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Review

ATP-dependent potassium channels and type 2 diabetes mellitus

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ABSTRACT

Diabetes mellitus is a public health problem, which affects a millions worldwide. Most diabetes cases are classified as type 2 diabetes mellitus, which is highly associated with obesity. Type 2 diabetes is considered a multifactorial disorder, with both environmental and genetic factors contributing to its development. An important issue linked with diabetes development is the failure of the insulin releasing mechanism involving abnormal activity of the ATP-dependent potassium channel, K_{ATP}. This channel is a transmembrane protein encoded by the *KCNJ11* and *ABCC8* genes. Furthermore, polymorphisms in these genes have been linked to type 2 diabetes because of the role of K_{ATP} in insulin release. While several genetic variations have been reported to be associated with this disease, the *E23K* polymorphism is most commonly associated with this pathology, as well as to obesity. Here, we review the molecular genetics of the potassium channel and discusses its most described polymorphisms and their associations with type 2 diabetes mellitus.

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Dear Editor

Introduction

Diabetes mellitus (DM) is one of the most intractable public health diseases in the 21st century, with an alarming incidence. The pathophysiological processes responsible for the development of this disorder are complex and unknown; however, information on diabetes genetics is

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being continuously published [1–6]. DM is not just considered one disease, but a defined group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both [7].

Candidate genes on different chromosomes have been associated with DM susceptibility, and their interactions with environmental factors increase the complexity of this disease's genetics and underlying molecular mechanisms. Among these genes, *KCNJ11* and *ABCC8* have been extensively associated with type 2 diabetes mellitus (T2DM, type 2 diabetes) [1,2,8–15], encoding the Kir6.2 and SUR1 proteins, respectively. These proteins form the subunits of ATP-dependent potassium channels (K_{ATP}) and are important components of the insulin release mechanism by pancreatic β-cells [16].

Although K_{ATP} polymorphisms have been associated with T2DM, the exact mechanism of how potassium channel variants promote this disease is still unclear [17–19]. This review aims to describe the molecular genetics of ATP-dependent potassium channels and reports the most described polymorphisms and their association with type 2 diabetes mellitus.

Type 2 diabetes mellitus

Among those with diabetes mellitus worldwide, 90%–95% have type 2 diabetes mellitus, including subjects who have insulin resistance (IR) and usually a relative deficiency in insulin production [7].

T2DM has been described as a complex metabolic disorder and reported to have a global distribution. In 2010, nearly 250 million people were diagnosed as having type 2 diabetes, and this number is expected to double by 2030 [7,20,21]. This type of diabetes is associated with obesity, which is defined as a chronic disease that leads to an excessive fat tissue accumulation, compromising the health of individuals [22]. Obesity is linked to insulin resistance, which potentiates T2DM development [7,23].

Long-chain polyunsaturated fatty acids maintain cell membrane fluidity and facilitate the signaling mechanism. Long periods of high-fat diet, particularly saturated fat and trans-fatty acids, alter cell membrane lipid composition, compromising transmembrane insulin receptor signaling and consequently glucose uptake in peripheral tissues [24]. Through a compensatory mechanism, this condition initially stimulates pancreatic β-cells to produce more insulin to control glucose homeostasis. The overproduction of this hormone or its decreased clearance in obesity characterizes hyperinsulinemia [23]. Chronic insulin overproduction, in addition to gluco- and lipotoxicity, may result in β-cell failure compromising this hormone's release [25–27].

Several genes have been reported as candidates for diabetes development and the identification of DM-associated variants has contributed to the understanding of this disease [28–32]. Type 2 diabetes mellitus is a multifactorial pathology, in which genetic and environmental factors are crucial for its development [33]. Despite the studies investigating genetic variations, the mechanisms of some polymorphisms located in genes that encode key components for the insulin control are still unknown [34].

More than 120 published reports have described associations between genetic variations and type 2 diabetes mellitus, and the list of susceptibility genes for this metabolic disorder has been increasing since 2007 thanks to Genome-Wide Association Studies (GWAS) [35]. There are about 70 candidate genes which confer susceptibility to T2DM development; however, it is estimated that these variants identified by GWAS correspond to only 10% of the heritability of this disease [36,37]. Hundreds of thousands of variants, almost exclusively of Northern European ancestry, have been described and candidate genes such as *TCF7L2*, *SLC30A8*, *IDE-KIF11-HHEX*, *CDKAL1*, *CDKN2A-CDKN2B*, *IGF2BP2*, *FTO*, among others, confer a risk of type 2 diabetes development via unclear mechanisms [38]. Variants in the genes *NEUROD1*, *HNF1B*, *PDXD1*, *HNF1A*, *HNF4A*, *ISL1*, *MTNR1B*, *ADRA2A*, *TCF7L2*, *SLC2A*, *CDKN2A*, *CDKN2B*, *ABCC8*, *KCNJ1* and *ANK1* have been reported to be associated with defects in β-cell mass and/or β-cell function, leading to a reduced insulin secretion [5]. These findings are just the "tip of the iceberg," and other genes and polymorphisms have been and are being discovered [4,8,28,30,35,38–48].

Although ranking the β-cell relevant polymorphisms according to their frequencies and function would be of interest to further the understanding of the derangement of the β-cell functions, this exercise is difficult to perform as these genetic variations depend on the ethnic characteristics and on the environmental factors of the sample population studied [8]. Furthermore, the physiopathological effects of several variants known to affect β-cell function remain hypothetical. However, polymorphisms in the ATP-dependent potassium channel coding genes may also contribute to type 2 diabetes development [13,17,49–51].

To better understand how these polymorphisms might influence T2DM, it is necessary to realize the importance of K_{ATP}-coding genes, proteins, as well as functions.

ATP-dependent potassium channels

The normal potassium channel acts as a modulator of the insulin release mechanism and so contributes to blood glucose homeostasis [52]. K_{ATPs} are transmembrane proteins expressed in the muscle, brain, and pancreatic β-cells [53].

Their octameric structure is composed of a sulfonylurea receptor (SUR1) and Kir6.2 subunits, the latter constituting the selective pore for K^+ ions. Both subunits are in a 1:1 stoichiometric proportion (Fig. 1) and can be represented by the $(SUR/Kir)_4$ notation [16,54,55].

Kir6.2 subunit and KCNJ11 gene

Kir6.2 is a protein encoded by the *KCNJ11* gene (potassium inwardly rectifying channel, subfamily J, member 11 [*Homo sapiens* (human)]; NCBI Reference Sequence: NG_012446.1; OMIM: 600937). In humans, this gene is located in the 11p15.1 chromosome region [52], composed of 4,084 base pairs (bp), and encodes isoforms 1 and 2 with 390 and 303 amino acid residues (aa), respectively.

The Kir6.2 isoform 1 has two transmembrane domains, TM1 and TM2. The H5 region lies between these domains and contains *Gly–Tyr* motifs that are important to the channel's selectivity for potassium ions [56]. Kir6.2 binds to SUR1 to form K_{ATP}. Through a currently unclear mechanism, Kir6.2 cannot appear on the membrane surface without the SUR1 subunit [54,57–59].

SUR1 subunit and ABCC8 gene

SUR1 is a transmembrane regulatory protein of potassium channels with an intracellular domain comprising an ATP-binding site [60]. SUR1 is encoded by *ABCC8* (ATP-binding cassette, subfamily C (CFTR/MRP), member 8 [*H. sapiens* (human)]; NCBI Reference Sequence: NG_008867.1; OMIM: 600509).

This gene in humans is also located in the 11p15.1 chromosome region [52], composed of 83,961 bp and encodes, like *KCNJ11*, two isoforms: isoform 1 (1,582 aa) and isoform 2 (1,581 aa).

SUR1 has a molecular weight of 177 kDa [52,55]. Like other members of the ABC family, this protein has four structural domains: two nucleotide-binding domains (NBDs), which are involved in nucleotide binding/hydrolysis [52] and two transmembrane domains, TMD1 and TMD2 [54].

In addition, highly conserved domains known as Walkers A and B have been described for SUR1 [54]. The NBDs associate with each other to form two ATPase sites, where the second is more active than the first [54]. This high activity at site 2 is associated with MgADP, which induces changes in K_{ATP} activity [61,62].