Inherited β-Cell Dysfunction in Lean Individuals With Type 2 Diabetes

Anne E.W. Mathews[1] and Clayton E. Mathews[2]

The syndromes comprising diabetes mellitus share the common feature of β-cell failure. Inheritance of β-cell failure is clear in patients diagnosed with the MODY (maturity-onset diabetes of the young, also referred to as monogenic diabetes in youth) syndromes (1), as well as in permanent neonatal diabetes mellitus (2) where mutations in genes essential for insulin secretion associate with elevated blood glucose. Causative alleles for β-cell dysfunction have been identified for the monogenic forms of diabetes. Likewise, a role for genes impacting glucose-stimulated insulin secretion has been proposed for some polygenic forms of diabetes mellitus. Genome-wide association studies have not associated single nucleotide polymorphisms (SNPs) in genes required for optimal insulin secretion with autoimmune type 1A diabetes. In contrast, latent autoimmune diabetes of adults has been associated with *TCF7L2* (3), a gene associated with reduced insulin secretion (4). *TCF7L2* is one of the most significant loci for type 2 diabetes (5) and, along with *HNF1B/HNF4A* (6) and *KCNJ11* (7), tie genes involved in β-cell dysfunction to risk for developing type 2 diabetes in overweight individuals. In this issue of *Diabetes*, a new report (8) proposes that a recently identified type 2 diabetes risk gene is linked to dysfunctional glucose-stimulated insulin secretion (GSIS) in lean Japanese patients with type 2 diabetes.

Lean type 2 diabetes is highly prevalent in Japan where more than half of the patients with this condition are considered normal weight (BMI <25) (9,10). The contrasting general clinical phenotypes of obese individuals with type 2 diabetes compared with lean individuals with type 2 diabetes have recently been detailed (9). In this report of 40 case subjects with a diabetes duration of 10–12 years, patients had an average age of onset of 56 ± 2 years, low BMI (21 kg/m^2), HbA_{1c} of 6.7 ± 0.1%, and fasting blood glucose of 144 ± 9 mg/dL. Diabetes in lean Japanese patients has been associated with a low level of fasting insulin (32 ± 17 pmol/L) in addition to reduced peripheral glucose uptake (2.3 ± 0.6 mg/kg/min) and elevated endogenous glucose production (13.8 ± 1.8 μmol/kg/min) (11). These data suggest that this disorder in normal-weight individuals results from impaired insulin secretion and action.

Studies to identify the genes contributing to type 2 diabetes in lean individuals identified a region on chromosome 21q (12). Follow-up examination of this region led to the identification of *KCNJ15* (potassium inwardly-rectifying channel, subfamily J, member 15) as a susceptibility gene (13). *KCNJ15*, also known as Kir4.2, is expressed in a wide variety of tissues and cells including peripheral blood, kidney, and pancreatic islet cells (13). The risk allele mRNA is present at elevated levels due to increased mRNA stability. Overexpression of *KCNJ15* in the rat β-cell line INS1 resulted in a significant reduction in GSIS. These data support a role for the *KCNJ15* risk allele as causative in β-cell dysfunction observed in lean type 2 diabetic patients.

In this issue of *Diabetes*, Okamoto et al. (8) examined the mechanism whereby KCNJ15 inhibits GSIS using both in vitro and in vivo approaches and made several important observations. First, expression of *KCNJ15* is positively regulated by glucose. Second, the expression of *KCNJ15* was higher in the pancreatic islets of patients with type 2 diabetes. Additionally, knockdown of *KCNJ15* in INS1 cells resulted in an approximate twofold increase in GSIS. Likewise, using a small inhibitory RNA approach, the authors were able to convincingly improve GSIS in both euglycemic and diabetic mouse models through knockdown of *KCNJ15*. However, it should be noted that while the suppression of this gene in diabetic mice did increase insulin secretion, it did not fully correct blood glucose levels to within the normal range. Finally, it is reported that KCNJ15 associates with calcium-sensing receptor in the plasma membrane, and the authors proposed that this interaction blocks the KCNJ15 activity allowing for stabilization of "post-prandial" membrane potential.

Unlike the MODY syndromes in which a single genetic defect results in decreased insulin secretion, the pathogenesis of type 2 diabetes in normal-weight individuals likely requires the contribution of multiple genetic regions (12). The data by Okamoto et al. (8) provide an important step forward in our understanding of β-cell function/dysfunction and offer a paradigm to study the singular impact of a risk gene within the pathology of diabetes. Once a mechanistic role has been elucidated, this provides a further platform to investigate interactions with other identified risk alleles. Moving toward expression of the specific risk allele in human β-cells, primary or a cell line that secretes insulin (such as the recently developed EndoC-βH1 [14]), will provide a further understanding of how a synonymous SNP modifies protein function in a human system. It should also be pointed out that many of the SNPs associated with polygenic forms of diabetes are in noncoding regions or induce synonymous changes. Therefore, these studies provide a model for studying polymorphisms that impact protein activity or function but do not alter protein sequence or a promoter region.

From the [1]Department of Food Science and Human Nutrition, University of Florida, Gainesville, Florida; and the [2]Departments of Pathology, Immunology, and Laboratory Medicine, University of Florida, Gainesville, Florida.
Corresponding author: Clayton E. Mathews, clayton.mathews@pathology.ufl.edu.
DOI: 10.2337/db12-0373

See accompanying original article, p. 1734.

In light of these new data (8), the authors suggest KCNJ15 as a new pharmacological target for individuals with reduced insulin secretion. KCNJ15 depletion or inhibition with a small molecule may be an attractive therapeutic in any system where GSIS is decreased. This is strongly supported by the data provided by whole animal systems where knockdown of *Kcnj15* led to elevated insulin secretion in mice without diabetes and in mice with diabetes induced by a mutation in the insulin 2 (*Ins2*) gene, that is presumably independent of *Kcnj15*. However, caution should be exercised. KCNJ15 appears to have a major role in renal function (15,16), and diabetic patients represent a population at increased risk for renal failure (17).

In conclusion, Okamoto et al. (8) present compelling evidence that KCNJ15 plays a role in reduced insulin secretion and the C566T SNP is likely causative in type 2 diabetes. However, further work is required for a systematic understanding of how KCNJ15 blocks GSIS.

ACKNOWLEDGMENTS

This work was supported by grants from the National Institutes of Health (DK074656) (C.E.M.) as well as funding from the American Diabetes Association (C.E.M.), the Juvenile Diabetes Research Foundation (C.E.M.), and the Sebastian Family Endowment for Diabetes Research (C.E.M.).

No potential conflicts of interest relevant to this article were reported.

The authors thank Mr. Clive Wasserfall and Dr. Desmond Schatz for critical reading of the manuscript and valuable advice.

REFERENCES

1. Winter WE, Nakamura M, House DV. Monogenic diabetes mellitus in youth. The MODY syndromes. Endocrinol Metab Clin North Am 1999;28:765–785
2. Gloyn AL, Pearson ER, Antcliff JF, et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004;350:1838–1849
3. Grant SF, Hakonarson H, Schwartz S. Can the genetics of type 1 and type 2 diabetes shed light on the genetics of latent autoimmune diabetes in adults? Endocr Rev 2010;31:183–193
4. da Silva Xavier G, Loder MK, McDonald A, et al. TCF7L2 regulates late events in insulin secretion from pancreatic islet beta-cells. Diabetes 2009;58:894–905
5. Grant SF, Thorleifsson G, Reynisdottir I, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nat Genet 2006;38:320–323
6. Waters KM, Stram DO, Hassanein MT, et al. Consistent association of type 2 diabetes risk variants found in Europeans in diverse racial and ethnic groups. PLoS Genet 2010;6:e1001078
7. Tabara Y, Osawa H, Kawamoto R, et al. Replication study of candidate genes associated with type 2 diabetes based on genome-wide screening. Diabetes 2009;58:493–498
8. Okamoto K, Iwasaki N, Doi K, et al. Inhibition of glucose-stimulated insulin secretion by *KCNJ15*, a newly identified susceptibility gene for type 2 diabetes. Diabetes 2012;61:1734–1741
9. Tanaka S, Honda M, Wu B, Kazumi T. Clinical features of normal weight Japanese patients with type 2 diabetes who had formerly been obese. J Atheroscler Thromb 2011;18:115–121
10. Prato SD, LaSalle J, Matthaei S, Bailey CJ; Global Partnership for Effective Diabetes Management. Tailoring treatment to the individual in type 2 diabetes practical guidance from the Global Partnership for Effective Diabetes Management. Int J Clin Pract 2010;64:295–304
11. Takahara M, Kaneto H, Katakami N, Matsuoka TA, Matsuhisa M, Shimomura I. Impaired suppression of endogenous glucose production in lean Japanese patients with type 2 diabetes mellitus. Diabetes Res Clin Pract 2011;93:e1–e2
12. Iwasaki N, Cox NJ, Wang YQ, et al. Mapping genes influencing type 2 diabetes risk and BMI in Japanese subjects. Diabetes 2003;52:209–213
13. Okamoto K, Iwasaki N, Nishimura C, et al. Identification of KCNJ15 as a susceptibility gene in Asian patients with type 2 diabetes mellitus. Am J Hum Genet 2010;86:54–64
14. Ravassard P, Hazhouz Y, Pechberty S, et al. A genetically engineered human pancreatic β cell line exhibiting glucose-inducible insulin secretion. J Clin Invest 2011;121:3589–3597
15. Sindic A, Huang C, Chen AP, et al. MUPP1 complexes renal K+ channels to alter cell surface expression and whole cell currents. Am J Physiol Renal Physiol 2009;297:F36–F45
16. Pessia M, Imbrici P, D'Adamo MC, Salvatore L, Tucker SJ. Differential pH sensitivity of Kir4.1 and Kir4.2 potassium channels and their modulation by heteropolymerisation with Kir5.1. J Physiol 2001;532:359–367
17. Ueda H, Ishimura E, Shoji T, et al. Factors affecting progression of renal failure in patients with type 2 diabetes. Diabetes Care 2003;26:1530–1534