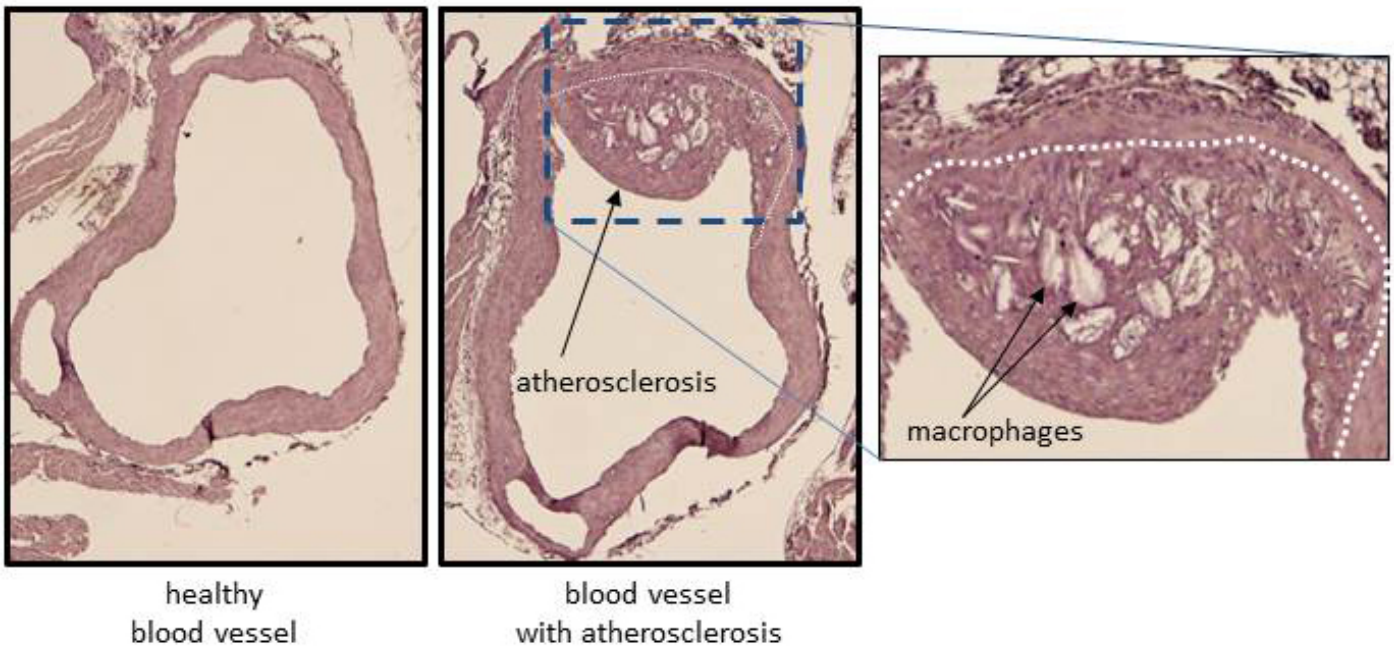
Finding new drug targets to prevent heart attacks and strokes

Heart attacks and strokes are responsible for more deaths than any other disease in the world. The underlying cause of most heart attacks and strokes is a disease of the blood vessels called atherosclerosis. Atherosclerosis involves accumulation of cholesterol and white blood cells (called macrophages) in the walls of large blood vessels (see figure). This accumulation causes thickening of the blood vessel wall that can eventually lead to a blockage of blood flow. When a blood vessel is blocked, the parts of the body that are supplied by that vessel are damaged. When blockages occur in blood vessels that supply the heart or the brain, the result is a heart attack or stroke.



Cross sectional view of blood vessels from a healthy mouse (left panel) and a mouse with atherosclerosis (center panel). The diseased area of the vessel wall is expanded to show the macrophage accumulation (right panel).

We know that smoking, obesity, high blood cholesterol, diabetes, and high blood pressure increase the risk of heart attack and stroke. However, we do not know how these risk factors cause atherosclerosis. If we knew how these risk factors actually cause atherosclerosis, then we could design better ways to slow, stop, or reverse disease development.

In this research paper we are looking for the pathways that link the risk factors for heart attacks and strokes to the development of atherosclerosis using unique mouse models.

Our research has led to the discovery of a factor, known as glycogen synthase kinase-3? (GSK3?), which may play an important part in the development of atherosclerosis. To directly investigate this possibility, we created special mice that were genetically altered so that they could not make GSK3? in specific cell types. We found that eliminating GSK3? in white blood cells (macrophages) significantly reduced the amount of atherosclerosis in mice.

These results suggest that risk factors, like obesity, high blood cholesterol, and diabetes, require the presence of macrophage GSK3? to cause atherosclerosis.

But what does GSK3? actually do?

Our results suggest that GSK3? acts as a switch that controls the function of the macrophage. Risk factors, like obesity, cholesterol and diabetes turn the switch (GSK3?) on. When GSK3? is turned on, the macrophage causes the atherosclerosis to progress (get worse), and the likelihood of a heart attack increases. When the switch (GSK3?) is turned off, the macrophage actually helps to repair the blood vessel and recover from atherosclerosis.

These findings are important because they have identified a new target for drugs to prevent atherosclerosis. Specifically, we predict that a drug that can turn GSK3? off will protect the blood vessel wall from atherosclerosis and reduce the risk of heart attack and stroke, even if the risk factors are still there. The next steps will involve finding new effective drugs that specifically block GSK3? activity in humans. Studies are currently underway to find these drugs and test this new strategy to protect people from heart attack and stroke.

Cameron S McAlpine, Aric Huang, Geoff H Werstuck
Thrombosis and Atherosclerosis Research Institute, McMaster University
Hamilton Ontario Canada

Publication

Deletion of Myeloid GSK3? Attenuates Atherosclerosis and Promotes an M2 Macrophage Phenotype.
McAlpine CS, Huang A, Emdin A, Banko NS, Beriault DR, Shi Y, Werstuck GH
Arterioscler Thromb Vasc Biol. 2015 May