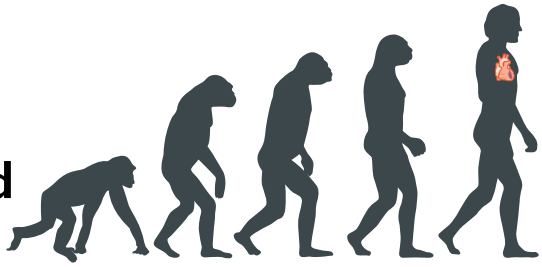
ATHEROSCLEROSIS

Enzyme loss during evolution linked to atherosclerosis predisposition



Credit: Carl Conway/ Springer Nature Limited

Cardiovascular events associated with atherosclerosis, such as myocardial infarction and stroke, are the most common cause of death worldwide in humans. However, these events are rare in other animals, even in closely related species, such as chimpanzees, despite having some of the same risk factors. Environmental and behavioural factors probably contribute to these differences. A new study shows that the loss of a single enzyme in humans during evolution might be another contributing factor.

Humans have a species-specific deficiency of the sialic acid *N*-glycolylneuraminic acid (Neu5Gc) caused by the loss of a functional form of cytidine monophosphate-*N*-acetylneuraminic acid hydroxylase (CMAH). This loss occurred in hominin ancestors 2–3 million years ago, an adaptation possibly linked to a malaria parasite that used Neu5Gc to invade cells. However, Philip Gordts, Nissi Varki, Ajit Varki and colleagues now show that the loss of CMAH might also predispose to atherosclerosis.

> “loss of CMAH also explains the increased risk of cardiovascular disease associated with red meat consumption”

The researchers found that *Ldlr*$^{-/-}$ mice with CMAH deficiency that were fed a sialic-acid-free, high-fat diet (HFD) had a ~1.9-fold increase in atherosclerosis compared with *Ldlr*$^{-/-}$ mice with CMAH. The increased risk seemed to be driven by higher levels of macrophage-derived cytokines and hyperglycaemia, given that triglyceride, cholesterol and lipoprotein levels did not change.

Interestingly, loss of CMAH also explains the increased risk of cardiovascular disease associated with red meat consumption in humans, which does not seem to occur in other carnivorous animals. Neu5Gc is present in red meat and can act as a ‘xeno-autoantigen’ in humans via metabolic incorporation into cellular glycoproteins and glycolipids, which by interaction with circulating anti-Neu5Gc antibodies potentiates chronic inflammation (termed xenosialitis). *Cmah*$^{-/-}$*Ldlr*$^{-/-}$ mice immunized with Neu5Gc antigens (to induce the generation of human-like anti-Neu5Gc antibodies) had a ~2.4-fold increase in atherosclerosis when fed a Neu5Gc-rich HFD compared with a Neu5Ac-rich diet or a sialic-acid-free HFD. Blood lipoprotein and glucose profiles were unchanged.

In summary, evolutionary loss of CMAH and Neu5Gc in humans might be a contributor to atherosclerosis susceptibility via intrinsic and extrinsic (that is, consumption of Neu5Gc, primarily from red meat) mechanisms.

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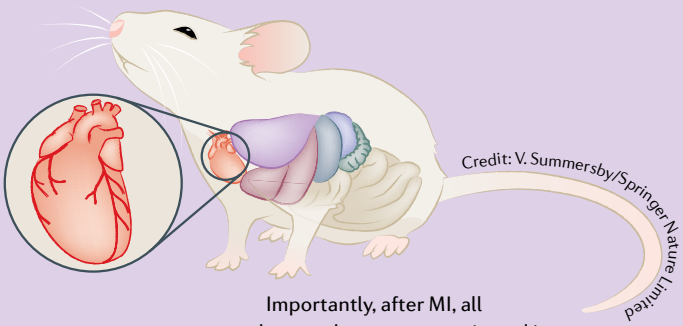
ORIGINAL ARTICLE Kawanishi, K. et al. Human species-specific loss of CMP-*N*-acetylneuraminic acid hydroxylase enhances atherosclerosis via intrinsic and extrinsic mechanisms. *Proc. Natl Acad. Sci.* https://doi.org/10.1073/pnas.1902902116 (2019)

CARDIAC REGENERATION

Distinct regulatory pathways are involved in coronary vessel growth



Credit: V. Summersby/Springer Nature Limited

Three independent regulatory pathways involved in the development of the coronary vasculature are activated in the hearts of embryos and neonatal mice after myocardial infarction (MI) but repressed in adult mice. “[This finding] strongly indicates a fundamental divergence between the regulatory pathways intrinsically employed in the healthy and injured adult heart,” summarize the researchers.

The generation of new coronary vessels after MI can attenuate ischaemic injury and cardiac dysfunction, but the mechanisms underlying vessel growth in the ischaemic heart are not well understood. The cellular processes involved in coronary vessel formation in the embryonic heart are well characterized, but whether these pathways can be reactivated in the adult heart is unclear. By analysing numerous gene enhancers that drive gene expression to endothelial cells of coronary vessels, Nicola Smart, Sarah De Val and colleagues identified three distinct signalling cascades implicated in coronary vessel growth.

First, sustained expression of the homeobox protein HLX3:*lacZ* transgene, which is activated by vascular endothelial growth factor A (VEGFA)–myocyte-specific enhancer factor 2 (MEF2) signalling in endothelial cells, was detected in both neonatal and adult endocardial-derived coronary vessels, confirming the role of this pathway in coronary vessel formation. Development of sinus venosus (SV)-derived coronary arteries required activation of the SOXF/RBPJ transcriptional programme. Finally, the bone morphogenetic protein (BMP)–mothers against decapentaplegic homologue (SMAD) pathway was found to be active in SV-derived coronary veins.

> “the mechanisms underlying vessel growth in the ischaemic heart are not well understood”

Importantly, after MI, all three pathways were activated in neonatal mouse hearts, which have regenerative potential, but repressed in the injured hearts of adult mice. “These findings were unexpected and highly relevant given that the VEGFA pathway has been the main pathway targeted in preclinical and clinical studies,” comments Smart.

To conclude, these results indicate that distinct pathways are involved in neovascular growth during developmental coronary vessel formation and ischaemic injury.

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ORIGINAL ARTICLE Payne, S. et al. Regulatory pathways governing murine coronary vessel formation are dysregulated in the injured adult heart. *Nat. Commun.* **10**, 3276 (2019)