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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New Pathway for Tissue-Type Plasminogen Activator Regulation

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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.6 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.7 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=0.3,8 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.9 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.
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References


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