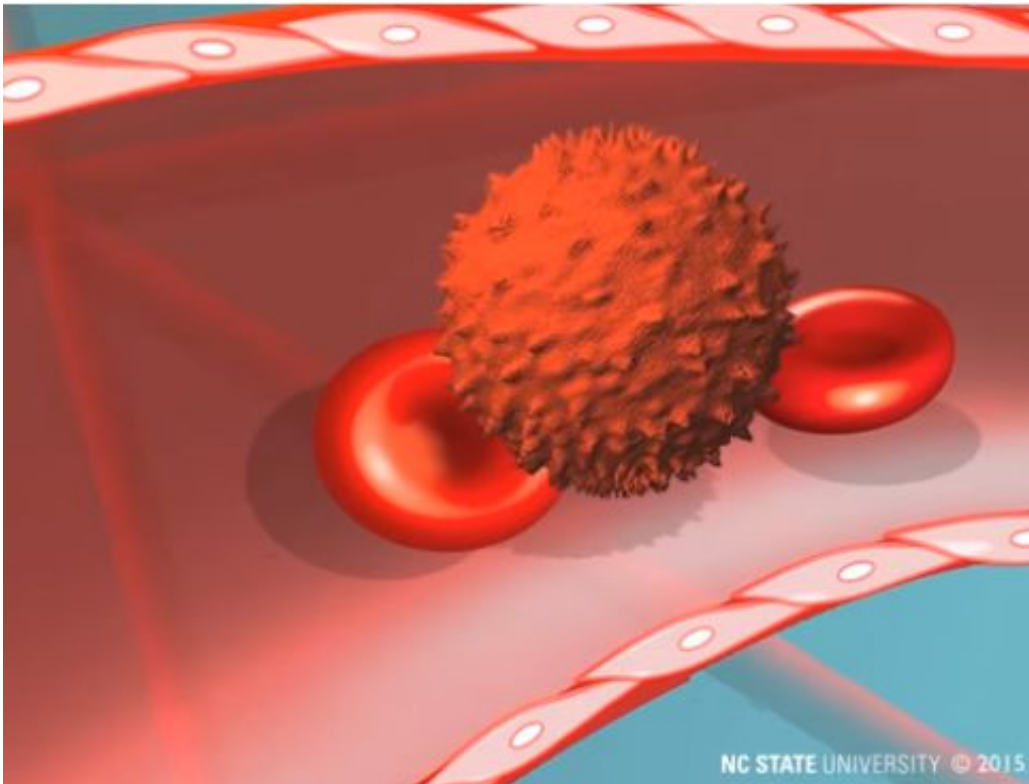


New way out: Researchers show how stem cells exit bloodstream

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Researchers at North Carolina State University have discovered that therapeutic stem cells exit the bloodstream in a different manner than was previously thought. This process, dubbed angiopellosis by the researchers, has implications for improving our understanding of not only intravenous stem cell therapies, but also metastatic cancers.

When white [blood cells](#) need to get to the site of an infection, they can exit the bloodstream via a process called diapedesis. In diapedesis, the white blood cell changes its shape in order to squeeze between or through the epithelial cells that form the walls of the blood vessel. Diapedesis is a well-understood process, and researchers believed that other types of cells, like therapeutic stem cells or even metastatic cancer cells, exited blood vessels in a similar way - with the cells pushing or squeezing themselves out.

But a group of researchers led by Ke Cheng, associate professor of molecular biomedical sciences at NC State with a joint appointment in the NC State/UNC-Chapel Hill Department of Biomedical Engineering, found that these stem cells behaved differently.

Therapeutic stem cells share the same ability to exit the bloodstream and target particular tissues that white blood cells do. But the precise way that they did so was not well understood, so Cheng and his team utilized a zebrafish model to study the process. The genetically modified zebrafish embryos were transparent and had fluorescently marked green blood vessels. Researchers injected the embryos with white blood cells and cardiac stem cells from humans, rats and dogs. These cells had all been marked with a red fluorescent protein.

Through time-lapse three-dimensional light sheet microscopic imaging, Cheng and his team could trace the progress of these cells as they left the blood vessel. The white blood cells exited via diapedesis, as expected. When stem cells exited the blood vessel, however, the endothelial cells lining the vessel actively expelled them. Membranes surrounding the endothelial cells on either side of the stem cell stretched themselves around the stem cell, then met in the middle to push the stem cell out of the vessel.

"When you're talking about diapedesis, the white blood cell is active

because it changes its shape in order to exit. The endothelial cells in the blood vessel are passive," Cheng says. "But when we looked at therapeutic stem cells, we found the opposite was true - the stem cells were passive, and the endothelial cells not only changed their shape in order to surround the stem cell, they actually pushed the [stem cells](#) out of the blood vessel. We've named this process angiopeliosis, and it represents an alternative way for cells to leave blood vessels."

The researchers found two other key differences between angiopeliosis and diapedesis: one, that angiopeliosis takes hours, rather than minutes, to occur; and two, that angiopeliosis allows more than one cell to exit at a time.

"Angiopeliosis is really a group ticket for cells to get out of [blood vessels](#)," Cheng says. "We observed clusters of cells passing through in this way. Obviously, this leads us to questions about whether other types of cells, like metastatic cancer [cells](#), may be using this more effective way to exit the bloodstream, and what we may need to do to stop them."

More information: Tyler A. Allen et al, Angiopeliosis as an Alternative Mechanism of Cell Extravasation, *STEM CELLS* (2016). [DOI: 10.1002/stem.2451](https://doi.org/10.1002/stem.2451)

Provided by North Carolina State University

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