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Angiogenesis and Antiangiogenic Therapy: Revisited

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Angiogenesis is complex process that involves series of events including endothelial cell survival, proliferation, migration, differentiation, and morphological changes, such as tube formation. It is a crucial process in many pathological conditions, such as tumor growth, diabetic retinopathy, and inflammation, as well as in embryonic development and wound healing. The formation and development a new blood supply or angiogenesis is essential to the development and maintenance of any living tissue. Tumors can also stimulate nearby normal cells to produce angiogenesis signaling molecules. The resulting new blood vessels "feed" growing tumors with oxygen and nutrients, allowing the cancer cells to invade nearby tissue, to move throughout the body, and to form new colonies of cancer cells, called metastases. Normal vasculature is architecturally structured to bring oxygen and nutrients to cells, allow for specific exchange of contents, and remove waste in a streamlined, efficient fashion. Diffusion of nutrients over small distances is sufficient for cellular function, but in order for tumor growth to exceed in volume, new vessels must be recruited. Tumor cells generate angiogenic factors that promote new vessel formation and recruit supporting cells. The resulting vasculature, however, is disorganized and heterogeneous with tortuous blood flow. The understanding of the tumor microenvironment and the interactions that provide a survival advantage for developing malignancy leads to investigation of tumor profiling and emerging of target therapies.

One of the key molecules in angiogenesis signaling is Vascular Endothelial Growth Factor (VEGF) which binds to its receptor on endothelial cells and stimulates formation of new blood vessels. Angiogenesis requires the binding of signaling molecules, such as vascular endothelial growth factor. Therefore, anti-angiogenic therapies targeting VEGF or VEGF receptors (VEGFRs) were designed and thought to be an effective tool for controlling the growth of malignant tumors and have been used in clinical trials with varying degrees of success. Recent studies suggest that inhibition of angiogenesis is even a driving force for tumor conversion to a greater malignancy, reflected in heightened invasion and dissemination into surrounding tissues and, in some cases, increased lymphatic and metastatic activities. Prolonged treatment with these receptor blockers also impacted negatively on the outcome of the treatment. Most of antiangiogenic treatment alters blood vessel integrity causing dramatic hypoxia which could increase VEGF production allowing significant invasiveness of tumor cells. New developed angiogenesis inhibitors, which interrupt critical cell signaling pathways involved in tumor angiogenesis and growth, will focus on tyrosine kinase inhibition of multiple proangiogenic growth factor receptors, and production of antibodies directed against specific proangiogenic growth factors and/or their receptors. Using new natural and synthetic angiogenesis inhibitors, we might prevent or slow the growth of cancer. Angiogenesis inhibitors interfere with various steps in this process, specifically, recognize and bind to VEGF. When VEGF is attached to new inhibitor, it is unable to activate the VEGF receptor. Other angiogenesis inhibitors bind to receptors on the surface of endothelial cells or to other proteins in the downstream signaling pathways, blocking their activities. In addition to the angiogenesis inhibitors that have already been approved by the FDA, we are preparing to test new angiogenesis inhibitors that target VEGF through inhibiting different signal pathways that are currently being approved by FDA to tested in clinical trial. Small noncoding RNAs, called microRNAs (miRNAs), are newly discovered regulators of angiogenesis and may prove useful for prognostic efforts in many types of cancer. MiRNAs negatively affect protein translation at the posttranscriptional level and may affect many pathways relevant for tumor progression and metastasis. It is well known that one miRNA may affect many targets, and thus, many processes. As a result, it is challenging to determine how differential expression of a miRNA specifically affects tumor cell function. As new mechanistic information on tumor angiogenesis and new targeted therapies are available, it is expected that an organizing principle of antiangiogenic therapy would be more effective by employing different classes of drugs to overcome resistance.

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