Is There a Sweet Spot for Nrf2 Activation in the Treatment of Diabetic Kidney Disease?

Diabetes-associated chronic kidney disease (CKD) continues to be a major contributor to morbidity and mortality in the U.S. and the world. Diabetic kidney disease is the most common reason that Americans are started on renal replacement therapy (1), and as the incidence of diabetes continues to increase, the health and economic consequences of nephropathy and other complications will rise in parallel (2). Unfortunately, there are no known treatments to reverse or arrest progression of diabetic kidney disease. Current treatment guidelines recently published by the National Kidney Foundation demonstrate the paucity of targeted therapies (3). The main recommendations include treatment of hyperglycemia, hypertension, and dyslipidemia, and use of inhibitors of the renin-angiotensin system if the patient has significant albuminuria. Thus, there is significant interest in identifying new therapeutic targets to prevent both development and progression of diabetic kidney disease.

Oxidative stress and inflammation have been implicated as contributors to the progression of CKD from a variety of causes, including diabetes. Recently, a particularly active area of investigation has focused on modulation of the transcription factor Nrf2 (nuclear factor erythroid 2–related factor 2). Nrf2 induces protective, so-called phase 2 antioxidant genes by interacting with cis-acting response elements in their respective promoters (4). This transcription factor is degraded by a ubiquitin ligase complex, which includes Keap1 (Kelch-like ECH-associated protein 1). A series of synthetic oleane triterpenoid compounds, including bardoxolone methyl and dh404 (the compound used by Tan et al. [5]), inhibits Keap1-dependent Nrf2 ubiquitination, stabilizes and increases nuclear translocation of Nrf2, and subsequently induces Nrf2 target genes (6).

Initial human studies of bardoxolone methyl were promising. In the Bardoxolone Methyl Treatment: Renal Function in CKD/Type 2 Diabetes (BEAM) trial, a phase II, dose titration, randomized, placebo-controlled trial of patients with moderate-severe CKD and type 2 diabetes, patients receiving the drug were noted to have a significantly increased glomerular filtration rate (GFR) compared with their pretreatment baseline, although participants were also noted to have increased albuminuria, which is associated with worsening kidney disease (7). Bardoxolone methyl was associated with a variety of side effects, but most were mild-moderate in severity. Based on these encouraging results, the Bardoxolone Methyl Evaluation in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus: the Occurrence of Renal Events (BEACON) trial, a larger phase III study, was conducted. Unfortunately, the BEACON trial was terminated early due to a significantly increased incidence of heart failure among those receiving the active drug (8). The mechanism underlying the apparent toxicity remains unclear, but concerns over the drug’s safety have significantly tempered initial enthusiasm for bardoxolone methyl (9).

In this issue, Tan et al. (5) administered a bardoxolone-related compound, dh404, to streptozotocin-treated ApoE(−/−) mice susceptible to the development of diabetic kidney disease. Bardoxolone methyl itself is metabolized to a toxic substance in rodents, so use of an analogous compound is necessary in rodent models (10). The new findings suggest that dh404 induced production of antioxidant genes and reduced mesangial proliferation and tubulointerstitial injury. Administration of the study drug also decreased albuminuria in the experimental mice, an observation that is in direct contrast to its reported effects in humans (7,8). However, the study mice received the drug shortly after initiation of diabetes; whereas the humans received the drug after years of CKD. Three significant findings from this study are: 1) dh404 appears to be an appropriate compound to study the effects of Nrf2 target genes in this mouse model; 2)
compound was suggested to have significantly reduced atherosclerosis compared with control mice, thereby expanding the therapeutic potential of this drug class; and 3) there was an inverse relationship of the drug dose to atherosclerosis and reductions in inflammatory markers. In this study, many of the end points were observed at low doses of dh404, and despite dose-dependent increased expression of the Nrf2-associated genes, higher doses were certainly not better and were possibly harmful. These observations suggest that there may be a narrow therapeutic window associated with use of this drug (Fig. 1). This is consistent with findings of the BEAM trial, which showed that human GFR did not continue to increase after a threshold dose. The in vitro experiments from Tan et al. demonstrate increased expression of proinflammatory genes and production of proinflammatory compounds at higher drug doses. One plausible hypothesis for this relationship is that the higher doses promote counterregulatory proinflammatory pathways.

This area of research continues to hold relevance and promise despite the major setback of cardiovascular toxicity noted in the BEACON trial. It is unfortunate that bardoxolone methyl is converted to a toxic metabolite in rodents because it confounds extrapolation of the study of toxicity and off-target effects to human subjects. Furthermore, there have been discordant results with this drug class among different diabetic rodent models. A study of two different Nrf2 activators (RTA 505 and dh404) in the Zucker rat suggested increased glomerulosclerosis and interstitial inflammation in the kidney; however, there was also increased GFR in treated animals at similar doses, although there were potential impurities in the experimental compounds (11). A recent follow-up study did not demonstrate deleterious effects in multiple rat and mouse models using the same compounds (12). Whether we can extrapolate these or other results in rats to humans is unclear. One possible way to address the concerns of off-target effects raised in BEACON would involve isolating the narrow therapeutic window of Nrf2 activation and/or developing specific activators of downstream targets of Nrf2 to avoid transcription of proinflammatory genes.

Other currently unresolved issues include the mechanisms of increased (rather than stabilized) GFR and the clinical significance and mechanisms of increased albuminuria in human subjects treated with Nrf2 activators. Studies in bardoxolone-treated monkeys implicate decreased megalin production and, thus, decreased albumin uptake in the proximal tubule (10). Overall, further work in rodent and other animal models with bardoxolone-like compounds is needed.

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Figure 1—Potential narrow therapeutic window for bardoxolone methyl–like triterpenoid compounds. In the study by Tan et al. (8), increasing doses of dh404, an inhibitor of Nrf2 degradation, predictably increased production of antioxidant enzymes but also increased proinflammatory mediators. Higher doses were not associated with more reduction in renal injury and the beneficial effects on atherosclerotic lesions observed at low doses were notably absent.