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Selective agent keeps blood vessels in check

Blood vessels in the eye that grow out of control and damage the retina may cause blindness in certain affected people. Scientists from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now discovered that a molecule, called semaphorin 3C (Sema3C), may halt this process. Sema3C is produced by the body and its normal function is to control the growth of neurons. In an animal model, this protein effectively inhibits pathogenic angiogenesis.

During wound healing or embryonic development, the body needs to form new blood vessels. In certain diseases, however, this process – called angiogenesis – can get out of control. Cancer cells, for example, grow new blood vessels to make sure that the tumor's high nutrient needs are met. Blood vessels that grow out of control can also become a problem in the eye: when these blood vessels grow over the retina, this may lead to retinal detachment and blindness in the affected person.

Prematurely born babies often develop a disease of the eye called retinopathy, which is difficult to treat. It is caused by elevated oxygen levels that result from oxygen therapy used in neonatal care. The vessels in the eyes of premature infants are still immature and may respond to the treatment by developing abnormally. In serious cases, physicians have to treat retinopathy invasively using laser obliteration. Despite successful surgery, the risk remains that the condition may later progress to retinal detachment.

Researchers are currently trying to find methods that offer an alternative to laser obliteration, namely by using specific inhibitors to treat the abnormal blood vessels. So far, the focus has been on a vascular growth factor called VEGF. However, this growth factor can only be administered at very low doses because the remaining vascular system is also dependent on it. Searching for an alternative, the Heidelberg researchers have now found a potential solution – on nerves.

"It has been known for some time that the growth processes of nerve tracts and blood vessels are regulated in very similar ways," says Andreas Fischer, who leads the Division of Vascular Signal Transduction and Cancer at the DKFZ and also works as a physician at the Department of Endocrinology, Metabolism and Clinical Chemistry at Heidelberg University Hospital. "Sema3C is naturally found on nerve tracts, but it can also bind to newly formed blood vessels. This means that we have found a specific factor that selectively prevents (only newly formed) immature vascular cells from growing." Sema3C binds to receptors on the surface of immature vascular cells, thus transmitting a growth-inhibiting signal to them. In the retina, the two receptors for Sema3C are only present on immature vessels that form during retinopathy. Therefore, Sema3C might selectively inhibit the growth of these blood vessels. The DKFZ researchers have successfully used Sema3C to treat artificially induced retinopathy in mice. For this research, they closely collaborated with the Division of Vascular Oncology led by Hellmut Augustin, who works at the DKFZ as well as at the Medical Faculty Mannheim of Heidelberg University.

"We were able to reconstruct the blood vessel growth in cell culture and, in this way, observe it as an isolated process," Fischer explains. "We used a novel hydrogel matrix that allows vascular cells to grow under tissue-like conditions." This matrix puts the vascular cells into a

resting state, just as they would also normally occur in the body. The researchers were thus able to investigate how Sema3C impacts human cells before treating mice with the molecule. The scientists are currently determining whether or not Sema3C is, in fact, more effective than conventional inhibitor therapy.

Sema3C might also be useful for treating other diseases. Macular degeneration, a condition usually affecting older adults, also involves uncontrolled sprouting of blood vessels from the retina. Furthermore, Israeli scientists have recently discovered that Sema3C can also suppress the formation of lymph vessels in tumors. Lymph and blood vessels supply the tumor with nutrients; therefore, tumors promote the growth of these vessels. Even though new approaches that aim to cut off tumors from their vascular supply exist, these therapies also affect resting vascular cells. Sema3C might interfere more selectively and, thus, effectively cut the tumor off from its growth supply.

Wan-Jen Yang, Junhao Hu, Akiyoshi Uemura, Fabian Tetzlaff, Hellmut G Augustin, Andreas Fischer: Semaphorin-3C signals through Neuropilin-1 and PlexinD1 receptors to inhibit pathological angiogenesis. EMBO Molecular Medicine 2015, DOI 10.15252/emmm.201404922

A picture for this press release is available at:
www.dkfz.de/de/presse/pressemitteilungen/2015/bilder/Fischer-PM-Sema3C.jpg
Source: Andreas Fischer /DKFZ
Caption: Immature vessels sprouting during premature retinopathy (red: endothelial cells; green: mural cells (pericytes))

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