

COAGULATION DEFECTS IN CERTAIN TYPES OF MALIGNANCY

Thesis

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ASHRAF MAHMOUD MOURAD

Assistant Lecturer of Biochemistry Faculty of Medicine El-Minia University

Biochemistry Department Faculty of Medicine Ain Shams University



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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

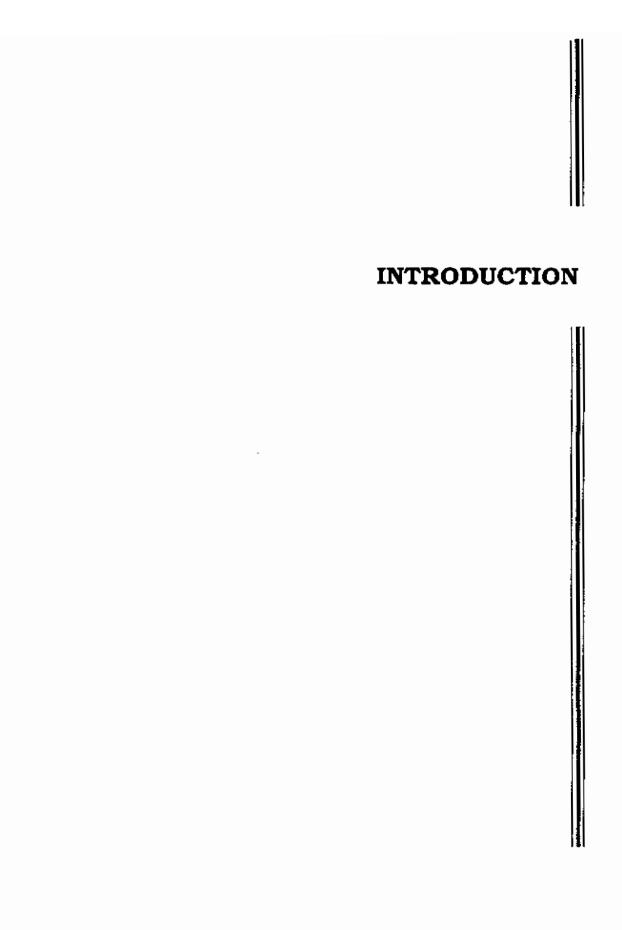
PVDF Polyvinylidene diflouride

Mr Molecular rate of migration.

Central Library - Ain Shams University Complementary Deoxyribonucleic acid.

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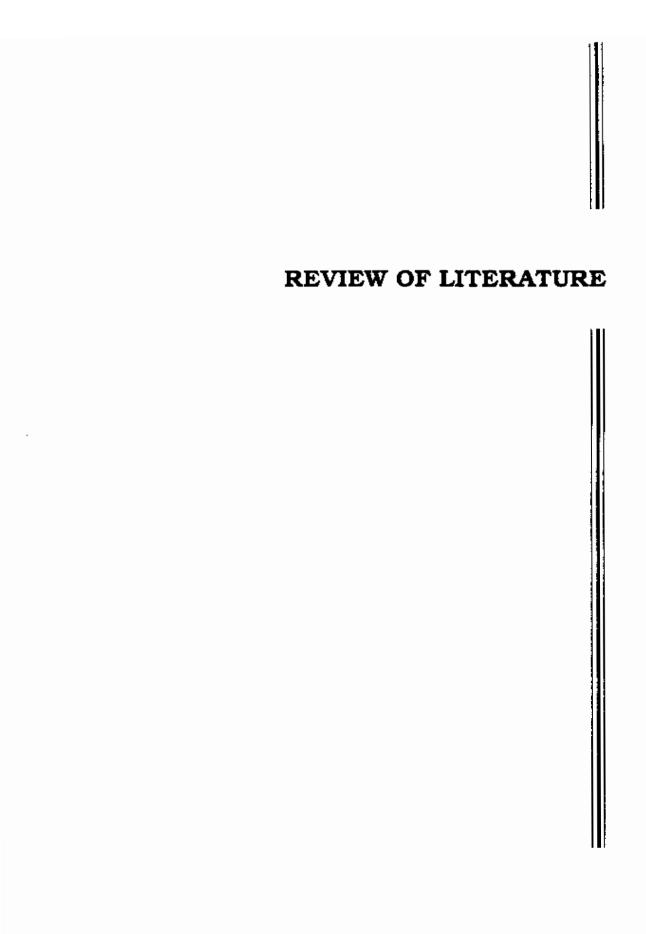


INTRODUCTION

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.



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. XIIa) 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 VIIIa, IXa, and X complex when VIIIa 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 Factor X Factor IX Factor VII Factor VIII Factor XI Factor XI Factor XII Fibrinogen Aa chain BB chain chain Protein C Protein S	72,000 56,000 56,000 50,000 330,000 330,000 160,000 80,000 340,000 66,000 52,000 46,000 62,000 80,000	21 22 34 31 185 23 12	2.1 1.5 2.8 2.4 9.0 7.0 2.4	100.0 10.0 5.0 0.5 0.1 10.0 5.0 30.0 3000.0	Proteinase zymogen Proteinase zymogen Proteinase zymogen Proteinase zymogen Cofactor Cofactor Proteinase zymogen Proteinase zymogen Structural Proteinase zymogen Cofactor
vWF Tissue factor	225,000x n ^a 37,000	175	8.5 2.1	10.0 0.0	Adhesion Cofactor/initiator

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