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Review Article

Oncology Section

Tumour Angiogenesis and Angiogenic Inhibitors: A Review

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ABSTRACT

Angiogenesis is a complex process depending on the coordination of many regulators and there by activating angiogenic switch. Recent advances in understanding of angiogenic mechanism have lead to the development of several anti-angiogenic and anti-metastatic agents that use the strategy of regulation of angiogenic switch. Antiangiogenic therapy is a form of treatment not cure for cancer and represents a highly effective strategy for destroying tumour because vascular supply is the fundamental requirement for growth of tumour. Because of the quiescent nature of normal adult vasculature, angiogenic inhibitors are expected to confer a degree of specificity when compared to nonspecific modalities of chemo and radiotherapy, so it has the advantage of less toxicities, does not induce drug resistance and deliver a relatively non toxic, long term treatment of tumour.

Keywords: Angiogenic switch, Angiostatin, Interleukin,VEGF

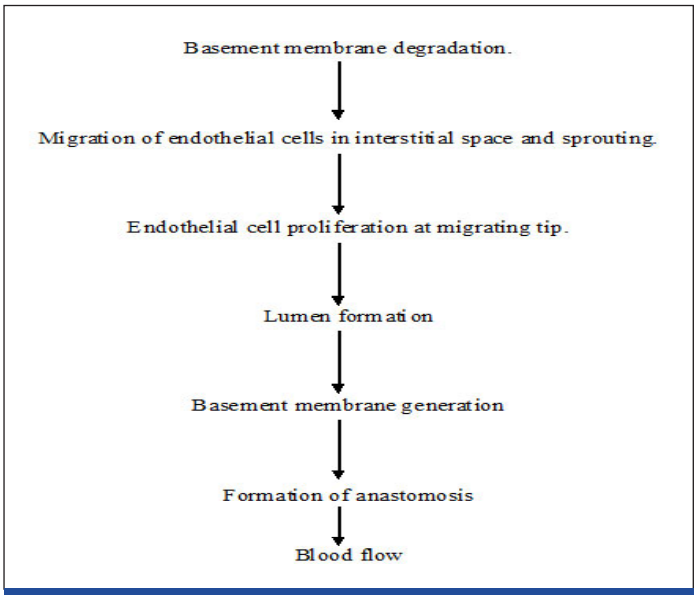
INTRODUCTION

Angiogenesis is a complex process in which there is growth of new blood vessels from the pre-existing ones and is an essential phenomenon for the growth and survival of solid neoplasms [1]. Tumour angiogenesis is the proliferation of blood vessels penetrating the cancerous growth for the supply of nutrients and oxygen [2]. Angiogenesis is a requisite not only for continued tumour growth, but also for metastasis [3]. Because adequate vascular response is critical for the initial development as well as the continued growth of solid tumours, much attention is focused on the use of angiogenesis inhibitors as an adjunct to other forms of therapy for preventing development of malignant neoplasms [4].

TEXT

Physiological Angiogenesis Mechanism

Vasculogenesis is a process in which blood vessels are assembled during embryonic development and further transformation of vascular net which proceed during angiogenesis, it is a complex multistep process where new vessels are formed from the pre-existing ones [3]. Steps in angiogenesis are shown in [Table/Fig-1].



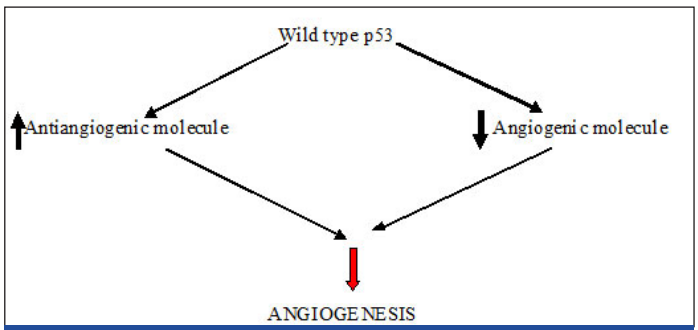
[Table/Fig-1]: Steps in angiogenesis

Tumour angiogenesis

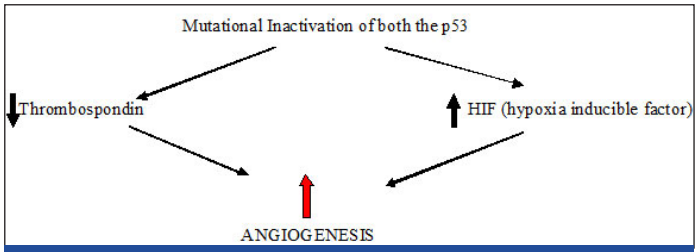
Angiogenesis is the process of new vessel formation and hallmark of tumour progression [5]. Folkman and colleagues demonstrated that solid tumours cannot grow larger than 2-3 mm diameter without inducing their own blood supply [6]. Tumour angiogenesis starts with the release of molecules by tumour cells that send signals to the surrounding normal host tissue, activates certain genes to make protein that encourage growth of new blood vessels [2].

Angiogenic Switch Mechanism

According to the experimental and clinical data most human tumours do not induce angiogenesis and exist in situ, without blood supply for months to years, when some cells within small tumour change to an angiogenic phenotype by a phenomenon known as angiogenic switch. The molecular basis of this mechanism may be increased production of angiogenic factors or loss of angiogenesis inhibitors [Table/Fig-2,3] [3]. Thus, the switch to an angiogenic phenotype is regulated by a change in the equilibrium between positive and negative regulators of angiogenesis [7].



[Table/Fig-2]: Normal angiogenic mechanism



[Table/Fig-3]: Angiogenic switch (Tumour induced)

Factors in Tumour Angiogenesis

Most blood vessels in an adult organism remain quiescent but have the capability to divide in response to stimulus and result in angiogenic process. The molecules that are the positive regulators of angiogenesis are:

A. Vascular endothelial growth factor (VEGF)
B. Platelet Derived Growth Factor (PDGF)
C. Fibroblast growth factor (FGF)
D. Epidermal growth factor (EGF)
E. Transforming growth factor (TGF)
F. Matrix metalloproteinase's (MMP's)
G. TNF (Tumour necrosis factor)
H. Angiopoietins [8].

A-VEGF (Vascular endothelial growth factor): VEGF also known as vascular permeability factor (VPF) is a heparin binding protein and its level is increased in various tumours [9].

Actions of VEGF

- Powerful inducer of angiogenesis [10].
- Stimulates growth and proliferation of endothelial cells [8].
- Act as survival factor for endothelial cells [11].
- Prevent the apoptosis of endothelial cells [12].
- Regulates the vascular permeability [13].

Structure of VEGF

VEGF is a secreted protein which promotes angiogenesis in tumours, chronic inflammation and healing of wounds. Gene encoding the human VEGF consists of 8 exons and 7 introns [3,14]. Alternative splicing of VEGF gene results in 4 different isoforms VEGF 121, VEGF165, VEGF 189, VEGF 206 [14] and less frequent spliced isoforms are VEGF 145 and VEGF 183 [8]. First 26 AAs in VEGF constitute signalling peptide [14]. The most frequent isoform is VEGF 165 which is a homodimer and has a molecular mass of 45 kD [15].

Hypoxia is one of the important factors inducing VEGF expression. [16] Other inducing agents are EGF, TGF α & β, IGF-1, FGF and PDGF [17]. Hypoxia induced transcription of VEGF mRNA is mediated by the hypoxia inducible factor -1 (HIF-1), the binding site of which is located in the VEGF promoter region [18].

VEGF Family & Receptors

Consist of closely related factors that are VEGF A (VEGF), VEGF B, VEGF C, VEGF D, VEGF E and placental growth factor (PlGF) [19]. VEGF family members signal through three tyrosine kinase receptors VEGF R1, VEGF R2, VEGF R3 [3]. Like all RTK, VEGF receptors are transmembranous proteins with a single transmembrane domain. Extracellular region are formed by seven immunoglobulin - like domain. Intracellular region exhibits tyrosine kinase activity and separated to two fragments (TK1and TK2) by an inter kinase insert [20]. VEGF R2 is located in endothelial cells and is the main receptor for the vasculogenic and angiogenic effects of VEGF.

B- Platelet Derived Growth Factor (PDGF): Family of PDGF ligand is composed of 4 structurally related soluble peptides in the form of 5 different homodimers & heterodimers and involved in vessel maturation and recruitment of pericytes [19].

C- Fibroblast Growth Factor (FGF): It is comprised of 23 different proteins and classified in to 6 different groups. These ligands are among the earliest angiogenic factors and involved in promoting cell proliferation, migration and differentiation of vascular ECs [2].

D-Epidermal Growth Factor (EGF): It is comprised of 11 members and 4 EGF receptors. Activation of EGFR pathway results in up regulation of proangiogenic factors such as VEGF and thus viewed as indirect regulator of angiogenesis [5].

E- Transforming Growth Factor-β (TGF β): TGF β is produced by nearly every cell type and participates in angiogenesis, embryonic development & wound healing and has potent growth inhibition properties. It has both pro and anti angiogenic properties, depending on its levels. Low levels promote angiogenesis by up regulating angiogenic factors & proteases and high levels inhibit ECs growth and proliferation by preventing phosphorylation of pRB and thereby arresting endothelial cells at late G1 phase [2].

F-Matrix Metalloproteinases (MMPs): MMPs induce tumour angiogenesis by degrading ECM and releasing angiogenic mitogens that are stored in the matrix. MMP-9 and MMP-2 proteolytically cleave and activate latent TGF-β and promote tumour angiogenesis [2].

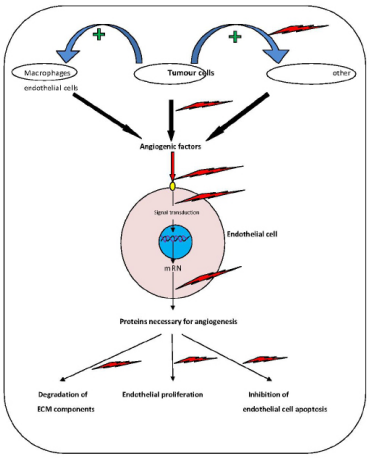
G-TNF (Tumour necrosis factor): TNF is a cytokine released from macrophage, mast cells and T-lymphocytes. It acts as a macrophage activating factor and activates these cells to secrete angiogenic factors.

H-Angiopoietins: Angiopoietin 1 and 2 can act both as proangiogenic and anti angiogenic because of their respective agonist and antagonist signal through Tie receptors. Ang 1 stimulates Tie 2 while Ang 2 does not activate receptor and act as competitive inhibitor of Ang 1.

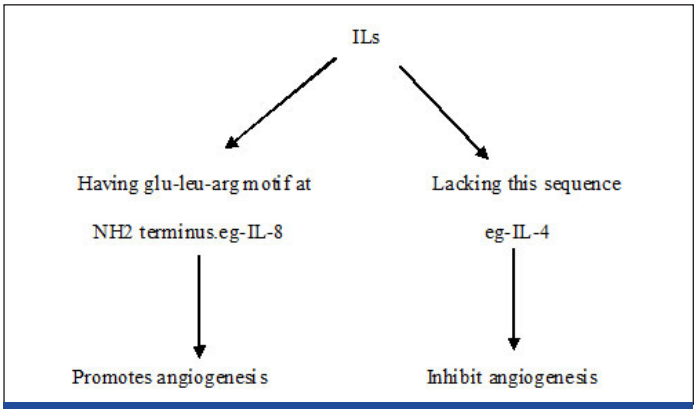
Angiogenesis Inhibitors

Because an adequate vascular response is essential for the initial development and the continued growth of the solid tumours so now a day's anti angiogenic therapy is an attractive modality for preventing the development of malignant neoplasm [21]. The angiogenic inhibitors can be either endogenous (present within the body) or synthetic (drugs).

Different mechanisms of antiangiogenesis are based on the step of angiogenic cascade that is inhibited which can be as under [Table/Fig-4].



[Table/Fig-4]: Angiogenesis cascade and steps blocked by angiogenesis inhibitors



[Table/Fig-5]: Role of Interleukins in angiogenesis

- Prevent or decrease the secretion of angiogenic factors by tumour cells e.g.-interferon [22].
- Increase the secretion of antiangiogenic factors e.g.: retinoids [1]
- Prevent the activation of macrophages and other endothelial cells by the tumour cells [23].
- Targeting the actions of VEGF [24].
- Inhibition of proteases that is essential for penetration of basement membrane and degradation of surrounding ECM to create space in which endothelial cells can proliferate and form new vessels [24]. E.g.- Merimastat, Neovastat
- Induce the EC apoptosis [24].
- Inhibition of EC survival [24].
- To make the endothelial cells refractory to angiogenic stimulus [1]. E.g.-Thalidomide, endostatin, squalamine,TNP-470

The various Endogenous Angiogenesis inhibitors are as follows:

A. Interferon

B. Interleukins

C. TIMP

D. Angiostatin

E. Endostatin

A. Interferon

Interferon is the members of secreted glycoproteins which directly or indirectly inhibit the tumour angiogenesis and growth [25]. Administration of optimal dose of IFN α/β decrease the expression of β - FGF m RNA and protein, microvessel density and also induces the apoptosis of endothelial cells [25]. IFN γ induces its antiangiogenic effects through the secretion of IFN γ – inducible protein 10 (IP-10) and monokine [26].

B. Interleukins [27]

The structure of interleukins (ILs) determines its function to play a role in either promoting or inhibiting angiogenesis [Table/Fig-5].

IL1a is a cytokine secreted by activated macrophage induces angiogenesis through the increased expression of angiogenic factors [28]. IL 12 suppresses the expression of VEGF mRNA, promotes the apoptosis and inhibits proliferation rate in human tumours and reduce tumour vessel density [29,30]. IL-10 down regulate the synthesis of VEGF, IL-1β, TNFα, IL-6, MMP 9 in tumour associated macrophages [31].

C. Timp

Degradation of basement membrane and remodelling of ECM is required to create a space in which endothelial cells can migrate and proliferate [32]. In the process of remodelling of ECM, matrix metalloproteinases (MMPs) have the central role and tissue inhibitors of matrix metalloproteinase's (TIMP) inhibit the neovascularisation by inhibiting the breakdown of surrounding matrix. The migration of ECs through gelatine is inhibited by TIMP-1.TIMP-2 inhibits the β FGF induced EC proliferation [33]. Because of the multiple effects of TIMPs, MMPs are the attractive targets for tumour therapy.

D. Angiostatin

It is a 38 KDa internal fragment of plasminogen and its antiangiogenic effect is due to down regulation of VEGF expression within tumours [34]. Binding of angiostatin to plasma membrane localized ATP synthatase suppress the endothelial –surface ATP metabolism and thus down regulate the EC (endothelial cell) proliferation and migration [35]. According to many studies angiostatin treatment significantly increases the apoptosis of EC [36].

E. Endostatin

It is a 20 KDa fragment of type XVIII collagen and inhibits ECs proliferation, angiogenesis and tumour growth.

Mode of action of Endostatin

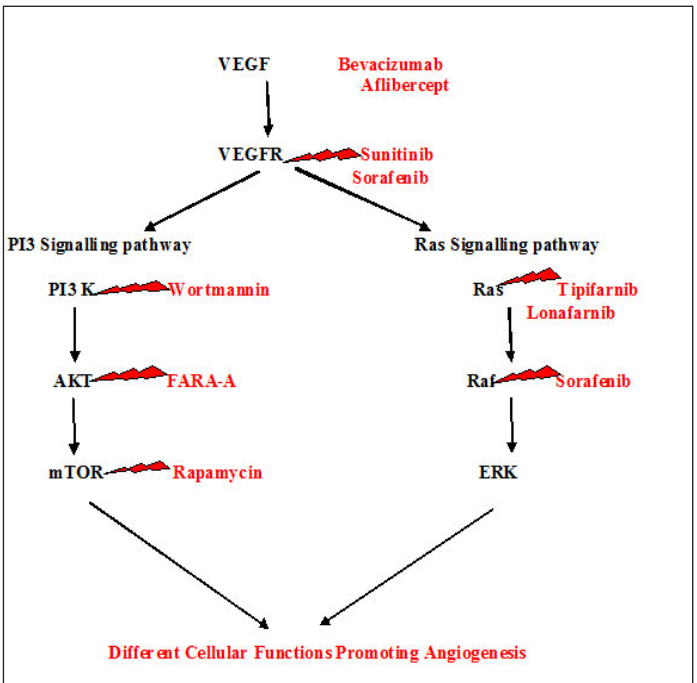
1) Inhibits the binding of VEGF to ECs.
2) Directly binds to receptors but not to VEGF.
3) Blocks the VEGF induced tyrosine phosphorylation.
4) Suppresses the VEGF induced downstream events of KDR/Flk-1 signalling which are involved in the mitogenic activities of VEGF [37].

Drugs That Target VEGF

Mode of action of VEGF includes ligand binding to the extracellular domain of transmembrane tyrosine kinase receptor which induces the autophosphoryation of an intracellular kinase domain and then subsequent downstream signalling by the kinases.

Drugs that inhibit the action of VEGF can act by any of the following mechanisms that can disrupt the above sequence as follows [Table/Fig-6]:

1. Anti VEGF mAb - Which directly neutralises the VEGF proteins and inhibits the biological actions of VEGF [38]? E.g. -Bevacizumab, Aflibercept.
2. Drugs which are soluble VEGF receptors that specifically bind to VEGF and block the binding of VEGF with actual receptors [39].
3. Drugs that is able to bind to VEGF receptors and thus act as inhibitors of VEGF receptors. E.g. -Sunitinib, Sorafenib
4. Inhibitors of VEGF signal transduction pathway by blocking autophosphorylation of VEGF receptors. e.g. -LY294002, Wortmannin, FARA-A, Rapamycin, Temsirolimus, Everolimus, Tipifarnib, Lonafarnib.
5. Drugs with a specific nucleotide sequence which is VEGF antisense and bind to VEGF mRNA and then interferes with the translation process and blocks the VEGF protein formation [40].



[Table/Fig-6]: Drugs targeting Actions of VEGF

1. Drugs that Target Growth Factors

- **BEVACIZUMAB:** It is a humanized monoclonal antibody, binds to VEGF A and prevents it from binding to receptors thus blocks the further signal transduction. Currently tested in various clinical trials for a variety of different tumours and in 2009 was approved for colorectal cancer, breast cancer and RCC [41].

- AFLIBERCEPT-(VEGF-Trap, AVE 0005): It is a soluble fusion protein of extracellular domains of VEGFR1 and R2 and Fc portions of human IgG. Binds to VEGF A & PIGF and renders the ligands unavailable to bind and activate receptors [42].

2. Drugs That Target Receptor Trasncriptase Kinase (RTK)

- SUNITINIB (SU 11248): Orally available tyrosine kinase inhibitor with activity against VEGFR, PDGFR, Flt-3, C-kit& RET, CSF 1R. Studies reported with sunitinib showed no significant antitumor activity in monotherapy. This drug has got FDA approval in 2006 for gastrointestinal stromal tumours and advanced metastatic RCC [43].
- SORAFENIB (BAY 43-9006): Orally available inhibitor of intracellular Raf kinase and targets MAPK, Raf/MEK/ERK signalling pathways. It also inhibits VEGF R, PDGFR-β and C-kit [44].

3. Drugs that Target PI3K/ AKT/ m -TOR Pathway

This signalling pathway is responsible for many processes including angiogenesis, proliferation, and survival and is initiated by RTK activation [45].

- LY294002 and wortmannin are inhibitors of PI3K pathway but demonstrated unacceptable level of toxicity in animals [46].
- Temsirolimus (CCI-779) and Everolimus (RAD001) are inhibitors of mTOR. Clinical trials demonstrated improved survival in advanced RCC leading to FDA approval [47].

4. Drugs that Target MAPK - Farnesyltransferase Rho and Ras

MAPK signalling can lead to increased angiogenesis, thus making it a logical target for Antiangiogenic therapy [48]. The drugs that inhibit MAPK signalling are Tipifarnib (R115777) [49] Lonafarnib (SCH66336) [50].

5. Other drugs

- Tnp-470 inhibits methionine aminopeptidase, prevents endothelial activation and arrest cell cycle [51].
- Thalidomide inhibits TNF α synthesis leading immunomodulatory and anti – inflammatory effects, thus contributing to its Antiangiogenic effect [52].

CONCLUSION

Because fundamental requirement of tumour growth is vascular supply so antiangiogenic therapy for cancer is a highly effective strategy which represent a treatment, not cure and expected to be cytostatic, so particularly effective in combination with cytotoxic agents. One of the major challenges in designing of antiangiogenic therapy is to include each of the possible mechanisms by which tumours can induce new blood vessel growth.

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