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Researchers find promising new angle for drugs to prevent stroke and heart attack

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Platelets, which allow blood to clot, are at the heart of numerous cardiovascular problems, including heart attacks and stroke. New research has uncovered a key platelet protein that could offer a new angle for developing drugs to prevent thrombosis, or dangerous blood clots, in patients who are at high risk such as those with atherosclerosis or a history of heart problems.

"I think we're at the start of an exciting journey of drug discovery for a new class of antithrombotic therapies," said lead study author Stephen Holly, PhD, assistant professor of biochemistry and biophysics at the University of North Carolina School of Medicine. This work was performed in collaboration with senior authors Leslie Parise, PhD, at UNC and Benjamin Cravatt, PhD, at The Scripps Research Institute.

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In the human circulatory system, platelets are something of a double-edged sword. Without their clotting abilities, even a minor injury could result in potentially fatal bleeding. But during a heart attack or stroke, platelets form a clot that can potentially block blood flow through our veins and arteries, a dangerous condition called thrombosis, which can deprive tissues of oxygen and lead to death.

Several antithrombotic drugs are available, but some have been found to

cause bleeding—a side effect that is particularly troublesome when these drugs are used to prevent thrombosis in people undergoing heart surgery. "There's still room for improvement, in terms of making an ideal drug that can block platelet function without initiating bleeding," said Dr. Holly.

Dr. Holly and his colleagues uncovered several potential drug targets using a screening technique that has never before been applied to the cardiovascular system. The technique, called activity-based protein profiling, has been used in cancer research and allows researchers to track the actual activities of proteins operating within a cell. The team first pre-screened human platelets to narrow the field of drug-like compounds, then generated an activity-based protein profile using one of these compounds to single out proteins that play a role in platelet activation.

The hunt was successful. "Using this technique, we discovered both novel inhibitors of platelet activation and a novel enzyme involved in platelet signaling," said Holly.

This new knowledge of platelets' natural "on-off" switches could be exploited to develop drugs that keep platelets from forming pathological blood clots. As a next step, the researchers hope to investigate the proteins' roles in animal models before potentially pursuing clinical trials in humans.

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