Stefanie Schwab

Title: Characterizing Altered Protein Acetylation in Diabetic Nephropathy

Diabetes is currently the seventh leading cause of death in the United States. According to the Center for Disease Control (CDC), approximately 30.3 million people have diabetes. An astounding 84.1 million adults are believed to have prediabetes, where 90% of those individuals remain undiagnosed. Numerous health complications arise from diabetes, including nephropathy. Diabetic nephropathy (DN) is defined by both structural and functional changes of the kidneys; including mesangial expansion, glomerular basement membrane thickening, and podocyte injury. Progression of DN can ultimately lead to chronic kidney disease (CKD), end-stage renal disease, and kidney failure. Although there are well-known structural changes of DN at the glomerulus, alterations occurring at the proximal tubule are often overlooked. Recent findings suggest that persistent damage at the proximal tubule contributes to the progression of CKD. A potential mechanism underlying proximal tubule dysfunction is the result of aberrant post-translational modifications (PTM). One such PTM of particular interest is lysine acetylation, which has been linked to cellular metabolic flux. Dysregulated acetylation can result in altered protein function. To better understand how protein acetylation is distorted during DN, whole cell lysates were prepared from kidney tissue isolated from mice that were injected with streptozotocin (STZ) to induce diabetic hyperglycemia. Mice were sacrificed at 1, 3 or 32 weeks of life post-STZ injection. Western blots, immunohistochemistry (IHC), and activity assays were employed to examine the acetylation pattern of proteins, including SOD2. Our data demonstrates that protein acetylation is increased in diabetic mice, with increased SOD2 acetylation at lysine residue 68 (acK68). This corresponded with decreased SOD2 activity after 32 weeks of diabetic hyperglycemia. Increased acetylation also corresponds with elevated glycated hemoglobin (HbA1c), a known marker of diabetic hyperglycemia. Furthermore, these results corroborate our findings from human kidney tissue biopsies from patients with moderate to severe diabetes. Total acetyllysine and SOD2 acK68 were increased at the proximal and distal tubules in patients with moderate diabetes. The correlation between this STZ mouse model and human data represents a translational link that supports the need for further investigation to determine if hyperacetylation may play a role in the pathogenesis of DN.