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Absence of transcription factor unleashes blood vessel growth

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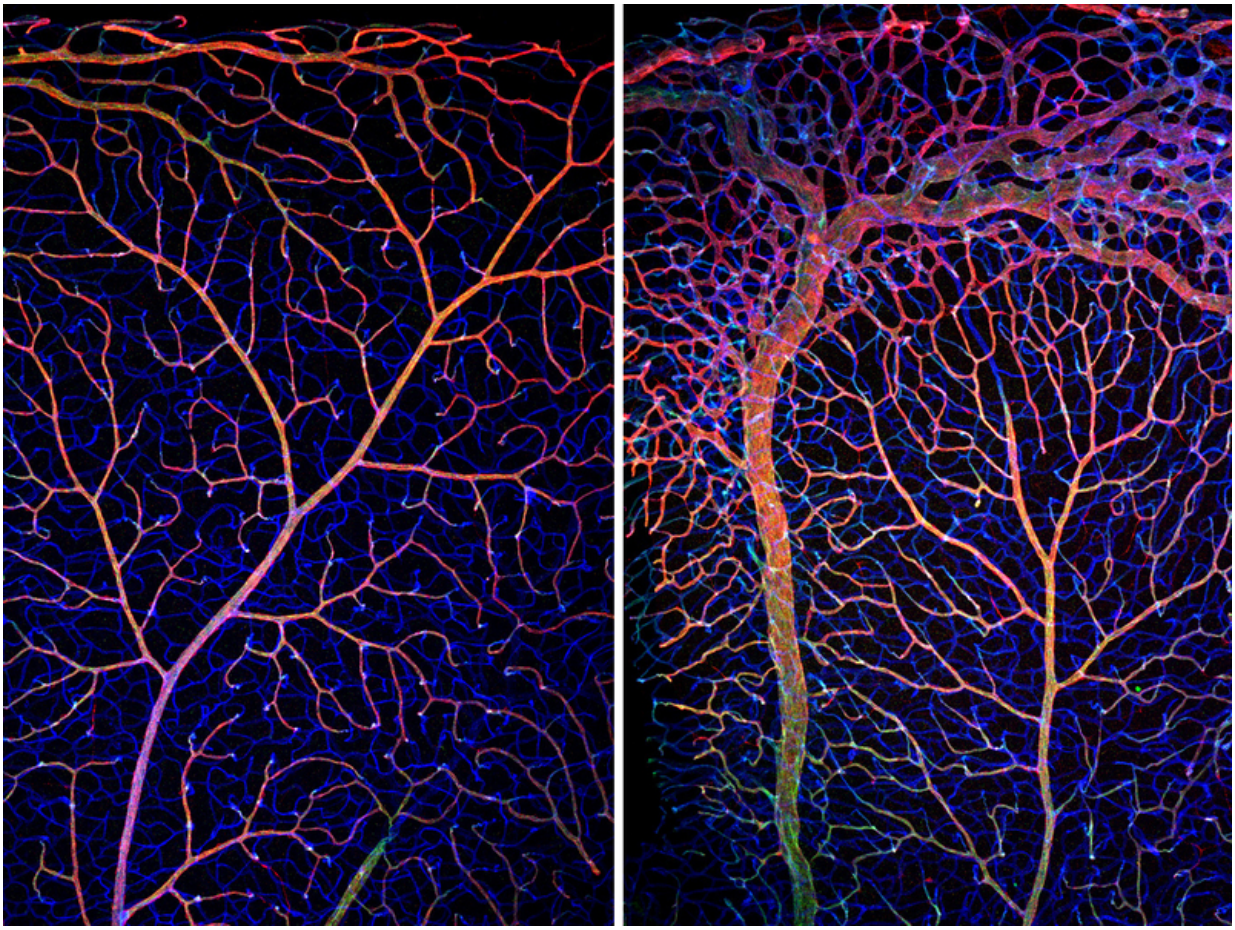

Unfettered blood vessel growth without FOXO1. The micrographs show developing blood vessels in the retinas of mice. In the control animals (left), the vascular network shows a high degree of organization. When the FOXO1 gene is absent, excessive and persistent growth of blood vessels is observed. In particular, the venous part of the vascular network is affected by inactivation of FOXO1, resulting in increased vessel size and density. The colours represent

various blood vessel markers. Credit: MPI for Heart and Lung Research

Blood vessels play an important role throughout life. Their growth determines whether organs are supplied with nutrients in a timely manner during embryonic development. In adulthood, the development of new blood vessels is instrumental in repair and regeneration processes. When blood vessel growth is disturbed, it can be an important factor in the progression of cancer, diabetes and eye diseases. Scientists from the Max Planck Institute for Heart and Lung Research in Bad Nauheim have now discovered that the growth of the innermost cell layer in blood vessels can be controlled via its metabolism. The results could serve as a basis for new treatments of diseases in which blood vessel growth plays a role.

Blood vessels are often compared to water lines: a pipe system that supplies organs with oxygen and nutrient-rich blood; however, this analogy has a serious flaw. Unlike water pipes, blood vessels do not form a rigid, static network of conduits but a complex and highly dynamic system – one that responds rapidly to changing requirements resulting, for example, from long-term increases in oxygen and nutrient requirements within tissues. If organs are persistently undersupplied with oxygen, this stimulates the growth of new blood vessels.

In this process, endothelial cells play an important role. Endothelial cells line the insides of blood vessels. As elements of the smallest vessels, the capillaries, they also have direct contact with organs. When endothelial cells receive a growth signal from tissue requiring more oxygen and nutrients, the cells switch within a short time from a resting state to a state of accelerated cell division. This switching process requires extensive adaptation of the their metabolism, as sufficient energy and building blocks must be supplied to support cell division.

The Research Group led by Michael Potente at the Max Planck Institute for Heart and Lung Research has now discovered a molecular switch that is involved in blood vessel growth and coordinates the division and metabolism of endothelial cells: the transcription factor FOXO1, which controls how genes are read in the cell nucleus. "When we inactivated FOXO1 in mice in the lab, we observed uncontrolled growth of vascular cells. Conversely, activating the molecule slowed blood vessel growth," Potente explains.

Together with European and US colleagues, the scientists also shed light on the underlying mechanism. Evidently, FOXO1 slows metabolism and cell division in endothelial cells. "In normal physiological states, FOXO1 prevents uncontrolled cell division, which would impair vascular function. However, when the growth of blood vessels is necessary, FOXO1 allows greater metabolic activity in endothelial cells," Potente explains. In this way, sufficient cellular building blocks can be supplied for the expanding vascular network.

The importance of FOXO1 in the endothelium is reflected in the fact that the molecule has been highly conserved throughout evolution. "The protein molecule is found in a broad range of species – from threadworms to fruit flies to humans – and in most cell types," says Potente. He believes that the fact that FOXO1 has such an important function in endothelial cells is due to the special metabolic environment in which these cells reside. "Vascular cells are in direct contact with oxygen and nutrient-rich blood and have to release these substances to the surrounding tissues." Optimum regulation of the cells' metabolism is therefore crucial.

The Max Planck researchers believe that FOXO1 could play an important role in the treatment of various diseases in future. It is known, for example, that FOXO1 is often inactivated in tumours, which could contribute to the uncontrolled vascular growth that is characteristic of

malignancies. "The growth of tumours could potentially be brought under control by the targeted pharmacological activation of FOXO1," Potente speculates. FOXO1 may also be implicated in metabolic diseases such as diabetes. "The observed disturbance of vascular growth could be due to impaired regulation of FOXO1 in endothelial cells," says Potente.

More information: Kerstin Wilhelm et al. FOXO1 couples metabolic activity and growth state in the vascular endothelium, *Nature* (2016). DOI: 10.1038/nature16498

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