Novel therapeutic approaches for chronic kidney disease due to glomerular disorders


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Over the past 5 years, four studies published in Nature Medicine (4, 5, 11, 13) have identified novel mechanism-based therapies designed specifically for glomerular disease and CKD associated with proteinuria. These new mechanism-based strategies can be broadly divided into two categories: those that involve administration of novel therapeutic agents, and others that involve depletion of a pathogenic circulating protein. The unique feature of all of these therapeutic strategies is that they have been developed specifically to treat glomerular disease and are not merely existing agents that are repurposed to treat kidney disease.

Administration of Novel Therapeutic Agents

Recombinant mutated human angiopoietin-like 4. Angiopoietin-like 4 (Angptl4) is the first member of the circulating glomerulophilic proteome (6) in which all of Koch’s postulates have been fulfilled. This class of therapeutic agents was developed by Chugh and colleagues to manipulate novel physiological feedback loops identified by this group to a therapeutic advantage (2, 5, 6, 8). As part of the progression from proteinuria to nephrotic syndrome, the rise in the plasma free fatty acid (FFA) to albumin ratio due to asymmetric urinary loss of low FFA containing albumin beyond a threshold level promotes entry of FFA into skeletal muscle, adipose tissue and heart, followed by secretion of the soluble sialylated glycoprotein Angptl4 from these organs into the circulation. Angptl4 secreted in this manner has two major effects: In the capillaries of organs from where it is secreted, it inhibits the activity of lipoprotein lipase, an endothelium-bound enzyme that breaks down triglycerides to release FFA for uptake in these organs, causing reduced triglyceride derived FFA entry and resulting in hypertriglyceridemia. This forms a local feedback loop that controls the entry of FFA into, and secretion of Angptl4 from these organs. In glomeruli, it binds to endothelial αvβ3 integrin (at the very least) and modifies putative endothelial - podocyte feedback loops to reduce proteinuria. This is the systemic feedback loop initiated by the development of proteinuria. Recombinant Angptl4 is eminently suited for development as a biological therapeutic agent for proteinuric disorders, since it naturally forms very high order oligomers (glycosylated monomer 65–70 kDa) with an effective size larger than the largest plasma proteins, thereby reducing significantly the likelihood of urinary losses following parenteral administration. Chugh and colleagues developed several forms of mutated human Angptl4 that are modified at normal cleavage sites to increase the half-life of the intact protein, and at sites important for its interaction with lipoprotein lipase to avoid hypertriglyceridemia. A single intravenous dose of recombinant mutated human Angptl4 significantly reduces proteinuria without causing hypertriglyceridemia by participating in the systemic feedback loops of the disease.
Additional animal models demonstrating the pathogenicity of secreted hyposialylated form of Angptl4 is proproteinuric, and podocytes in minimal change disease (1, 4). This podocyte-sialic acid residues (hyposialylated Angptl4) secreted only by podocytes in minimal change disease (1, 4). This podocyte-secreted hyposialylated form of Angptl4 is proproteinuric, and repletion of sialylation using N-acetyl D-mannosamine (ManNAc), an orally bioavailable precursor of sialic acid, improves sialylation and reduces proteinuria in rat models of MCD. Partial efficacy of ManNAc is also noted in diabetic nephropathy (2). Mild upregulation of podocyte Angptl4, which is not associated with production of the hyposialylated form, also occurs in membranous nephropathy, and therefore the efficacy of sialic acid or its precursor is not anticipated in this condition. The production of hyposialylated Angptl4 selectively in podocytes appears to be related to a demand-supply imbalance in these cells during the development of glomerular disease (2). Whereas the concept of sialylation-based therapeutics remains the dominant orally bioavailable therapeutic strategy for the future, the efficacy of the sialic acid precursor compound ManNAc in humans is not known, since activity of the sialic acid synthesis pathways in the podocyte in humans and rodents may be very different. Based on the knowledge of molecular pathways, alternative sugar derivatives more likely to have efficacy in humans are being developed.

Bis-T-23 and related compounds. Bis-T-23 is a small molecule of relatively short half-life that promotes actin-dependent dynamin oligomerization, noted by Sever and colleagues (11) to have efficacy in improving podocyte ultrastructure and proteinuria in rodent models. Two mouse models of FSGS and chronic kidney disease (α-actinin 4 and CD2AP mutant mice) and one model of type 1 diabetes and diabetic nephropathy (streptozotocin model) had significant improvement in proteinuria following administration of Bis-T-23. Since Bis-T-23 does not have chemical characteristics of a potential drug, high-throughput screens combining in vitro and in cell assays will be developed to identify novel lead compounds with the potential to become novel human therapeutics.

Depletion of Pathogenic Proteins

Depletion of circulating the soluble urokinase receptor using affinity columns. Reiser and colleagues (13) showed a pathogenic role of the soluble urokinase receptor (SuPAR) in experimental FSGS and documented elevated levels in FSGS patients. Using a combination of in vitro and animal studies, they were able to correlate the development of albuminuria and FSGS-like lesions in animal models with selective activation of α3β1-integrin in podocytes. Injection of recombinant SuPAR, but not a nonintegrin binding mutant, in animals induced albuminuria. Substantial effort is being devoted to the identification of SuPAR glycovariants and fragments with greatest efficacy in binding activated podocyte α3β1-integrin (12). Additional animal models demonstrating the pathogenicity of high circulating SuPAR levels from adipose tissue-specific overexpression are being characterized (14). Another recent study by Reiser and colleagues (7) shows plasma SuPAR levels to be the earliest known independent predictor of incident CKD and furthermore a predictor of a decline of glomerular filtration rate in prevalent CKD. Other studies have noted elevated SuPAR levels in renovascular hypertension (10) and highlight a role of SuPAR in cardiovascular disease in patients with mild to moderate CKD (9). Based on this data, strategies to immune-deplete circulating SuPAR using monoclonal antibody-based affinity columns are currently being developed.

Conclusion

Given the diversity and complexity of human glomerular disease, it is unlikely that a single novel therapeutic strategy will emerge to treat the broad spectrum of CKD due to glomerular disorders. Since many different pathways are being targeted, it is more likely that some or all of the above therapeutic strategies will emerge after clinical trials in the form of combination therapy, as has been standard practice in the cancer field for decades. The next generation of drugs must have greater efficacy and more specificity for kidney disease, so as to minimize off-target effects. The road to successful therapeutics is long and winding, but the goals are achievable by staying on focus. A positive outcome is always priceless.

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DISCLOSURES

S. S. Chugh is founder, president, and chief executive officer of GDTHERAPY LLC and has filed patents related to the use of Angptl4 mutants (PCT/US2011/039255) and sialic acid-related compounds (PCT/US2011/039058) for the treatment of glomerular diseases. S. S. Chugh may benefit financially from these patents in the future.

AUTHOR CONTRIBUTIONS

M.D.N.-A., H.D.-B., and M.K.S. drafted manuscript; C.B.M. edited and revised manuscript; L.C.C., C.E.M., and S.S.C. provided conception and design of research.

REFERENCES


