Walking a fine line between β-cell secretion and proliferation

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Of the many common genetic variants associated with type 2 diabetes, that in TCF7L2 remains the most studied because it has the greatest effect size. However, the mechanism by which this variant alters diabetes risk remains elusive. A new study adds another layer of complexity, suggesting that the effects of TCF7L2 are context-dependent, and highlights a novel interaction that might bias a β-cell to a secretory or proliferative phenotype. This in turn might open up new avenues to the restoration of insulin secretion in people with type 2 diabetes.

Diabetes is a disease that is characterized by hyperglycemia and broadly categorized into type 1 and type 2 diabetes. In the former, near absolute insulin deficiency arises from immune-mediated destruction of insulin-producing β-cells. On the other hand, type 2 diabetes is more heterogeneous, and its pathophysiology is less clearly defined. Broadly speaking, type 2 diabetes is also characterized by impaired insulin secretion for the prevailing hyperglycemia. The insulin deficiency in type 2 diabetes is relative, not absolute, but it is compounded by multiple other abnormalities such as a decreased ability of insulin to stimulate glucose uptake and suppress glucose production (insulin action) and an impaired ability of glucose per se to stimulate its own uptake and suppress its own production and release (glucose effectiveness). Abnormal secretion of glucagon, which produces effects opposite to those of insulin, by the pancreatic α-cells is also present. The advent of genome-wide association studies (GWAS) has led to the identification of more than 70 loci with moderate-to-weak effects on predisposition to diabetes. These variants have provided clues as to the pathways involved in the pathogenesis of type 2 diabetes (1).

Unfortunately, follow-up genotype–phenotype studies have been limited by the relatively weak effects on complex phenotypes (which are difficult and expensive to measure in large cohorts) and by the fact that the variants identified by GWAS are sometimes not the causative variants and indeed may not reside within or close to the physiologically relevant target gene. Of the common variants associated with type 2 diabetes, the rs7903146 variant in TCF7L2 has the largest effect on diabetes pathogenesis (1, 2). More importantly, detailed fine-mapping in multiple populations has established that if rs7903146 is not the causal variant, it is indistinguishable from the causative variant (3).

TCF7L2 is a transcription factor that is part of the Wnt signaling system and was first described as a regulator of proglucagon expression in enteroendocrine cells, which secrete proglucagon-derived peptides such as glucagon-like peptide-1 (GLP-1) in response to food ingestion (4). GLP-1 in turn stimulates insulin secretion; as a result, it was initially suggested that diabetes predisposition conferred by the diabetes-associated allele (T) at rs7903146 was a reflection of decreased GLP-1-stimulated insulin secretion (2). However, although insulin secretion is decreased in individuals carrying a T-allele at rs7903146, GLP-1 secretion and action are unchanged by the diabetes-associated variant (5). More recent data further suggest that the diabetes-associated allele also impairs post-prandial suppression of glucagon (6), perhaps by influencing proglucagon expression (and glucagon content) in α-cells. These combined data point to an upstream, but still poorly defined, role for this mutation.

The importance of TCF7L2 to β-cell and α-cell function (7) has been confirmed at the cellular level, via targeted gene deletion. Inhibition or deletion of TCF7L2 impairs glucose-stimulated insulin secretion. It also impedes the expansion of β-cell mass, necessary for adaptation to a high-fat diet. In this issue of JBC, Nguyen-Tu et al. (8) examined the effect of Tcf7l2 deletion in a mouse model of β-cell expansion and report some unexpected findings when liver kinase B1 (LKB1), a tumor-suppressor gene mutated in Peutz-Jeghers syndrome is deleted in the β-cell. Although LKB1 has not been associated with diabetes, β-cell–specific deletion of this gene increases β-cell mass and insulin secretion. LKB1 also inhibits mammalian target of rapamycin (mTOR), which drives protein synthesis and cell division. Like TCF7L2, it is part of the Wnt signaling system and inactivates glycogen synthase kinase-3 (GSK3).

In contrast to its usual effects, on an Lkb1-null background, deletion of both copies of Tcf7l2 to yield Blkb1-Tcf7l2-dKO mice (further) increased insulin secretion, β-cell size, and β-cell mass. Consistent with the increase in β-cell mass, the dKO mice exhibited a significant increase in mitosis and mTOR activation, as monitored via levels of phosphoribosomal protein subunit S6 (rpS6). β-Catenin (which activates the TCF family) and axin-2 (a negative regulator of Wnt signaling) levels are normally decreased by Lkb1 deletion. However, in the dKO mice,
axin-2 levels were increased, raising the possibility that LKB1 and Wnt/TCF7L2 cross-talk regulates β-cell proliferation in a context-specific manner. Another novel observation is that the disruption in β-cell glucose-sensing and cytosolic Ca2+ induced by loss of LKB1 is not rectified by loss of Tcf7l2, despite improved insulin secretion. This suggests mechanisms downstream of glucose-sensing are responsible for the enhanced islet function observed in this model (Fig. 1). Rosette formation, a surrogate for within-islet cellular connectivity, is increased in βLkb1-KO mice and βLkb1-Tcf7l2-dKO mice, but the significance of this finding is uncertain.

It is also notable that, in this model system, there is enhanced β-cell growth and the increased islet mass is accompanied by enhanced glucose-stimulated insulin secretion. Immature β-cells are able to proliferate but are not glucose-responsive. The converse is true for fully differentiated β-cells (9). Indeed, in uncontrolled diabetes, β-cells often exhibit characteristics similar to immature β-cells. mTOR is a key regulator of cell growth and proliferation and, in response to nutrients and specific regulators, increases β-cell mass and proliferation albeit at the expense of insulin secretion. In contrast, AMP-activated protein kinase (AMPK) promotes energy production and limits the expense of insulin secretion. In mature rodent (but not human) β-cells, AMPK disruption impairs insulin secretion and may enhance β-cell proliferation (reviewed in Ref. 10).

Nuclear co-localization of TCF7L2 and β-catenin activated by the canonical Wnt signaling pathway typically increases β-cell proliferation. This pathway can be initiated by GLP-1, although there is little data to suggest that GLP-1 can drive β-cell proliferation in humans. However, in βLkb1-KO mice, where β-cell proliferation is already increased, both β-catenin (a positive regulator of growth in this pathway) and axin-2 (a negative regulator of growth in this pathway) are decreased. Tcf7l2 expression was increased. Unexpectedly, in these mice, mTOR signaling was unchanged, perhaps restrained by TCF7L2, given the subsequent increase in Tcf7l2-null mice. This was accompanied by an increase in axin-2. Perhaps these findings suggest that the balance between growth and function in β-cells is ultimately determined by the relative activity of TCF7L2, mTOR, and axin-2.

Understanding the regulation of the balance between β-cell maturation (and the ability to secrete insulin in a glucose-responsive manner) and proliferation might enable simultaneous enhancement of both processes. Although these mechanisms cannot replicate the subtle effects of genetic variation in TCF7L2 on TCF7L2 function and predisposition to type 2 diabetes in humans, they might prove to be mile markers on the road to restoring insulin secretion in type 2 diabetes, a road illuminated by better understanding of TCF7L2 function.

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