

former editor of *Cell* and *PLoS Biology* will provide a workshop on how to write a scientific paper.

Given the experience of the organizers with similar hands-on courses, both at MDIBL and elsewhere, we believe the training in this course will strengthen the research of participants, enhance their potential as future investigators, and effectively reach others. We are hopeful that graduates will also contribute to the teaching of mechanisms of fluid and electrolyte disturbances at our national medical centers. Fellows interested in taking the course and their fellowship directors can log on to the course website for further information: <http://www.mdibl.org/courses/renal08.shtml>.

Integrins and Matrix in the Glomerulus: Old Mysteries and New Insights

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The proper interaction of integrins with glomerular basement membrane (GBM) is essential for normal glomerulogenesis. In addition, there may be interactions more relevant to glomerular injury. Recent findings provide new insights into the nature and role of these interactions.

The role of the extracellular matrix (ECM) in kidney biology and disease has been the subject of vast numbers of studies. Indeed, the GBM is one of the classic models for studying basement membrane function and structure, in part because of its important role in glomerular disease. Thus, we know quite a lot about its components and receptors. For example, there are interesting shifts in expression of laminin and type IV collagen isoforms during maturation of the GBM.¹ Why might these changes in the constitution of the GBM be important? First, they reflect different functional requirements for the GBM as the glomerulus matures, related to ultrafiltration or protecting podocytes from potentially damaging agents in the circulation. Second, because integrin receptors for the ECM transduce signals to the inside of the cell upon interaction with their respective ECM ligands, the GBM must be viewed not only as a structural component of the glomerulus but also as information to the podocyte about its surroundings. Therefore, changes in the constitution of the GBM are likely to modulate signals trans-

duced into podocytes that conceivably effect gene expression, cytoskeletal assembly, and cellular metabolism.

These possibilities remain mostly speculative for the time being, however. For example, interactions between the GBM and its receptors, primarily members of the integrin family, are essential for podocyte foot process assembly. Mice carrying mutations in either $\alpha 3$ integrin or some isoforms of laminin and type IV collagen are unable either to assemble or to maintain foot processes.^{2–5} Sometimes these phenotypes are evident at birth; in other cases, they take time to manifest. The same is true of mutations in GBM-encoding genes in humans. It would follow from these observations that shifts in expression of laminin and type IV collagen isoforms lead to differences in signal transduction by integrins that modulate specific steps in foot process assembly. Although intriguing, there has yet to be any evidence for this possibility.

A study reported in this issue of *JASN* by Borza *et al.*⁶ brings renewed attention to the interactions of the GBM with integrins on podocytes. Using immortalized human podocytes, these authors show that a KRGDS motif located adjacent to the $\alpha 3$ NC1 domain of type IV collagen is ligand for $\alpha v\beta 3$ integrin. This is particularly interesting for two reasons. First, this motif is present only in $\alpha 3$ type IV collagen in humans and other primates but not in other mammals, including rodents. Did this motif confer a selective advantage during primate evolution? Second, KRGDS is a potential phosphorylation site for an extracellular kinase, GPBP, and perhaps other as-yet-unidentified kinases.⁷ Although Borza *et al.* did not examine KRGDS phosphorylation in this study, other reports suggested that phosphorylation of this RGD motif augments cell attachment and, conversely, that dephosphorylation decreases attachment. In considering the GBM as “an information pallet” for podocytes and endothelial cells, variable phosphorylation of these moieties adds an additional level of complexity beyond that provided by the differential gene expression of distinct isoforms of collagen and laminin.

The knockout of the $\alpha 3$ integrin gene in mice immediately indicated an important role for $\alpha 3\beta 1$ integrin in podocyte foot process assembly,⁴ and loss of $\alpha 1\beta 1$ integrin renders glomeruli more sensitive to injury.⁸ The role of other integrins expressed by podocytes remains more enigmatic. This is especially true of the αv -containing integrins, including $\alpha v\beta 3$ and $\alpha v\beta 5$. Much of the early work on these two integrins, using blocking antibodies, suggested their crucial role in basic processes of angiogenesis and vasculogenesis.⁹ Thus, it was a surprise when a portion of embryos with αv integrin null alleles underwent relatively normal embryogenesis and then succumbed to hemorrhage of major vessels (although the great majority die mid-gestation, probably as a result of placental defects).¹⁰ Importantly, because of possible functional redundancies among integrins, the lack of very early vascular abnormalities in the αv null embryos should not be interpreted to indicate that αv -containing integrins are not important in vascular development.

Where does this leave us in considering a role for αv -

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containing integrins in glomerular function? There has not been a detailed examination of kidneys in αv null mice or in conditional knockouts of the gene encoding αv integrin in any kidney lineages; therefore, it is possible some kidney defects have been missed. Conversely, much of the αv -containing integrin in the glomerulus is thought to be $\alpha v\beta 3$, and $\beta 3$ integrin null mice have relatively normal kidneys¹¹ that would argue against a developmental role for $\alpha v\beta 3$ in kidneys. Borza *et al.* also demonstrated that $\alpha 3\beta 1$ integrins bind the $\alpha 3$ NC1 collagen domain and transdominantly inhibit adhesion mediated by $\alpha v\beta 3$ integrin,¹² suggesting regulatory interplay between integrins on podocytes. In addition, some recent evidence posits an important role for $\alpha v\beta 3$ integrin in kidney injury.¹¹ It is known that GPI-linked urokinase-type plasminogen activator receptors (uPAR) interact with several integrins that modulate their ligand-binding activities.¹³ Wei *et al.*¹¹ showed that uPAR and $\alpha v\beta 3$ integrin co-localize in podocyte foot processes and that uPAR-deficient mice are resistant to LPS-induced foot process effacement. $\alpha v\beta 3$ integrin is among those that are modulated by uPAR, and activation of $\alpha v\beta 3$ integrin in glomeruli (engaged by an activation-specific antibody) is decreased in uPAR-deficient mice.¹³ Finally, expression of a constitutively active $\beta 3$ integrin in podocytes results in proteinuria.

Together, the studies of Borza *et al.* and Wei *et al.* now indicate a role for $\alpha v\beta 3$ integrin in glomerular disease and indicate a binding site for $\alpha v\beta 3$ integrin in the KRGDS motif of human and primate $\alpha 3$ type IV collagen. Although the latter study indicates a role for $\alpha v\beta 3$ in glomerular disease even in the absence of this motif in rodents, this does not preclude a role for the motif in modulating glomerular function in humans or from its having a role in human kidney disease. Further studies will need to examine the phosphorylation of this site in various models of glomerular disease and the effects of mutagenizing this site to prevent phosphorylation or integrin binding. Genetic studies in animals are difficult because this motif is not found in rodents. Perhaps immortalized human podocytes can be used as an *in vitro* model for additional studies.

DISCLOSURES

None.

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See related article, "Human Podocytes Adhere to the KRGDS Motif of the $\alpha 3\alpha 4\alpha 5$ Collagen IV Network," on pages 677–684.

Are Podocytes Passive or Provocative in Proteinuric Glomerular Pathology?

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Podocytes are highly specialized epithelial cells with unique structure and function that are essential to maintenance of the

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