PLASMA FIBRONECTIN CONCENTRATION IN PATIENTS WITH VARIOUS MALIGNANCIES

THESIS

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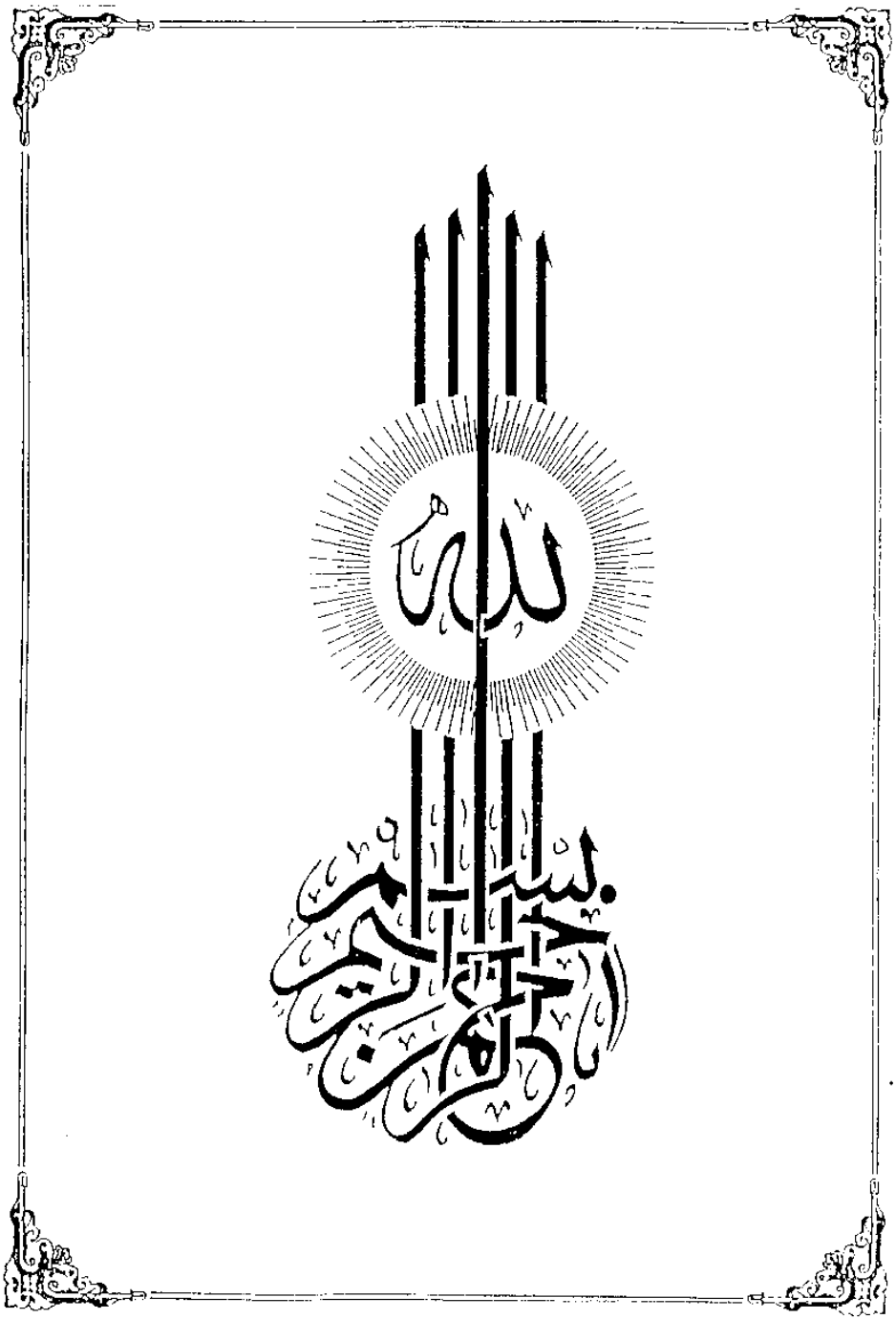
بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا

إِنَّكَ أَنْتَ الْعَلِيمُ الْحَكِيمُ

صدق الله العظيم



TO MY FATHER AND

MY MOTHER

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Mohamed Amin

INTRODUCTION AND AIM OF WORK

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Plasma fibronectin is a glycoprotein of molecular weight 440.000 and present normally in plasma. Its exact function is not completely understood. However, it has been reported that plasma fibronectin has many interactions and binding especially with elements of haemostasis, collagen, and fibrin **(Mosher et al., 1980).**

The concentration of plasma fibronectin in normal subjects and patients with various diseases have been determined by many workers **(Fyrand and Solum, 1976) (Forkman et al., 1972).** However, some of the data are contradictory and inadequate especially in malignant diseases.

Aim of the Work

The aim of the present work is to study the variations of plasma fibronectin level in patients with different solid tumours (e.g. breast, colon, lung, liver), Whether clinically non metastatic or metastatic.

An attempt to correlate the level of plasma fibronectin with the stage of the disease will also be done.

REVIEW OF LITERATURE

FIBRONECTIN

Fibronectins are a family of glycoproteins which are present in soluble form in plasma and other body fluids. They are also present in insoluble form in many tissues, such as interstitial connective tissue, in many basement membranes, around smooth muscle cells, fibroblasts, and in the sarcolemma of striated muscle fibres **(Cohler et al., 1985).**

The fibronectin molecule is composed of two apparently identical peptide chains which are held together with one disulphide bridge and has a molecular mass of 440,000 Daltons **(Mossesson et al., 1980).**

Although the functions of soluble fibronectin are not completly understood, it circulates in significant quantities 300:400 ug/ml, and it has been shown to have many interactions especially with elements of haemostasis. Fibronectin binds to collagen, fibrin, fibrinogen and heparin and it has been reported to be a part of normal blood clot. It also interacts with hyalouronic acid, gangliosides, and components of bacterial cell wall **(Mosher et al., 1980).**

Thus fibronectin is suitable for the role of a non specific opsonin for clearence of particulate debris from the circulation by fixed macrophages **(Blumenstock et al., 1978).**

Historical events

In ***1948, Morrison and Co-workers*** *described a protein component of fibrinogen which was not thrombin coagulable. It had a more rapid anodal electrophoretic migration rate and higher sedimentation coefficient than did fibrinogen.*

Later, in ***1957, Smith and Van Korff*** *described a protein with properties similar to the cold insoluble protein which was found in heparin induced cold precipitate plasma.*

In ***1968, Mosseson and Co-workers*** *investigated patients with chronic intravascular coagulation secondary to an occult neoplasm. The illness was characterized by the persistance of cold induced plasma precipitate termed "cryofibrinogen". The solubilized cryofibrinogen was partially coagulable by thrombin, thus proving that fibrinogen was present. Another major component resembling cold insoluble globulin was also found in the fractions and was shown to be immunochemically identical with a normal serum protein unrelated to fibrinogen.*

Follow up studies by ***Mosseson and Umfleet in 1970*** *presented a method for isolation and purification of cold insoluble globulin and provided clear evidence that it was a unique and major plasma protein (300 $\pm$ 100 ug/ml).*

In early 1970, a number of investigations had focused on the changes that occured in cell surface protein of fibroblast as a consequence of transformation by oncogenic viruses. Particular attention was paid a large transformation-sensetive glycoprotein that was released from the fibroblast cell surface into culture medium **(Hynes et al., 1974).**

Moreover, **Ruoslahti (1975)** reported that cold insoluble globulin was antigenically identical to the transformation sensetive glycoprotein brought to light the uniquness of fibronectin as both a cell-surface matrix protein and a blood protein and has stimulated numerous investigations on all forms of the protein.

Nomenclature:

Prior to the suggesion of the name fibronectin it has been known by variety of terms including opsonic protein **(Saba, 1970),** soluble fibroblast antigen **(Rouslahi et al., 1974),** cell surface protein **(Yamada et al., 1974),** cold insoluble globulin **(Chen et al., 1976),** and cell adhesion factor **(Pearlstein, 1976).**

Structure:

Structural studies of fibronectin derived from cell surfaces, tissue culture medium, or extracellular fluid pointed to the presence of molecular heterogenicity **(Chen et al., 1977).** Despite this,

the outline of basic molecular architecture can be sketched. (Fig. 1).

Plasma fibronectin molecule has a molecular weight of 440,000 Daltons and is composed of two similar but non identical polypeptide chains with estimated molecular weights of 220,000 and 210,000 **(Mosher, 1975).** The two chains are disulphide linked at the carboxyl-end of the molecule **(Balian et al., 1979).**

Intrachain disulphide bridges are clustered in the terminal thirds of each chain, most of them located at the amino terminal end **(Iwanga et al., 1978).**

There is also a significant number of free sulfhydryl groups **(Pearlisten et al., 1980).** Blocking of these groups interferes with binding to the cell surface **(Wagner and Hynes, 1979).**

Several minor fibronectin components of smaller size than the two-chain structure have been identified in plasma and most of them range in size from 250,000 to 146,000 Daltons. They may be derived by catabolic processes from large parent molecules **(Chen et al., 1977)** and it is not yet known whether the degradative processes occur intravascularly or not **(Mossesson, 1980).**

Plasma fibronectin contains also 5% carbohydrate **(Fukuda and Hakomori, 1979).** All oligosaccharide units are linked to

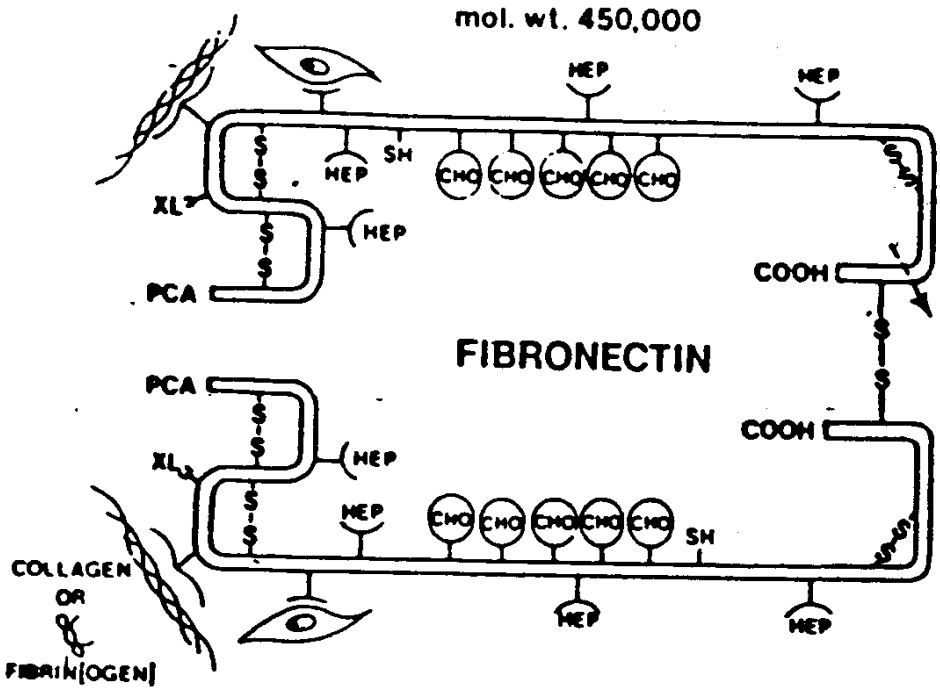

Figure (1)

Diagramatic representation of structure of plasma fibronectin molecule.

Most circulating molecules are composed of two more-or-less identical chains of approximate mol. wt. 220,000 Daltons, each linked near the C00H-terminal end by disulfide bridging (S-S). The NH2 terminus is designated PCA (Pyrrolidone Carboxylic Acid). The general location of intrachain disfluide bridging is also depicted as are the approximate locations of sulfhydryl groups (SH), Carbohydrate groups (CH0), and collagen-binding, fibrinogen-binding, cell-binding, Cross linking (XL), and Heparin (HEP) - binding sites. The dashed arrow indicate a region in the dimeric molecule which is cleaved during the course of hydrolysis by several proteolytic enzymes ***(Mossesson & Amrani, 1980).***