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THROMBOSIS

Novel target with antithrombotic potential and low bleeding risk

Current antithrombotic agents impair haemostasis, which increases the risk of bleeding. A new study now reveals a novel target with antithrombotic potential and with reduced risk of bleeding. "We have identified a pathway that regulates thrombosis, but not haemostasis," says corresponding author, Daniel Simon. The pathway involves the interaction of the leukocyte integrin Mac-1 (also known as integrin $\alpha_M\beta_2$) with the platelet surface receptor GPIbα.

Previous work by this group showed that Mac-1 binds GPIbα, regulating inflammation in various models. Taking this work forward, the researchers now show that Mac-1–GPIbα interaction is critical for regulation of thrombosis. Mac-1 deficiency or mutations in the Mac-1 binding site for GPIbα delayed thrombus formation in mouse models of large-vessel (carotid artery) and small-vessel (cremaster microcirculation) arterial thrombosis, without affecting haemostasis parameters such as tail bleeding time. Adoptive transfer of wild-type leukocytes rescued the thrombosis defect. Mechanistically, Mac-1–GPIbα binding induced phosphorylation of protein kinase C-δ and downregulation of forkhead box protein P1 (FOXP1) in leukocytes. FOXP1 signalling contributed to thrombosis, as shown by delayed thrombosis in mice with monocyte and macrophage-specific overexpression of FOXP1.

Finally, in a set of experiments highlighting the therapeutic potential of targeting this pathway, Simon and colleagues showed that blocking Mac-1–GPIbα binding with an antibody or with the small-molecule glucosamine delayed thrombosis after carotid artery injury in mice, without altering haemostasis. The research team is now planning clinical studies to assess the anti-inflammatory and antithrombotic effects of the humanized antibody.

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ORIGINAL ARTICLE Wang, Y. *et al.* Leukocyte integrin Mac-1 regulates thrombosis via interaction with platelet GPIbα. *Nat. Commun.* **8**, 15559 (2017)
FURTHER READING Franchi, F. *et al.* Antithrombotic therapy for patients with STEMI undergoing primary PCI. *Nat. Rev. Cardiol.* **14**, 361–379 (2017)