How life-threatening blood clots take hold

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When plaques coating blood vessel walls rupture and expose collagen, platelets spring into action to form a blood clot at the damaged site. Now, a new report in the April 17th issue of the journal *Cell*, a Cell Press publication, reveals how those life-threatening clots—a leading cause of death in the United States, Europe and other industrialized countries--get an early grip. The discovery might offer a new way to fight clot formation before it can even begin, according to the researchers.

"Compared to other diseases, blood clotting has been very well understood," said Athan Kuliopulos of Tufts Medical Center and Tufts University School of Medicine. Nevertheless, he continued, many people still suffer from heart attacks, ischemic stroke and death as a result of clot formation.

"Drugs designed to inhibit clots through known pathways are widely used by millions. They work well, but not perfectly. There is still an unmet need." Those drugs include aspirin and the so-called thienopyridines, including Clopidogrel (trade name Plavix).

Scientists have known that a protein called thrombin plays an important role in clot formation as a potent activator of platelets. It also cuts fibrinogen into fibrin, a fibrous protein that works together with platelets to form a clot.

But thrombin isn't the whole story. Enzymes known as matrix metalloproteases have recently emerged as important players in platelet

function and the biology of blood vessels. Two of those enzymes, MMP-1 and MMP-2 can actually encourage platelet activation, according to earlier studies, although the means were unknown. In cancer cells too, MMP-1 activates a receptor known as PAR1 - the same receptor that is also responsible for receiving the thrombin signal on human platelets.

"There is abundant proMMP-1 coating platelets," Kuliopulos said. "We thought maybe it was on the outside waiting to be activated by something. Maybe it could be involved in an early event in blood clotting, before thrombin is around."

Indeed, Kuliopulos' team has now connected those dots. They show that exposure of platelets to collagen activates MMP-1, which in turn directly cut PAR1 on the surface of platelets. Collagen is the first thing a platelet "sees" when a blood vessel ruptures or is cut.

The MMP-1-PAR1 pathway activates another set of molecular players known to be involved in early clot formation, he said. Those activated platelets change their shape, sending out spikes and membrane sheets. "Within seconds, they become more sticky," adhering to the vessel surface and then other platelets.

Moreover, they show that treatments that block the MMP1-PAR1 pathway prevent blood clots from forming in the presence of collagen, suggesting that drugs targeting this metalloprotease-receptor system could offer a new way to treat patients with acute coronary syndromes.

According to the new results, PAR1 inhibitors already being tested in clinical trials might have an added benefit, Kuliopulos said. It's also possible they might work a little too well, since there is a careful balance between the risk of dangerous blood clots and the risk of bleeding. "An MMP-1 inhibitor might be better tolerated," he said.

Source: Cell Press (news : web)