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Angiogenesis inhibitors undermined by immune cells, says study

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Angiogenesis inhibitors—a widely used class of cancer drugs designed to shrink tumors by preventing them from forming new blood vessels—often work in the short term, but usually become ineffective within months. Now, a team led by UC San Francisco scientists has discovered a possible reason, one that could lead to a way to address the problem and prevent cancer relapse.

Working with laboratory models of pancreatic and breast cancer, the scientists found that myeloid cells, which originate in bone marrow and are part of the body's first-line of defense—the so-called "innate" immune system—at first work in concert with the therapy but then switch roles and undermine it.

As reported in the April 16, 2015 online issue of *Cell Reports*, the researchers, under the direction of senior investigator Gabriele Bergers, PhD, UCSF professor of neurological surgery, and first author Lee B. Rivera, PhD, a UCSF postdoctoral scholar in the Bergers laboratory, also identified a potential way to stop myeloid cells from sabotaging the therapy and prevent relapse. The key to the discovery, said Bergers, lies in the dual nature of myeloid cells, which exist in two basic states.

In one state, myeloid cells are immunity-enhancing and angiostatic - that is, they prevent the formation of new blood vessels. "This is important in the early stages of wound healing," she explained, "when they need to be immune-stimulatory and attack when bacteria, for example, are invading." But during the later stages of healing, "they need to switch to

their other state, in which they are angiogenic"—generating new blood vessels—"and immune-suppressive, because new blood vessels need to form as part of tissue repair, and you don't want cells around that are in attack mode."

During anti-angiogenic therapy, said Bergers, the Neill H. and Linda S. Brownstein Endowed Chair in Brain Tumor Research and a member of the UCSF Helen Diller Family Comprehensive Cancer Center, "the tumor hijacks the second stage of the natural process we see in wound healing for its own advantage. But we have learned that we can also manipulate this process to make therapy more effective."

Angiogenesis inhibitors approved for clinical use, which include bevacizumab (Avastin), sunitinib (Sutent), and everolimus (Afinitor), work by blocking the vascular endothelial growth factor (VEGF) signaling pathway, which prevents the tumor from forming new blood vessels, thereby shrinking it.

The researchers found that during the initial phase of therapy, VEGF inhibition stimulates myeloid cells within the tumor to release the signaling protein CXCL14, which is angiostatic and stimulates immunity. During this phase, myeloid cells complement the therapy to prevent the creation of new blood vessels, and the tumor shrinks.

But then—probably in response to reduced oxygen flow within the tumor—myeloid cells switch to their opposite state "and become real bad guys," said Bergers. At this stage the cells activate the PI3-kinase (PI3K) signaling pathway, which neutralizes CXCL14 and promotes angiogenesis and tumor growth.

"Once the PI3K pathway is activated, therapy becomes ineffective, and you have relapse," she said.

In breast cancer, Bergers noted, anti-VEGF therapy is not very effective to begin with. "This tells us why," she said. "In a laboratory model of breast cancer, about 45 percent of myeloid cells are already activated, so the cancer just ignores the therapy."

The researchers found that targeting specific innate immune cells within the tumor did not reverse the negative effects of PI3K activation. Eliminating macrophages - one type of white blood cell - resulted in an increase in neutrophils, another type of white blood cell. But eliminating neutrophils brought on an increase in macrophages. This so-called myeloid-cell oscillation maintained the tumor's resistance to the therapy.

Instead, said Bergers, "we found that what you need to do is target the central signaling node, which is PI3K." Ultimately, the researchers demonstrated that combining a PI3K inhibitor with anti-VEGF therapy prevented relapse and significantly increased survival in a mouse model of pancreatic neuroendocrine tumor.

Bergers noted that the discovery potentially gives physicians a way to determine how effective anti-VEGF therapy might be in individual patients, as well as to monitor the course of therapy. "In some new patients, we could test to determine how many myeloid cells in the tumor were already activated, which could tell us to what extent the tumor would still be responsive to anti-VEGF therapy," she said.

In patients undergoing therapy, "we could take advantage of the fact that myeloid cells occur not only in the tumor, but also in the blood," said Bergers. "A simple blood test would give us a non-invasive biomarker to check on the state of myeloid activation. Right now, one of the major issues in anti-VEGF therapy is that there are no biomarkers for response and relapse."