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PTEN: The Potential Therapeutic Target of Diabetes Mellitus

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***Abstract*—**Diabetes mellitus is a metabolic disease characterized by high blood glucose levels. The cause of glucose control failure is decreased insulin production by pancreatic β-cells and insulin resistance. Both lead to the obstacle of glucose uptake into cells. The mechanism of glucose uptake into cells is crucial in carbohydrate metabolism. This mechanism aims to produce energy in the form of ATP. The main signaling pathway after the process of glucose uptake is the PI3K/Akt pathway. This pathway involves many proteins activated by phosphorylation mechanisms. One of the proteins involved in this pathway is PTEN, a PI3K regulator. PTEN activity can dephosphorylate PI3K so that the insulin signaling pathway becomes blocked and glucose cannot be uptaken into cells. It causes blood glucose levels to increase. The role of PTEN in inhibiting the PI3K/Akt pathway seems to be a crucial matter to observe. By inhibiting PTEN activity, the insulin signaling pathway is expected to work properly. We have searched, read, analyzed, and summarized various studies regarding the potential of PTEN to reduce diabetes mellitus cases. In some research articles, the use of active compounds and therapy using stem cells to inhibit PTEN activity has shown good progress in the insulin signaling pathway. Based on these, it can be an option to make PTEN a target for diabetes mellitus therapy.

***Keywords*—**Diabetes mellitus, Insulin Resistance, Blood Glucose, PTEN, PI3K/Akt

I. INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by increased blood glucose levels. The development of diabetes mellitus can lead to microvascular and macrovascular damage. It can affect various organs, such as the heart, eyes, brain, and kidneys. In addition, diabetes mellitus sufferers are very susceptible to infection from microorganisms that can interfere with the digestive and respiratory systems (Berbudi et al., 2019; Galicia-Garcia et al., 2020).

According to the International Diabetes Federation (IDF), in 2019, the number of diabetes mellitus cases in adults aged 20-79 years was around 463 million, while the death rate as a consequence of diabetes mellitus reached 4.2 million. (Berbudi et al., 2019; Galicia-Garcia et al., 2020). From IDF data, about 75% of diabetics come from low and middle-income countries. In addition, World Health Organization (WHO) states that diabetes mellitus is the third highest risk factor that causes premature death (Oguntibeju, 2019). It is estimated that by 2045 diabetes mellitus cases will increase to 700 million (Berbudi et al., 2019; Galicia-Garcia et al., 2020).

Diabetes mellitus is classified into two types, type 1 diabetes mellitus, and type 2 diabetes mellitus. Type 1 diabetes mellitus is associated with genetics and there is an abnormality in the function of the pancreas so that it cannot secrete insulin. Meanwhile, type 2 diabetes mellitus is more likely to lead to insulin resistance, and more than 90% of diabetics have type 2 diabetes (Galicia-Garcia et al., 2020; Xu et al., 2022).

Insulin resistance is a condition marked by cells that cannot recognize the insulin (Berbudi et al., 2019). Insulin resistance occurs when the insulin receptor cannot bind to insulin as its ligand (Roden & Shulman, 2019). The bond between insulin and its receptor is crucial for creating a signal within the cell to translocate glucose transporter (GLUT) from the cytosol to the cell membrane. It aims to facilitate the entry of glucose from blood circulation into cells (Berbudi et al., 2019). High blood glucose levels give a signal to the β cells of the pancreas to produce insulin. The goal is to increase glucose uptake into cells. Insulin resistance causes failure in glucose transport into cells so that the blood glucose concentration remains high. Instead, there is an increase in the mass of pancreatic β cells to produce more insulin. As a result, insulin levels can also increase in the blood. Type 2 diabetes mellitus occurs when these compensatory efforts fail and result in pancreatic dysfunction (Berbudi et al., 2019; Roden & Shulman, 2019).

Carbohydrates from food are the primary cause of increased blood glucose levels. To be absorbed by cells of the small intestine, polymers of glucose in carbohydrates must be broken down. It requires α-glucosidase and amylase. Based on this mechanism, one way that can be done to prevent an increase in blood glucose levels is to reduce the amount of glucose that can be absorbed by the cells of the small intestine (Gong et al., 2020). Various compounds have been investigated for diabetic activity to lower blood glucose levels (Xu et al.,

2022). Many studies have focused on blocking receptors such as α-glucosidase and amylase to prevent glucose absorption in the gut (Gong et al., 2020; Hossain et al., 2020). There are other alternatives to overcome hyperglycemia, namely through increasing glucose uptake into cells and increasing insulin signaling pathways. It begins with insulin binding to its receptors (Xu et al., 2022).

The binding of insulin with its receptors in the cell membrane activates a phosphorylation cascade in the insulin signaling pathway, known as the PI3K/Akt pathway. The cell's mechanism of uptaking glucose via the insulin signaling pathway involves many proteins (Kushi et al., 2021). One of them is PTEN, a negative regulator of the insulin signaling pathway, that dephosphorylates phosphatidylinositol 3,4,5-triphosphate (PIP3) to phosphatidylinositol-4, 5-bisphosphate (PIP2) thereby inhibiting the phosphorylation cascade and translocation of GLUT to the cell membrane (C. Y. Chen et al., 2018; Yin et al., 2018). Many studies show that PTEN expression is upregulated in diabetes mellitus cases (G. Chen et al., 2020; McLoughlin et al., 2018). Thus, the downregulation of PTEN appears to lead to better insulin signaling (H. Wang et al., 2018). This review article aims to collect various information regarding the role of PTEN as a target for diabetes mellitus therapy from various recent studies so it can provide an overview of new methods related to the prevention of diabetes mellitus so that research regarding the potential of PTEN or PI3K/Akt pathway intermediates as therapeutic targets will further develop in the future.

II. Methodology

The review process begins with conducting research articles using the keywords PTEN, diabetes mellitus, and diabetes mellitus therapy. Based on the search results, we analyzed the compounds and their molecular mechanisms of action in diabetes mellitus treatment. Furthermore, this mechanism is associated with the function and work of PTEN in carbohydrate metabolism to obtain the potential of PTEN in diabetes mellitus treatment. Then the results of the analysis are compiled into an article.

III. Result and Discussions

A. *Phosphatase and Tensin Homologous Deleted on Chromosome 10 (PTEN)*

Phosphatase and Tensin Homologous Deleted on Chromosome 10 (PTEN) or MMAC1/TEP1 is a protein that acts as a tumor suppressor (McLoughlin et al., 2018). PTEN has protein and lipid phosphatase activity. It is composed of 403 amino acids encoded by a gene on the 10q23 chromosome. Phosphatase and tensin homologs in the name PTEN refer to the amino end of PTEN. It shares sequence homology with tensin, actin filament capping protein, and auxilin (C. Y. Chen et al., 2018).

The transcription of the PTEN gene is increased by several transcription factors. They are EGR-1, p53, ATF2, and PPARγ. They increase PTEN expression by binding to the promoter of the gene (McLoughlin et al., 2018). In contrast, SNAIL inhibits PTEN expression by competing with p53. NFKB also binds to the PTEN promoter and suppresses its expression. At the protein level, PTEN activity is affected by post-translational modification mechanisms. One is the phosphorylation of threonine at the C-terminus which stabilizes the protein (Maity et al., 2019). In addition, PTEN can also undergo ubiquitination, oxidation, acetylation, and sumoylation (McLoughlin et al., 2018). There are two main domains in the PTEN protein structure, the PTPase domain (having phosphatase activity) and the C2 domain (having activity for phospholipids). In addition, there are other domains, PEST and PDZ, that play a role in the stability and subcellular localization (C. Y. Chen et al., 2018).

Post-translational modification of PTEN through phosphorylation of amino acid residues at the C-terminus can stabilize PTEN. Proteins involved in PTEN phosphorylation include casein kinase 2 (CK2), GSK3β, RhoA kinase, and P110δ. On the other hand, it can also cause a closed PTEN conformational change and decrease PTEN activity. K289, K254, and K255 residues in the C2 domain can be sumoylated and helps PTEN bind to the cell membrane. Other modifications that can occur in PTEN are acetylation at K125 and K128 and oxidation at C71 and C124. This modification decreases PTEN activity. Meanwhile, PTEN degradation depends on lysine residues (K289 and K13) which can undergo ubiquitination (C. Y. Chen et al., 2018). The structure and regulation of PTEN is shown in Figure 1.

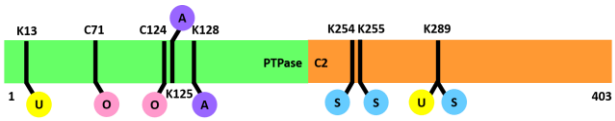

Figure 1. PTEN protein structure and protein modification binding site. U, ubiquitination; O, oxidation; A, acetilation; S, sumoylation

B. *Insulin Signaling Pathway*

Insulin is a hormone secreted by pancreatic B cells into the bloodstream when blood glucose levels are high, for example, after eating. This hormone plays a role in the process of glucose uptake into cells. The mechanism of insulin signaling in cells involves a variety of proteins. The main signaling pathway activated due to insulin binding to its receptor is the PI3K/Akt signaling pathway, which involves various phosphorylation cascades (Saltiel, 2021). Activation of the PI3K/Akt pathway leads to the translocation of GLUT, a glucose transporter, to the cell membrane. In the cell membrane, GLUT acts as a gateway for glucose to enter the cell. Thus, the level of glucose in the blood decrease (Berbudi et al., 2019).

The PI3K/Akt pathway activation begins when insulin binds to its receptor (Saltiel, 2021). The insulin receptor consists of two α subunits (extracellular proteins) and two β subunits (transmembrane proteins). When insulin binds to the α subunit, a conformational change occurs. It leads to the activation of the β subunit, causing autophosphorylation of insulin receptor substrate (IRS). Activated IRS

undergoes translocation to the cell membrane, then PI3K is phosphorylated and becomes active. When PI3K is in action, it will phosphorylate PIP2 to become PIP3, followed by PDK1 activation through a phosphorylation process. The phosphorylation of Akt by PDK1 on the Thr308 residue causes Akt to be activated. Consequently, the Akt can activate the GTPase domain on the Rab protein (Khokhar et al., 2020; Kushi et al., 2021).

Rab is the central regulator of intracellular transport because it is the dominant protein carrier of vesicles containing proteins and other molecules needed by other organelles and cells (Kjos et al., 2018). One of the roles of Rab related to the PI3K/Akt signaling pathway is membrane trafficking from GLUT. Rab helps GLUT translocation from the cytosol to the cell membrane. It mediates the transport of glucose to enter the cell. Thus glucose homeostasis can be maintained (Kushi et al., 2021; Saltiel, 2021).

C. The Role of PTEN In Insulin Signaling Pathway

PTEN was initially discovered as a tumor suppressor. In subsequent developments, it is known to be involved in metabolism. PTEN is involved in one of the insulin signaling pathways, namely the PI3K. As the name suggests, PTEN acts as a phosphatase, an enzyme that works in the dephosphorylation (Saltiel, 2021). PTEN is a negative regulator in the upstream part of the PI3K pathway. It dephosphorylates PIP3 at the 3' position. As a result, PIP3 formed through the activity of the kinase of PI3K returns to its inactive form, namely PIP2. It leads to a decrease in PIP3 required to activate PDK1. It becomes an obstacle in the PI3K signaling pathway. Thus, the transport of GLUT to the cell membrane is disrupted (C. Y. Chen et al., 2018). The role of PTEN in the insulin signaling pathway can be seen in Figure 2.

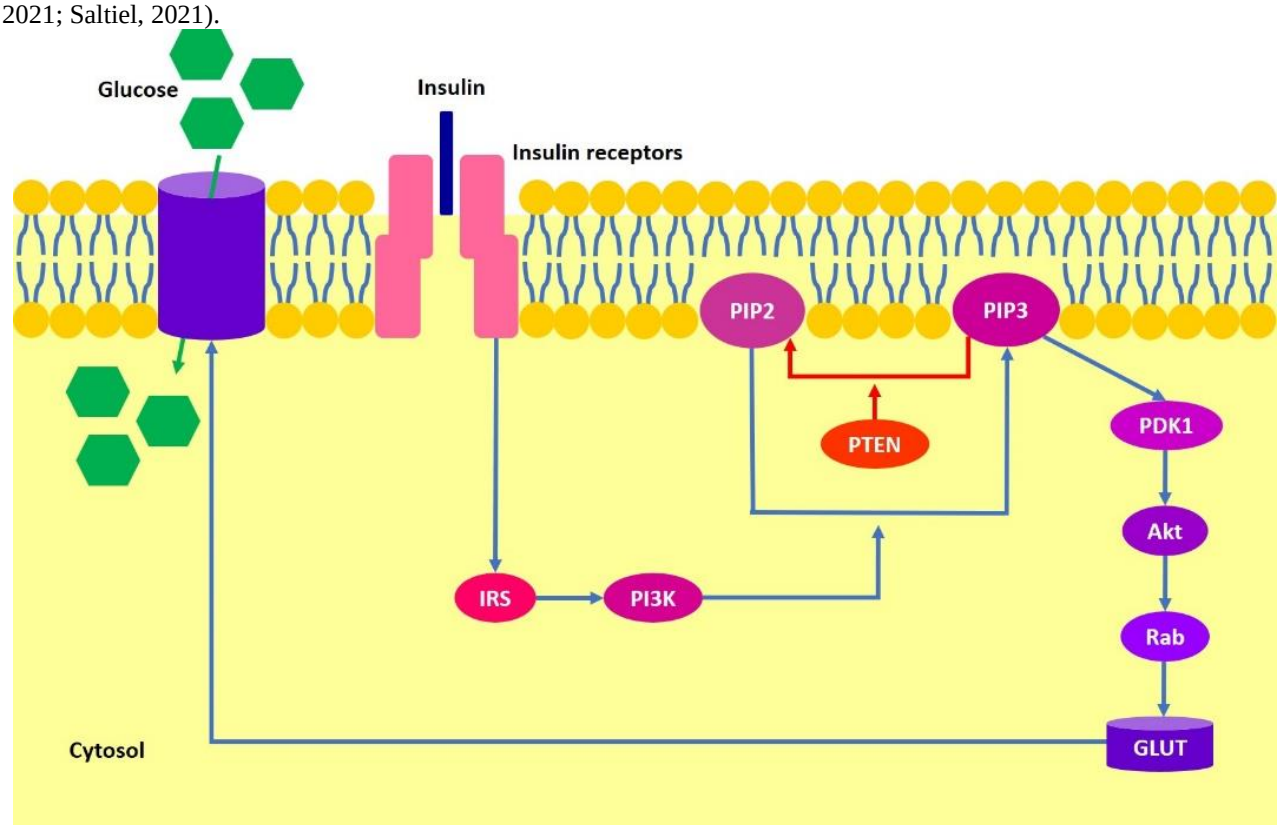

Figure 2. PTEN inhibit insulin signaling pathway by dephosphorylate PIP3 to PIP2.

D. PTEN As A Target For Diabetes Mellitus Therapy

Studies focusing on metabolic diseases has shown that PTEN activity is associated with increased insulin resistance, and the polymorphisms in PTEN are associated with the risk of developing diabetes mellitus. This polymorphism can increase PTEN levels. Polymorphisms in PTEN related to the incidence of insulin resistance, for example, experienced by Japanese individuals change from C to G at position 9 of the 5'untranslated region in PTEN (Y. Z. Li et al., 2020). Another polymorphism experienced by the Uyghur population is hypomethylation of the PTEN promoter, that thought to be the cause of diabetes mellitus. Methylation of the promoter leads to the downregulation of PTEN in metabolic syndrome. Thus, the hypomethylation in the Uyghur population increases PTEN expression (Yin et al., 2018).

The PI3K/Akt signaling pathway is involved in the insulin signaling pathway. It's activation can increase sensitivity to insulin (Gao et al., 2019). Given the role of PTEN as a negative regulator of insulin signaling pathways involving PI3K, high PTEN can inhibit Akt phosphorylation. Furthermore, it can inhibit glucose transport into cells (Y. Z. Li et al., 2020). Activation of the PI3K/Akt signaling pathway provides an opportunity for glucose uptake into cells. This process indirectly plays a role in lowering blood glucose levels (Zhang et al., 2019). In other words, the downregulation of PTEN is

thought to prevent high blood glucose levels (Y. Z. Li et al., 2020).

Diabetes mellitus is a disease characterized by high blood glucose levels that can lead to complications that cause the dysfunction of various organs (Gu et al., 2019). Various methods have been explored to control diabetes mellitus cases. Most of the discussion is about inhibitors for enzymes involved in carbohydrate absorption in the small intestine (Gong et al., 2020)., the main problems in diabetes mellitus cases occur in cells' ability to uptake glucose, the downstream also needs to be increased to achieve a high-minded therapeutic effect.

Diabetic patients can have hyperlipidemia and vascular complications leading to organ damage, such as cardiovascular problems, kidney failure, and peripheral vascular complications. It is related to endothelial progenitor cells (EPC), a subpopulation of mononuclear cells, to form tube structures in launching blood vessels. In Gu et al. study using palmitic acid-induced EPC from Sprague-Dawley rats, there was a decrease in proliferation, migration, and tube of EPC formation. Metformin can stop it by upregulating miR-130a. mi-RNA-130a in EPC is known to be downregulated in diabetes mellitus patients. It decreases migration and increases the apoptosis of EPCs. The miRNA-130a binding site was found in the 3'-UTR of PTEN mRNA. Therefore, the binding of this mi-RNA to its binding site inhibits PTEN expression. As a result, p-Akt expression as a target of PTEN, and a regulator in proliferation, migration, and angiogenesis, has increased (Gu et al., 2019).

Some research focused on inhibiting PTEN expression has also been carried out using experimental animals (El-Zeftawy et al., 2019). The results show that PTEN knockout can improve the glucose tolerance (Yin et al., 2018). Li et al. examined the effect of PTEN inhibition in diabetic mice with corneal epithelial cell damage. Administration of PTEN inhibitors caused corneal epithelial cell regeneration and reactivation of Akt, the downstream of PTEN. It proves that PTEN inhibition in diabetic conditions can accelerate the wound-healing process (J. Li et al., 2020).

Another cause of diabetes mellitus is insulin resistance (Hu et al., 2020). Recent diabetes mellitus therapy research by epigenetic studies used human umbilical cord-derived mesenchymal stem cells (HUC-MSCs). These cells are believed can control blood sugar levels through their ability to differentiate and proliferate, thereby improving insulin resistance (G. Chen et al., 2020; Xue J, Gao J, Gu Y, Wang A, Yu S, Li B, Yin Y, Wang J, Su W, Zhang H, Ren W, Gu W, Lv Z, Mu Y, 2022). The study by Chen et al. proved that intramuscular transplantation of HUC-MSCs increased the expression of p-PI3K, p-Akt, and GLUT-4 mRNA. It is due to PTEN mRNA and protein downregulation that upregulates the PI3K/Akt signaling pathway. Thus, therapy using HUC-MSCs in diabetes mellitus may increase insulin sensitivity (G. Chen et al., 2020).

Along with the times, many researchers are directing their research to molecular research to target certain proteins. One who did was Maity et al. As previously mentioned, PTEN is an inhibitor of Akt activation, an upstream of mTORC1. In their research, Maity et al. used rodent models of type 1 and type 2 diabetes. They investigated the proteins involved in the PI3K/Akt signaling pathway, including mTORC1 and PTEN. Raptor expression, a component of mTORC1, is known to increase mTORC1 activity and decrease PTEN expression. Interestingly, the overexpression of raptors at high glucose had no other effect. In addition to testing raptor expression to suppress PTEN expression, Maity et al. also tested the involvement of miRNA-214 in PTEN expression. miRNA-214 expression increased due to mTORC1 activity. Thus, the action of miRNA-214 provides a positive feedback loop on Akt activity by suppressing PTEN expression. Although research regarding the association of mTOR with PTEN in high glucose conditions is limited, it seems to be one way to repress PTEN activity in the hyperglycemia (Maity et al., 2019).

It has been mentioned that one of the causes of diabetes mellitus can be a disturbance in insulin secretion. Cells that play a role in this are pancreatic β-cells. Glucose homeostasis is highly dependent on pancreatic β-cell function. In several studies, β-cell dysfunction has been associated with PTEN upregulation in cases of diabetes mellitus that causes pancreatic β-cell dysfunction. Cheng et al. bioinformatically tested miRNAs related to PTEN expression. Based on the results of their research, miR-296-3p experienced a decrease in expression. They attempted to transfect a miR-296-3p mimic into mouse insulinoma Min6 cells to target PTEN. As a result, the expression of PTEN mRNA and protein decreased. In addition to targeting PTEN, miR-296-3p also targets Bax and Bcl-2, proapoptotic proteins involved in the apoptotic mechanism that causes cell injury. Thus, miR-296-3p mimic may be an alternative for diabetes mellitus therapy by targeting PTEN (Cheng et al., 2022).

Targeting a protein can also be done by utilizing natural compounds. Chemical compounds derived from plants have been widely studied as an alternative to drugs. One is Berberine (BER), a natural isoquinoline alkaloid from plants such as Berberis vulgaris. In El-Zeftawy et al.'s research, female albino Sprague-Dawley rats were treated with HFD for eight weeks to get a picture of hepatic cells with insulin resistance. The treatment continued with BER-chloride for two weeks. The results showed a decline in the PTEN gene and protein expression in rat liver cells. In addition, the PI3K and p-Akt genes and protein expressions increased. The mechanism of BER-chloride in reducing PTEN expression is thought to involve the downregulation of RBP4 and the upregulation of PI3K, but there was no significant difference in RBP4 expression between the control and the test group. However, PTEN downregulation is a prime focus as a therapeutic target to reduce insulin resistance. Thus, BER-chloride can be a therapeutic alternative to enhance hepatic function and

insulin signaling pathways by targeting PTEN (El-Zeftawy et al., 2019).

Research on PTEN has been around for the past two decades, but research focusing on the use of PTEN as a therapeutic target for metabolic diseases, especially diabetes mellitus, is still very limited, so we have limitations in comparing better methods. However, we hope that the research on PTEN as a target for DM therapy will further develop, considering the results shown from several studies show an improvement.

IV. CONCLUSIONS

PTEN is one of the regulatory proteins of the insulin signaling pathway through the PI3K/Akt pathway. In diabetes mellitus cases, PTEN activity was known to increase, and PTEN inhibition can improve the quality of insulin signaling pathways. Various studies using HUC-MSCs, raptors, and active compounds such as metformin or berberine gave positive results for Akt expression in insulin signaling pathways. It makes PTEN a target for insulin resistance therapy in diabetes mellitus.

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