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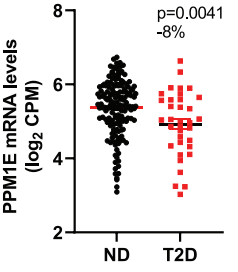
In This Issue of *Diabetes*

By Max Bingham, PhD

Phosphatase PPM1E Identified as Central to Maintaining Insulin Secretion in Type 2 Diabetes: A Treatment Option?

Reduced expression of a protein phosphatase termed PPM1E appears to be central to maintaining insulin secretion in type 2 diabetes, according to Gheibi et al. (**p. 455**). Based on a series of cell-based studies, they suggest that modulation of phosphatase expression and activity in general terms, and particularly toward PPM1E, represents a therapeutic target for type 2 diabetes. Specifically, they suggest this would target the preservation and restoration of β-cell function in patients with type 2 diabetes—a key process in maintaining insulin secretion. Initially targeting mRNA expression of type 2C family protein phosphatases in islets of donors with type 2 diabetes, they found that expression overall was changed compared with that of equivalent islets from donors without diabetes. In particular, expression of *PPM1E* was "markedly" downregulated (−8%) in the context of diabetes, with the authors noting a level of inverse correlation between its expression level and both HbA_{1c} and BMI. In cell-based studies they found that silencing *PPM1E* resulted in increased glucose-stimulated insulin secretion, while overexpression had the opposite effect. On the mechanistic level, they found that *PPM1E* silencing (i.e., increased insulin secretion) was associated with decreased oxidative stress, elevated Ca^{2+} level and ATP-to-ADP ratio, and a series of changes at the mitochondrial level. Notably, the actual insulin content in cells did not change following silencing. Follow-up experiments then led the authors to conclude that reduced expression of *PPM1E* in the context of type 2 diabetes is likely a compensatory response to uphold insulin secretion under conditions of metabolic stress. While the authors suggest they have uncovered a new therapeutic route for type 2 diabetes, they caution that more studies are needed. For example, they cannot currently exclude a role for the many other phosphatases in the family, and they suggest that establishing a causal role for PPM1E activity will require extensive studies in vitro and in vivo.

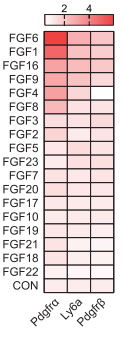


mRNA expression level of *PPM1E* in islets from donors with no diabetes (black) and type 2 diabetes (red). CPM, counts per million; ND, no diabetes; T2D, type 2 diabetes.

Gheibi et al. Reduced expression level of protein phosphatase *PPM1E* serves to maintain insulin secretion in type 2 diabetes. Diabetes 2023;72:455–466

FGF6: A Potential Treatment Target for Obesity

Fibroblast growth factor 6, or FGF6, appears to be a specific proliferative factor that controls adipocyte progenitor cells (APCs), according to Liu et al. (**p. 467**). Based on the findings, they suggest that FGF6 serves as a therapeutic target for obesity- and aging-induced metabolic dysfunction. Previously, the roles of specific fibroblast growth factors (FGFs) in regulating APC proliferation and the effects on metabolic health remained unclear. The findings come from a series of experiments with cells and mice and from molecular analyses that initially looked to screen how the various FGFs function in APC proliferation. The authors then used cell and mouse experiments to variously upregulate or downregulate FGF function or expression in a bid to establish the likely role of FGFs in the context of obesity and aging. They found that of the 18 FGFs they screened, FGF6 exerted the strongest effect on cell proliferation. With further experiments, they found that it induced APC proliferation and enhanced adipogenesis to form new adipocytes, and this was most likely to happen via extracellular signal–regulated kinase signaling. Overexpression of FGF6 in inguinal white adipose tissue of lean mice then prevented high-fat diet–induced and aging-induced hypertrophy, obesity, and insulin resistance. In the opposite direction, FGF6 blockade, either via a neutralizing antibody or *Fgf6* expression deficiency, resulted in impaired adipose tissue expansion, glucose tolerance, and insulin sensitivity. Based on the findings, they conclude that FGF6 appears to control APC proliferation in adipose tissue, which sets it up as a potential target to prevent adipocyte hypertrophy in cases of overnutrition and aging and therefore potentially as a treatment target in obesity. "Our findings demonstrate for the first time that FGF6 controls APC proliferation, induces [inguinal white adipose tissue] expansion via hyperplasia, and improves insulin sensitivity in response to overnutrition or aging," they write. "These results indicate that FGF6 is a strong paracrine FGF with potential in the treatment of metabolic diseases." Commenting further, author Cheng Hu said, "We hope to develop a long-acting FGF6 analog in the near future and believe that local delivery of FGF6 is a promising strategy to maintain adipose tissue homeostasis and protect against obesity- and age-associated metabolic diseases."



Heat map illustrating strong FGF6 gene expression in cells in response to a series of stimulatory recombinant FGFs. CON, control.

Liu et al. Fibroblast growth factor 6 promotes adipocyte progenitor cell proliferation for adipose tissue homeostasis. Diabetes 2023;72:467–482

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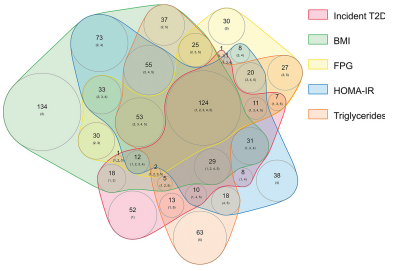
Proteomics Study Reveals Hundreds of Novel Protein Leads Related to Diabetes Development in African Americans

A proteomics study by Chen et al. (**p. 532**) that targeted self-identified African Americans in the Jackson Heart Study found 325 proteins associated with incident diabetes. Notably, a minority of the identified proteins were independent of established markers of diabetes pathways, such as adiposity, glycemia, and insulin resistance. According to the authors, this suggests that there are (many) novel biological processes associated with diabetes development that are yet to be discovered. Particularly in relation to U.S. African Americans, these processes also might start to explain, beyond the established inequalities in socioeconomic determinants of health, why African Americans have consistently higher type 2 diabetes incidence than White individuals. Using proteomics based on single-stranded DNA aptamer affinity–based technology applied to stored plasma samples, the authors examined a subset of the volunteers in the Jackson Heart Study as the discovery set. They then used equivalent data sets from a series of other cohorts as the replication sets. In addition to identifying the original 325 proteins, they found that 36 associations remained significant after adjustments for factors such as BMI, fasting plasma glucose, cholesterol, and hypertension. Top associations included complement factor H, formimidoyltransferase cyclodeaminase, serine/threonine protein kinase 17B, and high-mobility group protein B1 (among others). Notably, they replicated the results in the largely White cohorts under a meta-analysis. The authors suggest that this point means the biomarkers have generalizability. They continue the detailed analysis by examining how some of the proteins appear associated with diabetes risk factors but others did not, depending on the cohorts they looked at. What emerges is a picture of a wide variety of leads for further research studies, and particularly some that seem highly relevant to their original cohort of African Americans with diabetes in the U.S. The authors note that they have provided all the data from the study for the wider scientific community to take forward.



Proteins that share associations with incident diabetes and select baseline diabetes risk factors. FPG, fasting plasma glucose; HOMA-IR, HOMA of insulin resistance; T2D, type 2 diabetes.

Chen et al. Protein markers of diabetes discovered in an African American cohort. Diabetes 2023;72:532–543

Chronic Kidney Disease Not Directly Caused by Obesity but Mediated by Hypertension, Blood Glucose Levels

Obesity is likely not an independent cause of chronic kidney disease (CKD), according to Nguyen et al. (**p. 496**). Rather, its effects on CKD are likely mediated by hypertension and elevated blood glucose levels. Establishing whether obesity is truly an independent factor after adjusting for hypertension and elevated glucose would, according to the authors, help inform strategies to prevent or treat CKD, including the optimal amount of weight loss needed to protect against CKD. In a dual approach, the authors initially used Mendelian randomization (MR) to investigate whether BMI was independently associated with either CKD or microalbuminuria. They also looked at whether weight loss following bariatric surgery influences >50% reduction in estimated glomerular filtration rate (eGFR, an indicator of CKD) or hospitalization due to CKD, with <20% weight loss as a comparator. They found that increases in BMI appeared to be causally associated with increased CKD and microalbuminuria, but not after adjustment for hypertension and glucose. Indeed, nearly all the effects of increasing BMI on CKD were mediated by the two factors. Looking at weight loss following surgery, they found that 30% to <40% weight loss did result in a >50% decline in eGFR, but weight loss of 20–30% and above 40% did not. In terms of hospitalizations for CKD, they found weight loss above 30% resulted in reductions in hospitalizations, but below 30% no reduction was apparent. “This study suggests that obesity increases the risk of kidney disease via hypertension and elevated glucose,” said author Satya Dash. “Prospective well-powered randomized studies will be needed to confirm whether lowering blood glucose and blood pressure into the normal range, which can be safely achieved with newer medications, reduces kidney disease in people living with obesity. Randomized controlled trials of bariatric surgery, which are currently underway, will also inform us on the optimal weight loss threshold to prevent CKD.”

Nguyen et al. Association between obesity and chronic kidney disease: multivariable Mendelian randomization analysis and observational data from a bariatric surgery cohort. Diabetes 2023;72:496–510

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