Scientists find link between immune system suppression, blood vessel formation in tumors

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Targeted therapies that are designed to suppress the formation of new blood vessels in tumors, such as Avastin (bevacizumab), have slowed cancer growth in some patients. However, they have not produced the dramatic responses researchers initially thought they might. Now, research from the Perelman School of Medicine at the University of Pennsylvania might help to explain the modest responses. The discovery, published in the July 14 issue of *Nature,* suggests novel treatment combinations that could boost the power of therapies based on slowing blood vessel growth (angiogenesis).

The Penn investigators, led by George Coukos, MD, PhD, Celso-Ramon Garcia Professor of Reproductive Biology, found that ovarian cancer cells grown under low oxygen conditions – which promote blood vessel formation – secrete chemical signals that suppress the patient's immune system, preventing it from killing off the abnormal cancer cells.

"For the first time, we are realizing that the two programs – angiogenesis and immune suppression – are co-regulated and the two programs are mediated by the same cell types," Coukos says. "This creates new therapeutic opportunities, since the study reveals that in order to effectively suppress angiogenesis, one should also suppress a type of immune cell, called regulatory T cells.Thus, commonly used anti-angiogenesis therapies should be combined with therapeutic maneuvers that eliminate regulatory T cells."

Following hints that there might be cross-talk between the two systems, first author Andrea Facciabene, PhD, research assistant professor of Obstetrics and Gynecology, and colleagues grew ovarian cancer cells under normal oxygen conditions or low oxygen (hypoxic) conditions. When the team looked for differences in the proteins called chemokines secreted under the two growth conditions, they found that one signaling molecule, CCL28, was more abundant in low oxygen cultures. CCL28 was also commonly expressed in hypoxic areas of tumors in animal models.

The Penn investigators found that CCL28 recruited regulatory T cells (called T-regs) in experimental situations. Because T-regs suppress local immune responses, including immune cells that kill tumor cells, the researchers hypothesized that CCL28 signaling could induce immune tolerance. In fact, when they looked at tumors grown in animal models, they found that tumors engineered to express CCL28 grew significantly faster than tumors lacking CCL28 expression.

Together the data suggest that hypoxic conditions suppress the immune reaction through T regulatory cells while promoting blood vessel formation. Therefore, to get the most out of anti-angiogenesis drugs, clinicians might need to combine them with drugs that block T-regs.

"The tools to eliminate T-regs effectively are not presently available in the clinic, but the field is definitely advancing, with several candidate strategies currently being tested," Coukos said.

"The other implication of this study is that if anti-angiogenesis therapy induces tumor hypoxia, that could create a rebound increase in regulatory T cells," he continued. "That rebound could account for some of the resistance that is commonly seen in the clinic after anti-angiogenesis therapy is instituted."