Decreased blood vessel leakage can improve cancer therapy and reduce tumor spread

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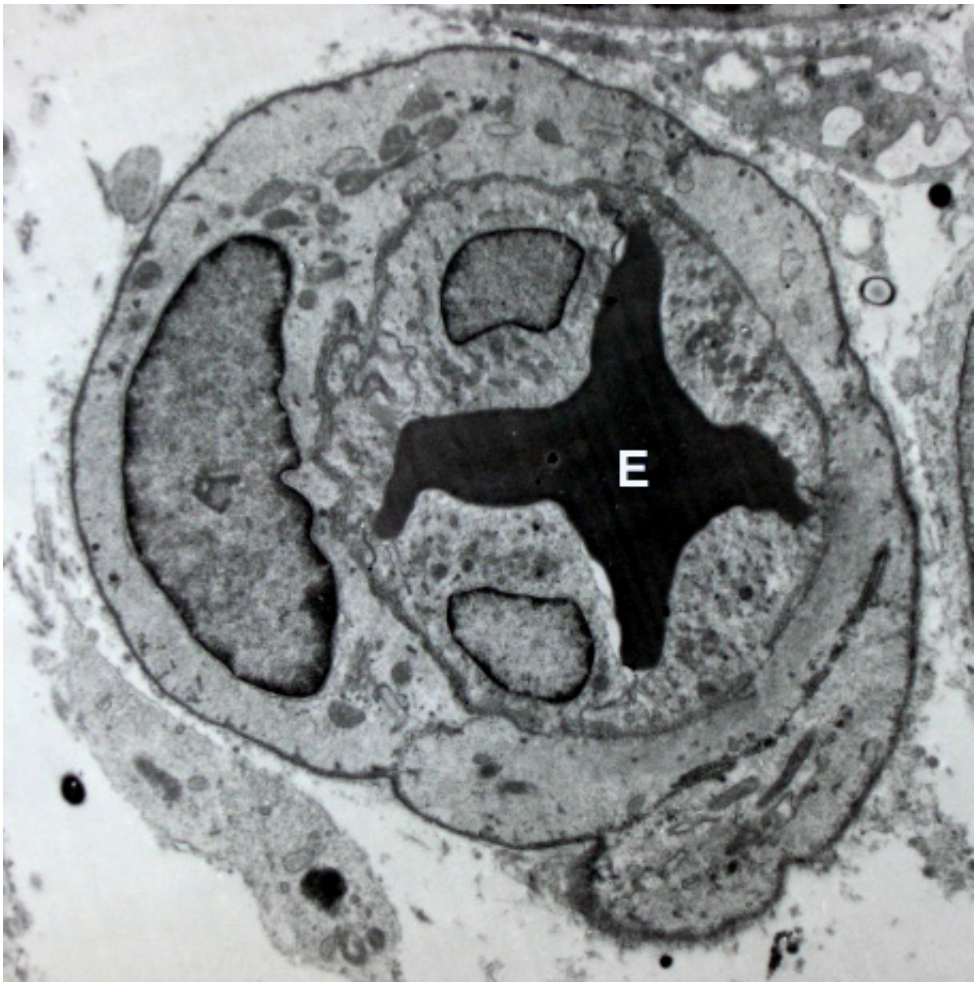

Blood vessel with an erythrocyte (red blood cell, E) within its lumen, endothelial cells forming its tunica intima (inner layer), and pericytes forming its tunica adventitia (outer layer) Credit: Robert M. Hunt/Wikipedia/CC BY 3.0

Cancer therapy is often hampered by the accumulation of fluids in and around the tumour, which is caused by leakage from the blood vessels in the tumour. Researchers at Uppsala University now show how leakage from blood vessels is regulated. They have identified a novel mechanism whereby leakage can be suppressed to improve the result of chemotherapy and reduce the spread of tumours in mice. The results have been published in the scientific journal *Nature Communications*.

When a tumour grows, new blood vessels are formed that supply the tumour with nutrients and oxygen. However, these vessels are often malfunctioning and fluids and other molecules leak out of the vessels. This results in edema in the tissues, which in turn makes it more difficult for drugs to reach into the tumour during cancer therapy. The malfunctioning vessels can also contribute to the spread of metastases from the tumour.

The leakage from the blood vessels is controlled by specific protein complexes that connect the cells in the blood vessel walls. By regulating these protein complexes, the cells are joined more or less tightly, which affects the leakage from the vessels.

Recent findings from Uppsala University show how a specific alteration of the protein complex in the vessel walls can reduce leakage, without affecting any other vessel functions.

'We have studied mice that have a mutation in a certain part of one of the proteins in the protein complex. The regular blood vessels in these mice function normally, but vessels in tumours showed less leakage, and there was a decrease in edema formation. In addition, the mutant mice responded better to treatment with chemotherapy', says Lena Claesson-Welsh, professor at the Department of Immunology, Genetics and Pathology,at Uppsala University and Science for Life Laboratory, who led the study.

The growth factor VEGFA functions as a signalling molecule, regulating the protein complexes in the blood vessel walls. One way of treating cancer is by inhibiting VEGFA, which decreases leakage and edema and improves the effects of chemo- and radiation therapy. However, VEGFA affects blood vessels in several ways and sustained anti-VEGFA therapy deteriorates vessel function and can cause increased metastasis.

'The specific mutation that we have studied allowed us to examine one of the signalling pathways in which VEGFA is involved. An important finding was that mice with the mutated protein complex also showed a reduced spread of metastases. We therefore believe that a targeted inhibition of this specific signalling pathway, which controls how the cells in the vessel walls are connected, might work better as a cancer therapy than the more general VEGFA inhibition that is used today,' says Lena Claesson-Welsh.

More information: Dr. Xiujuan Li , Dr. Narendra Padhan , Dr. K. Elisabet Ohlin , Dr. Frank Roche , Dr. Chiara Testini , Dr. Naoki Honkura , Dr. Miguel Sáinz-Jaspeado , Emma Gordon , Katie Bentley , Dr. Andrew Philippides , Prof. Vladimir Tolmachev , Prof. Elisabetta Dejana , Radu Stan , Prof. Dietmar Vestweber , Prof. Kurt Ballmer-Hofer , Prof. Christer Betsholtz , Prof. Kristian Pietras , Prof. Leif Jansson, Prof. Lena Claesson-Welsh (2016) VEGFR2 pY949 signaling regulates adherens junction integrity and metastatic spread, *Nature Communications*, DOI: 10.1038/ncomms11017

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