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Review article

Cytokines in the pathogenesis of hemophilic arthropathy

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ABSTRACT

Hemophilic arthropathy (HA) is one of the most common and typical manifestation in the course of recurrent bleeding episodes in patients with hemophilia. Clinical and subclinical joint bleeding episodes gradually lead to irreversible changes manifesting themselves as pain, progressing ankylosis, marked limitation of the range of motion, muscle atrophy and osteoporosis commonly concomitant with joint deformity resulting from chronic proliferative synovitis and both cartilage and bone degeneration leading to the final functional impairment of the joint. In spite of numerous studies, the pathophysiology of HA has not been fully elucidated, especially as regards immunopathological mechanisms which are associated with the subclinical and early stage of the disease and to be more precise, with chronic joint inflammation. It needs to be emphasized that the pathophysiological processes occurring in a joint with HA are most probably highly mediated by interactions within the cytokine network and other inflammatory mediators present in the tissues of affected joint. Among numerous compounds participating in the induction of an inflammatory process in the pathogenesis of HA, cytokines seem to play a leading role. The most important group controlling the disease seems to be well known inflammatory cytokines, including IL-1β, TNFα and IL-6. The second group with antagonistic effect is formed by anti-inflammatory cytokines such as IL-4 and IL-10. The role of inflammatory and anti-inflammatory cytokines in the pathogenesis of HA with respect to cellular and intracellular signaling pathways is still under investigation. This review, summarizes and discusses the current knowledge about cytokine network in the pathogenesis of HA, indicating possible molecular and cellular mechanisms that may provide potential new therapeutic directions.

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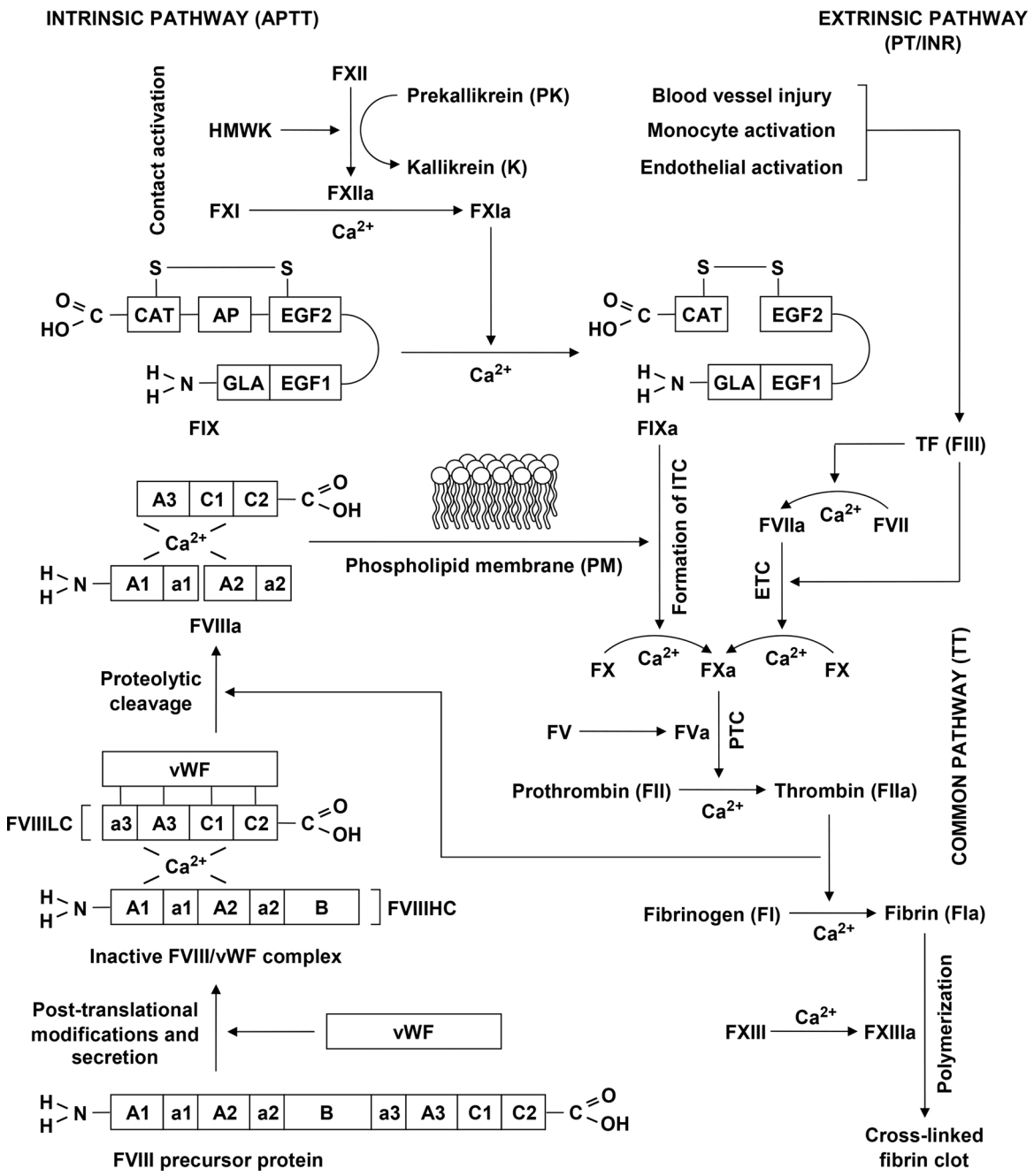

Fig. 1. Schematic representation of the coagulation cascade and simplified life cycle of FVIII and FIX including their domain structure and processing under physiological conditions. Hemostasis mechanisms defined as a system of proteolytic reactions, are activated by two distinct pathways, through intrinsic pathway associated with the formation of ITC (FVIIIa/FIXa/FX/PM/Ca^{2+}) and by extrinsic pathway associated with the formation of ETC (FVIIa/FX/TF/PM/Ca^{2+}). Both of these converge on the activation of common pathway associated with the formation of PTC (FII/FVa/FXa/PM/Ca^{2+}) and catalytic generation of FIIa which is essential for conversion of FI into FIa. Ultimately, FIa monomers polymerization along with platelet aggregation leads to formation of a stable cross-linked fibrin clot. The tightly controlled process such a hemostasis can be disrupted by genetic deficiency or reduction in the activity of FVIII or FIX. In this conditions assembly and functioning of ITC is impaired leading to prolonged bleeding (APTT ≥ 30–40 s). This types of congenital disturbances in hemostatic system are known as hemophilia A and B. Abbreviations: APTT activated partial thromboplastin time, HMWK high molecular weight kininogen (Fitzgerald factor), PK prekallikrein (Fletcher factor), K kallikrein, FXII coagulation factor XII (Hageman factor), FXIIa active coagulation factor XII, FXI coagulation factor XI (plasma thromboplastin antecedent), FXIa active coagulation factor XI, FIX coagulation factor IX (Christmas factor), GLA gamma-carboxyglutamic acid-rich domain (1–40 aa), EGF1 epidermal growth factor 1-like domain (47–83 aa), EGF2 epidermal growth factor 2-like domain (88–127 aa), AP activation peptide (146–180 aa), CAT catalytic domain (181–415 aa), FIXa active coagulation factor IX, FVIII coagulation factor VIII (anti-hemophilic factor), A1 A1 domain (1–336 aa), a1 a1 acidic region (337–372 aa), A2 A2 domain (373–710 aa), a2 a2 acidic region (711–740 aa), B B domain (741–1648 aa), a3 a3 acidic region (1649–1689 aa), A3 A3 domain (1690–2019 aa), C1 C1 domain (2020–2172 aa), C2 C2 domain (2173–2332 aa), vWF von Willebrand factor, FVIIIHC coagulation factor VIII heavy chain (A1-a1-A2-a2-B), FVIIILC coagulation factor VIII light chain (a3-A3-C1-C2), FVIIIa active coagulation factor VIII, PM phospholipid membrane, ITC intrinsic tenase complex, PT prothrombin time, INR international normalized ratio, TF (FIII) tissue factor (coagulation factor III), FVII coagulation factor VII (proconvertin), FVIIa active coagulation factor VII, ETC extrinsic tenase complex, TT thrombin time, FX coagulation factor X (Stuart factor), FXa active coagulation factor X, FV coagulation factor V (proaccelerin), FVa active coagulation factor V, PTC prothrombinase complex, FII prothrombin, FIIa thrombin, FI fibrinogen, FIa fibrin, FXIII coagulation factor XIII (fibrin-stabilizing factor), FXIIIa active coagulation factor XIII.