THE EFFECT OF SURGICAL INTERFERENCE ON PLASMA FIBRONECTIN

Thesis

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by

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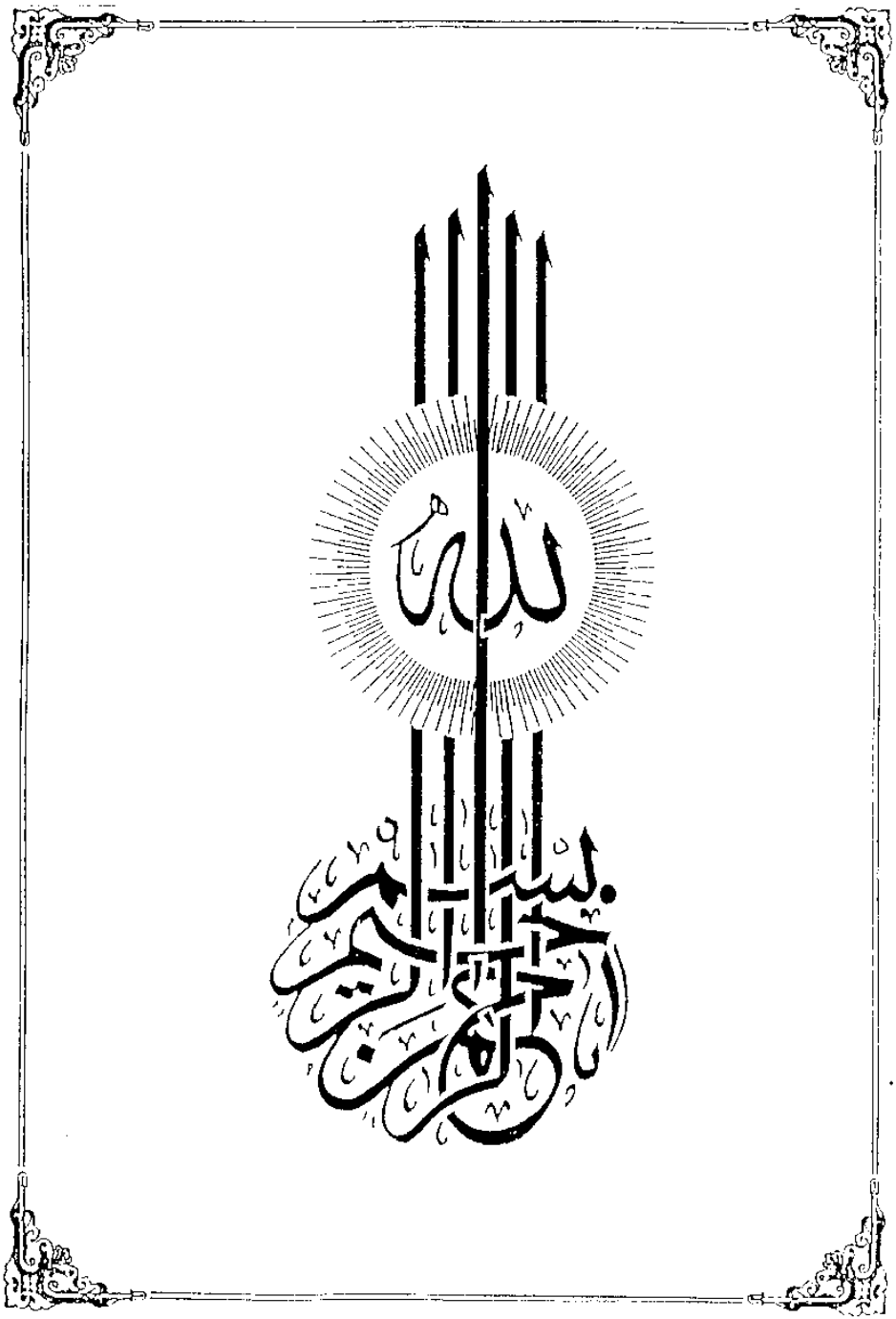
بسم الله الرحمن الرحيم

سُبْحَانَكَ لَا عِلْمَ لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
أَنْتَ الْعَلِيمُ الْحَكِيمُ ★

"صدق الله العظيم"
(سورة البقرة آيه ٣٢)



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AND

AIM OF THE WORK

levels of fibronectin were reported in patients developing septicemia following major surgery and burns, considerable interest was focused at the possible role of fibronectin in host defence mechanism. However, so far it is still not clear whether the depression of fibronectin levels reported after surgery really predisposes to septic postoperative complications.

The reasons for the rapid postoperative decrease in serum fibronectin levels may be multiple (Hogstrom et al., 1985). An increased proteolytic degradation in combination with decreased synthesis may be responsible. However, there are reasons to believe that sequestration of fibronectin at the site of tissue injury is the main mechanism behind the reduction of fibronectin levels (Gauperaa et al., 1985). This sequestration of fibronectin into damaged tissue may be of benefit for normal wound healing, as it helps clearing the wound tissue debris by monocytes and tissue repair by fibroblasts. As wounds and traumas are known to contain many cellular and monocellular materials which need to be cleared off prior to complete healing, a suspected relationship may exist

between plasma fibronectin levels and the process of healing. The aim of this work is to determine the fibronectin levels in patients exposed to major surgical interference to find out if there is any relationship between extensive healing process and plasma fibronectin levels.

REVIEW OF LITERATURE

II. REVIEW OF LITERATURE

1. FIBRONECTIN, GENERAL CONSIDERATIONS

Distribition:

Fibronectin is a major glycoprotein found in extracellular space of most body tissues, blood and other fluids. It has been known by many other names, including cold-insoluble globulin, surface binding opsonic protein, antigelatin factor, large external transformation sensitive (L.E.T.S.) protein and cell surface protein. It occurs in both soluble and insoluble forms. Insoluble fibronectin is found in connective tissue and is associated with basement membrane. Soluble fibronectin is found in plasma (Mosesson and Umfleet, 1970), amniotic fluid (Chen et al., 1976), seminal fluid (Vuento et al., 1980; Gressnet and Wallraff, 1981), joint fluid (Carsons et al., 1981) and cerebrospinal fluid (Vartio et al., 1981).

Plasma fibronectin has been described in 1948 as a major contaminant of fibrinogen (Morrison et al.,

1948). It is found in granules of platelets and may help to mediate adhesion to collagen and artificial surface. It is synthesized by endothelial cells and is a component of subendothelium and may contribute to thrombogenicity of subendothelial connective tissue. It is derived from hepatocytes. Patients with decompensated cirrhosis (Matsuda et al., 1982) or fulminant hepatic failure (Gonzalez et al., 1982) have low concentration of plasma fibronectin.

The fate of fibronectin leaving the circulation is obscure. Immunofluorescence and tissue extraction studies, however, indicate that some of the protein is deposited in extracellular matrices. Fibronectin concentration varies among individuals and females tend to have lower concentration than males. Its concentration is normal in pregnant women but the concentration can increase several fold in recurrent cholestasis of pregnancy. New born have 35% of the normal adult concentration of plasma fibronectin (Mosher, 1984).

Structure:

Fibronectin is a modular with multiple binding sites. It is composed of subunits that are approximately 2000 amino acid residues and 5% carbohydrates. Analysis of the amino acid sequence of the subunit and of the nucleotide sequence of the messenger RNA and genomic DNA that code for the subunit are incomplete.

Fibronectin is a paradigm of molecular protein (Fig. 1). The gene for fibronectin is composed of more than 40 exons and 40 introns. The introns are variable in size where as the exons are of constant size each able to code for a sequence of 45 to 50 amino acids (Hirano et al., 1983). Plasma fibronectin synthesized by cultured cells are dimers of subunits held together at the extreme carboxyl terminal end by a pair of disulfide bonds (Fig.1.) . When deposited on a surface and analysed by electron microscopy, plasma fibronectin looks like a "V" with two arms of length 2X60 nm at angle 70 degrees. Areas of the arms bind to one or more substances of biological interest. The amino-terminal region, composed of five blocks of the 45 residue

homology, binds to fibrin, heparin and staphylococcus aureus. An adjacent region, composed of six blocks of 45 residue homology, binds to gelatin and collagen. The carboxyl-terminal region composed of three blocks of 45 residue homology binds to fibrin, whereas several blocks of 90 residues homology binds to heparin (Petersen et al., 1983).

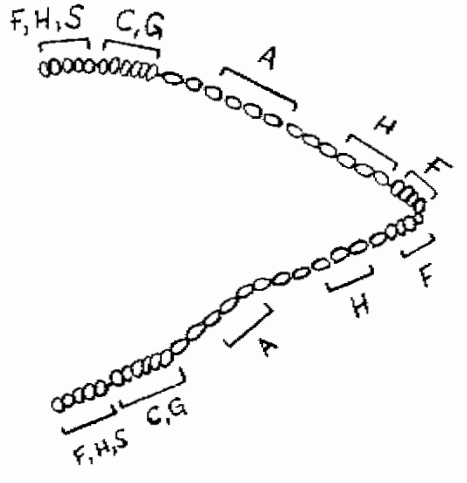

Fig. 1 : Schematic diagram of disulfide-bonded fibronectin dimer (after Mosher, 1984).

A. Cell adhesion and spreading.
C. Collagen binding.
F. Fibrin binding.
G. Gelatin binding
H. Heparin binding.
S. Binding to staphylococcus aureus.

In addition, fibronectin has been reported to bind to complement components (Menzel et al., 1981; Bing et al., 1982 and Pearistien et al., 1982), C3 (Hautanen and Keski, 1983), Streptococci (Beachey and Simpson, 1982), viral glycoprotein (Julkunen et al., 1983), Treponema pallidum (Peterson et al., 1983) and various carboxyl-group modified protein (Vuento et al., 1982).

Function:

Fibronectin is important for tissue remodelling and wound healing. In healing wounds and areas of inflammation, there are at least three sources of fibronectin. Plasma fibronectin is deposited as part of the blood clot (Grinnel and Feld, 1981) and accumulates at times of increased vascular permeability (Clark et al., 1981). Fibronectin is also produced by cells of blood vessels in response to injury (Clark et al., 1982).

Fibronectin may play a number of other roles in tissues. For instance, it is required for optimal macrophage immobilization by migration inhibitory

factor (Remold et al., 1981) and it stimulates the production of a cell growth factor by monocytes and macrophages (Martin et al., 1983). It enhances expression of FC receptors by monocytes and macrophages (Bevilacqua et al., 1981) and allows these cells to ingest particles opsonized with C3 b (Pommier et al., 1983). Finally, fibronectin coats cellular and tissue debris e.g. in the uterine lumen after parturition (Grinnel et al., 1982) and may play a role in the removal of this debris by phagocytic cells (Saba et al., 1978).

Plasma fibronectin concentration is depressed during starvation (Dillon et al., 1982 and Scott et al., 1982), profound liver failure (Matsuda et al., 1982 and Gonzalez et al., 1982) and defibrination syndrome (Stathakis et al., 1981). Repletion of plasma fibronectin either in the form of cryoprecipitate or purified protein may serve defects of phagocytosis in severely ill patients (Rubli et al., 1983; Mosher and Grossman, 1983).

Fibronectin interacts with collagen , fibrin and heparin and functions as both an adhesive (Grinnel,