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

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.

REFERENCES


