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VEGF inhibition in the therapy of malignant tumors: From theory to hope

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More than a century ago, pathologists made the observation that some human tumors contained unusually high numbers of blood vessels and suggested that blood vessels may contribute to the growth of cancer. The dependence of tumor growth on the development of neovascularisation is now a well-established aspect of cancer biology (1). In 1989 Ferrara and his collaborators made a crucial discovery to our understanding and treatment of cancer, cardiovascular disorders and tissue repair. This discovery was the identification and cloning of a gene termed vascular endothelial growth factor, or VEGF, now known as VEGF-A. VEGF is key regulator of physiological angiogenesis during embryogenesis, skeletal growth and reproductive functions. Many others molecules have been implicated as positive regulators of angiogenesis, including acid fibroblast growth factor (FGF), basic FGF, transforming growth factor (TGF)-α, TGF-β, hepatocyte growth factor (HGF, or scatter factor), tumor necrosis factor-α, angiogenin, interleukin (IL)-8 and angiopoietins (2,3). Angiogenesis is important for supply of oxygen, nutrients, growth factors and hormones, proteolytic enzymes, influences on hemostatic factors that control the process of blood coagulation and fibrinolytic system, and dissemination of tumor cells to in the metastatic process (4,5). Our understanding of angiogenesis has improved dramatically over past two decades. VEGF activity promotes growth of vascular endothelial cells (ECs) derived from arteries, veins and lymphatics. In the tumor angiogenesis this process involves recruitment of sprouting vessels from existing blood vessels and incorporation of endothelial progenitors into the growing vascular bed (6). VEGF is a survival facto for ECs, both in vitro and in vivo by inducing expression of the anti-apoptotic proteins Bcl-2 and A1 in ECs. Although ECs are the primary target of VEGF, several studies have reported mitogenic effects on certain non-EC types (7). VEGF has also effects on bone marrow-derived cells. It promotes monocyte chemotaxis and induces colony formation by mature subsets of granulocite-macrophage progenitor cells. In mice inhibits dendritic cell development and increases production of B cells and generation of immature myeloid cells. VEGF-deficient hematopoietic stem cells and bone-marrow mononuclear cells did not repopulate lethally irradiated hosts (8). VEGF is known also as vascular permeability facto, based on its ability to induce vascular leakage and play significant roles in inflammation and other pathological circumstances (9-11). Investigation of the molecular basis of angiogenesis identified a number of growth factor receptor pathways that promote tumor angiogensis and one of the major is VEGF family of proteins and receptors. The VEGF-related gene family of angiogenic and lyphangiogenic growth factors comprises six related glycoproteins referred as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor PlGF- 1 and PlGF-2 (9,12,13). Initially, VEGF binding sites were identified on the cell surface of vascular ECs. Two receptors were originally identified and characterized as the specific tyrosine kinase receptors (TKR), VEGFR-1 and VEGFR-2. Subsequently, it become that this receptors also occur on various hematopoietic bone marrow-derived cells (14). More recently, an additional TKR, VEGFR-3 was identified and has been found to be primary associated with lymphangiogenesis (15). The various members of the VEGF family have differing binding specificities for each o this receptors, which have helped in elucidating their function (Figure 1).

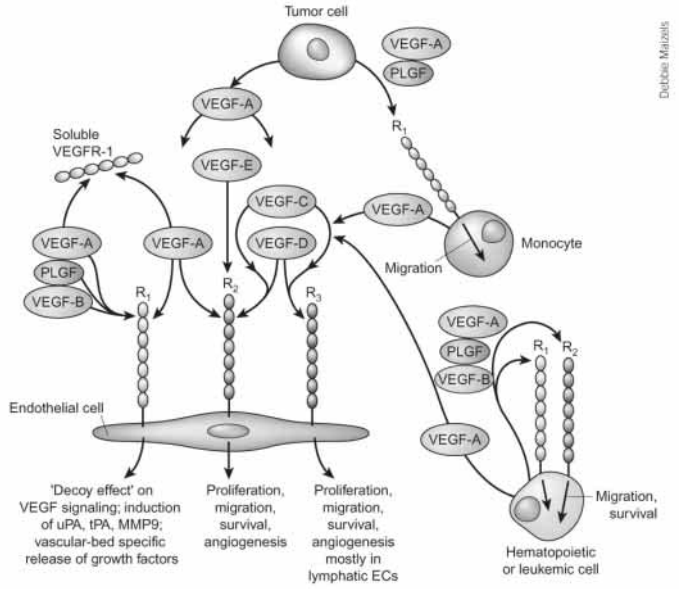

Figure 1. Role of the VEGFR tyrosine kinases in different cell types. (VEGFR-1, -2, -3 = R1, R2, R3). R1 and R2 are expressed in the cell surface of most blood endothelial cells (ECs). R3 is expressed in lymphatic EC. VEGF-A binds both R1 and R2, PLGF and VEGF-B interact only with R1. VEGF-D is a selective R2 agonist. VEGF-C and D bind R2 and R3

EGF play crucial role in physiological angiogenesis during embryonic and early postnatal development, skeletal growth and endochondral bone formation, wound healing and female reproductive function during follicular growth and development of the corpus luteum (9,16). The role of VEGF in the process of tumor angiogensis via stimulation of VEGFRs on tumor endothelium is well established. However, it could be hypothesized that various VEGF ligands support tumor growth, not only by inducing angiogensis, but also by acting directly through VEGFRs expressed by vast majority of solid tumor cells. VEGF is also expressed in a variety of cell lines derived from various hematological malignancies, including multiple myeloma, T-cell lymphoma, ALL, Burkitt lymphoma and CLL (17). All this basic and preclinical investigations found their therapeutic implications and perspectives. It is therefore, not surprising that most of the antiangeogenesis treatment strategies currently in preclinical and clinical development focus on inhibition of the VEGF pathway. As a key regulator of angiogensis, VEGF inhibition has become an attractive therapeutic approach for the treatment of malignant tumors in which aberrant angiogenesis is thought to contribute to disease development or progression. Several anti-VEGF strategies have developed, including neutralizing antibodies to VEGF or VEGFRs, soluble VEGFR/VGFR hybrids, and tyrosine kinases inhibitors to VGRFs.

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Table 1. Drugs currentlly in development as inhibitors of VEGF

Agent	Class	Target	Company
Bevacuzimab	MAb	VEGF-A	Genethech
IMC-1121B	MAb	VEGFR-2	ImClone Systems
CDP-791	Pegylated DiFab	VEGFR-2	Celthec
2C3	MAb	VEGF-A	Peregrine
PTK-787	TKInh	VEGFR-1 -2	Novartis
AEE 788	TKInh	VEGFR-2 EGFR	Novartis
ZD6474	TKInh	VEGFR-1,2,3 EGFR	AstraZeneca
AZD2171	TKInh	VEGFR-1, -2	AstraZeneca
SU11248	TKInh	VEGFR-1, - PDGFR	Pfizer
AG13925	TKInh	VEGFR-1, -2	Pfizer
AG013736	TKInh	VEGFR-1, -2	Pfizer
CEP-7055	TKInh	VEGFR-1, -2, -3	Cephalon
CP-547,632	TKInh	VEGFR-1, -2	Pfizer
VEGF-trap	Sol. hybrid receptor	VEGF-A, PlGF	Aventis/Regeneron
GW786024	TKInh	VEGFR-1, -2, -3	GlaoSmithKline
Bay 93-4006	TKInh	VEGFR-1,2 PDGFR	Bayer/Onyx
AMG706	TKInh	VEGFR-1, -2, -3	Amgen

Abbreviations: MAb - monoclonal antibody; TKInh – tyrosine kinase inhibitor; DiFab – two antibodies fragment consisting of antigen combining site. VEGF – vascular endothelial growth factor; VEGFR – VEGF receptor; PDGFR – platelet-derived growth factor receptor; PlGF – placenta growth factor; EGFR – epidermal growth factor receptor.

Table 1 summarized the classes of drugs currently in development as inhibitors of VEGF pathway. Some of these agents are investigating in clinical trials. The initial aim of antiangiogenic therapy was to "starve" tumor and thus inhibit their grow, but targeted therapy alone had modest objective response up to 10% (16). Therefore these therapies required additional cytotoxic therapy that directly targets rapidly proliferating neoplastic cells. A major question is what impact VEGF inhibition will have in human patients, especially with advanced malignancies. This question will be answered by the various clinical trials, which targeting colorectal (18,19), lung (20), head and neck (21), renal-cell carcinomas (22,23), and breast carcinoma (24). What mechanisms are responsible for the enhanced antitumor activities when combining with VEGF-targeted agents with conventional therapies? The answer to this question is not readily clear. Further understanding of the VEGF and VEGFRs family and their role in tumor angiogensis is necessary.

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