THE REGULATION OF BLOOD COAGULATION FACTOR XIII BY HUMAN NEUTROPHIL PROTEASES

Zsuzsa Bagoly, MD
University of Debrecen, Medical and Health Science Center, Clinical Research Center

Blood coagulation factor XIII (FXIII) is a protransglutaminase of tetrameric structure (A_2B_2). The first step in the activation of pFXIII is the cleavage of R37-G38 bond in the A subunit (FXIII-A) by thrombin, which makes the subsequent formation of an active transglutaminase possible. No active form of FXIII-A, other than G38-FXIII-A* has been identified. The main task of activated FXIII (FXIIIa) in hemostasis is the cross-linking of fibrin chains, which, together with the cross-linking α_2 plasmin inhibitor to fibrin renders the clot resistant to fibrinolysis. Although all activated clotting factors have known pathways of inactivation, in the case of FXIII, no such mechanism has been reported. As the hemostatic plug contains polymorphonuclear granulocytes (PMNs) rich in proteolytic enzymes, we tested if these proteases are released in fibrin clots and if they become involved in the regulation of FXIII activity.

Purified human neutrophil elastase (HNE) induced a limited cleavage of the inactive FXIII, resulting in the rapid activation of FXIII, followed by a much slower inactivation. HNE-activated FXIII cross-linked fibrin γ- and α-chains in the clot formed by batroxobin moojeni. MALDI-TOF analysis and N-terminal sequencing identified V39-N40 as the primary cleavage site and N40-FXIII-A* as a novel active form of FXIII.

The supernatant of stimulated PMNs proteolytically degraded FXIIIa, resulting in the parallel loss of transglutaminase activity. It was demonstrated that in the fibrin clot HNE, cathepsin G and matrix metalloprotease-9 (MMP-9) were released from PMNs, they exerted a fibrinolytic effect and degraded both FXIII subunits. It was shown that HNE is involved in the down-regulation of FXIIIa within the fibrin clot, while the task of MMP-9 and to a lesser extent that of cathepsin G is the further degradation of the split products. The proteolytic degradation of FXIII by PMNs was also significant when clots were made from whole plasma or from fibrinogen supplemented with α_1-antitrypsin (α_1AT). In the presence of α_1AT the degradation of FXIIIa by PMN proteases occurred significantly faster than that of cross-linked fibrin. These results suggest that proteases released from PMNs could effectively be involved in the

inactivation of FXIIIa within the fibrin clot. For the first time, a mechanism, which down-regulates FXIIIa in the clot, was described. This mechanism could prevent the formation of over-cross-linked fibrin clot difficult to eliminate when it is no longer needed.

Keywords:
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