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Renström, Erik

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Commentary

Impact of transcription factor 7-like 2 (TCF7L2) on pancreatic islet function and morphology in mice and men

E. Renström

Lund University Diabetes Center, Inga-Marie Nilssons gata 53 floor 3, SE-205 02 Malmö Sweden

Corresponding author: E. Renström, email erik.renstrom@med.lu.se

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Abbreviations:

GLP1	Glucagon-like peptide 1
GWAS	Genome-wide association study
SNP	Single-nucleotide polymorphism
TCF7L2	Transcription factor 7-like 2

Abstract

Common genetic variations in the gene encoding the Transcription factor 7-like 2 TCF7L2 reveal the strongest association with type 2-diabetes known to date. These lead to impaired insulin production and output, but the mechanisms of disease remain incompletely known. In this issue of Diabeteologia two publications provide new insights into *TCF7L2*-dependent diabetes.

The heterogeneity of type 2 diabetes, taken together with the number of genetic risk variants involved in the pathogenesis of the disease, calls for reflection when singling out the most important diabetes gene. Even so, few would object to the transcription factor *TCF7L2* being given that status. After the initial discovery of the strong association of genetic variation in *TCF7L2* with type 2 diabetes in 2006 [1], the subsequent genome-wide association studies (GWASs) for type 2 diabetes identified the single-nucleotide polymorphism (SNP) rs7903146 in intron 4 as the genetic variation most strongly associated with disease in European–American populations [2-5]. The importance of genetic variation in *TCF7L2* for type 2 diabetes has been replicated in numerous studies in populations of diverse ethical backgrounds, although the exact location of the genetic variation associated with the disease is different in cohorts of Asian descent [6].

The general lesson learnt from the GWASs is that the vast majority of genetic risk variants associated with type 2 diabetes reduce the capacity for insulin secretion. Likewise, the clinical phenotype of *TCF7L2*-related type 2 diabetes is that of insulin deficiency. As for any genetic risk variant that associates with insulin deficiency, it may result from cellular factors that reduce beta cell mass and/or lower insulin output by impairing beta cell function. At present, we lack methods to unequivocally determine the predominant mechanism of reduced insulin production at different stages of disease. Be that as it may, the genetic discoveries have prompted intense activity in the area of islet biology. Despite the collective efforts by many different groups we are still far from having a unifying view on which functions transcription factor 7-like 2 (TCF7L2) protein fulfils under normal conditions, or how these fail during the development and progression of type 2 diabetes. The report by da Silva and colleagues in this issue of *Diabetologia* [7] adds another important facet to the evolving understanding of this transcription factor in glucose homeostasis. The present study clarifies several of the outstanding issues concerning the fundamental actions of *TCF7L2* and its products on beta cell performance.

TCF7L2 is part of a transcriptional complex with broad target specificity. Furthermore, transcription of target genes may either be suppressed or activated depending on cellular conditions. Compounding this, *TCF7L2* is subject to tissue- and perhaps context-dependent alternative splicing. This is likely to affect target gene specificity, as well as the degree of activation vs repression of target gene expression. The authors and the Maedler laboratory have previously reported that silencing small interfering (si)RNAs expected to prevent formation of all TCF7L2 isoforms affects the capacity for insulin secretion in rodents [8, 9]. Collectively, these studies point to a role of the transcription factor in the later stages of the insulin stimulus secretion coupling. This is associated with downregulation of several exocytosis-regulating proteins, but also an increased rate of apoptosis. The latter effect was demonstrated by the Hansson group to involve the tumour suppressor protein p53 pathway

[10], and it suggests that TCF7L2 may play a role in maintaining an appropriate beta cell mass.

Furthermore, patients with the risk T allele in rs7903146 display a clearly deteriorated incretin effect (i.e. the normal amplification of insulin output in response to a glucose load when given orally instead of intravenously is compromised) [11]. In this context, it is of particular interest that several lines of evidence suggest cross-talk between TCF7L2 and the incretin hormone glucagon-like peptide 1 (GLP1). Initially, the proglucagon gene was suggested as a potential target of TCF7L2 and impaired GLP1 production in the intestinal L cells was, for a while, the prime suspect in TCF7L2-dependent diabetes. This hypothesis was later abandoned, but there are repeated reports that the levels of the GLP1 receptor (GLP1r) transcript are suppressed when *TCF7L2* expression is silenced [8, 12, 13]. GLP1 amplifies glucose-induced insulin secretion and maintains beta cell mass by suppressing apoptosis and stimulating proliferation. In fact, the latter effect has been specifically demonstrated to depend on TCF7L2 [14], offering a potentially specific mechanism for how TCF7L2 may affect beta cell mass.

TCF7L2 is widely expressed, with particularly high levels in, for example, certain regions of the brain; in contrast, expression in the pancreas is relatively modest. Although clinical data without doubt favour a pancreatic origin of TCF7L2-dependent diabetes, it is impossible to unequivocally rule out that metabolically active tissues other than the pancreas are the relevant ones for diabetes pathology. Here, mouse models may offer important keys to a better understanding and also allow for direct studies of beta cell mass. Mice with global ablation of *Tcf7l2* have previously been generated[15]. However, homozygous *Tcf7l2*-null mice die shortly after birth, and study of heterozygous mice with one intact allele cannot help to establish the specific role of the pancreas in *Tcf7l2*-dependent pathology.

To overcome these shortcomings, the authors generated a pancreas-specific *Tcf7l2*-null mouse strain (*pTcf7l2*) by crossing *pTcf7l2*-flox mice with mice expressing Cre recombinase under the control of the pancreatic and duodenal homeobox 1 (PDX1). Interestingly, these mice had impaired oral glucose tolerance from week 12, and later, at week 20, also developed intolerance to intravenous glucose loads. Moreover, glucose- and GLP1-stimulated insulin secretion in islets from *pTcf7l2* mice was markedly reduced. Interestingly, this coincided with reduced GLP1-receptor (*Glp1r*) and insulin (*Ins2*) gene expression. Finally, the authors demonstrated that *pTcf7l2* mice maintained on a high-fat diet failed to expand the beta cell volume to the same degree as their control littermates. These results provide direct evidence for the importance of pancreatic TCF7L2 for maintaining glucose tolerance. They also provide strong evidence for the involvement of GLP1 signalling in that respect.

This work clarifies the physiological role of pancreatic TCF7L2 and provides a solid platform for further endeavours to understand how genetic variation in the human *TCF7L2* gene generates the increased risk of type 2 diabetes. Intriguingly, another report in the current issue of *Diabetologia*, by Le Bacquer and colleagues [16], investigates the functional and morphological consequences of rs7903146 in human islets. Homozygous T/T risk allele carriers exhibit slightly reduced insulin release under both basal and glucose-stimulated conditions. Moreover, a reduction in islet density is accompanied by an increased islet size and, importantly, an apparent increase in the ratio of alpha to beta cells in the islets. These observations call for further mechanistic studies and the *pTcf7l2* mouse strain may be a useful tool for such endeavours.

Several questions remain to be answered: for example, we are still at a loss as to how the appropriate type 2 diabetes mouse model should be constructed. Whereas several reports of increased *TCF7L2* transcript expression in human islets from patients with type 2 diabetes have emerged, this does not necessarily translate to TCF7L2 protein production. By contrast, islet TCF7L2 protein production has been suggested to be reduced in type 2 diabetes [9]. Furthermore, the isoform pattern in different tissues is beginning to unravel [12, 17, 18] and needs to be determined according to genotype. When effects on target specificity and downstream transcriptional activity have finally been determined before and after onset of type 2 diabetes, there will be better prospects for specific intervention.

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Contribution statement

The author was responsible for the conception, design and drafting of the manuscript and approved the final version for publication

Duality of interest

The author declares that there is no duality of interest associated with this manuscript.

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