New Pathway for Tissue-Type Plasminogen Activator Regulation

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Circulating levels of tissue-type plasminogen activator (tPA) are correlated with risk of incident cardiovascular disease (CVD) among individuals with clinical atherosclerosis and in the general population, but a simple causal interpretation of this association belies epidemiological and regulatory complexity (eg, Ref. 1 and references therein). tPA, encoded by the PLAT gene, is an enzyme that is secreted from the vascular endothelium and cleaves circulating plasminogen to form plasmin, an enzyme with fibrinolytic activity. Most of the circulating tPA is bound in an inactive complex with its inhibitor PAI-1, encoded by the SERPINE1 gene. The association of higher levels of tPA with increased risk of incident CVD may thus seem paradoxical because formation rather than dissolution of a thrombus is the critical clinical event in clinical progression of atherosclerosis. Similarly, in the therapeutic setting, exogenous administration of tPA is an approved treatment for both myocardial infarction and acute ischemic stroke. The apparent discrepancy may be resolved by recognizing that elevated tPA may reflect, in part, a balance between risks of clotting and bleeding that, for example, may be shifted by underlying atherosclerosis. Thus, despite tPA’s intimate role in incident CVD, its regulation is not completely understood.

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Of course, genetics may be an alternative source of interindividual variation in circulating tPA and in fact the heritability of tPA levels is estimated to be $\geq43\%$. In the current issue, Huang et al. describe genome-wide genetic analysis of tPA levels conducted by meta-analysis across 14 cohorts including a total of almost 27,000 participants. The authors identify single nucleotide polymorphisms (SNPs) at 3 loci reaching the stringent significance thresholds required by genome-wide analysis. Significant SNPs at one of the loci span not only PLAT as expected but also the POLB gene encoding RNA polymerase B $\geq100$ kb away. Follow-up analysis suggests that association at POLB may be related through linkage disequilibrium to additional, nonredundant signals at the PLAT locus. The remaining associations strongly implicate the genes STX2, encoding syntaxin 2, and STXBP5, encoding syntaxin-binding protein 5. Strangely, none of the associations, including those near PLAT, was replicated in an additional sample that had moderate statistical power. Nevertheless, the validity of the discovery associations was affirmed by additional experimental analysis. The lead SNPs at STX2 and STXBP5 were associated with the transcripts of these 2 genes but not other neighboring genes in several cell types. Moreover, RNAi knockdown of STX2 or STXBP5 transcripts in endothelial cells in vitro led, respectively, to increased or decreased release of tPA after histamine stimulation. Finally, candidate gene analysis identified a SNP in the SERPINE1 gene that was associated with tPA levels, lending further credibility to the design of the discovery meta-analysis.

Remarkably, SNPs at STXBP5 had been identified previously in genome-wide genetic association with levels of both von Willebrand factor and FXIII, 2 additional hemostatic components, while SNPs in STX2 were associated with levels of von Willebrand factor alone. The proteins encoded by these 2 genes are likely part of soluble NSF attachment protein receptor complexes that target intracellular vesicles to the plasma membrane and facilitate release of their contents into the extracellular space. A separate syntaxin protein, syntaxin-4 (STX4), is critical for the release of von Willebrand factor from intracellular Weibel–Palade vesicles from the endothelium on stimulation, suggesting potential regulation of tPA by release from the endothelium through soluble NSF attachment protein receptor–related mechanisms. It still remains unknown the extent to which a common secretory pathway may contribute to the correlation between plasma levels of tPA and von Willebrand factor, which is estimated as $r=0.3$, because the associations at STXBP5 and STX2 do not account for this covariation.

Identification of the new genetic associations provides an opportunity to revisit the relationship between tPA levels and ischemia. It can be argued that genetic control of a cardiovascular biomarker may be used to investigate its potential causal contribution to incident CVD. This epidemiological construct turns on the idea that inherited genetic variation establishes, at random, a determinate and lifelong exposure to the biomarker without the possibility of reverse causation, because inherited genetics is practically immutable. Huang et al do not detect an association between any of their 3 genome-wide significant loci and CVD in large, existing genome-wide meta-analyses for either CAD or ischemic stroke. However, their finding may be consistent with previous studies suggesting that the association between tPA levels and CVD is weak enough that a genetic association between SNPs at STX2 or STXBP5 and CVD would have been difficult to detect. Nevertheless, as the authors note, the new genetic findings ought to focus attention on intracellular endosomal vesicle trafficking for further understanding the role of tPA in thrombosis risk related to atherosclerosis.
Disclosures

None.

Sources of Funding

The author’s research is supported by funding from the NHLBI for the MAPGen Consortium (U01 HL108630), the PARC Consortium (U01 HL069757), and R01 HL118305.

References


Key Words: Editorials ▪ atherosclerosis ▪ brain ischemia ▪ myocardial infarction ▪ SNARE proteins ▪ tissue plasminogen activator
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Arterioscler Thromb Vasc Biol. 2014;34:964-965
doi: 10.1161/ATVBAHA.114.303499
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

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