Comment on Matafonov et al, page 1739

No contact, no thrombosis?

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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 primate thrombosis model.1 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.2-4 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.5 Furthermore, low levels of fXII increased the risk of myocardial infarction,6 and there was an inverse correlation between fXII levels and death from all causes.7 This suggested discrepant roles for the contact system in thrombosis between mice and humans. To shed light on this discrepancy, Matafonov et al produced 2 monoclonal antibodies against human fXII.1 Careful in vitro and ex vivo characterization demonstrated that these antibodies inhibited surface-initiated coagulation in human plasma, and reduced ex vivo fibrin formation in collagen-coated tubes perfused with human blood. The authors then went on to in vivo characterization and took advantage of the fact that one of the anti-fXII antibodies inhibited baboon fXII. Using a collagen-coated graft model in baboons, it was clearly shown that inhibition of fXII resulted in a significant reduction of platelet deposition downstream from the graft. At the same time, fibrin deposition was reduced both at the graft and downstream. At least part of the effect was via a reduction in thrombin generation because thrombin-antithrombin levels were lower in the presence of the inhibitory antibody. So, this work importantly confirmed earlier observations in mice that fXII deficiency protects against fibrin and thrombus formation, and that reduction in fXII may be an attractive option for antithrombotic therapy.

However, several key issues remain. How can we explain the apparent discrepancy with human epidemiological data? First, the fact that individuals deficient in one of the contact factors do experience thrombotic events could be explained by both other risk factors and by underreporting because these persons are usually asymptomatic and only diagnosed with some other disease. The first person identified with fXII deficiency, John Hageman, had a pulmonary embolism, but incited by severe trauma. It could still be that fXII deficiency protects against thrombosis 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.1 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 Meijers8). Although it remains to be established whether targeting fXI 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.

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REFERENCES

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