Racial difference in blood clotting warrants a closer look at heart attack medications

November 10 2013

Thomas Jefferson University researchers have discovered that the formation of blood clots follows a different molecular route in African Americans versus European Americans, providing a new understanding of the effects of race on heart disease. The finding could one day help doctors provide more individualized treatment of heart disease and other blood-clot-related illnesses, according to research publishing online November 10th in *Nature Medicine*.

The finding may also provide an additional explanation for the disparity between outcomes in black and white patients with heart disease, which is the most common killer of white and black Americans. Compared to white patients, blacks have a two-fold increased incidence of heart disease and have a lower long-term survival. The reasons for this racial disparity are complex, and include racial bias, a higher prevalence of traditional risk factors such in blacks, and differences in socioeconomic status, management and environment. However, even when these factors are considered, the survival of black heart attack patients is 2 and a half times lower than white patients. This suggests there are yet-to-be identified factors accounting for the racial disparity in heart disease.

"We may need to consider our patient's race when using certain heart disease therapies," said lead author of the research Paul Bray, M.D., Director of Thomas Jefferson University's Cardeza Foundation for Hematologic Research.

Anti-platelet medications, such as aspirin, are commonly prescribed to

prevent heart attack or stroke. These medications function by blocking the clot-forming activity of platelets – small cells that normally circulate in the blood stream and congeal around damaged or atherosclerotic blood vessels. The plaques in atherosclerotic vessels can occasionally rupture, causing the formation of a platelet plug that clogs blood vessels and can lead to heart attack or stroke. However, there is considerable variability in how patients respond to these medications, which confounds physicians who must deduce the appropriate drug and proper dose for each patient. Now, researchers from Thomas Jefferson University have identified some of the genetic differences behind these variations, which could help doctors treat racial groups with a more personalized and effective approach.

"Differences in platelet biology could be part of the explanation of the disparity," says Dr. Bray.

To investigate whether the variation among different individuals had a racial component, Dr. Bray and collaborators from Baylor Medical College, Harvard Medical School and the New York and Puget Sound Blood Centers analyzed platelets from blood samples of 154 young healthy subjects that included 70 blacks and 84 whites. Self-reported race was confirmed with genetic tests that verified geographic (African or European) ancestry. Unexpectedly, the researchers found that platelets from black donors clotted faster and to a greater extent in response to the naturally occurring clotting agent, thrombin that specifically triggered one of the platelet-activating receptors, called PAR4. No racial differences were seen with other clotting agents.

Thrombin is the most potent platelet activator in the body, and it is targeted for suppression by numerous blood-thinning medications. However, newer drugs that target thrombin inhibit specific members of the PAR family of receptors. For example, the drug vorapaxar, currently in development for patients with a history of heart disease, specifically

inhibits the PAR1 receptor. If PAR1 is blocked by vorapaxar, then PAR4 is the only means by which thrombin can activate platelets, and the Jefferson scientists showed that in this setting thrombin more potently activated platelets from blacks. It remains to be determined how or if these findings relate to drugs that are currently prescribed or to those currently in development.

Further molecular studies identified a novel gene called PCTP that mediated platelet activation through PAR4. PCTP was expressed at higher levels in platelets from blacks and appears to be a major contributor to the racial difference in blood clotting. Furthermore, a microRNA was identified that silenced the expression of PCTP; this microRNA was expressed at higher levels in platelets from whites than blacks and may contribute to the lower levels of thrombin activation through the PAR4 receptor in whites.

In fact, the researchers found many silencing microRNAs were more actively expressed in whites than in blacks, at least in platelets, suggesting that other aspects of platelet biology may be regulated differently depending on race. Uncovering the genes that these microRNAs suppress could help researchers hone in on individual differences in platelet function, and eventually how these differences contribute to disease and response to anti-clotting treatments.

"In this age where there is such a focus on delivering personalized medicine, we should embrace these differences to try to give our patients better care," says Dr. Bray.

More information: L.C. Edelstein, et al., "Racial differences in human platelet PAR4 reactivity reflect expression of PCTP and miR-376c," *Nature Medicine*, DOI: 10.1038/nm.3385, 2013