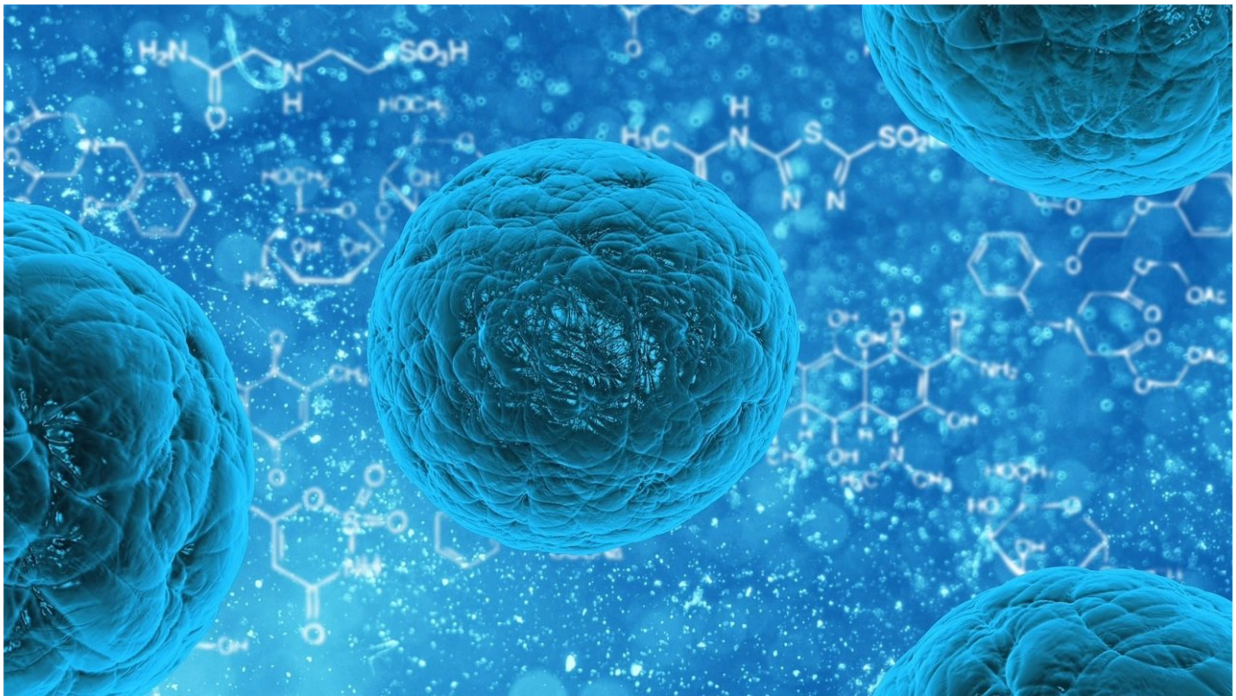
Probing the secret forces of pericytes

May 29 2020



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Leiden researchers found a way to measure the tiny forces exerted by pericytes, one of the most elusive, hard to research cell types, which occur in tiny blood vessels. Building on this fundamental science, researchers may eventually find treatments for medical conditions like ischaemia.

You could call them the secret cells because they are so very hard to study, find, or even distinguish from other cells. Olga Iendaltseva is the first author of an article in *Stem Cell Reports* that finally provides a way to study pericytes, which form part of the small blood vessels called capillaries.

Pericytes play an important role in many organs by regulating how much blood flows through the capillaries. "In the brain, pericytes help local and precise regulation of the blood flow to supply some regions with oxygen," says Iendaltseva. This is what is made visible in fMRI brain scans. In other organs, the main purpose is regulation of swelling or fortifying the tissues against high blood pressure, like in the penis or legs.

At least, this is what people think they do, because the exact functions of pericytes are still debated. "Pericytes are very hard to study," says Iendaltseva. One reason is that they are very small: the capillaries that they are part of are about 8 micrometres thick, and the pericytes are embedded within the capillary wall. This is not easily studied under regular microscopes.

Hard to Research

Another reason is that pericytes look very much like similar cells in thicker veins. In fact, there is a gradual change from the smooth muscle cells surrounding larger vessels to pericytes, depending on the amount of a protein called smooth muscle actin. As the blood vessels branch into ever thinner capillaries, the amount of smooth muscle actin decreases.

Iendaltseva, together with the groups of Erik Danen of LACDR and Thomas Schmidt of LION, now describes a new way to study these mysterious cells, by growing them in vitro.

"This was hard to do because they cannot be cultured in normal ways," explains Iendaltseva. Instead, the researchers obtained pericytes derived from Induced Pluripotent Stem Cells, generated by Valeria Orlova and Christine Mummery in the LUMC. "The Mummery lab had developed a protocol to generate functional pericytes from pluripotent stem cells, which have the capacity to grow into any cell type."

Pillar tops

In tissues, pericytes are joined to endothelial cells, which form the inner wall of the capillary. In between is a layer consisting of the protein laminin. It had been suggested, based on electron microscopy, that pericytes may attach to micrometre-sized spots of the sturdier protein fibronectin embedded in the laminin layer.

"We built a micropatterned substrate by stamping small dots of fibronectin to mimic this complex architecture and found that pericytes indeed strongly prefer such small deposits of fibronectin over laminin for attachment."

The next question to be addressed was whether such fibronectin deposits could serve as anchoring points for application of forces by pericytes. For this, the researchers used a system of micrometre-sized micropillars to measure the forces that pericytes develop.

"It works like this: the cell is laying on top of the micropillars like on a bed of needles. When the cell applies forces, the micropillars bend. We coated the tips of the pillars with fluorescently labelled fibronectin. The pericytes could attach to those pillars as they would to fibronectin deposits in real tissue. Then, we could use a fluorescence microscope to see the tops of the pillars. By measuring the bending of the pillar tops, we could calculate the force that pericytes applied to the micropillars."

Therapeutic strategies

After much fiddling, Iendaltseva got this to work. "It turns out that the force depends on the stiffness of the underlying material," says Iendaltseva. The force is the smallest when the stiffness is in the range of 15-25 kilopascals. Above or below this range, the force increases and pericytes drastically change their shape. "This makes sense for a capillary: when the pressure of the blood increases, the capillary wall becomes stiffer, and the pericyte force increases to counter the widening of the capillary."

"Our model now allows experimenting with abnormal circumstances, such as low oxygen content." In ischaemia, a medical condition where blood supply is restricted, the action of pericytes may play a large role in the extent of the damage. The model can be used to unravel such medically relevant mechanisms, and help develop new therapeutic strategies.

"There has been a lot of conflicting research findings. Our model certainly indicates that pericytes can really exert forces on the capillaries by using the fibronectin deposits," says Iendaltseva. "Moreover, our model provides a well-controlled, in vitro method to research pericyte functions under normal and pathological conditions."

More information: Olga Iendaltseva et al. Fibronectin Patches as Anchoring Points for Force Sensing and Transmission in Human Induced Pluripotent Stem Cell-Derived Pericytes, *Stem Cell Reports* (2020). DOI: 10.1016/j.stemcr.2020.05.001

Provided by Leiden University

Citation: Probing the secret forces of pericytes (2020, May 29) retrieved 27 April 2024 from https://phys.org/news/2020-05-probing-secret-pericytes.html

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