer models.58 Radiation can damage the tumour cells within the centre of the tumour, but can upregulate hypoxia inducible factor, which can increase the expression of VEGF. The combination of antiangiogenic drugs and radiation has been shown to have potent antitumour effects.59 During this treatment modality, angiogenesis based drugs may work as radiation sensitisers, facilitating the entrance of radiation into the tumour. Angiostatin in combination with radiation therapy is being evaluated in a phase I clinical trial.60 Anti-VEGF treatment can potentiate radiation therapy as well as decrease resistance of tumour cells.61

CONCLUSION AND FUTURE RESEARCH DIRECTION

We are faced with the challenge of angiogenesis based treatments. It is not easy to define the optimal treatment dose and schedule, the optimal combination of antiangiogenic therapy, and other anticancer modalities. Newer angiogenic factors are still being discovered raising the possibility of multiple factors involved in different cancers/pathological conditions. While these newer factors complicate the already complex milieu of angiogenesis, at the same time they provide additional therapeutic targets, taking us a step closer to finding an ultimate solution. With at least two approved angiogenesis based drugs (bevacizumab and PDGF-BB) being used in the clinical setting, we are hopeful that more angiogenesis based treatments will be available to patients in the near future.

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