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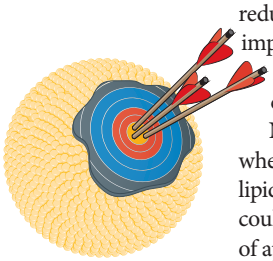
DYSLIPIDAEMIA

Monoclonal antibody targeting lipoprotein-bound human apoC-III

A novel monoclonal antibody that targets lipoprotein-bound human apolipoprotein C-III (apoC-III) promotes the clearance of circulating apoC-III in mice expressing human *APOC3*, thereby increasing the catabolism of triglyceride-rich lipoproteins, and reducing circulating triglyceride levels. These findings, published in *Nature Medicine*, suggest that an antibody to apoC-III would be an effective therapeutic approach to protect against coronary heart disease (CHD).

"Humans with heterozygous loss-of-function mutations in *APOC3* have lower triglyceride levels and reduced risk of CHD," explains Daniel Rader, senior investigator of the study. "Therapeutic antibodies are an alternative approach to inhibiting proteins, but the general opinion has been that apoC-III would be very difficult to target with a therapeutic antibody due to its relatively high concentration in blood." Four protective *APOC3* variants that were associated with reduced apoC-III and triglyceride levels have previously been identified; of these, only the A43T variant was a missense variant, rather than a protein-truncating variant. The study investigators sought to assess the mechanisms underlying the reduced levels of circulating apoC-III in carriers of the A43T variant by developing a mouse model expressing human *APOC3* A43T. These mice had reduced levels of apoC-III, owing to impaired binding of A43T apoC-III to lipoproteins, and enhanced renal catabolism of free apoC-III.

> "an antibody to apoC-III would be an effective therapeutic approach to protect against coronary heart disease"



Next, the investigators tested whether monoclonal antibodies to lipid-associated human apoC-III could promote the catabolism of apoC-III from lipoproteins. Using mice expressing human apoC-III, they generated an antibody that successfully reduced apoC-III and triglyceride levels by accelerating the clearance of apoC-III in the circulation; this enhanced apoC-III clearance could be partially explained by increased splenic uptake.

Together, these findings show that the naturally occurring *APOC3* A43T missense variant and a monoclonal antibody to apoC-III can both decrease apoC-III and triglyceride-rich lipoprotein levels in the circulation. Given that "apoC-III is perhaps the best-validated target for triglyceride reduction to reduce CHD, an antibody to apoC-III would be one therapeutic approach to reducing CHD risk in patients with controlled LDL-cholesterol levels who remain at risk," concludes Rader.

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ORIGINAL ARTICLE Khetarpal, S. A. *et al.* A human *APOC3* missense variant and monoclonal antibody accelerate apoC-III clearance and lower triglyceride-rich lipoprotein levels. *Nat. Med.* http://dx.doi.org/10.1038/nm.4390 (2017)
FURTHER READING Reiner, Z. Hypertriglyceridaemia and risk of coronary artery disease. *Nat. Rev. Cardiol.* **14**, 401–411 (2017)