Commentary

MOLECULAR METABOLISM

Beyond association: A functional role for Tcf7l2 in β-cell development*

Adriana Migliorini [1,2], Heiko Lickert [1,2,3,4,5,*]

Tcf7l2, also known as Tcf4, is a member of the HMG-box containing T-cell factor (Tcf)/Lymphoid enhancer factor (Lef) transcription factor family of DNA binding proteins downstream of the canonical Wnt pathway [1]. In addition to its well known role during development recent evidence suggests that the Wnt pathway is implicated in stem cell homeostasis, cancer development and metabolic disorders [2]. Thus, it is not surprising, that genome wide association studies (GWAS) have identified *TCF7L2* as a locus conveying an increased risk for developing type 2 diabetes (T2D) for the homozygous carrier of the minor allele [3]. Since this finding, several studies have focused on understanding the mechanism underlying the metabolic function of Tcf7l2 in organs and in pancreatic β-cells. In the small intestine, Tcf7l2-dependent Wnt signaling is essential for maintenance of proliferating cells located in the "intervillus pockets" as well as for the differentiation towards the hormone-producing enteroendocrine lineage [2]. In these cells, Tcf7l2 regulates pro-glucagon expression, precursor of glucagon-derived hormones. In the adult pancreas, cumulative evidence suggests that Tcf7l2/β-catenin signaling is critical for Glucagon-like peptide 1 (Glp-1) induced β-cell proliferation and Stromal-derived factor 1 (Sdf-1)-mediated β-cell survival [4]. Moreover, recent data indicate that alternative splicing isoforms of *TCF7L2* differently regulate β-cell proliferation and glucose-dependent insulin secretion in adult human islets [5]. Despite all these efforts, many questions remain, e.g. which metabolic organ requires Wnt/Tcf7l2 signaling for its function, when is Tcf7l2 function required for organ development and homeostasis, and is Tcf7l2 function conserved between the pre-clinical mouse model and human patients? Answers to these questions will unravel the contribution of TCF7L2 to the development of diabetes.

In the April 2015 issue of *Molecular Metabolism*, Shao et al. provide new insight on the function of TCF7L2 in pancreatic β-cells [6]. The authors used an adenoviral vector system expressing a dominant-negative (DN) variant of TCF7L2 (TCF7L2DN) to attenuate canonical WNT/β-catenin signaling in insulinoma cells (Ins-1) and during pancreas development as well as in the adult islet. Specifically, forced expression of TCF7L2DN in Ins-1 cells represses β-cell proliferation, glucose-dependent insulin secretion and down-regulates key β-cell genes, such as *MafA*, *Isl1*, *Pdx1* and the canonical Wnt target gene *Axin2*. Despite the lack of mechanistic data, this is an interesting starting point to investigate if *MafA*, *Isl1 and Pdx1* represent novel pancreas specific target genes of TCF7L2/β-catenin signaling pathway. Additionally, Shao et al. observed the down regulation of *Glp-1* receptor and Glucose-dependent insulin tropic polypeptide (*Gip*) receptor following the expression of *TCF7L2DN*. This is consistent with a previous study where the correlation between Glp-1 and TCF7L2/β-catenin pathway was already established [7]. Specifically, it was shown that activation of Glp-1 increased canonical Wnt signaling in Ins-1 cells and overexpression of TCF7L2DN was found to repress Glp-1 mediated β-cell proliferation. Existing data from human T2D islets revealed the correlation between decreased levels of TCF7L2 and incretin hormone receptor expression [8]. Collectively, these data support the hypothesis that WNT/β-catenin signaling via TCF7L2 regulates GLP-1 effects in β-cells by transcriptionally controlling its receptor.

Surprisingly, the *in vitro* results from the Ins-1 insulinoma system cannot be confirmed directly *in vivo* by the postnatal expression of *TCF7L2DN* under the Insulin 2 promoter (*βTCFDN* mice) [6]. Specifically, attenuation of Wnt/β-catenin signaling shortly after birth resulted in down regulation of *MafA* and *Pdx1* expression in islets. No alteration of β-cell mass, homeostasis and glucose control during adulthood was noted either when TCF7L2DN was expressed before or after weaning. Boj et al. found similar results when using a rat insulin promoter (RIP)-driven inducible Cre-ER^{T2} recombinase approach to ablate *Tcf7l2* specifically in adult β-cells at weaning and did not observe β-cell dysfunction either on normal chow or high-fat diet [9]. Moreover, this study revealed that full body knock-out of *Tcf7l2* had no effect on embryonic development of the endocrine pancreas, the expression of β-cell genes and β-cell proliferation. The authors of this study conclude that Tcf7l2 is not important for β-cell function in mice but controls the hepatic response to perinatal and adult metabolic

*This commentary refers to "The expression of dominant negative TCF7L2 in pancreatic beta cells during the embryonic stage causes impaired glucose homeostasis by Weijuan Shao et al.", http://dx.doi.org/10.1016/j.molmet.2015.01.008.

[1]Institute of Stem Cell Research (ISF), Helmholtz Center, Munich, Germany [2]Institute of Diabetes and Regeneration (IDR), Helmholtz Center, Munich, Germany [3]Technical University Munich (TUM), Germany [4]German Center for Diabetes Research (DZD), Germany [5]Helmholtz Alliance ICEMED – Imaging and Curing Environmental Metabolic Diseases.(ICEMED), Helmholtz Zentrum München, Deutsches Forschungszentrum für Gesundheit und Umwelt (GmbH), Ingolstädter Landstr. 1, 85764 Neuherberg, Germany

*Corresponding author. Helmholtz Zentrum München, Am Parkring 11, D-85748, Business Campus Garching, Germany. Tel.: +49 89 3187 3760; fax: +49 89 3187 3761. E-mail: heiko.lickert@helmholtz-muenchen.de (H. Lickert).

Received March 7, 2015 • Accepted March 7, 2015 • Available online 17 March 2015

http://dx.doi.org/10.1016/j.molmet.2015.03.002

demand, besides its function for intestinal stem cell homeostasis and endocrine lineage formation in the gut. This is in stark contrast to the study of Xavier et al. who reported that the ablation of *Tcf7l2* in Pdx1$^+$ progenitor cells during pancreas development resulted in glucose intolerance and altered β-cell function [10]. The work of Shao et al. is in line with these results and found that embryonic expression of *TCFL2DN* affects β-cell development and homeostasis [6]. In particular, a reduced number of pancreatic Pdx1$^+$/Nkx6.1$^+$ double positive cells were formed, which caused an altered β-cell mass and abnormal insulin secretion in adult mice. These findings are comparable to previous data from Mitchell et al. where embryonic Tcf7l2 ablation using an Ins1-Cre driver line which is active already at embryonic day (E) 11.5 led to impaired β-cell mass and secretory function [6,11]. These observations emphasize that Tcf7l2 function is required when β-cells are born during pancreas development, but might also be needed to maintain β-cell homeostasis in the adult islet. Specifically, ectopic stabilization of β-catenin in pancreatic epithelium during the first transition leads to loss of *Pdx1* expression, whereby inducing the stabilized form of β-catenin during the second transition positively influences pancreatic progenitor proliferation, resulting in increased pancreas organ size [12]. Collectively, these findings suggest that temporal and spatial regulation of the Wnt/β-catenin signaling pathway plays a critical role during pancreatic development and islet homeostasis and that compensatory mechanisms might be in place in the Tcf7l2 knock-out model [4,13]. Additional mechanistic studies are needed to explain the discrepancies among the different mouse models in terms of compensation in the Lef/Tcf transcription factor family, genetic background and efficiency of gene ablation or inhibition.

Overall, accumulating evidence has emphasized the importance of Wnt/β-catenin signaling pathway in β-cell development and homeostasis. In human, genetic and metabolic phenotyping clearly reveals that subjects carrying *TCF7L2* polymorphisms display insulin secretion defects in the presence of normal incretin plasma levels [14], suggesting an autonomous role of WNT/TCF7L2 signaling in β-cells and making it an attractive target for development of novel therapies for diabetes. In the future, the key to mechanistic understanding will lie in the investigation of a suitable human model system to unravel WNT/TCF7L2 function in β-cell homeostasis.

REFERENCES

[1] Lickert, H., et al., 2000. Wnt/(beta)-catenin signaling regulates the expression of the homeobox gene Cdx1 in embryonic intestine. Development 127(17):3805–3813.

[2] Schepers, A., Clevers, H., 2012. Wnt signaling, stem cells, and cancer of the gastrointestinal tract. Cold Spring Harbor Perspectives in Biology 4(4):a007989.

[3] Grant, S.F., et al., 2006. Variant of transcription factor 7-like 2 (TCF7L2) gene confers risk of type 2 diabetes. Nature Genetics 38(3):320–323.

[4] Liu, Z., Habener, J.F., 2010. Wnt signaling in pancreatic islets. Advances in Experimental Medicine and Biology 654:391–419.

[5] Le Bacquer, O., et al., 2011. TCF7L2 splice variants have distinct effects on beta-cell turnover and function. Human Molecular Genetics 20(10):1906–1915.

[6] Shao, Weijuan, Xiong, Xiaoquan, Ip, Wilfred, Xu, Fenghao, Song, Zhuolun, Zeng, Kejing, et al., 2015. The expression of dominant negative TCF7L2 in pancreatic beta cells during the embryonic stage causes impaired glucose homeostasis. Molecular Metabolism 4(4):344–352. http://dx.doi.org/10.1016/j.molmet.2015.01.008 [in press].

[7] Liu, Z., Habener, J.F., 2008. Glucagon-like peptide-1 activation of TCF7L2-dependent Wnt signaling enhances pancreatic beta cell proliferation. Journal of Biological Chemistry 283(13):8723–8735.

[8] Shu, L., et al., 2009. Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP-1 receptors and impaired beta-cell function. Human Molecular Genetics 18(13):2388–2399.

[9] Boj, S.F., et al., 2012. Diabetes risk gene and Wnt effector Tcf7l2/TCF4 controls hepatic response to perinatal and adult metabolic demand. Cell 151(7):1595–1607.

[10] da Silva Xavier, G., et al., 2012. Abnormal glucose tolerance and insulin secretion in pancreas-specific Tcf7l2-null mice. Diabetologia 55(10):2667–2676.

[11] Mitchell, R.K., et al., 2015 Mar 1. Selective disruption of Tcf7l2 in the pancreatic beta cell impairs secretory function and lowers beta cell mass. Human Molecular Genetics 24(5):1390–1399. http://dx.doi.org/10.1093/hmg/ddu553.

[12] Heiser, P.W., et al., 2006. Stabilization of beta-catenin impacts pancreas growth. Development 133(10):2023–2032.

[13] Puri, S., Hebrok, M., 2010. Cellular plasticity within the pancreas—lessons learned from development. Developmental Cell 18(3):342–356.

[14] Schafer, S.A., et al., 2007. Impaired glucagon-like peptide-1-induced insulin secretion in carriers of transcription factor 7-like 2 (TCF7L2) gene polymorphisms. Diabetologia 50(12):2443–2450.

