Team finds a new way to inhibit blood clotting and inflammation

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(Medical Xpress)—Scientists have identified a group of small molecules that interfere with the activity of a compound that initiates multiple steps in blood clotting, including those that lead to the obstruction of veins or arteries, a condition called thrombosis. Blocking the activity of this compound, polyphosphate, could treat thrombosis with fewer bleeding side effects than the drugs that are currently on the market.

Their findings appear in the journal *Blood*.

Blood clots are formed at the site of an injured blood vessel to prevent blood loss. Sometimes, however, blood clots completely clog an artery or vein and the surrounding tissues are damaged. The U.S. Centers for Disease Control and Prevention reports that annually, 300,000 to 600,000 Americans are afflicted with deep vein thrombosis or pulmonary embolism, a blocked lung artery that often results from thrombosis, and 60,000 to 100,000 people die each year as a result of these conditions.

There are two pathways that trigger blood clotting. The tissue factor pathway helps stop bleeding if a person is injured. If any of the proteins of this pathway are missing, a bleeding problem will develop. In contrast, the contact pathway is activated when blood comes into contact with some artificial substances. Although this pathway can cause pathological blood clots, humans who lack proteins in this pathway do not have bleeding problems. These two pathways eventually converge to form a common pathway.

In 2006, the researchers found that compounds called polyphosphates can, when released from cell fragments called platelets, activate the contact pathway, said University of Illinois biochemistry professor James H. Morrissey, who led that study and the new analysis.

Because the contact pathway is not essential for normal blood clotting after an injury, interrupting polyphosphate "wouldn't have the bleeding side effects that touching anything downstream of it in the clotting cascade (would) have," Morrissey said.

The researchers found a variety of positively charged molecules that can bind to the negatively charged polyphosphate molecule and inhibit its ability to induce blood clotting. By adding these compounds to human blood and plasma isolated from the body, Morrissey and his colleagues were able to measure their effectiveness in inhibiting polyphosphate's pro-thrombotic and pro-inflammatory activities.

The researchers also tested these inhibitors in mice that were afflicted with venous and arterial thrombosis or inflammation, and found that these inhibitors prevented or reduced these negative effects.

"What this shows is that you could put really potent inhibitors of polyphosphate in and interrupt the clotting system by decreasing thrombotic risk, but probably not increasing (a person's) bleeding risk," Morrissey said. "This is the proof of principle that it works."

Although the compounds identified would not, by themselves, be good drug candidates, Morrissey said, the new study offers clues for developing more suitable drugs to target polyphosphates.

"I think that the work going forward would be to identify compounds that would be better drug candidates," he said.

More information: The paper, "Inhibition of Polyphosphate as a Novel Strategy for Preventing Thrombosis and Inflammation," is available online.

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