

Invited Review

Dynamic interactions of the extracellular matrix

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Summary. The extracellular matrix (ECM) is a dynamic assemblage of interacting molecules that reorganise and regulate cell functions in response to endogenous and exogenous stimuli. Matrix components may affect cell behaviour directly or indirectly through growth factor sequestration and transmembrane signalling, by controlling the speed of various molecules through the ECM, and the access of growth factors, hormones and neurotransmitters to the cell surface.

Key words: Extracellular matrix, Growth factors, Transmembrane signalling

Introduction

The extracellular matrix (ECM) is a dynamic assemblage of interacting molecules that reorganise and regulate cell functions in response to endogenous and exogenous stimuli. In particular, the ECM modulates cell attachment, shape, spreading characteristics, migration, differentiation and gene expression by providing different extracellular microenvironments (Slavkin, 1982; Bravo, 1990; Mark et al., 1990). Matrix components may affect cell behaviour directly or indirectly through growth factor sequestration and transmembrane signalling (Couchman et al., 1994), by controlling the speed of various molecules through the ECM, and the access of growth factors, hormones and neurotransmitters to the cell surface (Banno, 1994).

The major constituents of the ECM are collagens, proteoglycans and adhesive glycoproteins. In addition to binding many cytokines, proteases and protease inhibitors, the ECM acts as a reservoir for a number of growth factors and their binding proteins, which are selectively accumulated and released. These include transforming growth factor α (TGF α), transforming growth factor β (TGF β), epidermal growth factor (EGF), insulin growth factor (IGF) I and II, and IGF binding protein (IGFBP) 5 (but not IGFBP 3 or 4)

(Raghow, 1994). It has been suggested that growth factors in the ECM are particularly active when complexed with other ECM molecules, this interaction often being essential to their activity (Flaumenhaft and Rifkin, 1991; Lortat-Jacob et al., 1991). For instance, the binding of IGF to ECM via IGFBP5 is important in mediating cellular responses to the IGF's (Jones et al., 1993). Some ECM molecules, such as fibronectin and C3, are multifunctional and have one domain that binds adhesion receptors and another that binds separate, mitogenic receptors (Levesque et al., 1991).

ECM components

Collagens provide strength and form, and also interact with other ECM molecules and cells. In addition to the more well-known collagens (I-VII), a group of collagens (types IX, XII and XIV) with unique structural characteristics has also been defined, and named FACIT (fibril-associated collagens with interrupted triple helices) collagens. These collagens are not secreted as procollagen nor do they form polymers but are associated only with the fibrils of the fibrillar collagens. Type IX collagen contains a glycosaminoglycan (GAG) side chain that is thought to interact with chondroitin sulphate GAG and also regulate the interaction of fibrillar type 1 collagen with chondroitin sulphate GAG. There is evidence that the FACIT collagens may serve as molecular bridges that are important for the organisation and stability of extracellular matrices (Shaw and Olsen, 1991). The GAG side chains themselves are also known to affect cell growth and differentiation (Uhman et al., 1990).

Proteoglycan molecules (PG) and their GAG side chains are ECM molecules that contribute to tissue strength, molecular migration rates and also bind growth factors and other ECM molecules. They regulate the growth, cross-linking and alignment of collagen fibrils (Junqueira et al., 1981) and act as matrix receptors on the cell surface. In particular, the PG proteins laminin and fibronectin control cell attachment, migration, differentiation and synthetic activity. For instance, fibronectin is involved in cell-ECM signalling events that control osteoblast differentiation (Thesleff et al.,

1991).

Angiogenesis may be stimulated by a number of substances, including fibroblast growth factors, vascular endothelial growth factor, platelet endothelial growth factor, E series prostaglandin, angiogenin and monobutyrin (Díaz-Flores et al., 1994).

Thrombospondin, which is also found in the ECM, may also be an important stimulator of angiogenesis (Nicosia and Tuszynski, 1994), wound healing and modulation of growth factor activity (Slater and Mason, 1995). Thrombospondin, in conjunction with c-kit ligand, is a developmental signal that synergistically modulates haemopoietic stem cell function (Long et al., 1992).

Adhesive glycoproteins

An important group of cell receptor adhesive glycoproteins are the integrin family. They are involved in cell-matrix, cell-cell, and ECM-cytoskeleton interactions as well as cellular differentiation through signal transduction. The expression of integrins is controlled by ECM molecules and also growth factors, notably TGF β (Uitto and Larjava, 1991; Bellon et al., 1994). Several types of a receptor may bind to different forms of a single ECM component. In monolayer cultures of mouse epiphyseal chondrocytes, for example, different forms of integrins label to different types of collagen (Shakibaei, 1995).

CD44 is another multifunctional adhesion protein that binds growth factors and promotes cell attachment. It also acts as a receptor for hyaluronan, which regulates embryonic morphogenic events (Wheatley et al., 1993).

Syndecan

Syndecan is a transmembrane protein, composed of chondroitin sulfate and heparan GSG side chains, which is thought to modulate cell development and morphogenesis. It may act as matrix receptor, binding ECM components such as fibronectin, collagens, I, III and IV, thrombospondin and basic fibroblast growth factor to the spectrin/actin cytoskeletal network (Bernfield and Sanderson, 1990; Hinkes et al., 1993). It is also associated with the preservation of morphology and differentiation (Inki et al., 1994), restriction of cancer growth (Jalkanen, 1994), and modulation of growth factor and cell-matrix interaction (Mali et al., 1993). Syndecan is thought to effect this modulation by binding with ECM molecules and growth factors, such as basic fibroblastic growth factor (bFGF) (Salmivirtti et al., 1992; Mali et al., 1993).

ECM to cell signalling systems

Interactions of ECM components with cell surface molecules, transmembrane molecules, integrin, syndecan, proteoglycans and growth factors initiate signal transduction mechanisms that lead to short and

long term cellular responses. Syndecan and tenascin represent a cell surface receptor/ECM ligand signalling system that is involved in morphogenesis of teeth (Thesleff et al., 1991). The expression of ECM components and growth factors such as fibroblastic growth factor (FGF), IGF, TGF β and their receptors, appears to be highly coordinated.

Mechanical forces may also be transmitted to the cell from the ECM, producing a metabolic response. ECM receptors on the cell membrane play a vital role in development by transmitting mechanical signals to and from the cytoskeleton. The cellular transmembrane ECM receptors such as syndecan, cadherin and integrin, physically link actin-associated proteins to adhesion molecules on the cell surface.

Integrin molecules are a group of dimeric cell receptor proteins characterised by non-covalently bound α and β chains. It is thought that ligand specificity is dictated by the α chain transmembrane signalling to the cytoskeleton via the β chain. In this way one ECM protein could deliver different signals to the cell at different times (Gani and Burns, 1990; Ingber, 1991). Integrin molecules maintain the stability of mechanical forces between tensile actin filaments, microtubular struts and ECM anchoring supports. Transmembrane cell surface integrin receptors run from the interior of the cell, where they connect to the cytoskeleton, to the exterior of the cell where they physically link to the molecules of the extracellular matrix (Ingber, 1991). In addition to acting as a mechanoreceptor, integrin also provides a molecular mechanism to transduction of physical stimuli into a chemical response. In this way ECM molecules can directly influence cellular metabolism. Examples of this include the transfer of energy from muscle stretch receptors, to sensory cells via the ECM, and the exocytosis of surfactant from lung epithelial cells (Ingber, 1991). Cell binding to ECM molecules has been shown to alter phosphatidylinositol metabolism, release intracellular calcium and activate the sodium/proton antiporter. In this way, integrin molecules may act as growth factor receptors (Ingber, 1991).

ECM degraders

Interleukin 1 (IL-1) degrades and modifies the ECM. This action is mediated by metalloproteinases and prostaglandins (Mauviel et al., 1994). In turn the expression of metalloproteinases is modulated by cytokines, growth factors, oncogenes and hormones (Matrisan, 1992; Mauviel, 1993). For instance, expression of the metalloproteinase collagen message is increased by IL-1, tumor necrosis factor (TNF), and EGF. TGF β on the other hand, inhibits production (Richards et al., 1991). EGF and TGF α are also known to stimulate metalloproteinase production (Ganser et al., 1991). Degradation of the ECM PG/GAG lattice by proteases probably precedes mineralisation (Slater et al., 1994b).

As neuronal, embryonic and bone cell ECM have been most studied, I will discuss them as examples.

Neuronal Tissue

Neuronal ECM molecules regulate development, survival, migration, axon growth and synapse formation (Engelmann, 1993; Venstrom and Reichardt, 1993). Some studies have shown that growth factors and cytokines function as signalling molecules between neurones and Schwann cells, using the ECM as a signalling conduit. ECM molecules produced by neurones are responsible for Schwann cell proliferation, cell survival and differentiation (Reynolds and Woolf, 1993). Both fibronectin and laminin play a fundamental role in the differentiation of quiescent astrocytes into the proliferating phenotype (Nagano et al., 1993).

Cytokines also act in concert with ECM proteins to anchor blood stem cells. HB-GAM (heparin-binding growth-associated molecule) binds to N-syndecan in the same manner as bFGF. It is suggested that this system regulates axonal growth by the transmission of the HB-GAM signal via N-syndecan to the cytoskeleton of growing neurites (Raulo et al., 1994).

Embryonic tissue

Just prior to and then following blastocyst attachment, the basal uterine epithelial cell (UEC) membrane ECM is dramatically altered. Prior to attachment, the rigidity of the UEC ECM is maintained by dense collagen, particularly collagen type VI. These components are subsequently removed and replaced by laminin, entactin, collagen type IV and heparin sulfate GSG (Mulholland et al., 1992). The latter components have also been found on the blastocyst (Haimovici and Anderson, 1993b). The UEC ECM is thus altered in preparation for invasion by the trophoblast.

Hormonal modulation of the plasma membrane transformation may be mediated by locally produced growth factors and cytokines (Murphy, 1993). Cytoskeletal elements such as adducin and the spectrin-actin network are also transmembrane proteins that interact with ECM proteins and growth factors to modulate cell shape, phagocytosis, cell locomotion, cell junction organisation and cell-to-substratum interactions (Bretscher, 1991; Amsterdam et al., 1992; Bennett and Gilligan, 1993). Transmembrane proteins such as syndecan provide a link between the cytoskeleton, ECM proteins and locally-produced growth factors. Fluctuations of the labelling intensity and location of syndecan and heparan sulphate GSG in mouse uterus at the time of implantation, have previously been studied by immunolocalisation using monoclonal antibodies and have been shown to alter in distribution during pregnancy (Potter and Morris, 1994). Cytokines such as granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage-colony-stimulating factor (GM-CSF) induce changes in cell shape and cytoskeletal

reorganisation (Bussolino et al., 1991; Couchman, 1993). Growth factors such as IGF-I, IGF-II, EGF, platelet derived growth factor (PDGF) are known to have marked effects on the reorganisation of the cytoskeleton during development and morphogenesis (Wang et al., 1992; Heldman and Goldsmith-Clermont, 1993; Livnat et al., 1993; Hill et al., 1994; Watson et al., 1994). One study has also shown that a receptor for ECM proteins behaves similarly to a growth factor receptor, activating a signalling pathway implicated in growth control (Schwartz et al., 1991). In fibroblasts, growth factors also trigger a complex genetic response involving at least 100 genes, that code for cytoskeletal and ECM elements as well as nuclear proteins and secretory molecules (Bravo, 1990).

At the site of blastocyst implantation, cytokines and growth factors and their receptors have been found on both the trophoblast and UEC membrane (Haimovici and Anderson, 1993a), as have IGF I and II, IGFBP, EGF, IL-1, TNF α , colony stimulating factor (CSF), GM-CSF, TGF β , FGF and PDGF. In particular, IGF-I and II probably play a major role in the regulation of implantation and placental development. Then, in turn, are regulated by the IGFBP. Immunohistochemical studies have demonstrated the presence of IGF-I, IGF receptor and IGFBPs 1-4 in human (Boomsa et al., 1994; Tang et al., 1994) and rat uterine tissue (Ghahary et al., 1993). IGF-I acts synergistically with EGF and PDGF and may play a role in the autocrine/paracrine regulation of trophoblast implantation and growth (Boomsa et al., 1994; Tang et al., 1994). Immunohistochemical studies in mice and rabbits have shown that other substances such as leukemia inhibitory factor (LIF) (Yang et al., 1994) and TGF α (Paria et al., 1994) as well as variety of cytokines, growth factors and ECM proteins, also act synergistically at different stages of implantation and development (Haimovici and Anderson, 1993a). Platelets appear to be an important source of cytokines and growth factors for the implantation process while immunoelectronmicroscopy has shown that the ECM collagens I, III, IV, V, as well as laminin, fibronectin and the GSG/PG, modulate growth factor expression and hence trophoblast attachment. It has been suggested that the uterine ECM may, in fact, direct the initiation of implantation and development by control of these substances (Haimovici and Anderson, 1993a). One study in rats has shown that EGF can even replace estrogen as an initiator of implantation (Johnson and Chatterjee, 1993). These processes are little understood, however.

Bone tissue

In bone tissue the osteoblast ECM affects cell function by binding growth factors such as TGF β 1 (Fig. 1) (Kjellen and Lindhal, 1991). These may be released during osteoclastic resorption and act as coupling agents between the processes of bone resorption and formation (Bonewald and Mundy, 1990; Strong et al., 1991). Specific growth factors have been shown to influence

production of individual ECM proteins (Mohan and Baylink, 1991). In turn, these proteins are thought to regulate bone cell function and modulate cytokine-induced differentiation in cells of the osteoblastic lineage (Traianedes et al., 1992).

In a recent study (Slater et al., 1994a), incubation of osteoblast-like cell cultures with 17β estradiol resulted in an increase in multilayer depth (cell plus ECM) and a 2-fold increase in TGF β and IGF-I. A maximal 3-fold increase in labelling for the ECM protein thrombospondin was also noted. The dose-response relationship for these responses to estradiol treatment were biphasic with maximal increases at 10^{-11} and to lesser extent 10^{-10} M of added estradiol (Fig. 1). Minimal increases were noted at 10^{-9} M. Treatment with 17α estradiol produced labelling intensities that were not significantly different from controls.

Another study in our laboratory, using immunocytochemistry and cultures of human osteoblast-like cells to study TGF β , IGF I, IGFII and bFGF incorporation into the ECM, indicated that the previously reported

increases in growth factor production seen with estrogen treatment were accompanied by increased growth factor incorporation into the matrix. It has been proposed that growth factors incorporated into the ECM of bone act as coupling factors (Canalis et al., 1988; Bonewald and Mundy, 1990; Jennings and Mohan, 1990). The results of the study were consistent with the possibility that, in the presence of reduced sex steroid concentrations, there is reduced growth factor incorporation into the matrix. When this matrix is eventually resorbed, less growth factor coupling agents are released, which in turn may result in lower than expected new bone formation. The resultant «uncoupling» would eventually result in bone loss.

In a study to determine the role of chondroitin sulfate GSG (CSGAG) in mineralisation, a monoclonal anti-chondroitin sulfate antibody (CS-56) which recognises native CSGAG was used to quantify changes in CSGAG labelling levels in mineralising human fetal osteoblast-like cell multilayers up to 40 days postconfluence. Labelling was markedly increased in the

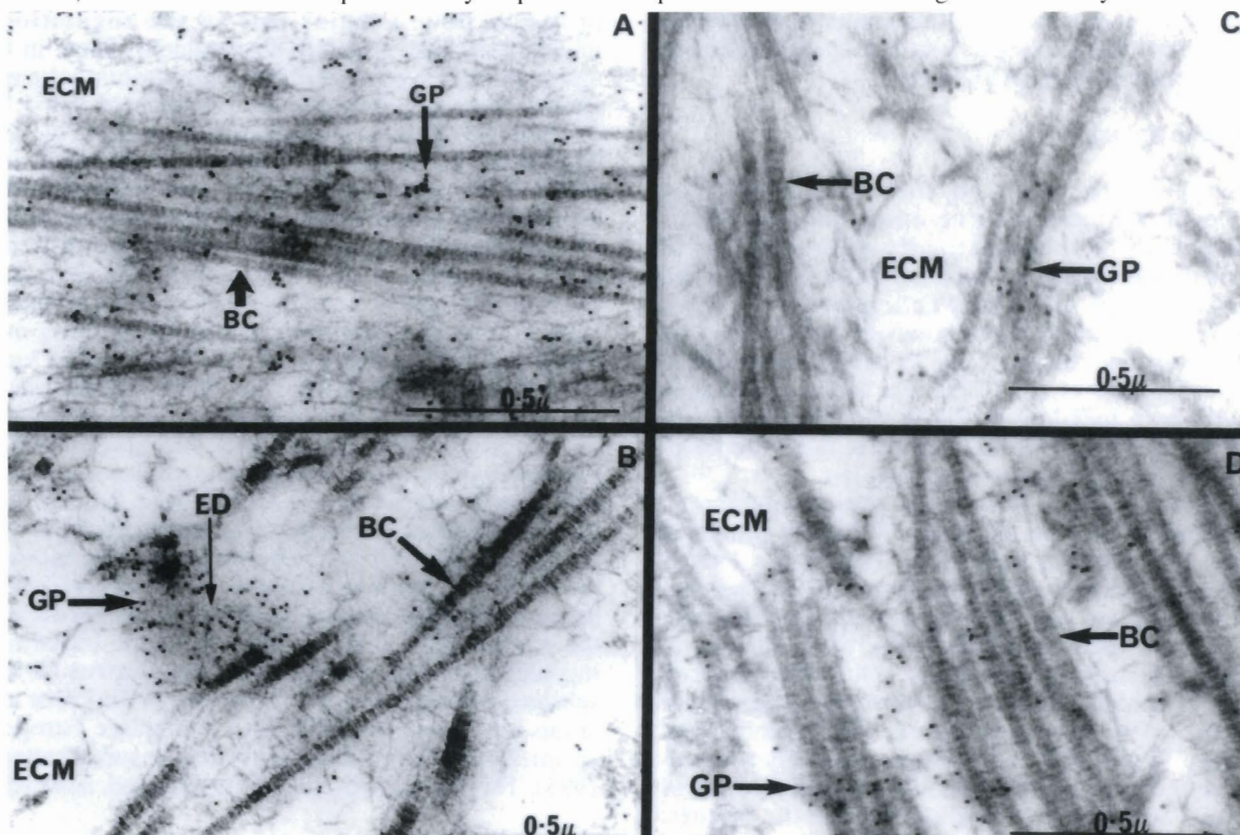


Fig. 1. Transmission electron micrograph of banded collagen (BC arrow) and its associated extracellular matrix (ECM) in a mineralising 30 days post confluence culture of osteoblast-like cells. **A.** Labels for the bone cell markers alkaline phosphatase and osteocalcin were not focally incorporated in discrete areas but were distributed diffusely throughout the extracellular matrix (ECM) and banded collagen (BC). Protein A conjugated to 10 nm colloidal gold (GP). **B.** In contrast, the bone growth factors were distributed in discrete, localised concentrations. Insulin-like growth factor 1 is labeled with a 10 nm gold probe (GP) conjugated to Protein A. The label is locally restricted to electron dense areas (ED) of the extracellular matrix and its associated banded collagen (BC). **C and D.** Transmission electron micrograph of banded collagen (BC arrow) and its associated extracellular matrix (ECM) in a section of 20 day post confluence culture of osteoblast-like cells. Insulin-like growth factor 1 is labelled with a 10 nm gold probe (GP) conjugated to Protein A. Without the addition of 17β estradiol (C); and with the addition of 10^{-9} M 17β estradiol to the culture medium (D). Note the increased number of gold probes in the section from a culture treated with 17β estradiol (D). The tissue was sub-optimally fixed using 1% glutaraldehyde in 0.1 M cacodylate buffer pH 7.3, in order to preserve antigenicity. Uranyl acetate and lead stain. Bar = 0.5 μ m.

mineralised tissue. These results indicate that an increase in immunoreactive CSGAG is associated with mineralisation in this culture system. One possible interpretation of these findings is that PG molecules or at least their CSGAG side chains, may be involved in the mineralisation process (Slater et al., 1994b).

Conclusion

In conclusion, the relatively few studies that have been carried out on dynamic interactions between the ECM and cells, have shown that the ECM plays a role in the functioning of the tissue concerned. This area will undoubtedly be a source of an expanded number of studies in the future.

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