have advanced disease and require such aggressive induction therapy. In a series published by Hogan et al., a 22% of patients in their cohort were treatment resistant largely as a consequence of advanced glomerular and interstitial scarring. Nephrologists must educate primary care physicians to recognize and quickly refer these patients. Second, if the antibody removal is useful, then it stands to reason that diminishing circulating B cells and therapy to reduce circulating ANCA titers may be of therapeutic advantage. A number of anecdotal experiences have been reported using rituximab or the anti-CD20 mAb that depletes B cells in ANCA small-vessel vasculitis. Many of these patients have had treatment-resistant disease. The use of this expensive therapy, although of potential interest, must be critically tested to determine whether it, too, can preserve normal glomeruli.

When the practicing physician confronts patients with ANCA small-vessel vasculitis and kidney injury that is complicated by life-threatening pulmonary hemorrhage, prompt induction of therapy with plasmapheresis is essential. On the basis of current reports, physicians should also add plasmapheresis to induction therapy in patients who have advanced renal insufficiency and dialysis dependence. The complications of this therapy, particularly the high mortality of plasmapheresis and oral cyclophosphamide, should limit this therapy only to dialysis patients with severe disease.

DISCLOSURES
None.

REFERENCES


See the related articles, “Randomized Trial of Plasma Exchange or High-Dosage Methylprednisolone as Adjunctive Therapy for Severe Renal Vasculitis,” on pages 2180–2188, and “Chances of Renal Recovery for Dialysis-Dependent ANCA-Associated Glomerulonephritis,” on pages 2189–2197.

Renin and Its Putative Receptor Remain Enigmas

Friedrich C. Luft
Medical Faculty of the Charité, Franz-Volhard Clinic, Max Delbrück Center for Molecular Medicine, Berlin, Germany


In this month’s issue of *JASN*, Takahasi et al. report that renin receptor blockade causes diabetic nephropathy to regress. The authors performed uninephrectomy in mice; induced diabetes with streptozotocin; and treated these mice with a prorenin receptor blocker (PPRB), an angiotensin converting enzyme (ACE) inhibitor, or vehicle. PPRB was nigh to curative, whereas ACE inhibition was solely ameliorative. This
report follows a series of publications from this group that comprises most remarkable findings rivaling those of Tigerstedt, Goldblatt, Braun-Menendez, Pickering, Helmer, and more recent giants in the renin-angiotensin system (RAS) field. I would not dare to challenge such a supposition lightly.

Luetscher et al. published a remarkable report more than 20 yr ago that an inactive form of renin, prorenin, was present in the plasma of patients with diabetes and target organ damage to levels that substantially exceeded those found in normal individuals. Furthermore, the high levels of prorenin were closely associated with the severity of diabetic complications. The findings were important because patients with diabetes have relatively low plasma renin activity, an indirect reflector of active renin. Furthermore, no one knew exactly what prorenin was. Luetscher et al. viewed it as an inactive zymogen that could be activated by acid. Sealey et al. demonstrated the existence of prorenin and activation by freezing. That group found salivary prorenin in normal, hypertensive, and anephric patients. Weinberger et al. found “renin-like” activity in 19 anephric patients. More recent observations indicating that patients with diabetes and low plasma renin activity benefit from ACE inhibition or AT1 receptor blockade, as well as the interesting finding that the mouse salivary gland renin gene (REN2) causes profound hypertension when transgenically introduced into the rat, give us pause for reflection.

Renin is a protease that consists of two homologous lobes. The cleft between the lobes contains the active site with two catalytic aspartic residues. Renin is monospecific and cleaves only angiotensinogen to generate angiotensin I (AngI). Prorenin circulates in the plasma in higher concentrations than renin. Prorenin is outfitted with a N-terminal propeptide that covers the enzymatic cleft of the molecule, rather like a trap door. Prorenin can be activated by proteolysis, cold temperature, or acid. Proteolysis occurs in vivo through the actions of kallikrein or other serine proteases. Renin that is released acutely from the juxtaglomerular apparatus is activated and ready to go, suggesting that an active storage form of renin exists. However, chronic stimulation results in the release of more prorenin than renin. The extrarenal sources of chronic prorenin release seem multiple, including ovaries, salivary glands, eyes, testes, adrenal glands, and mast cells. The relationship between prorenin and renin differs in various clinical conditions. A high plasma renin activity to prorenin ratio is seen in patients with Bartter syndrome, ACE inhibitor treatment, and cirrhosis. A low plasma renin activity to prorenin ratio, with occasionally astounding amounts of prorenin, is seen in low-renin hypertension, diabetes, late pregnancy, and patients with ovarian tumors.

Nguyen et al. first observed that renin binds to human mesangial cells in culture and caused these cells to express plasminogen activator inhibitor-1 as an AngII-independent effect. The significance of this became evident with the cloning of a (pro)renin receptor that binds both renin and prorenin. Receptor binding does not involve the enzymatically active site. Binding of prorenin to the renin receptor activates the molecule in a nonproteolytic manner. The catalytic angiotensinogen to AngI actions of the enzyme are increased four-fold with binding. Prorenin seems to bind to the receptor via the handle region of the prosent, thereby exposing the enzyme’s active site. Furthermore, the (pro)renin receptor complex is not internalized and signals even in the presence of losartan. Rapidly activated is the extracellular signal–regulated kinase 1/2 (ERK1/2), demonstrating the first AngII–independent actions of renin. Huang et al. pursuing in the same direction showed renin induces mesangial cells to produce TGF-β that in turn increases plasminogen activator inhibitor-1, fibronectin, and collagen. The group used small inhibitory RNA to show that the effect occurs through the putative (pro)renin receptor. In a follow-up study, the same group showed that the TGF-β1 expression is regulated by mitogen-activated protein kinases; an ERK1/2 blocker abrogated the effects.

The Ichihara group, responsible for this month’s report, gave us insight into how the renin receptor might work. The activation of prorenin was inhibited in endotoxin-induced uveitis by using a decoy peptide (PRRB) that corresponded to the handle region of prorenin. PRRB saved the eyes of the rats, suggesting that prorenin and renin receptor are pivotal to endotoxin-induced uveitis. The handle (prosegment) of prorenin hypothetically binds to the receptor and opens the enzyme cleavage site. The decoy prevents this binding. Thus, only prorenin could bind the renin receptor because only prorenin is outfitted with the prosegment handle. There is confusion as to this issue; Ichihara et al. interpreted the receptor as a prorenin receptor; Nguyen et al. have suggested that either prorenin or renin can bind to the receptor.

Ichihara et al. next reported that diabetic nephropathy could be inhibited by the administration of PRRB. In this remarkable study, PRRB produced a veritable cure of diabetic nephropathy, similar to the regression observed in the report of Ichihara’s group. The authors next reported that nonproteolytic activation of prorenin contributes to the development of cardiac fibrosis in spontaneously hypertensive rats (SHR), a genetic model of hypertension. Perhaps the most exciting publication by the group appeared in this journal 1 yr ago: PRRB in AT1 receptor gene–deficient mice practically cured diabetic nephropathy. In a very recent JASN report, Ichihara et al. also showed that SHR (sp) that are prone to stroke feature prorenin activation in the kidneys. The handle region was hypothesized to bind to sites in the kidney, thereby activating the molecule. Immunohistochemistry of an area adjacent to the handle region, termed the “gate region,” demonstrated that the majority of nonproteolytically activated prorenin was present in podocytes of the kidneys. Continuous subcutaneous administration of PRRB completely inhibited both nonproteolytic
activation of tissue prorenin and activation of tissue renin-angiotensin without affecting the circulating RAS or arterial pressure and significantly attenuated the development and progression of proteinuria and glomerulosclerosis. Their studies indicate that nonproteolytic activation of prorenin in glomeruli is critically involved in activation of the RAS in renal tissue, leading to renal damage in hypertensive animals. Amen to that! The authors also used prorenin receptor transgenic rats that overexpress the prorenin receptor. These rats developed proteinuria and glomerulosclerosis upon aging. Furthermore, mitogen-activated protein kinases stimulated through the renin receptor were activated in these animals. Expression of TGF-β1 was increased. ACE inhibitors did not help these animals much, despite a decrease in circulating AngII. These provocative findings gave the renin receptor a major role in aging.

The report by Ichihara’s group is fairly mild and refreshing stuff compared with the complexity of the previously reports. Here, heminephrectomized rats were made diabetic and glomerulosclerotic for up to 12 wk and then treated with ACE inhibition or PRRB. Would you care to guess which treatment was better? The data taken at face value indicate that the renin receptor is the greatest therapeutic drug target for cardiovascular disease identified in the past 100 yr. Are there flies in the ointment?

Is the (pro)renin receptor a prorenin receptor, or is that its main job? Burcklé and Bader recently reported on this issue. The prorenin receptor, correctly termed RR/ATP6ap2, seems to be a pivotal protein for survival. RR/ATP6ap2 is a single transmembrane domain protein with a large unglycosylated and hydrophobic N-terminal domain and a short cytoplasmic tail. RR/ATP6ap2 does not display domain homology, either with known protein families in general or with cell surface receptors in particular. Orthologs of RR/ATP6ap2 occur in vertebrates and invertebrates. The N-terminal part of the protein corresponding with the extracellular domain displays a high amino acid sequence identity exclusively in vertebrates. The C-terminal part of the protein is strikingly conserved in vertebrates and invertebrates, raising the proposal that the two domains might have a divergent evolutionary fate, namely a recently acquired renin binding capacity for the N-terminal domain and a more conserved ancestral function for the C-terminal domain. Burcklé and Bader attempted to generate mice that were deficient in RR/ATP6ap2 (and additional unpublished observations obtained by permission, M. Bader, 2006) and failed, suggesting an essential function of the protein in cell proliferation and differentiation. In other words, the “prorenin-receptor” job may be a trivial or side activity. We do not really know what this receptor does; however, it is surely of major importance to survival, clearly above and beyond prorenin.

Recently, Susic et al. were unable to substantiate the report by Ichihara in SHR in which osmotic minipumps were implanted subcutaneously. Susic et al. could not demonstrate any effect of prorenin blockade on myocardial collagen content, left ventricular function, and coronary and renal hemodynamics. Model and protocol differences can always be raised for interpretation; nonetheless, the failure does not inspire confidence. Finally, the reader will have noticed that I have used various terms for the receptor as taken from the literature. Is the receptor a renin receptor; a prorenin receptor; or a (pro)renin receptor, meaning both? Nguyen et al. indicated that the receptor responds to both renin and prorenin. The Ichihara group suggests that the receptor responds only to prorenin by the handle peptide region. Huang et al. showed a specific renin-based signal transduction. Our unpublished results show signaling when the receptor is exposed to either renin or prorenin. Were that the case, Ichihara’s handle model is probably incorrect or at least incomplete. Final agreement will require consensus; the term (pro)renin receptor has appeal if signaling by both the active renin and activatable prorenin is substantiated.

The implications of the work presented by the Ichihara group are profound and would surely stand muster next to the legionnaires of the RAS whom I mentioned previously. We and numerous other investigators have been scrambling to replicate their results. We have used the decoy peptide in cell-based systems and in animal models (transgenic and 2K1C) to no avail (unpublished data, D.N. Müller, 2007). Let us sincerely hope that the reason is related to our incompetence and technical failures rather than some other reason. Taken together, the data presented by this group would promise major advances in ameliorating cardiovascular disease. Flies are in the ointment? No problem—give us better ointments or better flies!

DISCLOSURES
None.

REFERENCES

See the related article, “Regression of Nephropathy Developed in Diabetes by (Pro)renin Receptor Blockade,” on pages 2054–2061.

Improving Outcomes from Acute Kidney Injury

Bruce A. Molitoris,* Adeera Levin,† David G. Warnock,‡ Michael Joannidis,§ Ravindra L. Mehta,¶ John A. Kellum,‖ Claudio Ronco,** and Sudhir Shah;†† on behalf of the Acute Kidney Injury Network

*Division of Nephrology, Indiana University School of Medicine, Indianapolis, Indiana; †Division of Nephrology, University of British Columbia, Vancouver, British Columbia, Canada; ‡Division of Nephrology, University of Alabama School of Medicine, Birmingham, Alabama; §Medical Intensive Care Research Unit, Department of Internal Medicine, Innsbruck Medical School, Innsbruck, Austria; **Division of Nephrology, University of California, San Diego, California; ††Departments of Critical Care Medicine and Medicine, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; ¶¶Department of Nephrology, San Bortolo Hospital, Vicenza, Italy; and ‖‖Division of Nephrology, University of Arkansas, Little Rock, Arkansas

Acute kidney injury is a common clinical problem that is defined by an abrupt increase in serum creatinine over 48 h resulting from injury or insult that causes a functional or structural change in the kidney. Recent epidemiologic studies demonstrate wide variation in causes and risk factors associated with acute kidney injury1–3 and increased hospital mortality that worsens when dialysis is required.1,2,4 Even minor short-term changes in serum creatinine are associated with increased mortality.5–9 Other important consequences of acute kidney injury are progression of preexisting chronic kidney disease and development of end-stage renal disease.1,5–7

A major limitation in improving outcomes from acute kidney injury has been the lack of common standards for diagnosis and classification. Recognizing that future clinical research in acute kidney injury requires a multidisciplinary collaborative network of investigators, a group representing members from the Acute Dialysis Quality Initiative, nephrology, and critical care societies recently established the Acute Kidney Injury Network (AKIN). The purpose of this network is to facilitate international, interdisciplinary, and intersociety collaborations to ensure progress in the field of acute kidney injury. The fundamental goal is to improve best outcomes for patients who are at risk. The first AKIN conference, held in Amsterdam in September 2005, focused on the development of uniform standards for definition and classification of acute kidney injury. Although the complete report is published elsewhere, key elements are summarized here as recommendations.

First, there need to be uniform standards for definition and classification of acute kidney injury. Previous studies have used a variety of definitions, including change in serum creatinine, absolute levels of serum creatinine, changes in urine output or blood urea nitrogen, or need for dialysis.

The wide variation in definitions has made it difficult to compare information across studies and populations. AKIN’s diagnostic criteria for acute kidney injury include an abrupt (within 48 h) reduction in kidney function currently defined as an absolute increase in serum creatinine of ≥0.3 mg/dl (≥26.4 μmol/l), a percentage increase of ≥50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of <0.5 ml/kg per h for >6 h). These diagnostic criteria are based on the following considerations: The definition should depend on...