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Role of Pink1 knockout gene on GLUT4 expression, glucose metabolism and type 2 diabetes

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Abstract

There are about 30,000 to 35,000 genes in a human genome. Different genes are expressed in different tissues of the body (formation of the protein) a process called gene expression or gene function. After the formation of a protein in a cell, proteins are involved in different cellular functions. Glucose molecule is an energy of a cell, but this energy cannot be produced directly because glucose cannot enter in cells without the involvement of different receptors, there is a process called glucose uptake. Glucose uptake is one of the important processes takes place in cells (a cell cannot survive in the absence of glucose). For this uptake many proteins are involved in the cell signaling pathway. Some proteins activate other proteins to perform smoothly any biological process. On the other hand, few proteins also inactivate some other proteins to interfere any metabolic process. So nowadays scientist think if we knockout repressor genes (that affects molecular signaling pathway), then glucose uptake or some other processes going well without any hindrance. A portion of a gene is deleted by crisper technology called knockout mice or transgenic mice. In this review we have focused on GLUT4 expression in the absence of Pink1 gene also called Pink1 knockout mice, because some previous studies described that loss of pink1 gene improves glucose susceptibility and decrease the risk of type 2 diabetes.

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Introduction

Type 2 diabetes: Type 2diabetes is a common metabolic disease affects over 256 million individuals across the world. The mechanism under this disease is insulin resistance in metabolic tissues such as muscle, liver and adipose tissue related with deficiency in insulin secretion. In normal conditions, the alpha and beta cells of the pancreas monitor blood glucose levels. When blood glucose level is increased, these cells take up glucose through the GLUT2 glucose transporter results to an enhanced in glucose metabolism within the cells [1]. An approximately 30.3 million American citizens have diabetes (9.4% of the total population). One of these, 23 million individuals has detected diabetes and 7.2 million people have undiagnosed diabetes. The occurrence of diabetes in the U.S. peoples has increasing intensely over the last 50 years. About 40% of American peoples with diabetes are 65 years old or older. The figure of individuals with type 2 diabetes is probable to enhance by 2030, the number of individuals in the United States with diagnosed or undiagnosed diabetes is expected to enhance to 55 million [2]. Diabetes is approximately accounts for 90%-95% of diabetes cases and is considered by insulin deficiency, insulin resistance, and high glucose levels. In type 2 diabetes peoples, insulin production is inadequate to compensate for insulin resistance. Several hazard factors for type 2 diabetes are over age, overweight, genetics, less physical exercise and reduced glucose metabolism (Anthony Cannon 2018). In Mexico, the frequency of diabetes has been growing. The occurrence of diabetes enhanced from 8.2% in 1993 to 11.8% in 2000. In Mexico City, the incidence of diabetes increased to 14% [3].

Glucose transporter 4 (GLUT4): The Glucose transporter 4 is the insulin-sensitive glucose transporter protein their important function is to offer the insulin induced glucose uptake by adipose tissue, skeletal muscle and the cardiac tissues that exactly makes this protein [4] The GLUT4 glucose transporter is a main mediator of glucose removal from the blood circulation and a vital regulator of entire body glucose check and balance. GLUT4 is tremendously expressed in cardiac muscle, adipose tissue and skeletal muscle tissues [5]. GLUT4 perform an important crucial role in glucose metabolism and signifies 90% of glucose transporters [6]. The human Skeletal muscle is the key location of insulin-mediated glucose uptake and is very important in investigative whole body glucose levels [7]. Glucose uptake by contracting skeletal muscle occurs on the existence of GLUT4 in the cell membrane and an internal diffusion gradient for glucose. There are three different processes that can be controlled: glucose delivery, glucose transport, and glucose metabolism [8]. Muscle tissues express two glucose transporter proteins, GLUT1 and GLUT4. In striated muscle, the key glucose transporter protein is the GLUT4, which undergoes to translocation in to the cell surface membrane in reply to insulin [9]. The primary insulin-sensitive glucose transporter in muscle is the GLUT4, which is involved to the sarcolemma resulting insulin stimulation [10].

Gene expression: A gene is the basic molecular unit of heredity material. In the arrangement of DNA or RNA, it conveys the genetic information that can be formed usually proteins. The level of involvedness of the organism is accomplished by regulating available genes, not merely by presenting more genes. The central dogma of molecular biology of gene expression includes two consecutive steps: transcription (formation of mRNA) and translation (formation of protein). Transcription is the process that controls the on and off" of genes and highlights the identity of the cell. After the translation proteins are involved in the cellular functions. The mechanism of gene expression is helping us to understand the development and evolution of life and to identify the treatment for diseases [11]. Protein synthesis is an essential process for biological systems to achieve a different function. A variety of proteins control the organism's structure or functions as enzymes catalyzing definite metabolic pathways to control different cellular processes. These cellular functions include responding to stimuli, transportation of molecules and catalyzing carbohydrate and lipid metabolic reactions. In order to perform the desired functions in a cell, one should control the protein synthesizing agents called transcription factors [12]. For gene expression Histone modification and transcription factors are required. Every cell has a different protein formation occurs because of different transcription factors present in a cell.

Genetics and Type 2 diabetes: Over the last thirty years, the prevalence of type 2 diabetes and related complications has been quickly increased globally. Type 2 diabetes is a complex metabolic disease that is produced by several factors. The genetic analyses achieved in family and twin studies have undoubtedly shown that about 70% of the alteration in type 2 diabetes susceptibility in the people is caused by genetic factors. Peoples with T2D-affected relations have a two-three times enhanced risk of developing T2D likened with the normal population [13].

Knockout mouse and gene modification: The process of gene knockout means to modify a specific part of gene in response to improve its biological function. By the homologous recombination, a mutation can be focused to a selected genetic position. The aim of genetic engineering is to overexpress a gene present in a human cell to find its genetic function in vivo, homologous recombination is generally hired to produce a damage of function. Nowadays the application of gene targeting is to create a knockout mouse, where a drug resistance marker

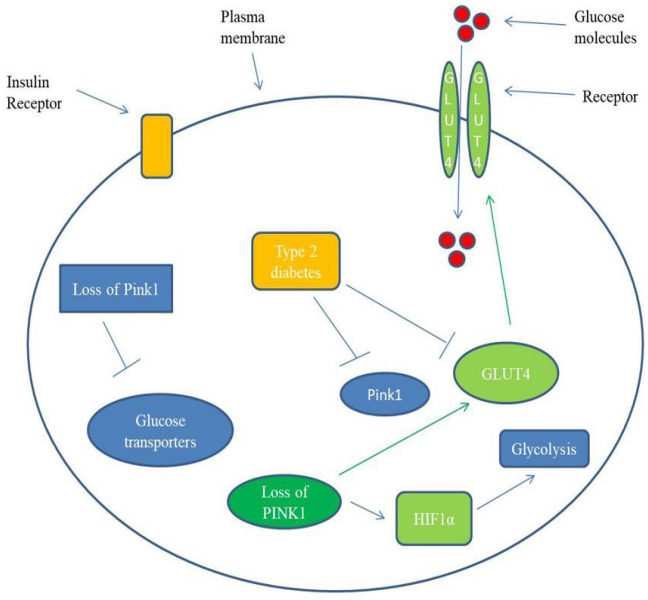

Figure 1: (a) Previous studies defined that loss of Pink1 stimulates Glycolysis via HIF1alpha (b) Some previous reports also suggested that Loss of Pink1 decreases Glucose transporters. (c) Our present review explained that the Loss of PINK1 up regulates GLUT4 expression but the molecular mechanism is still unclear. (d) In type 2 diabetes, Pink1 and GLUT4 expression both are decreased. Pink1: PTEN induced kinase 1, GLUT4; Glucose transporter 4, HIF1 alpha: Hypoxia-inducible factor 1-alpha.

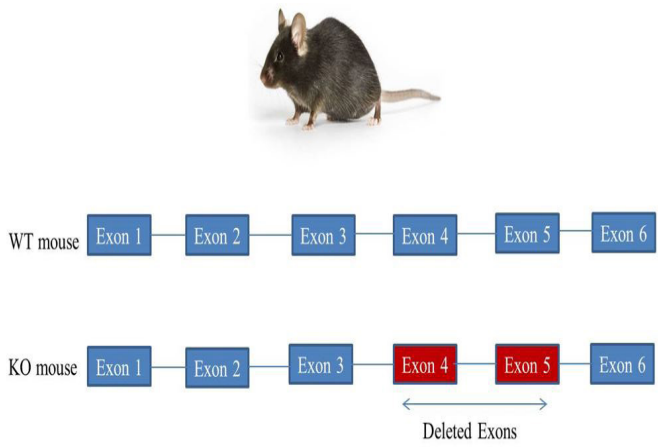

Figure 1: The deleted portion (4th and 5th) exon of Pink1 Knockout mouse. Now this mouse doesn't contain PINK1 protein. WT; Wild type, KO; knockout.

exchanges a vital coding area in a genetic position. During the two decades that gene targeting methods have been accessible, several of genes have been knocked out. Approximately 11,000 genes have been deleted in mice, which based on nearly 50% of the mouse cell genome. Through the combination of gene targeting, a worldwide struggle is ongoing to make a knockout mouse genome for the whole 25,000 mouse genes. Mouse perform as a good correspondent for the many human life biological processes because both mouse and human share approximately 99% of the similar genes [14].

The first knockout mouse was made in a year 1989; design a most important innovation in mouse genetic engineering. Gene targeting in mouse embryonic stem cells allowed the removal of any gene from the mouse genome, which would classically be shadowed by an examination of the consequences on development, structure and physiology [15]. To understand a gene role can describe the disease phenotypes detected in transporters of common genetic variants and deleterious mutations. Great improvement is being completed; interpreting the roles of the ~20,000 human genes, but the activities of several genes is still not clearly understood. To identify molecular mechanisms of any disease, genes give understandings for possible treatments. Although, mice are the best-established models for human disease [16]. Changes in gene expression variability have been related with numerous human diseases, including schizophrenia, Parkinson's disease, muscular dystrophy, dilated cardiomyopathy, and lung and colorectal adenocarcinoma. Certainly, hyper-variability of gene expression may be a general property of malignancies, providing the source for innovative variability-based cancer diagnostics [17]. At present the human and mouse genome sequences are identified, attention has turned to explaining gene function and detecting gene products that might have therapeutic value. The laboratory mouse has had a prominent function in the research of human disease pathways through the rich, 100 years history of traditional mouse genetics. Latest technology also allows the insertion of 'reporter' genes into the knocked-out gene, which can be used to detect the temporal and spatial expression of the knocked-out gene in the mouse tissues [18].

On November 25, 2018, Jiankui an associate professor from Southern University of Science and Technology, China, declared that two babies with modified C-C chemokine receptor type 5 (CCR5) genes had been born in South China. This genetic make-up alteration would make safe these babies from HIV disease. He presented their experimental data of his research project at the second World Summit of Human Genome modification. The compact indication of his experiment remains to be exposed and the accuracy of such rights discovered, the experimental data presented at the summit exposed serious delinquency on both the scientific research and ethical levels. Some other researchers working in the gene-editing field in China, they were totally surprised by this news [19]. Because this is so early to make these genetic modifications in humans [20].

PINK1 and type 2 diabetes: One research study has reported a relation between mRNA expression of the pink1 gene and type 2diabetes. Specially, pink1 transcription was inhibited in the skeletal muscle of type 2 diabetic individuals. The transcription of pink1 was also down-regulated under the circumstances of low physical exercise and obesity in diabetic patients. From this research, the researcher suggested a role for PINK1 in glucose metabolic process. The latest findings that the loss of PINK1 suppresses the glucose transporter are therefore inspiring. Surprisingly, pink1 transcription was exposed to be up-regulated by FOXO3a protein a downstream target of insulin and PI3K/Akt pathway. These both explanations show us a different subsequent studies regarding PINK1's function in type2 disease [21].

Scheele et al first detected decreased PINK1 expression in the skeletal muscle of type 2 diabetic individuals. This was similarly seen in the hearts of type 1 diabetes and in diabetic brains, the later resulting to the lipid accumulation and diminished oxidation of mitochondrial fatty acids [22].

Role of Pink1 KO gene: The PTEN-induced kinase 1 (PINK1) has been studied widely because this is a first protein to target the damaged mitochondria by the autophagosome for lysosomal degradation [20]. PTEN-induced putative kinase 1 (PINK1) is a mitochondrial based serine/threonine protein kinase which defends tissues in contrast to stress stimulated apoptosis. Homozygous mutations in the PINK1 gene (PARK6) and deficiency of PINK1 role have been revealed to be an original reason of early onset autosomal recessive Parkinson's disease [23]. PINK1 located at the mitochondrial external membrane, where it cooperates in a phosphorylation dependent way with PARKIN, both perform on the similar path as a quality control system to reserve mitochondrial stability on mitochondrial membrane potential failure [24]. The PINK1 protein is predicted to comprise a mitochondrial aiming motif and has been exposed to be localized to mitochondria, though a cytosolic pond of PINK1 has also been defined. PINK1 is slashed by the mitochondrial protease PARL, and this process is vital for the role of both PINK1 and mitochondria [25].

Some previous studies demonstrated that the loss of PINK1 animals have improved glucose tolerance. These findings showed that the increased basal insulin level is enough to stimulate the presentation of glucose transporter receptors at the cell surface and then the peripheral tissues to take up glucose from the blood stream with the faster rate [23]. Another study showed that the HIF1a stimulates glycolysis in the loss of Pink1, and the elevation of intracellular glucose metabolic process by HIF1a stabilization is needed for cell proliferation in Pink1 knockout mice. This research identified that the absence of Pink1 reprograms glucose metabolism via HIF1a, supporting enhanced cell proliferation [24]. These both studies suggest that the Pink1 knockout mice have the lower risk of type 2diabetes as compared to wild type controls.

Discussion

There are thousands of genes present in a human genome, some genes activate or inhibits other genes activity is called epigenetics without changing the structure of a gene. Pink1 is also a disease related gene that is involved in different types of diseases such as type 2 diabetes [26]. The mutations in PINK1 gene is a mitochondrial serine/threonine kinase, lead to autosomal recessive Parkinson's disease. An in vitro finding has exposed that PINK1 is recruited to destroyed mitochondria, resulting to phosphorylation of Parkin and ubiquitin to remove dysfunctional mitochondria through autophagy, a process named mitophagy that controls the quality of Mitochondria [27]. Previous studies demonstrated that the regulation of the PINK1 locus associated to neurodegenerative disease is changed during obesity and type 2diabetes. PINK1 may have a function in cell glucose metabolism [28]. After the induction of type 2 diabetes few studies suggested that the Pink1 expression is decreased in type 2diabetes (Fig.1), but the mechanism of decreased Pink1 expression in type 2diabetes is still unclear.

Some previous research suggested that the loss of Pink1 reprograms glucose metabolism via HIF1a and maintains enhanced cell division and proliferation (Fig.1) [24]. On the other hand the deficiency of pink1 in pancreatic beta cells also induces basal insulin secretion and maintains the blood glucose levels in mice [23]. The major glucose transporter protein that facilitates glucose uptake is through GLUT4, which plays an important function in regulating entire body glucose homeostasis [5].

Conclusion

Knockout mice are used to study the gene function, generally by investigating the effect of gene loss. In Pink1 KO mouse the 4th and 5th exons are deleted from the existing gene (Fig.2). Previous studies suggested that the GLUT4 expression has been decreased in diabetes. Still we do not know why GLUT4 dysexpression occurs in diabetes. An In vitro study is needed to explore the mechanism of decreased expression of the GLUT4 in type 2 diabetes. In conclusion for the first time, we have suggested that the loss of Pink1 gene may be increased the GLUT4 expression inside the cells and reduce the risk factor for type 2 diabetes. Higher the GLUT4 expression and translocation, more glucose uptake occurs and has low chances of type 2diabetes in humans. We also suggested that PINK1 and GLUT4 both are decreased in type 2diabetes but the mechanism of action is still unclear.

Conflict of Interest: There is no Conflict of Interest.

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