Vessel-thwarting antibody might help starve cancerous tumors

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An antibody might offer a safe and effective complement to anti-cancer therapies designed to starve malignant tumors by pruning the blood vessels that feed them, researchers report in the November 2 issue of the journal *Cell*.

The scientists found in studies of mice that an antibody against so-called placental growth factor (PlGF) blocks the growth and spread of many types of tumors. The antibody also enhances the effects of chemotherapy and of other drugs that block angiogenesis--the process by which new blood vessels sprout from preexisting vessels. Those other anti-angiogenic drugs work by acting on vascular endothelial growth factor (VEGF) or its receptor.

Such VEGF inhibitors have prolonged the survival of cancer patients, but without cure and at the expense of side effects, said Peter Carmeliet of K. U. Leuven in Belgium. The drugs effects are often short-lived, with many patients having or developing resistance to them.

“The vast majority of anti-angiogenic agents inhibit VEGF or its main receptor,” Carmeliet said. “Since they work in essentially the same way, a combination treatment of these agents hasn’t added much benefit in prolonging survival of cancer patients. We need complementary drug targets and we believe PlGF might be one. It needs to stand the test of time and rigorous clinical testing, but the findings in mice look promising.”

While VEGF plays an important role in blood vessel formation in both health and disease, the closely related protein PlGF switches on the production of new blood vessels only in disease, earlier studies showed. That raised the question whether PlGF inhibitors might reduce pathological angiogenesis but, unlike VEGF inhibitors, without affecting healthy blood vessels--thus providing an attractive drug with a better safety profile, the researchers explained.

Studies had linked PlGF levels with tumor stage, recurrence and survival, among other characteristics. Notably, they added, PlGF levels rise in cancer patients treated with VEGF-blocking therapies, as well as in human tumors after radio-immunotherapy, suggesting that the growth factor might “rescue” tumors and contribute to drug resistance.

In the current study, the researchers generated a PlGF-neutralizing antibody (aPlGF) and evaluated its potential for preventing the growth of solid tumors. They now report evidence from more than 12 mouse models of cancer that the antibody can slow the growth of tumors, including those that are resistant to VEGF-inhibiting therapies.

The PlGF antibodies blocked angiogenesis and the ability of tumor cells to move. They also prevented infiltration of blood vessel-promoting immune cells, called macrophages, and the development of severe oxygen deprivation within tumors. As a result, the PlGF antibodies did not switch on an “angiogenic rescue program,” which results from an enhanced release of other angiogenic factors, responsible for resistance to VEGF receptor blockers.

The antibody treatment also came with essentially no observed side effects, the researchers report. By contrast, they said, VEGF inhibitors cause blood clots, high blood pressure, blood vessel pruning in healthy organs, interruption of pregnancy, and other side effects.

The lack of ill effects of the antibody treatment may be explained by the fact that PlGF levels are virtually undetectable and dispensable in normal, healthy tissue, Carmeliet said. “PlGF knockout mice survive and are healthy,” he noted. “With no VEGF, they die before birth.” The vessels in healthy tissues also need VEGF, but not PlGF, even when they are not actively growing.

Somewhat paradoxically, aPlGF might have other advantages because, while it inhibits blood vessels in tumors as VEGF inhibitors do, it does so less dramatically, he said. The loss of tumor blood vessels that occurs when VEGF is blocked produces severe oxygen deprivation, or hypoxia, a strong stimulus for the production of other angiogenic factors, including PlGF, to come in and take the place of the primary growth factor. The PlGF antibody seems to allow a “critical threshold” of oxygen to remain, precluding such a rescue operation.

“Because of the excellent safety profile, aPlGF could be combined with VEGF receptor inhibitors to increase efficacy without increased toxicity or resistance,” the researchers concluded. “Besides, single aPlGF therapy may also offer novel opportunities for the treatment of pathological conditions, for which the adverse effects of VEGF receptor inhibitors may be excessive and prohibitive, such as cancer in children and young (pregnant) women, or perhaps in patients at risk for [blood clots], cardiac, or other complications.”

Carmeliet said that antibody therapies have gained ground in recent years as an alternative to the small chemical compounds that can be delivered in the form of a pill. In general, antibodies require an injection about once every three weeks, but usually have more specific effects than chemicals do.

He said he expects it would take at least five to six years, and perhaps closer to 15, to finalize clinical trials of the PlGF antibody alone and in

combination with other drugs in human patients. He added, however, that a “humanized” version of the antibody has already been developed. In principle, a small Phase I clinical trial, designed only to test for drug safety, could begin very soon.

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