CANCER CONUNDRUM

NEOVASCULARIZATION AND CANCER

New vessel growth in the vascular network of a tumor is important for proliferation as well as for metastatic spread of the cancer cells.[1] Tumor vessels grow by various mechanisms, either through vasculogenesis (i.e. recruitment of bone derived endothelial cell progenitor cell to form new vessel), angiogenesis (i.e. the sprouting and growth of new vessels from existing vasculature) or intussusceptions (tumour vessels remodel and expand by the insertion of interstitial tissue columns into the lumen of pre-existing vessels by division or splitting blood vessel into two or more new vessels).[2] The most common pathway for new vessel growth in malignancy is angiogenesis. Tumor angiogenesis is necessary for delivery of oxygen and nutrients to growing tumors and also plays a key role in other aspects of cancer such as metabolic deregulation and tumor dissemination, which facilitates angiogenesis to be considered as the most essential pathological feature of cancer.[3]

In 1971, Folkman first advanced the hypothesis that tumor growth depends on angiogenesis. According to this hypothesis, endothelial cells may be switched from a resting state to rapid growth phase by diffusible chemical signal emanating from the tumor cells.[4]

The tumour can attain a maximum size of 1-2 cm in diameter without the formation of new vascular system. Upto this size tumour cells can get oxygen and nutrients required for the growth through a simple passive diffusion. Angiogenesis is stimulated when tumour tissue requirement of oxygen and nutrients increases.[1]

The tumour angiogenesis is a four step process. 1) Local injury to basement membrane. 2) Activation of endothelial cells by angiogenic factors. 3) Proliferation and stabilization of endothelial cells. 4) Continued influence of angiogenic factors on angiogenesis.[5]

STRUCTURE AND FUNCTIONAL ABNORMALITIES OF TUMOR BLOOD VESSELS

Tumor blood vessels display structural abnormalities like high tortuosity and sinusoidal appearance, poor coverage by vascular supportive cells (pericytes and smooth muscle cells), lack of venous or arterial identity, less diameter of vessels and heterogeneous vascular density. These blood vessels also show dysfunctional features like unusual leakiness, potential for rapid growth, remodelling and poor perfusion. These abnormalities contribute to chaotic and heterogeneity in tumor blood flow. The pressure generated by proliferating cancer cells compresses intra-tumoral blood vessels and lymphatics which leads to impaired blood supply, interstitial hypertension, hypoxia and acidosis. This leads to interference in the delivery of therapeutic drugs that renders the tumor cells resistant to both radiation and cytotoxic therapies.[1,2,5]

Access this article online

Quick Response Code:

Website: www.jomfp.in

DOI: 10.4103/0973-029X.180902

How to cite this article: Bavle RM, Sudhakara M. Cancer Conundrum. J Oral Maxillofac Pathol 2016;20:5-8.

Angiogenesis is regulated by both angiogenic activators and inhibitors. Pro and anti-angiogenic molecules can emanate from cancer cells, endothelial cells, stromal cells, blood and the extracellular matrix.[2]

The balance between activators and inhibitors play a crucial role in tumor angiogenesis. The prevailing evidences suggest that tumor angiogenic switch is triggered as a result of a shift in the balance between stimulators and inhibitors[1] [Figure 1].

Angiogenic signals lead to preferential differentiation of certain endothelial cells into tip- cells, which start migrating and exit at the leading front of the growing vessels. In healthy angiogenesis, during development, the number of tip-cells is limited leading to an organized orderly expansion of vasculature. In tumor angiogenesis, this process is usually disrupted by excess production of pro-angiogenic signals, lack of angiogenic inhibitors, path finding signals or maturation factors thus leading to excessive tip-cell formation and migration of endothelial cells.[3]

PROMOTERS OF ANGIOGENESIS

The various pro-angiogenic factors have been identified like vascular endothelial growth factor [VEGF], basic fibroblast growth factor [FGF], angiogenin, transforming growth factor-α and β [TGF-α and β], tumor necrosis factor- α [TNF-α], platelet derived growth factor (PDGF), granulocyte colony stimulating factor, placental growth factor, interleukin-8 (IL), hepatocyte growth factor and epidermal growth factor.

In the field of neovascularisation in cancer, VEGF family and their receptors are receiving increasingly more attention. Its function in vascular permeability was first described by Dvorack *et al*. and first molecularly defined by Ferrara *et al*. VEGF is a powerful angiogenic agent in neoplastic and normal tissue. Under the influence of certain cytokines and growth factors, the VEGF family appears in the cancerous tissue and adjacent stroma.

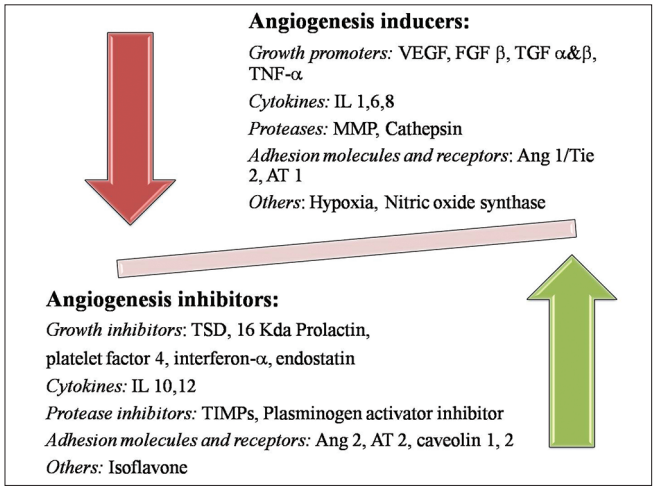

Figure 1: Illustration to depict factors affecting angiogenesis

Many angiogenic phenotypes are triggered by hypoxia which induces the expression of VEGF and its receptors via hypoxia inducible factor -1α (HIF-1α). The binding of VEGF to its receptors activates relay proteins that transmits the signal to nucleus of endothelial cell, which prompt a group of genes to make products needed for new endothelial cell growth.

VEGF-A is a potent and a specific mitogen for vascular endothelial cells and also functions as pro-survival factor in newly formed vessels, which stimulates full cascade of events required for angiogenesis. Endothelial cells activated by VEGF-A produce matrix metalloproteases [MMPs]. The MMPs break down the extracellular matrix which fills the space between the cells made up of protein and polysaccharides. This matrix breakdown permits migration of endothelial cells to surrounding tissue. Soon they will organise into hollow tubes, that evolves eventually as mature network of blood vessels with help of adhesion factors like integrin α and β and angiopoietin -1,-2 (ang) and their receptor Tie-2.

VEGF-B exists in two protein isoforms and binds specifically to VEGFR-1, which is widely expressed in heart, skeletal muscles and vascular cells, but its biological functions remains unclear. VEGF-C has a mature form that consists of VEGF homology domains and receptor binding sites. Its expression is restricted to early development and some pathological conditions like tumor angiogenesis and lymphangiogenesis. VEGF-D is also known as c-FOS induced growth factor. Its mature form has 61% identical amino acid sequence with VEGF-C and both bind to receptors on endothelial cell through VEGFR -2 and -3 which regulate lypmhangiogenesis as well as angiogenesis in mid-stage of embryogenesis. VEGF-E is encoded by the parapoxvirus- Orf which interacts with its receptor and promotes the endothelial growth. There is a significant overlap between binding of VEGF-A and VEGF-B on VEGFR-2 which suggests alliance of two molecules in final response of angiogensis.

Among VEGF family VEGF A, B, C and E act on their respective receptors and cause proliferation of blood vessels while VEGF C and D are involved in lymphangiogenesis.[1,5,6]

A second family of ligands and receptors specific for vascular endothelial cells are Tie-1, Tie-2 receptors and angiopoietin (Ang) 1 and 2 ligands. Ang 1 acts as agonist and Ang 2 acts in a contrary manner, but in the presence of VEGF, Ang 2 acts in collaboration to promote angiogenesis. But in the absence of VEGF, Ang 2 causes regression of newly formed blood vessels by inducing endothelial cell apoptosis.[1,5,6]

INHIBITORS OF ANGIOGENESIS

There are many naturally occurring proteins that can inhibit angiogenesis, including angiostatin (AT), endostatin, interferon, platelet factor-4, thrombospondin (TSD), prolactin 16kd fragment and tissue inhibitors of metalloproteinase

(TIMP)-1,2, and 3. Angiostatin and endostatin are most potent anti-angiogenic factors and play a key role in inhibition of neoangiogenesis. Angiostatin induces apoptosis in endothelial cells and tumor cells and inhibits migration and the formation of tubules in endothelial cells. It has also shown to inhibit tumor growth factors like VEGF and basic FGF. Endostatin binds to the $\alpha5\beta1/\alpha v\beta3$ integrin, the fibronectin receptor in endothelial cells, thus blocking the endothelial cell focal adhesions leading to unstabilized vessels.[1,5]

REGULATION OF TUMOR ANGIOGENESIS

Upregulation of the activity of angiogenic factors itself is not sufficient for angiogenesis in a neoplasm, negative regulators or inhibitors of vessel growth need to be downregulated. The tumor releases diffusible activators of angiogenesis that could signal a quiescent vasculature to begin capillary sprouting. Tumor cells also show much lower levels of inhibitors. In some conditions, the absence of angiogenic inducers may keep the angiogenesis switch off, while in others the angiogenesis inducers are present but are held in check by high levels of angiogenesis inhibitors. Their relative contribution is likely to change with tumor type, site, growth, regression and relapse.[2] Activation of oncogenes such as mutant ras and erb proteins; and deletion of tumor suppressor genes such as p53 results in increase in angiogenesis promoting factors. Loss of p53 expression is associated with decreased expression of thrombospondin. At the same time when the wild type tumor suppressor genes are expressed in a tumor microenvironment viz., expression of non-mutant wild type von hippel-lindau (VHL) gene and p16 gene, they block tumor angiogenesis by inhibiting VEGF.[5] The molecular signals involved in proangiogensis (pro-tumorogenic) and antiangiogenesis (anti-tumorogenic) is depicted using the concept of Yin and Yang [Figure 2].

ANTI-ANGIOGENIC THERAPY

Angiogenesis is regulated by both activator and inhibitor molecules. The change of equilibrium to positive regulators can switch to pro-angiogenic phenotypes leading to tumour cell proliferation and metastasis. In this context, angiogenic inhibitors provide hope for reducing the mortality and morbidity of carcinomas. Examples of targeted drugs are bevacizumab (monoclonal antibodies against circulating VEGF), aflibercept (against fusion proteins that trap angiogenic factors), sorefenib, sunitinib, pazopanib, regorafenib or axitinib (tyrosine kinase

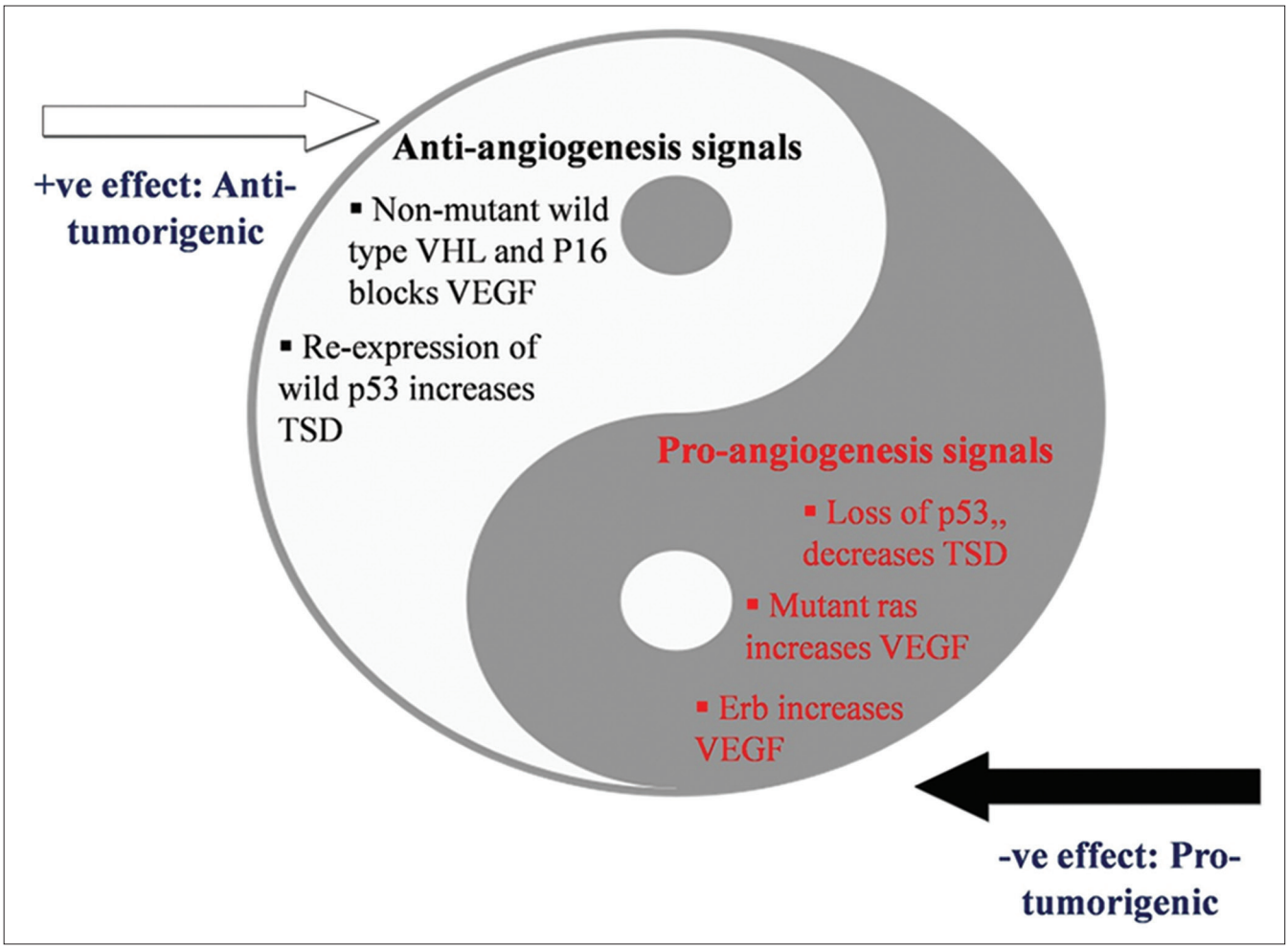

Figure 2: Yin and Yang depicting the various promoters and inhibitors of tumor angiogenesis affecting tumor progression.

inhibitors), paclitaxel, doxorubicin and thalidomide (inhibiton of VEGF and bFGF) and rapamycin analogues like temsirolimus and everolimus (inhibition of HIF-1alpha by blocking mTOR activity). Angiogenic inhibitors currently under clinical trial include: Inhibitors of proteases [act on MMPs], endothelial cell migration and proliferation, angiogenic growth factors; and inhibitors with unique mechanisms, have shown moderate positive outcome. However combination of these anti-angiogenic drugs with cancer chemotherapy or radiation therapy tends to increase the overall survival rate. Hence simultaneously hitting multiple aspects of tumor angiogenesis with cocktail of drugs might create a more effective treatment strategy especially in the frames of cancer prevention in high risk settings or maintenance therapies.[3]

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Radhika M Bavle, Sudhakara M
Department of Oral and Maxillofacial Pathology, Krishnadevaraya College of Dental Sciences, Bangalore, Karnataka, India.
E-mail: rad.iaomp@gmail.com

REFERENCES

1. Nishida N, Yano H, Nishida T, Kamura T, Kojiro M. Angiogenisis in cancer. Vasc Health Risk Mang 2006;2:213-219.
2. Carmeliet P and Jain RK. Angiogenesis in cancer and other diseases. Nature 2000;407:249-257
3. Wang Z, Dabrosin C, Yin X, Fuster MM, Arreola A, Rathmell WK, *et al*. Broad targeting of angiogenesis for cancer prevention and therapy. Seminars in Cancer Biology 2015;35:S224-S243.
4. Hanahan D and Folkman J. Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 1996;86:353-364.
5. Robert S. Kerbel. Tumor angiogenesis: Past, present and the near future. Carcinogenesis 2000; 21(3):505-515.
6. Lauri Eklund, Maija Bry, Kari Alitalo. Mouse models for studying angiogenesis and lymphangiogenesis in cancer. Molecular Oncology 2013; 7: 259-282.