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Pivotal Role of Both TNF-α 238G/A and TCF7L2 C/T Gene Polymorphisms in Type 2 Diabetes

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Abstract

Single nucleotide polymorphism (SNP) studies in the promoter region of tumor necrosis factor-alpha (TNF-α (238)) have suggested its role in increased insulin resistance and also in the progression from prediabetes to type 2 diabetes (T2DM). It has been reported that genetic variations in the promoter region regulate TNF-α production and transcription, and they influence susceptibility to inflammatory-related diseases. Impairment of normal functioning of the β-cells of pancreatic islets is one of the main causative factors for the suppression of insulin secretion. TNF-α is among the main stimuli that induce the inflammation in pancreatic islets which lead to the induction of apoptosis in β-cells of pancreatic islets. Transcription factor 7-like 2 (TCF7L2) gene has been found to be one of the most risky genes for prediabetes and progression toT2DM. However, the underlying mechanism of this is still unknown. This is a review article demonstrating the possible mechanisms of both TNF-α G/A 238 and TCF7L2 C/T gene polymorphisms in prediabetes and type 2 diabetes mellitus.

Introduction

TNF-α, along with other pro-inflammatory cytokines, plays a central role in the pathogenesis and development of obesity-induced insulin resistance as evidenced by the augmented levels of TNF-α in systemic circulation, liver, and adipocytes [1], [2], [3], [4]. The phenomenon of TNF-α-induced insulin resistance is dependent on the intracellular and molecular mechanisms that involve the activation of stress-related protein kinases such as inhibitor kappa-beta kinase beta (IKKβ), Jun N-terminal kinase (JNK), and nuclear factor kappa-beta (NF-κB pathway) [5].

Insulin Resistance in Adipose Tissues

In diabetic individuals, the level of messenger ribonucleic acid (mRNA) of TNF-α and its protein increases in adipose tissues. Another way by which TNF-α impairs insulin sensitivity in adipose tissues consists of downregulation of protein level of insulin receptor substrate1 (IRS-1) and glucose transporter 4 (GLUT4). TNF-α also decreases fatty acid oxidation and increases plasma free fatty acid levels [6]. TNF-α alters lipid metabolism and protein in adipose tissues [7]. In isolated adipocyte, TNF-α suppresses the action of genes that are responsible for regulating the level of fatty acids uptake within the tissues. TNF-α is also responsible for the inhibition of lipoprotein lipase and starts lipolysis in adipose cells. As a result of this lipolysis, non-esterified fatty acid level increases, which results in the development of insulin resistance [8].

Insulin Resistance in Peripheral Tissues

TNF-α produced by the muscles also induces insulin resistance in skeletal muscles by inhibiting insulin action in peripheral tissues. Mostly, the muscles are accounted for glucose disposal, and it has been

reported that TNF-α increases the phosphorylation of JNK, and IRS-1 which is linked with the cascade of insulin signaling impairment in peripheral tissues [9].

TNF-α and Dysfunctioning of β-Cells of Pancreatic Islets

Impairment of normal functioning of the β-cells of pancreatic islets is one of the main causative factors for the suppression of insulin secretion. TNF-α is among the main stimuli that induce the inflammation in pancreatic islets which lead to the induction of apoptosis in β-cells of pancreatic islets [10], [11], [12]. TNF-α does this job by activating the transcriptional factor, that is, NF-κB which is an important modulator of pancreatic cell death [13], [14], [15].

Role of TCF7L2 Gene Polymorphism in T2DM

Genetic mutation in TCF7L2

A previous work [16] had illustrated the biological impact of the TCF7L2 in type 2 diabetes and the study suggested that this risk variant was due to the ancestral T allele of an SNP, rs7903146, through replication in West African and Danish with type 2 diabetes case–control studies and another Icelandic study. Then, other authors [17] had evaluated about 43 SNPs and the previously identified DG10S478 microsatellite in African American and suggested again that rs7903146 was the trait-defining polymorphism linked to the development of type 2 diabetes. These previous studies interpret the intron 3 SNP rs7903146 as the causal variant in the TCF7L2 gene. However, the underlying mechanism of it is still elusive [15].

Because the mutations in risk-related variants were present in an intronic region, rather an exon, it was reasonable to suggest that this regulatory process was associated with conferring the risk of T2DM [18]. The previous researchers found that the locus conferred its T2DM risk by transcriptional protein complex binding across rs7903146 within TCF7L2 in a self-regulating manner [18], [19] and provided that the intronic TCF7L2 variants might regulate alternative transcript isoforms, which, in turn, might have a distinct physiologic process in inducing T2DM. One of them may be Acyl-CoA synthetase 5 (ACSL5) which has an important role in both the fatty acid degradation and lipid biosynthesis and which, in turn, might correlate with the insulin resistance [15]. Many previous researches found better maintenance regard to glucose levels [20], [21] and also, improvement in insulin sensitivity [19] in the whole body of the ACSL5 knockout mice. A previous study found that a causal variant within TCF7L2 resides in an element that controls the expression of ACSL5 and suggests that TCF7L2 regulates ACSL5 expression [22].

Effector of Wnt signaling pathway

TCF7L2 exerts its regulatory effect on the Wnt signaling pathway. This pathway may play a key role in both islet cell proliferation and differentiation [15]. In humans, it had been suggested that T2DM may have a link to a mutation in the TCF7L2 gene associated with the Wnt pathway [23]. TCF7L2 affects proglucagon gene transcription in the endocrine L-cell lines of the gut by mean of the signaling of the Wnt pathway. The proglucagon gene is important as it encodes the incretin hormone glucagon-like peptide-1 [24]. GLP-1 affects glucose by stimulating insulin secretion, inhibiting glucagon secretion, and slowing gastric emptying [25]. Furthermore, GLP-1 provides other effects such as promoting the transcription of the insulin gene, inhibiting β-cell apoptosis**,** promoting β-cell neogenesis, and also promoting its proliferation [26].

Because there was a previous work suggesting that the β-catenin has a pivotal effect in regard to modulating the secretion of insulin, it was exerted that the overexpression of TCF7L2, as one of the transcriptional coactivator of β-catenin, will attenuate the secretion of insulin [27].

Proinsulin conversion and β-cell responsivity

β-cells are involved in the production of proinsulin. If proinsulin levels relative to the level of the mature insulin hormone are increased, this might suggested impending insulin resistance and the progression to T2DM [28]. TCF7L2-induced β-cell apoptosis might occur through obstructing with the proinsulin processing. Moreover, it has been confirmed that the impairment of insulin vesicle trafficking could be done by silencing TCF7L2 [29]. The T-allele of the TCF7L2 rs7903146 was an important risk factor for impaired proinsulin conversion, as has been found by a previous meta-analysis [30].

Conclusion

We concluded that these polymorphisms had a role in the progression of prediabetes to type 2 DM, particularly TNF by affecting insulin resistance and TCF7L2 by affecting mainly insulin secretion. Also, we concluded that type 2 DM can be prevented or at least

delayed by managing prediabetes by regular exercises and keeping ideal body weight.

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