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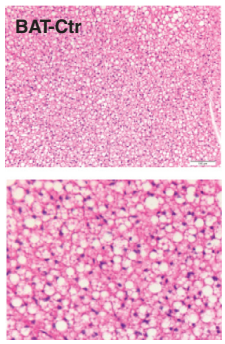
In This Issue of *Diabetes*

By Max Bingham, PhD

Rapamycin Blocks a Key Thermogenesis Pathway in White Adipose Tissue: Diabetes/Obesity Implications

Mechanisms underlying the action of rapamycin are the focus of a set of studies by Tran et al. (**p. 927**) that reveal the blocking of thermogenic gene expression in white adipose tissue (WAT) by the drug. The results, the authors say, may explain why rapamycin predisposes patients to diabetes and might support a potential intervention in obesity to induce a type of adipocyte that can metabolize glucose and lipids and dissipate the resulting energy as heat. The authors report that rapamycin likely blocks the ability of β3-adrenergic signaling that normally induces so-called beige adipocytes in WAT and subsequently the expression of genes involved in thermogenesis. Beige adipocytes are strongly induced by cold temperatures (and certain agonists), converting glucose and lipids to heat, which is why they are interesting targets for obesity interventions. By blocking mTORC1 (the target of rapamycin) at specific time points and intervening with a β3-adrenergic signaling agonist, the authors show how the beiging process of WAT can be inhibited and how the steps in the pathway likely link up. To illustrate the effects, mice were exposed to cold temperatures (4°C) for approximately three days, and while all mice experienced a drop in body temperature, those treated with rapamycin experienced greater decreases in temperature and lost more body weight in comparison to controls. The rapamycin-exposed mice also became significantly more glucose intolerant upon exposure to cold. Finally, deletion of a subunit of mTORC1 in mice also blocked the β3-adrenergic signaling underlining the effects previously seen in relation to rapamycin. Commenting further on the study, author Joseph A. Baur said: "There's great hope right now that increasing the number of beige adipocytes will be a viable strategy to treat obesity and diabetes. Our work reveals that mTORC1 plays a positive role in this process and may help explain why rapamycin has detrimental effects on metabolism."

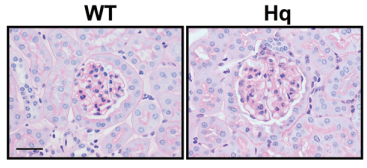


Dietary rapamycin attenuates CL316,243-induced thermogenic gene expression in WAT. BAT, brown adipose tissue; Ctr, control.

Tran et al. Rapamycin blocks induction of the thermogenic program in white adipose tissue. Diabetes 2016;65:927–941

Apoptosis-Inducing Factor as a Key Mediator of Chronic Kidney Disease in Diabetes

The massive levels of energy required by the kidneys to do their job of filtering what is needed or not needed may come down to one particular protein called apoptosis-inducing factor (AIF). According to Coughlan et al. (**p. 1085**), deficiencies of AIF may explain many aspects of kidney disease and particularly diabetic nephropathy. Animal and human studies reveal that AIF deficiency results in a disruption in oxidative phosphorylation and because the kidney relies on this process for homeostasis, all sorts of potentially crucial molecules might be lost to urinary excretion. The authors reveal that partially knocking out the genes related to AIF expression in mice resulted in emerging chronic kidney disease features. A series of follow-up experiments detail the likely mechanisms involved. To understand the impact of diabetes, the authors then imposed a diabetes background on the same AIF-deficient mice and found that there were extensive changes in mitochondrial metabolism that resulted in worsening kidney damage. Subsequent experiments then focused on the kidney cells from patients with diabetes, which revealed a decrease in AIF within the renal tubular compartment and a lower level of expression of the gene *AIFM1*. This significantly correlated with lower glomerular filtration rate, indicating there was a loss of kidney function. Finally, the authors write that lentiviral-induced overexpression of AIF resulted in a rescue of the kidney tubular cells and their reaction to glucose by improving the efficiency of mitochondrial respiration. According to author Melinda T. Coughlan: "Diabetic kidney disease is associated with reduced AIF expression, however the underlying mechanisms are yet to be unraveled. This study highlights the importance of AIF in the maintenance of kidney homeostasis and further research in this area is warranted. It is possible that AIF may represent a new therapeutic target for the treatment of chronic kidney diseases, particularly diabetic kidney disease."



Knockdown of AIF recapitulates nephropathy. Photomicrographs of periodic acid Schiff–stained renal cortex. WT, wild type; Hq, Harlequin.

Coughlan et al. Deficiency in apoptosis-inducing factor recapitulates chronic kidney disease via aberrant mitochondrial homeostasis. Diabetes 2016;65:1085–1098

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Treg Gene Signature as a Biomarker for Type 1 Diabetes

A gene signature that discriminates between regulatory T cells (Tregs) and conventional T cells regardless of their activation states has been identified, indicating that it might be possible to develop a biomarker-based test for Tregs to track the progression of type 1 diabetes. According to Pesenacker et al. (**p. 1031**), changes in Treg function are difficult to track because of a lack of exclusive markers that set them apart from conventional T cells. The ability to track Tregs is important since the insufficient function of Tregs is thought to be a major contributor to the development of type 1 diabetes and specifically to the immune system–mediated destruction of insulin-producing β-cells. Using cell sorting and mRNA expression analyses, the authors measured gene expression in a panel of 31 genes found in the Tregs from children with type 1 diabetes and age-matched control subjects. They discovered that six genes could successfully differentiate the groups. The genes included three that have previously been linked to T-cell receptor activation and three that are likely involved in Treg signaling. The authors suggest that this discovery could potentially be very useful in terms of monitoring and identifying Tregs in humans, and it could be used to track changes over time in Tregs and thus identify individuals who would benefit from Treg-targeted therapies. Author Megan K. Levings said: "We are very excited that this may be a useful test to monitor the status of Tregs in patients with type 1 diabetes. There is a real need for simple tests to measure changes in these cells because so many Treg-targeted therapies are being tested clinically. We believe that similar gene signatures will also be useful in other diseases caused by an imbalance in Tregs, including autoimmunity and cancer. We are currently validating the Treg signature in new cohorts of individuals with type 1 diabetes and exploring the utility of the gene signature in other disease settings."

Pesenacker et al. A regulatory T-cell gene signature is a specific and sensitive biomarker to identify children with new-onset type 1 diabetes. Diabetes 2016;65:1031–1039

Thiamine Transporter Gene Variations Are Associated With Type 1 Diabetes Microvascular Complications

Some individuals with type 1 diabetes appear to suffer less than others from microvascular complications such as diabetic retinopathy and nephropathy. And according to an analysis by Porta et al. (**p. 1022**), genetic variations in a thiamine transporter may be key to understanding why this occurs. Hypothesizing that variants in two thiamine transporters (*SLC19A2/3*) were associated with diabetic retinopathy and/or nephropathy, the authors investigated 134 single nucleotide polymorphisms (SNPs) in both the transporters and their transcription factors. It was significant that the study was carried out first in the Finnish Diabetic Nephropathy (FinnDiane) type 1 diabetes cohort and then was followed up in two subsequent type 1 diabetes cohorts, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study and the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR). The result was that the authors identified two SNPs in the *SLC19A3* transporter that were associated with diabetic retinopathy alone as well as a combined phenotype of retinopathy and end-stage renal disease (ESRD). In this case, it was possible to replicate the association in the WESDR cohort but not in the DCCT/EDIC as there were too few patients with ESRD. While complete replication of the associations was not possible, the authors suggest the outcome is still important and likely explains why some patients with diabetes suffer less from microvascular complications than others. Finally, they suggest this may help with the early identification of individuals at risk of complications. Author Per-Henrik Groop commented further on the study: "First of all, the results do not suggest that all patients should start to take B1 vitamins, but they give us the mandate to further study whether targeted intervention with vitamin B1 agents may reduce the risk of complications. It is reassuring that B1 agents such as thiamine and its derivative benfotiamine have been shown to reduce the risk of retinopathy and nephropathy in animals with experimental diabetes, and some clinical trials with thiamine have also shown successful results for treating nephropathy in humans. However, these preliminary data need to be proven in double-blind controlled trials."

Porta et al. Variation in *SLC19A3* and protection from microvascular damage in type 1 diabetes. Diabetes 2016;65:1022–1030

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