New drug targets clots: A potential treatment for heart attack and stroke prevention

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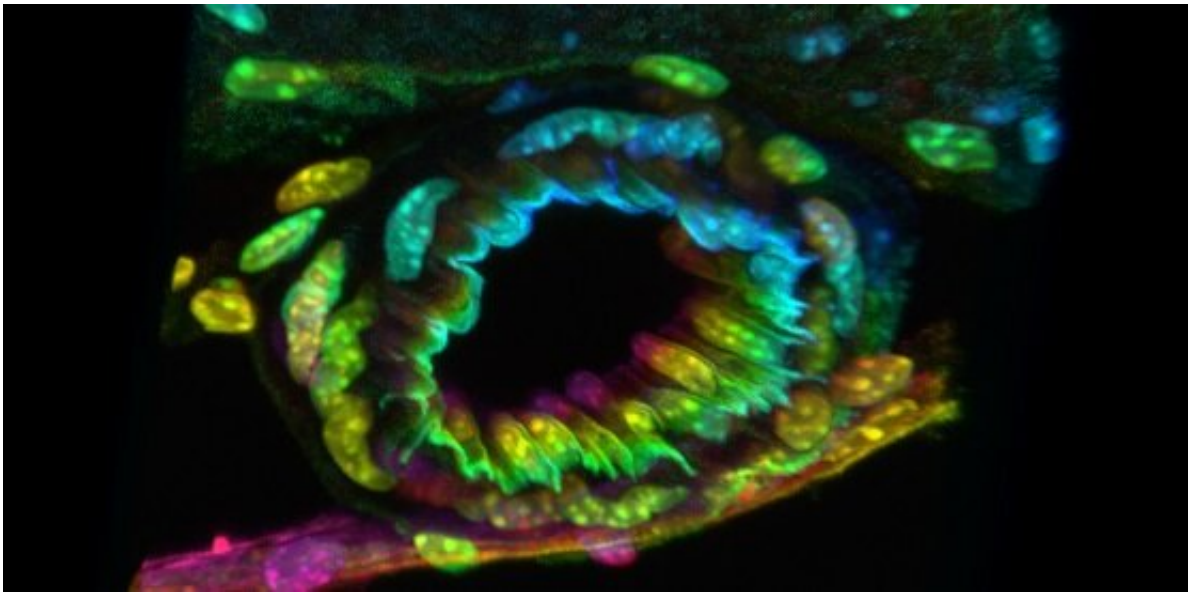

Cross-sectional image of a damaged blood vessel immediately prior to it triggering the formation of a thrombus (blood clot) inside. Credit: (C) Justin Hamilton

Monash researchers have developed a drug that can be potentially given as a preventative against heart attack. The drug—which has been studied in human cells and animal models—literally blocks the minute changes in blood flow that preempts a heart attack and acts on the platelets preventing the platelet-triggered clot before it can kill or cause damage.

Importantly, the drug may have a role in preventing the clotting that is

the hallmark of COVID-19.

One third of all deaths globally—18 million a year—are caused by cardiovascular disease, largely heart attack or stroke, both of which are triggered by clots blocking the vessels in the brain or heart.

While drugs like aspirin, given at the time of the attack, can prevent further clots forming, they only work in 25 per cent of cases, and these drugs can cause serious side effects from bleeding. According to the lead scientist on the paper, published in the prestigious journal, *Science Translational Medicine*, Associate Professor Justin Hamilton, from the Monash University Australian Centre of Blood Diseases, "there has been no new drugs to treat, let alone prevent, heart attack or stroke in more than 15 years," he said.

Associate Professor Hamilton said the researchers stumbled across the potential drug by accident. They were looking at changes within platelets that occur around the time of what is called a pathological setting, ie a heart attack or stroke. They found an enzyme of interest, isolated the gene responsible and developed a mouse that was missing just that gene.

The mice—to their surprise—were completely protected against heart attack. But why this enzyme provided protection remained a mystery for two years. "It drove us mad," Associate Professor Hamilton said.

The researchers used electron microscopy to cut ultrathin "slices" of the platelets from these mice to see what was going on. What they saw was a slightly modified membrane, which appears to prevent these platelets from attaching to each other or to blood vessel walls, the minute that there is a change in blood flow. "It is this blood flow perturbation which is a hallmark and predictor of a heart attack," Associate Professor Hamilton said.

"This enzyme allows the platelets to respond to this blood flow change and to "gear up" their capacity to clot, causing an attack."

Once the researchers were aware of the importance of the enzyme, they developed a drug that could shut this process down, in animal models and in laboratory models using human blood. This drug has the potential to be given to patients at risk of heart attack and stroke, to prevent blood clots forming when there is a risk of attack.

The next step is to develop a more suitable drug candidate that could be taken into a clinical trial, according to Associate Professor Hamilton. Initially he is hoping to test the drug on patients who have a higher risk of cardiovascular disease, such as those with diabetes.

These same clots—targeted by the Monash drug—have recently been linked to COVID-19 as a key cause of death from the disease. Associate Professor Hamilton said that, while it is early days, "the possibility of using our newly developed anti-thrombotic to improve the treatment of COVID-19 patients is an appealing idea we would like to explore."

More information: Disrupting the platelet internal membrane via PI3KC2α inhibition impairs thrombosis independently of canonical platelet activation, *Science Translational Medicine* (2020). DOI: 10.1126/scitranslmed.aar8430

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