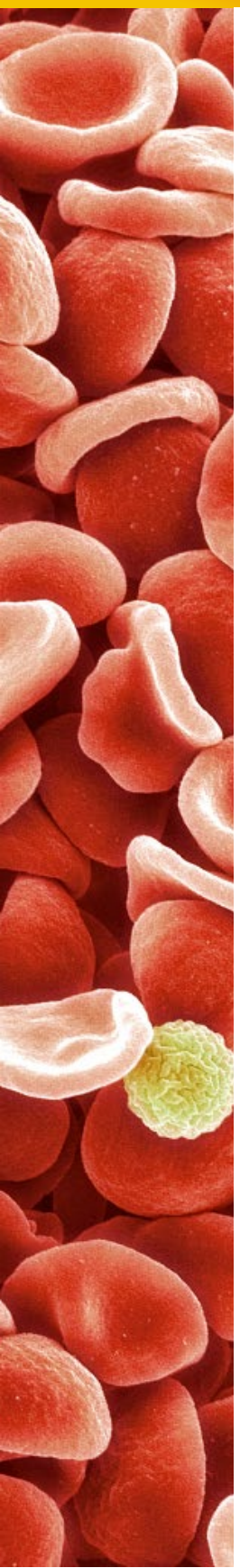
Lipid-Lowering tPA-K2 to Reduce Atherogenic Lipoproteins to Lower Residual Cardiovascular Risk



In Brief

The novel link between the intracellular function of tissue-type plasminogen activator (tPA) and Apolipoprotein B (apoB) in hepatocytes shows great promise for developing a drug to lower *all* bad atherogenic lipoproteins by tPA fragments and reduce cardiovascular risk.

Description

The invention is an approach to lowering all bad atherogenic lipoproteins. Tissue plasminogen activator (tPA) is a serine protease that initiates fibrinolysis to remove excessive blood clots and restore blood flow. We found that silencing or deleting tPA expression in the hepatocytes of mice resulted in higher plasma apoB and cholesterol levels, independent of any changes in hepatic LDLR or apoE expression or Apob mRNA level. The K2 domain of tPA binds to the N terminus of apoB, blocking the interaction between apoB and microsomal triglyceride transfer protein (MTP) in hepatocytes. This process reduces VLDL assembly and plasma apoB-lipoprotein cholesterol levels.

Currently, a patent application has been filed and we are developing therapeutic strategies to use this mechanism to lower atherogenic apoB-lipoproteins and cardiovascular risk.

Benefits

- Technology lowers *all* atherogenic lipoproteins
- Does not cause liver steatosis
- No bleeding risk or hepatic toxicity

Inventor

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Patent protection

- US Provisional Application filed May 2023: Recombinant Tissue Plasminogen Activator (TPA) Fragments and Uses Thereof
- Corresponding PCT Application filed May 2024

Publications

Wen Dai et al., Intracellular tPA-PAI-1 interaction determines VLDL assembly in hepatocytes. Science **381**, eadh5207 (2023). DOI: 10.11 26/science.adh5207

Keywords

Tissue plasminogen activator, tPA, K2, VLDL, IDL, LDL, hepatocyte, residual, cholesterol, dyslipidemia, atherosclerosis, cardiovascular disease, chylomicron, Lp(a)

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