Genes & Diseases (2016) 3, 48–55

HOSTED BY

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://ees.elsevier.com/gendis/default.asp

REVIEW ARTICLE

Current understanding and dispute on the function of the Wnt signaling pathway effector TCF7L2 in hepatic gluconeogenesis

Tianru Jin

Department of Medicine, University of Toronto, Toronto, Canada

Received 25 September 2015; accepted 27 October 2015
Available online 17 November 2015

KEYWORDS
β-Catenin;
Gluconeogenesis;
Insulin;
TCF7L2;
Transgenic mice;
Type 2 diabetes;
Wnt

Abstract Approximately 10 years ago, the Wnt signaling pathway effector TCF7L2 (=TCF-4) was recognized as a type 2 diabetes (T2D) risk gene through a genome wide association study (GWAS). As the correlation between *TCF7L2* polymorphisms and T2D susceptibility has been reproducibly observed by numerous follow-up investigations among different ethnic groups, great efforts have been made to explore the function of TCF7L2 in metabolic organs including the pancreas, liver and adipose tissues. Although these explorations have enriched our general knowledge on the Wnt signaling cascade in metabolic homeostasis, studies conducted to date have also generated controversial suggestions. Here I will provide a brief review on the Wnt signaling pathway as well as the milestone GWAS discovery and the follow-up studies. I will then discuss the two different opinions on the correlation between *TCF7L2* variants and T2D risk, a gain-of-function event versus a loss-of-function event. This will be followed by summarizing the relevant investigations on the metabolic function of hepatic TCF7L2 and presenting our view on the discrepancy and perspectives.

The recognition of *TCF7L2* as a diabetic risk gene

Although several early investigations have indicated the role of Wnt signaling pathway in the production and function of certain metabolic hormones,[1–4] the intensive global attention to the function of this pathway on glucose homeostasis started in 2006, after a genome wide association study (GWAS) performed by Grant and colleagues revealed the linkage between the polymorphisms of the Wnt signaling pathway effector TCF7L2 and the risk of type 2 diabetes (T2D).[5]

E-mail address: tianru.jin@utoronto.ca.
Peer review under responsibility of Chongqing Medical University.

http://dx.doi.org/10.1016/j.gendis.2015.10.002

Back to 1999 and 2003, investigators had revealed that a region on chromosome 10q is linked to T2D susceptibility.[6,7] Briefly, using a variance-components technique for conducting multi-point linkage analyses in a Mexican American population, Duggirala et al obtained evidence that there is a T2D susceptibility locus on chromosome 10q.[6] In 2003, a genome wide linkage study performed by Reynisdottir et al in an Icelandic population yielded the linkages of T2D susceptibility to regions on chromosome 5q34-q35.2, 12q, as well as10q.[7] Three years later, Grant et al defined the genetic linkage on chromosomal 10q.[5]

Grant et al genotyped 228 microsatellite markers in a cohort of Icelandic subjects with T2D and healthy controls across a 10.5-Mb interval on the chromosome 10q. The microsatellite, DG10S478, located within the intron 3 region of the *TCF7L2* gene (previously known as *TCF-4*) was found to be associated with the T2D susceptibility. This correlation was then replicated in a U.S. cohort as well as a Danish cohort. Furthermore, two single nucleotide polymorphisms (SNPs) known as rs12255372 and rs7903146 were found to be in strong linkage disequilibrium with DG10S478 and also showed similar robust associations with T2D susceptibility. By comparing with the non-carriers, they calculated that heterozygous and homozygous carriers of the at-risk alleles have relative risks of T2D of 1.45 and 2.41, respectively.[5] Importantly, this association has been replicated by numerous investigations among different ethnic populations.[8–14] Studies have also revealed the linkage between these T2D susceptibility SNPs with cardiovascular and other complications of T2D.[15,16]

Wnt signaling pathway and its key effector β-catenin/TCF

The Wnt signaling pathway was initially identified in cancer research and embryologic developmental studies[17,18]; while the physiological role of Wnt signaling in metabolic homeostasis and its implications in metabolic disorders have received broad attention since last decade,[1,19,20] especially after TCF7L2 is recognized as an important T2D risk gene.[5]

The key effector of Wnt pathway is β-catenin (β-cat)/TCF (cat/TCF), formed by free β-cat and a member of the TCF transcription factor family, including TCF7L2.[21] TCFs possess a high mobility group box (HMG) DNA binding domain while β-cat provides the transcriptional activation domain. In resting cells, free β-cat levels are tightly controlled by the proteasome-mediated degradation process (Fig. 1A, left panel). This involves the actions of the degradation complex on β-cat. The key components of this degradation complex are two tumor suppressors, adenomatous polyposis coli (APC) and axin/conduction; as well as two protein kinases, the serine/threonine kinase glycogen synthase kinase-3 (GSK-3) and casein kinases 1α (CK-1α). Following binding of a canonical Wnt ligand to the Frizzled receptor and LRP5/6 co-receptor, the degradation complex is dissociated, with the participation of the protein namely dishevelled (Dvl). This will prevent the degradation of free β-cat, which will accumulate and enter the nucleus, resulting in the formation of cat/TCF and the activation of cat/TCF (or Wnt signaling pathway) downstream target gene expression (Fig. 1A, right panel). Importantly, in the absence of β-cat, however, TCFs may repress Wnt target gene expression via recruiting nuclear co-repressors, such as histone deacetylases (HDACs), C-terminal binding protein 1 (CtBP1) and transducin-like enhancer of split (TLE), the mammalian homologue of Drosophila Groucho.

Fig. 1A also shows that in addition to serving as the effector of Wnt ligands, cat/TCF can mediate the function of certain hormonal factors, such as the two important metabolic hormones, insulin and glucagon-like peptide-1 (GLP-1).[22,23] This can be achieved by regulating TCF7L2 expression and by stimulating the phosphorylation on β-cat C-terminal serine residues (S675 and S552) (Fig. 1B).[22,24–29] Our experimental results demonstrated that feeding increased hepatic Tcf7l2 mRNA and protein levels in mice, while *in vitro* insulin treatment in primary hepatocytes increased both Tcf7l2 expression and β-cat S675 phosphorylation.[22] In pancreatic β-cells, Liu and Habener, as well as my team demonstrated the effect of GLP-1 on β-cat S675 phosphorylation.[30,31]

Mouse brain was shown to express dominant negative Tcf7l2 molecules during the early embryonic developmental stage.[32] Whether such native dominant negative molecules are expressed during adulthood in any peripheral organ is unknown. Scientists, however, can generate dominant negative TCF7L2 (TCF7L2DN) for attenuating Wnt signaling in various systems or cell lineages.[2,24,31,33–38]

TCF7L2 structure and the positions of T2D risk SNPs

Fig. 2 shows the intron-exon structure of *TCF7L2* and the SNPs that were found to be associated with T2D susceptibility. In addition to rs12255372 and rs7903146 which are known to be strongly associated with T2D risk in Caucasian populations, two other SNPs, known as rs290487 and rs11196218 were also indicated. They were recognized as the risk SNPs for an Asian population study and a study in a Hong Kong Chinese population.[12,13] The *TCF7L2* gene consists of 17 exons. Among them, exon 4, 13, 14, 15 and 16 can be alternatively spliced, leading to the generation of 13 different transcripts. Such overall organization is conserved between humans and rodents. However, the sizes of protein products detected by Western blot for most tissues are 78 kDa and 58 kDa, respectively. A recent mouse embryonic study revealed the existence of brain specific promoters Ex1b-e, located within intron 5.[32] Transcripts from these promoters will lead to the generation of TCF7L2 that lack the N-terminal β-cat interaction domain, anticipating function as native dominant negative molecules.[32] We cannot detect such transcripts in adult mouse liver or pancreas, although it is expressed in the mouse brain (data not shown). Whether such transcripts exist in any of the human tissues remains unknown.

TCF7L2 variants in T2D risk, gain-of-function or loss-of-function?

TCF7L2 T2D risk SNPs are located within the intron regions (Fig. 2). These SNPs may affect TCF7L2 expression, although it is difficult to determine the underlying