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Wnt Pathways are Related to Type 2 Diabetes

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ABSTRACT

This paper shows the Wnt pathways, which are related to type 2 diabetes mellitus. Two main Wnt pathways have been described, canonical pathway and noncanonical pathway. Canonical pathway is related to a protein called β-catenin. In presence of Wnt, β-catenin is accumulated in cytoplasm and can be transported to nucleus to produce activation of gene transcription through TCF/LEF. In absence of Wnt, β-catenin is phosphorylated and ubiquinated and degradated in proteasomes. Thus, in nucleus no activation of gene transcription is observed. Two noncanonical pathways have been described, both not involving β-catenin. The noncanonical Planar Cell Polarity (PCP) is related to a MAP kinase (JNK) ending in a change in actine modification. The noncanonical Wnt/calcium pathway is related to a calcium release from endoplasmic reticulum.

ABBREVIATIONS

APC: adenomatous polyposis coli; Axin2: adenomatous polyposis coli tumor suppressor; CaMKII: calcium-calmodulin-dependent protein kinase II; CK1: casein kinase 1; CRD: cysteine-rich domain; DAAM1: dishevelled-associated activator of morphogenesis; DAG: dyacylglycerol; Dsh: dishevelled (an adaptor protein); Fzd receptor: Frizzled receptor; GLUT4: glucose transporter 4; GSK3β: glycogen synthase kinase-3β; IDDM: insulin-dependent diabetes mellitus; IP3: inositol 1,4,5-triphosphate JNK: c-Jun N-terminal kinase; LRP: low density lipoprotein receptor; MAP: MYH-associated polyposis; MAPK: mitogen-activated protein kinase; NIDDM: non-insulin-dependent diabetes mellitus; PCP: planar cell polarity (or Wnt/JNK pathway) PDE: phosphodiesterase; PIP2: phosphatidylinositol 4,5-bisphosphate; PK: protein kinase; PK-C: protein kinase C; PK-G: protein kinase G; PLC: phospholipase C; ROCK: Rho associated coiled-coal containing protein kinase; SIRT1: sirtuin 1; TAK1: transforming growth factor beta-activated kinase 1; TCF / LEF: T-cell factor / lymphoid enhancing factor; b-TrCP: b-transducin repeats-containing protein

INTRODUCTION

Diabetes is the common name for diabetes mellitus, which is defined as a group of metabolic disorders presenting high blood glucose levels. Diabetes is based either on the low production of insulin in the pancreas, or to a non-properly response of body cells to the insulin produced. Symptoms of diabetes include a frequent urination and increased thirst and hunger, and if not treated can cause ketoacidosis, as well as cardiovascular and kidney diseases, stroke, foot ulcers, damage to the eyes, and even the death in cases of acute complications.

Three main types of diabetes have been described:

1) Type 1, also called "Insulin-Dependent Diabetes Mellitus (IDDM)" or "juvenile diabetes". This type results from a damage in beta cells, which will not produce enough insulin, although the cause is unknown [1].

2) Type 2, also called "Non-Insulin-Dependent Diabetes Mellitus" (NIDDM) or "adult-onset diabetes". This type results in a fail to insulin response in the cells and it is usually due to a high body weight and a low exercise [2].

3) Gestational diabetes, which occurs when pregnant women develop diabetes, without a previous history of diabetes. This type usually resolves after the birth [3].

Insulin action is a process partially mediated by activation of the MAP kinase pathways, related with the Wnt-β-catenin signalling. In fact, phosphorylated Erk1/2 (a MAP kinase) is inhibited by glycogen synthase kinase-3β (GSK3β), which forms a complex with Frizzled receptor (Fzd receptor) in Wnt signalling. Other proteins related to Wnt pathways are also related to the glucose transporter GLUT4 exocytosis, presenting in this way an interrelation with insulin sensitivity, and thus showing that Wnt pathways are related with type 2 diabetes.

Type 2 diabetes is associated with a combination of pancreatic β-cell disfunction and insulin resistance [4], and these effects can be compensated by increasing insulin secretion, leading to hyperglycemia and insulin resistance, in a process called "glucose toxicity" [5]. Under these conditions, oxidative stress and endoplasmic reticulum stress are produced, and the c-Jun N-terminal Kinase (JNK) pathway is activated in various tissues. There is evidence of a genetic component to the risk of type 2 diabetes, and in fact there are some clinical evidences of Wnt pathways in type 2 diabetes related with the effect of TCF7L2 gene, formerly TCF-4 [6-8]. The objective of this paper is to review the Wnt signalling pathways, that seem to be very important in type 2 diabetes. In the following sections the Wnt pathsways will be described.

Wnt pathways

The name Wnt comes originally from a wingless gene very well characterized in Drosophila melanogaster, the Wnt gene. Nineteen Wnt genes have been described in mammalian genomes (WNT1, WNT2, WNT2B, WNT3, WNT3A, WNT4, WNT5A, WNT5B, WNT6, WNT7A, WNT7B, WNT8A, WNT8B, WNT9A, WNT9B, WNT10A, WNT10B, WNT11, WNT16), and their functions differences are defined by mutations that lead to various developmental abnormalities [9]. Wnts are secreted proteins that contain a palmitoylated cysteine [10]. The lipid is important in their activity, as an enzymatic removal of the palmitate or a site-directed and natural mutation of the cysteine results in a loss of Wnt activity. Signalling is initiated by Wnt ligand binding to two receptor molecules: Frizzled proteins (FZD1-10) and low density lipoprotein receptor-related proteins 5 or 6 (LRP5 or LRP6) [11]. In humans, several Wnt proteins have been described. Aberrant activation of the Wnt/β-catenin signalling pathway is a necessary initiating event to generate the type 2 diabetes. Signal begins when a Wnt protein binds to the N-terminal extracellular cysteine-rich domain of a Frizzled family receptor.

Frizzled proteins (Fzd receptors) are a family of ten G-protein-coupled receptors, with seven transmembrane domains. All Frizzled proteins share a conserved region of 120 amino acids in the extracellular domain, with a motif of 10 invariantly spaced cysteines (called the cysteine-rich domain, CRD) [12]. The CRD domain is necessary and sufficient for Wnt ligand binding [13]. The ten members of the Fzd receptors interact with the nineteen Wnt to activate canonical and/or non-canonical Wnt signalling.

Fzd receptors can respond to Wnt proteins only in the presence of the low density lipoprotein receptor related proteins 5 or 6 (LRP5 or LRP6) or tyrosine kinase receptors (RTK or ROR2) to activate the phosphoprotein Dishevelled (Dsh), which is located in the cytoplasm. Activation of Dsh will activate the noncanonical and the canonical β-catenin pathway [14,15].

The three best characterized Wnt signalling pathways are the canonical Wnt pathway, the noncanonical planar cell polarity (PCP, or Wnt/JNK) pathway and the noncanonical Wnt/calcium pathway. The main difference between canonical and noncanonical pathways is that a canonical pathway involves the protein β-catenin, while a noncanonical pathway operates in absence of this protein.

Canonical Wnt pathway: Wnt-b-catenin pathway

Canonical pathway is shown in Figure 1. The main point of the Wnt pathway is that in absence of Wnt, b-catenin is sequestered in a "destruction complex" that contains APC (adenomatous polyposis coli), adenomatous polyposis coli

tumour suppressor (Axin2), Glycogen Synthase Kinase-3β (GSK3β), and Casein Kinase 1 (CK1), also formed when Wnt proteins are unable to bind to their receptors. The formation of this "destruction complex" induces the phosphorylation of β-catenin by CK1 and GSK3β, in particular at serine-675 [16]. Phosphorylated b-catenin is recognised by b-TrCP (b-transducin repeats-containing protein), an F-box component of the E3 ubiquitin ligase complex, which promotes b-catenin ubiquination and degradation by the ubiquitin-proteasome system [17]. Without Wnt, β-catenine is not accumulated in cytoplasm.

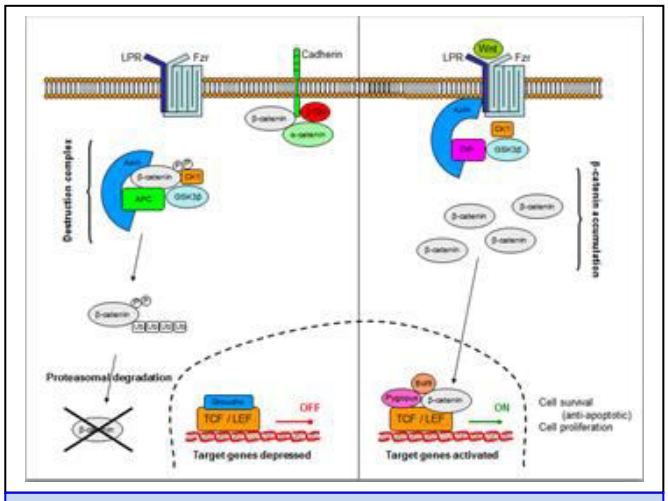

Figure 1: Canonical Wnt-β-catenin pathway.

Wnt signalling pathway is shown in the "OFF" (left hand side) and "ON" (right hand side) states. In the absence of a Wnt signal, the destruction complex phosphorylates and ubiquinates β-catenin, being therefore destroyed by the proteasome. In the presence of a Wnt signal, as the dishevelled protein (Dsh) recruits the Axin2 and inhibits GSK-3, β-catenin is not phosphorylated and therefore not destroyed. It can translocate to the nucleus and activate transcriptions genes.

The binding of Wnt to receptors to form the ternary complex (Wnt-Fzd-LRP5/6) leads to downstream evasion by β-catenin from degradation in the cytoplasm [18]. The adaptor protein dishevelled (Dsh) is activated and recruits Axin2, which forms a complex with Dsh [19]. In this complex, Dsh is activated and GSK3β inhibited. These events reduce b-catenin phosphorylation and its consequent degradation. Thus, β-catenin is accumulated in cytoplasm. Mammalians contain three dishelled proteins, named Dsh-1, Dsh-2 and Dsh-3. Sirtuin 1 (SIRT1) is a NAD+-dependent histone deacetylase that regulates Dsh and Wnt signalling [20].

β-Catenin accumulation in cytoplasm allows to this protein to enter in the nucleus and subsequently induce a cellular response via gene transduction alongside the transcription factors TCF/LEF (T-cell factor/lymphoid enhancing factor). Other co-activators, such as Bcl9 and Pygopus, can be recruited also by β-catenin to activate transcription of several genes.

Noncanonical Wnt pathway: Wnt-b-catenin pathway

Despite the Wnt canonical pathway, there are many other Wnt non-canonical pathways, but the two best-studied pathways are the noncanonical planar cell polarity (PCP, or Wnt/JNK) and the noncanonical Wnt/calcium pathway [21,22] (see Figure 2). Identified in colon carcinoma cells and named colon carcinoma kinase-4, PTK7 (protein kinase 7) has recently been analysed as a Wnt coreceptor in the non-canonical PCP [23]. This pathway is related to JNK (c-Jun N-terminal kinase), that belongs to the Mitogen-Activated Protein Kinase (MAPK) family.

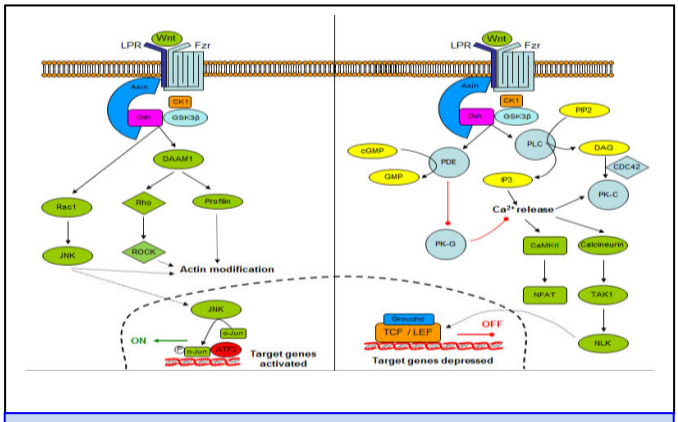

Figure 2: Noncanonical Wnt pathway.

Noncanonical Wnt signalling pathways are shown in the noncanonical planar cell polarity (PCP or Wnt/JNK) (left) and the noncanonical Wnt/calcium (right). Both noncanonical pathway require Wnt. PCP pathway is related with MAP kinase pathway and increases the MAP kinase JNK, and shows also actin modification. Non canonical Wnt/calcium increases a calcium release from endoplasmic reticulum.

The noncanonical Planar Cell Polarity (PCP) works at the beginning as the canonical pathways. Wnt activates the pathway by binding to the Frz receptor and to its co-receptor. The receptor then, recruites Dsh, that forms a complex with another protein called Dishevelled-Associated Activator of Morphogenesis 1 (DAAM1). DAAM1 is then able to activate Rho (a little G-protein), that activates Rho-associated coiled-coil containing protein kinase (ROCK), that is one of the major regulators of cytoskeleton. By the other hand, DAAM1 activates

also Profilin, a protein important for growth of actin microfilaments, which can restructure the cytoskeleton and change the cell shape. Another mitogen-activated protein kinase (JNK, c-Jun N-terminal kinase) phosphorylates c-Jun in the nucleus, another transcription factor. JNK is activated due to a complex of Dsh with Rac1. Despite this effect, Rac and Rho can form a TIAM-Rac-Rho complex [24].

The noncanonical Wnt/calcium pathway also does not involve β-catenin. This pathway controls intracellular calcium levels by helping calcium release from Endoplasmic Reticulum (ER). Wnt activates the pathway by binding to the Frz receptor and to its co-receptor, but in this case, a trimeric G-protein is involved. The receptor then, recruites Dsh and the G-protein can activate either a phospholipase C (PLC) or a cGMP specific phosphodiesterase (PDE). When phospholipase is activated, the enzyme hydrolyses phosphatidylinositol 4,5-bisphosphate (PIP2) to Diacylglycerol (DAG) and inositol 1,4,5-triphosphate (IP3). Calcium is released from endoplasmic reticulum when IP3 binds to its receptor at the endoplasmic reticulum membrane. DAG interacts with a GTPase protein from Rho family (Cdc42) and activates Protein Kinase C (PK-C), a serine-threonine kinase. Some PK-C are also activated by calcium. Increased calcium also activates calcineurin (also known as protein phosphatase 3) and calcium-calmodulin-dependent protein kinase II (CaMKII). CaMKII activates the transcription factor NFAT (nuclear factor of activated T-cells), whereas calcineurin activates TAK1 (transforming growth factor beta-activated kinase 1) and NLK (a serine threonine protein kinase), which can interfere with TCF/β-catenin canonical Wnt pathway [25]. However, if PDE is activated, calcium release from the ER is inhibited. PDE mediates this by inhibiting protein kinase G (PK-G), which subsequently causes the inhibition of calcium [26].

CONCLUSIONS

Although there are many studies related to insulin signal transduction, still a lot of research has to be done in order to understand the basis of diabetes. The study of the Wnt pathways can be a good challenge to prevent the non-insulin-dependent diabetes mellitus. Wnt canonical pathway is related to activation of gene transduction alongside the transcription factors TCF/LEF, while the noncanonical PCP pathway inhibits those gene transcription. More studies have to be performed in how are both pathways regulated.

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