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Study reveals a key to blood vessel growth and possible drug target

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Researchers have identified a molecular pathway that plays a critical role in the growth of blood vessels. The finding not only offers an important insight into the development of the vascular system during embryonic development but suggests a potential target for inhibiting the blood vessels that fuel cancers, diabetic eye complications and atherosclerosis, the researchers say.

The study, published online on Oct. 14 in *Nature Genetics*. was conducted in the zebrafish, the tiny, blue-and-silver striped denizen of India's Ganges River and many an aquarium.

A "News and Views" commentary on the paper will run in the same issue.

"We expect this finding will offer important insights into blood vessel formation in humans," says lead author Massimo Santoro, PhD, UCSF visiting postdoctoral fellow in the lab of senior author Didier Stainier, PhD, UCSF professor of biochemistry and biophysics. "The zebrafish has proven to be an important model for discovering molecules relevant to human disease."

Angiogenesis, or the growth of blood vessels, is active not only during embryonic development but throughout the life of the body, providing a source of oxygenated blood to tissues damaged by wounds.

However, it is also active in a number of disease processes, including

cancer. Without a blood supply, tumors cannot grow beyond the size of a small pea. Cancerous tumors release chemical signals into their environment that stimulate healthy blood vessels to sprout new vessels that then extend into the tumors. During the last decade, scientists have identified several molecules that promote angiogenesis. A drug that inhibits these molecules is now commercially available and others are being studied in clinical trials.

Scientists are also exploring strategies for stimulating the growth of new blood vessels in patients whose clogged arteries prevent a sufficient blood supply to the heart muscle.

In the current study, the UCSF team determined that two well known signaling molecules, birc2 and TNF, are crucial to the survival of endothelial cells -- which line the blood vessels and maintain the integrity of the blood vessel wall during vascular development -- in zebrafish embryos.

“The pathway these molecules make up during vascular development has not been looked at before,” says Stainier. “It offers a new target for therapeutic strategies.”

The birc2 gene belongs to a family of proteins that control the balance between cell survival and cell death (apoptosis). A cell induces apoptosis when it detects that it is irreparably damaged. The integrity of the blood vessel wall is determined by a dynamic balance between endothelial cell survival and apoptosis.

The scientists started the investigation by examining zebrafish with unusual physical characteristics and working to identify the mutated genes that were responsible for the traits.

“We began with a genetic mutant that displayed vascular hemorrhage

associated with vascular defects, and soon proved that the mutant had a defective birc2 gene," says Santoro. "Without the birc2 gene, hemorrhage and blood pooling occurred, resulting in vascular regression and cell death."

Next, through a series of genomic analyses and biochemical studies, the team discovered the critical role of birc2 and TNF in blood vessel health in the zebrafish embryo. They showed that birc2 is needed for the formation of the tumor necrosis factor receptor complex 1, a group of proteins and peptides that activate cell survival by initiating signals. Tumor necrosis factor promotes activation of NF-kB, a protein complex transcription factor involved in the transfer of genetic information. Further tests proved the existence of a genetic link between the birc2/NF-kB pathway, and that it is critical for vascular health and endothelial cell survival.

"Studies on vascular development are important so that we can better understand the molecular basis of how endothelial cell-related pathologies such as cancer, diabetic eye complications, known as retinopathies, atherosclerosis and system lupus develop," Santoro said. "It can also help us design new therapeutic strategies for these diseases."

The team hopes that future researchers will investigate other avenues and alternative pathways. "Because vascular health impacts many different diseases, understanding how to genetically control endothelial cell survival and apoptosis is critical to future work in these areas," Stainier said.

Source: University of California - San Francisco