Angiogenesis: A Literature Review

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***Abstract* - Angiogenesis, the formation of new blood vessels, plays critical roles in the human physiology, which range from fetal growth to tissue repair, and the female reproductive cycle. Contrary to this, imbalanced angiogenesis can result in vascular insufficiency and vascular overgrowth (retinopathies, hemangiomas, and vascularized tumors). The balance between pro-angiogenic and antiangiogenic growth factors tightly controls angiogenesis. As a result, in recent years, it has been found that through understanding and successful manipulation of these factors, angiogenesis can be used for therapeutic purposes. In this paper, we discuss the clinical implications of angiogenesis, and the pro-angiogenic and antiangiogenic agents that offer potential therapy for cancer and other angiogenic diseases.**

Keywords - Blood vessel, cancer, angiogenesis, disease, and agents.

I. Introduction

Angiogenesis, the word angio meaning blood vessel and genesis meaning creation, is the creation of new blood vessels. Angiogenesis is a crucial process, which occurs during health, as well as disease. The formation of new tissues involves the formation of new blood vessels. When new tissue is formed, it is essential that is has blood supply for its growth and livelihood. For this reason, the creation of new blood vessels or angiogenesis is important. Situations where angiogenesis is vital and necessary include the repair of wounds, as well as the formation of the placenta during pregnancy.

II. Angiogenic factors

A variety of signaling molecules such as Fibroblast growth factors (FGF), Vascular endothelial growth factors (VEGFs) and receptors (VEGFRs) , Ephrin-eph receptors, and angiopoietin-Tie have been identified as playing important roles in angiogenesis. The VEGFs and VEGFRs regulate angiogenesis and vasculogenesis, the development of blood vessels from precursor cells during the early embryogenesis.

The VEGFR family of genes contains 3 to 4 members, entirely dependent on the vertebrae species, whereas the VEGF family of genes contains at least 7 members. The members of VEGF family are VEGF-A VEGF-B, VEGF-C, VEGF-D, PIGF, VEGF-E, and svVEGF. Amongst these, the first 5 can be found in humans. The members of the VEGFR family are VEGFR-1, VEGFR-2, and VEGFR-3. Members of the VEGF family stimulate cellular responses by binding to the VEGFRs on the cell surface.

III. Processes in Angiogenesis

According to Yoo and Kwon, 2013, the process of angiogenesis occurs as follows:

1) Angiogenic factors FGF and VEGF bind to their receptors on endothelial cells and activate the signal transduction pathways.
2) Matrix metalloproteinases ae activated, and degrade the extracellular matrix.
3) Endothelial cells migrate out of the preexisting capillary wall and proliferate.
4) Integrins are expressed by endothelial cells, facilitating their adhesion to the extracellular matrix and their migration for tube formation.
5) Angiopoietin 1 binds to Tie-2 receptors and simulates pericyte recruitment and vessel stabilization.

IV. Angiogenesis in clinical trials

Unusual angiogenesis is said to be the major cause of many diseases. By unusual, we mean either excessive or insufficient angiogenesis. This is said to be the cause of conditions which include skin diseases, cancer, age-related blindness, hemangiomas, and cardiovascular disease. One can assume that with medical help, angiogenesis can be balanced, to reduce the effects or possibly nullify the effects of said disease that previously occurred as a result of imbalance.

We've reached the discovery that medical treatment can be used to stimulate or inhibit angiogenesis, which can prolong the lives of cancer patients, reverse vision loss, and improve general health. Depicted in Table 1, are instances where angiogenesis needs to be inhibited in areas where it is rampant, or stimulated in areas where it is lacking, depending on the disease. New research suggests that through therapeutic angiogenesis, we may be able to save limbs afflicted with poor circulation, and regenerate damaged or lost tissues.

The vast majority of the development in treatment inhibiting angiogenesis has been directed towards cancer because of tremendous heterogeneity of different cancers and only one common feature of increased angiogenesis among different cancers. Angiogenesis plays a major role in the development and spread of cancer, because a blood supply is required for tumor growth and metastases. Tumors secrete chemical signals that stimulate angiogenesis and thus stimulate nearby cells. For this reason, antiangiogenic agents have been studied to slow or prevent the growth of cancer. These agents can have various effects on angiogenesis.

Therapeutic goal	Diseases	Definitions/symptoms
Inhibition of angiogenesis	Hemangiomas	Benign and usually a self-involuting tumor (swelling or growth) of the endothelial cells that line blood vessels and is characterised by increased number of normal or abnormal vessels filled with blood
	Psoriasis	Immune-mediated disease that affects the skin. The immune system mistakes a normal skin cell for a pathogen and sends out faulty signals that cause overproduction of new skin cells
	Kaposi's sarcoma	Tumor caused by human herpesvirus 8 (HHV8)
	Ocular neovascularization	Abnormal or excessive formation of blood vessels in the eye
	Rheumatoid arthritis	Inflammatory response of the capsule around the joints (synovium), secondary to swelling (hyperplasia) of synovial cells, excess synovial fluid, and the development of fibrous tissue (pannus) in the synovium
	Endometriosis	A gynecological medical condition in which cells from the lining of the uterus (endometrium) appear and flourish outside the uterine cavity, most commonly on the membrane which lines the abdominal cavity
	Atherosclerosis	Artery wall thickens caused largely by the accumulation of macrophage white blood cells and promoted by low-density lipoproteins (LDL, plasma proteins that carry cholesterol and triglycerides)
	Tumor growth and metastasis	Tumor-associated neovascularization is involved in tumor growth, invasion, and metastasis
Stimulation of angiogenesis	Induction of collateral vessel formation: Myocardial ischemia, Peripheral ischemia, Cerebral ischemia	After blood vessels blockage (occulsion), collateral vessels can be developed to improve blood supply to the area.
	Wound healing	Intricate process in which the skin (or another organ-tissue) repairs itself after injury. Angiogenesis occurs concurrently with fibroblast proliferation when endothelial cells migrate to the area of the wound
	Reconstructive surgery	Surgery to restore the form and function of the body

Table 1: Clinical manipulation of Angiogenesis (Yoo and Kwon, 2013).

Bevacizumab (Avastin) was the first FDA-approved angiogenesis inhibitor that was shown to slow tumor growth, and prolong the lives of patients with some cancers. Bevacizumab is a monoclonal antibody that specifically recognizes and binds to VEGF, which prevents VEGF from activating VEGFR. In contrast, other angiogenesis inhibitors (depicted in table 2), including sorafenib and sunitinib, bind to receptors on the ECs or to other proteins in the downstream signaling pathways to block their activities (Yoo and Kwon, 2013). Zhang, 2005 provides us with some of the major advantages of angiogenesis based treatments are over others:

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) The endothelial cell is a normal diploid cell, which is unlikely to acquire genetic mutations that render it drug Resistant.
3) Blood flow, a surrogate marker for biological activity, is measurable in the clinic.
4) Temporary effects on vascular function may be sufficient to kill the endothelial cells.

5) A change of shape of local initiation of blood coagulation may be sufficient, other than killing the endothelial cells.

Inhibiting target	Drug	Sponsor	Clinical trials/mechanism
Epidermal growth factor receptor (EGFR)	Gefitinib (Iressa)	AstraZeneca and Teva	FDA-approved in 2003 for NSCLC/effective in cancers with mutated and overactive EGFR
	Lapatinib (Tykerb)	GSK	FDA-approved in 2007 for breast cancer/dual tyrosine kinase inhibitor which interrupts the HER2/neu and epidermal growth factor receptor (EGFR) pathways
	Erlotinib (Tarceva)	Genentech/OSI pharmaceuticals/Roche	FDA-approved in 2005/used to treat nonsmall cell lung cancer, pancreatic cancer, and several other types of cancer
	Canertinib (CI-1033)	Selleck Chemicals	Phase II/irreversible tyrosine-kinase inhibitor with activity against EGFR, HER-2, and ErbB-4
VEGFR	Vatalanib (PTK787 or PTK/ZK)	Bayer Schering and Novartis	Phase III/it inhibits all known VEGF receptors, as well as platelet-derived growth factor receptor-beta and c-kit, but is most selective for VEGFR-2
VEGFR-2	IMC-1C11	ImClone Systems	Phase I/chimerized monoclonal antibody
VEGFR-3	mF4-31C1	ImClone Systems	Phase I/rat monoclonal antibody to murine VEGFR-3, which potently antagonizes the binding of VEGF-C to VEGFR-3
Multiple growth factor receptors	Imatinib (Glivec)	Novartis	FDA-approved in 2001/competitive tyrosine-kinase inhibitor used in the treatment of multiple cancers, most notably Philadelphia chromosome-positive (Ph^+) chronic myelogenous leukemia (CML)
	Sunitinib (Sutent)	Pfizer	FDA-approved in 2006 for renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST)/the simultaneous inhibition of receptors for platelet-derived growth factor (PDGF-Rs) and vascular endothelial growth factor receptors (VEGFRs)
	Sorafenib (Nexavar)	Bayer and Onyx pharmaceuticals	FDA-approved in 2005/a small molecular inhibitor of several tyrosine protein kinases (VEGFR and PDGFR) and Raf kinases (more avidly C-Raf than B-Raf)
	Pazopanib (Votrient)	GlaxoSmithKline	FDA-approved in 2009 for advanced renal cancer/multitargeted receptor tyrosine kinase inhibitor of VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-α/β, and c-kit
VEGF	Bevacizumab (Avastin)	Genentech/Roche	FDA-approved in 2004 for metastatic colorectal cancer/humanized anti-VEGF mAb, licensed to treat various cancers including colorectal, lung, breast (outside the USA), glioblastoma (USA only), kidney, and ovarian
Integrin $\alpha_v\beta_3$	Vitaxin	Applied molecular evolution	Phase II as a treatment for colorectal cancer/humanized monoclonal antibody against the vascular integrin $\alpha_v\beta_3$

Table 2: Selected angiogenesis inhibitors in clinical trials (Yoo and Kwon, 2013).

V. 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, anti-angiogenic treatments target actively proliferating endothelial cells. However, the relative number of proliferating EC is far smaller in human tumours than it is in rodent tumour models. Mature vessels in human tumour at any given time may not undergo regression with the conventional anti-angiogenic 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. It is not yet feasible to monitor the antiangiogenic response in the patients. However, with the recent advances in magnetic resonance imaging it may be possible to do vascular imaging in patient (Zhang, 2005).

VI. Side effects of antiangiogenic therapy

A wide variety of side effects, such as renal dysfunction, hypertension, thrombosis, arrhythmia, proteinuria, cardiac failure, hair changes and bleeding, have been reported in patients under anti–VEGF-VEGFR therapy. Among these reports, the frequency of hypertension and proteinuria is higher than that of others, which suggests a direct relationship with the blockage of VEGF-A in tissues. A decrease in the level of VEGF-A in the kidney could induce damage to vascular endothelial cells in glomeruli, and such a dysfunction of glomerular microvasculature may cause proteinuria. In addition, in some preclinical and clinical trials, glioblastoma showed an enhanced invasiveness after anti-angiogenic therapy (Shibuya, 2011).

VII. Methods

For the gathering of information, I took the simplest of routes. I used the most basic form of text mining, using the find feature (ctrl-f) of pdf readers and webpages, to look for terms related to angiogenesis, which helped me select the review papers that I did. In addition to that, I read the review papers, and while reading I highlighted important areas that I wanted to include in my paper. Later on I will look at other tools that can help me identify more sources, in order to elaborate on angiogenesis.

VIII. Results

Gene products	Category	Major Function
VEGF-A	inducer	Induction of EC proliferation
VEGF-B	inducer	Induction of EC proliferation
Angiopoietin 1	inducer	Induction of EC proliferation
Angiostatin	inhibitor	Inhibit EC proliferation
Endostatin	inhibitor	Inhibit EC proliferation
interstitial collagenase (MMP-1)	Proteolytic enzyme	Degrading ECM components
collagenase-3 (MMP-13)	Proteolytic enzyme	Degrading ECM components
Ephrins	inducer	Induction of EC proliferation
Integrins	inducer	Induction of EC proliferation
Vasostatin	inhibitor	Inhibit EC proliferation

Table 3: Angiogenesis gene products.

IX. Discussion

As a result of this review, there is plenty to walk away with. I not only became familiarized with what angiogenesis is and the process, but also how it affects our livelihood and what factors can be used to control it. Furthermore, I've become acquainted with diseases and conditions that angiogenesis is associated with. I've identified uses for the clinical manipulation of angiogenesis, be it to induce, or inhibit EC proliferation, and the side effects of some of those manipulations. Lastly, I've identified gene products of angiogenesis. The most difficult part of this review was deciding where to focus because angiogenesis is involved in so many biological processes. One thing I wanted to come across but did not find was a hint to whether angiogenesis clinically manipulated or not can repair damage caused by heart conditions.

X. Conclusion

As a result of still being in the early stages of breakthroughs for angiogenesis, we face the challenge of creating a positive outlook for potential therapy for cancer and other angiogenic diseases. With every solution, there are repercussions and new factors that are discovered. Angiogenesis is already a complex process, so with every new factor, the complexity only increases. Despite this, angiogenic based drugs are still preferred over drugs like chemotherapeutic drugs.

XI. References

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