UCSD Scientists Find Gas Pedal - And Brake - for Uncontrolled Cell Growth

Discoveries offer promising new way to treat wide array of diseases and conditions

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Scott LaFee

Researchers at the University of California, San Diego School of Medicine have identified a new way to regulate the uncontrolled growth of blood vessels, a major problem in a broad range of diseases and conditions.

The findings are published in the online edition of *Nature Medicine* by David A. Cheresh, PhD, professor of pathology in the UC San Diego School of Medicine and associate director for translational research at the Moores UCSD Cancer Center, and colleagues at the cancer center and at the University of Michigan.

Blood vessels grow and expand in association with a number of diseases. In particular, new blood vessel growth (known as angiogenesis) occurs during the growth of tumors, enabling them to expand and metastasize or spread to other parts of the body. Uncontrolled vascular growth can lead to vascular malformations and hemangiomas, which may become life-threatening. According to the National Cancer Institute, as many as 500 million people worldwide could benefit from therapies targeting angiogenesis.

Researchers have been trying to identify the switch mechanism that converts normal blood vessels from the resting state to the proliferative or diseased state. Cheresh, along with the study's first author Sudarshan Anand, also of the UCSD School of Medicine and the Moores Cancer Center, and colleagues discovered how an "angiogenic switch" turns on and developed a strategy to turn it back off.

During normal blood vessel formation or regeneration, endothelial cells forming the inner layer of blood vessels are exposed to factors in the local microenvironment that initiate the switch, causing blood vessels to begin to expand. Cheresh and colleagues identified a small microRNA (miR-132) responsible for controlling the switch.

Cheresh described the process in terms of a car and its brakes: "In tumor vessels or in hemangiomas, this particular microRNA is abundant and capable of maintaining extensive vascular growth. The effect is similar to a car that's speeding out of control because its gas pedal is stuck to the floor and its brakes aren't working."

The researchers designed a complementary microRNA, or anti-miR, that binds to and neutralizes the original microRNA. "This anti-miR therapy in effect restores functionality to the brake pedal and uncontrolled blood vessel growth comes to a halt," said Cheresh, who noted the new anti-miR turned off the angiogenic switch controlling disease severity in mouse models of cancer and of retinal disorders.

As part of their study, Cheresh and colleagues designed a nanoparticle that's capable of delivering the microRNA or the anti-microRNA directly to the diseased or proliferating blood vessels. This delivery vehicle ensures the therapeutic benefit is maximized while reducing the possibility of toxicity or side effects. By delivering more of this microRNA, the scientists said, it may be possible to promote new blood vessel development in patients who have suffered tissue damage from stroke, heart attacks, or diabetes. Conversely, treating patients with the anti-miR might reduce or inhibit blood vessel development in tumors or help reduce inflammation.

Co-authors with Cheresh and Anand are Bharat K. Majeti, Lisette M. Acevedo, Eric A. Murphy, Rajesh Mukthavaram, Lea Scheppke, Miller Huang, David J. Shields, Jeffrey N. Lindquist and Sara M. Weis, all of the UC San Diego department of pathology and Moores Cancer Center; and Philip E. Lapinski and Philip D. King of the department of microbiology and immunology at the University of Michigan, Ann Arbor.

Media Contact: Scott LaFee, 619-543-6163, slafee@ucsd.edu