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Extracellular Matrix: Structure and Function

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A. Hari Reddi

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EXTRACELLULAR MATRIX: STRUCTURE AND FUNCTION

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Editor

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Preface

The extracellular matrix is a very early and necessary feature of multicellularity among animals. There is a growing realization that cell biology extends beyond the cell and cell membrane into the extracellular matrix. The interface of cell surface and matrix appears to be a biochemical continuum. This has resulted in increasing appreciation of the role of extracellular matrix in structure and function of animal cells. The UCLA Symposium on Extracellular Matrix: Structure and Function was held in Keystone, Colorado, April 22–29, 1984, and was attended by an international group of scientists representing various disciplines.

The conference was characterized by vitality and no small amount of late night discussion. The week began with plenary lectures and poster presentations in the areas of biology and chemistry of collagens, elastin, proteoglycans, fibronectins and laminin. It progressed with timely and informative presentations on the roles of these various constituents in development and disease states. Most of the contents of plenary lectures and selected poster presentations are presented in this volume to enable others to share the experiences of those of us fortunate enough to attend. Many of these papers are reprinted from the **Journal of Cellular Biochemistry**, from which they received rigorous reviews.

The travel and subsistence expenses of the invited speakers were defrayed in large part by a major contribution to the meeting through sponsorship funding provided by the Dow Chemical Company. Our special thanks go to Dr. William Riley, of Dow, for his enthusiasm and support. Additional funding was provided by grant HL32343-01 from the National Heart, Lung and Blood Institute, National Institutes of Health, Sandoz, Collaborative Research, and Collagen Corporation.

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Fibronectin and Wound Healing

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Critical to the continued existence of all multicellular organisms is their ability to respond to and repair traumatic injuries. In vertebrates, particularly mammals, the response to injury has been studied in great detail, and the various cells involved in wound healing have been identified (recently reviewed in [1] and [2]). While the overall features of wound healing are now well known, many important details remain to be clarified. For instance, the biochemical signals that initiate and terminate the wound healing response are still subjects of considerable debate. Cells of the organism recognize and migrate to the wound interface, and the wound healing response persists at least until this abnormal interface is replaced by new tissue.

Several years ago, I reviewed the evidence indicating that fibronectin is important in cutaneous wound healing [3]. Since then, considerable additional information in support of this idea has been forthcoming, and it now appears that fibronectin plays numerous roles in the wound healing situation, which will be discussed in this brief review.

CUTANEOUS WOUND HEALING

Skin normally is composed of a stratified epithelium (epidermis) separated from an underlying connective tissue stroma (dermis) by a basement membrane. Following formation of a full thickness wound, the defect produced in the skin is filled by a blood clot composed of platelets trapped in a fibrin meshwork. Platelets are important, not only in recognizing and physically occluding the defect, but also in promoting blood coagulation and in secreting growth factors for fibroblasts and possibly other cells involved in subsequent stages of wound healing. Following formation of the blood clot, the wound region is invaded almost immediately by neutrophils. These cells are responsible primarily for controlling infection, but in the absence of infection neutrophils do not seem to be necessary for normal healing of wounds. Next, monocytes migrate into the wound region where they are involved in removing tissue debris and secreting factors that promote the growth and biosynthetic activity of

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fibroblasts. Shortly after the appearance of monocytes, the region is invaded by fibroblasts and endothelial cells from the subdermis. The fibroblasts synthesize granulation tissue which is vascularized by the endothelial cells. Finally, the granulation tissue is covered by a neo-epidermis formed by keratinocytes migrating in from the wound edges. The keratinocytes migrate beneath the dried out portion of the blood clot through the upper region of the granulation tissue. This entire process takes about 1–2 weeks, and is followed by a gradual remodeling of the granulation tissue to a more normal neo-dermis, during which time the increased fibroblast population characteristic of granulation tissue markedly diminishes [1,2].

The above description (summarized in Table I) is somewhat superficial, and does not take into account important features such as wound contracture [4], but is sufficient to point out the main cell types that participate in the organism's response to wounding and their primary functions in wound healing. In the remainder of this paper the role of fibronectin will be described in relationship to the cells and functions listed in Table I.

THROMBOSIS

Platelets normally are nonadhesive to the intact endothelial surface of blood vessels. When there is a defect in the endothelium, platelet attachment to the underlying connective tissue appears to occur by at least two mechanisms, one involving direct interactions with polymerized collagen fibrils [5] and the other involving a von Willebrand factor-mediated interaction with the subendothelium [6]. While resting platelets do not normally express fibronectin on their surfaces, it has been shown that fibronectin can be detected on the surfaces of platelets attached to collagen [7] or enmeshed in blood clots [8] (Fig. 1). Apparently, there are specific and saturable receptors for fibronectin on the platelet surface [9,10] that are exposed after platelet activation [11,12].

Initial studies demonstrated that addition of fibronectin promoted platelet spreading on collagen substrata but did not enhance platelet attachment [13,14]. Fibronectin also has been found to enhance platelet spreading associated with von Willebrand factor-mediated platelet attachment to the subendothelium [15]. On the other hand, fibronectin does not appear to be important in platelet aggregation induced by ADP [12] or collagen [16]. The physiological significance of fibronectin-mediated platelet spreading has yet to be adequately explained, but studies on platelets isolated from a patient with a new form of Ehlers-Danlos syndrome [17] and patients with Glanzmann's thrombasthenia [18] have raised the possibility that fibronectin is necessary for normal platelet function.

TABLE I. Cells Involved in Cutaneous Wound Healing

Cell type	Function
Platelets	Thrombosis, coagulation, secretion of growth factors
Neutrophils	Management of infection
Monocytes	Removal of tissue debris, secretion of growth factors
Fibroblasts	Synthesis and remodeling of extracellular matrix
Endothelial Cells	Neo-vascularization
Keratinocytes	Re-epithelialization

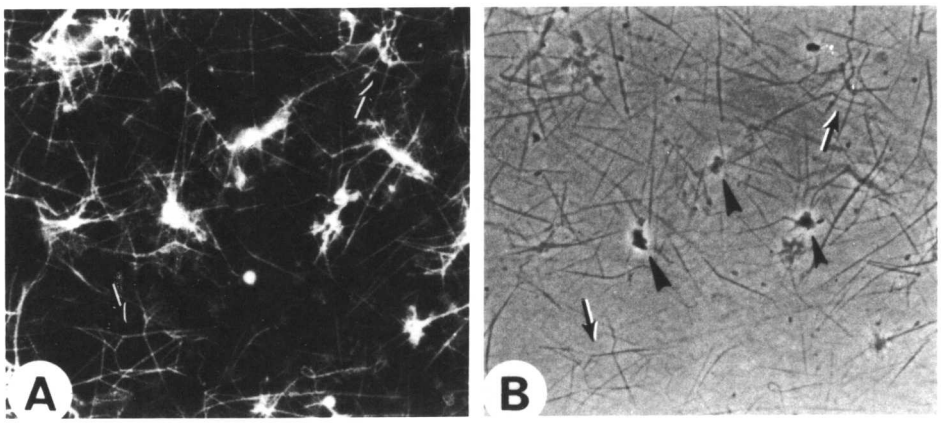

Fig. 1. Fibronectin distribution in blood clots formed ex vivo. Indirect immunofluorescence analysis with antifibronectin shows fibronectin coating fibrin strands (arrows) and platelets (arrowheads). A) Fluorescence. B) Phase contrast. See [8] for other details.

One other interesting possibility is that the presence or absence of fibronectin on material surfaces might determine the thrombogenicity of the surfaces [19]. If this were the case, it would be of considerable importance in understanding tissue reactions to artificial implant materials. Both the attachment and spreading of platelets on polystyrene is promoted by fibronectin [20], and the presence of fibronectin on a variety of material surfaces has been shown to promote thrombus deposition in an ex vivo shunt model [21].

FIBRONECTIN AT THE WOUND INTERFACE

The major structural component of the blood clot that fills the wound defect is a fibrin polymer cross-linked by the plasma enzyme transglutaminase (factor XIII), and fibronectin also can be covalently linked to the fibrin polymer by this enzyme [22]. As shown in Figure 1, the fibrin in blood clots formed ex vivo is uniformly coated with fibronectin [8], and a similar result has been found following wounding in vivo (Fig. 2) [23]. While the presence of fibronectin coating the fibrin does not appear to change the mechanical properties of clots formed from platelet-rich or platelet-free plasma [24], it does play an important role in the adhesive interactions of cells migrating into the clot region (see below).

One point of particular importance is that the fibronectin content of the wound matrix is much higher than that of the adjacent tissue [23]. This is consistent with the low concentration of fibronectin in the dermis of unwounded skin except where fibronectin is associated with dermal fibroblasts [23,25]. Although fibronectin has been found to bind collagen type I, the major collagenous component of dermis, this binding is relatively weak unless the collagen is denatured [26,27].

NEUTROPHIL FUNCTION

Several different studies have shown that fibronectin promotes neutrophil motility, chemotaxis [28] and adhesion to endothelial cells [29] or material surfaces [21].

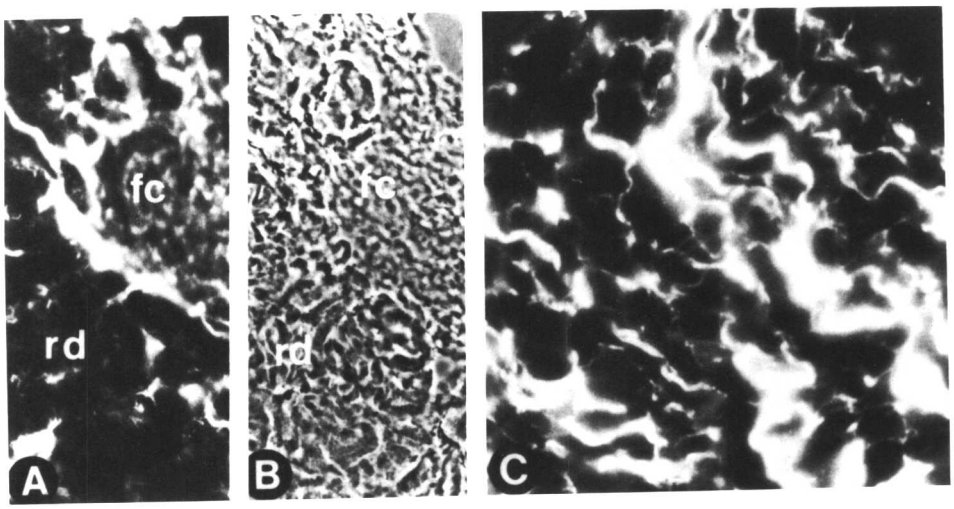

Fig. 2. Fibronectin distribution in blood clots formed in vivo after wounding. Indirect immunofluorescence analysis with antifibronectin shows that fibronectin was present throughout the fibrin clot (fc) (A,B), and at higher magnification fibronectin was found coating individual fibrin strands (C). In the reticular dermis (rd) adjacent to the blood clot, fibronectin was found associated with cells but not with the collagen matrix. See [23] for other details.

It also has been reported that neutrophils can enzymatically modify fibronectin to an altered form that enhances neutrophil adhesion [30]. Thus, although there are some conflicting data [31], it seems likely that the presence of fibronectin may be an important signal for neutrophil movement into the wound region.

The role of fibronectin in neutrophil phagocytosis is less clear. While fibronectin promoted binding of Streptococcus pyogenes to neutrophils [32], other evidence suggested that phagocytosis of bacteria was not enhanced by fibronectin [33,34]. In addition, although fibronectin promoted the phagocytosis of latex or yeast particles by neutrophils, opposite data were found regarding the activation of postphagocytotic metabolic activities [28,35].

MONOCYTE FUNCTION

In the case of monocytes, fibronectin appears to be important in both cell migration and phagocytosis. Fibronectin has been reported to promote monocyte adhesion to material surfaces [36], and both the intact fibronectin molecule [37] as well as fibronectin fragments [38] were found to be chemotactic for monocytes. In addition, although fibronectin does not itself function as an opsonin for phagocytosis by monocytes [33,36], it does enhance phagocytosis of particles opsonized by immunoglobulin [36] or complement [39,40]. In addition, fibronectin fragments have been found to augment the opsonin-independent pathway of phagocytosis by monocytes [41]. Finally, fibronectin also stimulated secretion of monocyte derived growth factor for fibroblasts [42].