Discovery Could Lead To Anti-Clotting Drugs With Less Risk Of Bleeding

Researchers at the University of Illinois at Chicago have discovered a molecular switch that causes small, beneficial clots that stop bleeding to enlarge further during wound healing. By blocking this switch in lab mice, the researchers prevented small clots from growing — a process that can pose a danger in humans — while preserving their ability to staunch bleeding. Their findings, published online in Nature, open up the possibility for developing potent anti-clotting drugs that don't raise the risk of bleeding.

"Existing anti-clotting drugs significantly reduce the body's ability to form blood clots, so people on these drugs are at risk of serious bleeding," says Xiaoping Du, professor of pharmacology in the UIC College of Medicine and lead author of the paper. "By exploiting this switch we found, we can develop very powerful drugs that prevent the big clots that cause heart attacks and strokes, while preserving the body's ability to form the smaller, primary clots you need to stop bleeding."

Anti-clotting drugs, also known as blood thinners, can help prevent strokes, heart attacks, and deep vein clots. They are also prescribed to reduce the risk of dangerous clots after surgery. But the drugs also increase the risk of bleeding, and must be used with great care.

Du and colleagues investigated a protein called integrin, found in the cell membrane of platelets, the specialized blood cells that form clots to stop bleeding. Signals given off by injured or torn blood vessels activate integrin, which directs the platelets to bind to the injured blood vessel and to other platelets through a linking-protein called fibrinogen. This cross-linking results in a primary clot, good enough to stop the bleeding in most minor cuts.

The UIC researchers discovered that once fibrinogen gets involved, another molecule called G-alpha-13 latches on to integrin and causes the clot to grow much bigger — to ensure the bleeding is stopped. Normally, the enlarged clot will shrink back. But in people prone to developing dangerous clots, or in those with narrowed arteries, the enlarged clots can lead to a heart attack or stroke.

Having found that G-alpha-13 is responsible for ramping up the clotting process, the researchers were able to develop a molecule that blocks G-alpha-13 from binding to integrin. Mice given the blocker-drug can form primary clots that stop bleeding but never enter the growth phase.

"This is exciting, because new drugs based on blocking G-alpha-13 can preserve the ability to form primary clots, which are necessary to heal wounds, but will prevent the clots from growing too large and clogging blood vessels," Du said.

Bo Shen, Xiaojuan Zhao, Kelly O'Brien, Aleksandra Stojanovic-Terpo, M. Keegan Delaney, Kyungho Kim, Jaehyung Cho, and Stephen C. T. Lam, all from UIC, are co-authors of the research paper.

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