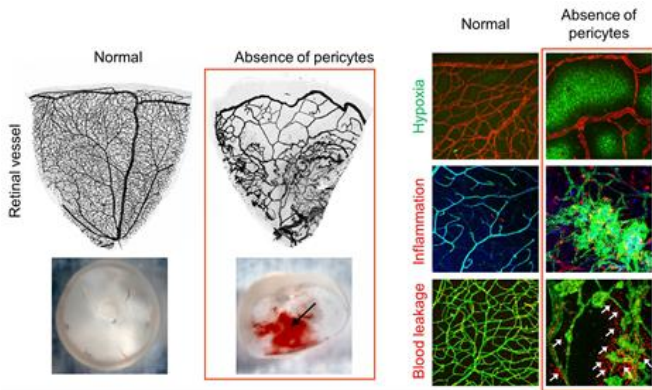


# Loss of pericytes deteriorates retinal environment

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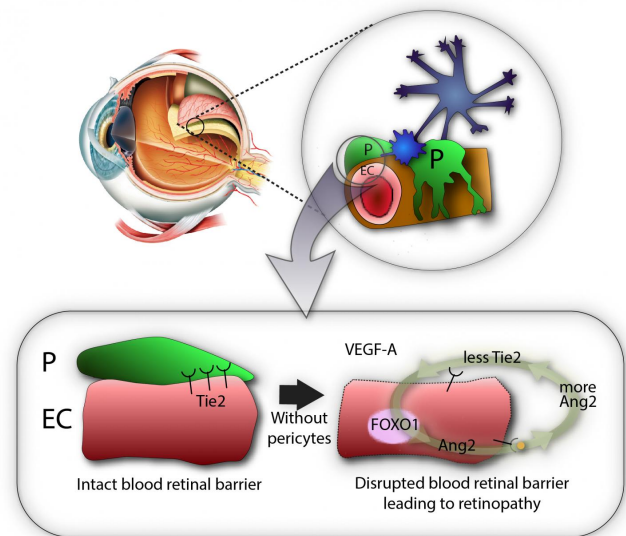
The experimental mouse model lacking pericytes in retinal vessels which demonstrates a damaged blood-retinal barrier showing blood leakage, inflammation, hypoxia (lack of oxygen), and loss of visual function, which are all hallmarks of diabetic retinopathy. Credit: IBS

Inside the eye, at the interface between blood vessels and the retina, lies a boundary that prevents harmful substances present in the blood from entering the retina. Researchers at the Center for Vascular Research, within the Institute for Basic Science (IBS) are studying the role of cells called pericytes, which protectively wrap the retinal vessels building up this blood-retinal barrier. This new study published in *Nature Communications*, revealed how the loss of pericytes aggravates the retinal environment and function in a mouse experimental model. These findings could contribute to the development of new therapies for blindness-causing diseases, such as diabetic eye disease (diabetic retinopathy).

Diabetic retinopathy, one of the major complications of diabetes, is considered a leading cause of blindness in adults. The loss of pericyte at the blood-retinal [barrier](#) is a hallmark of this disease, but its leading causes and exact roles are

still unclear. "We still do not know how pericytes influence the development of [diabetic retinopathy](#). Is the loss of pericytes the direct cause of this disease? Or the aftermath of other damages of the blood-retinal barrier? Or both of them? Knowing this information can help us tackle the disease," explains KOH Gou Young, corresponding author of this study.

Diabetic retinopathy can affect patients who have had diabetes for around 10-20 years. On the other hand, studying this disease on mouse experimental models is difficult because of their short lifespan. IBS scientists produced a new mouse model to study diabetic retinopathy and observed that young mice deprived of the growth factor responsible for proper attachment of pericytes to retinal vessels had severe retinal vascular leakage, impaired vascular network and visual loss similar to diabetic retinopathy. The research team confirmed that at the heart of these symptoms is the lack of pericytes at the blood-retinal barrier.



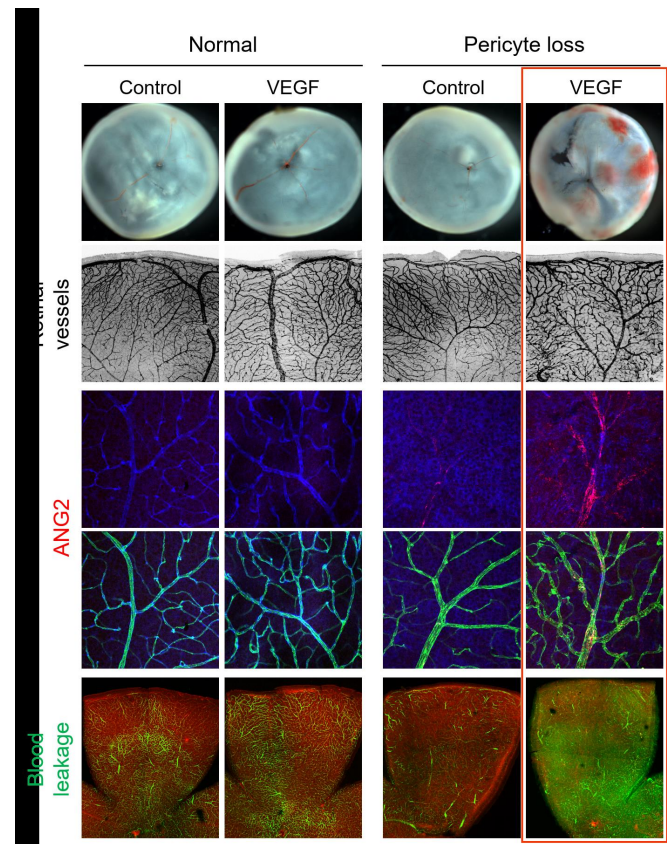
(Top) Pericytes (P, green) are cells tightly wrapped around the wall of the retinal capillaries, in close contact

with endothelial cells (EC, dark pink) and other supporting cells (blue). These form the blood-retinal barrier and prevent some substances from going from the blood stream to the eye. (Bottom) IBS scientists clarified that the lack of pericytes, a common hallmark of diabetic retinopathy, triggers a vicious cycle that causes an increase in vascular-destabilizing proteins, like Ang2, and a reduction of vascular-stabilizing proteins, like Tie2. Credit: IBS

Then, the researchers showed that pericytes play an important role in the vessels because they regulate a molecular pathway associated with vascular stabilization, which includes important proteins, such as Tie2, FOXO1, and Ang2. The loss of pericytes corresponds to the reduced production of Tie2, an essential protein for vascular stabilization, in par with the activation of FOXO1, which is responsible for the production of several proteins associated with vascular destabilization, such as Ang2. Ang2 inhibits the activity of Tie2, triggering a vicious cycle that increases deterioration of the retinal vascular environment and destroys the blood-retinal barrier.

IBS scientists then made a surprising observation: while young mice deprived of pericytes experienced such harmful effects, adult mice did not suffer from the same problems. Unexpectedly, when the scientists removed the pericytes from the retina of adult mice, the vessels kept resistant to vascular leakage. One thing the scientists could observe though, is that these adult healthy-looking retinas without pericytes were more sensitive to the vascular endothelial growth factor A (VEGF-A). VEGF-A causes the activation of FOXO1 and Ang2, leading to lesions that resembles diabetic retinopathy.

"The role of pericytes is still not fully understood, however these experiments show that once the blood-retinal barrier around the vessels is well established, as in adulthood, pericytes dropout is not the only cause of diabetic retinopathy. It is instead an aggravating factor that essentially accelerates the progression of the disease, sensitizes it to VEGF-A and further destabilizes retinal blood vessels," explains Koh. "We expect that the activation of Tie2, together with Ang2



When pericytes were removed from adult mice, the research team observed that the retina became more reactive towards the vascular endothelial growth factor A (VEGF-A), and increased the expression of Ang2 protein. As a result, the blood vessels became more unstable, leading to the destruction of the blood-retinal barrier. The image show substantial blood leakage in the cells without pericytes treated with VEGF-A. Credit: IBS

**More information:** Do Young Park et al, Plastic roles of pericytes in the blood–retinal barrier, *Nature Communications* (2017). DOI: [10.1038/ncomms15296](https://doi.org/10.1038/ncomms15296)

Provided by Institute for Basic Science

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