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Angiogenesis and Antiangiogenesis Therapies: Spear and Shield of Pharmacotherapy

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Angiogenesis, the growth of nascent blood vessels from pre-existing vessels, is a critically important process for both physiological (such as wound healing, reproduction and embryonic development) and pathophysiological conditions (such as solid tumor growth, psoriasis and diabetic retinopathy). Angiogenesis is a dynamic and complicated multistep process involving the activation, migration and invasion, proliferation, sprout formation, tube formation, and finally capillary network formation of vascular endothelial cells. All of these steps are essential for the success of angiogenesis and is therefore tightly controlled directly or indirectly by the dynamic balance between angiogenic stimulators and inhibitors. Therefore, insufficient and excessive angiogenesis contribute to the pathogenesis of many major diseases Angiogenesis and antiantiogenesis therapies become the latest sharp spear and strong shield for pharmacotherapies of many angiogenesis dependent diseases, in particular cancer.

Under pathologic conditions, insufficient angiogenesis occurs in diseases such as coronary artery disease, stroke, and chronic wounds. Currently several angiogenic stimulators based angiogenesis therapies are under development. In chronic inflammation and tumor growth, there is an imbalance between endogenous stimulator and inhibitor levels, which turn on "pro-angiogenesis switch". Most importantly, human body losses control over the balance between angiogenesis stimulators and angiogenesis inhibitors, which leads to excessive angiogenesis. Excessive angiogenesis mostly occurs when diseased cells, such as inflammatory cells and tumor cells, produce abnormal amounts of angiogenic stimulators, overwhelming the effects of endogenous angiogenesis inhibitors [1-3]. Decreased levels of angiogenic inhibitors in the vitreous and retina have been found in diabetic patients and diabetic animal models, which also contributes to the imbalance of "angiogenesis switch". Excessive angiogenesis is seen in diseases such as solid tumor cancers, diabetic retinopathy, age-related macular degeneration, rheumatoid arthritis, and psoriasis and other angiogenic diseases. In these conditions, new blood vessels feed diseased tissues and destroy normal tissues [4-6]. In the case of cancer, tumor cells produce and secrete excessive amounts of many potent angiogenic stimulators, VEGF, placental growth factor (PlGF), stromal-cell–derived factor 1, and angiopoietin-2. These angiogenic stimulators will activate the complicated multistep angiogesis process surround the tumor microenvironment. New evidence indicates that these angiogenic factors also stimulate the mobilization of cells at distant sites, including bone marrow, into circulation to promote vascularization [7-9]. Moreover, the newly formed angiogenic capillary networks might also provide the "super high way" for the spreading of tumor cells to distant site through circulation, which is blamed to be the major causes of high mortality in cancer patients [1].

Anti-angiogenesis therapy becomes one of the latest successful strategies for cancer treatment with the approval of bevacizumab (Avastin, Genentech) in the treatment of colorectal and other cancers by the Food and Drug Administration. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is the first FDA approved drug in the class of anti-angiogenesis therapy for cancer treatment. This strategy of stopping tumor growth and metastasis by blocking tumor angiogenesis was pioneered by Dr. Judah Folkman and his colleagues almost four decades ago. A tumor requires and stimulates persistent angiogenesis to supply oxygen and nutrients for its survival and growth. Anti-angiogenesis therapy inhibits tumor growth and kills tumor cells by cutting the fuel supply for the tumor cells through blocking tumor angiogenesis. Drugs based on blocking monoclonal antibodies and chemical inhibitors are being developed to neutralize the effect of angiogenesis growth factors [10-13]. In February 2004, bevacizumab (Avastin), a humanized blocking monoclonal antibody for VEGF, was approved to treat metastatic colorectal cancer in combination with 5-fluorouracil (5-FU). Since then, bevacizumab in combination with standard chemotherapy agents has been found efficacious in clinical trials of non–small-cell lung cancer, renal cell carcinoma, glioblastoma, ovarian cancer and breast cancer. More recently, aflibercept (VEGF Trap, Regeneron) in combination with standard chemotherapy regimens is undergoing phase II and phase III clinical trials in the treatment of five different advanced solid tumors: colorectal cancer, non-small cell lung cancer, prostate cancer, pancreatic cancer and gastric cancer. Aflibercept is a fused protein comprised of segments of the extracellular domains of human VEGF receptors 1 (VEGFR1) and 2 (VEGFR2), and constant region (Fc) of human IgG. Afilbercept inhibits angiogenesis by functioning as a soluble decoy receptor to trap VEGFs. Aflibercept may inhibit tumor growth and metastasis by blocking tumor angiogenesis through disrupting the binding of VEGFs from binding to their cell receptors. Furthermore, the VEGF receptor inhibitor PTK787/ZK222584 in combination with standard chemotherapy is in phase III clinical trials for colorectal cancer, and is also in phase II clinical trials for a number of other tumors, such as metastatic gastrointestinal stromal tumors, unresectable malignant mesothelioma [14-19].

In addition to the ligand blocking agents, anti-angiogenesis drugs are also being developed to block the signal transduction pathway for angiogensis stimulators by targeting at the receptor tyrosin kinase pathway for VEGF and other angiogenic stimulators. Several small molecular weight receptor tyrosine kinase (RTK) inhibitors, such as sunitinib and sorafenib, have been developed to target the signal transduction pathway of angiogenic stimulators. In 2006, both sunitinib (Sutent) and sorafenib (Nexavar) were approved by the FDA for advanced renal cell carcinoma [20-24].

In November 2007, the FDA granted approval of sorafenib for the

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treatment of inoperable hepatocellular carcinoma, and current trials are ongoing in ovarian, pancreatic, and thyroid cancers. A variety of other small-molecule RTK inhibitors targeting the VEGF receptors signal transduction pathway have been approved by FDA for the treatment of solid tumor cancers, including gefitinib (Iressa), Erlotinib (Tarceva), pazopanib (votrient), vatalanib, and vandetanib (Caprelsa) [25-29].

Unlike standard chemotherapy agents, anti-angiogenesis therapy does not easily cause tumor resistance. Tumors do not appear to easily develop a resistance to angiogenesis inhibitors, even when given over a long period of time. In the normal healthy body, the angiogenesis switch is kept "off" with the effect of inhibitors being dominant over stimulators. Since anti-angiogenesis therapy is a target therapy aimed specifically at the angiogenic stimulators and the angiogenic microvascular endothelial cells, anti-angiogenesis therapy usually produce only mild side effects and are non- toxic to most healthy cells. Interestingly, research on some of the previously approved chemotherapeutic agents, such as doxorubicin and cisplatin, demonstrate that they inhibit VEGF production. Thalidomide inhibits angiogenesis mediated by VEGF and bFGF. Studies have shown that thalidomide in combination with dexamethasone has increased the survival of multiple myeloma patients. The combination of thalidomide and dexamethasone, is now one of the most common regimens for patients with newly diagnosed multiple myeloma, with an improved response rate of up to 60-70%. There are at least 30 known endogenous angiogenesis inhibitors found in the body, they are also potential drug targets for anti-angiogenesis therapy. Angiogenesis inhibitors have also been discovered from natural sources, including: tree bark, fungi, shark muscle and cartilage, sea coral, green tea, and herbs (licorice, ginseng, cumin, garlic). In total, more than 300 angiogenesis inhibitors have been discovered to date [29].

In summary, antiangiogenesis therapy represents one of the most significant advances in clinical oncology. It has sparked tremendous interest in angiogenesis research in both academic research institutions and pharmaceutical industry for the past two decades. The FDA has approved over 10 anticancer drugs with recognized antiangiogenic properties. More research is needed to fully understand the biological mechanisms of tumor angiogenesis to optimize this new cancer treatment strategy. Next generation medications are in development to increase the target specificity and to investigate possible treatments across the spectrum of solid tumors. Although the majority of the currently approved antiangiogenesis drugs only offer a modest survival benefit in a limited patient population, they have pave the way for the development of an optimized antiangiogenesis strategy and improved cancer treatments. On the other hand, the effort of developing angiogenesis therapy for diseases with insufficient angiogenesis is relatively too little and too slow compared to the tremendous effort and great success of developing antiangiogenesis therapy.

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