CELLULAR EFFECTS OF ANGIOGENESIS INHIBITORS ON BLOOD VESSELS

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Blood vessels in tumors have multiple molecular and cellular abnormalities that provide targets for diagnostics and therapeutics. These abnormalities involve all components of the vessel wall, including endothelial cells, pericytes (mural cells), and vascular basement membrane. Endothelial cells of tumor vessels express abnormal proteins, undergo sprouting and proliferation, and have a defective barrier function. Many tumor vessels depend on vascular endothelial growth factor (VEGF) for survival. In addition, pericytes have an abnormal association with endothelial cells and may express abnormal proteins. The vascular basement membrane of tumor vessels has redundant loose layers that reflect the dynamic nature of the vasculature.

Leakiness of tumor blood vessels has important functional implications. Leakage of fibrin contributes to the provisional extracellular matrix that facilitates vessel growth. Leakiness also enables antibodies and other macromolecules to reach tumor tissue from the bloodstream. Yet, in tumors, vessel leakiness contributes to high interstitial pressure that restricts drug delivery to tumor cells. Also, because of heterogeneity of the leakiness, antibodies and other proteins extravasate in a patchy distribution and do not have uniform access to targets within tumors.

Integrin alpha5beta1 is among the proteins overexpressed on blood vessels in many tumors and increases during malignant progression. The integrin is also expressed on smooth muscle cells and certain other sites in normal tissues. Importantly, alpha5beta1 integrin on tumor vessels is rapidly accessible to antibodies in the bloodstream, but the integrin in most normal tissues is not. The rapid accessibility of the integrin on angiogenic blood vessels results from overexpression on the luminal (apical) surface of endothelial cells due to loss of cell polarity. The barrier function of normal blood vessels limits extravasation of the antibody and access to the integrin expressed by non-vascular cells in normal tissues. Overexpression combined with this distinctive distribution of the integrin on endothelial cells makes it a useful vascular target for diagnostics and therapeutics in cancer.

Studies of the cellular actions of VEGF inhibitors have shown robust and early changes in endothelial cells, pericytes, and basement membrane of blood vessels in mouse tumor models. Within 24 hours, endothelial fenestrations disappear, vascular sprouting is suppressed, and patency and blood flow cease in some vessels. By 7 days, many blood vessels regress, and expression of VEGF receptor-2 (VEGFR-2) is reduced in endothelial cells. Surviving tumor vessels acquire more normal structural features. Pericytes do not degenerate to the same extent as endothelial cells after inhibition of VEGF signaling. Pericytes on surviving tumor vessels have a more normal phenotype. Vascular basement membrane persists for several weeks after endothelial cells degenerate, providing a record of pretreatment vessel number and location, sites for growth factor binding, and a scaffold for blood vessel regrowth after cessation of therapy.

Normal blood vessels in the adult are generally thought not to require VEGF for survival. However, there are clues that some normal blood vessels may depend on VEGF. We sought to identify which normal vascular beds depend on VEGF for survival by treating normal adult mice with the same inhibitors of VEGF signaling as used in tumor models. A study of 17 normal organs after inhibition of VEGF signaling for 1 to 3 weeks revealed significant capillary regression in pancreatic islets, thyroid, adrenal cortex, pituitary, choroid plexus, small intestinal
villi, and epididymal adipose tissue. The amount of regression was dose-dependent and varied from organ to organ, with a maximum of 68% in thyroid, but was less in normal organs than in tumors in the mouse models studied. All VEGF inhibitors studied had this effect. VEGF-dependent capillaries in normal organs were fenestrated, expressed high levels of both VEGFR-2 and VEGFR-3, and had normal pericycle coverage. Surviving capillaries in affected organs had fewer fenestrations and less VEGFR expression. Strikingly, most capillaries in the thyroid grew back within 2 weeks after cessation of treatment for one week.

Our findings of VEGF-dependency of many tumor vessels as well as some normal capillaries, and rapid regrowth of both after cessation of treatment with VEGF inhibitors, illustrate the plasticity of the normal and pathological microvasculature and the role of VEGF in the maintenance of certain normal vascular beds in the adult.

References


