A National Course for Renal Fellows: The Origins of Renal Physiology

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A national course endorsed by the American Society of Nephrology for renal fellows will be held annually at Mount Desert Island Biologic Laboratories (MDIBL) on the coast of Maine. The 1-wk course seeks to reconnect renal trainees with the origins of kidney physiology and a systems approach to mechanisms of homeostasis in electrolyte disorders.

What is the rationale for such a course? As renal research focuses increasingly on specific regulatory processes, single molecules, or clinical outcomes, renal fellows and future junior nephrologists are losing touch with fundamental concepts of homeostasis and classical experiments forming the foundations of nephrology. A solid grounding in renal physiology and its history can only enhance the perspective of new renal investigators, and such knowledge will enrich the subsequent teaching moment with new medical students and trainees in medicine.

Our 1-wk course in renal physiology and its history will be conducted at MDIBL in mid-September of each year, starting in 2008. There are openings for 30 renal fellows. The curriculum will consist of six different 1½-d modules. Each trainee will be assigned to participate in three of the six modules.

Topics for the modules include water homeostasis, salt homeostasis and secretion, collecting duct sodium balance, and proximal tubular function. In each module, classical experiments using well-established model systems will be combined with modern cellular and molecular techniques. For example, the collecting duct sodium balance module will monitor salt transport in toad urinary bladders mounted in Ussing chambers, by measuring the amiloride-sensitive short circuit current. Similar studies will be performed using cultured renal epithelial cells such as A6, in similar chambers. The response of the currents to exposure of the bladders to aldosterone, antidiuretic hormone, insulin, and other agents will be examined. These studies will be linked to functional studies of epithelial sodium channels expressed in *Xenopus* oocytes. Two electrode voltage-clamp experiments will examine channel function under a variety of conditions. Linking studies that regulate salt transport in whole epithelia to measurements of currents across the channels themselves will cement in participants an understanding of distal nephron salt homeostasis.

The modules involve a long workday (Sunday, Tuesday, or Thursday) during which a topic is introduced and participants perform experiments and begin to analyze data. The next day (Monday, Wednesday, or Friday), participants work for half a day and, after lunch, present their experiments to the group. Each module progresses through the week. The initial presentations (Monday after lunch) focus on introduction and some data, as well as suggested experiments for the next group in the module. The second presentations (Wednesday after lunch) build on the introduction provided in the first presentations, summarize the data from the first two groups, and suggest experiments for the final group in the module. The final presentations (Friday after lunch) summarize the week’s work in the module and suggest future experiments. By participating in these three “group lab meetings,” the fellows will learn from each other and will follow the progress of all modules, including those in which they are only observers.

Participants will be provided a syllabus that describes each module, including the rationale, overall approach, and scientific questions to be addressed. Methods to be used will be spelled out in detail, with appropriate diagrams, so that the trainees understand fully what they will be doing in the lab. Reprints of classic articles using the approaches in the module will also be included in the notebook, as well as an extensive bibliography. It is hoped these articles and references will help give participants access to the classic literature of nephrology. Senior, nationally prominent renal physiologists drawn from around the United States will lead each module. Aside from imparting effectively the perspective of their individual module, their close interaction with participants in the laboratory will help the fellows gain important perspectives on careers in nephrology. During the week, one or two eminent guest lecturers will also discuss the development of our understanding of areas such as glomerular filtration or tubular transport. Dr. Vivian Siegel, executive editor of *JASN*, editor-in-chief of *Disease Models and Mechanisms*, and
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. 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 transduced 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 α3 integrin or some isoforms of laminin and type IV collagen are unable either to assemble or to maintain foot processes. 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. 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 α3NC1 domain of type IV collagen is ligand for αvβ3 integrin. This is particularly interesting for two reasons. First, this motif is present only in α3 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? 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 α3 integrin gene in mice immediately indicated an important role for α3β1 integrin in podocyte foot process assembly, and loss of α1β1 integrin renders glomeruli more sensitive to injury. The role of other integrins expressed by podocytes remains more enigmatic. This is especially true of the αv-containing integrins, including αvβ3 and αvβ5. Much of the early work on these two integrins, using blocking antibodies, suggested their crucial role in basic processes of angiogenesis and vasculogenesis. 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 midgestation, probably as a result of placental defects). 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-