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GLOMERULAR DISEASE

PROTECTIVE ROLE OF TGR5 ACTIVATION

Activation of the G-protein-coupled bile acid receptor TGR5 (also known as GPBAR1) protects against diabetic nephropathy (DN) and obesity-related glomerulopathy (ORG), say researchers. TGR5 is downregulated in response to high levels of glucose and/or fatty acids, which are common metabolic perturbations in diabetes and obesity.

Moshe Levi and colleagues previously reported that bile-acid-induced activation of the nuclear receptor FXR prevents the development of kidney disease related to diabetes and/or obesity by inhibiting renal lipid synthesis and accumulation, inflammation, oxidative stress and fibrosis. In their new study they investigated whether activation of TGR5 might exert similar beneficial effects.

The researchers found that *TGR5* mRNA expression was decreased in kidney biopsy samples from patients with DN or ORG, compared with normal kidney biopsy samples. Moreover, low levels of *TGR5* mRNA were associated with kidney disease progression, as evidenced by inverse correlations with glomerulosclerosis, proteinuria and decline in estimated glomerular filtration rate, and direct correlations with expression of podocyte markers.

To investigate whether TGR5 activation protects against DN and ORG, Levi and colleagues used mouse models of diabetes (db/db) and diet-induced obesity (DIO). Although renal *TGR5* mRNA expression was downregulated in these models, treatment with the TGR5 agonist INT-777 prevented all of the major phenotypic characteristics of DN and ORG. In kidneys from db/db mice and in human podocytes cultured in high glucose conditions, INT-777 increased mitochondrial biogenesis and fatty acid β-oxidation, and decreased oxidative stress and lipid accumulation. Similarly, the agonist enhanced mitochondrial function, prevented weight gain and reduced renal lipid accumulation in DIO mice.

"Our study is the first to show that a TGR5 agonist prevents the development of obesity and diabetes-associated kidney disease in part by modulation of mitochondrial function," concludes Levi. "We plan to test this pathway in additional models and eventually to conduct clinical trials."

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