

New angiogenesis finding may help fight cancer growth

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A researcher at the University of Wisconsin-Madison School of Medicine and Public Health has discovered a new part of the complicated mechanism that governs the formation of blood vessels, or angiogenesis.

The finding may help halt tumor growth in cancer patients, says Emery Bresnick, the senior author on the study, a professor of pharmacology and member of the UW-Madison Paul P. Carbone Comprehensive Cancer Center.

The research, published in the *Journal of Cell Biology* on Sept. 25, is the first to connect a particular nervous-system chemical to the regulation of blood vessels.

Normally, blood vessels form when wounds heal and during menstruation, pregnancy and fetal development. But impaired blood-vessel development and function are also a major cause of blindness, and tumors rely on new blood vessels as they develop.

Like most critical body processes, angiogenesis is tightly controlled by multiple balancing mechanisms. When Bresnick and colleagues, including postdoctoral fellow Soumen Paul, began the new study, they were not looking into angiogenesis. Instead, they were studying a protein that regulates the maturation of blood cells, and noticed that it turns on a gene that makes a compound called neurokinin-B, or NK-B.

Aware that NK-B affects cells in the nervous system, Bresnick wondered, "Why would a protein involved in blood-cell formation turn on the gene for a compound that is supposedly involved in regulating the nervous system?"

The researchers searched for NK-B receptors - molecules that can "recognize" and respond to NK-B - and found great numbers of them on endothelial cells, which line the inside of blood vessels.

Endothelial cells form the internal structure of a blood vessel, and during angiogenesis, they migrate, starting an extension of the blood-vessel network. When Paul added NK-B to endothelial cells, "They lost the capacity to organize in three dimensions, to form the tubes that are the precursors to new blood vessels," Bresnick says. "Then we got excited."

Further tests showed that NK-B could inhibit angiogenesis in four ways. It prevents the production of vascular endothelial growth factor (VEGF), a key stimulator of blood-vessel formation, and also reduces the number of receptor molecules that respond to VEGF. NK-B also slows the movement of endothelial cells, which is necessary to form new vessels, and raises the level of a newly discovered angiogenesis inhibitor.

"It's premature to call it a master switch, but intriguingly, it regulates at least four different processes, each of which individually would be anti-angiogenic," says Bresnick.

Angiogenesis inhibitors, Bresnick observes, are a fast-growing field of medicine. This June, the Food and Drug Administration approved an angiogenesis inhibitor as the first drug that can restore some vision in the more severe ("wet") form of age-related macular degeneration (AMD). Wet AMD occurs when leaky blood vessels form in the retina. Along with a similar growth of new blood vessels in diabetes, it is the major cause of blindness in older adults.

But the "holy grail" of angiogenesis inhibition concerns cancer treatment. Before solid tumors start to grow, they must create a new blood supply, and since adults need angiogenesis only during pregnancy and to heal wounds, blocking angiogenesis could be a promising way to halt tumor growth. Also in June, the FDA approved a compound that inhibits VEGF for treating colon cancer, the second-leading cause of cancer death in the United States. The VEGF-inhibitor reduces the formation of blood vessels, helping starve tumors.

But angiogenesis regulation is a two-way street, and there are some diseases in which it might be desirable to stimulate angiogenesis. The new research shows that the NK-B system can work both ways: Reducing inhibition seems to increase angiogenesis.

"Activating the NK-B receptor blocked angiogenesis, and blocking the receptor stimulated angiogenesis," Bresnick says. In theory, selectively stimulating angiogenesis could help treat heart attacks by restoring blood flow to the heart, increasing the blood supply to threatened heart muscle.

NK-B also plays a role in a mysterious but common syndrome called preeclampsia, in which soaring blood pressure and low blood oxygen levels harm or even kill pregnant women and their babies. Philip Lowry, at the University of Reading in the United Kingdom, has found that NK-B levels spike in preeclampsia, and the new understanding of NK-B's role in angiogenesis suggests that faulty blood-vessel formation may be to blame.

Because NK-B prevents endothelial cells from organizing into blood vessels, Bresnick says, "Maybe excess levels of NK-B are responsible for or contribute to impaired vascular development/function and certain symptoms of preeclampsia." According to the Preeclampsia Foundation, the condition affects about 200,000 American women each year.

Many angiogenesis inhibitors are under study at this point, but finding a regulatory molecule that affects four separate mechanisms "makes for an interesting package," Bresnick says.

The Wisconsin Alumni Research Foundation has applied for a patent on the discovery, which, says Bresnick, reflected the work of "outstanding collaborators at the University of Wisconsin-Madison, who facilitated this multidisciplinary study and co-authored this paper." Authors included Patricia Keely in the Department of Pharmacology; John Fallon and Tim Gomez in the Department of Anatomy; and Sam Gellman in the Department of Chemistry.

Bresnick and his collaborators are looking further into how the molecule works in human cells and in mouse models of angiogenesis.

Eventually, after years of basic research and drug development, the multitasking compound NK-B could wind up playing a major role in treating cancer and other diseases where blood vessel formation goes awry, Bresnick says. "We have discovered a new peptide that clearly suppresses angiogenesis via a novel multi-component mechanism," he says. "A key question is whether we can exploit it to develop therapeutics."

Source: University of Wisconsin-Madison

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