Staying Connected: Transcriptomics in the Search for Novel Diabetic Kidney Disease Treatments

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Diabetic kidney disease (DKD) is the most common cause of end-stage renal disease in the U.S. Nephrologists and primary care providers are quite familiar with this diagnosis and the standard of care for slowing its long-term progression. Current treatment is highly reliant on nonspecific measures such as strict blood pressure and glycemic control. Until recent promising data showing benefits of sodium–glucose cotransporter 2 inhibitors (1), it had been more than two decades since specific pharmacological therapy with angiotensin-converting enzyme inhibitors or AT1 receptor blockers had been shown to be effective (2,3) in slowing progression of this disease. Morbidity and mortality remain high, and despite recent successes in the field, our current therapeutic armamentarium remains vastly inadequate to combat a disease of this magnitude. There remains a great need for discovery of further novel treatments.

In this issue of *Diabetes*, Zhang et al. (4) use an innovative approach to identify new therapeutics for DKD. Rather than initiating their study with a targeted hypothesis focused on the role of a single signaling pathway, they used data from several publicly available gene expression data sets to perform an in silico screen of potential therapeutic agents. They conducted a transcriptome-wide search to define DKD "gene signatures" based on data from 11 independent studies. These signatures contained the top 500 differentially expressed genes in diabetic kidneys as compared with controls in the individual studies. They then used a connectivity mapping approach to query each gene signature in the L1000CDS^2 search engine to identify the top 50 pharmacological agents that would predictably reverse these signatures. Providing some validation for their approach was the identification of multiple compounds that have been shown to slow progression of diabetic and other forms of kidney disease in previous studies. While many of their "top 10" compounds

have been previously studied in preclinical models of DKD, the third compound on their list, BI-2536, which inhibits polo-like kinase 1 (PLK1), has not been. Therefore, they decided to focus their analysis on this drug.

Their group subsequently used a combination of in vitro and in vivo studies to validate their in silico findings by showing efficacy of this compound in the OVE26 mouse model of type 1 diabetes. They demonstrated protection from albuminuria, elevated blood urea nitrogen, and pathological changes. Mechanistic studies further implicated NF-κB and Smad3 signaling downstream of PLK1.

While the biological findings surrounding PLK1 in this study are potentially of great importance for the pathogenesis of DKD, perhaps the most significant aspect of this study stems from its methodology. They took advantage of several publicly available data sets to identify BI-2536 without performing a "wet lab" experiment. They then used traditional experimental techniques to validate their findings. If this approach can reliably identify additional therapeutics for DKD or other disease states, it could revolutionize the process by which we screen drugs and small molecules. It could minimize, or potentially eliminate, cumbersome high-throughput screens that are commonly used for this purpose and would provide time, effort, and cost savings.

While their novel approach could open up a new world of pharmacological screens, this study also raises multiple questions about PLK1 in both type 1 and, potentially, type 2 diabetic nephropathy. Little has previously been reported on this kinase in diabetic glomerular disease, but their findings suggest a deleterious role for PLK1 in its pathogenesis. The most well-described roles of PLK1 have been in regulating the cell cycle and cell proliferation (5). It is interesting that the authors identified increased PLK1 abundance in mesangial cells of diabetic kidneys, as

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mesangial cell proliferation is a hallmark of DKD. BI-2536 may therefore specifically inhibit mesangial cell proliferation, a mechanism of action different from current DKD treatments. Further studies are needed to comprehensively characterize the role of PLK1 in glomerular physiology and disease.

Despite these advances, many questions persist to drive future studies. First, their connectivity mapping approach is based on short-term cell culture studies using a limited sample of cell types. If this approach is to be successful for DKD, or kidney disease more generally, the method should be expanded to include broader kidney cell phenotypes that have been analyzed under several conditions. Secondly, they only used the OVE26 model of type 1 diabetes to evaluate their compound. Given the prevalence of type 2 diabetes, it will be interesting to see if their PLK1 inhibitor also works in type 2 models or other models of type 1 diabetes. Thirdly, while they showed phenotypic improvement using several parameters, they did not show a benefit for glomerular filtration rate, which is the gold standard for kidney function. This will be of great importance, as it is an important measure used clinically to assess disease progression. Lastly, their inhibitor will need to be tested in PLK1 knockout mice to demonstrate true drug specificity.

DKD continues to be the biggest driver of morbidity and mortality among all kidney diseases. A large part of the reason for this has been the lack of new treatments for decades. While there have been recent successes in this field, we are still in great need of new medications. Looking toward the future, the hope is that when patients are diagnosed, we will be able to immediately prescribe a therapeutic package that consists of multiple medications, each of which has proven benefit but acts at a different node in the pathological progression of DKD. This resembles how we currently treat other conditions, such as congestive heart failure. The technique reported in this issue by Zhang et al. may be useful in the search for these treatments. The hope is that it can serve a launching pad to aid in their discovery.

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