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Integrative proteogenomic analysis identifies COL6A3-derived endotrophin as a mediator of the effect of obesity on coronary artery disease

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Obesity strongly increases the risk of cardiometabolic diseases, yet the underlying mediators of this relationship are not fully understood.

Given that obesity strongly influences circulating protein levels, we investigated proteins mediating the effects of obesity on coronary artery disease, stroke and type 2 diabetes. By integrating two-step proteome-wide Mendelian randomization, colocalization, epigenomics and single-cell RNA sequencing, we identified five mediators and prioritized collagen type VI α3 (COL6A3).

Levels of these proteins, including COL6A3, could potentially be decreased through reduction in body fat; this indicates their potential clinical actionability. COL6A3 levels were strongly increased by body mass index and increased coronary artery disease risk. Notably, the carboxyl terminus product of COL6A3, endotrophin, drove this effect. COL6A3 was highly expressed in disease-relevant cell types and tissues.

Finally, we found that body fat reduction could reduce plasma levels of COL6A3-derived endotrophin, indicating a tractable way to modify endotrophin levels.

In summary, our study provides evidence that endotrophin acts as a causal mediator in the relationship between obesity and CAD in humans. Given our finding that reducing levels of COL6A3 and its cleaved product endotrophin can reduce the risk of CAD without apparent adverse health outcomes, directly targeting endotrophin could be an attractive therapeutic approach that may be particularly effective in individuals with obesity. We provide actionable insights into how circulating proteins mediate the effects of obesity on cardiometabolic diseases and prioritize endotrophin as a potential therapeutic target.

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