The extracellular matrix can regulate vascular cell migration, proliferation, and survival: relationships to vascular disease

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Summary. The extracellular matrix (ECM) of the normal artery wall is a collection of fibrous proteins and associated glycoproteins embedded in a hydrated ground substance of glycosaminoglycans and proteoglycans. These distinct molecules are organized into a highly ordered network that are closely associated with the vascular cells that produce them. In addition to providing the architectural framework for the artery wall that imparts mechanical support and viscoelasticity, the ECM can regulate the behaviour of vascular cells, including their ability to migrate, proliferate and survive injury. The composition of the ECM is different within intimal lesions of atherosclerosis, which are composed of monocytes and lymphocytes from the circulation and smooth muscle cells (SMC) that migrate from the media to the intima (Ross 1993, 1999), and these differences may contribute to the altered phenotype of vascular cells within lesions. This review will briefly outline the ECM changes observed in atherosclerosis and restenosis and the potential relationship of these changes to altered vascular cell functions.

Keywords: smooth muscle, endothelial cell, monocyte, macrophage, phenotype

Vascular extracellular matrix in normal vessels

Normal blood vessel walls are composed of endothelial cells, SMC (smooth muscle cells), and ECM (the extracellular matrix) that vary within the different layers of the vessel wall (reviewed in Wight 1996). They are arranged in concentric layers: the intima, composed of the lining endothelial cells with minimal subendothelial ECM enriched in proteoglycans and hyaluronan (HA); the media, separated from the intima by a dense elastic membrane (internal elastic lamina), and composed of smooth muscle cell layers embedded in an ECM comprising elastic elements, collagen and proteoglycans (Table 1); and the adventitia, separated from the media by the external elastic lamina, and composed of fibrillar collagen, fibroblasts, and vasa vasora that nourish the vascular wall. The ECM of each of these layers imparts different properties to the vessel (Figure 1), with compressible inner layers allowing expansion of the vessel during systole and elastic recoil during diastole.

Collagens are composed of a triple helix of three polypeptide α chains, each having a gly-x-y repeating sequence (Prockop & Kivirikko 1995). In vessels, types I and III are predominant and assemble into cross-banded fibrils that provide tensile strength to the vessel wall. Collagens type IV, VI and VIII are nonfibrillar collagens. Within basement membranes beneath endothelial cells and surrounding media SMC, collagen types IV and VIII form 3-dimensional networks (Yurchenco & Schittny 1990; Shuttleworth 1997) that serve as an anchoring

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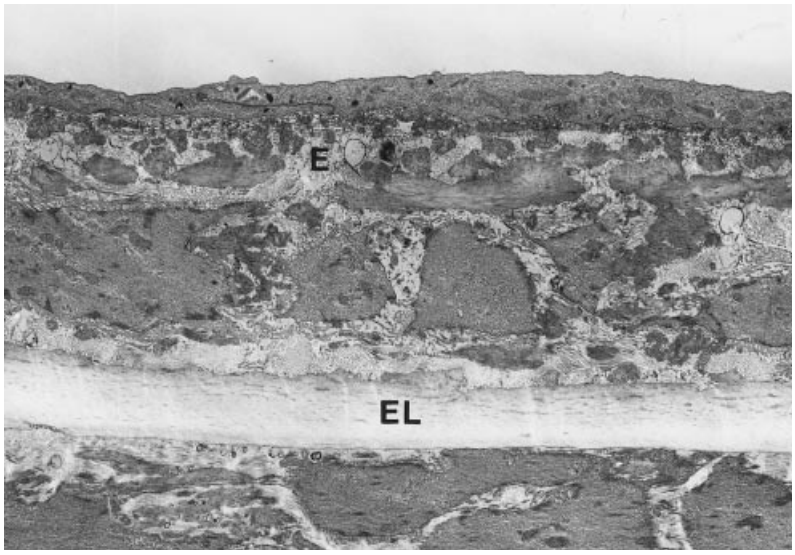

Figure 1. A transmission electron micrograph of a developing monkey aorta. Within normal vessels, smooth muscle layers are embedded in a matrix composed of elastic elements, collagen and proteoglycans. Two endothelial cells can be seen at the lumen (although their nuclei are not apparent in this thin section). Beneath the endothelial cells are newly forming elastic fibres (E) that are separated from the endothelium by basement membrane and collagen fibrils. A layer of smooth muscle lies beneath the forming elastic fibres, which is separated from another layer of smooth muscle by well-formed elastic laminae (EL). Reprinted with permission from Ross R. (1988) In *Heart Disease: A Textbook of Cardiovascular Medicine*, 3rd edition. (Ed. E. Braunwald) Philadelphia: W.B. Saunders Co.,

Table 1. Comparison of the extracellular matrix in the normal media and in lesions of atherosclerosis*

	Normal media	Atherosclerosis		
		SMC remodeling	Macrophages	Fibrous cap
Collagen				
collagens type I, III	+++			+++
collagen type IV	+	++		++
collagen type V	–	++	++	
collagen type VI	+	+	+	
collagen type VIII	+	++	++	
collagen XVIII	+			
Elastic fibers				
elastin	+++	+/–		++
Proteoglycans and hyaluronan				
biglycan	++	+++	+	–/+
decorin	++	+	+++	+
glypican	+			
hyaluronan	+	+++	+++	+++
perlecan	++	+++	++	+
syndecan	+	+		
versican	++	+++	–	+++
Adhesive glycoproteins				
fibronectin	+	+++		
laminin	++	++		
Matricellular proteins				
osteopontin	–	++	+++	
SPARC	–	++	+++	
tenacin	–		++	
thrombospondin	+	++		

*Expression levels have been summarized from the available data: -, none detectable; ±, variably detectable; +, detectable; ++, detectable at moderate levels; and +++, detectable at high levels.

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substrate and help form a permeability barrier. Self-association and disulphide bonding of type VI collagen result in high molecular weight aggregates that are localized between fibrils of collagens type I and III (Katsuda *et al*. 1992). Collagen XVIII, the precursor of the endothelial cell inhibitor endostatin, is also expressed in normal media and associated with elastic fibres in the multiple elastic membranes of the aorta and large arteries (Miosge *et al*. 1999).

While collagens provide tensile strength, elastin assembled into elastic fibres provides elastic recoil needed to accommodate the pulsatile nature of blood flow as well as haemodynamic and pressure changes (Rosenbloom *et al*. 1993). Fibrillin, a 350-kDa glycoprotein which associates with itself or with other components of the ECM, forms a microfibrillar network that serves as scaffolding for deposition of elastin and assembly of elastic fibres (Reinhardt *et al*. 1995). Expression of emilin, an extracellular matrix glycoprotein, also precedes elastin deposition and is thought to be involved in elastogenesis (Bressan *et al*. 1993). Elastic fibres are synthesized by SMC and are arranged in concentric lamellae that separate the different layers of the vessel and form boundaries between layers of SMC. Mice made hemizygous for the elastin gene are normal in terms of arterial compliance, but to be compliant they increase the number of rings of elastic lamellae and SMC 2.5-fold (Li *et al*. 1998a).

Proteoglycans and HA are hydrophilic molecules that represent the third general component of the ECM. Proteoglycans consist of a core protein linked to one or more polysaccharides that have diverse roles in regulating connective tissue structure and permeability (Iozzo & Murdoch 1996; Rosenberg *et al*. 1997). HA is a huge molecule that consists of many repeats of a simple disaccharide stretched end-to-end, which often serves as a backbone for large proteoglycan complexes (Fraser *et al*. 1997). HA binds a large amount of water forming a viscous hydrate gel, which allows the ECM to resist compression forces. In addition to interacting with other matrix constituents, proteoglycans and HA interact with vascular cells.

The adhesive glycoproteins fibronectin and laminin form connections between other ECM and cells via specific integrin receptors. Fibronectin is a multifunctional adhesive protein present in the plasma and also synthesized by vascular cells. Fibronectin is a large (approximately 450 kDa) disulphide-linked, glycoprotein dimer that binds collagen, fibrin and proteoglycans via specific domains as well as vascular cells through specific integrins (Ruoslahti 1988). Laminin, an even larger (approximately 820 kDa) trimeric glycoprotein, is the most abundant glycoprotein in endothelial and SMC basement membranes (Timpl & Brown 1994). Laminin binds cells through specific integrins and interacts with other ECM, such as collagen type IV and heparin sulphate.

Another group of glycoproteins, termed matricellular proteins (Bornstein 1995), are a class of secreted proteins that interact with other ECM constituents, multiple specific cell surface receptors, as well as growth factors, to modulate cell–matrix interactions (Sage & Bornstein 1991). This group includes osteopontin, SPARC (also known as osteonectin), tenascin and thrombospondin. As indicated in Table 1, their expression in normal vessels is limited.

The extracellular matrix surrounding vascular cells is altered after injury and in developing lesions of atherosclerosis

After balloon injury of a normal or diseased vessel and in atherosclerosis, the physiologic healing response results in the formation of a neointima. The neointima after balloon injury of a normal vessel is composed primarily of SMC that migrate from the media into the intima (Clowes *et al*. 1986). In contrast, in atherosclerosis, the inflammatory response initiates neointimal accumulation of monocytes and lymphocytes followed by SMC migration and proliferation (Ross 1993, 1999). In both cases, analysis of experimental models of balloon injury and atherosclerosis, as well as of more advanced human lesions, has demonstrated alterations in the ECM within the neointima (Table 1). With the formation of intimal lesions, the phenotype of the SMC changes from a ‘contractile’ state, in which the SMC are filled with myofilaments and contain a relatively poorly developed Golgi apparatus and rough endoplasmic reticulum, to a ‘synthetic’ phenotype (Figure 2) characterized by an abundance of rough endoplasmic reticulum and Golgi bodies with few and sometimes no evident myofilaments (Thyberg *et al*. 1990).

Lipid- and macrophage-rich areas of lesions contain less collagen (Voss & Rauterberg 1986). In contrast, fibrous plaques contain areas rich in types I and III collagen (Voss & Rauterberg 1986). Type V and VI collagen are observed diffusely distributed in the intimal space associated with cross-banded collagen fibres and beaded filaments respectively (Katsuda *et al*. 1992), while type IV collagen increases in multilayered basement membrane beneath endothelial cells and around SMC in lesions (Shekhonin *et al*. 1985; Katsuda *et al*. 1992). Type VIII collagen is expressed in response to balloon injury(Sibinga *et al*. 1997), and was identified in a

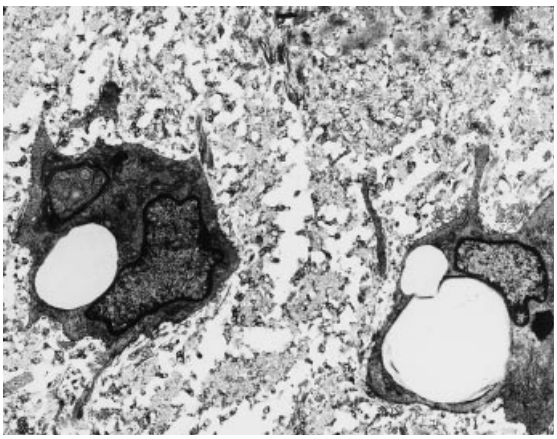

Figure 2. Smooth muscle cells within atherosclerotic lesions have abundant rough endoplasmic reticula. A transmission electron micrograph of a deep layer of a fatty streak in the thoracic aorta of a nonhuman primate six months after initiation of a high cholesterol diet. The extracellular space between the smooth muscle cells in the deep layer of the fatty streak contains collagen, elastin and numerous extracellular liposomes. The smooth muscle cells have abundant rough endoplasmic reticula and few myofilaments. Reprinted with permission from Masuda J. & Ross R. (1990) *Arteriosclerosis* **10,** 164–177.

differential screen of the rat carotid artery four days after injury in which the migratory response was enhanced (Bendeck *et al*. 1996). Type VIII collagen has also been demonstrated to accumulate in the intimal space in response to cholesterol diet in rabbits (Plenz *et al*. 1999a), in both SMC (Plenz *et al*. 1999b) and macrophages (Weitkamp *et al*. 1999).

Disruption or loss of elastic fibres is frequently observed in atherosclerosis (Fulop *et al*. 1998), while the content and distribution of proteoglycans and HA also change (Table 1). In lesions from hypercholesterolemic nonhuman primates at different stages of lesion development, strong immunostaining for decorin, biglycan, versican and HA is observed in both intermediate and advanced lesions, with decorin being more predominant in macrophage-rich areas and versican most prevalent in areas rich in SMC (Evanko *et al*. 1998). Selective deposits of versican (Wight *et al*. 1997) and biglycan and decorin (Riessen *et al*. 1994) are also observed in the ECM of restenotic human vessels. The cell surface proteoglycans syndecan-1 and syndecan-4 are also increased after vascular injury (Cizmeci-Smith *et al*. 1997).

In situ fibronectin assembly by neointimal SMC has been demonstrated in tissue sections from balloon-injured rat carotid artery 12 days after injury (Pickering *et al*. 2000). Electron microscopic analysis also demonstrates newly deposited fibronectin assembled into a fibrillar network associated with the surface of synthetic SMC during early atherosclerotic and restenotic lesion development (Kakolyris *et al*. 1995; Thyberg *et al*. 1997).

Expression of the matricellular proteins is significantly increased in developing lesions (Table 1). Osteopontin (Giachelli *et al*. 1993), SPARC (Raines *et al*. 1992), tenascin (Hedin *et al*. 1991; Wallner *et al*. 1999), and thrombospondin (Wight *et al*. 1985; Reed *et al*. 1995; Riessen *et al*. 1998) are all increased after arterial injury in the atherosclerotic lesions. In addition to being localized to lesions of atherosclerosis and balloon-injured vessels, antibody blockade of osteopontin (Liaw *et al*. 1997) and thrombospondin (Chen *et al*. 1999) reduces neointimal thickening after carotid denudation and thrombospondin-enhanced re-endothelialization.

In addition to changes in the ECM composition after injury and in atherosclerotic lesions, there is evidence of matrix degration by matrix metalloproteinases (MMPs) (Galis *et al*. 1994; Halpert *et al*. 1996; Nikkari *et al*. 1996; Sukhova *et al*. 1999) and cathepsins (Sukhova *et al*. 1998). MMP expression is particularly elevated in the shoulders and cores of lesions and may contribute to plaque destabilization. Cleaved type I collagen is localized in atheromatous lesions with MMP-1- and MMP-13-positive macrophages (Sukhova *et al*. 1999). Macrophage-derived proteinases have the capacity to degrade every component of the extracellular matrix, even in the presence of high-affinity proteinase inhibitors (Jones & Werb 1980; Owen & Campbell 1999). The proteinases are required for the response after injury, as evidenced by: 1) MMP blockade inhibits SMC migration in the rat carotid (Bendeck *et al*. 1996); 2) gene transfer of tissue inhibitor of metalloproteinase (TIMP)-2 into SMC after rat carotid balloon injury inhibits SMC migration and accumulation (Forough *et al*. 1996; Cheng *et al*. 1998); 3) the accumulation of SMC after electric injury of the mouse femoral artery is impaired in animals deficient in TIMP-1 (Lijnen *et al*. 1999). Conversely, overexpression of MMP-9 enhances SMC migration and alters remodelling in the injured rat carotid artery (Mason *et al*. 1999). In many cases, the proteolytic events are probably concentrated near the cell surface where they will be effective even in the presence of high concentrations of inhibitors of apoptosis (Werb 1997). Thus, new ECM deposition, as well as localized ECM degradation, is observed in neointimal lesions.

Cellular response to the extracellular matrix is regulated by specific matrix receptors

The principal matrix receptors on vascular cells include: integrins, members of the diverse family of

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Table 2. Integrins expressed in normal vessels*

Integrins	Matrix bound	Endothelium	Smooth muscle
$\alpha1\beta1$	collagen, laminin	++	++
$\alpha2\beta1$	collagen, laminin, tenascin	++	−
$\alpha3\beta1$	collagen, fibronectin, laminin, thrombospondin	+	+
$\alpha5\beta1$	fibronectin, thrombospondin	++	+/−
$\alpha6\beta1$	laminin	+	−
$\alpha8\beta1$	fibronectin, tenascin,vitronectin	−	++
$\alpha v\beta1$	fibronectin, osteopontin, tenascin, vitronectin	++	++
$\alpha v\beta3$	fibronectin, osteopontin, tenascin, thrombospondin vitronectin	++	+/−
$\alpha v\beta5$	osteopontin, vitronectin	++	++

*Expression levels have been summarized from the available data: -, none detectable; ±, variably detectable; +, detectable at low levels; and ++, detectable at higher levels.

transmembrane heterodimers that lack any inherent kinase activity (Shattil & Ginsberg 1997); CD44, a broadly expressed cell surface protein that is a receptor for hyaluronate (Aruffo *et al*. 1990); receptor for HA-mediated motility (RHAMM), which has been implicated in the regulation of SMC migration (Cheung *et al*. 1999); and the discoidin domain receptors, previously, orphan tyrosine kinases that have been identified as collagen receptors (Schlessinger 1997). The integrin profiles of endothelial cells and SMC in the normal vascular wall have been characterized (Conforti *et al*. 1992; Skinner *et al*. 1994), and are shown in Table 2. Both the adhesive and signalling properties of the integrins are critical for their biological activities (Shattil & Ginsberg 1997). Changes in integrin and other adhesion receptors during atherogenesis have not been well defined.

The effects of different extracellular matrices on vascular cell functions

When normal medial SMC are placed in culture, within a few days they lose their contractility and myofilaments and develop an extensive rough endoplasmic reticulum and a large Golgi complex (Hultgardh-Nilsson *et al*. 1997), similar to the features of SMC in developing lesions (Thyberg *et al*. 1990). Interestingly, laminin, a constituent of normal media, has been shown to inhibit the shift of cultured SMCs from the 'contractile' phenotype, while fibronectin promotes the shift to the 'synthetic' phenotype (Hedin *et al*. 1988). Culture of SMC on polymerized collagen type I inhibits SMC proliferation and mimics many of the properties of medial SMC (Koyama *et al*. 1996; Raines *et al*. 2000), and on rigid gels of type IV collagen may even more closely reproduce the phenotype of medial SMC (Hirose *et al*. 1999). Four other matrix-associated glycoproteins (osteopontin, SPARC, thrombospondin and tenascin) present in lesions of atherosclerosis (Table 1), have been shown to exert common 'antiadhesive' functions involved in cell migration and proliferation (Sage & Bornstein 1991) and osteopontin and vitronectin promote SMC adhesion and migration (Liaw *et al*. 1995; Slepian *et al*. 1998). Thus, different ECM environments of the SMC can modulate SMC phenotype and responsiveness.

Each of the types of ECM listed in Table 1 within the local environment surrounding vascular cells creates distinct environments for these cells. Collagens, specifically polymerized collagens type I and IV surrounding SMC, promote a more quiescent and 'contractile' SMC phenotype similar to normal medial SMC *in vivo* (Koyama *et al*. 1996; Hirose *et al*. 1999; Raines *et al*., in press). However, evaluation of calcification of cultures of bovine SMC has shown that films of monomeric type I collagen enhance mineralized nodule formation, calcium incorporation, von Kossa staining, and alkaline phosphatase activity, while films of type IV collagen inhibit mineralization parameters (Watson *et al*. 1998). Addition of soluble type VIII collagen, which accumulates in developing lesions, stimulates SMC migration *in vitro*, and attachment to type VIII collagen increases production of MMP-2 and MMP-9 in rat SMC isolated from carotid neointima after balloon injury, but fails to alter MMP production in rat SMC isolated from normal media (Hou *et al*. 2000). Similarly, mutation of one allele of elastin, previously thought to play a purely structural role, is sufficient to induce subendothelial proliferation of SMC (Li *et al*. 1998b).

Collagens also modulate monocytes/macrophages that infiltrate the artery wall early in lesion initiation and are present throughout lesion development (Ross 1993, 1999). Monomeric films of collagen type I enhance acquisition of resident macrophage traits, such as expression of CD71, cell spreading, uptake of modified

lipoproteins, and release of MMP-9 (Wesley *et al*. 1998). Integrin engagement of ECM, such as with fibronectin, has also been shown to be a primary signal transduction pathway regulating monocyte immediate-early gene induction, including a number of inflammatory mediators (Yurochko *et al*. 1992).

Heparan sulphate species produced by SMC have long been recognized as potent inhibitors of SMC proliferation (Fritze *et al*. 1985). In addition to direct effects, a number of growth factors bind to heparin sulphate-rich ECM (Taipale & Keski-Oja 1997), and thus can serve as a local site of storage. Heparin has also been critical for oligomerization of fibroblast growth factor (FGF) and subsequent stimulation of endothelial cells and SMC (Spivak-Kroizman *et al*. 1994). Recently, heparanase degradation of syndecan-1 ectodomain, soluble heparan sulphate proteoglycan shed from vascular cell surfaces after injury, produces heparin sulphate fragments, which activate FGF-stimulated proliferation (Kato *et al*. 1998). Glypican-1, the only member of the family of glycosylphosphatidylinositol-anchored cell surface heparan sulphate proteoglycans expressed in vascular cells, binds vascular endothelial growth factor and acts as an extracellular chaperone that enhances its activity (Gengrinovitch *et al*. 1999). In addition, the proteoglycans biglycan and versican and HA have been involved in migration and proliferation of vascular cells (Wight *et al*. 1992). Biglycan expression is upregulated in migrating endothelial cells, and is localized to the tips and edges of lamellopodia on migrating cells (Kinsella *et al*. 1997) and in lesions of atherosclerosis (Evanko *et al*. 1998). All migrating and proliferating human SMC display abundant HA- and versican-rich coats whose appearance is coordinated with cell detachment and mitotic cell rounding (Evanko *et al*. 1999). Reduction in this coat is sufficient to enhance adhesion and decrease SMC migration and proliferation. In animal models of balloon injury of vessels, administration of HA has inhibited neointimal macrophage influx (Ferns *et al*. 1995) and SMC accumulation (Savani & Turley 1995).

Fibronectin fibril assembly, another feature of atherosclerotic lesions (Thyberg *et al*. 1997; Pickering *et al*. 2000) is necessary for SMC growth (Mercurius & Morla 1998; our unpublished observations), but is also important as an adhesion substrate for the survival of endothelial cells (Meredith *et al*. 1993; Chen *et al*. 1997). Multiple splice variants of fibronectin have been identified, and differential regulation of the multiple splice variants may further modulate vascular cell adhesion, migration and proliferation (Schwarzbauer 1991). A film of fibronectin also promotes calcification of SMC *in vitro* (Watson *et al*. 1998).

The matricellular proteins – SPARC, tenascin and thrombospondin – promote antiadhesive and antiproliferative responses in endothelial cells and SMC (Sage & Bornstein 1991), while osteopontin promotes adhesion and migration of SMC (Liaw *et al*. 1995), but also inhibits calcification (Wada *et al*. 1999) and apoptosis (Scatena *et al*. 1998). The modular domain structure of matricellular proteins allows them to independently bind cells and matrix components and a multiplicity of binding partners simultaneously. However, their ability to bind a large number of integrins and other receptors has made it difficult to assess the relative contribution of specific binding interactions. Loss of either of these binding partners may have significant impact on the ECM and vascular cell behaviour. In embryonic *mov 13* mice that lack type I collagen, SPARC is not observed in the ECM despite normal levels of synthesis by *mov 13* cells (Iruela-Arispe *et al*. 1996). The ability of matricellular proteins to bind growth factors, as shown for platelet-derived growth factor binding to SPARC (Raines *et al*. 1992), provides an alternative mechanism for the matricellular proteins to modulate vascular cell responses.

Fragments of the extracellular matrix have distinct activities from the native molecules

ECM fragments generated as a result of local release of MMPs and cathepsins have different effects on vascular cells than their native counterparts, including the generation of novel regulators of angiogenesis (Sage 1997). A 20-kDa C-terminal fragment of collagen XVIII, endostatin, specifically inhibits endothelial proliferation and blocks angiogenesis (O'Reilly *et al*. 1997). Administration of endostatin to apolipoprotein E -/- mice (20–36 weeks), which develop lesions of atherosclerosis, reduces intimal neovascularization and decreased plaque area at the aortic origin (Moulton *et al*. 1999). The noncollagenous domains of α2(IV), α3(IV), and α6(IV) chains of collagen type IV regulate endothelial cell adhesion and migration and potently inhibit angiogenesis (Petitclerc *et al*. 2000). In cultured human SMC, addition of fragments of type I collagen induces cell rounding through calpain-mediated cleavage of focal adhesion proteins (Carragher *et al*. 1999). This effect is dominant irrespective of the ECM, to which the SMC are adherent, and may provide a mechanism for de-adhesion of cells from ECM. Elastin peptides promote monocyte migration (Senior *et al*. 1980), and induce a dose-dependent and endothelium-dependent vasorelation mediated by the elastin/laminin receptor and by endothelial nitric oxide production (Faury *et al*. 1998). On human monocytes, elastin peptides also

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mobilize calcium and stimulate a respiratory burst and enzyme secretion (Fulop *et al*. 1986). In SMC, elastin peptides stimulate production of MMPs and decrease secretion of their inhibitors, TIMPs (Tummalapalli & Tyagi 1999).

The extracellular domain of the cell surface proteoglycan syndecan-1 is shed after injury, and heparanase treatment of the shed ectodomain generates heparin sulphate fragments that markedly enhance FGF activity (Kato *et al*. 1998). HA in its native form exists as a high molecular weight polymer, but during inflammation lower molecular weight fragments accumulate. In macrophages, the HA fragments induce chemokine gene expression (McKee *et al*. 1996), including MMP regulation (Horton *et al*. 1999), and stimulate nitric oxide synthase through a nuclear factor-κB-dependent mechanism (McKee *et al*. 1997).

Several examples exist for cleavage-induced exposure of cryptic binding sites in vascular glycoproteins. Cleavage of fibronectin results in the release of a 120-kDa cell-binding fragment that is chemotactic for human monocytes (Clark *et al*. 1988). The same fibronectin fragment stimulates tumour necrosis factor secretion by human monocytes (Beezhold & Personius 1992). More recently, it has been shown that this fragment also modulates integrin α5 expression, which has been proposed to promote monocyte accumulation (Trial *et al*. 1999). Thrombin cleavage of osteopontin promotes endothelial cell attachment and spreading (Senger *et al*. 1994). This cleavage exposes a cryptic adhesive sequence recognized by α9 β1, an activity not found in native osteopontin (Smith *et al*. 1996). Plasminolysis of SPARC produces a copper-binding peptide that stimulates angiogenesis (Sage 1997).

Perspective

Vascular ECM is critical for maintenance of vascular integrity and imparts tensile strength, viscoelasticity, elastic recoil and compressibility through the distinct properties of the different constituents. As reviewed here, the ECM composition is altered during the formation of intimal lesions, which changes the physical properties of the ECM, including the generation of fragments with distinct activities. However, in addition to changing the physical nature of the ECM, the composition of the ECM can regulate vascular cell responses, including survival, migration and proliferation, all of which can significantly contribute to remodelling of the vascular wall. An outgrowth of our increasing knowledge of the molecular interactions of ECM receptors with different ECM constituents is the development of peptide mimetics that can interfere specifically with some of these processes. Further understanding of these cell–matrix interactions promises to provide novel therapeutic targets for the prevention of unfavourable remodelling of the artery wall in atherosclerosis and restenosis.

Acknowledgements

This manuscript is dedicated to the memory of the late Russell Ross who would have enjoyed writing a review in honor of his dear friend and colleague, Neville Woolf. Russ's first studies as a young investigator focused on cellular interactions with the extracellular matrix in wound repair. Within the last five years, our laboratory has returned to extracellular matrix to examine how it may alter cellular responses in atherogenesis. Although he left us much too soon, a wonderful legacy remains in the people he trained, the colleagues he inspired, and our memories of a truly caring and supportive mentor, colleague and friend and an enthusiastic scientist who was passionate in his pursuit of understanding the cellular and molecular mechanisms involved in the formation of lesions of atherosclerosis.

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