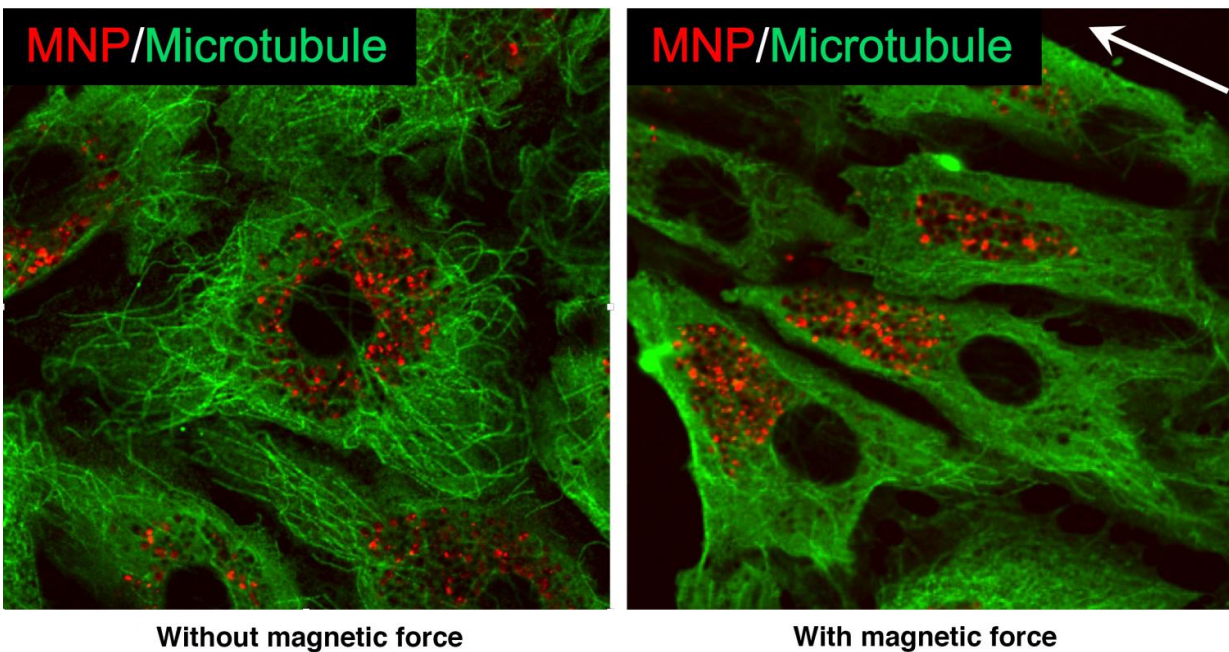


Making vessels leaky on demand could aid drug delivery

June 8 2017

Microtubules



Fluorescent iron-oxide nanoparticles glow in endothelial cells in an experiment at Rice University. At left, the nanoparticles are evenly distributed among the microtubules that help give the cells their shape. At right, after a magnetic field is applied, the nanoparticles are pulled toward one end of the cells and change their shapes. The researchers believe this offers a way to make the endothelial barrier "leaky" enough to allow drug molecules to pass through to reach tissues. Credit: Laboratory of Biomolecular Engineering and Nanomedicine/Rice University

The endothelial cells that line blood vessels are packed tightly to keep blood inside and flowing, but scientists at Rice University and their colleagues have discovered it may be possible to selectively open gaps in those barriers just enough to let large molecules through—and then close them again.

Rice bioengineer Gang Bao and collaborators at Emory University and the Georgia Institute of Technology reported using magnets to help iron-oxide nanoparticles invade [endothelial cells](#) both in the lab and in vivo. Then they use the same magnets to make vessels temporarily "leaky."

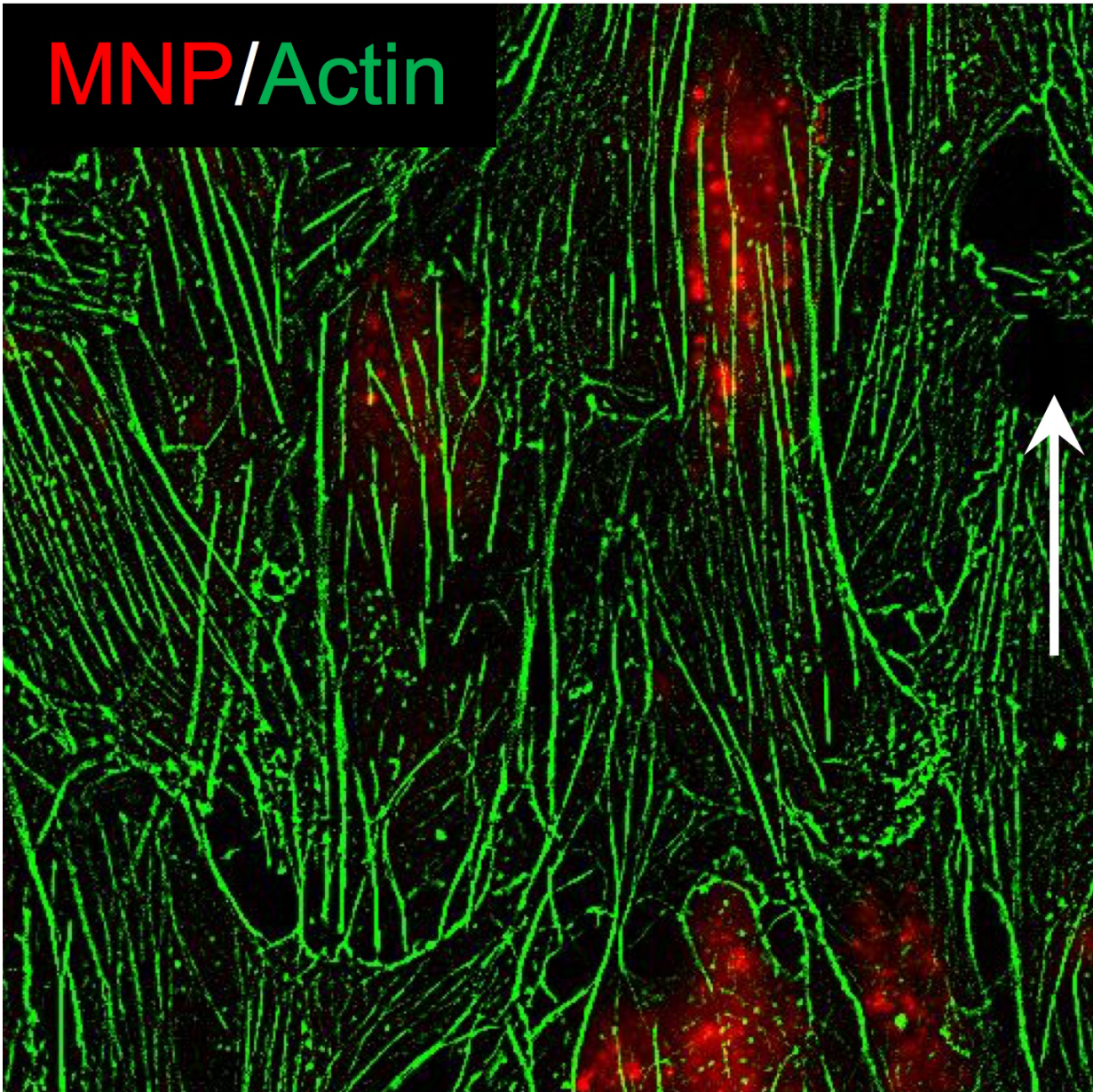
This permeability would allow large-molecule drugs to reach target tissues, Bao said. Strong magnets may be able to lead nanoparticle-infused stem cells or drug-laden nanoparticles themselves to targeted areas, even in deep tissues like organs that current therapies cannot reach, he said.

The study appears today in *Nature Communications*.

"For many diseases, systemic delivery through the blood stream is the only way to deliver molecules to the site," Bao said. "Small molecules can penetrate the blood vessel and get into the [diseased cells](#), but large molecules like proteins or drug-loaded nanoparticles cannot pass the endothelium effectively unless it is leaky."

Blood vessels in cancerous tumors typically have holes in the endothelial barrier, but they don't close on demand like Bao and his team hope to make them do.

Actin filaments



With magnetic force

Under the influence of a magnet, nanoparticles realign actin filaments in endothelial cells. Rice University researchers suspect such realignment can disrupt the junctions between endothelial cells and increase vascular permeability. Credit: Laboratory of Biomolecular Engineering and Nanomedicine/Rice University

Along with drug molecules, Bao wants to use magnets to deliver nanoparticle-infused stem cells to injured tissues. "Unless you can do direct injection of stem cells, let's say into the heart, you have to do systemic delivery and you have no control over where they go.

"Our initial idea was to deliver magnetic nanoparticles into stem cells and then use a magnet to attract the stem cells to a particular location," he said. "In doing so, we also discovered that by applying a [magnetic field](#), we could generate changes in the cell's skeletal structure in terms of the actin filament structures."

These structural elements give cells their shape and help keep neighboring cells tightly compacted. "We thought if we could alter the cell-cell junction by using magnetic force, there was a possibility that we could engineer the leakiness of the vessel," Bao said.

The lab created a microfluidic flow chamber that mimicked the vascular system and lined its tubes with real endothelial cells. Experiments proved their hypothesis: When a magnetic field was applied to the nanoparticle-infused cells, the gaps opened. Relaxing the force allowed most gaps to close after 12 hours.

Microscopic images showed that fluorescent-tagged nanoparticles were evenly distributed inside the endothelial channel when a magnetic field was not applied. When it was, the particles redistributed, and the force they applied distorted the cytoskeleton.



Rice University researchers prepare a batch of iron-oxide nanoparticles for experiments. They have discovered the particles, along with strong magnets, can be used to open gaps for drug delivery between the endothelial cells that line blood vessels. From left, Gang Bao, Sheng Tong and Linlin Zhang. Credit: Jeff Fitlow/Rice University

In some images, actin filaments that help give a cell its shape were observed lining up with the force. "It's a pretty dramatic change," Bao said. "Once you apply the force, given enough time, the structure of the cells changes. That leads to the opening of the cell-cell junction."

Bao said the magnetic force also generates a biological signal that alters the cytoskeletal structure. "It also contributes to the leakiness," he said. "We're still trying to understand what kind of signal we give to cells and

how the [individual cells](#) are responding."

While there are methods to facilitate two types of transport across the endothelial barrier - paracellular (between cells) and transcellular (through cells) - neither has the ability to target specific areas of the body. Bao said his team's approach offers a solution.

He said his group is part of an ongoing collaborative project on knee repair with the lab of Dr. Johnny Huard, a professor of orthopedic surgery at the University of Texas Health Science Center at Houston. "The problem is how to accumulate therapeutic [stem cells](#) around the knee and keep them there," Bao said. "After injecting the nanoparticle-infused [cells](#), we want to put an array of magnets around the knee to attract them.

"But if you want to treat the heart or liver, you'd need a pretty large device to have the required magnetic field," he said. "We don't have that yet. To drive this to a clinical setting will be a challenge."

More information: *Nature Communications* (2017). [DOI: 10.1038/NCOMMS15594](#)

Provided by Rice University

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