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A Historical Review on Current Medication and Therapies for Inducing and Inhibiting Angiogenesis

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ABSTRACT

Angiogenesis means the growth of new capillary blood vessels in the body is an important natural process used for healing and reproduction. The body controls angiogenesis by producing a precise balance of growth and inhibitory factors in healthy tissues. When this balance is disturbed, the result is either too much or too little angiogenesis. Excessive angiogenesis occurs in diseases such as cancer, diabetic blindness, age-related macular degeneration, rheumatoid arthritis, psoriasis, and more than 70 other conditions for these Anti angiogenic therapies are aimed to halt new blood vessel growth there by using angiogenesis inhibitors have been also discovered from natural sources to treat cancer. Insufficient angiogenesis occurs in diseases such as coronary artery disease, stroke, and chronic wounds. Therapeutic angiogenesis aimed to stimulate new blood vessel growth with growth factors is being developed to treat these conditions. Angiogenic gene therapy is also being developed as a method to deliver angiogenic growth factors to the heart, limbs, and wounds. Currently there is no angiogenic gene therapy and drugs approved by FDA for the treatment of ischemic cardiovascular disease. But FDA approved device is used to stimulate NBV to grow in diseased hearts is a laser used in a technique called Direct Myocardial Revascularization. The present review will helpful for the discovery of potent angiogenesis growth factors and further research findings from various sources is to be encouraged to alternate the recombinant protein, monoclonal antibody, device and cell based therapies.

KEYWORDS: Angiogenic growth factors, Angiogenesis inhibitors, Anti-angiogenic therapies, Therapeutic angiogenesis, VEGF

INTRODUCTION

Angiogenesis means for the growth of new capillary blood vessels in the body is an important natural process in the body used for healing and reproduction. The body controls angiogenesis by producing a precise balance of growth and inhibitory factors in healthy tissues. When this balance

is disturbed, the result is either too much or too little angiogenesis. Abnormal blood vessel growth either excessive or insufficient is now recognized as a “common denominator” underlying many deadly and debilitating conditions including cancer, skin diseases, age related blindness, diabetic ulcers, cardiovascular disease, stroke and many others. The list of diseases that have angiogenesis as an underlying mechanism grows longer every year [1].

Body Control Mechanism of Angiogenesis

Angiogenesis the growth of new blood vessels is an important natural process occurring in the body both in health and in disease. Angiogenesis occurs in the healthy body for healing wounds and for restoring blood flow to tissues after injury or insult. In females angiogenesis also occurs during the monthly reproductive cycle (to rebuild the uterus lining, to mature the egg during ovulation) and during pregnancy (to build the placenta, the circulation between mother and foetus). The healthy body controls angiogenesis through a series of "on" and "off" switches: The main "on" switches are known as angiogenesis stimulating growth factors and the "off switches" are known as angiogenesis inhibitors, When angiogenic growth factors are produced in excess of angiogenesis inhibitors the balance is tipped in favours of blood vessel growth. When inhibitors are present in excess of stimulators angiogenesis is stopped. The normal healthy body maintains a perfect balance of angiogenesis modulators. In general angiogenesis is "turned off" by the production of more inhibitors than stimulators [2].

ANGIOGENESIS BASED DISEASES

In many serious diseases states the body loses control over angiogenesis and angiogenesis dependent diseases result when new blood vessels either grow excessively or insufficiently.

Excessive Angiogenesis

Excessive Angiogenesis occurs in diseases such as cancer, diabetic blindness, age related macular degeneration, rheumatoid arthritis, psoriasis and more than 70 other conditions. In these conditions new blood vessels feed diseased tissues, destroy normal tissues and in the case of cancer the new vessels allow tumour cells to escape into the circulation and lodge in other organs (tumour metastases). Excessive angiogenesis occurs when diseased cells produce abnormal amounts of angiogenic growth factors overwhelming the effects of natural angiogenesis inhibitors. Anti-angiogenic therapies are aimed to halt new blood vessel growth there by used to treat these conditions.

Insufficient Angiogenesis

Insufficient Angiogenesis occurs in diseases such as coronary artery disease, stroke and chronic wounds. In these conditions blood vessel growth is inadequate and circulation is not properly restored leading to the risk of tissue death. Insufficient angiogenesis occurs when tissues cannot produce adequate amounts of angiogenic growth factors [3-5]. Therapeutic angiogenesis is aimed to stimulate new blood vessel growth with growth factors is being developed to treat these conditions.

ANGIOGENESIS BASED THERAPIES

Angiogenesis dependant therapies restoring the body’s natural control of angiogenesis are new and comprehensive approach to fighting disease. By using new medical treatments that either inhibit or stimulate angiogenesis, doctors are prolonging the lives of cancer patients, preventing limb amputations, reversing vision loss and improving general health.

Anti-angiogenic Therapy

All cancerous tumour release angiogenic growth factor proteins that stimulate blood vessels to grow into the tumour, providing it with oxygen and nutrients, Anti-angiogenic therapies literally starve the tumour of its blood supply by interfering with this process. New classes of cancer treatments that block angiogenesis are now approved and available to treat cancers of the colon, kidney, lung, breast and liver, as well as multiple myeloma and bone gastrointestinal stromal tumours. Some older drugs have been rediscovered to block angiogenesis as well. These are being used to treatment angiogenesis dependent conditions, such as hemangiomas, colon polyps and precancerous skin lesions.

Angiogenic Therapy

Else called as Therapeutic angiogenesis, in contrast stimulates angiogenesis where it is required but lacking. This technique is used to replenish the blood supply to chronic wounds to speed healing and it prevents unnecessary amputations. New research suggests this approach can be also used to save limbs afflicted with poor circulation and even oxygen starved hearts. Therapeutic angiogenesis may even help to regenerate damaged or lost tissues in ways that were previously considered impossible such as with nerves and brain tissue [1, 2].

ANGIOGENESIS GROWTH FACTORS

There are at least 20 different known angiogenic growth factors (Tab.1) out of that five angiogenic growth factors are being tested in humans for growing new blood vessels to heal wounds and to restore blood flow to the heart, limbs and brain [6-8]. Angiogenic gene therapy is also being developed as a method to deliver angiogenic growth factors to the heart, limbs and wounds [1, 4, 5, 9, 10].

Table 1: List of Known Angiogenic Growth Factors

Sl. No.	Known Angiogenic Growth Factors
1.	Angiogenin
2.	Angiopoietin-1
3.	Del-1
4.	Fibroblast growth factors: acidic (aFGF) and basic (bFGF)
5.	Follistatin
6.	Granulocyte colony-stimulating factor (G-CSF)
7.	Hepatocyte growth factor (HGF) /scatter factor (SF)
8.	Interleukin-8 (IL-8)
9.	Leptin
10.	Midkine
11.	Placental growth factor
12.	Platelet-derived endothelial cell growth factor (PD-ECGF)
13.	Platelet-derived growth factor-BB (PDGF-BB)
14.	Pleiotrophin (PTN)
15.	Progranulin
16.	Proliferin
17.	Transforming growth factor-alpha (TGF-alpha)
18.	Transforming growth factor-beta (TGF-beta)
19.	Tumor necrosis factor-alpha (TNF-alpha)
20.	Vascular endothelial growth factor (VEGF)/vascular permeability factor (VPF)

ANGIOGENESIS INHIBITORS

There are at least 28 known natural angiogenesis inhibitors found in the body (Tab. 2). Other than this Angiogenesis inhibitors have also been discovered from natural sources in total more than 300 angiogenesis inhibitors have been discovered to date [1, 4, 5, 10].

Table 2: List of Known Angiogenic Inhibitors

Sl. No.	Known Angiogenic Inhibitors
1.	Angioarrestin
2.	Angiostatin (plasminogen fragment)
3.	Antiangiogenic antithrombin III
4.	Cartilage-derived inhibitor (CDI)
5.	CD59 complement fragment
6.	Endostatin (collagen XVIII fragment)
7.	Fibronectin fragment
8.	Gro-beta
9.	Heparinases
10.	Heparin hexasaccharide fragment
11.	Human chorionic gonadotropin (hCG)
12.	Interferon alpha/beta/gamma
13.	Interferon inducible protein (IP-10)
14.	Interleukin-12
15.	Kringle 5 (plasminogen fragment)
16.	Metalloproteinase inhibitors (TIMPs)
17.	2-Methoxyestradiol
18.	Placental ribonuclease inhibitor
19.	Plasminogen activator inhibitor
20.	Platelet factor-4 (PF4)
21.	Prolactin 16kD fragment
22.	Proliferin-related protein (PRP)
23.	Retinoids
24.	Tetrahydrocortisol-S
25.	Thrombospondin-1 (TSP-1)
26.	Transforming growth factor-beta (TGF-b)
27.	Vasculostatin
28.	Vasostatin (Calreticulin fragment)

HISTORICAL HIGHLIGHTS IN THE FIELD OF ANGIOGENESIS

***1787*:** British surgeon Dr. John Hunter first uses the term "angiogenesis" (new blood vessel growth) to describe blood vessels growing in the reindeer antler.

***1935*:** Boston pathologist Dr. Arthur Tremain Hertig describes angiogenesis in the placenta of pregnant monkeys.

***1971*:** Surgeon Judah Folkman hypothesizes that tumour growth is dependent upon angiogenesis. His theory, published in the New England Journal of Medicine, is initially regarded as heresy by leading physicians and scientists.

***1975*:** The first angiogenesis inhibitor is discovered in cartilage by Dr. Henry Brem and Dr. Judah Folkman.

***1984*:** The first angiogenic factor (basic fibroblast growth factor, b-FGF) is purified by Yuen Shing and Michael Klagsbrun at Harvard Medical School.

***1989*:** One of the most important angiogenic factors, vascular endothelial growth factor (VEGF), is

discovered Dr. Napoleone Ferrara. It turns out to be identical to a molecule called Vascular Permeability Factor (VPF) discovered in 1983 by Dr. Harold Dvorak.

***1989*:** The first successful treatment of an angiogenesis dependent benign tumor (pulmonary haemangioma) using interferon alfa2a is reported by Dr. Carl White, a paediatric radiologist in Denver.

***1992*:** The first clinical trial of an anti angiogenic drug (TNP-470) begins in cancer patients.

***1994*:** The Angiogenesis Foundation is founded to improve global efforts by facilitating the development and application of angiogenesis-based medicines.

***1997*:** The first angiogenesis-stimulating drug (becaplermin, Regranex) is FDA-approved for treatment of diabetic foot ulcers.

***1997*:** Dr. Michael O'Reilly publishes research finding in the journal Nature showing complete regression of cancerous tumours following repeated cycles of anti angiogenic therapy using angiostatin and endostatin.

***1998*:** The first angiogenesis-stimulating laser is FDA-approved for the treatment of severe, end-stage coronary disease.

***1999*:** The first vascular targeting therapy is FDA-approved for treatment of age-related macular degeneration.

***1999*:** Massive wave of anti-angiogenic drugs enter clinical trials: 46 anti-angiogenic drugs for cancer patients; 5 drugs for macular degeneration; 1 drug for diabetic retinopathy; 4 drugs for psoriasis.

***1999*:** Massive wave of angiogenesis-stimulating drugs enter clinical trials: 5 drugs for coronary artery disease; 5 drugs for peripheral vascular disease; 1 drug for stroke; 10 drugs for wound healing.

***1999*:** Laboratory research led by Dr. Robert Kerbel and Dr. Judah Folkman shows that some traditional cytotoxic chemotherapy may inhibit tumour angiogenesis when given at low-doses.

***1999*:** Dr. Richard Klausner, Director of the U.S. National Cancer Institute, designates the development of anti-angiogenic therapies for cancer as a national priority.

***2003*:** The monoclonal antibody drug Avastin (Bevacizumab) becomes the first anti-angiogenic drug to demonstrate in large-scale clinical trials that inhibiting tumor blood vessel growth can prolong survival in cancer patients.

***2004*:** A pivotal phase 3 trial published in the New England Journal of Medicine shows that the addition of bevacizumab (Avastin), an anti-VEGF monoclonal antibody, to chemotherapy significantly improves survival in patients with metastatic colorectal cancer.

***2004*:** Bevacizumab is FDA approved for the treatment of advanced colorectal cancer. At the time of bevacizumab's approval, FDA Commissioner Mark McClellan declares anti-angiogenic therapy "the fourth modality for cancer treatment."

***2004*:** Pegaptanib (Macugen), an anti-VEGF aptamer, becomes the first anti-VEGF drug to be FDA approved for the treatment of age-related macular degeneration.

***2004*:** Erlotinib (Tarceva), a small molecule inhibitor of EGFR tyrosine receptor kinase, receives FDA approval for treatment of non-small cell lung cancer (NSCLC).

***2005*:** Endostatin (Endostar), an agent that inhibits metastasis and angiogenesis by down regulating multiple pro-angiogenic growth factors, is approved in China for the treatment of advanced lung cancer.

***2005*:** Sorafenib (Nexavar), a multi-tyrosine kinase inhibitor, demonstrates significantly longer progression-free survival vs. placebo in patients with advanced renal cancer in a randomized phase 3 trial.

***2005*:** Sorafenib is FDA approved as second-line therapy for advanced renal cancer.

***2005*:** Lenalidomide (Revlimid), and agent with both immunomodulatory and anti-angiogenic

properties, is FDA approved for treatment of myelodysplastic syndrome.
***2006*:** Sunitinib (Sutent), a multi-tyrosine kinase inhibitor, receives FDA approval as first-line therapy for advanced renal cancer and gastrointestinal stromal tumor (GIST).
***2006*:** Ranibizumab (Lucentis), a fragment of the bevacizumab molecule, is FDA approved for the treatment age-related macular degeneration.
***2006*:** Bevacizumab in combination with paclitaxel and carboplatin is shown to significantly improve progression-free survival, overall survival, and response rates in treatment-naïve patients with advanced NSCLC. This is the first time an anti-angiogenic agent plus chemotherapy has been shown to prolong survival in NSCLC patients.
***2007*:** Results from a randomized phase 3 trial published in the New England Journal of Medicine show a significant survival benefit for sorafenib vs. placebo in patients with advanced renal cancer who fail first-line therapy.
***2007*:** Temsirolimus (Torisel), an inhibitor of mTOR, is approved for the treatment of advanced renal cancer after a pivotal phase 3 trial published in the New England Journal of Medicine shows significantly improved progression-free survival in previously untreated mRCC patients with poor prognosis.
***2007*:** Results from a randomized phase 3 trial published in the New England Journal of Medicine show that sunitinib doubles progression-free survival in previously untreated patients with metastatic renal cancer.
***2007*:** Results announced at ASCO 2007 from a randomized phase 3 study show that sorafenib extends overall survival by 44% vs. placebo in patients with advanced liver cancer. Based on these findings, in November the FDA approves sorafenib to treat unresectable advanced hepatocellular carcinoma. Sorafenib is the first systemic agent to show efficacy for advanced liver cancer.
***2008*:** Angiogenesis pioneer Dr. Judah Folkman passes away suddenly on January 14 while traveling to a conference. At the time of Dr. Folkman's death, an estimated 1.2 million patients had been treated with anti-angiogenic therapy, a concept he first conceived of almost 4 decades prior. He is widely recognized as one of the most important figures in modern medicine.
***2008*:** In February, bevacizumab (Avastin) becomes the first anti-angiogenic agent approved to treat breast cancer. The approval is based on phase 3 trial results in which BV/paclitaxel doubled median progression free survival versus paclitaxel alone (PFS: 11.8 mo. vs. 5.9 mo., $P<0.0001$) in women with locally recurrent or metastatic breast cancer [7- 12].

DISCUSSION ON CURRENT AND FUTURE PERSPECTIVES

This review clearly describes the basic concepts, historical highlights involved in angiogenesis field and list of up to date known angiogenic growth factors and inhibitors. Discussions on Current and Future perspectives in the field of angiogenesis are listed below.

Oncology

In the field of oncology angiogenesis inhibitors are used to treat Cancer. In U.S. there are currently eight approved anti-cancer therapies with recognized anti angiogenic properties agents. These agents which interrupt critical cell signalling pathways involved in tumour angiogenesis and growth involve three categories: 1) monoclonal antibodies directed against specific pro-angiogenic growth factors and/or their receptors; 2) small molecule tyrosine kinase inhibitors (TKIs) of multiple pro-angiogenic growth factor receptors; and 3) inhibitors of mTOR (mammalian target of rapamycin). In addition, there are two other approved anti angiogenic agents may indirectly inhibit angiogenesis through mechanisms that are not completely understood. Angiogenesis inhibitors have also been discovered from natural sources, including tree bark, fungi, shark muscle and cartilage, sea coral, green tea and herbs (liquorices, ginseng, cumin,

garlic). In total, more than 300 angiogenesis inhibitors have been discovered to date. Near about 184 million patients in World could benefit from some form of anti angiogenic therapy [1, 6, 13, 14].

Dermatology

In the field of dermatology there are several anti angiogenic agents used for neoplasm of the skin.

Ophthalmology

In the field of ophthalmology angiogenesis in the eye underlies the major causes of blindness in both developed and developing nations particularly age related macular degeneration (AMD), proliferative diabetic retinopathy (PDR), diabetic macular edema (DME), neovascular glaucoma, corneal neovascularization (trachoma) and pterygium. Presently approved anti-angiogenic therapies for ophthalmic conditions are biologic agents that inhibit VEGF. There are currently two approved anti angiogenic therapies for ophthalmic diseases an anti-VEGF aptamer (pegaptanib, Macugen) and a Fab fragment of a monoclonal antibody directed against VEGF-A (ranibizumab, Lucentis). The first FDA-approved blood vessel therapy for eye disease is a type of photodynamic therapy called Visudyne (QLT Therapeutics/CIBA Vision), which has shown effectiveness, for treating macular degeneration [13, 15].

Diabetalogy

In the field of diabetics the first angiogenesis stimulating medicine is a prescription gel called Regranex (recombinant human platelet-derived growth factor-BB, Ortho-McNeil Pharmaceuticals) that became FDA-approved to heal diabetic foot ulcers in December 1997.

Cardiology

In the field of cardiology angiogenic agents are used as a therapeutic angiogenesis for tissue repair and regeneration. Therapeutic angiogenesis modalities represent a broad range of interventions that generate new blood vessel growth to promote neovascularization and tissue repair. Near about 314 million patients in world would benefit from some form of angiogenesis stimulating pro-angiogenic therapy [1, 4, 9, 10]. Presently, there are three major indications for which angiogenic therapies are in clinical use: 1) chronic wounds (e.g. diabetic lower extremity ulcers, venous leg ulcerations, pressure ulcers and arterial ulcers); 2) peripheral arterial disease; and 3) ischemic heart disease. In such conditions, the therapeutic goal is to stimulate angiogenesis to improve perfusion, deliver survival factors to sites of tissue repair, mobilize regenerative stem cell populations and ultimately restore form and function to the tissue; More than 2,000 patients with heart disease have received some form of experimental angiogenic therapy. But currently there are no FDA-approved angiogenic drugs for the treatment of ischemic cardiovascular disease. The first FDA-approved device is used to stimulate new blood vessels to grow in diseased hearts is a laser used in a technique called Direct Myocardial Revascularization (DMR) or called as trans myocardial revascularization (TMR). [12, 16]. So it is necessary to determine the potent angiogenic growth factors as well as research findings from natural sources are to be encouraged to alternate the recombinant protein, monoclonal antibody, device and cell based therapies.

REFERENCES

[1] Folkman J, Braunwald E, Fauci AS, Kasper DL. Tumor angiogenesis, Harrision's Texbook of Internal Medicine, 15th Edition, McGraw-Hill, New York, **2000**; 132-152.
[2] Li W, Talcott K, Zhai A, Kruger E, Li V. *Adv Skin Wound Care*, **2005**. 18, 491-500.

[3] Folkman J. *Nat Med*., **1955**, 1, 27-31.
[4] Li WW, Li VW, Casey R. Clinical trials of angiogenesis based therapies: overview and new guiding principles, Angiogenesis: Models, Modulators and Clinical Application, Maragoudakis M. Edition, Plenum Press, New York, **1998**, 475-492.
[5] Li WW, Li VW, Tsakayannis D. Emerging concepts and lessons from clinical trials of angiotherapy, The New Angiotherapy, Fan TP, Kohn EC. Edition, Humana Press, **2001,** 547-571.
[6] Folkman J, Devita VT, Hellman S, Rosenberg SA. Antiangiogenesis agents, Cancer: Principles & Practice of Oncology, 6th Edition, Lippincott Williams & Wilkins, Philadelphia, **2001**; 509-519.
[7] Folkman J, Klagsbrun M. *Science.* **1987**, 235, 442-447.
[8] Kerbel RS. *N Engl J Med*. **2008,** 358, 2039-2049.
[9] Li W. *Acad Radiol*. **2000**, 7, 800-811.
[10] White CW, Sondheimer HM, Crouch EC. *N Engl J Med*., **1992**. 326, 1456-1463.
[11] Ingber D, Fujita T, Kishimoto S. *Nature.* **1990**, 348, 555-557.
[12] Smiell, JM, Wieman TJ, Steed DL. *Wound Repair Regen*., **1999**. 7, 335-346.
[13] Andreoli CM, Miller JW. *Cum op in Opthalmol*., **2007**, 18(6), 502-508.
[14] Li WW, Hutnik M, Gehr G. *Br J Haematol*. **2008**, 7372, 1365-2141.
[15] Jager RD, Mieler WF, Miller JW. *N Engl J Med*. **2008,** 358(24), 2606-2617.
[16] Li VW, Kung EF, Li WW. Molecular therapy for wounds: modalities for stimulating angiogenesis and granulation, Manual of Wound Management, 5th Edition, McGraw Hill, **2004**, 17-43.