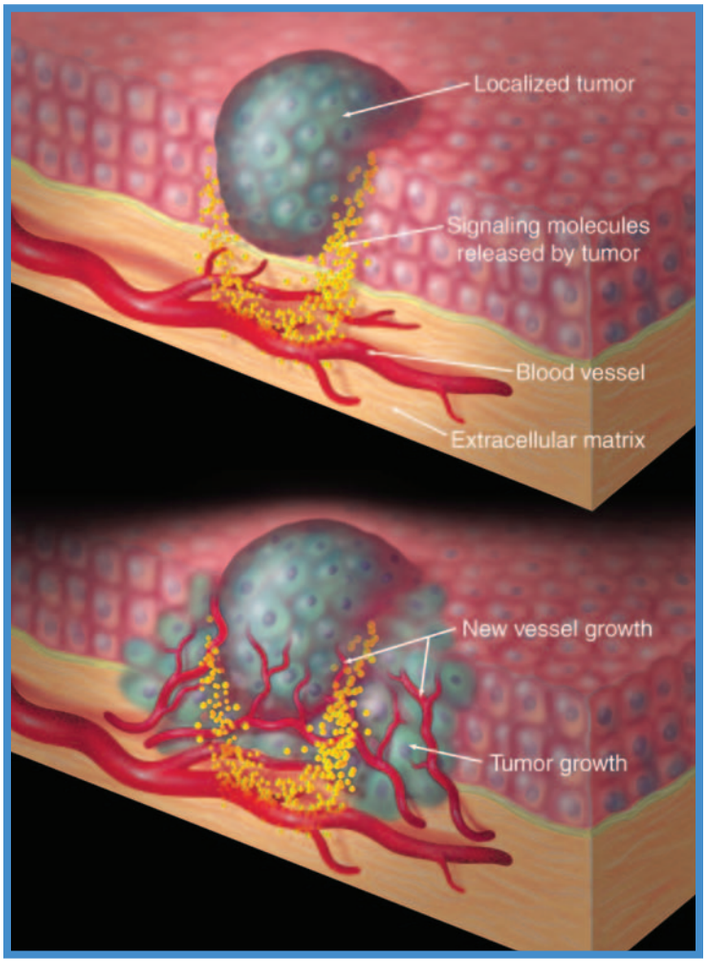
Targeting Angiogenesis

Cutting off a tumor's blood supply is one strategy for treating cancer



In tumor angiogenesis, a small, localized tumor sends out signals that lead to the formation of new blood vessels around the tumor. The cells that make up the new blood vessels are recruited from the bone marrow. New vessel growth allows the tumor to increase in size and potentially spread to other parts of the body.

A tumor, like any other part of the body, needs nutrients to thrive. Cut off the tumor's blood supply, and it shrinks and dies. This is the idea behind development of angiogenesis inhibitors, a cancer-fighting strategy that is under investigation at Memorial Sloan-Kettering and other institutions throughout the world.

The formation and growth of new blood vessels, a process called angiogenesis, is crucial to the development and spread of cancer. Angiogenesis also plays a role in many normal, essential processes in the body, including embryonic development, the healing of wounds, and a woman's menstrual cycle. Tumor angiogenesis occurs when cancer cells begin sending signals to surrounding tissue, activating proteins that encourage the growth of new blood vessels. These blood vessels supply oxygen and nutrients to the tumor so that it can grow. They also allow cancer cells to enter the bloodstream and spread to other parts of the body, a process called metastasis.

"The idea behind focusing on angiogenesis as a cancer therapy is that, without a network of blood vessels, the tumor can't grow beyond a very limited size," said Robert Benezra, head of the Molecular Mechanisms of Differentiation Laboratory in the Sloan-Kettering Institute and an expert on angiogenesis. "Also, because the blood vessels that feed the tumors are normal blood vessels, they are genetically stable and less likely to develop resistance to drugs." Cancer cells, on the other hand, contain many genetic mutations, so they often are able to adapt to avoid destruction by chemotherapy.

The development of drugs that inhibit angiogenesis as a means of controlling cancer is moving forward, but slowly. Basic research to understand the science behind angiogenesis, including work by several investigators at MSKCC, is important in determining which proteins in the angiogenesis process might make the best targets for drug therapies.

Filippo Giancotti, head of SKI's Cell Adhesion and Signaling Laboratory, is studying how molecules called integrins are related to angiogenesis. Integrins are a family of receptors that allow cells to attach to the extracellular matrix (the support structure surrounding cells that is often referred to as connective tissue). Upon binding to specific proteins in the matrix, integrins deliver to the cell's interior signals that affect cellular growth. Dr. Giancotti recently published a paper in the journal *Molecular and Cellular Biology* demonstrating that an integrin called $\alpha 5\beta 1$ activates a cascade of genes that were already known to be players in angiogenesis. He envisions that blocking the function of this integrin may curb angiogenesis.

Dr. Giancotti is also studying another integrin, $\alpha 6\beta 4$, which he believes is important for angiogenesis. He has created mouse models

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that make a mutant version of α6β4, which is unable to signal, and he plans to crossbreed them with mice that are genetically engineered to be susceptible to certain kinds of cancer. "Now we will be able to look at tumors that are developmentally very similar to human tumors and study what happens in the mice if their blood vessels lack signaling by this integrin," Dr. Giancotti said.

Dr. Benezra and his colleagues have focused much of their research on a set of proteins called Id proteins, which were known to be important for the development of blood vessels in the developing brain. In 1999, they published work showing that if three of four copies of the genes *Id1* and *Id3* were removed, or "knocked out," in mice, the animals were resistant to cancer. More recently, they used Id-deficient mice to show that the cells that contribute to blood vessel formation are recruited from the bone marrow.

Dr. Benezra now is studying ways to block the function of Id. He has found a molecule that inhibits the protein and is working with MSKCC structural biologist Nikola P. Pavletich to learn how the molecule binds to Id, with the goal of developing a better molecule with enhanced activity to inhibit Id's function. In addition, Dr. Benezra's work has indicated that one of the Id proteins may regulate the activation of α6β4 integrin, and Drs. Benezra and Giancotti plan to further study this connection.

MSKCC's Richard N. Kolesnick, head of the Laboratory of Signal Transduction, and radiation oncologist Zvi Fuks also have published research shedding light on aspects of angiogenesis. Last year in the journal *Science*, they showed that destruction of the endothelial cells that line small blood vessels is the cause of the tissue damage in the gastrointestinal (GI) tract that results from chemotherapy and radiation therapy. This damage is a limiting factor to the highest doses of therapy that patients can safely receive.

By blocking a cell-signaling pathway called the sphingomyelin pathway, Drs. Kolesnick and Fuks and their colleagues found that GI damage could be prevented. They believe they may be able to use that knowledge not only to protect the blood vessels of healthy tissue during therapy, but also to more effectively target the blood vessels that feed tumors by making them more susceptible to destruction from chemotherapy and radiation.

Several drugs that inhibit angiogenesis are already in clinical trials at Memorial Hospital and elsewhere, according to Jakob Dupont of MSKCC's Developmental Chemotherapy Service. Many of these drugs focus on blocking the protein vascular endothelial growth factor (VEGF, pronounced "veg-eff"). VEGF is a molecule that is sent out by tumors to recruit blood vessels. Some VEGF inhibitors block the protein itself by binding to it, thereby preventing it from binding to its receptors. Others VEGF inhibitors focus on blocking other molecules that make up the signaling pathway that leads to the growth of new blood vessels.

Basic research to understand the science behind angiogenesis is important to determine the best targets for potential cancer therapies.

However, drugs that block VEGF activity on rare occasion can have harmful side effects. Some of these side effects may be due to the fact that VEGF also plays a role in functions not related to cancer. In addition, tumor angiogenesis is complex, and different types of tumors rely on different molecules to generate a blood supply. There are other targets that are being investigated for the development of anti-angiogenesis therapies. These include Cox-2, a protein that is the target of many drugs used to treat the inflammation of arthritis and may also be involved in angiogenesis; metalloproteinases, enzymes that are essential to the formation of the extracellular matrix; and epidermal growth factor receptors, which already are the focus of many cancer drugs in development, including gefitinib (Iressa™) for the treatment of non-small cell lung cancer.

Another angiogenesis inhibitor that is showing promise for treating certain kinds of cancer, especially the blood cancer multiple myeloma, is thalidomide. Thalidomide was first used to treat nausea during pregnancy and became infamous in the late 1960s when it was found to cause profound birth defects. Those birth defects, a shortening or absence of arms and legs, are believed to be due to thalidomide's anti-angiogenic effects. "However, researchers are not sure of the exact molecular mechanism by which thalidomide inhibits tumor growth," Dr. Dupont said, "and more studies are needed."

Investigators think that some types of cancer might be better targets for angiogenesis inhibitors than others. For example, much of the success of these drugs so far has been seen in kidney cancer. This success is probably due to the fact that kidney tumors generate extremely high levels of VEGF and significant angiogenesis. In addition, some anti-angiogenesis drugs may turn out to be good agents for preventing the growth and spread of tumors but may not actually reduce tumor size.

Much evidence is showing that angiogenesis inhibitors may work best in combination with other, more traditional chemotherapy drugs that kill tumor cells directly. "There's a notion that combination therapies very much like the ones used to treat AIDS will be developed," Dr. Benezra said, "where the tumors are attacked from different angles at the same time. This could be much more effective than using any one therapy alone."

"We still don't understand the best way to use these drugs," Dr. Dupont explained. "And we not only have to think about the most effective way to use them, meaning alone or in combination with other drugs, but also on which patients they will work best: Will they work with metastatic cancer, or is it better to give them to patients after surgery as a preventive measure to avoid recurrence? There is a lot of enthusiasm about the science, but we have many things to learn." ☼