Inhibition of factor XIIa, a new approach in management of thrombosis

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Thrombosis is an unfavorable condition of blood clot formation that may happen in arteries or veins. Although arterial and venous thromboses are different in content and mechanism of formation, both conditions have a large impact on community health with significant clinical consequences. Venous thrombosis is associated with inappropriate activation of coagulation cascade, and has high fibrin content and low platelets, whereas activation of platelets plays a major role in arterial thrombosis (1,2). Several efforts have been made so far to resolve this pathological condition or at least minimize the mortality and morbidity of thrombosis in patients. Many anticoagulants have been developed with different clinical applications. Immediate acting anticoagulants like heparin are commonly used for initial treatment of thromboembolism while slower acting vitamin K antagonists are largely used for long term therapy (3).

The intrinsic coagulation pathway is initiated by contact activation of factor XII (FXII), which consequently activates plasma factor XI (FXI). Activated FXI (FXIa) then triggers factor IX activation and eventually leads to thrombin-mediated fibrin formation. Although FXIIa is an indispensable component for in vitro assessment of coagulation, congenital FXII deficiency is not associated with abnormally excessive bleeding, which may give the impression that FXII is not involved in the physiologic pathway of coagulation (4,5). However, blood contact with surfaces like extracorporeal membrane oxygenation (ECMO) system, hemodialysis membrane and catheters potentially leads to the activation of FXII and a subsequent high risk of thrombus formation (6). Since the use of conventional anticoagulants including heparin is associated with bleeding, new strategies seem to be necessary in this setting to avoid excessive bleeding after surgical operation. Considering these facts, one could imagine that FXII targeting is one of the promising strategies to fulfill this aim. Recently, in a study by Larsson et al. in Science Translational Medicine journal entitled “A factor XIIa inhibitory antibody provides thromboprotection in extracorporeal circulation without increasing bleeding risk”, it was attempted to evaluate this strategy (7). They developed a recombinant antibody against FXII by phage study. This antibody, also known as 3F7, specifically binds to the activated FXII and not to the zymogen form, and thereby inhibits its proteolytic activity (7).

Although the mentioned study was not the first attempt in this respect, it resulted in valuable findings by using both human and animal plasma. There is also a previous series of experiments mainly on animal models assessing different inhibitors of FXII or FXIIa. According to a valuable review by Kenne et al., currently available inhibitors include antibodies (such as 15H8, C6B7, B7C9, etc.), biological inhibitors (such as C1 INH, Ir-CPI, dimiconin, etc.), small molecules (e.g., bicyclic peptide 3) and oligonucleotides (e.g., RNA-aptamer) (6). However, the study of Larsson et al. is the most recent experiment introducing a new anti-
FXIIa neutralizing antibody.

In the mentioned study, analysis of clotting activity using rabbit and human blood showed that 3F7 prolongs activated partial thromboplastin time (aPTT) in both species with more efficiency in rabbit but was not effective upon prothrombin time (PT) (7).

The authors then investigated in vivo function of 3F7 action. They induced thrombosis in mice using FeCl$_3$, which results in the formation free radicals followed by vascular endothelium injury. 3F7 protected mice from thrombosis, and the blood collected from mice showed prolonged aPTT with no effect on PT. This result was comparable with FXII$^−/−$ mice, which were all protected from vessel-occlusive thrombus formation. Subsequently, 3F7 effect was assessed in larger animals, which provides more predictive values on anticoagulant associated bleedings in humans. For this purpose, the rabbits were treated with microglass chamber containing shunt to assess thrombus formation. Chamber occlusion was inhibited in the animal treated with 3F7 and heparin, but not in saline-treated control group. However, 3F7 and heparin both provide similar thromboprotection but the effect of heparin on hemostasis was associated with prolonged bleeding time and increased bleeding from skin and kidney wounds compared with 3F7. These data are consistent with prolonged PT induced by heparin but not by 3F7 (7).

Finally, the authors presented a model of cardiopulmonary bypass using an ECMO system in rabbits to analyze the clinical application of 3F7. Circulation of blood in this system is subject to thrombotic events without the use of anticoagulants. Administration of heparin in the same dose used for patient prevents thrombotic occlusion, whereas a single dose of 3F7 introduces a similar thromboprotection. As patients undergo heparin therapy, administration of heparin to rabbits is associated with impaired hemostasis and increased blood loss at wound sites, which was not observed in animals treated with 3F7 (7).

According to these findings, inhibition of FXIIa seems to be a new approach of anticoagulation, as 3F7 showed the same efficacy of heparin but did not lead to excessive hemorrhage during invasive procedures. However, further experimental studies especially on human models are necessary for better investigation of the efficacy and probable risks of FXII inhibition methods for preventing thrombosis.

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**References**
