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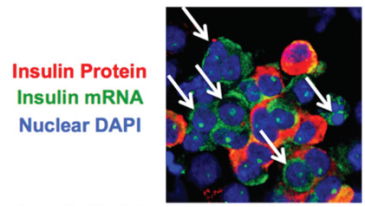
In This Issue of *Diabetes*

By Max Bingham, PhD

Transcriptomics of Pancreatic α- and β-Cells via Highly Purified Cell Subsets

A molecular analysis reported in this issue of *Diabetes* (**p. 3172**) details the transcriptomes of human adult and fetal pancreatic α- and β-cells and reveals that a range of transcription factors implicated in islet cell development, but only previously observed in rodent models, appear in human fetal cells as well. Blodgett et al. also report the intriguing observation that adult α-cells also express insulin mRNA (but not the corresponding protein), which they suggest raises the possibility that the adult α-cells might somehow be reprogrammed to produce insulin. That is likely to have clear therapeutic implications, according to the authors. Previously such studies have not been possible because obtaining homogenous, highly purified cell populations has been so difficult. To overcome these issues, the authors report a range of new approaches toward cell sorting and next-generation RNA sequencing and show that it is now possible to obtain the highly purified samples of α-, β-, and other islet cell types that are needed for subsequent molecular studies. Certain genes of known function were highly up- or downregulated in the study, but many others of unknown function were also disproportionally expressed, suggesting there is still much to learn about islet cell behavior in diabetes. Commenting more widely on the study, senior author David Harlan said: "We have long recognized human islets are very heterogeneous 'mini-organs' comprised of many different cell types. And yet, our techniques for studying the individual cell types have been limited. To make matters worse, the pancreatic β-cell might represent as few as 25% of the islet cells in one individual, or as many as 75% of the islet cells in another. Therefore, studies that have assumed a 'human islet is a human islet' have been based on a faulty premise. Our studies even show that β-cells from a *single* donor can be quite different with widely varying insulin mRNA content. Thus, while the technique we have developed has limitations—including that the cells are killed during sorting—we are excited by the novel insights we have gained. Our technique, coupled with complementary live-cell sorting techniques developed by others, will open new vistas into our understanding of islet subcellular structure and function with the promise that we will gain the knowledge to prevent the loss of β-cell function underlying diabetes."

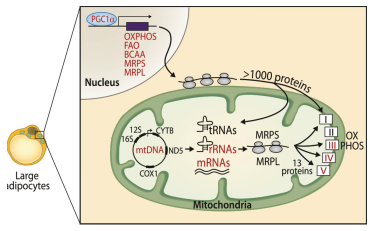


α-Cells express insulin mRNA. Arrows denote insulin mRNA+ cells negative for insulin protein staining.

Blodgett et al. Novel observations from next-generation RNA sequencing of highly purified human adult and fetal islet cell subsets. Diabetes 2015;64:3172–3181

Mitochondrial Function Impaired in Obesity: Twins Study

A study of identical twin pairs where one had obesity and the other did not suggests that downregulation of mitochondrial biogenesis in adipose tissue may be important in obesity and associated with metabolic abnormalities already at the preclinical stage. Low mitochondrial activity has been suspected as an underlying factor in obesity, type 2 diabetes, and metabolic syndrome but until now the details have remained elusive. Heinonen et al. report the study in this issue of *Diabetes* (**p. 3135**) and now suggest that "obesity-related disease development may be halted by improving mitochondrial activity in subcutaneous adipose tissue." Using transcriptomics analyses, the researchers show a global downregulation of mitochondrial oxidative pathways in the obese co-twins compared with their lean siblings. Subsequent pathway analysis suggested all sorts of associated metabolic outcomes being downregulated in obese co-twins and inversely correlated with adiposity, insulin resistance, and markers of inflammation. The unique nature of the studies in identical twins means that genetic background can be excluded as a confounding factor, which is a major advantage for drawing conclusions about metabolic pathways in obesity. These authors suggest that such impaired mitochondrial biogenesis may well explain the range of symptoms typically associated with obesity—low-grade inflammation, insulin resistance, and perhaps even weight gain being key among many. Without exclusion of variations in genetic background, these conclusions would have been difficult to make. Commenting on the wider implications of the study, author Kirsi Pietiläinen stated: "These data clearly show the power of lifestyle. Staying slim and exercising are very effective ways of keeping mitochondria active; even in fat, which is typically considered to be an energetically 'lazy' tissue. The effects of obesity were surprisingly robust. The twins were young and healthy and had only mild degrees of obesity. Yet, the downregulation of the mitochondria was clear, with strong associations to prediabetes. We believe that mitochondrial dysfunction is at the heart of metabolic problems in obesity."



Downregulation of mitochondrial biogenesis in the subcutaneous adipose tissue of monozygotic obese twins.

Heinonen et al. Impaired mitochondrial biogenesis in adipose tissue in acquired obesity. Diabetes 2015;64:3135–3145

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Reduced Levels of HDL Cholesterol Are Not a Causal Risk Factor for Type 2 Diabetes: Mendelian Randomization Study

According to a 47,000 strong general population study from Denmark reported in this issue of *Diabetes* (**p. 3328**), genetically reduced HDL cholesterol is not associated with the increased risk of type 2 diabetes. Moreover, low HDL cholesterol is more likely to be a consequence of type 2 diabetes. Observations from many studies indicate that low levels of HDL cholesterol are consistently associated with the increased risk of type 2 diabetes. However, no study has ever managed to establish whether low HDL cholesterol is a cause or a consequence of type 2 diabetes. Using a Mendelian randomization strategy, Haase et al. have now established likely "reverse causation," meaning that low HDL cholesterol is likely a consequence of type 2 diabetes. Mendelian randomization helps to untangle confounding factors by taking a two-step approach towards establishing a relationship, for example, between an environmental trigger and a health outcome via a genetic trigger. In this case, the researchers looked at whether HDL cholesterol levels correlated with related genetic variants and then tried to establish the likelihood of a relationship between the genetic components and finally the health outcome—type 2 diabetes. As genetic components are lifelong, they essentially act as unconfounded proxies and therefore get around confounding factors such as diet or disease status. The authors established statistically significant relationships between low HDL cholesterol and the risk of type 2 diabetes and also HDL cholesterol gene scores with HDL cholesterol levels. However, they could not establish significant genetic risk ratios leading to the conclusion of no causal relationship. Commenting more widely on the study, author Ruth Frikke-Schmidt said: "These findings suggest that low levels of HDL cholesterol per se do not cause type 2 diabetes and thus that the corresponding observational association may be due to the dyslipidemia observed as a consequence of type 2 diabetes—so-called reverse causation. Consequently, this questions plasma HDL cholesterol increasing as a novel therapeutic option for treatment or prevention of type 2 diabetes, as recently suggested."

Haase et al. HDL cholesterol and risk of type 2 diabetes: a Mendelian randomization study. Diabetes 2015;64:3328–3333

Plasma microRNA May Predict Progression of Renal Function in Type 1 Diabetes: Prospective Study

A set of microRNA biomarkers detectable in blood plasma may hold the key for predicting the risk and speed of the progression toward end-stage renal disease (ESRD) in type 1 diabetes patients, according to a prospective study reported in this issue of *Diabetes* (**p. 3285**). Pezzolesi et al. compared plasma samples of proteinuric patients with type 1 diabetes that had normal renal function at enrollment but rapid decline in follow-up with equivalent patients who maintained renal function over the same period. Both groups were also compared with type 1 diabetes patients with no proteinuria and normal/stable renal function. The follow-up period in which renal function and other clinical characteristics were monitored was 7–20 years, depending on the groups. All baseline samples were screened for a bank of transforming growth factor (TGF)-β–regulated microRNAs. The authors focused on five microRNAs and found that two were significantly associated with protection against rapid progression and two others were associated with increased risk of ESRD. After controlling for HbA_{1c} and other covariates, there was an ~50% reduction in the risk of rapid progression of renal decline associated with two of the microRNAs. While cautioning that more research is needed, the authors conclude that "TGF-β–regulated microRNAs detectable in plasma could be preclinical indicators of early renal decline and therefore might have utility in identifying patients most at risk for renal function decline and progression to ESRD." The authors also hint that microRNAs might represent therapeutic targets in the future: "Pending further studies, therapeutic augmentation of these and perhaps other microRNAs may prove useful in inhibiting fibrogenesis and modifying the risk of renal function decline in type 1 diabetes."

Pezzolesi et al. Circulating TGF-β1–regulated miRNAs and the risk of rapid progression to ESRD in type 1 diabetes. Diabetes 2015;64:3285–3293

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