How 'bad' cholesterol causes atherosclerosis in humans: Stem cells play a key role

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Cimato says the research opens up a potential new approach to preventing heart attack and stroke. Credit: Douglas Levere, University at Buffalo

University at Buffalo translational researchers are developing a richer understanding of atherosclerosis in humans, revealing a key role for stem cells that promote inflammation.

The research was published last month in *PLOS One*. It extends to

humans previous findings in lab animals by researchers at Columbia University that revealed that high levels of LDL ("bad") cholesterol promote atherosclerosis by stimulating production of hematopoietic stem/progenitor cells (HSPC's).

"Our research opens up a potential new approach to preventing heart attack and stroke, by focusing on interactions between cholesterol and the HSPCs," says Thomas R. Cimato, MD, PhD, lead author on the *PLOS One* paper and assistant professor in the Department of Medicine in the UB School of Medicine and Biomedical Sciences.

He notes that the finding about the importance of these stem cells in atherosclerosis could lead to the development of a useful therapy in combination with statins, or one that could be used in place of statins in individuals who cannot tolerate them.

The study demonstrated for the first time in humans that high total cholesterol recruits stem cells from the bone marrow into the bloodstream, via increases in IL-17, which has been implicated in many chronic inflammatory diseases, including atherosclerosis. IL-17 boosts levels of granulocyte colony stimulating factor (GCSF), which releases stem cells from the bone marrow.

They also found that statins do reduce the levels of HSPCs in the blood but not every subject responded similarly, Cimato says.

"We've extrapolated to humans what other scientists previously found in mice about the interactions between LDL cholesterol and these HSPCs," explains Cimato.

The demonstration that a finding in lab animals is equally relevant in humans is noteworthy, adds Cimato, a researcher in UB's Clinical and Translational Research Center (CTRC).

"This is especially true with cholesterol studies," he says, "because mice used for atherosclerosis studies have very low total cholesterol levels at baseline. We feed them very high fat diets in order to study high cholesterol but it isn't easy to interpret what the levels in mice will mean in humans and you don't know if extrapolating to humans will be valid."

Cimato adds that the degree of increased LDL cholesterol in mouse studies is much higher than what is found in patients who come to the hospital with a heart attack or stroke.

"The fact that this connection between stem cells and LDL cholesterol in the blood that was found in mice also turns out to be true in humans is quite remarkable," he says.

Cimato explains that making the jump from rodents with very high LDL cholesterol to humans required some creative steps, such as the manipulation of the LDL cholesterol levels of subjects through the use of three different kinds of statins.

The study involved monitoring for about a year a dozen people without known coronary artery disease who were on the statins for two-week periods separated by one-month intervals when they were off the drugs.

"We modeled the mechanism of how LDL cholesterol affects stem cell mobilization in humans," says Cimato. The UB researchers found that LDL cholesterol modulates the levels of stem cells that form neutrophils, monocytes and macrophages, the primary cell types involved in the formation of plaque and atherosclerosis.

The next step, he says, is to find out if HSPCs, like LDL cholesterol levels, are connected to cardiovascular events, such as heart attack and stroke.

Provided by University at Buffalo