PROTEIN C
ITS FUNCTIONAL ROLE
AND SIGNIFICANCE IN VARIOUS DISEASES

Essay
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By

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A C K N O W L E D G E M E N T

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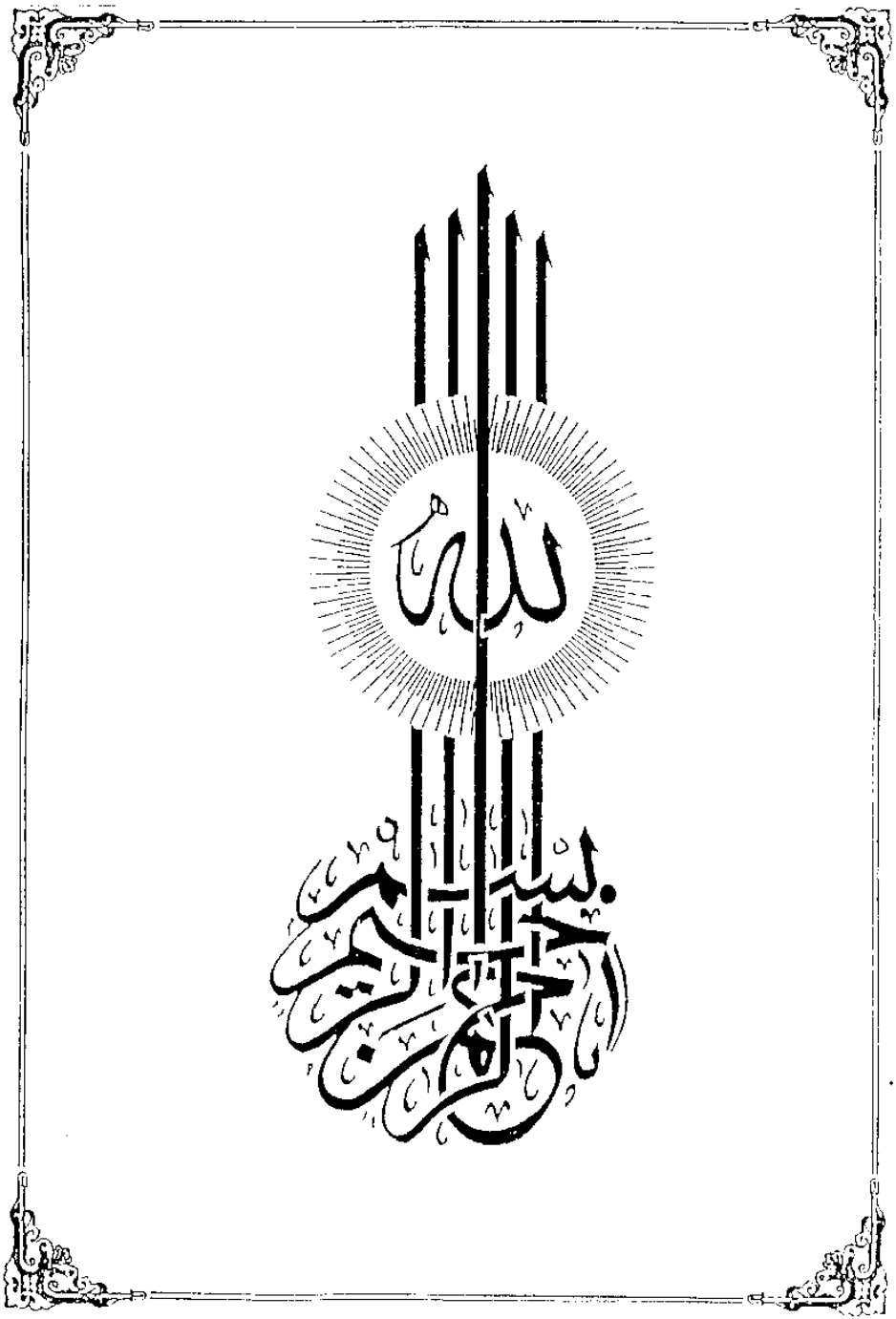

C O N T E N T S

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INTRODUCTION

NORMAL HAEMOSTASIS

The functions of the normal haemostatic process are to prevent blood loss from intact vessels and to arrest bleeding from injured vessels. This is maintained through a complex series of interactions and a balance between several plasma proteins, which posses a procoagulant or anticoagulant tendencies, in the presence of suitable surface (platelet or endethelial cell).

Haemostasis involves three main processes which are :

1. The vascular response.
2. Platelet adhesion & aggregation.
3. Activation of blood coagulation mechanisms.

1. Role of blood vessels :

Immediately following injury, the injured blood vessel undergoes a temporary reflex nervous vasoconstriction, resulting in slowing of blood flow & giving a chance for platelets and coagulation factors to react

forming the blood clot. Also, the escaping blood comes in contact with the damaged vessel wall and the subendothelial collagen which initiates the processes of platelet adhesion, platelet aggregation and blood coagulation.

Platelets adhere to the subendothelial collagen and release adenosine diphosphate (ADP) which cause aggregation of the adherent platelets.

The subendothelial collagen also activate factor XII which starts both coagulation and fibrinolysis.

Moreover, the vascular endothelial cell secretes VonWillebrand's factor (F VIII - VW) which mediates platelet adhesion and helps in clot formation.

Recently, the vascular endothelium has been shown to participate actively in inhibiting clot formation so that clot is limited to the injured site and not propagated to occlude the vessel and block the blood flow. Both endothelial cell surface and intra-cellular factors contribute to this regulation.

Two distinct anticoagulant mechanisms are triggered by contact with the cell surface. One involves cell surface heparin like molecules that can function to accelerate the inactivation of coagulation proteases by antithrombin III (Busch et al., 1982). The other involves thrombomodulin, a thrombin binding protein that changes the specific procoagulant effect of thrombin to an anticoagulant effect, by decreasing the ability of thrombin to catalyse clot formation (Esmon et al., 1982), and at the same time converting thrombin into a potent protein C activator (Esmon & Owen, 1981). Protein C then functions as an anticoagulant by inactivating factor Va and VIIIa (Walker, 1979; Fulcher et al., 1983a).

Intracellular components also contribute to the vascular regulation of the clotting process. Prostacyclin (Moncada et al., 1976), an inhibitor of platelet activation, and plasminogen activator (Sakata et al., 1985) are both synthesized and released from endothelium.

Thus the endothelial cell contributes to the control of clotting, platelet activation and clot dissolution.

2. Role of platelets :

Platelets have a central role in the regulation of haemostasis, preventing spontaneous leaking of blood cells through capillary walls. Together with the blood vessel wall, they maintain a balance between thrombosis and haemostasis by maintaining a balance between the production of prostacyclin which interferes with platelet aggregation, and thromboxane A_2 which promotes it.

3. Coagulation mechanism :

It is formed of three related systems : the coagulation system itself, the fibrinolytic system and the coagulation inhibitory system ..

(1) The coagulation system :

According to the coagulation cascade or waterfall hypothesis (Davie and Ratnoff, 1964;

MacFerlane, 1964), coagulation is initiated by two fundamental different mechanisms : The process of contact activation & the action of tissue factor, which proceeds via two separate (intrinsic & extrinsic) pathways with the end result of factor X activation then they converge by activating a third pathway leading to fibrin formation . (Figure 1).

A) Intrinsic pathway :

This involves activation of factors XII, XI, IX in addition to Kinin System. It ends by formation of intrinsic F X activator complex by the interaction of F IX_a, PF(3), Ca^{++} and F VIII.

Factor XII activation, can be achieved by two ways, either by contact activation (by contact with the subendothelial collagen),

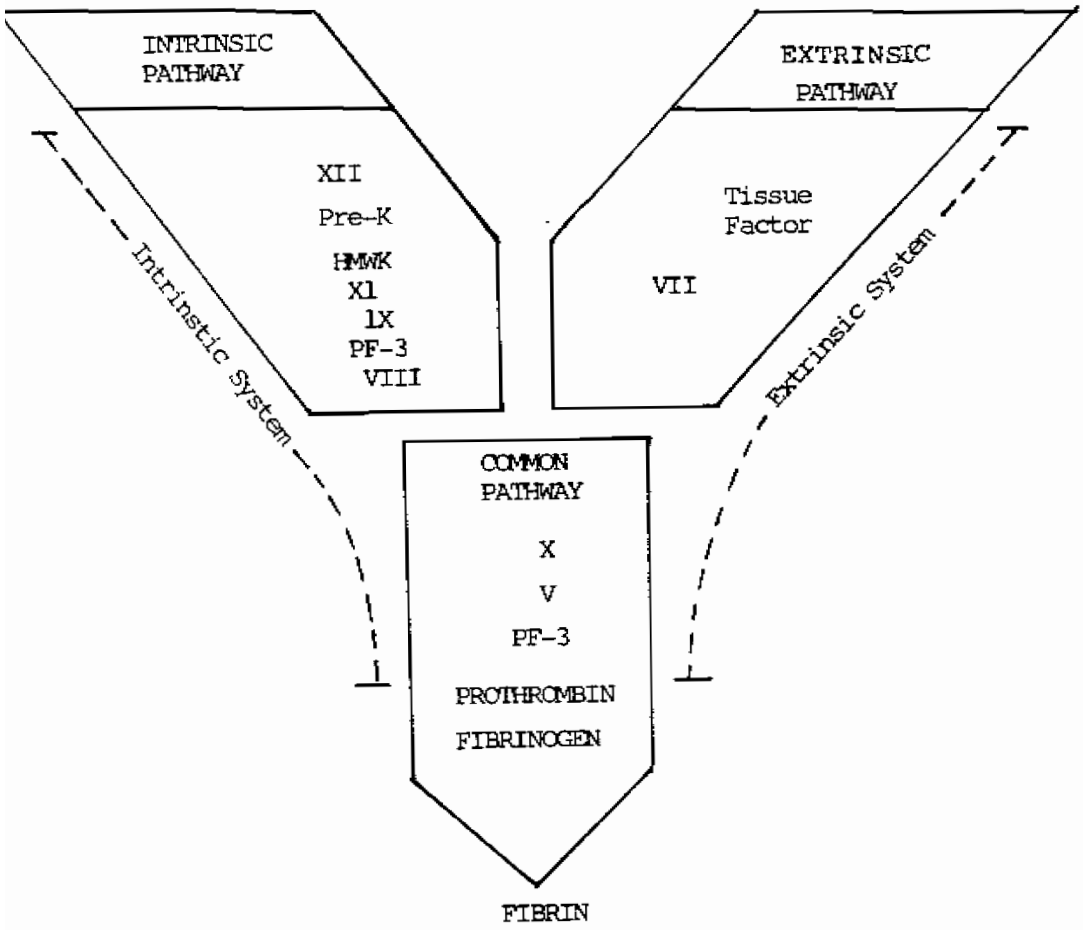

Fig.1: Pathways of coagulation. The terms intrinsic system and extrinsic system are widely used with reference to the reactions indicated by dashed lines. The following abbreviations are used:- PF-3: platelet factor 3, pre K; prekallikrein, HMWK: high molecular weight kininogen.
(Quoted from Wintrobe Clinical Hematology, 1981)

or proteolytic cleavage & fragmentation (mainly by the action of kallikrein) (Kaplan, 1978).

Activation of kinin system (PK, HMWK) :

It was found that optimum activation of intrinsic pathway of coagulation requires the participation of kinin system (Saito, 1977), however the exact mechanism is unclear. Prekallikrein (PK) activation is achieved by proteolytic action of F XII_a, plasmin (Bagdasarian, 1973). Kallikrein accelerates several coagulation reactions in vitro (Kaplan & Austen, 1975) including the conversion of F XII to F XII_a & F XII fragmentation thus amplifying the activation of F XII (Weiss, 1974). It may directly activate factor XI (Osteurd, 1975) and plasminogen (Mandle & Kaplan, 1977). The high molecular weight kinin (HMWK) acts mainly to enhance F XII_a action on its natural substrates FXI (Meier, 1977).

Factor XI activation into F XI_a occurs by the enzymatic action of F XII_a (Ratnoff & Miles, 1964), and the serine protease F XI_a subsequently activate F IX into F IX_a in a calcium dependent reaction (Davie & Fujikawa, 1975).

Formation of intrinsic F X activator : It is achieved through the interaction of F IX_a, F VIII, $PF_{(3)}$ in a calcium dependent reaction. The reaction is accelerated by the action of traces of thrombin on F VIII. Factor IX_a is the active enzyme acting on F X while F VIII is a cofactor.

B) Extrinsic pathway :

This involves the interaction of tissue factor and F VII in the presence of Ca^{++} ions to form a complex which behaves as "enzyme" activating F X (Williams & Norris, 1966), but

neither of two factors alone can activate F X (Jesty & Newerson, 1974).

C) Common pathway :

It starts with activation of F X in a Ca^{++} dependent reaction to yield F X_a (Discipio, 1977) which interacts with F V, Ca^{++} & $PF_{(3)}$ to form "prothrombinase complex" (Papahad-Jopoulos & Hañahan, 1964). Factor X_a is the active enzyme, while F V is a cofactor that forms a receptor site for F X_a binding to $PF_{(3)}$ by Ca^{++} bridges (Miletich et al., 1978). Factor V must be activated by thrombin before F X_a binding is optimal (Kane et al., 1980).

The prothrombinase complex then activates prothrombin in a calcium dependent reaction to yield thrombin, which itself enhances prothrombin activation (Aronson, 1977).

Then Thrombin-fibrinogen reaction proceeds in three steps :

* Enzymatic proteolysis leading to formation of fibrin monomer + 2 fibrino-peptide (A) & 2 fibrinopeptide (B). (Nossel, 1976).
* Poly-merization of the fibrin monomer (Krakow, 1972).
* Stabilization of soluble fibrin into insoluble fibrin by the action of F XIII (Curtis & Lorand, 1977). Factor (XIII) is activated by thrombin (Curtis, 1974).

(2) The Fibrinolytic system :

Fibrinolysis is the major physiological way for fibrin degradation after performing its haemostatic function, thus it is an important mechanism in wound healing and recanalization of thrombosed vessels. In blood, fibrinolysis results from conversion of the pro-enzyme (plasminogen)