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Racially different DLK1-DIO3 miRNA expression levels in platelets reflect differential thrombin receptor PAR4 reactivity

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Abstract

Myocardial infarction and stroke typically result from an occlusive platelet thrombus formed at the site of atherosclerotic plaques. There is reproducible variation in platelet reactivity among different individuals – a variation that likely contributes to thrombosis risk. The Platelet RNA And eXpression-1 (PRAX1) study was designed to identify novel genes and miRNAs responsible for inter-individual variation in platelet reactivity. We assessed platelet aggregation in 70 black and 84 white healthy subjects and profiled miRNA and mRNA from highly purified blood platelets. The richness of these data provided unique opportunities to establish miRNA-mRNA-physiology relationships that led to a number of novel and unexpected results. This includes the discovery of racial differences in PAR4-mediated platelet activation and a genetic regulatory module in which racial differences in expression of miRNAs located in the DLK1-DIO3 locus and their target mRNAs account for this racial difference in platelet function. Compared to whites, blacks have a 2-fold increase in the incidence of CHD and a lower long-term survival. In addition, it is unknown whether the racial difference in platelet reactivity impacts the benefits and risks of anti-platelet therapies. Because novel inhibitors of PAR1 and 4 are currently in clinical development, it is critical to know whether dosing of such agents should be adjusted by race to maximize benefit and avoid toxicity. Lastly, since PAR4 is expressed in tissues other than platelets, it is possible that these expression differences have consequences for non-thrombotic diseases known to show racial differences.

Biography

Leonard C. Edelstein has completed his PhD from Rutgers University and postdoctoral studies from Harvard Medical School. He is a Research Assistant Professor in the Cardeza Foundation for Hematologic Research at Thomas Jefferson University. He has published 14 papers in reputed journals in the field of gene expression.