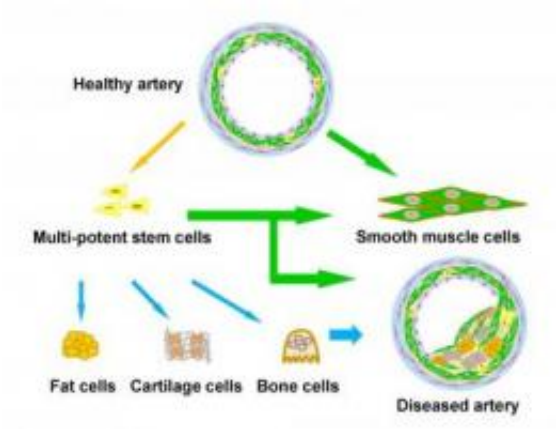
The real culprit behind hardened arteries? Stem cells, says landmark study

June 6 2012



Within the walls of blood vessels are smooth muscle cells and newly discovered vascular stem cells. The stem cells are multipotent and are not only able to differentiate into smooth muscle cells, but also into fat, cartilage and bone cells. UC Berkeley researchers provide evidence that the stem cells are contributing to clogged and hardened arteries. Credit: Song Li illustration

One of the top suspects behind killer vascular diseases is the victim of mistaken identity, according to researchers from the University of California, Berkeley, who used genetic tracing to help hunt down the real culprit.

The guilty party is not the smooth muscle cells within blood vessel walls, which for decades was thought to combine with cholesterol and fat that can clog arteries. Blocked vessels can eventually lead to heart attacks and

strokes, which account for one in three deaths in the United States.

Instead, a previously unknown type of stem cell — a multipotent vascular stem cell — is to blame, and it should now be the focus in the search for new treatments, the scientists report in a new study appearing June 6 in the journal *Nature Communications*.

"For the first time, we are showing evidence that vascular diseases are actually a kind of stem cell disease," said principal investigator Song Li, professor of bioengineering and a researcher at the Berkeley Stem Cell Center. "This work should revolutionize therapies for vascular diseases because we now know that stem cells rather than smooth muscle cells are the correct therapeutic target."

The finding that a stem cell population contributes to artery-hardening diseases, such as atherosclerosis, provides a promising new direction for future research, the study authors said.

"This is groundbreaking and provocative work, as it challenges existing dogma," said Dr. Deepak Srivastava, director of the Gladstone Institute of Cardiovascular Disease at UC San Francisco, who provided some of the mouse vascular tissues used by the researchers. "Targeting the vascular stem cells rather than the existing smooth muscle in the vessel wall might be much more effective in treating vascular disease."

It is generally accepted that the buildup of artery-blocking plaque stems from the body's immune response to vessel damage caused by low-density lipoproteins, the bad cholesterol many people try to eliminate from their diets. Such damage attracts legions of white blood cells and can spur the formation of fibrous scar tissue that accumulates within the vessel, narrowing the blood flow.

The scar tissue, known as neointima, has certain characteristics of

smooth muscle, the dominant type of tissue in the blood vessel wall. Because mature smooth muscle cells no longer multiply and grow, it was theorized that in the course of the inflammatory response, they revert, or de-differentiate, into an earlier state where they can proliferate and form matrices that contribute to plaque buildup.

However, no experiments published have directly demonstrated this de-differentiation process, so Li and his research team remained skeptical. They turned to transgenic mice with a gene that caused their mature smooth muscle cells to glow green under a microscope.

In analyzing the cells from cross sections of the blood vessels, they found that more than 90 percent of the cells in the blood vessels were mature smooth muscle cells. They then isolated and cultured the cells taken from the middle layer of the mouse blood vessels.

After one month of cell expansion, the researchers saw a threefold increase in the size of the cell nucleus and the spreading area, along with an increase in stress fibers. Notably, none of the new, proliferating cells glowed green, which meant that their lineage could not be traced back to the mature smooth muscle cells originally isolated from the blood vessels.

"Not only was there a lack of green markers in the cell cultures, but we noticed that another type of cell isolated from the blood vessels exhibited progenitor traits for different types of tissue, not just smooth muscle cells," said Zhenyu Tang, co-lead author of the study and a Ph.D. student in the UC Berkeley-UCSF Graduate Program in Bioengineering.

The other co-lead author of the study, Aijun Wang, was a post-doctoral researcher in Li's lab.

"The different phenotypes gave us the clue that stem cells were

involved," said Wang, who is now an assistant professor and the co-director of the Surgical Bioengineering Laboratory at the UC Davis Medical Center. "We did further tests and detected proteins and transcriptional factors that are only found in stem cells. No one knew that these cells existed in the blood vessel walls because no one looked for them before."

Further experiments determined that the newly discovered vascular stem cells were multipotent, or capable of differentiating into various specialized cell types, including smooth muscle, nerve, cartilage, bone and fat cells. This would explain why previous studies misidentified the cells involved in vessel clogs as de-differentiated smooth muscle cells after vascular injury.

"In the later stages of vascular disease, the soft vessels become hardened and more brittle," said Li. "Previously, there was controversy about how soft tissue would become hard. The ability of stem cells to form bone or cartilage could explain this calcification of the blood vessels."

Other tests in the study showed that the multipotent stem cells were dormant under normal physiological conditions. When the blood vessel walls were damaged, the stem cells rather than the mature smooth muscle cells became activated and started to multiply.

The researchers analyzed human carotid arteries to confirm that the same type of multipotent vascular stem cells are found in human blood vessels.

"If your target is wrong, then your treatment can't be very effective," said Dr. Shu Chien, director of the Institute of Engineering in Medicine at UC San Diego, and Li's former adviser. "These new findings give us the right target and should speed up the discovery of novel treatments for vascular diseases."

Provided by University of California - Berkeley