



## **Angiogenesis: Role in Tumor Growth and Metastasis**

Chandra Mohan, Ph.D., EMD Chemicals, San Diego, California 92121

Angiogenesis, a multi-step process consisting of degradation of basement membrane, proliferation and migration of endothelial cells to the tumor, canalization and branching, is not only a prerequisite for tumor growth and expression, but is also a major factor affecting the metastatic spread of malignant cells. Angiogenic growth factors secreted by tumors, endothelial cells, and supporting cells act as autocrine or paracrine growth factors to accelerate angiogenesis. Most tumors persist for years without any angiogenic activity, incapable of growing beyond 2 to 3 mm in size. However, rapid tumor growth ensues when they switch to the angiogenic phenotype. In the dormant stage, the rate of tumor cell proliferation is balanced by apoptosis of tumor cells.

Vascular endothelial growth factor (VEGF), one of the most potent angiogenic cytokines, regulates both vascular proliferation and permeability, and acts as an anti-apoptotic factor for newly formed blood vessels. Alternative splicing of a single VEGF gene results in the generation of five isoforms of VEGF that differ in their molecular weights and in their ability to bind to cell-surface heparan sulfate proteoglycans. VEGF<sub>121</sub> and VEGF<sub>165</sub> are reported to be the most dominantly expressed variants in all tumor cell lines investigated. The biological effects of VEGF are mediated mainly VEGFR-1 (Flt-1) and VEGFR-2 (KDR/Flk-1), whose expression is largely limited to the vascular endothelium. VEGF expression is enhanced in response to hypoxia, oncogenes, and several cytokines and it is associated with poor prognosis in several types of cancer. The obligatory neovascularization, a rather uncommon process under normal conditions, for tumor growth and metastasis makes angiogenesis a prominent target for therapeutic intervention. Most of the antitumor agents used in cancer therapy are cytotoxic in nature, designed mainly to prevent tumor growth. However, to be useful, an ideal therapeutic agent should exhibit selectivity and minimal acute or chronic toxicity. Selective effect of angiogenic inhibitors on vasculature not only reduces toxicity, but also helps to overcome drug resistance commonly seen in solid tumors. This presentation will highlight the role of angiogenesis in tumor growth and metastasis and introduce various investigative tools developed by EMD Chemicals to induce and block the angiogenesis process.