Genetic variability in the platelet linked to increased risk for clotting

In humans, study links genetic variation in a receptor on the platelet to an increase in the risk for thrombosis

Boston (March 31, 2015) – Coronary heart disease and stroke, two of the leading causes of death in the United States, are diseases associated with heightened platelet reactivity. A new study in humans suggests an underlying reason for the variability in the risk of clotting is due to a genetic variation in a receptor on the surface of the platelet. Additionally, the current study suggests that people expressing this genetic variant may be less protected from clotting and thrombosis when taking current anti-platelet therapies such as Aspirin and other blood thinning medications.

Antiplatelet therapy has helped to drastically reduce mortality associated with heart attacks and strokes; however, some individuals taking antiplatelet drugs are not fully protected from platelet clot formation. For example, black individuals are disproportionately burdened by these diseases compared to white individuals even after adjusting for clinical and demographic factors.

Benjamin Tourdot, Ph.D., a Postdoctoral Fellow on a research team led by Michael Holinstat, Ph.D., at the University of Michigan Department of Pharmacy recently discovered a genetic variant in a key platelet receptor, PAR4, which enhances platelet reactivity and is more frequently expressed in blacks than whites. The research will be presented at the American Society for Pharmacology and Experimental Therapeutics (ASPET) Annual Meeting during Experimental Biology 2015.

While the genetic variation is more common in blacks than whites it is still relatively common in both races with 76 percent of blacks and 36 percent of whites expressing at least one copy of the gene responsible for the hyper-responsiveness.

To determine if individuals with the hyper-responsive form of PAR4 may be less protected following a myocardial infarction or stroke even after receiving recommended antiplatelet therapy, the investigators compared healthy individuals and cardiac patients with and without the mutation for their responsiveness to PAR4 who were taking standard of care antiplatelet therapy (Aspirin and Plavix). The preliminary data demonstrated that independent of race individuals with a copy of the hyperactive variant of PAR4 have an increase in PAR4-mediated platelet reactivity compared to individuals without the variant even in the presence of antiplatelet therapy.
This work could identify the PAR4 T120A variant as a potential risk factor for thrombosis, and would require a new approach to treating patients with this genetic variant including the development of PAR4 antagonists.

A greater understanding of which patients benefit the most from current therapeutic strategies and which patients remain at elevated risk for a thrombotic event will aid in the development of new therapeutic targets for at-risk populations.

This study reinforces the personalized medicine approach to therapeutic intervention and challenges the one size fits all approach, which often leaves at risk populations without adequate protection from thrombotic events and stroke.

The study was funded by the National Institute for Minority Health and Health Disparities, National Institutes of Health.

Benjamin Tourdot will present the findings during the Experimental Biology 2015 meeting on Tuesday, March 31, from 12:30-2:30 p.m. at the poster session in Exhibit Hall AB, Boston Convention & Exhibition Center. Following the poster session, Tourdot will discuss his research findings at an oral presentation at the ASPET Division for Cardiovascular Pharmacology Trainee Showcase at 2:30 p.m. in Room 107AB of the Boston Convention & Exhibition Center.

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About Experimental Biology 2015
Experimental Biology is an annual meeting comprised of more than 14,000 scientists and exhibitors from six sponsoring societies and multiple guest societies. With a mission to share the newest scientific concepts and research findings shaping clinical advances, the meeting offers an unparalleled opportunity for exchange among scientists from across the United States and the world who represent dozens of scientific areas, from laboratory to translational to clinical research. [www.experimentalbiology.org](http://www.experimentalbiology.org)

About the American Society for Pharmacology and Experimental Therapeutics (ASPET)
ASPET is a 5,100 member scientific society whose members conduct basic and clinical pharmacological research within the academic, industrial and government sectors. Our members discover and develop new medicines and therapeutic agents that fight existing and emerging diseases, as well as increase our knowledge regarding how therapeutics affects humans. [www.aspet.org](http://www.aspet.org)

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