Type 2 Diabetes Susceptibility Gene *TCF7L2* and Its Role in β-Cell Function

Anna L. Gloyn, Matthias Braun, and Patrik Rorsman

Type 2 diabetes is associated with impaired insulin secretion. Both 1st- and 2nd-phase insulin secretion are reduced, but the effect is particularly pronounced for the 1st phase. The processes culminating in impaired insulin secretion are not fully understood, but both genetic and environmental factors are thought to play a role. Over the past 2 years, genome-wide association scans have transformed the genetic landscape of type 2 diabetes susceptibility, with the current gene count close to 20 (1). A couple of common themes have emerged from these studies. First, the majority of the genes identified thus far seem to affect diabetes susceptibility through β-cell dysfunction (2). Second, the risk alleles tend to be common in the population, but their effect on diabetes risk is relatively small (3,4).

TCF7L2, the susceptibility gene with the largest effect on disease susceptibility discovered to date, was identified pre–genome-wide association by Grant et al. in 2006, with rapid replication of its consequence on diabetes susceptibility in multiple populations (5–9). *TCF7L2* was a positional candidate gene that mapped to a region of genetic linkage to type 2 diabetes in the Icelandic population on chromosome 10. However, the identified *TCF7L2* risk allele, which was present in ~28% of control subjects and ~36% of type 2 diabetic individuals, could not explain this linkage, so the finding was actually serendipitous (5). The precise genetic defect that causes the association of *TCF7L2* with type 2 diabetes remains unclear. There is a large number of highly correlated variants, none of which are obvious functional candidates, that show association with diabetes (5). The most likely candidate is the single nucleotide polymorphism rs7903146, which shows the strongest association with diabetes and resides in a noncoding region with no obvious mutational mechanism. It is clear, however, that the effect of the *TCF7L2* risk allele is through a defect in insulin secretion (9).

There have been few studies investigating the role of TCF7L2 on insulin secretion in isolated islets. Recently, a study by Shu et al. (10) reported that silencing of *TCF7L2* by siRNA resulted in strong suppression of insulin secretion in human and mouse islets. Conversely, overexpression of *TCF7L2* stimulated insulin secretion. Exactly how TCF7L2 protein levels modulate insulin secretion was not established in the study by Shu et al.

The normal regulation of insulin secretion from pancreatic β-cells is well understood (Fig. 1*A* [11]). As reported in this issue of *Diabetes*, da Silva Xavier et al. (12) studied the effects of overexpression and knockdown of *TCF7L2* on β-cell function using an impressive battery of cell physiological techniques. They confirm that silencing of *TCF7L2* exerts a strong inhibitory effect on glucose-induced insulin secretion. By contrast, insulin secretion triggered by high extracellular K^+ was not affected. Unlike what was seen in the study of Shu et al., overexpression of *TCF7L2* did not affect insulin secretion. The inhibition of glucose-stimulated insulin secretion produced by *TCF7L2* silencing was not associated with any lowering of $[Ca^{2+}]_i$; if anything, the responses to glucose were larger in cells lacking TCF7L2. This suggests that glucose sensing in the β-cell was unaffected.

Given these functional data, the inhibitory action of *TCF7L2* gene silencing on glucose-induced insulin secretion seems paradoxical insofar as no part of the β-cell stimulus-secretion coupling was perturbed in a way that would suppress insulin release. This might indicate that the distal events involved in the fusion of the secretory granules might be involved (although the finding that insulin secretion elicited by high K^+ was unaffected seemingly militates against this notion). This would be consistent with the observation that *TCF7L2* silencing affected the levels of the exocytotic proteins syntaxin-1 and munc18-1. It is unlikely, however, that reduced expression of munc18-1 alone is responsible for the observed defect because knockdown of this protein in β-cells inhibited both glucose- and high-K^+–induced secretion and interfered with granule docking (13). The authors further investigated the secretory defect by capacitance measurements of the increase in cell surface area resulting from the addition of the granule membranes to the plasma membrane. When the β-cells were depolarized for 2.5 s, the inhibitory effect was limited to 40%. However, responses to depolarizations as short as 0.2 s were reduced by 80%. This is significant because the β-cell action potential is <100 ms (14). The observation that the inhibitory effect of *TCF7L2* silencing was particularly strong for the brief depolarizations suggests that TCF7L2 somehow affects the distribution of voltage-gated Ca^{2+} channels (Fig. 1*B*). There is evidence that interference with the association of Ca^{2+} channels and secretory granules principally affects exocytosis triggered by brief stimuli in β-cells (15). This would be in agreement with the observations that insulin secretion is evoked by high extracellular K^+. The latter condition produces a global elevation of $[Ca^{2+}]_i$ and triggers exocytosis of all release-competent granules at the plasma membrane regardless of whether they are associated with the voltage-gated Ca^{2+} channels (Fig. 1*C*).

From the Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, U.K.
Corresponding author: Patrik Rorsman, patrik.rorsman@drl.ox.ac.uk.
DOI: 10.2337/db09-0099

See accompanying original article, p. 894.

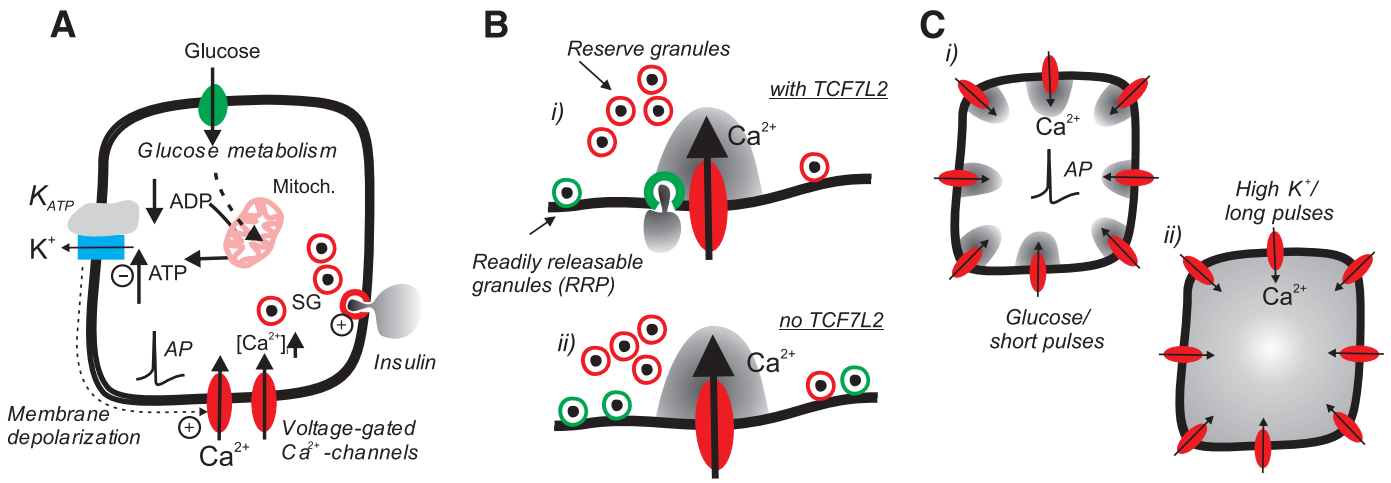

FIG. 1. Mechanisms by which *TCF7L2* silencing reduces glucose-stimulated insulin secretion. *A*: Stimulus-secretion coupling of the β-cell. Glucose, via mitochondrial (mitoch.) production of ATP and an increased ATP-to-ADP ratio, causes closure of ATP-sensitive K^+ (K_{ATP}) channels and elicits action potentials (APs) that are associated with the opening of voltage-gated Ca^{2+} channels. The increase in $[Ca^{2+}]_i$ stimulates exocytosis of insulin-containing secretory granules (SGs). *B*: The insulin granules belong to different functional pools, which differ with regard to release competence. The vast majority of granules did not attain release competence and belong to a reserve pool (red granules). A small fraction of the granules are immediately available for release: the readily releasable pool (RRP) (green granules). Many readily releasable pool granules are situated in close proximity of the voltage-gated Ca^{2+} channels (*i*). In the absence of TCF7L2, the Ca^{2+} channels may detach from the secretory granules and $[Ca^{2+}]_i$ increases in the wrong part of the β-cell (*ii*). *C*: Localized increases in $[Ca^{2+}]_i$ (gray zones) close to the Ca^{2+} channels during brief action potential–like stimulation (*i*) and the global elevation produced during protracted (e.g., high K^+) stimulation (*ii*).

Although it remains to be determined exactly how a reduction of TCF7L2 inhibits insulin secretion, the report of da Silva Xavier et al. is significant because it is one of the first detailed studies of the mechanisms by which the diabetes gene affects insulin secretion. The fact that the most strongly associated diabetes susceptibility variants in *TCF7L2* are all in the noncoding region suggests that they affect disease susceptibility by influencing the expression levels (16). The finding that silencing *TCF7L2* is associated with strong inhibition of insulin secretion whereas overexpression, if anything, stimulates insulin secretion makes it tempting to speculate that diabetes results from reduced *TCF7L2* expression. It is therefore unexpected that the only study thus far that has compared *TCF7L2* expression in nondiabetic and diabetic human islets found that type 2 diabetes is associated with a fivefold increase in *TCF7L2* mRNA levels (17). Clearly, the latter observation must be confirmed. Finally, we echo the authors' statement that the changes in *TCF7L2* expression used in this study (and an earlier study) are "likely to considerably exceed those observed in carriers of the at-risk T-allele of TCF7L2. Future studies will be required to assess how more subtle variations in TCF7L2 level impact on β-cell function. . . ." In addition, studies investigating the temporal and specific *TCF7L2* isoform expression profiles in human islets are required to fully elucidate the role of this key transcription factor in islet development and function.

ACKNOWLEDGMENTS

A.L.G. is a Medical Research Council New Investigator (81696). P.R. is a Wolfson-Royal Society Merit Award Fellow. This study was supported by the Wellcome Trust and Diabetes UK.

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

REFERENCES

1. Prokopenko I, McCarthy MI, Lindgren CM: Type 2 diabetes: new genes, new understanding. *Trends Genet* 24:613–621, 2008
2. Gloyn AL, McCarthy MI: Genetics: how the UKPDS contributed to determining the genetic landscape of type 2 diabetes. *Diabet Med* 25 (Suppl 2):35–40, 2008
3. Lango H, the U.K. Type 2 Diabetes Genetics Consortium, Palmer CN, Morris AD, Zeggini E, Hattersley AT, McCarthy MI, Frayling TM, Weedon MN: Assessing the combined impact of 18 common genetic variants of modest effect sizes on type 2 diabetes risk. *Diabetes* 57:3129–3135, 2008
4. Yasuda K, Miyake K, Horikawa Y, Hara K, Osawa H, Furuta H, Hirota Y, Mori H, Jonsson A, Sato Y, Yamagata K, Hinokio Y, Wang HY, Tanahashi T, Nakamura N, Oka Y, Iwasaki N, Iwamoto Y, Yamada Y, Seino Y, Maegawa H, Kashiwagi A, Takeda J, Maeda E, Shin HD, Cho YM, Park KS, Lee HK, Ng MC, Ma RC, So WY, Chan JC, Lyssenko V, Tuomi T, Nilsson P, Groop L, Kamatani N, Sekine A, Nakamura Y, Yamamoto K, Yoshida T, Tokunaga K, Itakura M, Makino H, Nanjo K, Kadowaki T, Kasuga M: Variants in KCNQ1 are associated with susceptibility to type 2 diabetes mellitus. *Nat Genet* 40:1039–1040, 2008
5. Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K: Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. *Nat Genet* 38:320–323, 2006
6. Groves CJ, Zeggini E, Minton J, Frayling TM, Weedon MN, Rayner NW, Hitman GA, Walker M, Wiltshire S, Hattersley AT, McCarthy MI: Association analysis of 6,736 U.K. subjects provides replication and confirms *TCF7L2* as a type 2 diabetes susceptibility gene with a substantial effect on individual risk. *Diabetes* 55:2640–2644, 2006
7. Cauchi S, Meyre D, Choquet H, Dina C, Born C, Marre M, Balkau B, Froguel P: *TCF7L2* variation predicts hyperglycemia incidence in a French general population: the Data From an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) study. *Diabetes* 55:3189–3192, 2006
8. Damcott CM, Pollin TI, Reinhart LJ, Ott SH, Shen H, Silver KD, Mitchell BD, Shuldiner AR: Polymorphisms in the transcription factor 7-like 2 (*TCF7L2*) gene are associated with type 2 diabetes in the Amish: replication and evidence for a role in both insulin secretion and insulin resistance. *Diabetes* 55:2654–2659, 2006
9. Weedon MN: The importance of TCF7L2. *Diabet Med* 24:1062–1066, 2007
10. Shu L, Sauter NS, Schulthess FT, Matveyenko AV, Oberholzer J, Maedler K: Transcription factor 7-like 2 regulates β-cell survival and function in human pancreatic islets. *Diabetes* 57:645–653, 2008

11. Rorsman P, Renström E: Insulin granule dynamics in pancreatic beta cells. *Diabetologia* 46:1029–1045, 2003
12. da Silva Xavier G, Loder MK, McDonald A, Tarasov AI, Carzaniga R, Kronenberger K, Barg S, Rutter GA: TCF7L2 regulates late events in insulin secretion from pancreatic islet β-cells. *Diabetes* 58:894–905, 2009
13. Tomas A, Meda P, Regazzi R, Pessin JE, Halban PA: Munc 18-1 and granuphilin collaborate during insulin granule exocytosis. *Traffic* 9:813–832, 2008
14. Ribalet B, Beigelman PM: Calcium action potentials and potassium permeability activation in pancreatic beta-cells. *Am J Physiol* 239:C124–C133, 1980
15. Barg S, Ma X, Eliasson L, Galvanovskis J, Gopel SO, Obermuller S, Platzer J, Renstrom E, Trus M, Atlas D, Striessnig J, Rorsman P: Fast exocytosis with few Ca(2+) channels in insulin-secreting mouse pancreatic B cells. *Biophys J* 81:3308–3323, 2001
16. Jin T, Liu L: The Wnt signaling pathway effector TCF7L2 and type 2 diabetes mellitus. *Mol Endocrinol* 22:2383–2392, 2008
17. Lyssenko V, Lupi R, Marchetti P, Del Guerra S, Orho-Melander M, Almgren P, Sjogren M, Ling C, Eriksson KF, Lethagen AL, Mancarella R, Berglund G, Tuomi T, Nilsson P, Del Prato S, Groop L: Mechanisms by which common variants in the TCF7L2 gene increase risk of type 2 diabetes. *J Clin Invest* 117:2155–2163, 2007