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The extracellular matrix: an active or passive player in fibrosis?

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Abstract

Fibrosis is characterized by excessive accumulation of collagen and other extracellular matrix (ECM) components, and this process has been likened to aberrant wound healing. The early phases of wound healing involve the formation of a provisional ECM containing fibrin, fibrinogen, and fibronectin. Fibroblasts occupy this matrix and proliferate in response to activators elaborated by leukocytes that have migrated into the wound and are retained by the ECM. This coincides with the appearance of the myofibroblast, a specialized form of fibroblast whose differentiation is primarily driven by cytokines, such as transforming growth factor-β (TGF-β), and by mechanical tension. When these signals are reduced, as when TGF-β secretion is reduced, or as in scar shrinkage, myofibroblasts undergo apoptosis, resulting in a collagen-rich, cell-poor scar. Retention of myofibroblasts in fibrosis has been described as the result of imbalanced cytokine signaling, especially with respect to levels of activated TGF-β. ECM components can regulate myofibroblast persistence directly, since this phenotype is dependent on extracellular hyaluronan, tenascin-C, and the fibronectin splice variant containing the "extra domain A," and also, indirectly, through retention of TGF-β-secreting cells such as eosinophils. Thus the ECM is actively involved in both cellular and extracellular events that lead to fibrosis. Targeting components of the ECM as cells respond to injury and inflammatory stimuli holds promise as a means to avoid development of fibrosis and direct the wound-healing process toward reestablishment of a healthy equilibrium.

Keywords: provisional extracellular matrix, myofibroblast, collagen, hyaluronan, proteoglycans

THE EXTRACELLULAR MATRIX (ECM) is a composite of collagens and elastic fibers embedded in a viscoelastic gel of proteoglycans, hyaluronan, and assorted glycoproteins. These molecules interact by entanglement, cross-linking, and charge-dependent interactions to form bioactive polymers that, in part, regulate the biomechanical properties of tissues and their cellular phenotypes. The relative contributions of different ECM molecules vary with tissue type and result in mechanical and chemical properties appropriate to each environment. The objective of this review is to address the roles of individual components of the prefibrotic ECM in cellular events that lead to tissue fibrosis.

ECM and Control of Cell Behavior

The ECM interacts with cells to influence adhesion, proliferation, migration, and survival (27). In turn, the cells remodel the ECM, allowing these events to take place (Fig. 1). Thus the composition of the ECM is in a constant state of flux during development and disease. In healthy tissue, the ECM provides an optimal environment for normal cell functions. The ECM interacts with cells through integrin and nonintegrin receptors that provide mechanical support for the cells and a mechanism for information exchange between the cells and their environment. Multiple receptors and ECM ligands create higher ordered complexes that, in turn, bind and retain specific ECM components such as matricellular proteins (e.g., SPARC, thrombospondin, osteopontin, periostin, and tenascin-C) (6) and the glycosaminoglycan hyaluronan (19). Often these different ECM components are linked to one another by bridging molecules such as proteoglycans. For example, versican, a chondroitin sulfate proteoglycan, can bind to hyaluronan, tenascin, thrombospondin 1, and fibrillin, forming higher ordered ECM complexes in the pericellular environment (19, 39, 42). These components can influence cell behavior through direct contact with cell surface receptors (66). They can also act as a reservoir for cytokines and growth factors to be released at a later time, establishing another level of control (22, 43).

ECM Remodeling Leading to Fibrosis

Any change in the balance among different ECM components leads to altered tissue architecture. Structural changes often affect the mechanical properties of tissues which, in turn, can be sensed by the cells, leading to altered cell behavior (30). For example, mechanical strain markedly alters the composition of the ECM produced by arterial smooth muscle cells (ASMC) providing the cells with a more deformable ECM to withstand the strain (40).

The composition of the ECM is controlled by the coordinate and differential regulation of synthesis and turnover of each of its individual components. Fibrosis results from the abnormal accumulation of the fibrillar collagens, primarily type I collagen, arising as a result of elevated synthesis and/or decreased turnover (71). Since many factors regulate collagen synthesis and turnover by a variety of cells in various metabolic states and in spatial and temporal patterns, developing strategies to interfere with fibrosis has been most challenging (28). However, some success has been achieved by targeting profibrotic cytokines such as transforming growth factor-β (TGF-β) (24). A fundamental question is whether fibrosis is the result of a series of ECM remodeling events that eventually end in fibrosis or whether fibrosis arises independently of previous ECM remodeling events (Fig. 2).

Fibrosis can be viewed as the result of a series of ECM changes that take place over time (9, 72). It is often considered to be an aberrant form of wound healing in which there is progression rather than resolution of scarring, resulting in excessive accumulation of ECM, thus causing disruption of normal tissue architecture and function (15). Classic wound healing starts with some insult to healthy tissue. Upon injury, the ECM scaffold is destroyed and the wound is filled with a wave of cytokines and growth factors originating from broken or leaky blood vessels and cells entering and originating within the damaged tissue. This first phase is defined as the “provisional ECM” phase and is formed by plasma proteins such as fibrin, fibrinogen, and fibronectin seeping into the wound site and forming a cross-linked ECM so that resident cells such as fibroblasts, as well as myeloid cells, can adhere and begin to repair the wound (73). Fibroblasts that enter the provisional ECM also synthesize and secrete other provisional ECM molecules, such as hyaluronan and proteoglycans, that interact and stabilize the fibrin-enriched ECM (35). The provisional ECM provides the proper microenvironment for resident and invading cells to proliferate and migrate during the repair process. These cellular events are driven by cytokines and growth factors. For example, platelet-derived growth factor (PDGF) promotes cell proliferation as part of the early growth response that occurs during the “provisional ECM” phase. PDGF also stimulates cells to produce an ECM enriched in hyaluronan and versican, which is secreted into the pericellular space around the cells forming a viscoelastic cell coat (Fig. 3). This cell coat allows the cells to change shape and facilitates cell division and migration (16, 17, 19, 54, 56, 57). In fact, interfering with the formation of this ECM coat by treating

the cells with short oligosaccharides of hyaluronan blocks their proliferation even in the presence of the PDGF mitogen (16). Thus this very specialized form of ECM, in part, regulates the proliferative and migratory activity of the cells.

Different types of ECMs can have different effects on events associated with tissue repair. During the early provisional phase of wound healing, inflammatory cells are drawn into the wound. Matrices that are enriched for hyaluronan and versican can bind and trap inflammatory cells. This is referred to by some as a second order of provisional ECM (7, 13). For example, we and others have shown that versican and hyaluronan-enriched ECMs can bind myeloid and lymphoid cells, causing them to accumulate (Fig. 4) within specific regions of the tissue (10a–12, 18, 26, 52, 58, 68). Thus specialized forms of the ECM may promote inflammation. The integrity of the ECM can also influence immune regulation. For example, intact hyaluronan interacts with regulatory T cells through CD44 and promotes their functional suppression of T cell responder proliferation, whereas degraded low molecular weight hyaluronan does not exhibit this activity (3, 4). In addition, high molecular weight hyaluronan promotes the induction of IL-10-producing TR1 regulatory cells from conventional T cell precursors. These TR1 are capable of abrogating IL-10-dependent colitis in a mouse model, whereas fragmented hyaluronan does not (5). These results indicate that specific components of the ECM can play an active anti-inflammatory role by promoting immunosuppression. Immune regulation is a critical component in many fibrotic diseases, including inflammatory bowel disease (10, 20).

Myeloid cell infiltration into the provisional ECM releases matrix metalloproteinases that degrade the existing provisional ECM, generating fragments of ECM that are biologically active (1). Degradation of ECM is often referred to as a “danger signal” alerting the cells to remodel and repair the ECM so that homeostasis can be restored (53). Some ECM fragments can promote vascularization as part of the repair process, such as is seen for hyaluronan fragments promoting new blood vessel growth (62). In addition, hyaluronan fragments can be proinflammatory by stimulating inflammatory cytokine release by myeloid cells (50, 51). The degradation of versican by members of the ADAMTS family of proteases generates fragments of versican that are proapoptotic (45). Furthermore, fragments of hyaluronan promote collagen production in some cells (55). These examples highlight the importance of ECM degradation as contributing to the events leading to fibrosis.

Fibrosis and the Myofibroblast

Once the proliferative phase has occurred and leukocytes have migrated into a wound, granulation tissue formed from the provisional ECM is remodeled (9). This coincides with the appearance of the myofibroblast, a specialized form of fibroblast whose differentiation is primarily driven by cytokines, such as TGF-β and mechanical tension (21, 28). A number of other cytokines such as connective tissue growth factor, insulin-like growth factor-1, and PDGF have been identified as profibrotic cytokines. Myofibroblasts are responsible for the closure of wounds and for the formation of a collagen-rich scar (21, 65). The myofibroblast is also dependent on the synthesis and secretion of specific ECM components, such as fibronectin splice variant containing the extra domain-A (ED-A) fibronectin (59). Insertion of the ED-A module into fibronectin changes its configuration and thereby increases cell adhesion to fibronectin (44). The interaction between the ED-A segment of fibronectin and the cell surface is essential for the TGF-β-mediated myofibroblast transdifferentiation (59, 65). Furthermore, the polymerization of fibronectin into the ECM is required for the accumulation of other types of ECM components, e.g., type 1 collagen (63). These findings indicate that changes in the deposition of noncollagen molecules within the ECM can influence the deposition and accumulation of collagens that characterize the fibrotic ECM.

Other ECM changes in collagen binding molecules also regulate the myofibroblast phenotype. For example, hyaluronan is a glycosaminoglycan that is secreted by fibroblasts and a number of other cells and associates with the cell surface through CD44, forming a pericellular coat around the cell (see review in Ref. 19). Hyaluronan secretion has been intimately connected with maintenance of the myofibroblast phenotype (34, 47, 48, 60, 69, 70). Association of hyaluronan with CD44 influences the positioning of

TGF-β receptors, which can have an impact on TGF-β signaling (31, 32). Furthermore, blocking the synthesis of hyaluronan in fibroblasts inhibits the increase in α-actin expression induced by TGF-β during the fibroblast to myofibroblast conversion (69). Since removal of cell surface hyaluronan is known to destabilize focal adhesions involved in cell attachment (66), these findings point to the possibility that hyaluronan, as a component of the cross-linked pericellular matrix, may cooperate with focal adhesions to provide the mechanical tension needed to maintain the myofibroblast phenotype. Molecules such as hyaluronan that interact with fibrillar collagens will modulate the mechanical properties of the collagen and alter the contractile forces that can be generated by the cells (2). Furthermore, release of mechanical tension in myofibroblasts can result in a wave of apoptosis and cell loss (23, 29), suggesting that pericellular hyaluronan may promote survival of the myofibroblast. In addition, the capacity of a cell to synthesize and secrete hyaluronan in response to TGF-β has been linked to a fibrotic cell phenotype. For example, fibroblasts isolated from human oral mucosa are resistant to TGF-β-driven myofibroblast conversion (47), and this difference has been associated with scar-free healing of the oral mucosa. However, human dermal fibroblasts are readily converted to myofibroblasts by TGF-β and readily form scars with healing. In dermal fibroblasts, myofibroblast conversion was associated with an induction of hyaluronan synthetic enzymes, HAS1 and HAS2, and formation of a pericellular coat. Changes in these enzymes and pericellular coat formation were not observed for the oral fibroblasts in response to TGF-β (47). Although it is not entirely clear how pericellular hyaluronan promotes events leading to fibrosis, one possibility is that the hyaluronan-enriched ECM that forms around cells in response to proinflammatory agonists attracts and retains inflammatory cells, thus driving the inflammatory component associated with fibrosis (11, 47, 52). The role of this noncollagenous ECM component in events associated with fibrosis needs further investigation.

Retention of myofibroblasts in fibrosis has been described as the result of imbalanced cytokine signals. Conversion of fibroblasts to myofibroblasts is mediated by elevated levels of TGF-β and myofibroblasts contribute to their own continued survival by secreting activated TGF-β. At the end of the normal healing process, IL-1β induces apoptosis in lung myofibroblasts through inducible NO synthase, but this pathway is blocked by TGF-β (74). Any condition that causes elevated levels of TGF-β can inhibit myofibroblast death and result in fibrosis. Sources of TGF-β can include eosinophils (49), which can, in turn, be retained by a hyaluronan-rich ECM (37). In addition, TGF-β causes increased retention of hyaluronan in the ECM (47, 69), and myofibroblasts secrete TGF-β, closing the loop on an autostimulatory cycle.

Myofibroblasts are responsible for the deposition of a dense, fibrotic collagen matrix (36). The widespread occurrence of myofibroblasts and the fact that they can originate from a spectrum of cellular sources indicates that the term “myofibroblast” should be considered as defining functional status rather than a fixed cell type (28). Eventually, myofibroblasts become surrounded and buried in collagen. Collagen can have adverse effects on the behavior of cells. For example, ASMC cultured on polymerized type 1 collagen fibrils are arrested in the G1 phase of their cell cycle and do not respond to growth factor stimulation, whereas ASMC cultured on monomeric collagen proliferate in response to growth factors (38). Furthermore, degraded collagens promote disassembly of cellular focal adhesions, reducing the ability of the cells to adhere (8), which, in turn, causes the cells to undergo apoptosis (41, 67). The impact of intact vs. degraded collagen on the survival of myofibroblasts has not yet been investigated.

The myofibroblast appears to derive from multiple sources: epithelial cells going through epithelial-to-mesenchymal transition, pericytes, mesenchymal stem cells, and circulating bone marrow-derived fibrocytes (reviewed in Refs. 28 and 72). The more common origin is thought to be conversion of resident fibroblasts to myofibroblasts by cytokines such as TGF-β, coupled with mechanical forces generated on the cell by the remodeled ECM (65). In addition, viruses act through TLR-3 receptors to promote the formation of myofibroblasts (64). TLR-3 may act by stimulating the formation of a hyaluronan-rich ECM around the cell (11, 52) and inducing TGF-β secretion (64). These observations may help explain why viral infection can exacerbate chronic diseases that have a fibrotic component, such as remodeling in asthma (46).

Fibrosis and Inflammation

Remodeling of the ECM toward a fibrotic phenotype may or may not involve an inflammatory component (14, 25, 61). Fibrosis is defined by the overgrowth, hardening, and scarring of various tissues and is attributed to excess deposition of ECM components, primarily the fibrillar collagens (71). Fibrosis is the end stage of many different diseases and often results from a chronic inflammatory insult. Although inflammation is no doubt a player in promoting fibrosis in some tissues, attempts at curbing fibrosis with anti-inflammatory therapy have usually been ineffective. This failure could result from the fact that the inflammatory component of the disease that drives the fibrotic response may have already passed when treatment is initiated. On the other hand, fibrosis can proceed without evidence of an inflammatory component in some tissues and is therefore looked at as an aberrant form of wound healing (25). This could be partially explained by the fact that several of the agonists that promote the fibrotic response, such as TGF-β, can be synthesized by noninflammatory cells resident in the tissues. Thus situations likely exist in which mechanisms driving fibrosis are distinct from those regulating inflammation (71). However, it is just as likely that fibrosis involves both inflammatory and noninflammatory stimuli occurring in a stage-specific manner over time.

Summary and Conclusions

ECM composition is relatively stable in healthy adult tissue, but this balance changes during events associated with disease. For many diseases, these changes involve a stepwise remodeling of specific ECM components such that the early remodeling phase (provisional matrix) is characterized by an ECM composition that creates loose and highly hydrated environments for cellular invasion and repair. Specific components of the ECM interact with cells during this phase and play an active role in controlling cell behavior critical to the repair process. In many diseases, the formation of a fibrotic ECM follows this early phase and involves turnover of the provisional ECM, generation of biologically active ECM fragments, and replacement by a more compact and rigid ECM enriched in collagens and other fibrous proteins. We do not yet understand the precise cellular and molecular mechanisms that control repair processes in healthy tissue to produce an ECM that is sufficient for tissue strength and elasticity without excessive deposition of fibrous proteins such as collagen. Components of the ECM do not passively follow events that lead to fibrosis, but rather play an active role in the cellular and extracellular events in this process. A significantly large percentage of deaths in the developed world can be attributed to some type of chronic fibroproliferative disease. Clearly, effective antifibrotic therapies would make a significant contribution to public health. Targeting specific components of the ECM and/or the enzymes that modify these components may be an effective strategy to treat fibrosis in the future (28, 33).

GRANTS

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DISCLOSURES

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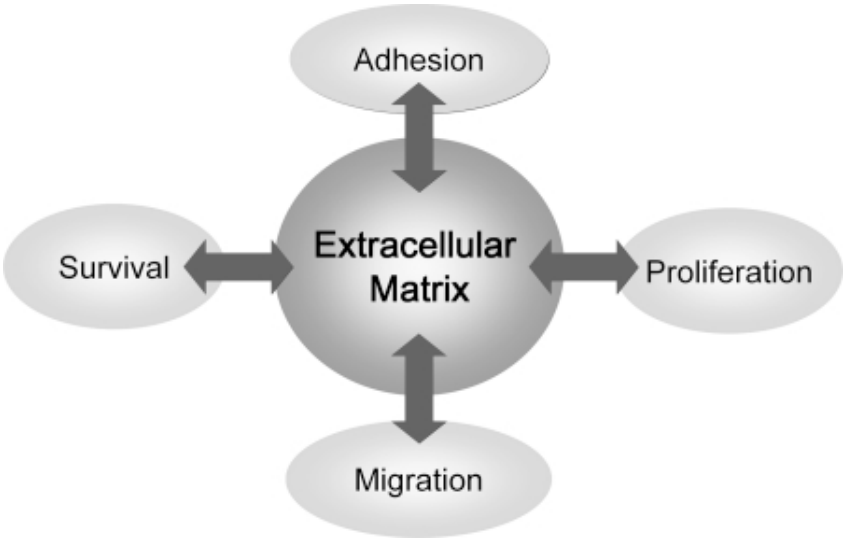
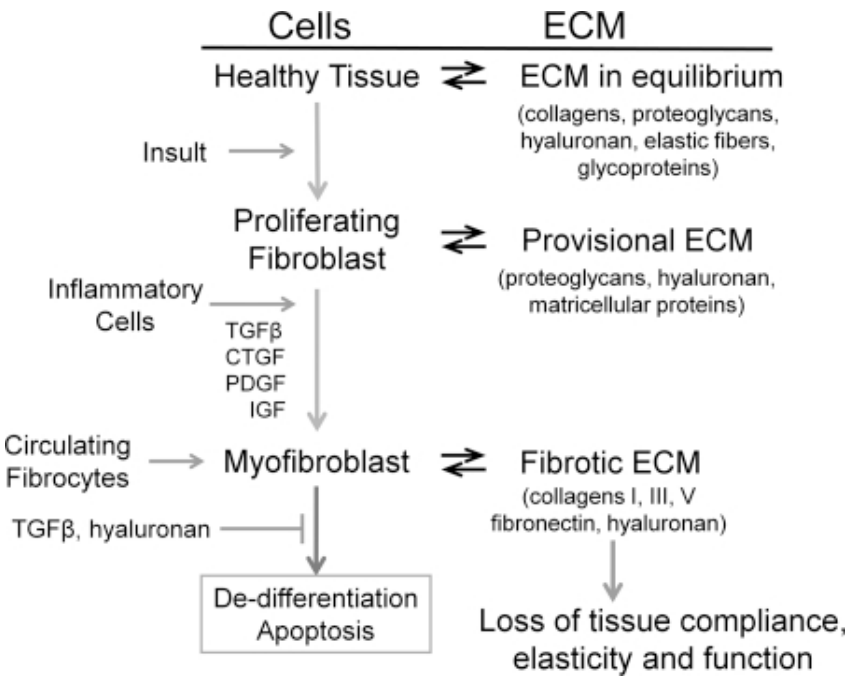
Figures and Tables

Fig. 1.



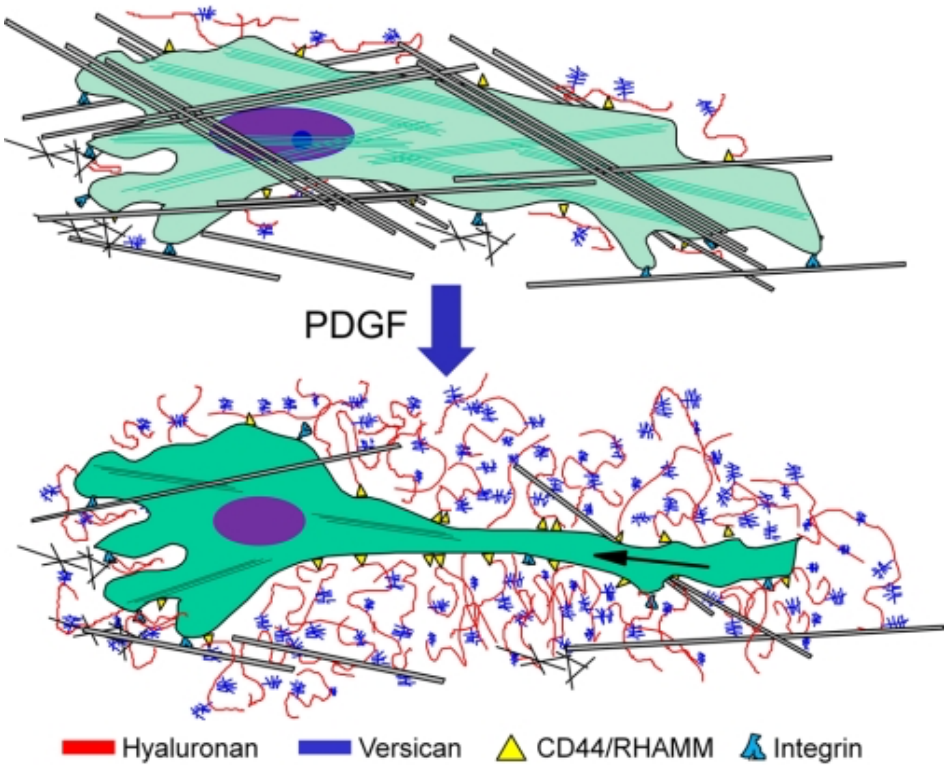
Influence of extracellular matrix (ECM) on cell behavior. Cells interact with specific components of the ECM. These interactions govern, to a large extent, the ability of cells to adhere to that ECM, proliferate, and migrate, as well as to survive and resist cell death. In turn, the cells remodel and produce new ECM, allowing these events to take place.

Fig. 2.



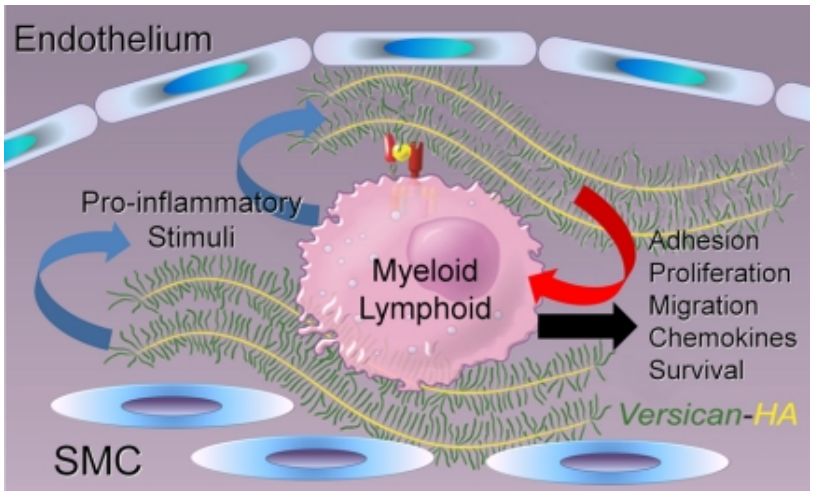
Transition of healthy tissue to fibrotic tissue. A proposed sequence of events highlighting a stepwise remodeling of the ECM that involves alterations in the composition of the ECM and effects on cell phenotype that eventually result in tissue fibrosis. A central component in this pathway is the temporal generation of the major collagen-secreting cell, the myofibroblast, from resident fibroblasts. As an alternative pathway, circulating cells such as fibrocytes or other stem cells may directly engraft into tissue and transdifferentiate into myofibroblasts, promoting fibrosis. TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor.

Fig. 3.



ECM transitions required for cell proliferation and migration. For cells to change shape so they can divide and/or migrate, they must modify their external environment by first degrading the existing ECM and replacing it with components that allow the cell to change shape and move. Two ECM molecules that are produced during these events and allow this to happen are hyaluronan and versican.

Fig. 4.



ECM and immune cell regulation. Immune cells come into contact with the ECM as they invade tissue as part of the inflammatory phase of tissue repair. Certain types of ECMs, including those that contain hyaluronan (HA) and versican, interact with myeloid and lymphoid cells through specific cell surface receptors to promote their invasion, accumulation, and activation. Such matrices may exhibit either pro- or anti-inflammatory properties. Targeting specific ECM components involved in these interactions may be one strategy to interfere with subsequent events driven by these cells that lead to fibrosis. This figure was prepared by Dr. Charles W. Frevert, University of Washington, Seattle, WA, and is used with permission.