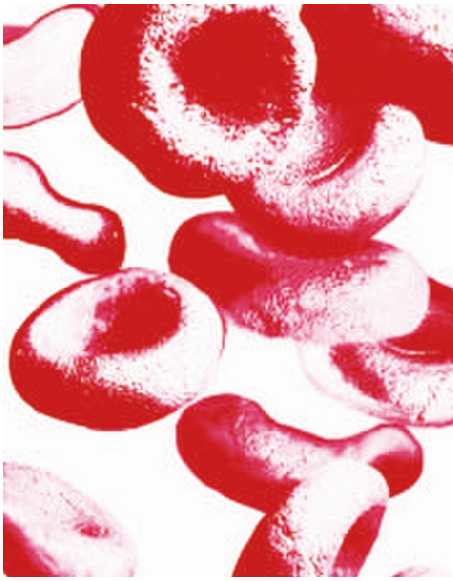
ANTITHROMBOTIC DRUGS

Sheer inhibition



The effects of thrombus formation can be devastating, and underlie two of the biggest killers in the developed world, myocardial infarction and stroke. Writing in *Nature Medicine*, Shaun Jackson, Alan Robertson, Hatem Salem and colleagues report the identification of a new potential target for antithrombotic drugs.

Various factors can precipitate the formation of a thrombus, such as the rupturing of atherosclerotic plaques. Changes in the rate of blood flow, and associated increases in shear stress, can raise the thrombogenic potential of a ruptured plaque, and *in vivo* studies have revealed that shear forces promote platelet activation and, consequently, thrombus formation.

The formation of platelet thrombi is crucially dependent on the adhesive and signalling functions of integrin αIIbβ3 (platelet GPIIb–IIIa), which mediates platelet–vessel and platelet–platelet adhesive interactions through several adhesive ligands. All existing antiplatelet agents target one or more key steps in the thrombotic pathway and ultimately downregulate the adhesive functions of αIIbβ3. Current therapies, however, can also lead to bleeding complications by affecting normal clotting functions.

An important signalling pathway underlying shear-induced platelet activation involves phosphatidylinositol 3-kinases (PI3Ks); however, the roles of various PI3K isoforms in the pathways have remained unclear. In addressing this problem, the authors developed a series of PI3K inhibitors, some of which were selective for PI3K isoforms. The PI3K inhibitor TGX-221, which is selective for the PI3K p110β isoform, reduced thrombus formation on a von Willebrand factor substrate at elevated shear rates, which led to an exploration of the *in vivo* effects of TGX-221.

Intravenous bolus injection of TGX-221 at a dose of 2 mg per kg abolished thrombus formation in rats and rabbits, whereas an inhibitor selective for the PI3K isoform p110δ had no effect. The onset of TGX-221 action was rapid (within 5 minutes), and was dose-dependent, with activity observed at doses as low as 0.5 mg per kg. In a rat carotid artery electrolytic injury model, TGX-221 (2 mg per kg) prevented the development of occlusive thrombi and was more effective than aspirin at preserving carotid blood-flow volume over a 60-minute period following injury.

An important issue with any drug designed to prevent the formation of blood clots is whether it causes unwanted bleeding when administered at therapeutic doses. Doses of 20 mg per kg of TGX-221 — 20 times the minimum dose required for therapeutic activity — did not prolong bleeding time in a rat tail bleeding model or the ear bleeding time in anaesthetized rabbits. Interestingly, from a clinical perspective, the co-administration of TGX-221 with the anticoagulant heparin had no significant effect on bleeding time, whereas the antiplatelet agents aspirin and clopidogrel both increase bleeding time on their own and prolong bleeding time in the rat tail bleeding model when combined with heparin by upwards of 20 minutes.

In addition to the demonstration of the potential of the PI3K p110β isoform as an antithrombotic drug target, the authors' findings provide further evidence for the functional specialization of different PI3K isoforms. The selective targeting of the role of other PI3K isoforms, such as p110α in oncogenesis, p110δ in immune function and p100γ in inflammation, might also be a strategy applicable to a wide range of diseases.

Daniel Jones

References and links

ORIGINAL RESEARCH PAPER Jackson, S. P. *et al*. PI 3-kinase p110β: a new target for antithrombotic therapy. *Nature Med.* **11**, 507–514 (2005)

FURTHER READING Jackson, S. P. & Schoenwalder, S. M. Antiplatelet therapy: in search of the 'magic bullet'. *Nature Rev. Drug Discov.* **3**, 775–789 (2003)