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Unexpected Lock and Key Mechanism Found For the Assembly of Tumor Blood Vessels

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A critical lock and key mechanism that allows the final step in the completion of new blood vessel formation has been identified by a UCSD School of Medicine team in research that promises to lead to a new way to halt tumor growth by cutting off the tumor blood supply.

The research team led by Judith Varner, Associate Professor of Medicine at UCSD and a member of the Rebecca and John Moores UCSD Cancer Center, made the surprising discovery that a receptor-ligand pair previously identified as key regulators of immune cell function puts the finishing touches on newly constructed blood vessels by allowing the two cell layers of blood vessels to recognize and "lock" together.

The study, which appears in the June 2005 issue of the Journal of Clinical Investigation, is the first to show how the two cell layers of blood vessels recognize and bind to each other during angiogenesis, which is the formation of new blood vessels.

The work also could yield new ways to diagnose and combat cancer. In fact, together with Dr. Barbara Parker, UCSD Professor of Clinical Medicine at the Moores UCSD Cancer Center, the researchers currently are conducting tests with breast cancer patients to see if measuring the activity of the receptor, or "lock," called integrin, could help diagnose the cancer earlier. They are also currently planning cancer clinical trials with an FDA approved drug directed against the integrin.

Angiogenesis has been an intensely studied field of cancer research for the past 10 years. Since cancer cells literally hijack the body's normal angiogenesis process to initiate blood vessel growth to fuel the growth of tumors, researchers believe that blocking angiogenesis may choke off a tumor's blood supply and kill the cancerous cell.

Varner and her team found that a specific integrin protein called a4b1 was produced at high levels in one part of a developing blood vessel, the interior area called the endothelia. The integrin was not produced in mature blood vessels, indicating a specific role in developing vessels. The team found that the integrin was produced in the endothelia of mouse and human blood vessels that feed tumors such as colon cancer, melanoma and lung cancer. Inhibitors of the integrin stopped new blood vessel growth and suppressed tumor growth, indicating that the integrin helped in the creation of tumors.

"Our study marks the first time this integrin was found to play a key role in angiogenesis," said Varner. "This integrin is known to regulate the body's inflammation response, but until this study it wasn't suspected of regulating angiogenesis. It's possible that since the integrin only works on developing blood vessels and in cancer, disrupting its ability to form blood vessels could starve the tumor and stave off cancer."

The research team discovered that the integrin brought the endothelia, the inside part of a blood vessel, together to bind with vascular smooth muscle, the outer portion of a blood vessel. Blood vessels only work when both endothelia and vascular smooth muscle are bound together. Previous work on integrin a4b1 showed that

the protein worked in the immune system by binding with another molecule called VCAM, so the researchers next looked for evidence of VCAM in the vascular smooth muscle cells, called pericytes.

Indeed, Varner's team found VCAM on the nascent blood vessel's pericytes, but not in mature vessel pericytes. The two molecules, Varner discovered, work together to bring the endothelial cells together with the outer pericytes to create new intact blood vessels, with integrin as the lock and VCAM as the key. Drugs that inhibit either the integrin or the VCAM molecule prevented intact blood vessels from forming.

"When the integrin meets with VCAM, both cell types receive survival signals at this active stage of blood vessel development, which occurs mainly in tumors in adults," said Varner. "This was a chance discovery, which was exciting, and we think it may have important clinical significance."

In their current studies of breast cancer patients for the presence of the integrin and VCAM, "We want to know if the integrins predict aggressive breast cancer. If so, this could become a valuable, non-invasive diagnostic tool for cancer," said Varner.

In addition, knowing how blood vessels are finally assembled could help lead to effective ways to stop the proliferation of cancer cells by cutting off their nutrient supply, Varner added. Drs. Varner and Parker are currently in discussions with pharmaceutical companies to test integrin inhibitors in cancer clinical trials at the new Moores UCSD Cancer Center.

Varner's colleagues in the study included Barbara Garmy-Susini, Hui Jin, Yuhong Zhu, Rou-Jia Sung and Rosa Hwang, all of UCSD.

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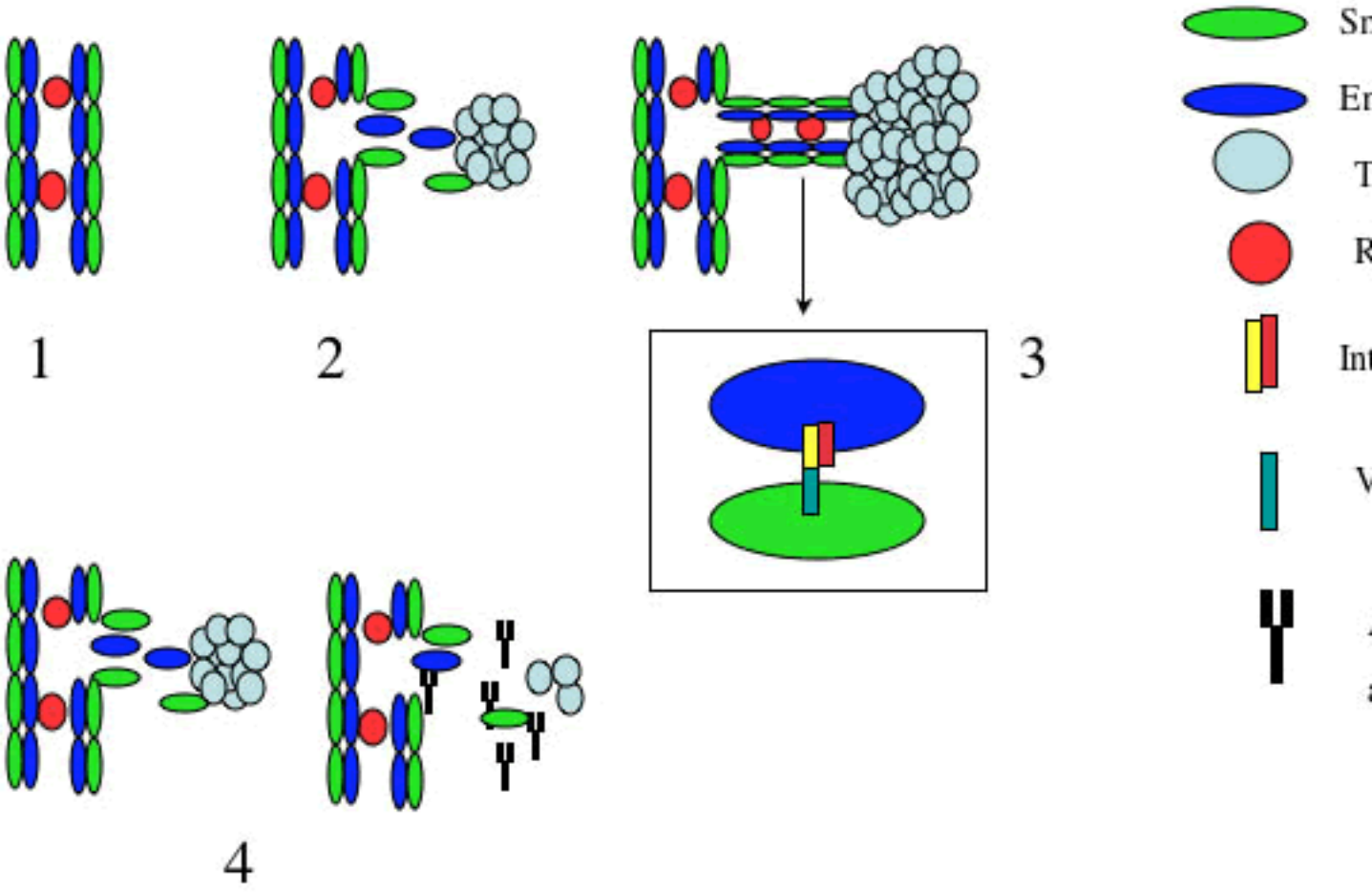

Lock and key mechanism promotes blood vessel formation:

In Panel 1, stable blood vessels are composed of two cell layers, the innermost endothelium and the outermost vasc
In Panel 2, a tumor begins to grow near a blood vessel and attracts a sprout to grow towards it. Endothelial cells an
cells both migrate towards the tumor. In Panel 3. for a new vessel to form completely, the endothelial cells and vas
must find each other and bind to each other. They do this through the interaction of endothelial cell $\alpha 4\beta 1$ and smoo
In Panel 4, a tumor initiates angiogenesis but in the presence of anti–$\alpha 4\beta 1$ antibodies, the the endothelium and smo
each other. Both cell types die and new vessels cannot be completed. The tumor then shrinks or disappears.