# Study reveals insights that could aid in therapeutic use of mesenchymal stem cells

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Mesenchymal stem cells (MSCs), are a newly emerging cellular therapy being tested in approximately 250 clinical trials worldwide to help repair damaged tissues, such as injured heart muscle following a heart attack. The problem is that when culture-expanded MSCs are injected into the circulation, they have trouble gaining access to the inflamed tissues—exactly where their help is needed.

Now, research led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and Brigham and Women's Hospital (BWH) reveals new insights into how MSCs "traffic" from the circulation into the tissue, providing important clues that could be used to improve the delivery of this promising therapy. The findings are published in the November issue of the journal *Stem* Cells.

MSCs have great clinical potential due to their convenient isolation, their lack of significant immunogenicity (allowing for transplantation between individuals), their lack of ethical controversy, their potential to differentiate into tissue-specific cell types, and their ability to promote blood vessel growth. The cells can seek out and repair damaged tissue and treat inflammation resulting from cardiovascular disease, brain and spinal cord injury, cartilage and bone injury, Crohn's disease, and other conditions. Given the systemic nature of many diseases and the desire for minimally invasive therapies, systemic infusion of MSCs holds considerable promise as an effective treatment in many conditions.

But, as senior author Christopher Carman, PhD, explains, in order for

MSCs circulating in the bloodstream to have any therapeutic effect, they must first cross the vascular endothelium, the layer of cells that line blood vessels and serve as the primary barrier between the blood and the tissues. Carman and co-corresponding author Jeffrey Karp, PhD, set out to answer the question, "How do MSCs interact with this layer?"

"Our basic approach was to grow isolated endothelial monolayers in the lab in ways that mimic the vascular barrier structure in the body and conduct dynamic high-resolution imaging studies of MSCs interacting with the endothelium under normal or inflamed conditions," explains Carman, an investigator in BIDMC's Center for Vascular Biology Research and Assistant Professor of Medicine at Harvard Medical School (HMS).

Their experiments revealed that, similar to white blood cells that act during an immune response, MSCs use inflammation-specific adhesion molecules called vascular cell adhesion molecule-1 (VCAM-1) to stick to the endothelium at sites of inflammation. "But," says Carman, "whereas white cells very efficiently crawl over the endothelial surface, apparently searching out weak spots to breach and migrate across this barrier, we discovered that MSCs are unable to mediate such crawling and are about 10 times slower to cross the endothelium." And that, he adds, may explain why MSCs are not efficient at entering inflamed tissues.

"This work suggests that the initial phase of the homing cascade—cell rolling—is the rate limiting step to achieve effective homing for MSCs," says Karp, Co-Director of the Center for Regenerative Therapeutics at BWH, and Associate Professor of Medicine at HMS. (Homing occurs when circulating MSCs target areas of injury in response to signals of cellular damage; cell rolling refers to the way that MSCs "decelerate" on this target tissue.)

"Clinically this would be a good place to focus efforts to enhance MSC homing—to improve the ability to roll on inflamed endothelium, since we showed that MSCs can efficiently adhere under static conditions and transmigrate on the endothelium in inflamed tissues," adds Karp, who is also a principal faculty member of the Harvard Stem Cell Institute.

The scientists further discovered that when MSCs do eventually cross the endothelium, they often do so through "membrane blebbing." During this unique process, an MSC uses hydrostatic pressure to create a bulge or bleb in the cell's outer membrane that exerts mechanical force against the endothelium, leading to the initial break in its barrier that initiates transmigration. "We demonstrated that MSCs can transmigrate between endothelial cells—called paracellular transmigration—and directly through a single endothelial cell—called transcellular migration," says Karp. "This is an exciting finding as it provides a new axis that potentially can be modulated for developing next-generation MSC therapy." During transcelluar migration, an MSC doesn't actually enter an endothelial cell, but rather forms a pore through which it then migrates.

Interestingly, say the researchers, these findings may also provide insights on how some tumor cells spread or metastasize, as migratory blebbing has been observed in a number of embryonic germ cells and in some tumor cells. "Our finding shows for the first time that blebbing may function in the critical barrier-breaching event of MSC migration through endothelial cells," says Carman. "This suggests that blebs could similarly function in cancer invasiveness."

For now, however, Carman and his colleagues will focus on MSCs. Among their next steps is to verify that the results generated in the lab hold true within the body. "From there, we wish to iterate back and forth between our in vitro and in vivo systems to explore a range of bioengineering approaches that build on the new knowledge from this

study to design improved delivery and efficacy of MSC therapeutics," says Carman, adding that as the understanding of the mechanisms of MSC movement grows, researchers' abilities to enhance homing to specific tissues through engineered approaches should help bring MSC therapy closer to the clinic.

**More information:** Teo GS et al. Mesenchymal Stem Cells Transmigrate Between and Directly Through Tumor Necrosis Factor-α-Activated Endothelial Cells Via Both Leukocyte-Like and Novel Mechanisms. *Stem Cells*. 2012 Nov;30(11):2472-86. doi: 10.1002/stem.1198

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