concentration is often only half the total urinary concentration of calcium, because of ligand binding. The EC_{50} for calcium of the human CaSR is approximately 5 to 6 mM at pH values in the range of human urine, 5.5 to 6.5,16 so expected concentrations of ionized calcium in urine would have only a weak effect to stimulate the CaSR unless pH were either much higher or much lower than the usual range. High ionic strength also decreases the sensitivity of the receptor.17

Although the effects of hypercalciuria to moderate urine volume or pH are not clearly evident in human calcium stone formers, a therapeutic modality that could stimulate urine acidification and increase urine volume would potentially be of benefit in patients with calcium stones, especially those with CaP stones, in whom a potentially destructive deposition of mineral in renal tubules exists as a result of urinary CaP supersaturation. There is no safe way to lower urine pH in these patients. Until such therapy exists, the use of increased fluid intake, low-salt diet, and thiazide remains the mainstay of preventive treatment.

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DISCLOSURES

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See related article, “The Calcium-Sensing Receptor Promotes Urinary Acidification to Prevent Nephrolithiasis,” on pages 1705–1713.

The SDF-1/CXCR4 Axis Is a Novel Driver of Vascular Development of the Glomerulus

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Spatial and temporal control of developing glomerular capillaries is complex and requires coordinated cross-talk between various cell types. Recent advances in our understanding of the processes that regulate glomerular morphogenesis reveal some
mediators are essential for the emerging tuft, particularly vascular endothelial growth factor (VEGF) and PDGF.1–4

In search of additional crucial mediators, Takabatake et al.5 examine the role of CXC chemokine ligand 12 (CXCL12; stromal cell–derived factor 1 [SDF-1]) and its receptor, CXCR4, in this issue of JASN. Traditional SDF-1 signaling is involved primarily in the homing of hematopoietic stem cells to their niche within the bone marrow and in hematopoietic stem cell quiescence. A role for SDF-1/CXCRI4 is also described for chemokinesis of T lymphocytes and monocytes, B cell development, cardiac and cerebellar development, and cancer stem cell migration.6 This study was triggered by a previous report, which analyzed mice deficient in SDF-1 or CXCR4 and the requirement for this ligand-receptor system in vascularization of the gastrointestinal tract.7 In their beautiful study, Takabatake et al.5 demonstrate the SDF-1/CXCRI4 axis is a novel and essential signaling system for blood vessel formation in the kidney, particularly within the glomerulus.

The significance of the SDF-1/CXCRI4 axis was investigated by expression analysis using embryonic kidney and conditional null mice for CXCRI4 and SDF-1, as well as endothelial and podocyte-specific CXCRI4 null mice. The authors first demonstrate that CXCRI4 and its ligand, SDF-1, exhibit similar spatial and temporal expression patterns and that SDF-1–secreting cells surround CXCRI4+ epithelial and endothelial structures. In the glomerulus, SDF-1–expressing podocytes are in close apposition to CXCRI4+ endothelial cells positioned within the vascular cleft in the S-phase of the developing glomerulus. Both conditional SDF-1 and CXCRI4 null mice exhibit defective blood vessel formation with disorganized patterning of renal vasculature and capillary ballooning of the glomerular tufts. For proving the observed phenotype is a direct signaling event from podocytes through SDF-1 secreted to endothelial cells, CXCRI4 expression was specifically inactivated in endothelial cells using Cre/lox technology; an identical glomerular phenotype was observed. In contrast, no apparent abnormalities were observed by deleting CXCRI4 specifically from podocytes. This finding suggests that SDF-1 produced by podocytes signals in a paracrine manner on endothelial cells.

How can these findings be integrated into the current knowledge of glomerular development? The recruitment of endothelial cells into the vascular cleft of the S-shaped body is mediated by the expression of angiogenic factors, which are released from early glomerular epithelial cells—the future podocytes—and parietal cells. VEGF is also essential for this process. A podocyte-specific deletion of VEGF results in small avascular glomeruli containing fully differentiated podocytes lacking endothelial cells.8 PDGF is a related growth factor of the cystine-knot family of signaling molecules. In PDGF-B–deficient mice, podocytes and endothelial cells differentiate normally, but mesangial cells are no longer recruited into the capillary convolute, resulting in capillary ballooning.2 These landmark experiments established a remarkable sequence of events whereby highly differentiated epithelia, the podocytes, recruit endothelial cells that in turn recruit stabilizing mesangial cells through PDGF-B, similar to the vascular wall where PDGF-B mediates pericyte recruitment and vascular stability.

As in PDGF-B–deficient mice, the abnormal glomeruli in CXCRI4 or SDF-1 null mice are characterized by glomerular capillary dilation or ballooning and decreased in-growth of mesangial cells. The glomerular phenotypes in both models are reminiscent of those observed in other genetically modified mice, in particular α3 integrin–deficient mice, and for the genes encoding the transcription factors Pod1, Lmx1b, and Foxc2, which are important for podocyte differentiation.9–11 These similar glomerular phenotypes, resulting from alterations in seemingly unrelated signaling pathways, suggest that a complex chain of events regulates glomerular development, whereby various interruptions result in similar downstream changes in pathology.

Besides such indirect interactions, recent studies on the role of SDF-1/CXCRI4 signaling in angiogenesis also suggest a more direct relationship between VEGF and other angiogenic factors. For example, VEGF, PDGF, and the angiopoietin-1 and CXCRI4/SDF-1 axis all are hypoxia responsive, and their expression is, in part, regulated by hypoxia-inducible factors, which are key drivers of angiogenesis.12–15 In addition, VEGF and SDF-1 induce angiogenesis in a synergistic manner,16 whereby SDF-1/CXCRI4 signaling induces VEGF expression through the phosphatidylinositol-3-kinase/Akt pathway in different cell types in vitro;17 however, it is still unclear whether and how SDF-1 and VEGF interact within the glomerulus. The study of Takabatake et al.5 does suggest that CXCRI4 signaling in podocytes is not required for VEGF production, given the absence of a phenotype in podocyte-specific CXCRI4 null mice.

Intriguing, after nephrogenesis is complete, podocytes continue to express SDF-1, even though endothelial cell proliferation and migration are low. VEGF expression also persists in mature podocytes and is important for maintaining normal glomerular capillaries or for glomerular endothelial regeneration after injury.18 Whether SDF-1 is also important for the maintenance of the glomerular structure still is unclear. SDF-1 expressed by mature podocytes might act not only on endothelial cells but also on other glomerular cells, such as parietal epithelial cells. Human progenitor cells from Bowman’s capsule, for example, demonstrate increased SDF-1–mediated migration and survival in vitro and in vivo.19 The latter study also reveals that, in addition to CXCRI4, a second SDF-1 receptor, CXCRI7,20 plays an essential role in SDF-1 bioactivity.

Many ontogenetic processes are recapitulated in response to injury. An understanding of the processes and crucial mediators of glomerular development, therefore, may provide new clues on how to stimulate glomerular regeneration after injury with the ultimate goal of establishing treatments for glomerular diseases that promote repair of the glomerular structure. Takabatake et al.5 establish a role for a novel mediator in vascular development of the glomerulus and provide more clues to reach this goal.

DISCLOSURES
None.
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A Novel Role for Nephrin in the Maintenance of Glomerular Structure

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The NF-κB family of transcription factors is a key mediator of the immune and inflammatory response to a diverse range of environmental and microbiological targets. The role of NF-κB extends beyond transcriptional control of the immune response, however; it is also involved in maintaining the structure and function of many tissues. To serve such a multitude of functions, NF-κB has developed the capacity to generate transcriptional responses that are both stimulus specific and cell specific. Because of this, NF-κB signaling is a paradigm in cell signaling research.

There are five proteins within the NF-κB group, which normally exist as homo- and heterodimers. The dimers are complexed with a member of the IκB complex, and is degraded. NF-κB signaling is a paradigm in cell signaling research.

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