No contact, no thrombosis?

Joost C. M. Meijers

In this issue of Blood, Matafonov et al demonstrate that an inhibiting monoclonal antibody against coagulation factor XII (fXII) reduces fibrin formation and platelet accumulation in a primatethrombosis model. Although the contact system (consisting of fXII, prekallikrein, and high-molecular-weight kininogen) has been known for decades, its role in coagulation has been limited to diagnostics where it plays an essential role in the activated partial thromboplastin time. Deficiencies in either fXII, prekallikrein, or high-molecular-weight kininogen have not been associated with a bleeding tendency, which makes their role in hemostasis questionable. However, in recent years, mice with deficiencies in these proteins have consistently shown reduced injury-induced thrombosis. These findings brought great excitement to the field because this would suggest that in vivo inhibition of one of these proteins would be ideal for treatment of (venous) thrombosis because these drugs may be effective against thrombosis and, at the same time, bear no risk of bleeding. The situation became complex when the contribution of the contact factors in human thrombosis could not be confirmed. Patients with deficiencies in one of the contact factors experience thrombotic events. Furthermore, low levels of fXII increased the risk of myocardial infarction, and there was an inverse correlation between fXII levels and risk of myocardial infarction, unless overruled by other major prothrombotic risk factors. Second, the inverse relationship between fXII and all-cause mortality was observed between the 10% and 100% factor level, but individuals between 1% and 10% did not have an increased mortality. In combination with the increased risk for myocardial infarction by low levels of fXII, this may point to a difference between deficiency and low levels of fXII: complete deficiency (<10%) protects, but low levels (10%-50%) increase risk. If true, this would make treatment with fXII inhibitors a delicate task because each patient has then to be carefully titrated to remain in the protecting target window. Third, the models that were used favored contact system-initiated coagulation. It remains to be established whether fXII inhibition is effective when thrombus formation is initiated via tissue-factor exposure. The death of John Hageman, albeit an n = 1 experiment, would argue against that. It remains therefore to be seen whether targeting fXII will be effective in humans.

One of the interesting experiments in the study of Matafonov et al was a direct comparison between fXII and factor XI (fXI) inhibition, and targeting fXI appears to be superior in the baboon model. Over the last few years, there have been numerous publications showing efficacy and safety of fXI inhibition in animal models (reviewed in van Montfoort and Meijers). Although it remains to be established whether targeting fXII or one of the other contact factors will be useful in humans, the targeting of fXI seems to be a promising option as an alternative approach for future effective and safe antithrombotic therapy.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

No contact, no thrombosis?

Joost C. M. Meijers