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THE ROLE AND REGULATION OF FOXO1 IN CARBOHYDRATE METABOLISM AND ITS TARGETING IN METABOLIC DISEASES

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ABSTRACT

Carbohydrate is the first energy source used in metabolic processes. Failure in carbohydrate metabolism can cause metabolic diseases, and many studies are focused on its therapy. Until now, there is no specific therapy approved. Despite that, one of the main alternatives is regarding the involvement of FOXO1 protein in metabolic disease progress. As a transcription factor for gluconeogenesis genes, FOXO1 can increase blood glucose levels. It also involves various signaling pathways in carbohydrate metabolisms such as PI3K/Akt and PKA in which many proteins act as FOXO1 regulators through posttranslational modification. The vital role of FOXO1 in carbohydrate metabolism provides an opportunity to make FOXO1 the main target of metabolic disease therapy. Various proteins and natural compounds can either directly or indirectly regulate FOXO1 activity. It can be an option to be used to control blood glucose levels by targeting FOXO1

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INTRODUCTION

Metabolic disease is one of the most common diseases today. One of the enormous metabolic diseases in the world is diabetes. This disease is one of the fastest-growing global health problems in the 21st century. Based on data from the International Diabetes Federation (IDF), about 463 million people in 2019 suffering diabetes, and this figure is expected to continue to increase to 578 million in 2030 and 700 million in 2045 with an estimated more than four million cases of diabetes deaths occurring in a population aged 20-79 years. Meanwhile, according to data from the World Health Organization (WHO), there were 422 million sufferers in 2014. The increase in the prevalence of diabetes from 1980 increased by 3.8% in 2014 and an estimated 629 million sufferers in 2045.[1] It is commonly caused by hyperglycemia.[2,1] The pathology includes abnormalities in insulin secretion and abnormalities in insulin action. This situation increases the risk of complications and can even lead to death.[1]

Hepatic glucose production (HGP) dysregulation increases blood glucose levels continuously and leads to hyperglycemia. This situation commonly occurs in diabetes mellitus cases characterized by an increase in glucose levels in the blood that stimulates excess gluconeogenesis. Glucose-6-phosphatase and Phosphoenolpyruvate carboxy-kinase (PEPCK) enzymes are the main gluconeogenesis enzymes that increase glucose production. Their expression is regulated by FOXO1. High FOXO1 expression is associated with the inactivation of Akt and activation of PKA as a protein involved in two major signaling pathways in carbohydrate metabolism. The role of FOXO1 in carbohydrate metabolism and its regulation involving two main pathways in carbohydrate metabolism can pave the way for metabolic disease control.[3]

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FOXO1

Forkhead Box O (FOXO) is a subfamily of the FOX protein that acts as a transcription factor involved in various mechanisms such as metabolism, cell differentiation, cell cycle, apoptosis, and oxidative stress.[4] In mammals, FOXO consists of four members, namely FOXO1 or forkhead in rhabdomyosarcoma (FKHR), FOXO3 or homologous forkhead rhabdomyosarcoma like protein 1 (FKHRL1), FOXO4 or acute leukemia fusion gene on chromosome X (AFX), and FOXO6. They have the same recognition site located on the promoter of the upregulated gene, that is TT(G/A)TT(G/T)(G/A)(C/T).[5]

Among four types of FOXO, FOXO1 plays an extensive role in metabolism, especially in gluconeogenesis. Analysis by x-ray crystallography showed that FOXO1 has two winged loops (W1 and W2) that cause the structure of FOXO1 to resemble a butterfly shape. Its secondary structure consists of α-helix and β-strand. The α-helix includes H1, H2, H3, and H4, while the β-strand comprises S1, S2, and S3. As a transcription factor, the primary structure of FOXO1 consists of DNA Binding Domain (DBD) forkheads, Nuclear Localization Signal (NLS), Nuclear Export Sequence (NES), and Transactivation Domain (TAD). The portions are arranged sequentially from the N terminal to the C terminal of the FOXO1.[6] The N terminal is rich in alanine. It is an essential part of FOXO1 repression, while the C-terminal is rich in proline, serine, and threonine for FOXO1 activation.[7] This structure is crucial for FOXO1 regulation and can affect carbohydrate metabolic pathways.

The regulation of FOXO1

FOXO1 can undergo activation and inactivation through a posttranslational modification. It can affect FOXO1 targets in the cell and be related to its function as a transcription factor by regulating its target, in the nucleus or cytosol. FOXO1 becomes active in the nucleus and binds to promoter of the target gene via its DBD. On the contrary, FOXO1 inactivation will occurs when it is translocated to the cytosol by exportin protein.[6] Many proteins are involved in FOXO1 regulation. It includes various mechanisms such as acetylation, phosphorylation, methylation, and ubiquitination (Figure 1).

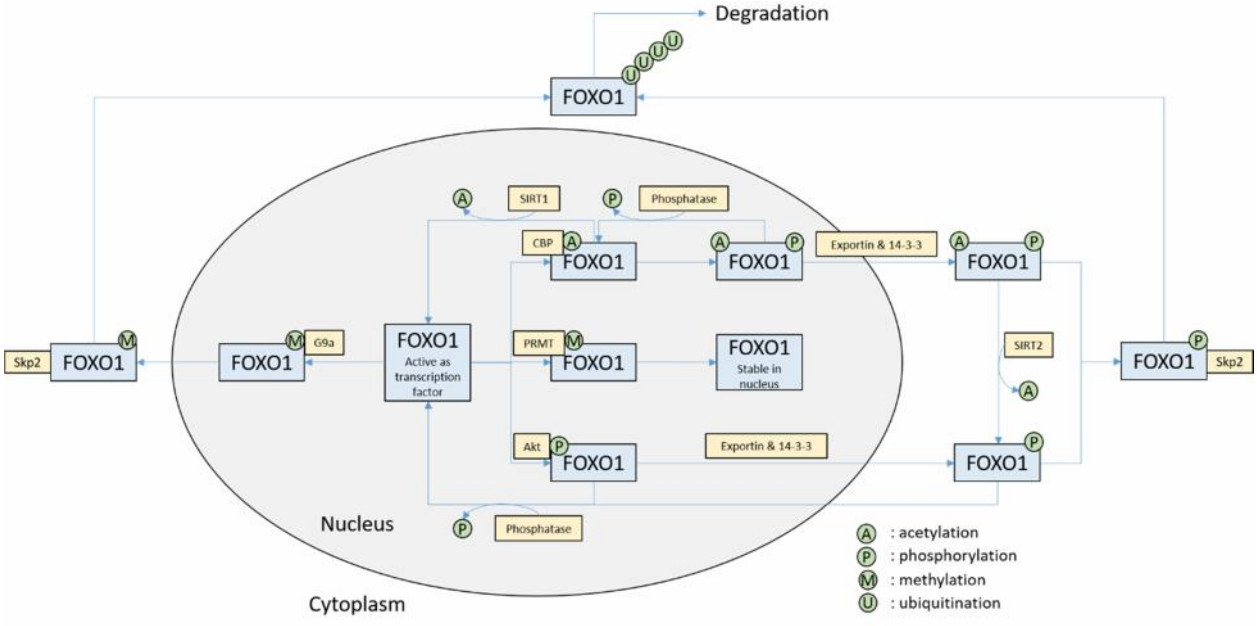

Figure 1. Regulation of FOXO1 by posttranslational modifications directs its localization in nucleus and cytosol. [4–6,8–13]

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Acetylation is the addition of an acetyl group. FOXO1 acetylation is regulated by lysine acetylation transferase (KATs) and histone deacetylase (HDACs). It occurs in K222, K245, K248, K262, K265, K274, and K294 in FOXO1 NLS.[6] One type of KATs that acetylates FOXO1 is CREB-binding protein (CBP) on residues of K242, K245, and K262. Moreover, Erythroblast Transformation Specific-1 (Ets1) also contributes to FOXO1 acetylation by forming a complex with CREB-binding protein (CBP/P300). The complex of Ets1 and CBP can increase histone acetyltransferase activity, thus reducing the affinity of FOXO1 to bind to the targeted genes.[10] Conversely, FOXO1 deacetylation in the nucleus is carried out by silent mating type information regulation 2 homologous 1 (SIRT1), but depends on the presence of NAD. Deacetylation prevents the translocation of FOXO1 to the cytosol therefore FOXO1 remains active in the nucleus to promote transcription of its target gene.[13] The acetylation of FOXO1 in murine can also occur in the cytosol by the FOXO1 Corepressor (FcoR).[14] In this state, deacetylation is carried out by SIRT2 so FOXO1 will be translocated to the nucleus (Figure 1).[5, 6]

Acetylation affects other types of regulation. Acetylation of FOXO1 by CBP can increase the sensitivity of FOXO1 to phosphorylation by Akt.[8] However, phosphorylation does not only occur when FOXO1 is acetylated. This mechanism can also occur independently. Phosphorylation occurs a lot in the signaling pathway of phosphoinositide 3- kinase/protein kinase B/Akt (PI3K/PKB/Akt). FOXO1 phosphorylation initiated at the S256 site by Akt causes the decrease of FOXO1 affinity to its target gene, followed by phosphorylation in T24 and S319 by the same protein. The phosphorylated FOXO1 is easily recognized by the 14-3-3 protein. It can phosphorylate FOXO1 in T24 and S256 sites. S256 being the phosphorylation site that influences the FOXO1 location because its located on the NLS. When 14-3-3 protein binds to FOXO1, there will be a conformational change. It makes the FOXO1 NES domain recognized by the exportin protein. As its name, exportin protein serves to export FOXO1 out of the nucleus. Meanwhile, FOXO1 dephosphorylation is accomplished by protein phosphatase (PP2A). It occurs both in the nucleus and cytosol (Figure 1.).[6]

The next type of modification is methylation. The two previous mechanisms suggest that the modification occurs in the posttranslational stage. In methylation, the modification also processed in the post-transcriptional stage. It is performed by methyltransferase 3 (METTL3). In the other hand, FOXO1 mRNA demethylation is accomplished by Fat mass and obesity-associated gene (FTO) in the N6-adenosine-modified (m6A) sites and N6,2'-O-dimethyladenosine-modified (m6Am) sites, resulting an increase in FOXO1 expression. This FTO activity will be destructed by its inhibitor that causes a decrease in FOXO1 expression, and the FOXO1 targeted genes cannot be upregulated.[15]

Methylation as a posttranslational modification process of FOXO1 occurs in arginine residues, precisely at R248 and R250 by arginine methyltransferase-1 (PRMT1) protein.[6] This modification helps FOXO1 remain stable in the nucleus by preventing phosphorylation. Another methylation occurs at the lysine residue (K273) by one of the histone methyltransferase, namely G9a in the nucleus. This methylation does not affect the translocation of FOXO1 to the cytosol. It is more about assisting the formation of the FOXO1-Skp2 complex. S-phase kinase-associated protein 2 (Skp2) is an E3 ligase protein that plays a role in the proteasomal degradation process.[11] Thus, methylation at different amino acid residues will have a different impact on the stability of FOXO1.

Degradation of FOXO1 is carried out through the ubiquitination-proteasome mechanism. This system is a degradation system for endogenous protein types. Before being ubiquitinated, FOXO1 will be translocated outside the nucleus. The process was mediated through phosphorylation by Akt in S256.[9] Ubiquitination occurs through a series of reactions

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that involve ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (UBC E2), and ubiquitin ligase (E3). FOXO1 and four ubiquitins will form a complex and gives a signal for proteasomal degradation.[4] The degradation mechanism involving Skp2 as E3 ligase is inhibited by the menin protein that binds to FOXO1 that causes the FOXO1-Skp2 complex becomes unstable. Menin also inhibits the phosphorylation of FOXO1 by Akt, therefore reducing the chance for FOXO1 to form a complex with Skp2.[12]

The role and regulation of FOXO1 in the PI3K/Akt signaling pathway

FOXO1 plays a role in PI3K/Akt signaling pathway. It is the major signaling pathway regulated by insulin. First, insulin is secreted by β-pancreatic cells when blood glucose levels are high, then the secreted insulin is bound to insulin receptor substrate (IRS) and triggers the signaling pathway. It also increases GLUT expression on the cell surface for glucose uptake into the cells and initiates glycolysis. Insulin binding to its receptor lead to IRS activates PI3K that catalyze phosphatidylinositol-4,5-bisphosphate (PIP2) to be phosphatidylinositol (3,4,5)-trisphosphate (PIP3). Then, PIP3 activates Akt through phosphorylation by phosphoinositide-dependent kinase-1 (PDK1) and PDK2 at Thr308 and Ser473. The phosphorylated Akt is the active state of Akt, but this activation is not completed without phosphorylation in Ser473 by mTORC2. Akt activation inhibited by phosphorylation of PIP3 by homologous phosphatase and tensin (PTEN), an inhibitor of the PI3K/Akt pathway that dephosphorylates PIP3 to PIP2, though PIP3 loses its ability to activate Akt.[16]

Phosphorylated Akt can activate mTORC1 that helps activate glucokinase (Gck). Glucose taken up by hepatocytes is phosphorylated to glucose-6-phosphate by glucokinase. Glucose-6-phosphate is a substrate for glycolysis and glycogenesis.[16] Glycogenesis occurs due to Akt phosphorylates glycogen synthase kinase (GSK3) and inactivate it. The inactive GSK3 cannot phosphorylate glycogen synthase (GS). Therefore GS becomes active to synthesize glycogen from glucose-6-phosphate.[17, 18]

The involvement of FOXO1 in metabolism occurs in the process of gluconeogenesis. FOXO1 is a transcription factor for gluconeogenesis enzyme genes such as glucose-6-phosphatase and phosphoenolpyruvate-carboxy-kinase. In addition to activating gluconeogenesis, FOXO1 inhibits glycolysis by decreasing glucokinase activity. This activity is opposite to Akt activity that declines FOXO1 exertion in the nucleus.[16]

In the case of insulin resistance, there is a decrease in glucose uptake by cells and an increase in the expression of gluconeogenic enzymes by the liver that causes an increase in blood glucose levels.[19] Insulin sensitivity can be escalated by estrogen through the induction of insulin receptors. Uniquely, estrogen can reduce High Glucose Production (HGP) in control mice, but it cannot decrease HGP in mice with FOXO1 knockout. It means that glucose production through gluconeogenesis and glycogenolysis can be reduced by estrogen when FOXO1 undergoes phosphorylation in Ser253 by Akt due to estrogen induction.[17]

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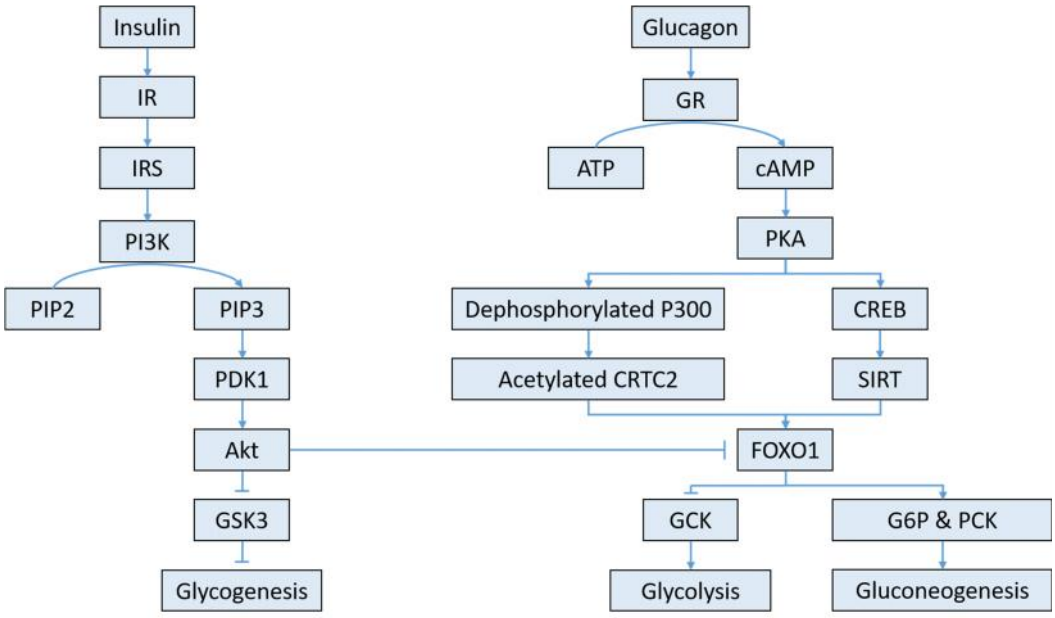

Figure 2. The role of FOXO1 in PI3K/Akt and PKA pathway. Glucose homeostasis is controlled by FOXO1 that downregulated by insulin and upregulated by glucagon.

The role and regulation of FOXO1 in the PKA signaling pathway

The hormone that has an antagonistic action to insulin is glucagon. Glucagon generally regulates glucose homeostasis via acetylation mechanisms that target FOXO1 via various proteins. Glucagon inhibits the acetylation of glycogen phosphorylase. It means glycogen phosphorylase actives to produce glucose.[20] Apart from the acetylation mechanism, glucagon also performs phosphorylation. Glucagon causes increased FOXO1 phosphorylation at S273, S153, and S276. Phosphorylation in S276 is crucial because it mediates the translocation of FOXO1 to the nucleus and maintains its stability. Without phosphorylation in S276, the 26S proteasome will degrades FOXO1. The existence of FOXO1 in the nucleus supports FOXO1 to carry out its transcription activity, and phosphorylation at S273 can control the increase in glucose production by the liver (Figure 2).[3]

The other mechanism regulated by glucagon is ~~through~~ the PKA signaling pathway. Low blood glucose levels cause glucagon secretion and its binding to the glucagon receptor activating PKA. The active PKA dephosphorylates p300 (an acetyltransferase) at the Ser89 site and makes it on. As acetyltransferase, p300 transfers acetyl to the CREB-regulated transcription coactivator-2 (CRTC2) Lys628 residue. It makes an increase in the expression of glucose-6-phosphatase and phosphoenolpyruvate-carboxy-kinase. CREB-regulated transcription coactivator-2 activity is related to FOXO1, and p300 downregulation reduces FOXO1 activity. Also, the instability of FOXO1 binding to its target gene occurs via acetylation by E26 transformation specific or Erythroblast Transformation Specific-1 (Ets-1) family. However, in the fasting state, glucagon activates Extracellular signal -Regulated Kinase (ERK) that can inhibit Ets-1.[20]

In prolonged fasting, PKA increases the expression of CREB. CREB will bind to the SIRT1 gene promoter and increase SIRT1 expression. SIRT1 is a deacetylase that targets CRTC2 and induces its degradation by ubiquitination. CRTC2 inhibition by SIRT1 will increases FOXO1 activity through deacetylation. Continuously SIRT1 expression can change the metabolic mechanism to the ketogenesis pathway.[20]

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FOXO1 as a target in metabolic disease

FOXO1 involvement in gluconeogenesis is of interest to study FOXO1 in metabolic diseases. It also aims to determine the other proteins involved and seek alternative therapies for metabolic diseases. In patients with diabetes mellitus, there is a decrease in serum spexin/neuro peptide Q (NPQ) levels. Spexin is a neuropeptide composed of 14 amino acids and functions to suppress glucose production by the liver. Decreased spexin is known to be in line with insulin resistance and contrast to FOXO1/PGC-1α, G6Pase, and PEPCK. In Gu et al experiment, exogenous spexin treatment in mice with a high-fat diet gives an increasing in p-Akt and p-FOXO1, so it can reduce hepatic glucose production up to 58% and increase insulin sensitivity.[2] The inhibition of glucose production in the liver is also executed by Ets1. Erythroblast Transformation Specific-1/Ets1 increases the acetylation of FOXO1 in the feeding state by complexing it with CBP. The acetylation that occurs in Lys242, Lys245, and Lys262 of FOXO1 disrupts the stability of DNA-binding FOXO1 to Insulin Response Elements (IREs) in the G6Pase and PEPCK gene promoters, causing FOXO1 nuclear exclusion. The increase in Ets1 expression is supposed to inhibit glucose production in the liver and prevent hyperglycemia in both physiological and diabetic conditions.[10]

Glucose homeostasis is not only carried out by the liver but also by the vascular system. In diabetes, adipose tissue metabolic dysfunction occurs due to failure of angiogenesis. Research using mice-induced high fat feeding showed that FOXO1 increased in endothelial cells, there is insulin resistance, and there is no capillary growth. Meanwhile, mutant mice, namely mice that lost FOXO1 in their endothelial cells and induced a high-fat diet, showed capillary growth, blood glucose levels similar to normal mice, good insulin sensitivity, and increased glycolysis gene mRNA levels. It suggests that the cause of angiogenesis in individuals with a high-fat diet is the downregulation of FOXO1. Along with the increase in glucose uptake, metabolism will move towards glycolysis which is crucial for increasing cell growth. These results give an approach in preventive therapy for obesity-related diseases from the point of view of endothelial cell metabolism that can impact body homeostasis.[21]

Glucose homeostasis is also regulated in muscles. Muscles regulate glucose uptake, storage, and metabolism. Therefore, muscles play a role in the pathogenesis of diabetes mellitus. FOXO1 in muscles regulates pyruvate dehydrogenase kinase in the myofibrils transitions from fast to slow glucose metabolism. High pyruvate dehydrogenase kinase-4 found in fasting and diabetes mellitus. Geniposide, a bioactive substance found in fruit, can reduce pyruvate dehydrogenase kinase-4 mRNA and FOXO1 expression to keep pyruvate dehydrogenase at a high level. Thus more pyruvate will be converted to acetyl coenzyme A. It proves that the mechanism of active glycolysis and fatty acids oxidation decreases.[22]

As a transcription factor that regulates metabolic changes towards gluconeogenesis which can worsen pathogenesis, FOXO1 can be the central target in metabolic disease treatment. The use of chlorogenic acid (CGA), a polyphenol with high antioxidant properties found in tea, coffee, fruit, and vegetables can reduce glucose production in diabetes mellitus. Chlorogenic acid can bound to the pleckstrin homology (PH) domain located at the N-terminus of Akt. Consequently, Akt becomes phosphorylated at S473. Generally, the phosphorylated Akt will be translocated to the membrane, but the activation of Akt by CGA does not cause Akt to the membrane. Although much literature says that active Akt can inhibit FOXO1, there has been no further research regarding the relationship between Akt activated by CGA and FOXO1. It may become a reason why Akt activation by CGA not optimal so that CGA consumption is only possible as a complementary therapy.[23]

CONCLUSION

FOXO1 is a protein that acts as a transcription factor for the gluconeogenesis gene in carbohydrate metabolism. This function is related to increase blood glucose production. It makes FOXO1 becomes a crucial target to control metabolic disease progression. Understanding the pathways that regulate FOXO1 and the proteins involved in its modifications will give new insight in metabolic disease therapy.

CONFLICT OF INTEREST

The authors convey that there is no conflict of interest in this paper.

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