

Introduction



Vicki Caligur
Market Segment Manager, Specialty Biochemistry
vicki.caligur@sial.com

Angiogenesis, the construction of new vasculature, has been recognized as a key step in cancer for over 100 years, but it was not until the 1970's that Judah Folkman suggested that the abnormal development of vasculature could be used to target

malignant tumors.¹ Anti-angiogenic therapies, including antibodies to key angiogenic growth factors and small molecule inhibitors, are now being developed by pharmaceutical companies as a way to stop angiogenesis and prevent tumor growth and metastasis.

The creation of new blood vessels is normal and occurs routinely as part of wound healing, pregnancy, and menarche. As with normal tissue, solid tumors require oxygen and nutrients to continue growth, and tumors obtain oxygen from a nearby circulatory capillary. Since the diffusion distance of oxygen is 100-200 μm , tumor cells farther than that distance from the capillary evolve into a hypoxic (oxygen-starved) state. This hypoxia leads to expression of vascular endothelial growth factor (VEGF) and other factors to initiate angiogenesis.

In general, tumor vasculature is more chaotic and less effective than normal vasculature. In normal tissue, new blood vessels are constructed in a systematic way, so circulation is able to deliver oxygen and nutrients, and remove waste products and excessive fluid (see **Figure 1**). Tumor vasculature is characterized by blood vessels connected in apparently random ways, creating loops and dead ends. The structure of the capillaries is also inconsistent due to recruitment of tumor cells and incomplete assembly of basement membrane. The resulting capillaries are "leaky" and inefficient in removing lymph fluid (see **Figure 2**).

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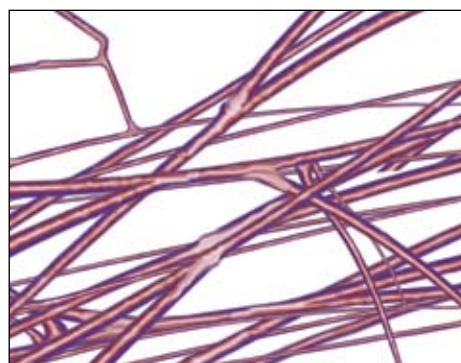


Figure 1. Illustration of normal vasculature.

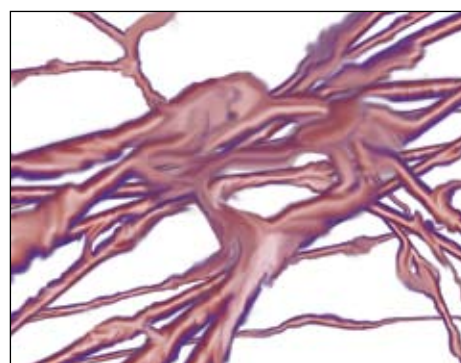


Figure 2. Illustration of tumor vasculature.

Angiogenesis is critical for tumors to evolve from a dormant (benign) to a malignant state. Those growths that do not initiate the growth of their own vasculature remain dormant. It is not until the composition of the tumor microenvironment shifts to encourage blood vessel growth that the tumor becomes malignant, increasing its growth rate and ability to metastasize. Hanahan and Folkman called this the "angiogenic switch", and hypothesized that the balance of angiogenic inducers and angiogenic inhibitors must shift from predominantly inhibitory to predominantly active.²

The tumor microenvironment is another crucial component in the development of vasculature. Changes in signaling and endothelial cell recruitment and evolution produce heterogeneous changes in the extracellular matrix of the tumor. Folkman suggested a two-compartment system to create vasculature, requiring both tumor cells and endothelial cells in the microenvironment. The endothelial cells go into a rapid-growth, vascular construction state.³ This has provided another route to developing therapies; instead of targeting the solid tumor with its physical challenges, alternative therapies target the endothelial cells and microenvironment to prevent the construction of new capillaries.

The National Cancer Institute of the U.S. NIH has identified four strategies being used to identify and design anti-angiogenic therapies.

- Block the ability of the endothelial cells to break down the surrounding matrix
- Inhibit normal endothelial cells directly
- Block factors that stimulate angiogenesis
- Block the action of the endothelial cell surface protein, integrin.⁴

Angiogenic pathways and mechanisms continue to be discovered. The secreted frizzled-related protein-2 (SFRP2) has been identified as an angiogenic activator protein, and FK506 (**Cat. No. F4679**) was successfully used to inhibit angiosarcoma by blocking SFRP2 signaling.⁵ Prosapondin, a protein secreted by tumor cells, stimulates the activity of the tumor suppressor enzyme p53, which subsequently increased the expression of the angiogenic inhibitor thrombospondin-1.⁶ Compounds that affect other cellular mechanisms not associated with cancer have been shown to have angiostatic or angiogenic properties. For example, the osteoclast-inhibiting bisphosphonates neridronate (**Cat. No. N6037**)

and clodronate (**Cat. No. D4434**) demonstrated inhibition of angiogenesis in both *in vitro* and *in vivo* experiments.^{7,8}

This issue of BioFiles discusses some of the main processes of angiogenesis, the contribution of the tumor microenvironment to angiogenesis, and recent theories and therapies being investigated to prevent angiogenesis or improve chemotherapeutic drug delivery to the tumor through changes in the microenvironment.

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4. "Angiogenesis inhibitors in cancer research", National Cancer Institute, U.S. National Institutes of Health, www.cancer.gov/newscenter/angio, accessed June 30, 2009
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