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In This Issue of *Diabetes*

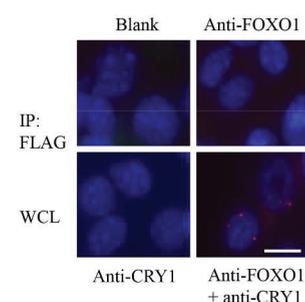
By Max Bingham, PhD

A Novel Pathway to Potentially Tackle Hyperglycemia in Type 2 Diabetes

A novel metabolic pathway relating to hepatic gluconeogenesis is reported by Tong et al. (p. 2571) with the suggestion that it may represent a target for controlling hyperglycemia in type 2 diabetes. Using a series of mouse models and cell-based experiments, the authors systematically uncover the role of DDB1, the scaffolding protein in the DDB1-CUL4A E3 ligase complex. Reportedly, DDB1 likely promotes FOXO1-driven gluconeogenesis in the liver via the degradation of the cryptochrome CRY1. CRY1 is normally used by insulin to suppress gluconeogenesis and hence to reduce or at least control blood glucose levels following meals. The authors hypothesized that under normal circumstances FOXO1-controlled gluconeogenesis is normally kept in check through CRY1-mediated degradation. However, in the case of high-fat diet-induced insulin resistance, induction of DDB1 leads to CRY1 degradation and consequently to FOXO1 stabilization and sustained glucose production. To prove the case, they initially demonstrate that the deletion of *Ddb1* (the gene that encodes DDB1) in the livers of mice impairs hepatic gluconeogenesis while protecting from high-fat diet-induced hyperglycemia. The deletion also reportedly downregulates FOXO1 protein expression and associated gluconeogenesis. They go on to demonstrate that DDB1 likely stabilizes FOXO1 by degrading CRY1. Depletion of *Cry1* also inhibited the ability of insulin to suppress FOXO1 and subsequent gluconeogenic gene expression. Finally, they highlight that *Cry1* depletion further increases hepatic levels of FOXO1 and gluconeogenesis in mice. Author Lei Yin told *Diabetes*: “Given the potent effects of *Ddb1* deletion on glucose production in the liver of high-fat diet-fed mice, DDB1-specific inhibitors might offer a tantalizing option for treating hyperglycemia. However, those inhibitors might have many off-target effects because the DDB1-CUL4A E3 ligase complex regulates ubiquitination and proteolysis of a variety of substrates. To improve specificity, a more feasible approach should aim to identify small molecules that specifically block DDB1 binding to CRY1 and subsequently suppress glucose production.”

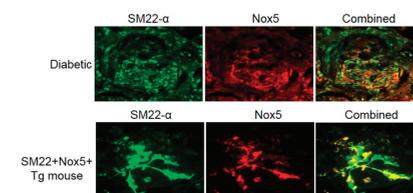
Nox5 May Be Central to the Development of Diabetic Nephropathy

The role of NADPH oxidases and specifically their production of reactive oxygen species (ROS) in the kidney appears to be a key step toward the development of diabetic nephropathy. According to Jha et al. (p. 2691), version 5 of the compound, Nox5, might be critical in terms of progression of the disease. Previously very little was understood in relation to Nox5 because of the limitations of mice models as Nox5 is not normally expressed in the species. Hence, the generation of mice that apparently can express the isoform appears to be a major step forward toward uncovering the role of the enzyme. According to the authors, human kidney biopsy samples taken from patients with diabetic nephropathy did demonstrate an increase in Nox5 expression in comparison to healthy control subjects. Likewise, isolated human mesangial cells also demonstrated Nox5 expression when exposed to high levels of glucose. After silencing Nox5 expression in the cells with a short hairpin RNA lentivirus approach, they found that Nox5 gene expression was heavily downregulated, and in turn, this reduced protein expression of Nox5, associated ROS generation, and the accumulation of a variety of extracellular matrix compounds. Moving to mice with enhanced mesangial-specific expression of Nox5 and diabetic nephropathy, they found that in comparison to controls, the mice had enhanced glomerular ROS production, accelerated glomerulosclerosis, and expansion of both mesangial mass and extracellular matrix proteins such as collagen and fibronectin. They say that, taken together, inhibition of Nox5 might represent a novel approach for halting the progression of diabetic nephropathy. Author Karin Jandeleit-Dahm said: “These studies using human biopsy samples, human kidney cells, and ‘humanized’ Nox5-expressing mice represent an important step forward toward our understanding of the role of Nox5 and derived reactive oxygen species in diabetic nephropathy and provide the impetus to develop novel Nox inhibitors with higher specificity toward Nox5.”



CRY1 interaction with FOXO1 in the nucleus by proximity ligation assay. After transduction with Ad-Foxo1 and Ad-Cry1, *Cry1*^{-/-}/*Cry2*^{-/-} mouse embryonic fibroblasts cells were incubated with both anti-CRY1 and anti-FOXO1 antibodies and subjected to proximity ligation assay. Scale bar = 20 μm. WCL, whole cell lysate.

Tong et al. DDB1-mediated CRY1 degradation promotes FOXO1-driven gluconeogenesis in liver. *Diabetes* 2017;66:2571–2582



Colocalization of Nox5 (red staining) and the marker of smooth muscle cells, transgelin (SM22-α [green staining]), in kidney biopsies obtained from individuals with diabetes (top) as well as in frozen kidney sections of SM22⁺Nox5⁺ transgenic (Tg) mice (bottom) (magnification ×20).

Jha et al. NADPH oxidase Nox5 accelerates renal injury in diabetic nephropathy. *Diabetes* 2017;66:2691–2703

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Persistent Organic Pollutants Inhibit β -Cell Function

The effects of common environmental pollutants on pancreatic β -cell function in healthy individuals are investigated by Lee et al. (p. 2669), and their conclusions point in one direction: greater exposure appears to limit insulin secretion and consequently might increase the risk of type 2 diabetes. As a result, they suggest prospective studies are needed urgently to fully investigate the link. The study, which mainly focused on 200 individuals without diabetes, assessed various insulin secretion indices and serum concentrations of various persistent organic pollutants (POPs)—notably, compound classes that have been largely banned from use in many countries around the world but still widely contaminate food chains and accumulate in human adipose tissue. The authors reveal an inverse correlation between static-phase insulin secretion rate and serum concentration of organochlorine pesticides (OCPs), a class of POP. Overall, they report that individuals with the highest levels of OCPs had insulin levels that were about 30% of those with low OCPs. Also, the inverse relationship between OCPs and dynamic-phase insulin secretion was observed only among insulin-sensitive people and not among insulin-resistant people, suggesting a compensatory overproduction of insulin might exist in some individuals. To back up the findings from the human study, the authors also report a series of outcomes from in vitro experiments with INS-1E β -cells showing that individual compounds belonging to POPs at low concentrations can inhibit insulin secretion. Authors Duk-Hee Lee and In-Kyu Le commented: “Asians and elderly have a high body burden of POPs. Therefore, POPs may explain why β -cell dysfunction—dominant type 2 diabetes are common in Asians and elderly. Also, as POPs are mechanistically related to dynamics of adipocytes and POPs in serum primarily reflect POPs stored in adipose tissue, disentangling the interrelationships between POPs and adipocytes would be an important research topic.”

Lee et al. Low-dose persistent organic pollutants impair insulin secretory function of pancreatic β -cells: human and in vitro evidence. *Diabetes* 2017;66:2669–2680

Physical Activity Can Modify Risk of Weight Gain Even in Individuals With High Genetic Risk for Obesity

Genetic susceptibility to long-term weight gain may be diminished by concurrent increases in physical activity in the longer term, according to Wang et al. (p. 2704). The authors suggest that promoting physical activity to prevent obesity, particularly with individuals that are genetically predisposed to the disease, should be a key message to patients. Taking advantage of long-term follow-up data from both the Nurses' Health Study (NHS) (~9,400 women) and the Health Professionals Follow-Up Study (HPFS) (~5,300 men), they link a series of single nucleotide polymorphisms (SNPs) to increased weight and asked whether physical activity could modify the relationship. Using genetic risk scores that summarized the risk of BMI increases (77 SNPs) and body fat percentage increases (12 SNPs), they found that both were associated with increases over a 20-year period. Significantly, physical activity changes did modify both BMI and body fat percentage. According to their analysis, small decreases in both BMI and weight could be expected with increased activity and the opposite was true when physical activity declined over the 20 years of follow-up. In individuals with greater genetic risk for weight gain, increasing physical activity led to the clearest reductions in BMI. As a result, they suggest that using genetic data to understand risk of weight gain and obesity might be helpful in terms of targeting individuals that would benefit most from increases in physical activity. They say that although the magnitude of changes in weight associated with the SNPs was modest, targeting individuals with the most to gain from increases in physical activity could have important health consequences at the population level. Indeed, they even suggest that in individuals that struggle with weight loss, a strategy of simply trying to maintain weight throughout adult life, as opposed to putting on weight, could still be significant.

Wang et al. Genetic susceptibility, change in physical activity, and long-term weight gain. *Diabetes* 2017;66:2704–2712

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