ISSN 0975-6299 **Vol.1/Issue-3/Jul-Sep.2010**

International Journal of Pharma and Bio Sciences

VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR ANTAGONIST- A TARGET FOR TREATING INFLAMMATORY DISEASE

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ABSTRACT

The present review of literature was done to check the influence of the main angiogenic factor vascular endothelial growth factor in the various physiological and pathological conditions like growth, development, tumor formation, arthritis etc. It was also seen that how VEGF are classified and produced as well as the mechanism of action. VEGF bind over the specific receptors and cause cascade of events of angiogenesis. So if the VEGF receptor antagonists are investigated they can block the VEGF receptor and prevent the process of angiogenesis which occurs in various chronic inflammations like solid tumor, rheumatic arthritis etc.

KEYWORDS

Angiogenesis, VEGF, Anti VEGF therapy, tumor, VEGF Receptor

INTRODUCTION

Angiogenesis is a process which occurs physiologically involves the growth of new blood vessels from pre-existing vessels. It is a normal and important process in growth and development, as well as in wound healing. However, it is also a fundamental step in the transition of tumors from a dormant state to a malignant one. [1,2]Vascular endothelial growth factor (VEGF) is a chemical signal produced by cells that stimulates the growth of new blood vessels. It is part of the system that restores the oxygen supply to tissues when blood circulation is inadequate. VEGF's normal function is to create new blood vessels during embryonic development, new blood vessels after injury, and new vessels (collateral circulation) to bypass blocked vessels.When VEGF is overexpressed, it can contribute to disease. Solid cancers cannot grow beyond a limited size without an adequate blood supply; cancers that can express VEGF are able to grow and metastasize. Overexpression of

VEGF can cause vascular disease in the retina of the eye and other parts of the body. Drugs such as bevacizumab can inhibit VEGF and control or slow those diseases.VEGF is a family of growth factors, specifically the platelet-derived growth factor family of cystine-knot growth factors. They are important signaling proteins involved in both vasculogenesis[3,4] (Fig 1)

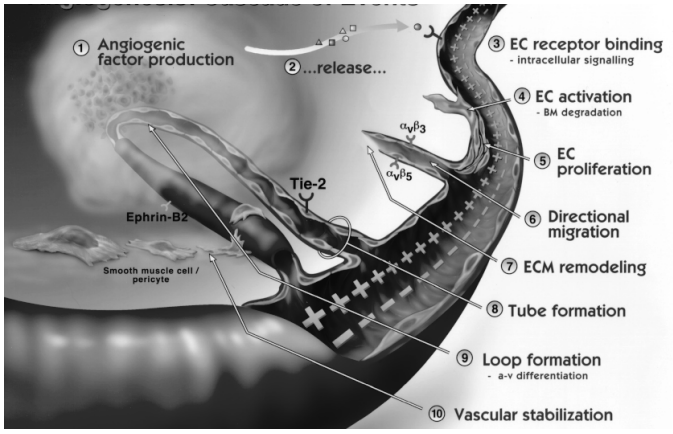
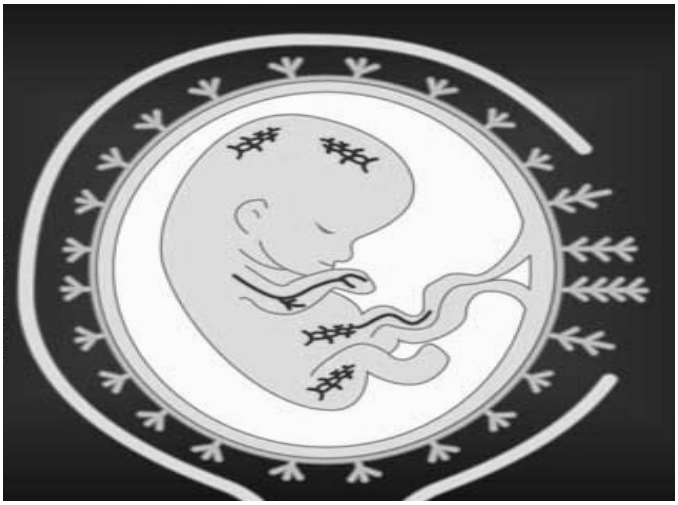


Fig 1*. (A) Angiogenesis cascade of events[5]*



(B) Angiogenesis in children[6]

Classification of Vegf

Angiogenesis is triggered by a change in balance between different pro- and anti-angiogenic activities that regulate the behavior of capillary endothelial cells[7]. In this regard, a

pre-eminent role has been established for the vascular endothelial growth factor (VEGF)-related family of angiogenic and lymphangiogenic growth factors, which currently includes VEGF-A, -B, -C, -D, -E, and placenta growth factor (PlGF). VEGF-A is believed to play an indispensable role in angiogenesis. Indeed, targeting of the *VEGF-A* gene in mice resulted in early embryonic lethality due to severe structural and functional abnormalities in the developing vasculature, even when only a single *VEGF-A* allele was inactivated[8,9]. Embryonic lethality is also induced by targeted disruption of either of the two main VEGF receptors expressed by endothelial cells, namely VEGFR-2 (Flk-1/KDR) and VEGFR-1 (Flt-1), the former regarded as the main transducer of positive pro-angiogenic signals[10]. The profound influence of the VEGF/VEGF receptor axis on vascular development and angiogenesis is likely linked to its role as a stimulator of endothelial cell survival, mitogenesis, migration, differentiation and self-assembly, as well as vascular permeability and mobilization of endothelial progenitor cells (EPCs) from the bone marrow into the peripheral circulation[11].

Alternative Classification of Vegf

The broad term 'VEGF' covers a number of proteins from two families, that result from alternate splicing of mRNA from a single, 8 exon, *VEGF* gene. (Fig -2) The two different families are referred to according to their terminal exon (exon 8) splice site - the proximal splice site (denoted $VEGF_{xxx}$) or distal splice site ($VEGF_{xxx}b$). In addition, alternate splicing of exon 6 and 7 alters their heparin-binding affinity, and amino acid number (in humans: $VEGF_{121}$, $VEGF_{121}b$, $VEGF_{145}$, $VEGF_{165}$, $VEGF_{165}b$, $VEGF_{189}$, $VEGF_{206}$; the rodent orthologs of these proteins contain one fewer amino acid). These domains have important functional consequences for the VEGF splice variants, as the terminal (exon 8) splice site determines whether the proteins are pro-angiogenic (proximal splice site, expressed during angiogenesis) or anti-angiogenic (distal splice site, expressed in normal tissues). In addition, inclusion or exclusion of exons 6 and 7 mediate interactions with heparan sulfate proteoglycans (HSPGs) and neuropilin co-receptors on the cell surface, enhancing their ability to bind and activate theVEGF receptors (VEGFRs) [12, 13, 14, 15]

Mechanism Of Action Of Vegf

All members of the VEGF family stimulate cellular responses by binding to tyrosine kinase receptors (the VEGFRs) on the cell surface, causing them to dimerize and become activated through transphosphorylation, although to different sites, times and extents. The VEGF receptors have an extracellular portion consisting of 7 immunoglobulin-like domains, a single transmembrane spanning region, and an intracellular portion containing a split tyrosine-kinase domain.(Fig. 3) VEGF-A binds to VEGFR-

1 (Flt-1)and VEGFR-2 (KDR/Flk-1). VEGFR-2 appears to mediate almost all of the known cellular responses to VEGF. The function of VEGFR-1 is less well-defined, although it is thought to modulate VEGFR-2 signaling. Another function of VEGFR-1 may be to act as a dummy/decoy receptor, sequestering VEGF from VEGFR-2 binding (this appears to be particularly important during vasculogenesis in the embryo). VEGF-C and VEGF-D, but not VEGF-A, are ligands for a third receptor (VEGFR-3), which mediates lymphangiogenesis.[16]

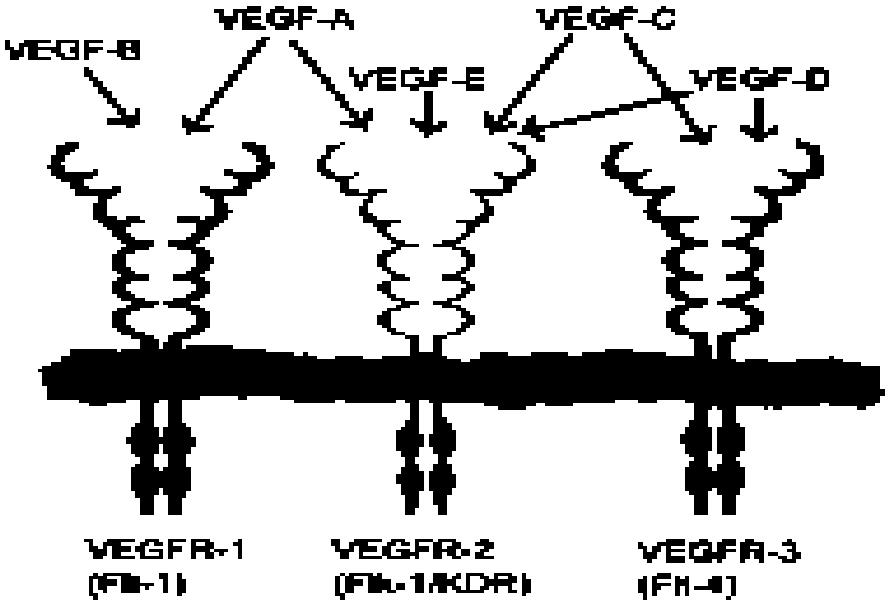


Fig.3 ***Mechanism of action of VEGF on VEGF receptors***[17]

Production Of Vegf

$VEGF_{xxx}$ production can be induced in cells that are not receiving enough oxygen. When a cell is deficient in oxygen, it produces HIF, hypoxia-inducible factor, a transcription factor. HIF stimulates the release of $VEGF_{xxx}$, among other functions (including modulation of erythropoeisis). Circulating $VEGF_{xxx}$ then binds to VEGF Receptors on endothelial cells, triggering a Tyrosine Kinase Pathway leading to angiogenesis. [18,19]

Clinical Significance Of Vegf

$VEGF_{xxx}$ has been implicated with poor prognosis in breast cancer. The overexpression of $VEGF_{xxx}$ may be an early step in the process of metastasis, a step that is involved in the "angiogenic" switch. Although $VEGF_{xxx}$ has been correlated with poor survival, its exact mechanism of action in the progression of tumors remains unclear. $VEGF_{xxx}$ is also released in

rheumatoid arthritis in response to TNF-α, increasing endothelial permeability and swelling and also stimulating angiogenesis (formation of capillaries). $VEGF_{xxx}$ is also important in diabetic retinopathy[20]. VEGF is a potential target for the treatment of cancer. Patients suffering from pulmonary emphysema have been found to have decreased levels of VEGF in the pulmonary arteries.[21]

Anti-Vegf Therapies

Anti-VEGF therapies are important in the treatment of certain cancers and in age-related macular degeneration. (Fig. 4). They can involve monoclonal antibodies such as bevacizumab (Avastin), antibody derivatives such as ranibizumab (Lucentis), or orally-available small molecules that inhibit the tyrosine kinases stimulated by VEGF: sunitinib (Sutent), sorafenib (Nexavar), axitinib, and pazopanib.[22]

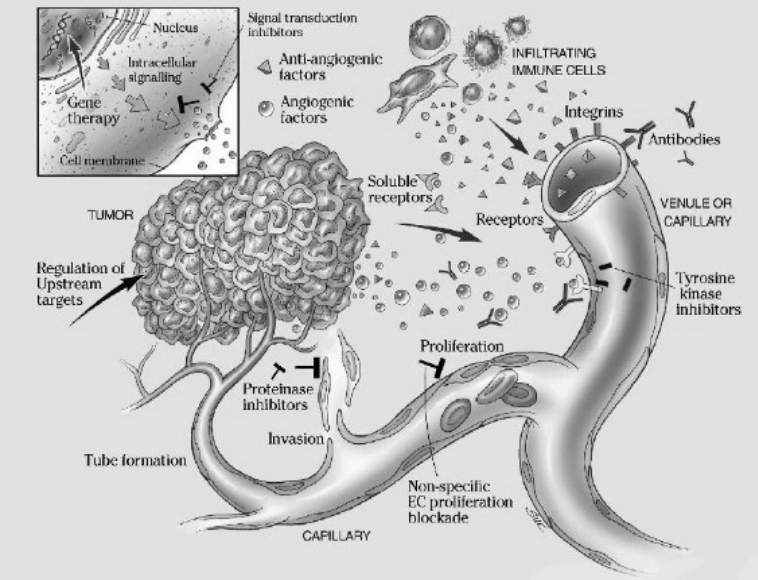


Fig. 4 *Anti angiogenic therapies*[23]

DISCUSSION

These studies suggest implicitly that not only is VEGF essential and indispensable for tumor growth and neovascularization, but also that tumor cells themselves constitute the major source of VEGF. Angiogenesis is triggered by a change in balance between different pro- and anti-angiogenic activities that regulate the behavior of capillary endothelial cells[24]. There are numerous reasons to suggest that VEGF also plays an important role in 'pathological' forms of angiogenesis, including tumor neovascularization[25]. For instance, VEGF expression is elevated in the majority of human cancers, and in many transformed cell lines in culture [26]. A causative role for VEGF in tumor angiogenesis has been implicated by numerous studies[27,28]. There are, however, experimental findings that seem to be at variance with the notion that VEGF is a non-redundant tumor angiogenesis factor that is predominantly produced by cancer cells. For example,

appreciable VEGF expression has been detected in tumor-associated fibroblasts[29,30,31] and inflammatory cells[32]. It has also been observed that reduction of VEGF expression in cancer cells may be functionally insignificant in certain advanced experimental tumors[33], and that tumor progression is associated with expression of an increasing number of different pro-angiogenic growth factors, in addition to VEGF[34]. Moreover, while the anti-tumor effects of neutralizing antibodies and pharmacological antagonists of VEGF or its receptors have been promising in many cases [35,36]

CONCLUSION

From the above review it was concluded that VEGF is an important angiogenic factor which is responsible for the growth of blood vessels inside the solid tumours, arthritis and other imflammation indued diseases. It was also seen that VEGF acts by VEGF receptors present in the endothelium cells. So, It these receptors are antagonized, the angiogenesis cascade of events can be stopped and thus the tumour cells will died without blood vessels and oxygen. So, it may be a better treatment if some antagonists (chemicals) can be synthesized or investigated from natural sources.

REFERENCES

1. Rubanyi, G.M. (Ed): Angiogenesis in health and disease. M.Dekker, Inc., New York – Basel, 2000
2. Raizada, M.K., Paton, J.F.R., Kasparov, S., Katovich, M.J. (Eds): Cardiovascular genomics. Humana Press, Totowa, N.J., 2005
3. Hlatky L, Tsionou C, Hahnfeldt P and Coleman CN (1994) Mammary fibroblasts may influence breast tumor angiogenesis via hypoxia-induced vascular endothelial growth factor up-regulation and protein expression. Cancer Res, 54, 6083–6086
4. Fukumura D Tumor induction of VEGF promoter activity in stromal cells. Cell (1998), 94, 715–725.
5. The Angiogenesis foundation, 2000, biomed.brown.edu/.../GROW2.HTM
6. A document (from internet), Angiogenesis in children, National Cancer Institute, 2000
7. Hanahan D and Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell, 86, 353–364.
8. Carmeliet P *et al*. (1996) Abnormal blood vessel development and lethality in embryos lacking a single VEGF allele. Nature, 380, 435–439.
9. Ferrara N, Carver-Moore K, Chen H, Dowd M, Lu L, O'Shea KS, Powell-Braxton L, Hillan KJ and Moore MW (1996) Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. Nature, 380, 439–442.
10. Carmeliet P (2000) Mechanisms of angiogenesis and arteriogenesis. Nat Med, 6, 389–395.
11. Ferrara N and Gerber HP (2001) The role of vascular endothelial growth factor in angiogenesis. Acta Haematol, 106, 148–156. |
12. Vascular endotelial growth factor, http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor
13. Stuttfeld E, Ballmer-Hofer K. "Structure and function of VEGF receptors". *IUBMB Life* (2009, 61 (9): 915–22
14. Patan S: Vasculogenesis and angiogenesis.Cancer Treat Res. 2004;117:3-32..
15. Napoleone Ferrara, Hans-Peter Gerber The Role of Vascular Endothelial Growth Factor inAngiogenesis, *Acta Haematol* 2001;106:148-156
16. Alicia VP, Lucile M, Joanne LY, Marina G, Capucine S, Linda M, Jack H, Contrasting

effects of *VEGF* gene disruption in embryonic stem cell-derived versus oncogene-induced tumors. The EMBO Journal (2003) 22, 4091 - 4102
17. Vascular endotelial growth factor, http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor
18. Minchenko A, Salceda S, Bauer T and Caro J (1994) Hypoxia regulatory elements of the human vascular endothelial growth factor gene. Cell Mol Biol Res, 40, 35–39.
19. Vascular endotelial growth factor, http://en.wikipedia.org/wiki/Vascular_endothelial_growth_factor
20. Enqi L , Masatoshi M, Shuji K, Tomonari K, Ying Y, Hideo S, Michio N[l], Teruo W J Am Soc Nephrol (2007) , Increased Expression of Vascular Endothelial Growth Factor in Kidney Leads to Progressive Impairment of Glomerular Functions,18: 2094-2104.
21. Liu E, Morimoto M, Kitajima S. (2007). "Increased expression of vascular endothelial growth factor in kidney leads to progressive impairment of glomerular functions". *J. Am. Soc. Nephrol.* 18 (7): 2094–104.
22. Bergers G, Hanahan D (2008). "Modes of resistance to anti-angiogenic therapy". *Nat. Rev. Cancer* 8 (8): 592–603.
23. Current Research, The University of Texas M. D. Anderson Cancer Center 1515 Holcombe Blvd, Houston, TX 77030, 1999, Basic Science Research in Colon Cancer Liver Metastasis, Fig.2 www.wentek.com/jean/research.htm
24. Hanahan D and Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell, 86, 353–36
25. Ferrara N, Carver-Moore K, Chen H, Dowd M, Lu L, O'Shea KS, Powell-Braxton L, Hillan KJ and Moore MW (1996) Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. Nature, 380, 439–442.
26. Dvorak HF, Brown LF, Detmar M and Dvorak AM (1995) Review: Vascular permeability factor/vascular endothelial growth factor, microvascular hyperpermeability, and angiogenesis. Am J Pathol, 146, 1029–1039
27. Claffey KP, Brown LF, del Aguila LF, Tognazzi K, Yeo K-T, Manseau EJ and Dvorak HF (1996) Expression of vascular permeability factor/vascular endothelial growth factor melanoma cells increases tumor growth, angiogenesis, and experimental metastasis. Cancer Res, 56, 172–181
28. Ferrara N and Gerber HP (2001) The role of vascular endothelial growth factor in angiogenesis.[28] Acta Haematol, 106, 148–156
29. Hlatky L, Tsionou C, Hahnfeldt P and Coleman CN (1994) Mammary fibroblasts may influence breast tumor angiogenesis via hypoxia-induced vascular endothelial growth factor up-regulation and protein expression. Cancer Res, 54, 6083–6086
30. Fukumura D *et al*. (1998) Tumor induction of VEGF promoter activity in stromal cells. Cell, 94, 715–725.
31. Kishimoto J, Ehama R, Ge Y, Kobayashi T, Nishiyama T, Detmar M and Burgeson RE (2000) *In vivo* detection of human vascular endothelial growth factor promoter activity in transgenic mouse skin. Am J Pathol, 157, 103–110
32. Coussens LM, Raymond WW, Bergers G, Laig-Webster M, Behrendtsen O, Werb Z, Caughey GH and Hanahan D (1999) Inflammatory mast cells up-regulate angiogenesis during squamous epithelial carcinogenesis
33. Yoshiji H, Harris SR and Thorgeirsson UP (1997) Vascular endothelial growth factor is essential for initial but not continued in

vivo growth of human breast carcinoma cells. Cancer Res, 57, 3924–3928.
34. M *et al*. (1997) Expression of the angiogenic factors vascular endothelial cell growth factor, acidic and basic fibroblast growth factor, tumor growth factor beta-1, platelet-derived endothelial cell growth factor, placenta growth factor, and pleiotrophin in human primary breast cancer and its relation to angiogenesis.
35. Kim KJ, Li B, Houck K, Winer J and Ferrara N (1992) The vascular endothelial growth factor proteins: identification of biologically relevant regions by neutralizing monoclonal antibodies. Growth Factors, 7, 53–64.
36. Ferrara N, Carver-Moore K, Chen H, Dowd M, Lu L, O'Shea KS, Powell-Braxton L, Hillan KJ and Moore MW (1996) Heterozygous embryonic lethality induced by targeted inactivation of the VEGF gene. Nature, 380, 439–442