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COMMENTARY

Properdin (factor P) as a new target cleaved by factor XIa: Intrinsic coagulation at the crossroads with inflammation

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The complement system and blood coagulation cascade, in particular, the contact activation pathway, are functionally related and exhibit crossover activities. Deficiency or altered function of complement proteins are associated with thrombo-inflammatory diseases. Factor XI (FXI), as part of the intrinsic pathway, is the zymogen, which can be activated to the plasma protease FXIa by FXIIa with the help of high molecular weight kininogen, and then continue to the downstream cascade of proteases that ultimately triggers the production of thrombin (FIIa). In addition to FXIIa, FXI can be feedback activated by thrombin, but also by autoactivation in the presence of surfaces such as sulfatides and glycosaminoglycans.[1] In past decades, multiple studies have tried to clarify the role of FXI in thrombin generation and its relationship to contact activation.

Patients with FXI deficiency rarely have spontaneous bleeding; even with trauma to susceptible tissues or major surgery, bleeding is mostly moderate, indicating that FXI has a limited role in hemostasis. Interestingly, there is emerging evidence from epidemiologic data, animal models experiments, and human clinical trials indicating that FXI has a more important role in thromboembolic disease. $FXI^{-/-}$ mice had normal tail bleeding time but exhibit attenuated clot formation at the sites of arterial or venous injury.[2] Likewise, treatment with FXI antisense oligonucleotides (FXI-ASO) or anti-FXI antibodies in rodent or rabbit models had shown resistance to experimentally induced thrombosis and a low risk of bleeding complications.[3] Epidemiological studies showed that patients with lower levels of FXI are at reduced risk of venous thromboembolism (VTE) and cardiovascular diseases such as stroke, transient ischemic attack (TIA), and myocardial infraction (MI).[4] Obviously, FXI is not involved in initiating thrombus formation, but rather contributes to the thrombus stabilization and growth through the amplification loop of thrombin feedback-activating FXI. This makes FXI(a) an attractive target for antithrombotic therapy. Novel FXI/FXIa inhibitor agents include inhibitors of biosynthesis, antibodies, and small molecules and are under development in clinical trials:

- *Antisense oligonucleotides*: FXI-ASO downregulates the FXI level by inhibiting its biosynthesis in liver. In a phase 2 study (NCT01713361), the FXI ASO IONIS-FXI_{RX} (200 mg or 300 mg) was compared with enoxaparin (40 mg) for prevention of VTE in patients undergoing total knee arthroplasty (TKA). The study showed that the higher does (300 mg) regimen (4%) was superior to enoxaparin (30%) for the prevention of VTE and had lower bleeding events than with enoxaparin (3% vs. 8%). Therefore, this trial demonstrated that factor XI contributes to postoperative VTE and that lowering factor XI levels was an effective method for its prevention and appeared to be safe.[5]

Presented at ESC Congress August 28th, 2022: Sharma M et al., AXIOMATIC-SSP: Antithrombotic treatment with factor XIa inhibition to Optimize Management of Acute Thromboembolic events for Secondary Stroke Prevention.

- *Abelacimab (MAA868)* is a fully human, inhibitory FXI antibody that binds the catalytic domain of both FXI (zymogen) and active FXIa. One of three regimens of abelacimab (30, 75, or 150 mg) administered postoperatively in a single intravenous dose was compared with 40 mg of enoxaparin administered subcutaneously once in 412 patients who were undergoing TKA.[6] Another trial comparing abelacimab (120, 180 mg) with placebo in patients with AF who are at low risk of thromboembolism (NCT04213807) is ongoing.
- *Osocimab (BAY 1213790)* is a long-acting, fully human monoclonal antibody that inhibits factor XIa. A total of 813 adult patients who were undergoing TKA were involved in this phase 2 noninferiority study (FOXTROT). Osocimab (0.6, 1.2, and 1.8 mg/kg) was compared with enoxaparin and apixaban for thromboprophylaxis.[7] Another trial is a 6-month study comparing subcutaneous osocimab at low or high doses with placebo in patients with end-stage renal disease undergoing hemodialysis is under way (NCT04523220). It is designed primarily to evaluate safety and the rates of the composite of major and clinically relevant nonmajor bleeding.
- *Milvexian (BMS-986177/JNJ-70033093)* is an oral small molecule, active-site inhibitor of FXIa. A phase 2 trial compared milvexian with enoxaparin for postoperative thromboprophylaxis in 1242 patients undergoing TKA (AXIOMATIC-TKR). Twice daily doses of milvexian ranging from 25 to 200 mg and once daily doses of 25, 50, or 100 mg were evaluated in patients undergoing knee arthroplasty, showing dose-dependent anticoagulation without significantly increasing the risk of bleeding.[8] The recently presented results of the phase 2 trial AXIOMATIC-SSP (NCT03766581) indicate that milvexian did not reduce the composite of covert brain infarction or ischemic stroke at 90 days compared with placebo in patients with ischemic stroke or TIA on a background of antiplatelet therapy.
- *Asundexian (BAY 2433334)*: An oral chemically synthesized small molecule that binds directly, potently, and reversibly to the active site of FXIa and thereby inhibits FXIa activity. In a phase 2 dose-finding clinical trial for the indication stroke prevention in atrial fibrillation, asundexian at doses of 20 mg and 50 mg once daily resulted in near-complete in vivo FXIa inhibition and in lower rates of bleeding compared with standard dosing of the active comparator, the FXa inhibitor apixaban.[9] Two more phase 2 clinical trials investigating asundexian in acute MI or noncardioembolic stroke are completed: PACIFIC AMI[10] and PACIFIC Stroke,[11] both demonstrating no significant increase in bleeding when added to antiplatelet therapy.

The clinical potential of FXI/FXIa-directed anticoagulant strategies are further evaluated in phase 3 clinical trials in atrial fibrillation and stroke and represent an exciting new era in anticoagulation. In this issue of RPTH, Heal et al. used the methods of surface plasmon resonance, substrate specificity analysis, and enzyme kinetics analysis to demonstrate that properdin (Factor P), an intrinsic activator of the alternative complement pathway, is cleaved by activated coagulation FXIa, binds with high affinity to FXI/FXIa and modulates FXIa activity with downstream functional consequences. They further demonstrate a direct interaction between Factor P and FXI suggesting a novel crosslink of intrinsic coagulation and the activation of the alternative pathway of complement. This implies a broader understanding of thromboinflammatory events, and a putative off-target protection from inflammation-mediated (vascular) injury, as suggested by preclinical models of polymicrobial sepsis,[12] or aggravation as seen in a model of *Streptococcus pneumonia*–induced sepsis.[13] Factor P cleavage may outbalance the inhibitory effect of FXIa on complement Factor H, an intrinsic inhibitor of the alternative complement pathway.[14] The discovery of properdin as target of FXIa adds to the list of even more off-target effectors of the protease FXI with implication in thromboinflammation, such as the adipokine and chemo-attractant chemerin[15] and high molecular weight kininogen.[16] These pleiotropic immune-modulatory sequalae of FXI-inhibition might explain, at least in part, the anti-inflammatory protection seen in models of atherosclerosis,[17] arterial hypertension,[18] and myocardial infarction.[19] It remains to be established whether the activity of Factor P has potential implications for the FXIa-thrombin feedback activation, another important contributor to vascular inflammation. Future in vivo studies will be required to prove a pathophysiological role of the FXIa dependent properdin cleavage, and whether the cleavage products of Factor P will have pro- or anti-inflammatory properties in the vasculature.

AUTHOR CONTRIBUTION

Qi Luo drafted the manuscript, Philip Wenzel wrote the manuscript and handled funding and supervision.

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RELATIONSHIP DISCLOSURE

Q. L. has no disclosures. P. W. reports serving as a consultant for Bayer and has received speaker honoraria from Bayer, Boehringer-Ingelheim, Pfizer, Daiichi Sankyo, Astra Zeneca, Abbot and Novartis.

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