THROMBOTIC DISORDERS

Seeking out better anticoagulants

Currently used anticoagulants — such as heparins, warfarin and factor Xa inhibitors — that target key enzymes required for the formation of fibrin can be associated with the drawbacks of an increased risk of bleeding and/or lack of antidotes. Two recent papers have identified potential new anticoagulants that could overcome these limitations.

The study by Xu *et al.* in *Nature Chemical Biology* identified a new synthetic low-molecular-weight heparin (LMWH) and, importantly, showed that its effects could be reversed by an approved antidote. The effects of currently available LMWHs, either isolated from animals (such as enoxaparin) or synthetically produced (such as fondaparinux) cannot be completely reversed.

The authors used recombinant heparan sulphate biosynthetic enzymes expressed in *Escherichia coli* to synthesize heparin oligosaccharides. Of the five molecules synthesized, the lead molecule had anticoagulant activity in an assay that measured the activity of factor Xa (a protease that converts prothrombin to active thrombin). The activity of the lead molecule was reversed by the approved antidote protamine to a greater extent than enoxaparin and to a similar level as unfractionated heparin. Moreover, in a mouse model of bleeding (a tail clip assay), the increase in bleeding time induced by the molecule was reversed by protamine — an effect that the authors attributed to the sulphation pattern and larger size of the lead molecule.

Future studies to develop the molecule as a therapeutic include structure–activity relationship studies and scale-up of the manufacturing process.

The paper by Larsson *et al.* in *Science Translational Medicine* identified a neutralizing antibody that targets factor XIIa (which initiates the intrinsic coagulation pathway). The knowledge that thrombus formation is defective in mice lacking factor XII but is not accompanied by excessive bleeding led the authors to pursue this target. They generated a fully human recombinant antibody that bound to the catalytic site of human factor XIIa by screening a human Fab (antigen-binding fragment)-based phage antibody library against human plasma-derived factor XIIa.

The antibody reduced clotting activity in human plasma and reduced thrombin formation in mouse and rabbit blood. Furthermore, in a mouse model of thrombosis, intravenous injection of the antibody reduced the rate of vascular occlusion, with higher doses almost completely preventing clotting activity without increasing bleeding time or blood loss from wounds.

The authors next tested the anticoagulant activity of the antibody in rabbit models. . In a model of cardiopulmonary bypass (mimicking the procedure that is used to provide pulmonary and circulatory support to infants), which is subject to thrombotic events without the use of anticoagulants, a single intravenous dose of the antibody induced similar thromboprotection as heparin. But whereas heparin largely prolonged bleeding time and impaired haemostasis at wound sites, these effects were not seen in antibody-treated rabbits.

The next steps of research include testing the antithrombotic effects of the antibody in more complex models, such as models of myocardial infarction, ischaemic stroke and pulmonary embolism.

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ORIGINAL RESEARCH PAPERS Xu, Y. *et al.* Homogeneous low-molecular-weight heparins with reversible anticoagulant activity. *Nature Chem. Biol.* http://dx.doi.org/10.1038/nchembio.1459 (2014) | Larsson, M. *et al.* A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk. *Sci. Transl. Med.* **6**, 222ra17 (2014)