CANCER RESEARCH

New Type of Blood Vessel Found in Tumors

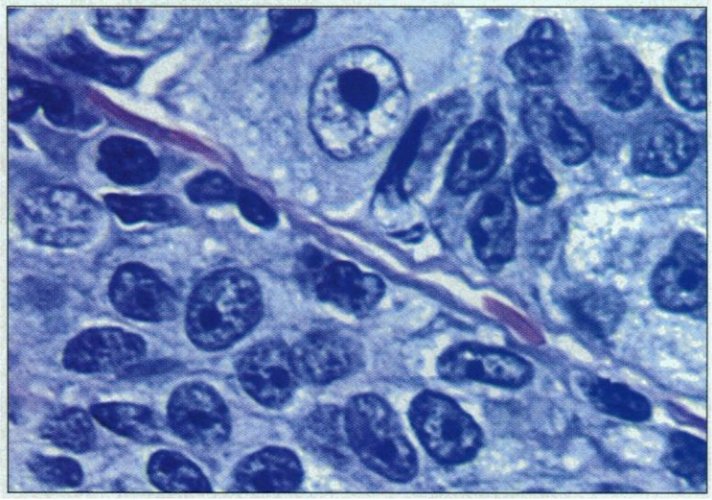
An army's supply lines are often its weak point. Some researchers think that the same goes for cancer. By cutting off angiogenesis —the growth of the new blood vessels that tumors need to nourish themselves—they hope to block tumor growth. But in a new twist that may require some retooling of that approach, a research team at the University of Iowa College of Medicine in Iowa City has found that at least some aggressive cancers have developed an unexpected way of ensuring a blood supply: Rather than inducing normal blood vessel formation, they apparently make new blood supply channels themselves.

New blood vessels are normally formed by a special type of cell called endothelial cells. But Iowa cancer biologist Mary Hendrix and her colleagues Andrew Maniotis and Robert Folberg report in the current issue of the *American Journal of Pathology* that highly malignant uveal melanomas, which develop in the eye, are full of networks of blood channels made by the melanoma cells themselves. The team's results suggest that this happens because melanoma cells, like other cancer cells, lose some of the characteristics of the tissue from which they were derived and acquire the ability to switch identities, turning on genes expressed by other cell types—in this case including key endothelial cell genes.

Avraham Raz, a cancer researcher at the Karmonas Cancer Institute in Detroit, finds the new discovery "very exciting." If the finding is correct, he adds, "then [the melanoma] cells don't have to rely on growth of endothelial cells, because they can [form blood vessels] by themselves."

The discovery may also help explain why the melanomas containing the channels tend to spread aggressively. To form tubes, cancer cells must be capable of burrowing through tissue, a trait also needed for metastasis. What's more, the blood vessels would provide the cells with direct access to the bloodstream. And if other types of cancer cells have similar capabilities, as preliminary work suggests, it would imply that tumors might be able to circumvent some antiangiogenesis drugs now under development, which are directed at endothelial cells. However, the work may also help researchers find genes needed for both types of vessel formation, which could provide new drug targets.

The discovery arose from a collaboration between Hendrix, whose lab has studied the metastatic properties of melanoma cells for many years, Folberg, a pathologist who specializes in uveal melanomas, and Maniotis, who recently moved to Iowa from the lab of Harvard angiogenesis researcher Judah Folkman. Folberg had identified fine web-like patterns of blood vessels in the melanomas and found that patients whose tumors had those patterns were very likely to develop metastases and die. To find out why, Maniotis compared the blood vessel–forming capabilities of cells cultured from the aggressive and nonaggressive tumors, using an assay developed in Folkman's lab at Harvard.



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Channeling. The micrograph shows a channel, clearly containing red blood cells—but not lined with the endothelial cells that would be found in ordinary blood vessels—in a primary uveal melanoma.

Maniotis wanted to see if the cells from aggressive tumors could induce endothelial cells in the cultures to form blood vessels. Instead, the researchers were "absolutely shocked," Hendrix says, to find that aggressive melanoma cells could form channels even in the absence of the endothelial cells. Maniotis repeated the test with a variety of uveal melanoma cell lines, and under a variety of culture conditions. And always, says Hendrix, the cells "formed a pattern that completely recapitulated what was seen ... in the patients." On closer examination of tumors taken from patients, Folberg found that their vessels, like those formed in the culture dishes, were devoid of endothelial cells and instead were completely coated with melanoma cells, easily identifiable by their melanin-containing pigment bodies.

To look for clues to how the melanoma cells had picked up this new skill, the team then collaborated with cancer geneticists Paul Meltzer and Jeff Trent, of the National Human Genome Research Institute in Bethesda, Maryland. Using microarrays that can survey the expression of thousands of genes simultaneously, they found that a host of genes not normally active in melanocytes, the skin cells that give rise to melanomas, are turned on in the tumor cells. "The highly aggressive cells ... have become embryonic-like," says Hendrix. "They are expressing genes that are characteristic of many different cell types." And counted among those genes were many that are characteristic of endothelial cells and may contribute to those cells' ability to form blood vessels.

Other researchers, such as tumor biologist Meenhard Herlyn of the Wistar Institute in Philadelphia, had already found that melanoma cells express some typical endothelial cell genes, but this new work goes further, Herlyn says, by showing that melanoma cells actually act like endothelial cells and form vascular channels. What's more, Hendrix says the team has found the channels in the more common skin-derived form of melanoma, and "we have preliminary evidence that this happens with aggressive prostate tumor cells [and] with aggressive glioblastoma," a brain cancer.

If further work confirms that the phenomenon is widespread, says Raz, "we may have to rethink our strategy of combating vessel formation." For example, some current antiangiogenesis efforts may target characteristics of endothelial cells not shared by the tumor cells and so might miss blood vessels made from the actual cancer cells. But Folkman, whose lab at Harvard has pioneered antiangiogenesis drugs, notes that endothelial cell growth must occur at the sites where the tumor vessels hook up to the surrounding vessels, and blocking that growth might be enough to starve a cancer. What's more, he points out, some of the antiangiogenic treatments home in on target proteins that have been identified in the vessel-forming melanoma cells and so may work against those cells as well.

Even if the drugs currently in development don't act against both types of vessel formation, the Iowa team's finding opens the door to identifying such common targets. Now, Herlyn says, the Iowa team can "sort out which genes are the most important ones" for blood vessel formation. So in time, researchers may be able to turn the devious adaptability of tumors back on themselves.

–MARCIA BARINAGA