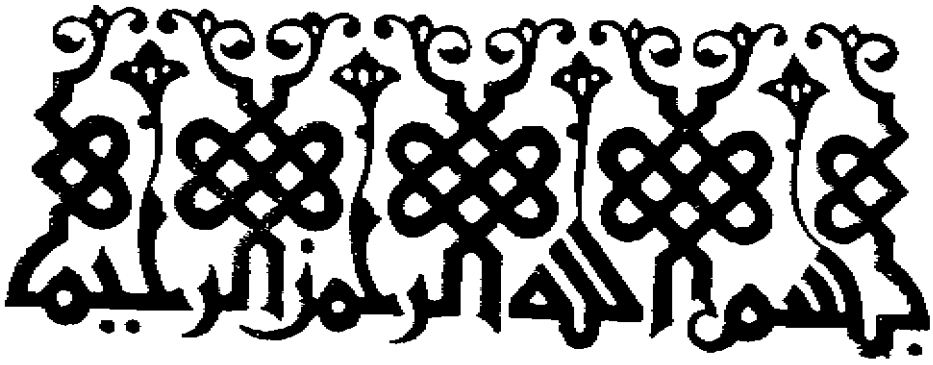

COAGULATION DEFECTS IN CERTAIN TYPES OF MALIGNANCY

Thesis

Submitted in partial fulfilment
for the M. D. Degree in Biochemistry

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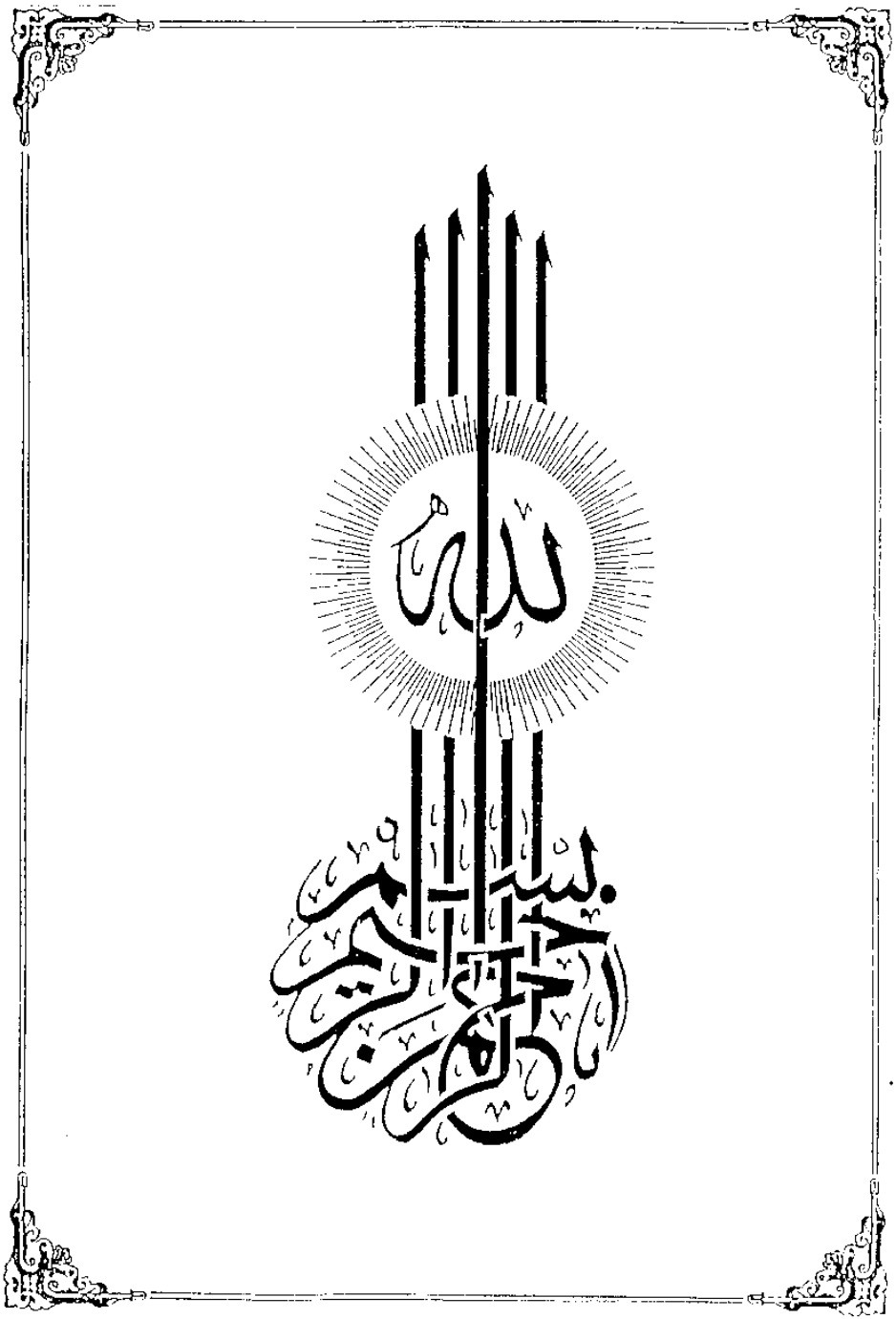

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LIST OF ABBREVIATIONS

vWF	von Willibrant Factor
EGF	Epidermal Growth Factor
LACI	Lipid-Associated Coagulation Inhibitor
RVV	The proteinase from Russell's Viper Venom
Gla	-carboxy glutamic acid
PCA	Procoagulant Activity
PCMB	P-chloro-mercurial-benzoate-agarose
NBT	Nitroblue tetrazolium
BCIP	5-Bromo, 4-chloro, 3-indolyl phosphate
SDS	Sodium Dodecyl Sulfate
SDS-PAGE	Sodium Dodecyl Sulfate-Polyacrylamide Slab Gel Electrophoresis
PVDF	Polyvinylidene diflouride
Mr	Molecular rate of migration.
cDNA	Complementary Deoxyribonucleic acid.

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INTRODUCTION

INTRODUCTION

Different effects on blood coagulation are known to be associated with malignancies in experimental animals, tissue culture cells, and human. Evidence has been accumulated to suggest that inhibition of blood coagulation is effective in decreasing the incidence of metastatic formation and can even cause suppression of the growth of the tumor. Malignant cells are known to produce various materials (procoagulants) that can affect blood coagulation at various sites of the cascade. Various types of these procoagulants have been described. In this review of the literature, I will describe the general mechanism of blood coagulation and the properties of some coagulation factors that are known to be affected in malignancy. I will also describe the properties of the proteins constituting a pathway that is important in the regulation of blood coagulation, the protein C anticoagulant pathway. Finally, I will discuss the different properties of cancer procoagulant.

This will explain the importance of studying the effect of cancer procoagulant on the blood coagulation human factor X and on the two cofactors of the protein C anticoagulant pathway, thrombomodulin and protein S.

Studying the effect of cancer procoagulant on its natural substrates could provide the information required to synthesize a specific substrate or inhibitor for cancer procoagulant that can be applied for the diagnosis and probably the treatment of malignancy.

REVIEW OF LITERATURE

BLOOD COAGULATION

Blood coagulation is a type of host defense system composed of a complex response of the vascular system, circulating platelets and monocytes, coagulation proteins, and the fibrinolytic system towards blood vessel injury. The activation of the proenzymes (designated by Roman numeral, e.g. XII) of blood coagulation to their active enzyme forms (designated by "a" after the Roman numeral, e.g. XII_a) proceeds through either the extrinsic or the intrinsic pathway (Davie and Ratnoff, 1964; and MacFarlane, 1964).

In these blood coagulation pathways many of the enzyme reactions take place within complexes that are associated with cell membranes; for example factor X activation takes place in factor $VIII_a$, IX_a, and X complex when $VIII_a$ is associated with a cell membrane or a phospholipid bilayer. Phospholipid in *in vitro* experiments replaces the cell membrane *in vivo*.

The intrinsic pathway: The intrinsic pathway of blood coagulation was given the name "intrinsic" because all of required proteins are in the blood. In contrast, the extrinsic pathway requires a glycoprotein associated with the cell membrane of many tissues. The intrinsic pathway (figure 1) is activated in the presence of a

Table 1. Properties of the genes, mRNA and gene products of the components of the blood coagulation cascade (Furie and Furie, 1988).

Component	Molecular weight	Gene (Kb)	mRNA (Kb)	Plasma conc. (μg/ml)	Function
Prothrombin	72,000	21	2.1	100.0	Proteinase zymogen
Factor X	56,000	22	1.5	10.0	Proteinase zymogen
Factor IX	56,000	34	2.8	5.0	Proteinase zymogen
Factor VII	50,000	31	2.4	0.5	Proteinase zymogen
Factor VIII	330,000	185	9.0	0.1	Cofactor
Factor V	330,000		7.0	10.0	Cofactor
Factor XI	160,000	23		5.0	Proteinase zymogen
Factor XII	80,000	12	2.4	30.0	Proteinase zymogen
Fibrinogen	340,000			3000.0	Structural
Aα chain	66,000				
Bß chain	52,000				
chain	46,000				
Protein C	62,000	11	1.8	4.0	Proteinase zymogen
Protein S	80,000		2.4	25.0	Cofactor
vWF	225,000x n^a	175	8.5	10.0	Adhesion
Tissue factor	37,000		2.1	0.0	Cofactor/initiator

n^a = number of subunits , where the subunit Mr is 225,000.