Antibodies could stop heart disease, study finds

Now in cancer trials, antibodies block atherosclerosis in mouse study

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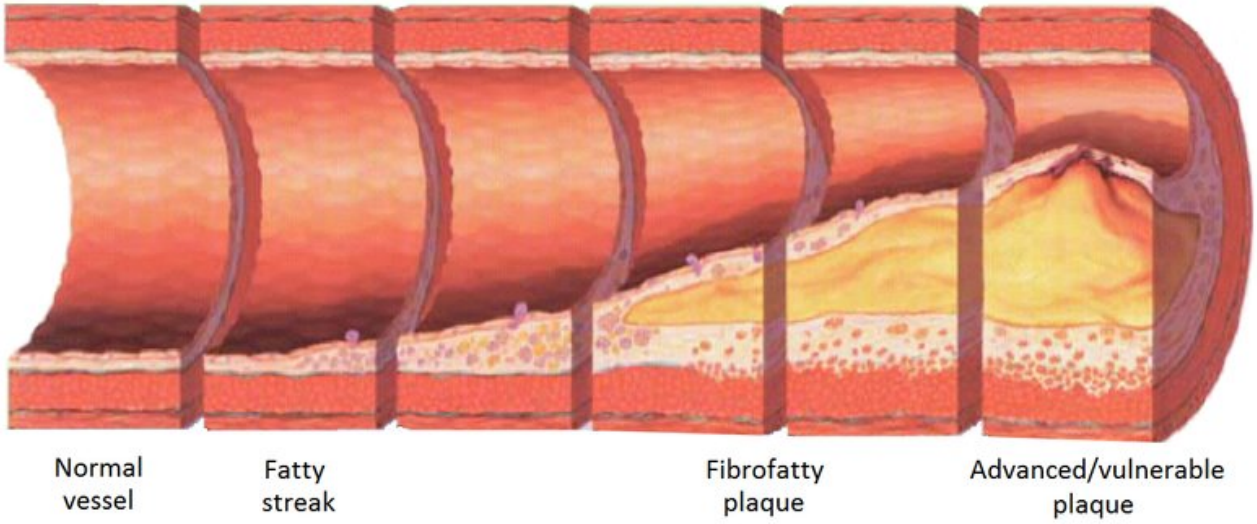

The progression of atherosclerosis as debris clogs arteries. — *Wikimedia Commons*

Antibodies that help the immune system remove dead and dying cells have been shown to reduce atherosclerosis in mouse models of cardiovascular disease, a study led by Stanford University researchers reports (http://www.eurekalert.org/emb_releases/2016-07/sumc-aac071716.php).

These antibodies are already being tested in people against cancer, raising the possibility that they could be repurposed for a clinical trial in heart disease relatively quickly.

The antibodies attack a molecule present on the cells called CD47, which signals macrophages not to destroy cells bearing that marker. This "don't eat me" molecule works with a cellular receptor called signal regulatory protein alpha, or SIRP α to inhibit the attack.

CD47 is normally removed in dead or dying cells, allowing the body's clean-up crew to remove debris. In cancer, CD47 is highly activated, enabling the malignant cells to evade immune system surveillance. The antibodies remove this shield, allowing immune cells to inspect and destroy them.

The researchers found that in cases of atherosclerosis, CD47 is present when it shouldn't be. After researchers gave the antibodies to mice, the macrophages resumed their normal role, removing the cells and associated debris. In many cases, this actually caused the plaques to shrink.

The study, led by Stanford's Nicholas Leeper, was published Wednesday in Nature. It can be found at http://j.mp/artantibodies (http://j.mp/artantibodies). Researchers at the David Geffen School of Medicine at UCLA and the Icahn School of Medicine in New York City contributed to the study.

"This is a very exciting study indeed," said heart researcher Klaus Ley of the La Jolla Institute for Allergy & Immunology. Ley is developing an anti-inflammatory vaccine to reduce heart attacks. Inflammation triggers the deposits of debris and accumulation of cells that result in atherosclerosis.

"We have known for years that macrophages in atherosclerotic plaque fail to take up dead and dying cells, a failure of efferocytosis," Ley said by email. "Here, the authors show that this is because CD47 expression is increased in plaque, perhaps through TNF (https://en.wikipedia.org/wiki/Tumor_necrosis_factor_alpha).

"Excitingly, blocking CD47 by antibodies reduces atherosclerosis burden," he said. "This is directly relevant for human disease, because CD47 antibodies are currently being developed for other indications (cancer)."

TNF is an inflammatory molecule involved in many disease processes.

Such a drug would intervene directly in the cardiovascular disease process. Existing drugs work indirectly by reducing risk factors, such as high levels of "bad" cholesterol and high blood pressure.

“It seems that heart disease may be driven by our immune system’s inability to ‘take out the trash,’” said Leeper, associate professor of vascular surgery and of cardiovascular medicine, in a statement.

Leeper's colleague, Dr. Irving Weissman, was a co-author on the study. Weissman is director of Stanford’s Institute of Stem Cell Biology and Regenerative Medicine and the Ludwig Cancer Stem Cell Institute.

Weissman and colleagues discovered that CD47 is overexpressed on tumor cells, leading to a Phase I clinical trial in solid tumors and blood cancers.

After Weissman heard of the Leeper lab's work, he gave them anti-CD47 antibodies to test for atherosclerosis. The researchers found that elevated levels of CD47 correlated with higher levels of TNF-alpha, which promotes inflammation. They found out that TNF-alpha preserves CD47, which would otherwise be removed on dying cells.

Leeper said in the Stanford statement (http://www.eurekalert.org/emb_releases/2016-07/sumc-aac071716.php) that the process could feed on itself.

“The problem could be an endless loop,” said Leeper, “in which TNF-alpha-driven CD47 overexpression prevents macrophages from clearing dying cells in the lesion. Those cells release substances that promote the production of even more TNF-alpha in nearby cells.”

In the mice, anti-CD47 produced a transitory anemia as older red blood cells with low levels of CD47 were removed. But new blood cells with higher levels of the protein replaced them.

Leeper and Weissman have filed for a patent on inhibition of CD47 to fight atherosclerosis. A company they co-founded, Forty Seven Inc., has licensed related intellectual property from Stanford for cancer therapy.

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