Kidney International, Vol. 51 (1997), pp. 1447–1453

Adhesion molecules in the glomerular mesangium

STEFAN GAUER, JIAN YAO, HARALD O. SCHOECKLMANN, and R. BERND STERZEL

Medizinische Klinik IV, Friedrich-Alexander Universität Erlangen-Nürnberg, Erlangen, Germany

Adhesion molecules in the glomerular mesangium. Experimental evidence indicates that extensive "cross-talk" exists between glomerular cells, extracellular matrix molecules and soluble mediator substances affecting the proliferative and secretory phenotype of glomerular mesangial cells. Both matrix and cytokines regulate mesangial cell behavior *in vitro* and *in vivo* after binding to specific cell surface receptors. It appears as if the concerted action of insoluble and soluble ligands on mesangial cells involves a reciprocal regulation of matrix molecules and cytokines as well as expression and affinity of their respective receptors. Elucidation of the potential biologic and clinical relevance of cell-matrix interactions in the glomerular mesangium represents a challenging goal in current kidney research. This brief review summarizes recent investigations concerning regulation of expression and function of adhesion molecules and matrix receptors in the mesangium. In addition to results from cell culture studies, descriptive findings on expression and regulation of adhesion molecules and their potential role for altered mesangial cell behavior in glomerular disease is considered.

The mesangium represents a specialized pericapillary tissue in the glomerulus. It consists of non-polarized, contractile, myofibroblast-like mesangial cells (MCs) and extracellular matrix (ECM). In the normal adult mammalian glomerulus, the mesangial space is mostly restricted to an axial or centrolobular position (Fig. 1).

However, in some parts of the glomerulus, MCs surround the circumference of capillaries [1]. This is in keeping with the concept that contractile, pericapillary MCs contribute to the regulation of the glomerular microcirculation and ultrafiltration. Structure and function of the mesangium have been reviewed [2–6]. This article attempts to summarize the available information on adhesion of MCs to ECM components, emphasizing findings on function and modulation of ECM adhesion receptors. The role of cell-cell adhesion in MC interactions with other cells (endothelial or inflammatory cells) has been the subject of recent reviews [7, 8] and will not be discussed here. Table 1 lists the main functional properties of MCs and the mesangium. All of them require to a larger or smaller extent interactions of MCs with ECM and with other cells. This is particularly obvious with respect to mesangial support and maintenance of the capillary tuft architecture.

Lobular disintegration of the mesangium with mesangial cell detachment and death (so-called mesangiolysis) is found in certain types of human glomerular disease and in experimental glomerulopathies [5, 9]. Mesangiolysis leads to aneurysms of the glomerular capillaries and loss of their lobular arrangement. As holds for all anchorage-dependent cells [10–13], adhesion of MCs to the surrounding ECM is a prerequisite for many functions and properties, including contraction and migration as well as survival, proliferation and expression of a differentiated phenotype [2, 3, 14–16].

MC adhesion molecules

Cell adhesion and other interactions of cells with components of the ECM are mediated by specific cell surface receptors, of which integrins are the most abundant. Integrins constitute a family of heterodimeric transmembrane glycoproteins consisting of non-covalently associated α and β subunits that both bind to ECM ligands and are linked to cytoskeletal elements [10, 13]. The β_1 subunit family of integrins has been shown to be most relevant for binding of cells to various components of the underlying or surrounding ECM. Studies of glomeruli in kidney tissue sections and of MCs in culture have confirmed that glomerular MCs as well as endothelial and visceral epithelial cells express multiple integrins (Table 2) [2, 3, 7, 8, 15–21].

This list of adhesion receptors is likely to grow once new integrins become identified. At present, the dominant α chains expressed by human and rat MCs are α_1, α_3, α_5, α_8, and α_v. These MC surface receptors can bind to and interact with a variety of ligands, some of which are listed in Table 3.

The number and diversity of ligands which can interact with one or more integrins is large and growing [10, 12, 13]. Besides many ECM components and cell surface proteins, pathogenic ligands have been identified, including bacterial and viral proteins [12]. It is presently unknown whether such exogenous ligands interact with MC integrins and are of relevance *in vivo*. Of conceptual interest are the so-called disintegrins, which are short ligands for integrins and appear to act as competitive inhibitors of ligand-integrin binding [12, 22]. First found in snake venoms, a number of endogenous soluble and cell surface disintegrins have been identified that may play a role in the physiologic or pathogenic regulation of cell-ECM interactions. However, their potential relevance in the mesangium is presently unclear.

β_1 integrins connect the ECM with the cytoskeleton and provide a mechanical or physical linkage. As receptors, they also transmit information from the ECM context into the cell and are involved in ECM-controlled signaling events that modulate multiple cellular functions. Conceptually, one can distinguish adhesion-related functions of integrins (including cell anchorage, development and organization of tissues, contraction and migration) from functions that induce cellular changes due to non-adhesion-dependent signaling initiated by ligand-integrin binding (Table 4). The latter includes induction of expression and/or

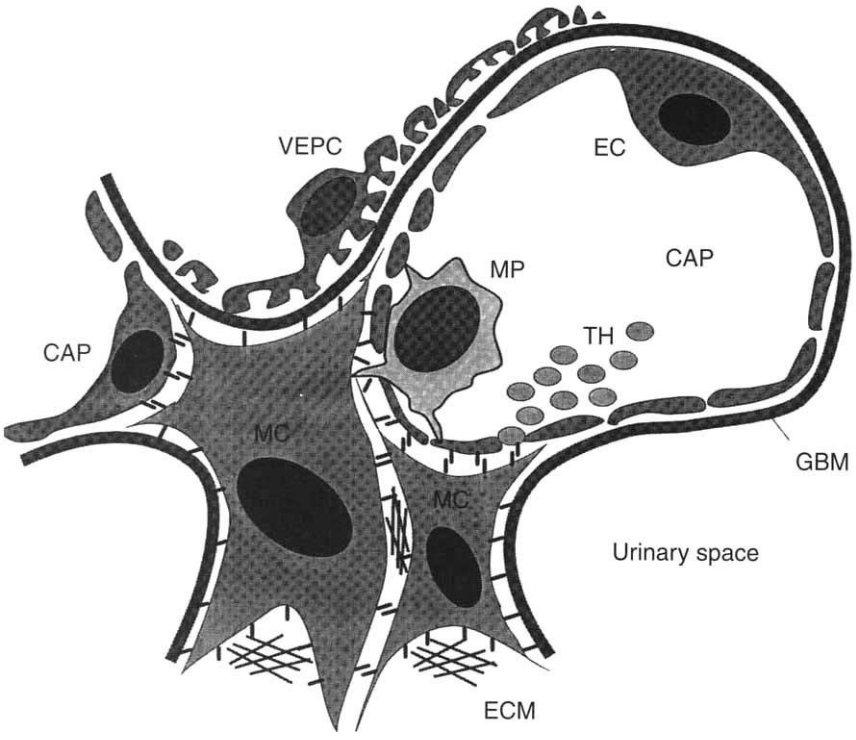

Fig. 1. *Schematic structure of mammalian glomerular capillary (CAP) lobule.* Abbreviations are: EC, endothelial cell; MC, mesangial cell; VEPC, visceral epithelial cell; MP, macrophage; TH, thrombocytes; ECM, extracellular matrix consisting of mesangial matrix and glomerular basement membrane (GBM); adhesion molecules on MC surfaces connect with EC and ECM components and with MP and TH during inflammatory processes.

Table 1. Functional properties of mesangial cells

1. Structural support of glomerular capillary tuft
2. Contractility allowing modulation of glomerular microcirculation and ultrafiltration
3. Migration during embryonic development and reconstitution of injured glomeruli
4. Endocytosis/clearing function
5. Endothelium-like properties and functions
   - anti-thrombogenic properties
   - non-leukocyte adherent surface
   - source of vasoactive molecules
6. Response to local injury
   - MC proliferation
   - formation of soluble regulator molecules with autocrine and/or paracrine effects
   - formation, breakdown, remodeling of mesangial matrix and GBM
7. Interaction of activated MCs with immune complexes and immune cells

Table 2. Expression of adhesion molecules in glomerular cells[a]

	Mesangial	Endothelial	Epithelial
Integrins			
β_1	α_1	α_1	
	α_2	α_2	α_2
	α_3	α_3	α_3
	α_5	α_5	α_5
	α_8		
β_3	α_v		
Cell surface proteoglycans	Syndecan 4 CD44	Syndecan 1 CD44	
Selectins		path.: E-selectin	
Ig superfamily	path.: ICAM-1	path.: ICAM-1 path.: VCAM-1	VCAM-1 path.: ICAM-1 path.: ELAM-1

[a] path., expression found in diseased tissue or stimulated cells in culture

activation of other cell surface receptors, gene expression, cell differentiation, survival as well as assembly and disassembly of ECM [23–27]. Thus, ligation and activation of the various β_1 integrin adhesion receptors on MCs are likely to play a critical role in the regulation of the MC phenotype in culture and *in vivo*.

Besides β_1 and β_3 integrins, cell surface proteoglycans also function in the mediation of cell-matrix and cell-cell interactions [24, 28–30]. They include the syndecan family [28, 29] and the cell surface antigen CD 44 [31]. Expression of both types of molecules has been demonstrated on MCs (Table 3). The available information on fibroblasts and MCs indicates that they bind to various ligands and can serve as co-receptors modulating the expression and affinity of other cell surface receptors, such as β_1 integrins [28, 29].

Formation of focal adhesions by MCs

As anchorage-dependent cells, MCs form focal adhesions or focal contacts when plated on ECM substrata. Focal contacts allow cells to anchor to their environment (Fig. 2). They are transmembranous assemblies of multiple molecules, including extracellularly the ECM ligand and clusters of the transmembranous integrin receptors. Intracellularly, a submembranous plaque is formed containing a complex of cytoskeletal proteins, including paxillin, talin, α-actinin, tensin and vinculin. These and other components provide linkage to actin filament bundles, important for cell shape change, contraction and migration. Elements involved in signal transduction via β_1 integrins include α-actinin,

Table 3. ECM receptor expression in the mesangium[a]

Receptor	Ligands	Human		Rat	
		Tissue	Cells[b]	Tissue	Cells
β_1-integrins					
α_1	Col I, Col IV, LN	+	++	++	++
α_2	Col I, Col IV, LN	+	(+)	(+)	(+)
α_3	Col I, FN, LN	+	+	+	+
α_4	VCAM-1, LN, FN	–	–	–	–
α_5	FN, RGD	+	++	+	++
α_6	LN (E8 fragment)	–	–	–	–
α_7	LN	–	–	–	–
α_8	FN, others	+	+	+	++
β_3-integrin					
α_v	VN, FN, RGD, others	+	+	+	++
Cell surface proteoglycans					
Syndecan 4	FN, VN, LN	?	+	(+)	+
CD44	Hyal, Col, FN, LN	(+)	+	(+)	+

Abbreviations are: Col, collagen; LN, laminin; FN, fibronectin; VN, vitronectin; Hyal, hyaluronan.

[a] Detected by immunochemistry on normal kidney sections or in cultured mesangial cells

[b] Results dependent on the ECM substratum used for MC culture; see text for references

Table 4. Functions of adhesion molecules/ECM receptors

Cell adhesion-related functions ("physical linkage")
- cell anchorage
- tissue organization and maintenance
- embryogenesis and tissue remodeling/repair
- transmission of contractile forces to cytoskeleton/reorganization of actin microfilaments/contraction
- cell shape change
- dynamic alterations of adhesion (attachment/detachment):
  - mitosis
  - migration

Signal transduction ("chemical linkage")
- (co-) receptor function with stimulatory or inhibitory signals for:
  - expression, conformation and affinity of cell surface receptors, including adhesion molecules ("inside-out signals")
  - cell polarity
  - cell differentiation
  - cell proliferation
  - cell survival/apoptosis
  - ECM metabolism and assembly/disassembly

vinculin, talin, tensin, PKCα, Grb2, syndecan-4 and p125^{FAK} [23, 24]. MCs organize only those β_1 integrins into focal adhesions, which are used to interact with the underlying matrix molecules. On collagen I, MCs organize $\alpha_1\beta_1$, $\alpha_2\beta_1$ and $\alpha_3\beta_1$, on EHS laminin $\alpha_1\beta_1$ and $\alpha_3\beta_1$, on fibronectin $\alpha_3\beta_1$ and $\alpha_5\beta_1$ into focal contacts [32]. No evidence is currently available showing that the expression of the β_1 integrins is regulated by the underlying substrate at the level of gene transcription [32].

Although interaction of integrins with ECM ligands has to take place in order to induce their organization into focal adhesion sites, this process does not necessarily achieve and mediate cell adhesion. For example, the $\alpha_v\beta_3$ integrin is moved into MC focal adhesions on contact with fibronectin, although this is not required to mediate MC adhesion to fibronectin.

In the signal transduction cascade following MC adhesion and focal contact formation, the phosphotyrosine kinase p125^{FAK} seems to be of particular importance [26, 33]. p125^{FAK} is phosphorylated after binding of β_1, β_2 or β_3 integrins to their respective substrate. In MCs, it was shown that p125^{FAK} is phosphorylated after integrin clustering induced by exposure to various stimuli, such as ET-1 or thrombin [33, 34]. The effect of ET-1 is likely to be mediated via PKC activation, since treatment with staurosporine or calphostin C and prolonged pre-treatment with TPA antagonizes the phosphorylation of p125^{FAK} in response to ET-1. In contrast, p125^{FAK} phosphorylation can be stimulated in MCs by short-term treatment with TPA activating PKC.

Regulation of MC adhesion receptors

At present, there is very little information with respect to the regulation of MC adhesion receptors. It has been demonstrated that MC-ECM interactions via specific adhesion receptors occur in concert with effects of soluble regulators, such as cytokines, which also specifically bind to MC surface receptors and affect cell behavior. Indeed, expression and activation of β_1 integrins appear to be modulated by cytokines. For example, TGF-β has been shown to elevate the α_1, α_5 and β_1 chains at the mRNA and protein level in fibroblasts and glomerular cells [14, 18].

TGF-β is one of the most extensively studied cytokines in the regulation of ECM metabolism and has been shown to be an important mediator of ECM build-up in several chronic diseases, including glomerulosclerosis [35]. TGF-β stimulates the production of various matrix components, inhibits matrix degradation and modulates ECM receptors to increase cell adhesion. In cultured MCs, TGF-β induces the production of the matrix components laminin and collagen I, as well as $\alpha_1\beta_1$ and $\alpha_5\beta_1$ integrin mRNA and protein. It stimulates MC adhesion to collagen I and fibronectin. In isolated normal glomeruli, TGF-β was shown to stimulate synthesis of $\alpha_1\beta_1$ and $\alpha_5\beta_1$ integrins [18]. In an experimental model of mesangioproliferative disease, elevated glomerular expression of the α_1, α_5, and β_1 integrin chains correlated with the up-regulation of TGF-β_1 in the mesangium. Furthermore, accumulation of laminin, collagen, and fibronectin, that is, ligands for $\alpha_1\beta_1$ and $\alpha_5\beta_1$ integrins, was observed [18]. These data suggest that TGF-β induces increased glomerular β_1 integrin expression and augments MC-matrix interactions by up-regulating the expression of matrix receptors and of their ligands. The mechanism how TGF-β regulates the expression of individual integrin subunits is presently unclear. Results from other cell lines indicate that the expression of integrin subunits is differentially regulated by TGF-β. For instance, in rat alveolar epithelial cells TGF-β_1 increased expression of $\alpha_6\beta_1$, while expression of the $\alpha_3\beta_1$ receptor was decreased [36]. Thus, TGF-β may influence cell function and differentiaton by causing switches in the pattern of ECM receptors. Other cytokines such as bFGF, PDGF, or EGF have also been shown to modulate integrin expression in different cell types [37, 38]. Similarly, IL-1β, IFNγ and TNFα can elevate the expression of various receptors of cell-matrix and cell-cell adhesion [7, 8].

Since the involvement of these and other cytokines in glomerular inflammatory processes has been demonstrated in experimental disease models and in human pathology [3–5], it is conceivable that the effects of cytokines on glomerular cell behavior may be partly due to altered expression and activation of adhesion receptors. This could affect the MC phenotype, for

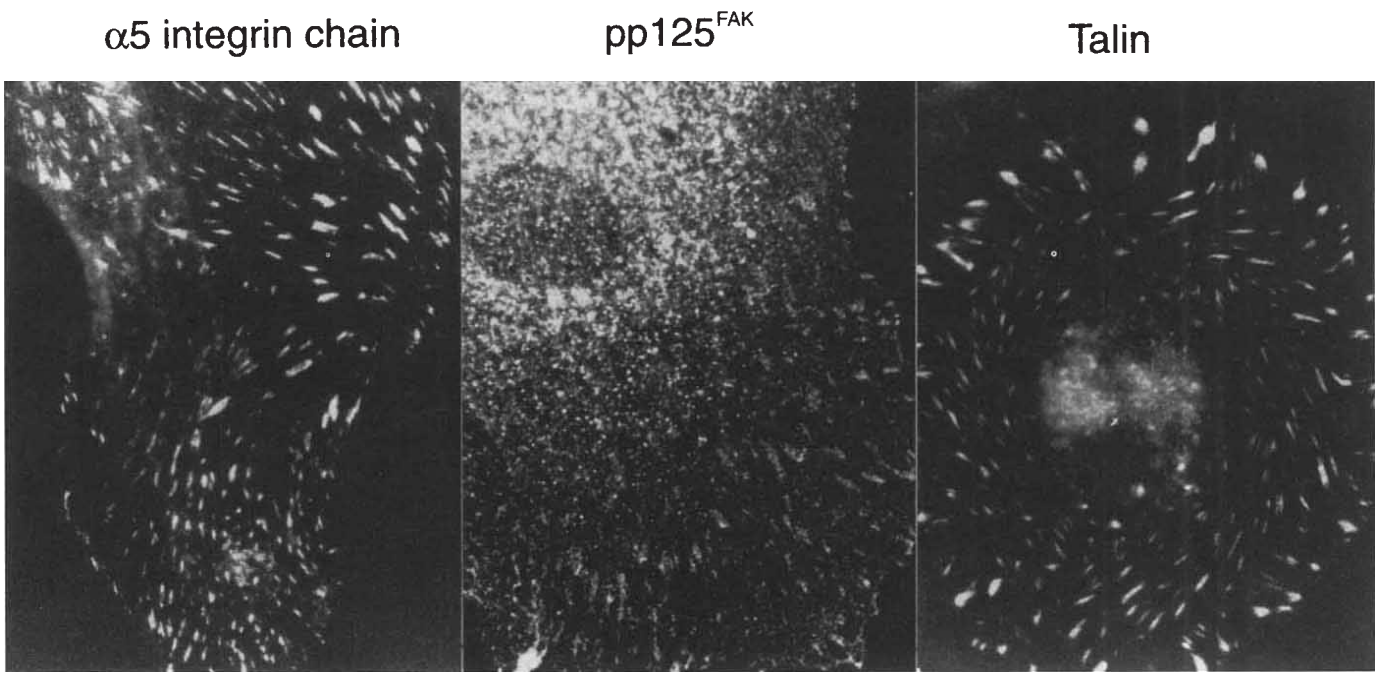

Fig. 2. *Immunocytochemical staining of focal adhesion components.* Human MCs were seeded onto fibronectin. After four hour adhesion time, MCs were stained with monoclonal antibodies to the α_5 integrin chain, focal adhesion kinase p125^{FAK} and talin. The microphotographs show that these components are localized in MC focal adhesions.

example with regards to cell proliferation, survival or apoptosis, as well as ECM assembly.

Besides soluble cytokines and growth factors, non-soluble ECM constituents can also affect localization and function of β_1 integrins [32]. This has been shown in various cell types grown on different ECM substrates, such as fibronectin, laminin and collagens. Based on these findings, it can be hypothesized that in glomerular disease when different ECM constituents are newly expressed, glomerular cells may also be induced to change their expression of adhesion receptors, allowing new kinds of MC-ECM interaction. Promoting further ECM production and assembly, this may be relevant for progressive mesangial ECM build-up and glomerular scarring. On the other hand, reduction or lack of physiologic ECM constituents may also lead to abnormal MC behavior, such as due to loss of tonic deactivating effects on the MC phenotype. In this context, recent findings are of interest which demonstrated that various glycosaminoglycans and proteoglycans can interfere with binding and adhesion of cells to ECM components. For example, the small dermatan sulfate proteoglycan, decorin, is able to inhibit fibroblast adhesion to several ECM proteins, including thrombospondin and fibronectin [39].

Since the heparan sulfate proteoglycan, perlecan, is a key constituent of the glomerular basement membrane and is also present in mesangial ECM, we explored whether it may act as a regulator for MC adhesion to ECM proteins in culture [21]. MCs readily attach to and spread on substrata containing fibronectin, laminin or collagens whereas they do not adhere to perlecan. Moreover, MC adhesion to fibronectin but not to laminin or collagen I was inhibited in a specific, dose-dependent fashion when perlecan was added to the substratum (Fig. 3).

Further experiments showed that perlecan exerted its anti-adhesive effects on MCs predominantly via a core protein-dependent mechanism that appeared to reduce the avidity of the fibronectin receptor, $\alpha_5\beta_1$ integrin. While induction of $\alpha_5\beta_1$ integrin organization into focal contacts was not impaired by

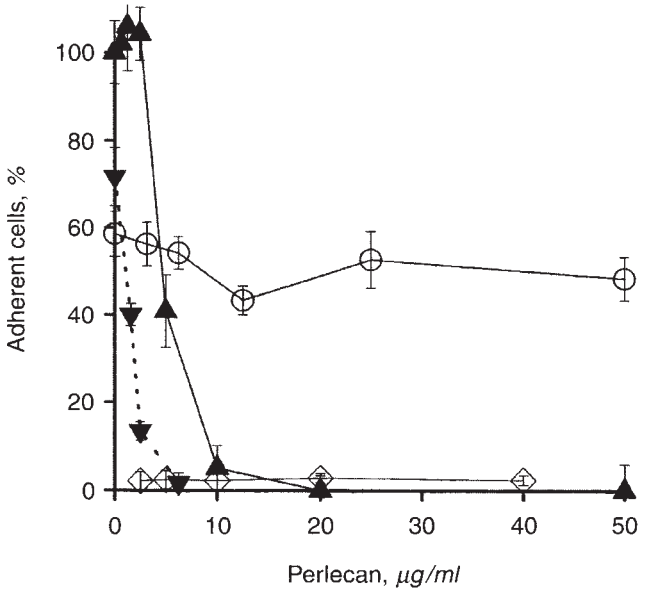

Fig. 3. *Perlecan specifically inhibits MC adhesion to fibronectin (FN; ▲) and to the 120 kDa cell-binding fragment of FN (▼).* Rat MCs were seeded onto culture dishes which had been coated with FN, laminin (LN; ○), or 120 kDa cell-binding fragment of FN. Uncoated culture plastic served as control (◇). Dishes were additionally coated with increasing concentrations of perlecan. Perlecan itself (◇) did not mediate MC adhesion (1 hr). Perlecan specifically inhibited the adhesion of MCs to FN and its 120 kDa fragment, but had no effect on the MC adhesion to LN.

perlecan, the resulting receptor avidity level seemed too low for mediating MC binding to and spreading on fibronectin [21]. These results are consistent with the concept that mesangial perlecan modulates the activating effects of fibronectin on the MC phenotype *in vivo*, thus contributing to the maintenance of the glomerular architecture. It remains to be elucidated whether perlecan down-regulates the affinity of the fibronectin-binding β_1 integrin in a direct or indirect fashion. Also, it is unclear whether loss of this anti-adhesive mechanism *in vivo* may facilitate fibronectin-induced MC proliferation and ECM increase in chronic glomerulopathies, where reduced perlecan abundance has been reported [40].

Regulation of MC proliferation by ECM

Growth of MCs is controlled by many soluble regulator molecules, including cytokines, growth factors, autacoids and hormones. Experimental evidence in different cell systems has revealed that the ECM components can also modulate the proliferative phenotype of MCs. *In vitro*, freshly seeded MCs do not only plate with higher efficiency on collagen types I, III and IV compared to plastic but may also show greater replication activity [41]. Thrombospondin (TSP) increases MC proliferation, an effect that might be mediated by up-regulation of EGF and PDGF secretion [42]. TSP has anti-adhesive effects on MCs in culture. Whether the decrease of MC-ECM attachment is related to the growth-promoting action of TSP is presently uncertain. Heparan sulfate was shown to dose-dependently inhibit MC proliferation in culture [43]. The inhibitory effect of perlecan on MC-fibronectin adhesion and its potential to modulate the MC phenotype has been discussed above. Also, proteoglycans are able to bind and sequester various cytokines. For example, bFGF as well as TGF-β strongly bind to heparan sulfate proteoglycans. Since bFGF has been reported to influence experimental kidney diseases, local storage could represent another regulatory function of glomerular proteoglycans. Morita and co-workers demonstrated that heparan sulfate proteoglycans show enrichment of bFGF-binding domains in fibrotic areas of glomeruli and peritubular interstitium [44]. Taken together, these reports demonstrate the ability of certain ECM molecules to bind and sequester growth factors, possibly providing a local "reservoir" of regulatory proteins and presenting them to adjacent cells in a biologically more active form. At present, however, the *in vivo* relevance of this notion is uncertain.

Considering the growth-regulatory potential of ECM for MCs, recent studies performed in fibroblasts are of interest which have explored the molecular basis of adhesion-dependent cell growth on the level of cell cycle regulation. Cell cycle progression is controlled by cyclin-dependent kinases (cdks), whose enzymatic activity activity is modulated by association with different cyclins, functioning as regulatory subunits. In mammalian cells, several classes of cyclins have been identified, which can associate with different cdk catalytic subunits [4, 45]. These include D-type cyclins (D1, D2, D3) and cyclin E which are involved in controlling G1 phase progression and entry into S phase. One major signaling event allowing progression through G1 phase is phosphorylation and inactivation of the retinoblastoma tumor suppressor protein [4, 45]. Zhu and coworkers demonstrated that adhesion of fibroblasts induces cyclin D1 mRNA and is required for activation of the cyclin E-cdk2 complex and subsequent phosphorylation of the retinoblastoma protein, an effect which is possibly mediated by down-regulation of the nuclear cdk inhibitor proteins, p21 and p27 [45]. Similarly, Fang et al showed that the cyclin E-cdk2 complex was activated in attached human fibroblasts but not in fibroblasts maintained in suspension. This lack of cyclin E-cdk2 activity in suspended cells appeared to result from an increased expression of cdk 2 inhibitors [46]. Taken together, these observations suggest a mechanism for anchorage-dependent cell growth that requires both, growth factors as well as an appropriate ECM context for the transit of cells through the G1 phase and entry into the S phase.

In addition to the requirement of cell anchorage for proliferation, the expression pattern of adhesion molecules may also directly influence cell cycle progression. For example, expression of integrin β_1C, an alternatively spliced variant of integrin β_1, inhibited growth of fibroblasts by blocking cell cycle progression in the late G1 phase, near the G1-S boundary [47]. Recent studies have provided new insight into MC growth control by soluble regulators. For example, TGF-β_1-induced cell cycle arrest in MCs involves inhibition of cdk2 activation and retinoblastoma protein phosphorylation [48]. Analogous studies are in progress to help clarify the nuclear signaling events which mediate ECM effects on MC survival and proliferation.

ECM and regulation of apoptosis of MCs

The abnormal mesangial ECM deposition and build-up in glomerular disease has been described in great detail [2, 3, 5, 16, 18, 35]. In contrast, few data exist concerning ECM involvement in repair mechanisms regulating recovery from injury and restoring structural and functional integrity of the glomerulus. A novel aspect concerning resolution of glomerular pathology points towards a possible role of MC-matrix interactions in the induction of cell removal by programmed cell death or apoptosis in the recovery phase of glomerulonephritic disease. Baker et al demonstrated MC apoptosis to be a major cell clearance mechanism counterbalancing cell division in self-limited anti-Thy 1.1 glomerulonephritis, thereby mediating decline of glomerular hypercellularity in experimental MC proliferation [49]. It has been shown in several cell types, including endothelial cells and epithelial cells, that loss of adhesion can induce apoptosis, an effect which is often abolished in tumor cells [11]. Recent data support the notion that apoptosis may be dependent on and regulated by the expression and signaling of distinct sets of cell adhesion molecules. For example, antibodies to β_1 integrins induced apoptosis in epithelial cells [50]. Moreover, Zhang et al found in CHO cells that expression of $\alpha_5\beta_1$ integrin but not of the closely related $\alpha_v\beta_1$ integrin, which binds fibronectin on the same RGD motif, appears to suppress apoptosis through the bcl-2 pathway [51]. Thus, it is conceivable that integrin-mediated signaling in MCs regulates cell survival or induction of apoptosis *in vivo* and may thereby contribute to glomerular repair processes.

Modulation of MC adhesion by nitric oxide

For survival and maintenance of structure and function, MCs depend on anchorage to ECM within the three-dimensional architecture of the glomerular capillary tuft. Detachment of various anchorage-dependent cell types has been shown to lead to apoptosis [11]. Recent investigations by Mühl, Brüne and Pfeilschifter [52] have demonstrated that donors of nitric oxide (NO) can induce apoptosis of rat MCs in culture. Moreover, it is known that the cytokine-inducible NO synthase can be expressed in MCs to produce large amounts of NO [53]. Interestingly, NO

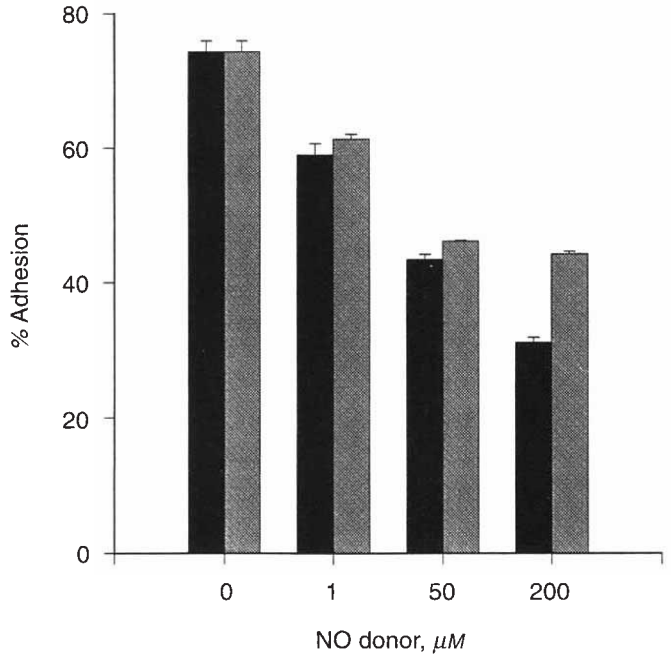

Fig. 4. *Effects of the NO donors SNAP and SNP on adhesion of rat MCs to collagen I.* MCs were seeded onto collagen I coated wells and incubated with the indicated concentrations of SNAP (■) and SNP (▨). Adherent cells were counted after one hour. After washing at one hour, the number of adherent cells was compared to the number of cells seeded and was expressed as percent adhesion (Yao et al, unpublished observations).

synthase inhibition with L-NMMA has been reported by Narita et al [9] to prevent early mesangiolysis in glomeruli of rats with anti-Thy 1.1 nephritis. Based on these different observations, we hypothesized that NO interferes with adhesion-related functions of ECM receptors in MCs. In the initial studies, we noted that various NO donors, including SNAP and SNP, inhibit rat MC adhesion and spreading on various substrata [54]. This anti-adhesive action of NO was most pronounced when MCs were seeded onto collagen I (Fig. 4), and was less obvious on fibronectin, laminin and collagen IV. The inhibitory effects were time and dose dependent. Importantly, cytotoxicity of the NO donors on MCs was negligible at the employed dosage and incubation time.

Additional experiments have shown that NO donors also cause rounding and detachment of adherent MCs. The precise mechanism involved in the observed anti-adhesive effect of NO on cultured MCs and its relevance for the regulation of the MC phenotype, such as for cell survival, proliferation, apoptosis and other adhesion-related functions, remain to be clarified. However, these *in vitro* findings support the hypothesis that local release of high NO concentrations might contribute to MC detachment and mesangiolysis *in vitro* [9].

In view of the remarkable abundance of adhesion molecules in MCs and because of MC embedding in ECM of varying composition in the normal or abnormal mesangium, the potential exists that the proliferative as well as apoptotic phenotype of MCs is greatly influenced by expression and activity of integrin receptors. It remains to be seen whether this concept is relevant for the regulation of MC behavior in glomerular development, maintenance and inflammation, and whether such processes of integrin-ligand interaction in the mesangium offer targets for experimental and, ultimately, therapeutic maneuvers.

Acknowledgments

Research data used for this article were obtained with the support of the Deutsche Forschungsgemeinschaft, Sonderforschungsbereich 263/B5. Dr. Jian Yao from the University of Nanjing, China is presently a research fellow funded by the Alexander von Humboldt-Stiftung, Bonn, Germany.

Reprint requests to R. Bernd Sterzel, M.D., Medizinische Klinik IV, Friedrich-Alexander Universität Erlangen-Nürnberg, Krankenhausstrasse 12, D-91054 Erlangen, Germany.

References

1. Inkyo-Haysaka K, Sakai T, Kobayashi N, Shirato I, Tomino T: Three dimensional analysis of the whole mesangium in the rat. *Kidney Int* 50:672–683, 1996
2. Sterzel RB, Schulze-Lohoff E, Weber M, Goodman SL: Interactions between glomerular mesangial cells, cytokines, and extracellular matrix. *J Am Soc Nephrol* 2(Suppl 1):S126–S131, 1992
3. Rupprecht HD, Schoecklmann HO, Sterzel RB: Cell-matrix interactions in the glomerular mesangium. *Kidney Int* 49:1575–1582, 1996
4. Schoecklmann HO, Rupprecht HD, Sterzel RB: Mesangial cell growth control in glomerular inflammation. *Proc R Coll Phys Edinb* 26:352–373, 1996
5. Kashgarian M, Sterzel RB: The pathobiology of the mesangium. *Kidney Int* 41:524–529, 1992
6. Mené P, Simonson MS, Dunn MJ: Physiology of the mesangial cell. *Physiol Rev* 69:1347–1424, 1989
7. Bruijn JA, de Heer E: Adhesion molecules in renal diseases. *Lab Invest* 72:387–394, 1995
8. Dal Canton A: Adhesion molecules in renal disease. *Kidney Int* 48:1687–1696, 1995
9. Narita I, Border WA, Ketteler M, Noble NA: Nitric oxide mediates immunologic injury to kidney mesangium in experimental glomerulonephritis. *Lab Invest* 72:17–24, 1995
10. Gumbiner BM: Cell adhesion: The molecular basis of tissue architecture and morphogenesis. *Cell* 84:345–357, 1996
11. Ruoslahti E, Reed JC: Anchorage dependence, integrins, and apoptosis. *Cell* 77:477–478, 1994
12. Haas TA, Plow EF: Integrin-ligand interactions: A year in review. *Curr Opin Cell Biol* 6:656–662, 1994
13. Hynes RO: Integrins: Versatility, modulation, and signaling in cell adhesion. *Cell* 69:11–25, 1992
14. Ruoslahti E, Noble NA, Kagami S, Border WA: Integrins. *Kidney Int* 45(Suppl 44):S17–S22, 1994
15. Adler S: Integrin matrix receptors in renal injury. *Kidney Int* 45(Suppl 45):S86–S89, 1994
16. Cosio FG: Cell-matrix adhesion receptors: Relevance to glomerular pathology. *Am J Kid Dis* 20:294–305, 1992
17. Baraldi A, Furci L, Zambruno G, Rubbiani E, Annessi G, Lusvarghi E: Very late activation-3 integrin is the dominant beta 1-integrin on the glomerular capillary wall: An immunofluorescence study in nephrotic syndrome. *Nephron* 62:382–388, 1992
18. Kagami S, Border WA, Ruoslahti E, Noble NA: Coordinated expression of beta 1 integrins and transforming growth factor-beta-induced matrix proteins in glomerulonephritis. *Lab Invest* 69:68–76, 1993
19. Cosio FG, Sedmak DD, Nahman NSJ: Cellular receptors for matrix proteins in normal human kidney and human mesangial cells. *Kidney Int* 38:886–895, 1990
20. Baraldi A, Zambruno G, Furci L, Manca V, Vaschieri C, Lusvarghi E: Beta-1 integrins in the normal human glomerular capillary wall: An immunoelectron microscopy study. *Nephron* 66:295–301, 1994
21. Gauer S, Schulze-Lohoff E, Schleicher E, Sterzel RB: Glomerular basement membrane derived perlecan inhibits mesangial cell adhesion to fibronectin. *Eur J Cell Biol* 70:233–242, 1996

22. WESKAMP G, BLOBEL CP: A family of cellular proteins related to snake venom disintegrins. *Proc Natl Acad Sci USA* 91:2748–2751, 1996
23. CLARK EA, BRUGGE JS: Integrins and signal transduction pathways: The road taken. *Science* 268:233–239, 1995
24. COUCHMAN JR, WOODS A: Transmembrane signaling generated by cell-extracellular matrix interactions. *Kidney Int* 47(Suppl 49):S8–S11, 1995
25. SCHALLER MD, PARSONS JT, SIEGEL PM, DANKORT DL, HARDY WR, MULLER WJ: Focal adhesion kinase and associated proteins. *Curr Opin Cell Biol* 6:705–710, 1994
26. JULIANO RL, HASKILL S: Signal transduction from the extracellular matrix. *J Cell Biol* 120:577–585, 1993
27. MAKGOBA MW, BERNARD A, SANDERS ME: Cell adhesion/signalling: Biology and clinical applications. *Eur J Clin Invest* 22:443–453, 1992
28. WIGHT TN, KINSELLA MG, QWARNSTROM EE: The role of proteoglycans in cell adhesion, migration and proliferation. *Curr Opin Cell Biol* 4:793–801, 1992
29. WOODS A, COUCHMAN JR: Signaling from the matrix to the cytoskeleton: Role of cell surface proteoglycans in matrix assembly. *Kidney Int* 49(Suppl 54):64–67, 1996
30. YAMAGATA M, SUZUKI S, AKIYAMA SK, YAMADA KM, KIMATA K: Regulation of cell-substrate adhesion by proteoglycans immobilized on extracellular substrates. *J Biol Chem* 264:8012–8018, 1989
31. CHAUDHURY PR, KHONG TF, WILLIAMS JH, HAITES NE, WU B, SIMPSON JG, POWER DA: CD44 in glomerulonephritis: Expression in human renal biopsies, the Thy1.1 model, and by cultured mesangial cells. *Kidney Int* 50:272–281, 1996
32. PETERMANN A, FEES H, GRENZ H, GOODMAN SL, STERZEL RB: Polymerase chain reaction and focal contact formation indicate integrin expression in mesangial cells. *Kidney Int* 44:997–1005, 1993
33. TROYER DA, BOUTON A, BEDOLLA R, PADILLA R: Tyrosine phosphorylation of focal adhesion kinase (p125FAK): Regulation by cAMP and thrombin in mesangial cells. *J Am Soc Nephrol* 7:415–423, 1996
34. HANEDA M, KIKKAWA R, KOYA D, SHIKANO T, SUGIMOTO T, TOGAWA M, SHIGETA Y: Endothelin-1 stimulates tyrosine phosphorylation of p125 focal adhesion kinase in mesangial cells. *J Am Soc Nephrol* 6:1504–1510, 1995
35. BORDER WA, NOBLE NA: Transforming growth factor beta in tissue fibrosis. *N Engl J Med* 331:1286–1292, 1994
36. KUMAR NM, SIGURDSON SL, SHEPPARD D, LWEBUGA MUKASA JS: Differential modulation of integrin receptors and extracellular matrix laminin by transforming growth factor-beta 1 in rat alveolar epithelial cells. *Exp Cell Res* 221:385–394, 1995
37. KIRCHBERG K, LANGE TS, KLEIN EC, JUNGTAUBL H, HEINEN G, MEYER INGOLD W, SCHARFFETTER KOCHANEK K: Induction of beta 1 integrin synthesis by recombinant platelet-derived growth factor (PDGF-AB) correlates with an enhanced migratory response of human dermal fibroblasts to various extracellular matrix proteins. *Exp Cell Res* 220:29–35, 1995
38. FUJII K, DOUSAKA NAKAJIMA N, IMAMURA S: Epidermal growth factor enhancement of HSC-1 human cutaneous squamous carcinoma cell adhesion and migration on type I collagen involves selective up-regulation of alpha 2 beta 1 integrin expression. *Exp Cell Res* 216:261–272, 1995
39. WINNEMÖLLER M, SCHON P, VISCHER P, KRESSE H: Interactions between thrombospondin and the small proteoglycan decorin: Interference with cell attachment. *Eur J Cell Biol* 59:47–55, 1992
40. SCHLEICHER ED, OLGEMOLLER B: Glomerular changes in diabetes mellitus. *Eur J Clin Chem Clin Biochem* 30:635–640, 1992
41. SIMONSON MS, CULP LA, DUNN MJ: Rat mesangial cell-matrix interactions in culture. *Exp Cell Res* 184:484–498, 1989
42. MARINIDES GN, SUCHARD SJ, MOOKERJEE BK: Role of thrombospondin in mesangial cell growth: Possible existence of an autocrine feedback growth circuit. *Kidney Int* 46:350–357, 1994
43. GROGGEL GC, MARINIDES GN, HOVINGH P, HAMMOND E, LINKER A: Inhibition of rat mesangial cell growth by heparan sulfate. *Am J Physiol* 258:F259–F265, 1990
44. MORITA H, SHINZATO T, DAVID G, MIZUTANI A, HABUCHI H, FUJITA Y, ITO M, ASAI J, MAEDA K, KIMATA K: Basic fibroblast growth factor-binding domain of heparan sulfate in the human glomerulosclerosis and renal tubulointerstitial fibrosis. *Lab Invest* 71:528–535, 1994
45. ZHU K, OHTSUBO M, BÖHMER RM, ROBERTS JM, ASSOIAN RK: Adhesion-dependent cell cycle progression is linked to the expression of cyclin D1, activation of cyclin E-cdk2, and phosphorylation of the retinoblastoma protein. *J Cell Biol* 133:391–403, 1996
46. FANG F, OREND G, WATANABE N, HUNTER T, RUOSLAHTI E: Dependence of cyclin E-cdk2 kinase activity on cell anchorage. *Science* 271:499–502, 1996
47. MEREDITH JRJ, TAKADA Y, FORNARO M, LANGUINO LR, SCHWARTZ MA: Inhibition of cell cycle progression by the alternatively spliced integrin beta 1C. *Science* 269:1570–1572, 1996
48. SCHOECKLMANN HO, RUPPRECHT HD, ZAUNER I, STERZEL RB: TGFβ1 induced cell cycle arrest in renal mesangial cells involves inhibition of cyclin E-cdk 2 activation and retinoblastoma protein phosphorylation. *Kidney Int* (in press)
49. BAKER AJ, MOONEY A, HUGHES J, LOMBARDI D, JOHNSON RJ, SAVILL J: Mesangial cell apoptosis: The major mechanism for resolution of glomerular hypercellularity in experimental mesangial proliferative nephritis. *J Clin Invest* 94:2105–2116, 1994
50. BOUDREAU N, SYMPSON CJ, WERB Z, BISSELL MJ: Suppression of ICE and apoptosis in mammary epithelial cells by extracellular matrix. *Science* 267:891–893, 1996
51. ZHANG Z, VUORI K, REED JC, RUOSLAHTI E: The $\alpha 5\beta 1$ integrin supports survival of cells on fibronectin and upregulates bcl-2 expression. *Proc Natl Acad Sci USA* 92:6161–6165, 1995
52. MÜHL H, SANDAU K, BRÜNE B, BRINER V, PFEILSCHIFTER J: Nitric oxide donors induces apoptosis in glomerular mesangial cells, epithelial and endothelial cells. *Eur J Pharmacol* 317:137–149, 1996
53. PFEILSCHIFTER J: Does nitric oxide, an inflammatory mediator of glomerular mesangial cells, have a role in diabetic nephropathy? *Kidney Int* 51(Suppl):50–60, 1995
54. YAO J, GAUER S, SCHOECKLMANN HO, STERZEL RB: Nitric oxide inhibits glomerular mesangial cell adhesion to extracellular matrix and phosphorylation of focal adhesion kinase. (submitted for publication)