Gut microbiota

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A perspective on thrombogenesis through gut microbiota-derived bile acids and platelet activation

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Cardiovascular arterial thrombosis poses a major health burden, despite intensive antiplatelet therapy, and platelet hyper-reactivity drives thrombus formation, yet its molecular mechanisms remain unknown. A study now shows that gut microbiota–derived deoxycholic acid modulates platelet activity and thrombosis risk in coronary artery disease.

Bile acids, which are primarily known for their role in lipid digestion and absorption, are increasingly being recognized as key regulators of metabolism and inflammation[1] and have been linked to cardiovascular diseases. However, their potential role in modulating platelet activation and blood clot formation, particularly in coronary artery disease (CAD), remains poorly understood.

Primary bile acids are synthesized in the liver, conjugated with taurine or glycine, stored in the gallbladder and released into the small intestine upon ingestion of fats. Excess bile acids either are reabsorbed by the ileum or undergo microbial transformation in the colon. Gut microbiota-mediated deconjugation, dehydroxylation and oxidation convert primary bile acids into secondary bile acids, which are known to be important modulators of liver function and risk of cancer[2]. Both primary and secondary bile acids bind receptors with important regulatory functions, such as the nuclear farnesoid receptor FXR and the Takeda G-coupled-protein receptor TGR5, both of which have crucial roles in regulating liver metabolism[2]. These receptors, though primarily expressed in the liver, are also expressed in other tissues, including the kidney and gastrointestinal tract but also, importantly, the vascular endothelium and blood cells[2]. This suggests that bile acids, the natural ligands of these receptors, must also affect signaling in extrahepatic tissues.

In this context, a study published in this issue of *Nature Cardiovascular Research* by Qi et al.[3] provides compelling evidence that gut microbiota-derived deoxycholic acid (DCA) modulates platelet activity and thrombosis risk in CAD, highlighting a previously unrecognized link between bile acid metabolism, the gut microbiota and cardiovascular pathology.

The authors first analyzed bile acid levels in patients with CAD and found that DCA concentrations were significantly lower than in healthy individuals[3]. DCA is formed by conjugation of cholic acid by 7α-dehydroxylation by gut bacteria[4]. Qi et al.[3] traced this reduction to decreased levels of *Bacteroides vulgatus*, a gut bacterium involved in bile acid metabolism. To explore the functional consequences of this imbalance, they conducted platelet activation studies and demonstrated that DCA effectively inhibited platelet aggregation in response to various clot-promoting stimuli[3] (Fig. 1a). Further mechanistic investigations revealed that DCA binds to the TGR5 receptor on platelets, triggering downstream signaling pathways that reduce platelet activation (Fig. 1b). This effect was abolished in genetically modified mice lacking TGR5 and in experiments using a TGR5 inhibitor, confirming the role of the receptor in mediating the effects of DCA.

A major strength of this study lies in its comprehensive approach, integrating human clinical data, microbiome analysis, in vitro platelet function studies and in vivo mouse models of CAD. Moreover, the authors went beyond mere correlation to establish causality. Indeed, administering deoxycholic acid (DCA), *B. vulgatus* or stool transplants from healthy donors to atherosclerotic mice resulted in decreased platelet reactivity and clot formation[3]. Importantly, these treatments conferred protection against ischemia–reperfusion injury, suggesting that they could have broader cardiovascular benefits (Fig. 1a). The findings also align with recent studies indicating that genetic deficiency of TGR5 in mice results in increased platelet activation and thrombus formation[5].

Several lines of evidence have indicated that liver diseases are associated with an increased risk of cardiovascular events, even in early stages of chronic liver disease[6], but underlying the mechanisms have so far been unclear. The data from Qi et al.[3] suggest that in the absence of TGR5 activation, a prothrombotic phenotype might develop. The data are also consistent with some of the many beneficial effects of TGR5 activation, which include increased GLP-1 secretion and which have led to a decades-long search for suitable TGR5 agonists[2].

The new findings also point to a precise mechanism behind various clinical observations linking liver disease to altered hemostasis[7]. Liver cirrhosis, for example, is associated with a complex, unstable rebalanced hemostasis, sometimes worsened by thrombotic events[7]. The authors' data[3] help explain the imbalance between fibrinolysis and thrombogenesis seen in individuals who have dysregulated TGR5, as is the case in some types of liver damage.

Despite its strengths, the study raises some questions. Although the mouse models provide strong preclinical evidence, translating these findings to humans will require further studies, including clinical trials to test whether targeting gut microbiota or bile acid metabolism can safely reduce clotting risk in patients with CAD. Furthermore, although the advantageous effects of TGR5 activation on liver and metabolic health are well established[8], it is difficult to argue for a positive effect of DCA on human health. In fact, higher levels of DCA are associated with impaired glucose metabolism[4], vascular calcification and increased risk of cardiovascular disease events in individuals with kidney disease[9], as well as increased progression

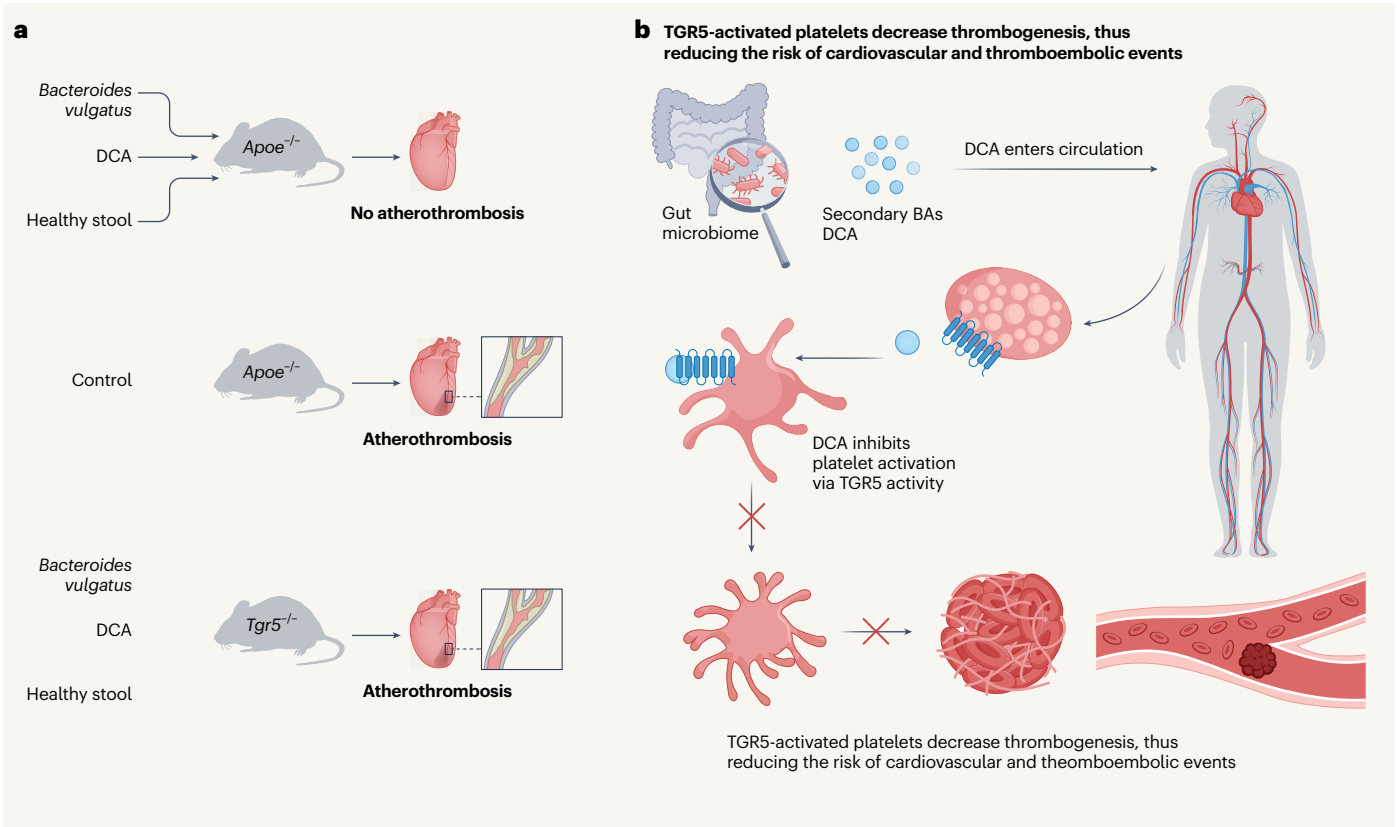

Fig. 1 | Role of bile acids in atherothrombosis. a, Experimental data from Qi et al.[3] showing that administration of *B. vulgatus*, DCA or stool transplants from healthy donors to atherosclerotic mice (homozygous for mutations resulting in the lack of functional apolipoprotein E) results in decreased platelet reactivity and clot formation. **b**, Mechanistic summary. Gut microbiome-derived DCA enters the circulation, inhibits platelet activation via the TGR5 receptor, and reduces thrombogenesis and cardiovascular and thromboembolic events.

of gallbladder cancer and increased risk of colon cancer. Therefore, although these findings open important avenues for understanding the role of TGR5 signaling as a regulator of platelet activation, they do not suggest DCA as a viable means to reduce the risk of thromboembolic events.

Looking ahead, this research opens up new avenues for exploring microbiome compounds, and in particular bile acid-based therapies, for cardiovascular disease. Various gut bacterial metabolites have already been implicated in cardiovascular disease[10]. For instance, trimethylamine-*N*-oxide (TMAO), short-chain fatty acids (SCFAs) and phenylacetylglutamine (PAG) have been extensively investigated for their effect on atherosclerosis, thrombosis and inflammation. TMAO, derived from dietary choline and carnitine via gut microbial metabolism, induces cholesterol metabolism alterations, inflammation, endothelial dysfunction and platelet activation and has been linked with an increased risk of cardiovascular events independently of traditional risk factors. SCFAs, produced through the fermentation of dietary fiber, influence blood pressure regulation and immune responses. PAG, a phenylalanine-derived microbial metabolite, has been linked to incident risk for major adverse cardiac events, including heart attack, stroke and death. These findings underscore the complex interplay between the gut microbiome and heart health, suggesting potential therapeutic strategies targeting microbial metabolism to reduce cardiovascular risk.

In general, beneficial gut microbial metabolites, such as SCFAs, are produced at higher levels in response to healthy diets such as the Mediterranean diet or other diets rich in plants. By contrast, at least on the basis of cross-sectional observational evidence, DCA levels appear to be elevated in individuals with unhealthy diets and to decrease with healthy diets such as the Mediterranean diet[1]. Therefore, dietary strategies known to be effective at reducing the risk of cardiovascular disease should actually decrease the levels of most secondary bile acids.

Pharmacological activation of TGR5, for liver and metabolic disease, is likely to translate into novel and effective drugs in the not-too-distant future. Based on the findings of Qi et al.[3], such therapies would also have anticoagulant effects, which might need to be considered when prescribing such therapies alongside non-steroidal anti-inflammatory drugs (NSAIDs), direct oral anticoagulants (DOACs), vitamin K antagonists and antiplatelet agents. Moreover, these data highlight the potential of gut microbial products to alter the effectiveness and safety of anticoagulation therapy. This has been recently reported in a pilot that found that gut dysbiosis is associated with lower time in the therapeutic range in individuals taking warfarin therapy for anticoagulation[11]. Although it was not tested specifically in that study, dysbiosis tends to be associated with high intakes of unhealthy fats, which are the same type of habitual diets that are associated with high levels of secondary bile acids. Such results would then be consistent

with a role for secondary bile acids in modulating response to anticoagulation therapy.

Future studies should aim to validate these findings in human populations and further unravel the complex interactions between the gut microbiota, bile acid metabolism and platelet function.

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References

1. Louca, P. et al. *Cell Rep. Med.* **4**, 100993 (2023).
2. Fuchs, C. D. & Trauner, M. *Nat. Rev. Gastroenterol. Hepatol.* **19**, 432–450 (2022).
3. Qi, Z. et al. *Nat. Cardiovasc. Res.* https://doi.org/10.1038/s44161-025-00637-x (2025).
4. Wahlström, A. et al. *Nat. Commun.* **15**, 4276 (2024).
5. Reusswig, F. et al. *Platelets* **35**, 2322733 (2024).
6. Roca-Fernandez, A. et al. *J. Hepatol.* **79**, 1085–1095 (2023).
7. Lisman, T., Caldwell, S. H. & Intagliata, N. M. *J. Hepatol.* **76**, 1291–1305 (2022).
8. Jin, W., Zheng, M., Chen, Y. & Xiong, H. *Eur. J. Med. Chem.* **271**, 116462 (2024).
9. Frazier, R. et al. *Kidney Med.* **4**, 100387 (2022).
10. Witkowski, M., Weeks, T. L. & Hazen, S. L. *Circ. Res.* **127**, 553–570 (2020).
11. Agosti, P. et al. *Arterioscler. Thromb. Vasc. Biol.* **44**, 2659–2661 (2024).

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Competing interests

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