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PROSPECTS

Effects of Soluble Factors and Extracellular Matrix Components on Vascular Cell Behavior In Vitro and In Vivo: Models of De-Endothelialization and Repair

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Abstract Vessel walls are comprised of several different cell populations residing in and on complex extracellular matrices. Each of the vascular cell types has diverse and sometimes unique functions and morphologies, and each has roles in repair processes following injury. Large vessel endothelial cells are known to respond to denudation injury by sheet migration and proliferation. This is in contrast to the migration through soft tissues with tube formation and subsequent lumen formation exhibited by microvascular endothelial cells in response to injury. Vascular smooth muscle cells of larger vessels respond to injury by migration from the arterial media into the intima, proliferation, and matrix biosynthesis, ultimately causing intimal thickening. Both these cell types exhibit "dysfunctional" phenotypes during their responses to injury. Microvascular cell responses to injury, while extremely variable, are less well documented. Specifically, responses to injury by microvascular endothelial vascular cells appear to be modulated, in part, by the composition and organization of the surrounding matrix as well as by the various soluble factors and cytokines found at sites of injury, suggesting that the extracellular matrix and soluble factors modulate each other's effects on local vascular cell populations following injury.

Key words: endothelial cell, smooth muscle cell, microvascular endothelial cell, angiogenesis, denudation injury, growth factors, autocrine, paracrine, migration, proliferation

Injury to the endothelium, followed by platelet aggregation and release of growth factors and vasoactive agents, such as PDGF, TGF-β1, serotonin, norepinephrine, and histamine, which promote vascular smooth muscle cell chemotaxis, migration, and proliferation, has been proposed as an important event in the development of arteriosclerosis [1]. Currently, several of the available invasive treatments of large and medium vessel occlusive disease (including autologous and synthetic grafting, angioplasty, endarterectomy, atherectomy, and laser ablation) cause significant de-endothelialization and medial injury of vascular segments. This injury elicits platelet adhesion, aggregation, and release of soluble factors and "activation" of local medial smooth muscle cells that are thought to contribute to the development of post-therapy stenosis that is noted in up to 50% of the patient populations studied [2]. For several years we have investigated the role of matrix components and selected soluble factors in the modulation of endothelial and vascular smooth muscle cell attachment, proliferation, and migration [1,3–5].

It is now widely accepted that matrix components have significant effects on bovine aortic endothelial cell (BAEC) migration in vitro. Using an in vitro migration assay that was developed in our laboratory, we have demonstrated that interstitial collagens elicit the most rapid migration rate, basement membrane components evoke intermediate migratory rates, while fibronectin was found to elicit the lowest migration rate [4,6–9]. Additionally, we found that migratory behavior on these substrates could be modulated by altering the amounts of matrix coated on the culture dishes, and migratory behavior could be correlated with the organizational patterns and dynamics of various cytoskeletal components such as fodrin [8], protein 4.1 [6], and vinculin and α-actinin [5]. BAEC cultured on substrates that elicit high to intermediate migratory rates (collagen types I, III, and IV

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and laminin) were also noted to reorganize the cortical cytoskeletal components fodrin and protein 4.1 following stimuli to migrate. In contrast, substrates that elicit low migratory rates (fibronectin) are not associated with reorganization of these cytoskeletal components following stimuli to migrate [6,8]. These data are consistent with the concept that the existing and newly synthesized extracellular matrix modulates cellular behavior, in part, by affecting the organization and dynamics of the cytoskeleton presumably via cell surface matrix binding proteins [1,4,5,7,8].

We have demonstrated that both integrin and non-integrin matrix binding proteins participate in in vitro BAEC adhesion and migration events [9,10]. Immunoprecipitation and immunoblot analyses revealed that BAEC express at least two different integrin heterodimers, β1 and β3 class integrins, and attachment assays using RGD-containing (arginine-glycine-aspartate-containing) peptides illustrated dose-dependent RGD sensitivity on fibrinogen, laminin, and fibronectin substrates. Immunofluorescence studies of BAEC integrins revealed rapid matrix protein-specific organization within 1 h of plating. β1 integrin molecules were observed to become arrayed in linear stress fiber-type patterns on fibronectin and laminin substrates. In contrast, β3 integrins were noted to organize into punctate patterns on a fibrinogen substratum at this early time point. In contrast, the non-integrin laminin binding protein LB69 was not observed to organize on any of these matrix components at this early time point [9]. At later time points LB69 was noted to organize following plating, suggesting a spatiotemporal segregation of integrin and non-integrin binding proteins during adhesive events [9,11]. Supporting this concept of a spatiotemporal segregation of integrin and non-integrin binding proteins during adhesive events in BAEC are the findings that both RGD-containing peptides and antibodies directed against integrins inhibit BAEC attachment *and* spreading, while antibodies directed against LB69 as well as YIGSR-containing peptides *only* affect BAEC spreading. In addition, selective disorganization of β1 integrins (but not LB69) is noted following RGD-containing peptide inhibition of BAEC sheet migration on a laminin substrate [9,11]. Although there is matrix-driven reorganization of endothelial cell surface integrins, recent studies have demonstrated that there are no changes in the sizes of cell surface pools of β1 or β3 integrins [12]. However, in contrast to the effects of extracellular matrix components, selected soluble factors (TGF-β1 and PDGF) were observed to modulate (increase) sizes of cell surface pools of BAEC β1 or β3 integrins and bovine aortic smooth muscle cells (BASMC) β3 integrins but do not alter integrin organization in these two cell types in vitro [12]. These data suggest a complex modulation of vascular cell behavior occurring, in part, through a coordination of soluble factor and extracellular matrix protein regulation of integrin expression and organization and extracellular matrix component synthesis (Fig. 1) [11–13].

BAEC have also been found to be sensitive to a variety of soluble factors, including those obtained from platelet releasates as well as autocrine factors such as angiotensin II [3,14]. In the past, several investigators have demonstrated effects on motility, proliferation, morphology, and surface protein expression when large vessel endothelial cells have been incubated with a variety of soluble factors, including PDGF, TGF-β1, serotonin, histamine, and a variety of cytokines [3,15–20]. In our studies, the soluble factors angiotensin II, histamine, serotonin, norepinephrine, PDGF, and TGF-β1 were all found to decrease BAEC sheet migration while having markedly different effects on BAEC proliferation [3,14] (Fig. 2). In addition, inhibition of proliferation with mitomycin C treatment did not alter the effects of these added factors, consistent with the concept that the processes of migration and proliferation are not linked [3]. It is important to recognize that platelets are not the sole cellular source for any of these factors, and it is conceivable that in vivo the physiologic sources for these factors may be non-platelet mesenchymal or circulating cells as well as the resident vascular cells themselves.

In addition to the pivotal roles thought to be played by the overlying endothelial cells in modulating the response to vascular injury and repair, medial smooth muscle cells also have important roles in modulating response to injury. Their response is one of migration from the media into the intima, where they proliferate and synthesize extracellular matrix. This response (driven by mononuclear cells, platelet factors, loss of overlying endothelial cells, and autocrine/paracrine factors produced by the smooth muscle cells themselves as well as by dysfunctional endothelium at or near the site of injury) is thought to lead to intimal thickening and ultimately to atherosclerosis [2,19]. Vascular smooth muscle cell migration and prolifera-

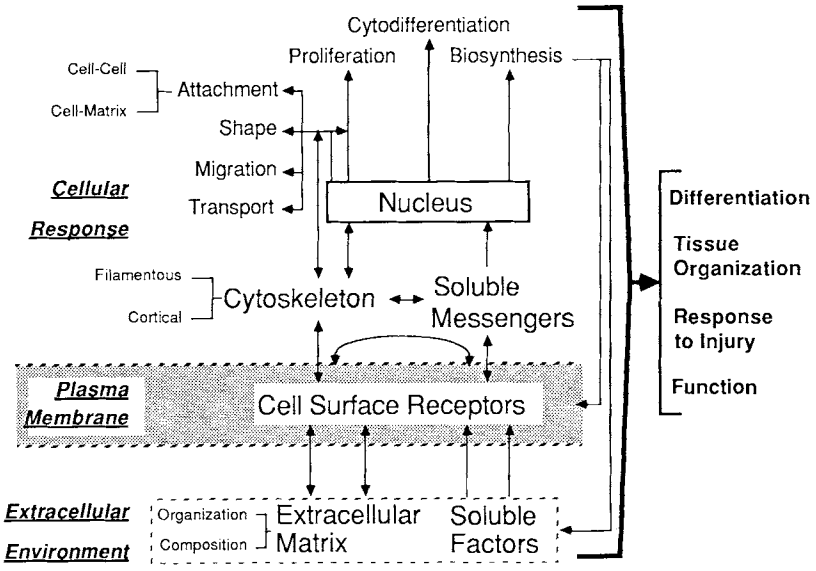

Fig. 1. General schematic representation of vascular cell-matrix-soluble factor interactions illustrating how information resident in the composition and organization of the extracellular matrix and soluble factors (such as TGF-β1 and TGF-β2) could be transduced into the interior of the cell. Cell surface matrix receptors (integrin and non-integrin) could be organized by the matrix and would in turn organize the cortical and filamentous cytoskeleton and/or initiate production of soluble second messengers. The ability of cells continually to respond to and modify the matrix and secrete soluble factors would allow for a flexible, coordinated cellular behavior resulting in a complex, dynamic response to injury. (Reproduced from Madri et al. [5], with permission of Raven Press.)

tion are modulated, in part, by the composition of the surrounding extracellular matrix and soluble factors (histamine, serotonin, norepinephrine, angiotensin II, PDGF, and TGF-β) [3,21]. In our studies, the platelet factors histamine, serotonin, norepinephrine, PDGF, and TGF-β1, as well as angiotensin II, all increase aortic medial smooth muscle cell migration while having markedly different effects on proliferation (Fig. 2). In addition, as noted in experiments using BAEC, inhibition of proliferation with mitomycin C treatment did not alter the effects of these added factors, supporting the concept that the processes of migration and proliferation are not linked [3]. Further studies have revealed that, in addition to increasing BASMC migratory rate, TGF-β1 treatment increases fibronectin mRNA and protein levels in confluent and migrating BASMC cultures and that TGF-β1 and PDGF treatment of cultured BASMC elicits an increase in the pool size of β3 integrins, supporting the concept that TGF-β1 may be eliciting its effects on migration, in part, via the selective modulation of matrix component(s) and cell surface matrix receptors, including the integrins [1,12].

Thus it appears that selected matrix components (fibronectin) and soluble factors (TGF-β1) elicit different effects in aortic endothelial and smooth muscle cells, *enhancing migration* in one case (BASMC) while *inhibiting migration* in another (BAEC), which may, in part, lead to the development of atherosclerotic lesions. In addition, TGF-β1 appears to be having its effects on these vascular cells, in part, by modulating the matrix synthetic profile of the cells, eliciting increases in fibronectin mRNA and protein levels in both aortic endothelial and smooth muscle cells as well as by selectively modulating the sizes of surface pools of β1 and β3 integrins in these cell types [9,12,13].

Ongoing studies investigating possible mechanisms by which extracellular matrix components and soluble factors (transforming growth factor β1 and angiotensin II) mediate changes in BAEC migratory behavior have revealed that both matrix composition *and* soluble factors modulate levels of BAEC plasminogen activator and plasminogen activator inhibitor-1. These data suggest that changes in this protease–protease inhibitor system may also play a role in modulating migratory behavior. Specifically, plasminogen activator activity levels are *decreased* by TGF-β1 treatment (which inhibits BAEC migration) and *increased* when the angiotensin II antagonist saralasin is used or when angiotensin II levels are decreased by inhibiting angiotensin converting enzyme using lisinopril

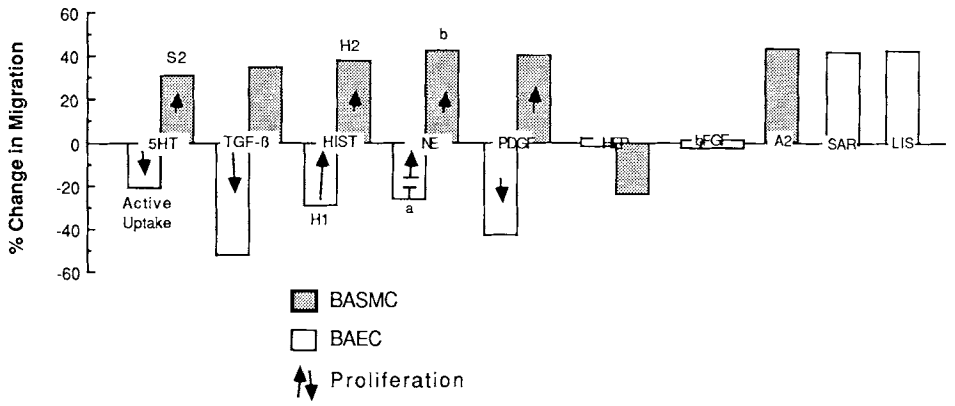

Fig. 2. Relative changes in migration rates of bovine aortic endothelial cells (BAEC) and bovine aortic smooth muscle cells (BASMC) cultured on type I collagen and treated with serotonin (5HT), transforming growth factor β1 (TGF-β), histamine (HIST), norepinephrine (NE), platelet-derived growth factor (PDGF), heparin (HEP), basic fibroblast growth factor (bFGF), or endogenous (BAEC) or exogenous (BASMC) angiotensin II (A2). All the tested factors except heparin and basic fibroblast growth factor decreased BAEC migration rates and increased BASMC migration rates. Heparin and basic fibroblast growth factor had no observable effect on BAEC migration, but heparin was observed to decrease BASMC migration. The activities of these factors was dose dependent and specifically blocked by antagonists or blockers. In BAEC cultures diphenhydramine (H2 receptor specific) blocked the HIST effect; imipramine (an uptake inhibitor) blocked the 5HT effect; phenoxybenzamine (a β blocker) blocked the NE effect; saralasin (an A2 antagonist) and lisinopril (an inhibitor of angiotensin converting enzyme) increased BAEC migration. In BASMC cultures cimetidine (H1 receptor specific) blocked the HIST effect; ketanserin (S2 receptor specific) blocked the 5HT effect; propanolol (an α blocker) blocked the NE effect; saralasin (an A2 antagonist) blocked the A2 effect. All factors manifested their effects on cell migration independently of their effects on cell proliferation. (Reproduced from Bell and Madri [3], with permission of the American Heart Association Scientific Publications Department.)

(which increases BAEC migration) [3,14]. In contrast to BAEC, BASMC plasminogen activator levels are *increased* in response to TGF-β1 (which increases migration) and *decreased* in cells treated with the angiotensin antagonist saralasin (which decreases migration) [3,14]. These data are consistent with the concept that modulation of vascular cell migratory behavior is complex and involves several mechanisms, including protease–protease inhibitor systems, changes in selected matrix component synthesis and organization, changes in expression and organization of cell surface matrix binding proteins (integrins and non-integrins), and cytoskeletal reorganization [1,5,9,11,12,13,22,23].

While useful, in vitro models of vascular cell injury may not closely mimic the in vivo situation. Therefore we have employed an in vivo model of large vessel denudation injury in our studies of vascular injury and repair. We have found that in a rat carotid balloon de-endothelialization model, in which there is incomplete re-endothelialization of the de-endothelialized area, there is increased fibronectin and TGF-β staining throughout the media and luminal surface of the chronically de-endothelialized region of the vessel [13]. These in vivo findings correlate well with in vitro studies in which BAEC migration on a type I collagen coating was *inhibited* and BASMC migration was *enhanced* by 1) addition of soluble fibronectin to the culture media, 2) coatings of increasing fibronectin concentration, and 3) TGF-β1 treatment of migrating cells in which there is a significant increase in fibronectin mRNA and protein levels [1]. Thus, both in vivo and in vitro, the composition of the existing and newly synthesized underlying extracellular matrix as well as the presence of soluble factors appear to have profound effects on the migratory abilities of large vessel endothelial and medial smooth muscle cells. Further studies using this in vivo model have revealed distinct differences in the localizational patterns of β1 or β3 integrins in the neointimal and luminal regions of both the chronically de-endothelialized and the re-endothelialized areas [12]. Specifically, in the chronically de-endothelialized area neointimal smooth muscle cells exhibited increased staining for β3 integrins but no changes in β1 integrins compared with normal and post-injury medial smooth muscle cells, while in the re-endothelialized area the neointimal smooth muscle cells nearer the lumen displayed less intense staining for β3 integrins (as well as for fibrinogen) than those deeper in the neointima [12]. These observations support the well-ac-

cepted concept of endothelial cell modulation of smooth muscle phenotype. These observations are consistent with the effects of TGF-β1 and PDGF on BASMC noted in vitro.

MATRIX COMPOSITION, ORGANIZATION, AND SOLUBLE FACTORS: MODULATORS OF MICROVASCULAR ENDOTHELIAL CELL DIFFERENTIATION IN VITRO

While large vessel endothelial cells undergo sheet migration in response to denudation injury, microvascular endothelial cells respond to injury by disrupting their investing basement membranes, migrating into and proliferating in the surrounding three-dimensional interstitial stroma, forming new microvessels, stabilizing them, and ultimately dismantling the newly formed microvascular bed following the conclusion of the repair response [24]. In studying the complex process of angiogenesis and microvascular endothelial cell differentiation, we have employed several in vitro culture systems [22,23, 25,26], including the culture of microvascular endothelial cells from the rat epididymal fat pad and bovine calf adrenal cortex *on* selected extracellular matrix components in two-dimensional culture, *on* the interstitial and basement membrane aspects of the amnion, and *in* three-dimensional type I collagen gels. Under all conditions studied, these microvascular endothelial cells retain von Willebrand factor positivity. When microvascular endothelial cells are placed in culture, they are removed from their three-dimensional environment where they have a significant arc of curvature and intimate associations with specific matrix basement membrane components and pericytes and placed in a two-dimensional environment in which they have no arc of curvature, dramatically different associations with the substratum, and no contacts or associations with pericytes. This change in environment contributes, in part, to the loss of their differentiated phenotype in culture. Placing these cells on basement membrane components or pre-existing basement membranes (amnion) elicits the return of a more differentiated phenotype, namely, tube formation with tight junctions and luminal and abluminal plasma membrane specializations [4,5,9,22–28]. In contrast, placement on the interstitial aspect of the amnion elicits a high proliferative rate, migration *into* the three-dimensional stroma, and ultimately formation of tube-like structures having junctional complexes and abluminal basal lamina formation [9,22]. Placement on interstitial collagen types I or III causes these cells to lose their tight junctions and ZO1 staining and to begin to express α-smooth muscle actin mRNA and protein and PDGF receptor protein and responsiveness, while still retaining their von Willebrand factor staining. These changes are consistent with a modulation of phenotype, driven, in part, by the composition and organization of the extracellular matrix [1,5,9,22,27,28]. Furthermore, when microvascular endothelial cells cultured on coatings of interstitial collagens are treated with TGF-β1, there is an eightfold induction of α-smooth muscle actin mRNA and a dramatic inhibition of proliferation, further supporting the concept that under certain conditions microvascular endothelial cells can be induced to exhibit smooth muscle/pericyte phenotypic features [1,5,27].

When microvascular endothelial cells are dispersed and cultured *in* a three-dimensional type I collagen gel their behavior, compared with that observed in two-dimensional culture systems, is quite different. In the presence of TGF-β1, TGF-β2, TGF-β3, or bFGF the cells organize into multicellular tube-like aggregates with lumina in a calcium-dependent process, form tight junctions between cell processes, and deposit an organized basal lamina abluminally [29]. Additionally, the cells no longer express α-smooth muscle actin mRNA or detectable protein and do not express PDGF receptor β chain or exhibit any proliferative response to any of the PDGF isoforms (see below), suggesting that the organization (architecture) of the surrounding matrix drives the cells to a differentiated endothelial phenotype having markedly different responses (and cell surface receptor repertoire) to cytokines produced during inflammatory, repair, and angiogenic processes.

Recently, when we re-examined microvascular endothelial cells grown *on* types I and IV collagen in two-dimensional culture and *in* a three-dimensional type I collagen gel using an antibody probe directed against the β chain of the PDGF receptor antibody in Western blot analyses, we found that microvascular endothelial cells cultured in the two-dimensional environment expressed the β chain of the PDGF receptor while cells cultured in the three-dimensional environment did not. Large vessel smooth muscle cells expressed this PDGF receptor chain under all the culture conditions used. In addition to finding this inducible receptor on the cell

surface, we demonstrated that microvascular endothelial cells were responsive to selected isoforms of PDGF when cultured in two-dimensional but not in three-dimensional culture. Namely, PDGF-BB elicited a dramatic increase in proliferation, while PDGF-AB caused a modest increase in proliferative rate and PDGF-AA had no effect on proliferation. No PDGF isoform had any effect on proliferation when tested on three-dimensional cultures (M. Marx, R. Perlmutter, and J.A. Madri, in preparation). These findings, together with our previous observations documenting the inducible presence of α-smooth muscle actin mRNA and protein in microvascular endothelial cells in two- but not three-dimensional cultures lend further support to the concept that microvascular endothelial cells may have the capacity to give rise to pericytes during the angiogenic process in response to particular stimuli, including extracellular matrix composition and organization (Fig. 3) [1,5,11,27].

CONCLUSIONS AND SPECULATION

In summary, it appears that specific extracellular matrix proteins elicit *organization* of integrin and non-integrin vascular cell surface matrix binding proteins and selected cytoskeletal elements while cytokines, such as PDGF and TGF-β1, modulate the *size* of surface membrane-associated vascular cell integrin pools, in addition to their effects on cytoskeletal organization and matrix synthesis and protease–protease inhibitor systems.

In an in vivo model of vascular endothelial and smooth muscle cell response to injury that results in incomplete re-endothelialization and intimal thickening following balloon catheter denudation of rat carotid artery, endothelial cells respond to the injury initially by migration and proliferation. However, following the acute platelet response, plasma fibronectin deposition and fibronectin synthesis by local vascular cells, secretion and activation of TGF-β1 by both endothelial and smooth muscle cells, endothelial cell

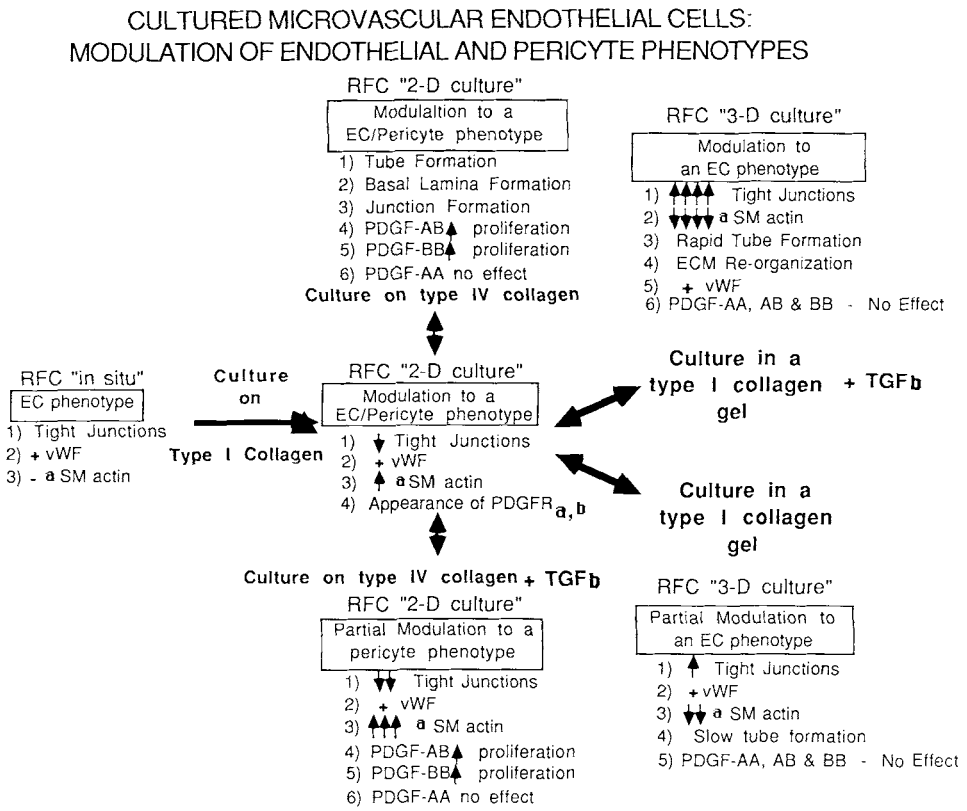

Fig. 3. Schematic representation of the modulation of microvascular endothelial cell phenotype mediated by changes in extracellular matrix (ECM) composition, organization, and soluble factors (TGF-β1). (*Reproduced with modification from Madri et al. [1,11], with permission of the publisher).*

migration/proliferation is inhibited, creating a chronically de-endothelialized region of vessel wall. In addition, the deposition of plasma fibronectin (as well as other plasma components such as fibrinogen and fibrin split products), the development of a platelet releasate, and the synthesis, secretion, and activation of TGF-β1 by both endothelial and smooth muscle cells stimulate medial smooth muscle cells to migrate to the area of injury, proliferate, synthesize, and deposit matrix components (such as fibronectin). These events further enhance smooth muscle cell migration into the injured area. Thus the complex interactions of particular vascular cell populations with surrounding and newly synthesized matrix components and a variety of cytokines elicit expression of "dysfunctional" phenotypes in local endothelial and smooth muscle cell populations that favor the development of arteriosclerosis (Fig. 4).

In contrast to large vessel vascular cells, the response of microvascular endothelial cells to changes in the *composition* and/or *organization* of the matrix is one of a reversible "change of phenotype." Namely, in three-dimensional culture microvascular endothelial cells (but not large vessel endothelial or smooth muscle cells) undergo an angiogenic response complete with tube formation [29]. However, in two-dimensional culture the same cells express cell surface receptors and cytoskeletal components and have responses to cytokines similar to those observed in vascular smooth muscle cells and/or pericytes [5]. Our in vitro data are consistent with the idea that the microvascular endothelial cell is capable of giving rise to pericytes, and, although our data suggest that the extracellular matrix may play an important role in this process in vivo, it is as yet not understood. Thus, like the large vessel endothelial and smooth muscle cells, the microvascular endothelial cell displays a "plastic" phenotype in response to injury, but, rather than the "dysfunctional" phenotypes displayed by the large vessel cells, the microvascular endothelial cell displays a variety of phenotypes normally observed in the microvasculature during development and in response to injury (Fig. 3).

Though still incomplete, our knowledge of how the extracellular matrix and soluble factors affect vascular cells is constantly growing. The mechanisms by which information is transduced across the cell membrane are complex, involving extracellular matrix, soluble factors, a

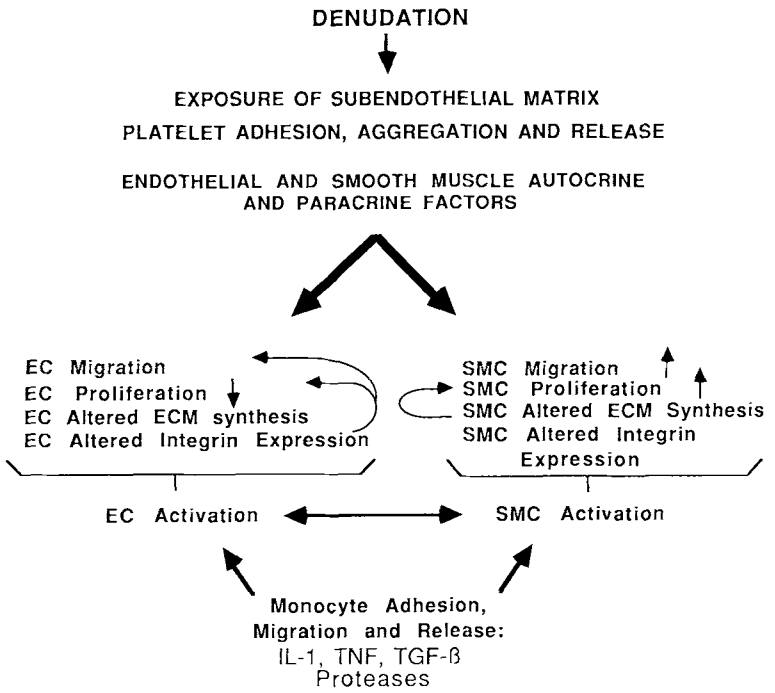

Fig. 4. Schematic representation of the modulation of medial smooth muscle cell (SMC) and endothelial cell (EC) behavior following denudation injury by soluble factors and extracellular matrix components. In this scheme, soluble factors elicit changes in matrix production and integrin expression, which in turn modulate cell migration and proliferation.

variety of matrix and soluble factor receptors, second messenger systems, and dynamic cytoskeletal organizations [1,5,11].

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