

REVIEW

The role of FoxO1 and its modulation with small molecules in the development of diabetes mellitus: A review

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Abstract

Diabetes mellitus type 2 (T2D) is one of the metabolic disorders suffered by a global human being. Certain factors, such as lifestyle and heredity, can increase a person's tendency for T2D. Various genes and proteins play a role in the development of insulin resistance and ultimately diabetes in which one central protein that is discussed in this review is FoxO1. In this review, we regard FoxO1 activation as detrimental, promote high plasma glucose level, and induce insulin resistance. Indeed, many contrasting studies arise since FoxO1 is an important protein to alleviate oxidative stress and promote cell survival, for example, also by preventing hyperglycemic-induced cell death. Inter-relation to PPAR γ , another important protein in metabolism, is also discussed. Ultimately, we discussed contrasting approaches of targeting FoxO1 to combat diabetes mellitus by small molecules.

KEYWORDS

Akt pathway, diabetes, FoxO1, modulators, small molecules

1 | INTRODUCTION

Diabetes mellitus, known as diabetes, is a metabolic disease characterized by high blood sugar. This disease is one of the ten diseases with the world's highest lethality rate. International Diabetes Federation counted that 463 million people have diabetes. This number will continue to increase, and it is estimated that in 2045, diabetes mellitus sufferers will increase of up to 51% and reach 700 million people. In general, diabetes consists of several types, namely type 1 diabetes mellitus (T1D), type 2 diabetes mellitus (T2D), and gestational diabetes mellitus (GDM). Globally, T2D is a type of diabetes that accounts for 85–95% of diabetes mellitus sufferers. Most countries show that diabetes increases along with rapid socio-cultural development such as urbanization, changing dietary patterns, to decreasing physical activity followed by unhealthy lifestyles (Goryakin et al., 2017). Without an

effective management program, the number of diabetes mellitus sufferers will continue to increase.

Our previous literature study (Nathanael et al., 2020) showed that several gene expressions changed when animal models, cell culture, or epidemiological study applied a diet with a high carbohydrate or MSG. However, such study is a comprehensive study in which no central genes which may become determining factor(s) in the formation of T2D are concluded. This study focuses on two central proteins which are very much related to the insulin signaling pathway (Akt/Protein kinase B(PKB) and mitogen-activated protein kinase (MAPK) pathway), forkhead box protein 1 (FoxO1) and peroxisome proliferator-activated receptor gamma (PPAR γ). Study compared *FoxO1* expression in average (non-obese) conditions and obesity with mild insulin resistance, in which *FoxO1* expression was found to increase in obese conditions and even higher when sustaining a combination of obesity with

acute insulin resistance relative to the non-obese group (Battiprolu et al., 2012). It was shown that *FoxO1* overexpression or gain-of-function studies increased blood sugar levels, which led to impaired insulin, glucose tolerance, and other various metabolic disorder such as obesity, glucose intolerance, hyperphagia, and impaired insulin secretion (Qu et al., 2006; Zhang et al., 2006). Other positive results also supported that *FoxO1* knockdown or knock-out can decrease blood sugar levels and increase insulin sensitivity and shows rescue of diabetes (Alharbi et al., 2018; Altomonte et al., 2003; Dong et al., 2008; Matsumoto et al., 2007; Nakae et al., 2002; Samuel et al., 2006). High expression of *PPARG* in pancreatic β -cell can be associated with a high-glucose profile (Hogh et al., 2014; Kanda et al., 2009). Additionally, mice lack *PPARG* result in hypotension, insulin resistance, and other metabolic-related disorder (Duan et al., 2007; Greenstein et al., 2017; Norris et al., 2003; Odegaard et al., 2007).

Those correlation experiments mentioned above can be the basis for the involvement of the *FoxO1* gene in body weight regulation and carbohydrate metabolism. Its inter-relation, several genes which regulate and are regulated by those two genes are discussed. Moreover, several small molecule ligands which have been reported to regulate the activity of two genes directly/indirectly will be discussed and mainly subjected to alleviate diabetes progression.

2 | REGULATION OF FoxO1: RELATION TO AKT SIGNALING AND REGULATION

2.1 | FoxO1 and Akt signaling pathway

When insulin is released by β -cell, it binds to a receptor known as insulin receptor (InsR). This receptor plays a vital role in a series of biochemical pathways such as carbohydrate and lipid metabolism. The abundance of this gene variant in humans is predominantly found in liver tissue, skeletal muscle, adipose tissue, and placenta (Benecke et al., 1992; Escribano et al., 2017). Binding of insulin to its receptor activates several insulin receptor substrate (IRS) proteins in which two proteins, IRS1 and IRS2, exert down-regulation activity toward various FoxO proteins, particularly focussing on FoxO1. The later was reported to give more dominant activity in various cells while IRS1 is mostly exerts its activity in skeletal muscle. Further signaling pathway activates the p110 α subunit of phosphoinositide-3-kinase (PI3K) and to Akt/Protein kinase B (Guo et al., 2006). As transcription factor, FoxO1 displays most of its activity in nucleus. This signaling promotes phosphorylation of FoxO1 by Akt, resulting in

an ejection of FoxO1 to cytoplasm and subsequently degraded by ubiquitin-mediated proteasome degradation (Huang & Tindall, 2011; Matsuzaki et al., 2003). Indeed, inactivation of Akt by a protein phosphatase 2A (PP2A) prevents FoxO1 deactivation and results in insulin resistance (Beg et al., 2016). Activated FoxO1, for example, in liver, promotes gluconeogenesis through activation of several genes such as *glucose-6-phosphatase(G6Pase)* and *phosphoenolpyruvate carboxykinase (PEPCK)*, which also confers an insulin resistance phenomenon by the inability of insulin to suppress glucose production (Nakae et al., 2001a).

Insulin receptor correlation with the onset diabetes was not consistent. One study proved that overexpression of *InsR* in diabetic mice significantly reduced body weight, alleviated hyperphagia, and improved blood sugar level compared to diabetes control although other growth parameters were compromised (Sasaki et al., 2015). The particular study also reported no improvement on insulin sensitivity. In contrast, other study explained that overexpressed *InsR* increased insulin sensitivity so that glucose transport and glycogen synthesis run effectively and reduce blood sugar (Besic et al., 2015; Kosaki et al., 1995). Moreover, prolonged insulin stimulation in *IRS1*^{-/-} mouse embryo fibroblasts (MEF) apparently failed to degrade FoxO1 in which IRS2 level itself was reduced (Guo et al., 2006). Additionally, FoxO1 activation can in turn give feedback by deactivating IRS1 by serine phosphorylation which promote the vicious cycle of metabolic disorder. Inactivation of FoxO1 reduced IRS2 level, but not IRS1 which plays more dominant role in metabolism (Battiprolu et al., 2012; Zhang, Li, et al., 2012). The negative impact of FoxO1 related to insulin sensitivity on another central protein such as *PPARG* (Armoni et al., 2006; Dowell et al., 2003) and thus toward more downstream protein such as glucose transporter type 4 (GLUT4) activity (Armoni et al., 2007; Gonzalez et al., 2011) proofs that FoxO1 is a central protein that can modulate whole Akt signaling pathway. General overview on the action of insulin via Akt signaling to modulate FoxO1 activity and its downstream effect can be seen in Figure 1.

Modulating FoxO1 requires a delicate approach in which FoxO1 activation itself is one mechanism to alleviate oxidative stress and promote wound healing by activating various antioxidant-related proteins such as manganese superoxide dismutase (MnSOD) (Kitamura et al., 2005; Mohseni et al., 2021; Yun et al., 2014). One mechanism to protect cells from oxidative stress includes induced apoptosis (Ning et al., 2015; Shen et al., 2012; Weng et al., 2016). Additionally, active FoxO1 itself is responsible for the expression of insulin receptor, thus creating self-feedback loop (Puig & Tjian, 2005).

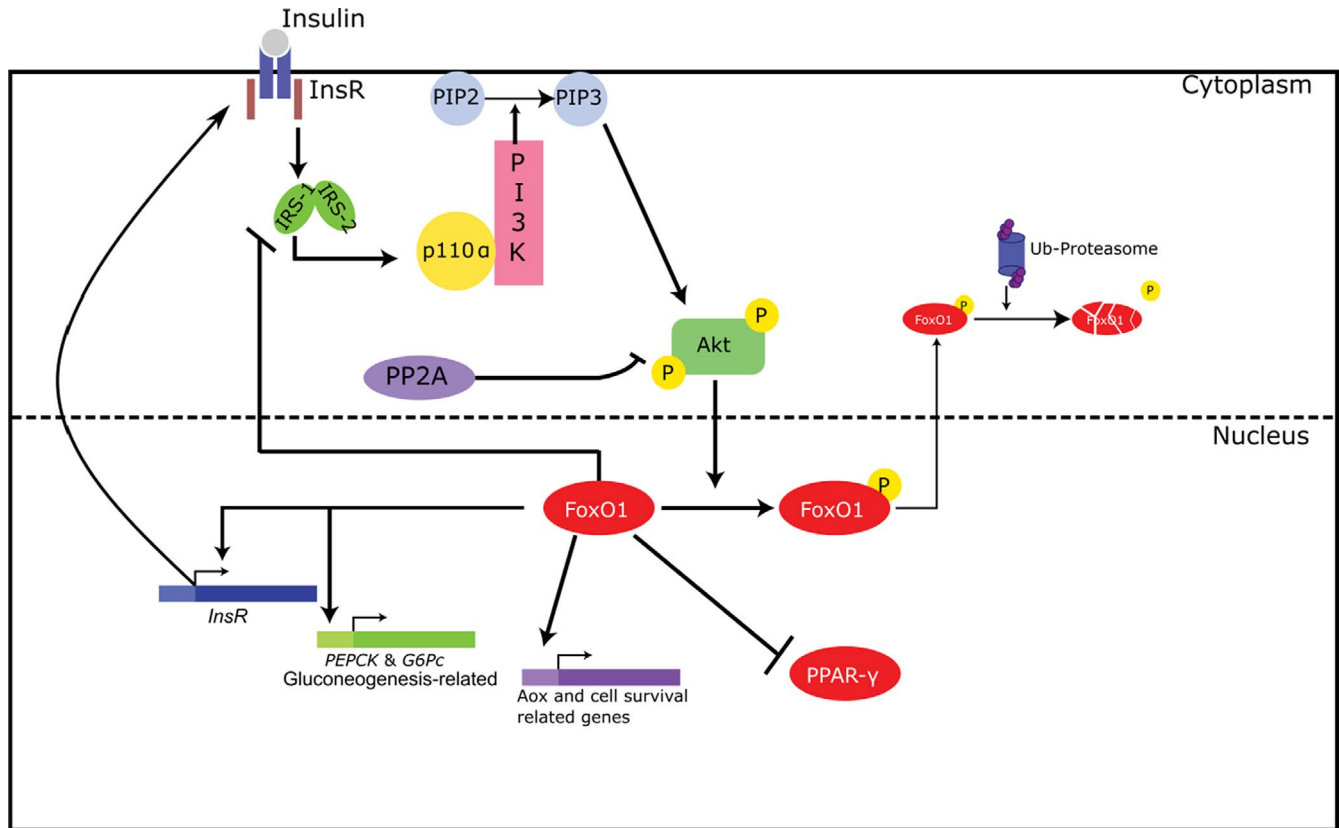


FIGURE 1 Overview of FoxO1 signaling pathway related to insulin response to Akt signaling cascade. InsR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide-3-kinase; PIP, phosphatidylinositol phosphate; PP2A, protein phosphatase 2A; FoxO1, forkhead box protein O1; Ub, ubiquitin; *PEPCK*, phosphoenolpyruvate carboxykinase-encoded gene; *G6Pc*, glucose-6-phosphatase-encoded genes; PPAR γ , peroxisome proliferator-activated receptor gamma

2.2 | Regulation of FoxO1 activity through post-translational modification

Although the basic concepts regarding FoxO1 regulation are that insulin activates cascades which ultimately deregulate FoxO1 activation through phosphorylation by Akt (Protein Kinase B), distinct phosphorylation sites by other protein kinase, various protein modification such as acetylation also plays a role on FoxO1 activity. Phosphorylation by Akt at S256, followed by T24 and S319 which seems Akt-independent, ultimately promotes degradation of FoxO1 by ubiquitination (Accili & Arden, 2004; Biggs et al., 1999; Guo, 2013; Matsuzaki et al., 2003; Nakae et al., 2001a, 2001b; Rena et al., 1999). However, its degradation is apparently regulated by 14-3-3 protein, in which 14-3-3 protein binding to the FoxO1 is promoted by phosphorylation, exporting FoxO1 out from the nucleus while subsequently protects FoxO1 from ubiquitin-mediated degradation (Saline et al., 2019; Tzivion et al., 2011). Other phosphorylation site is recently identified in S276 by protein kinase A (PKA), which is induced by glucagon (Wu et al., 2018). In contrast, phosphorylation of FoxO1 by MST-1 hinders binding of 14-3-3 protein

toward phosphorylated FoxO1 at S212, thereby promoting nuclear localization and in turns can be dephosphorylated and activated in nucleus by PP2A (Lehtinen et al., 2006; Yan et al., 2008; Yuan et al., 2009) which promotes FoxO1-mediated cell death and modulates longevity. Additionally, FoxO1 can be activated through phosphorylation by AMP-activated protein kinase (AMPK) although with a preference to FoxO3 (Greer et al., 2007, 2009).

FoxO1 can be modified by acetylation through CREB-binding protein (CBP)/p300 which can reduce its activity as transcription factor and promotes degradation through phosphorylation (Matsuzaki et al., 2005). On the contrary, FoxO1 can also be deacetylated by sirtuin (SIRT) proteins, both SIRT1 and SIRT2. It is generally known that deacetylation of lysine increase the amount of positive charge of the protein, thereby creating a condition of nuclear trapping and promoting the binding to the DNA although the degree of the effect is dependent on the acetylation of the protein DNA-binding interface (Matsuzaki et al., 2005). As such, the consensus is deacetylation of FoxO1 by sirtuin protein positively regulates FoxO1 activity as transcription factor, thereby further promoting gluconeogenesis in which in long terms may promotes diabetic condition,

for example, by repressing PPARG (Wang & Tong, 2009). On the contrary, FoxO1 is also related to the expression of genes, which seems to be important for the protection from cell death due to oxidative stress. Increased activity of FoxO1 by SIRT1 deacetylation apparently reduces the effect of diabetic nephropathy by autophagy (Xu et al., 2019, 2020).

Acetylation dynamic effects are rather conflicting and seem to be quite dependent on genes and cells, level of acetylation and acetylated protein and closely related to alleviating oxidative stress and promoting cell longevity (Brunet et al., 2004; Motta et al., 2004). One example in muscle cells was that *SIRT1* overexpression reduced FoxO1 activity and results in the protection and muscle atrophy (Lee & Goldberg, 2013). Acetylation of FoxO1 also creates a site competition for subsequent ubiquitination (Kitamura et al., 2005). It is worth to be mentioned that sirtuin itself asserts its effect to lots of protein, which are critical to metabolism and survival. Dynamics of FoxO1 acetylation is well discussed by Daitoku et al. (2011).

FoxO1 expression can be regulated by methylation both in protein and mRNA level. Methylation of FoxO1 in position K273 by G9a (known as euchromatic histone-lysine-N-methyltransferase) promotes its recruitment to S-phase kinase-associated protein-2 (SKP2), an E3 ubiquitin ligase and its degradation (Chae et al., 2019). In contrast, methylation at arginine position 248 and 250 by protein arginine N-methyltransferase 1 (PRMT1) turns out to block Akt binding to FoxO1, hinders its degradation, and subsequently promotes its activation. Methylation by PRMT1 can be promoted by oxidative stress and resulted in the FoxO1-mediated cell death (Yamagata et al., 2008). Methylation of *FoxO1* mRNA by m(Altomonte et al., 2003) A methyltransferase possibly by METTL3 (methyltransferase 3) and its demethylation by fat mass and obesity-associated protein (FTO) affects the dynamic of its translation, in which the later promotes FoxO1 production (Dominissini et al., 2012; Peng et al., 2019). Additionally, FoxO1 can be glycosylated by N-acetylglucosamine via O-linked β -N-acetylglucosamine transferase (OGT), which apparently increased its activity for gluconeogenesis (Kuo et al., 2008a, 2008b). O-glycosylation of FoxO1 by glucosamine can also be induced by high-glucose intake and apparently leads to an increase of hepatic *G6Pase* expression, thereby releasing glucose into blood circulation and creating a vicious cycle of glucotoxicity. The effect of glycosylation can also be found in mutant FoxO1 protein in which the phosphorylation sites are mutated by alanine, which hints to an independent regulation from phosphorylation. Overview of post-translational modifications of FoxO1 and its impact on FoxO1 activity is summarized in Figure 2 and Table 1.

2.3 | PPARG (Peroxisome proliferator-activated receptor gamma)

Peroxisome proliferator-activated receptor (PPAR) is a group of transcription factors and attached to PPAR response element (PPRE). PPAR itself comprises of PPARG, PPARG, and PPARG/B. PPARG and PPARG/B play a role in adipogenesis, while PPAR- α is involved in lipolysis. PPARG agonists, such as thiazolidinedione (TZD) or chiglitazar, are believed to improve glucose tolerance and obesity (Li et al., 2006). PPARG has three isoforms and mainly distributed in different tissues. Isoforms 2 and 3 are mainly expressed in adipose, and isoform two is usually found in the obese subject. Its activity is heavily dependent on various ligands, growth factors, protein complexes, and modifications on the protein.

The importance of PPARG can be extracted from several animal and transgenic studies. A high-glucose profile also showed overexpression of *PPARG* pancreatic β -cell-specific (Hogh et al., 2014). Meanwhile, mice lack PPARG result in hypotension, insulin resistance, and higher plasma-free fatty acid (Duan et al., 2007; Norris et al., 2003; Odegaard et al., 2007). Mice with PPARG deficient in adipose-specific bone marrow and liver-specific suffer from hepatomegaly and steatosis (Greenstein et al., 2017; He et al., 2003; Kanda et al., 2009). Furthermore, agonists applied to mice with obesity and insulin resistance have better results in improving conditions.

It is of note that PPARG signaling is also interrelated to adipogenesis and development of cancer. This is due to the signaling via MAPK-ERK kinase (MEK) pathway, which is related to cell division. In this case, phosphorylation of PPARG by MAPK/ERK (and janus kinases) inhibits its activity, which induces its export toward cytoplasm and its degradation by proteasome (Burgermeister & Seger, 2007; Kaplan et al., 2010) (Figure 3a). It is phosphorylated at position S84 in which its mutation to alanine increases the transcriptional activity of this protein (Adams et al., 1997). In mice, mutation S112A that inhibits PPARG phosphorylation indeed promotes weight gain but also manages to alleviate insulin resistance (Rangwala et al., 2003). PPARG exerts its activity by activating glucose transporter expression, mainly *GLUT4* which further stimulate glucose uptake (Liao et al., 2007; Michael et al., 2001; Wu et al., 1998). It is to be noted that PPARG activities depend on the bound ligands. Some contrasting studies were reported in which activation of PPARG inhibits *GLUT4* transcription in skeletal muscle cells (Miura et al., 2003) while PPARG knockout mice displayed better insulin sensitivity (Kubota et al., 1999; Miles et al., 2000). It turns out that retinoid X receptor (RXR) acted as ligands to

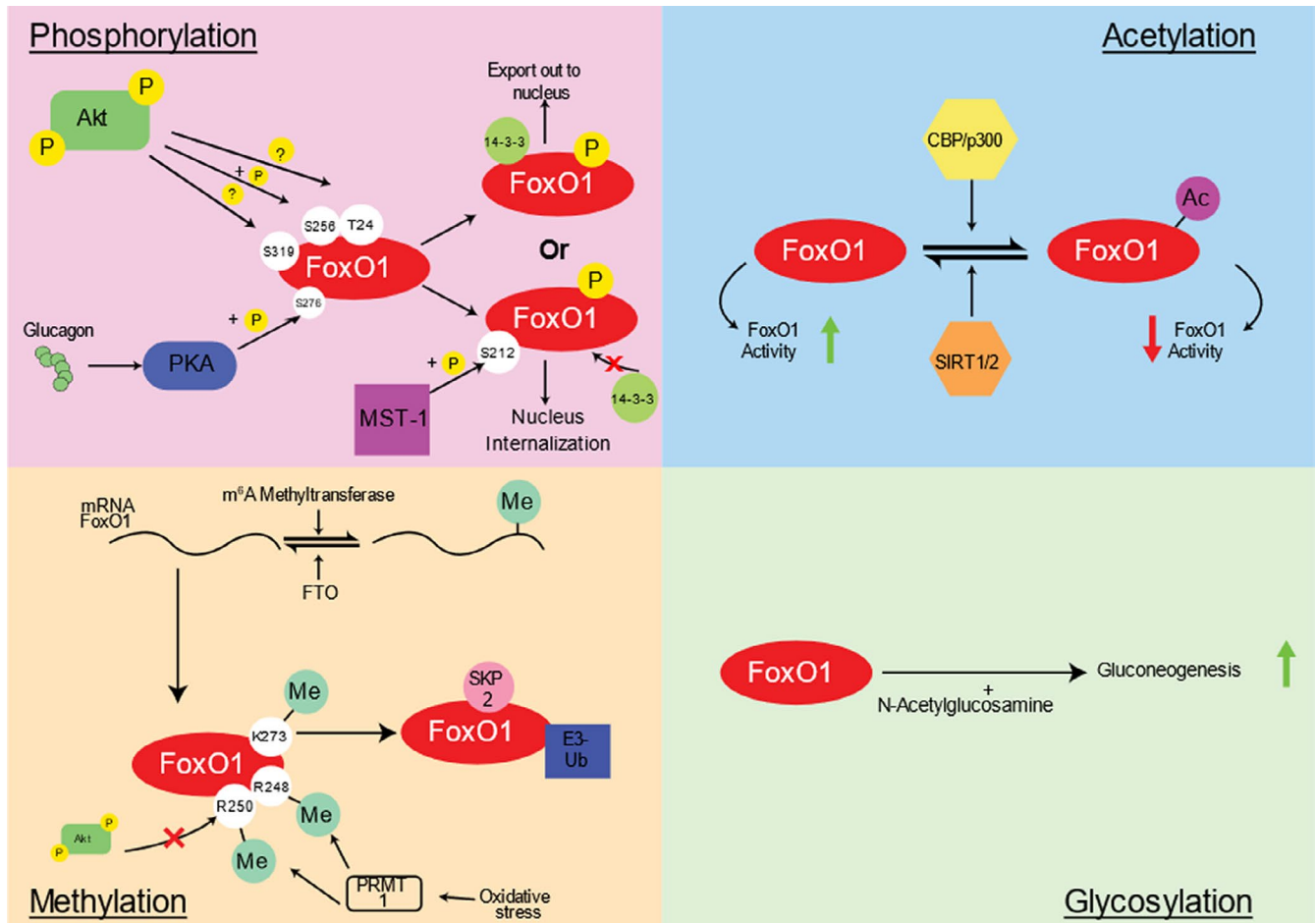


FIGURE 2 Various post-translational modification on FoxO1 protein / mRNA regulates its activity and response. PKA, protein kinase A; CBP, CREB-binding protein; SIRT, sirtuin; FTO, fat mass and obesity-associated protein; PRMT1, protein arginine N-methyltransferase 1

unphosphorylated S112 PPARG which suppress GLUT4 transcriptional activity while combination of PPARG agonist such as rosiglitazone displays the opposite phenotype (Armoni et al., 2003).

2.4 | PPARG entanglement with FoxO1 signaling

FoxO1 and PPARG itself are interrelated and also center proteins which bridges and can modulate or be modulated Akt and MAPK signaling that affects the activity of GLUT4 which is downstream of the insulin signaling pathway (Liao et al., 2007; Wu et al., 1998). Early reports about FoxO1 relationship with PPARG are quite contrasting (Daitoku et al., 2003; Dowell et al., 2003). However, further studies showed that FoxO1 reported to repress PPARG2 isoform production through binding to IRS promoter (Armoni et al., 2006) or direct inhibition (Fan et al., 2009). This would indicate that both proteins modulate cell sensitivity toward insulin in the order of PPAR

ligand-dependent activity. PPARG also displays crosstalk toward insulin signaling directly, in which administration of thiazolidinediones as PPARG agonist managed to increase *IRS2* gene expression (Smith et al., 2001). PPARG itself can possibly indirectly modulate FoxO1 by its interrelation to SIRT1. Apparently, PPARG is negatively modulated by SIRT1 in which SIRT1 can act as corepressor of PPARG in the promoter (Picard et al., 2004) or through the dynamic of acetylation by SIRT1 (Han et al., 2010). Interestingly, SIRT1 itself can also be back regulated by PPARG by reducing SIRT1 transcription level, thereby creating self-loop regulation (Han et al., 2010).

It is to be noted that the activities of both proteins are quite dependent on the type of the cells. One well studied that link FoxO1 and PPARG is in the kidney through Klotho protein (Figure 3b), a protein related to alleviating oxidative stress and nephropathy mostly in streptozotocin-induced or db/db diabetic rat/mice models (Asai et al., 2012; Cheng et al., 2010; Kim et al., 2016; Takenaka et al., 2019). Klotho protein managed to protect kidney from further destruction through

TABLE 1 Summary of post-translational modification of FoxO1 and its impact on FoxO1 activity

Post-translational modification	Modifying protein	Residues	Remarks
Phosphorylation	Akt	S256	Further phosphorylation which seems Akt-independent is at T24 and S319, promotes ejection of FoxO1 from nucleus, and subsequently degrades by proteasome in conjunction with ubiquitinylation
	PKA	S276	Induced by glucagon, promotes FoxO1 degradation
	MST-1	S212	Promotes nuclear localization and prevents FoxO1 ubiquitin-mediated degradation
	AMPK	–	Activate FoxO1
Dephosphorylation	PP2A	–	Dephosphorylate phosphate groups that have been added by various phosphate-modifying proteins; activate FoxO1
Ubiquitinylation	Ubiquitin	–	In conjunction usually with Akt-mediated phosphorylation to promote degradation of FoxO1 by proteasome
Acetylation	CBP/p300	–	Reduces FoxO1 activity
Deacetylation	SIRT1, SIRT2	Unknown lysine residue	Increase the activity of FoxO1, f.e. promotes gluconeogenesis but also protects cells from oxidative stress-related cell death
Methylation	G9a	K273	Promotes FoxO1 ubiquitin-mediated degradation
	PRMT1	R248 R250	Blocks Akt-mediated phosphorylation, promotes FoxO1 activity
	METTL3	adenine residue in FoxO1 mRNA	Decrease FoxO1 mRNA translation
Demethylation	FTO	adenine residue in FoxO1 mRNA	Increase FoxO1 translation
Glycosylation	OGT	unknown but different than Akt modification site	Modified with glucosamine, increase FoxO1 activity to promote gluconeogenesis

^aProtein abbreviations are given in the text.

its inhibition of MAPK and RelA, a protein related to the activation of inflammatory protein nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) (Zhao et al., 2011). It is known although FoxO1 is positively related to the onset of diabetes, FoxO1 activity also protects cell from oxidative stress via activating various antioxidant enzymes or induced apoptosis and autophagy as described above. This indicates that PPARG indirectly activates FoxO1 activity by preventing its phosphorylation in kidney through klotho protein (Kuro-o, 2008; Yamamoto et al., 2005; Zhang et al., 2008). It is also true then overexpression of *Klotho* in transgenic mice displays moderate resistant to insulin (Utsugi et al., 2000).

To summarize, FoxO1 and PPARG as a regulatory protein play a critical factor in modulating expression and activation of protein both downstream and upstream of the signaling pathway. While GLUT4 localization on the membrane, for example in muscle tissue,

can also be a biomarker to detect abnormality in the metabolism, aberrant *FoxO1* and *PPARG* expression, especially high level of FoxO1 protein, can be a good indicator for the onset of diabetes and other metabolic disorder.

2.5 | Chemical biology: Modulating FoxO1 activity by small molecules

One study made an opinion that targeting the expression or transient inactivation of FoxO1 by selective ligand may indeed be a promising technique for diabetes therapy and/or detection (Zhang, Li, et al., 2012). FoxO1 inhibitor such as AS1842856 remains a tool for molecular and chemical biologist for in vitro and in vivo study (Nagashima et al., 2010; Tanaka et al., 2010). It proves to be challenging to directly use FoxO1 inhibitor as drug since inhibition of FoxO1 can also induced cell death. Designing or derivating

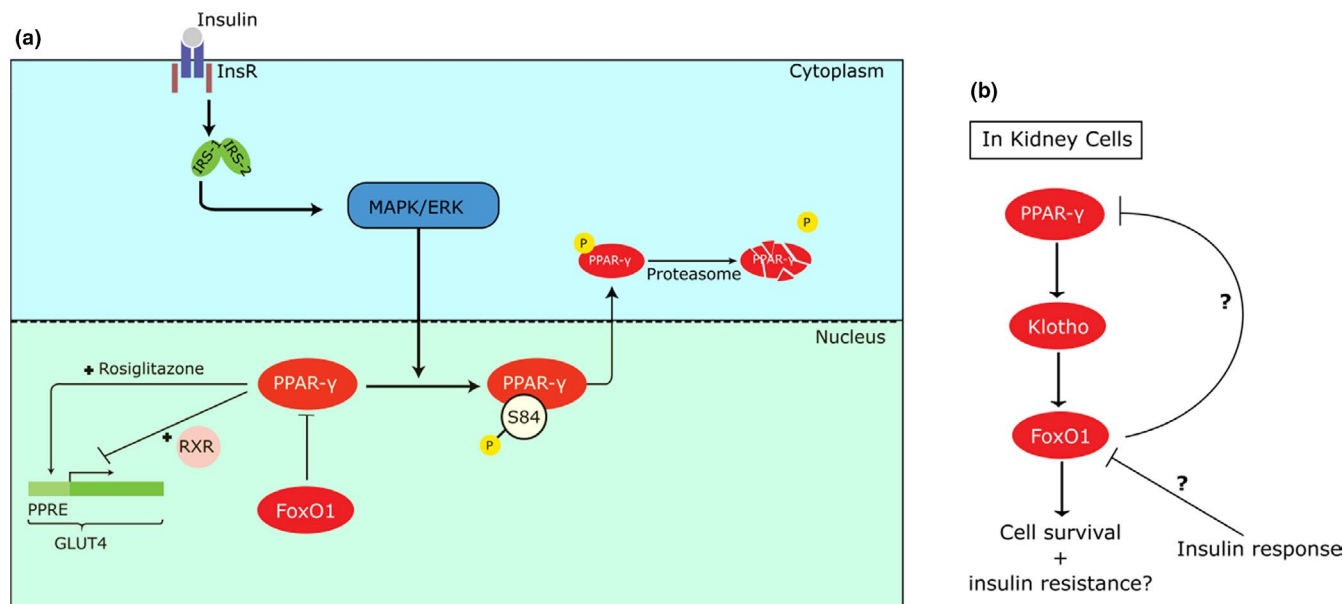


FIGURE 3 (a) Overview of PPARG signaling cascade, its relation to insulin response via MAPK/ERK pathway and interdependence to FoxO1. (b) Interrelation of FoxO1 and PPARG model in kidney cells through klotho protein. MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinases; RXR, retinoid X receptor; PPRE, PPAR response element; GLUT4, glucose transporter type 4

inhibiting ligands for specific binding on FoxO1 may open new therapeutic FoxO1 inhibitor ligands strategy to combat diabetes.

On the contrary, many PPARG agonists (and antagonists) have been developed for drugs as PPARG is heavily dependent on ligands. Many reviews have discussed and compiled PPARG ligands (Lamers et al., 2012; Takada & Makishima, 2020). Those include also various metabolites natural products (Grygiel-Górniak, 2014; Wang et al., 2014) and a study about structure to function correlation study (Peng et al., 2010). Trends between agonists and antagonists are also mixture and conflicting, for example in the case of anticancer drug antagonist GW9662 that manage to covalently binds to PPARG (Leesnitzer et al., 2002). GW9962 was reported to inhibit growth of breast tumor cells and reporting that rosiglitazone (PPARG agonist) cannot reverse the antagonist effect given by GW9962, and thus, the effects are independent from PPARG activation (Seargent et al., 2004). Meanwhile, recent paper using bladder cancer said otherwise (Lv et al., 2019) in which PPARG activation inhibits Akt signaling pathway and thus detrimental to cancer cells. On the contrary, various ligands from the same class (thiazolidinediones) were reported to not affect *Akt* expression but increase *IRS2* expression (Smith et al., 2001). Diverse effects can arise due to the multiple binding sites or structural arrangement upon ligand binding (Hughes et al., 2014; Sheu et al., 2005). Further discussion of PPARG ligands is out of the scope of this review. Excluding this topic, it is to be reminded that targeting

PPARG for the modulation of Akt and ERK signaling pathway directly or indirectly (using rapamycin) can be one strategy to combat metabolic disorder (Goetze et al., 2002; Kim & Chen, 2004).

2.6 | Small molecules modulated FoxO1 activities

Treating diabetes by targeting FoxO1 activity must be taken with great caution since FoxO1 is a central protein which regulates various metabolic processes, cell division, and longevity. Two big approaches are reported in various paper, which can also be biased on constructing the method to proof their initial hypothesis. A nice review that also includes various small molecules modulating FoxO1 activity is written by Calissi et al. (2021). Indeed, various ligands discussed in the aforesaid review act rather as anticancer drug. We focus our discussion on the ligands, which are relevant for diabetes treatment (Table 2).

Two common FoxO1 inhibitors that have been used in many studies are AS1842856 (Nagashima et al., 2010) and AS1708727 (Tanaka et al., 2010). Both small molecules proved to improve blood glucose level in db/db mice model by possibly inhibiting gluconeogenesis by PEPCK due to the inactivation of FoxO1. AS1842856 is also shown to selectively bind to FoxO1, but not the S256-phosphorylated one and shows considerably lower inhibition activity to FoxO3 and FoxO4. Antihypertriglyceridemia effects are also displayed by

TABLE 2 Structural formula of reported small molecules that exert antidiabetic activity through modulation of FoxO1 activity in this study

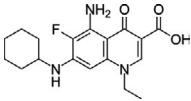
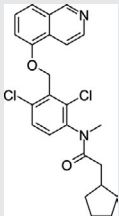
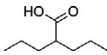
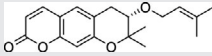
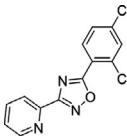
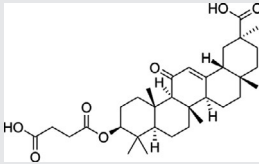
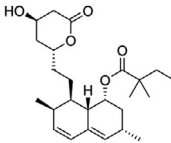
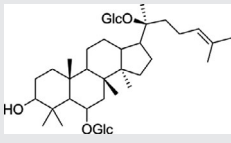
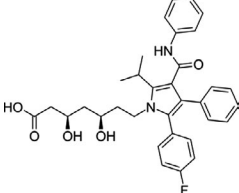
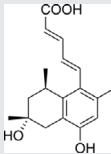
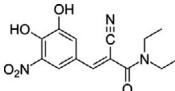
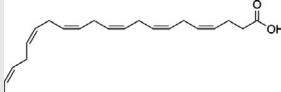
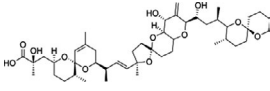
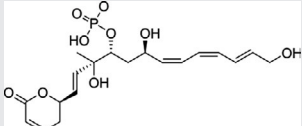
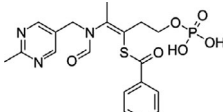
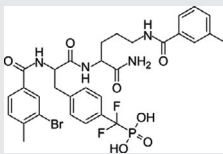
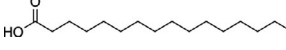
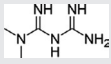
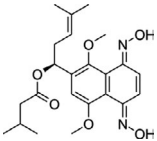
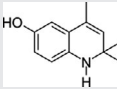
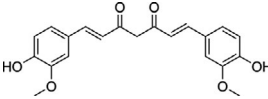
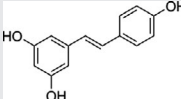
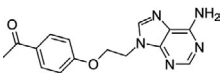
Chemical	Effect	Remarks	Concentration-dependent parameters	References
 <p>AS1842856</p>	Binds and inactivates FoxO1	Direct binding	IC ₅₀ by reporter gene assay to insulin response element = 0.03 μM. IC ₅₀ for FoxO3 and FoxO4 is above 1 μM	Nagashima et al. (2010)
 <p>AS1708727</p>	Inactivates FoxO1	Unknown	EC ₅₀ = 0.48 μM for FoxO1 one-hybrid assay and 0.1 μM for reporter gene assay to insulin response element DNA	Tanaka et al. (2010)
 <p>Valproic acid</p>	Inhibits FoxO1 activity	Unknown	Observed from animal treatment methods	Khan et al. (2016)
 <p>Decursinol derivative (compound 2b)</p>	FoxO1 inhibitor	Unknown	Compound 2b exhibits ~40% of FoxO1 activity at 100 μM	Joo et al. (2019)
 <p>JY-2</p>	FoxO protein inhibitor	Unknown	IC ₅₀ for FoxO1 transcriptional activity = 22 μM	Choi et al. (2021)
 <p>Carbenoxolone</p>	FoxO proteins binder, including FoxO1 but mainly FoxO3	Direct binding	Found to directly bind to FoxO3 (K _d = 53.4 nM) but can also quench fluorophore completely at 10 μM	Salcher et al. (2020)
 <p>Simvastatin</p>	Activates Akt thereby promotes FoxO1 phosphorylation	Unknown	Observed from animal treatment methods	Wu et al. (2008)
 <p>Rg1</p>	Activates Akt and promotes FoxO1 phosphorylation	Unknown	Observed from animal treatment methods	Liu et al. (2017)
 <p>Atorvastatin</p>	Activates Akt thereby promotes FoxO1 phosphorylation	Indirectly modulates FoxO1	Unknown, observed from incubating human umbilical vein endothelial cells with 1 μM atorvastatin	Park et al. (2018)

TABLE 2 (Continued)

Chemical	Effect	Remarks	Concentration-dependent parameters	References
 Hydroxylated tanzawaic acid D	Putative FoxO1 binder	Direct binding	Direct binding with $K_d = 37$ nM	Sun et al. (2017)
 Entacapone	Competitively inhibits FTO thereby increases FoxO1 mRNA methylation and inhibit transcription	Direct binding to FTO	$IC_{50} = 3.5$ μ M	Peng et al. (2019)
 Docosahexanoic acid	Reduce transcriptional level of FoxO1	Unknown	Observed from animal treatment methods	Chen et al. (2012)
 Okadaic acid	PP2A inhibitor, prevents FoxO1 dephosphorylation	Direct PP2A inhibitor	$K_i = 30$ – 40 pM	Takai et al. (1992)
 Fostriecin	PP2A inhibitor, more potent toward type 2A than type 1	Direct PP2A inhibitor	$IC_{50} = 3.2$ nM	Walsh et al. (1997)
 Benfotiamine	PP2A inhibitor	Indirectly inhibit PP2A activity	Unknown	Du et al. (2010)
 Compound 7	Selective PTP-MEG2 inhibitor than other protein tyrosine phosphatase types	Competitive inhibitor	$IC_{50} = 75$ nM; $K_i = 34$ nM	Zhang, Liu, et al. (2012)
 Palmitic acid	Induces insulin resistance, indirectly inhibits phosphorylation of FoxO1	Unknown, seems to be indirect modulation mode	Unknown, but cells were incubated with 750 μ M of palmitate for 24 h	Kumar & Tikoo, 2015)
 Metformin	Alleviates oxidative stress and increase cell survival through FoxO1 activation	Unknown	Unknown, various animal- and cells-based techniques were used rather to detect FoxO1 signaling pathway	Xu et al. (2019), Wang et al. (2018), Kalender et al. (2010), Zhou et al. (2001), Ren, Shao, et al. (2020)

(Continues)

TABLE 2 (Continued)

Chemical	Effect	Remarks	Concentration-dependent parameters	References
 DMAKO-05	Inhibits Akt phosphorylation and its signaling	Unknown	Unknown, but cells were treated with a concentration of 10 μM	Yang et al. (2016)
 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol	Antioxidant activity through FoxO1 activation	Unknown	Observed from animal treatment methods	Kryl'skii et al. (2021)
 Curcumin	Activates SIRT-FoxO1 but also Akt	Unknown	Unknown	Ren, Zhang, et al. (2020)
 Resveratrol	Activates SIRT1 and AMPK, indirectly promotes FoxO1 activity. Other reports include the activation of Akt pathway	Indirect modulation	Activates SIRT1 in vitro with a working concentration of 200 μM . As low as 1 μM can be used in a cell-based studies. Other mode concentration parameters are unknown	Borra et al. (2005), Chen et al. (2009), Costa et al. (2011)
 W2476	Dephosphorylate FoxO1, activating FoxO1 and subsequently repressing TXNIP	Unknown	Unknown, but cells were incubated with a concentration of 20 μM	Zhong et al. (2021)

these two ligands. Similar activity is displayed by valproic acid, a drug usually subjected to treat neuronal disorders (Khan et al., 2016), planar decursinol derivatives particularly named compound **2b** (Joo et al., 2019), and a non-planar aromatic heterocyclic compound named JY-2 (Choi et al., 2021). It is particularly intriguing that JY-2 is also the same compound that exhibits allosteric inhibition toward metabotropic glutamate receptor subtype 5 (mGluR5) (Raboisson et al., 2012). The IC_{50} to mGluR5 was found to be 10-fold lower than to FoxO1 although the difference in values might also be due to different kind of assays. An old ligand, carbenoxolone, which is initially reported as 11β -hydroxysteroid dehydrogenase inhibitor apparently also exerted antidiabetic activity (Andrews et al., 2003; Walker et al., 1995). It is recently reported that carbenoxolone can also bind to the several FoxO class protein DNA-binding domain including FoxO1 (Salcher et al., 2020) in which the main study is for FoxO3 inhibitors. While valproic acid might not interfere directly with FoxO1, the decursinol derivative, compound JY-2, and carbenoxolone intriguingly inhibits FoxO1 in concentration-dependent manner although both compounds have different electron distribution in the ring systems (chemical structures are provided in Table 2). Clearly, the binding

modes, intermolecular interactions between ligand and protein, and possibly the binding sites as well might not be similar and cannot be easily generalized for rational drug design. Another approach may also activate Akt which increase FoxO1 phosphorylation and its degradation, for example by various drugs that combat high lipid level such as simvastatin and even natural products such as Rg1, a saponin ginsenoside from *Panax ginseng* (Liu et al., 2017; Wu et al., 2008). In addition to activating Akt, atorvastatin enhances FoxO1 degradation by promoting the binding of SKP2 (Park et al., 2018).

Similar results in inhibiting hepatic glucose production by reducing FoxO1 activity were reported as well in a small compounds library screening study (Langlet et al., 2017). Moreover, various natural products derived from marine organism exert FoxO1 DNA-binding domain binder as well in which the largest affinity ($>10^7 \text{ M}^{-1}$) is displayed by hydroxylated tanzawaic acid D by fluorescence titration assay in the presence of DNA as competitor (Sun et al., 2017). Additionally, metabolite such as docosahexaenoic acid (DHA) also reduces the transcriptional level of FoxO1 (Chen et al., 2012).

Indirectly, FoxO1 can also be down-regulated by inhibiting FTO with entacapone by preventing adenine demethylation of FoxO1 mRNA (Peng et al., 2019, 2020).

Entacapone was found to act as competing substrates for FTO with IC_{50} of 3.5 μ M in which the hydroxyl groups bound to the phenyl seem important for inhibitory activity as also has been proven by crystal structure (PDB 6AK4). Insulin resistance and high-glucose-related drawbacks can also be alleviated by blocking PP2A, which hinders Akt activity (Galbo et al., 2011). Small molecules that are known to inhibit PP2A activities are okadaic acid, fostriecin, and benfotiamine (Cheng & Li, 2020; Du et al., 2010; Takai et al., 1992; Walsh et al., 1997). Similar FoxO1 inhibition activity is also shown by synthetic compound **7** that was found to competitively inhibit PTPN9 (protein tyrosine phosphatase non-receptor type 9/PTP-MEG2), which again in turn reduce the dephosphorylation of FoxO1 and promotes its destruction (Zhang, Liu, et al., 2012). This compound **7** is found to bind specifically to PTPN9 in particular in terms of inhibition constant and not the other protein tyrosine phosphatases (PTPs) protein. In opposite, palmitate rather induces insulin resistance not only by inhibiting the phosphorylation of Akt but also potentially through modification of mTOR activity (Kumar & Tikoo, 2015).

Opposite polar point of view is also proposed in which activating FoxO1 prevent diabetes-induced cell death. For example, metformin itself is a very common diabetes drug to improve insulin resistance conditions (Giannarelli et al., 2003). Metformin promotes the activation of FoxO1 via activation of AMPK, promoting deacetylation by SIRT1 or inhibition mTOR kinase (both mTORC1 and mTORC2) which in turn also inhibits Akt to promote longevity of cells and relieve oxidative stress (Kalender et al., 2010; Ren, Shao, et al., 2020; Wang et al., 2018; Xu et al., 2019, 2020; Zhou et al., 2001). Inhibition of Akt phosphorylation is also shown by shikonin derivative DMAKO-05 (Yang et al., 2016).

Similar to metformin result in alleviating oxidative stress through FoxO1 activation are 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (Kryl'skii et al., 2021) and curcumin (Ren, Zhang, et al., 2020). However, two contradicting results were reported in curcumin study in which curcumin managed to activate not only SIRT-FoxO1 pathways but also Akt in which phosphorylated FoxO1 by Akt is subsequently destroyed by proteasome. Specific discussion can also be directed to SIRT1-binder using natural product. It is also clear that SIRT1 promotes deacetylation of FoxO1, thereby activating its axis. In that case, resveratrol, a stilbenoid phenolic compound, activates SIRT1 (Borra et al., 2005) or AMPK (Yun et al., 2014) and subsequently FoxO1 which alleviates oxidative stress and promotes wound healing in various diabetes mice model such as with STZ treatment or db/db model (Chen et al., 2009; Huang et al., 2019; Kitada et al., 2011; Wu et al., 2012) and in turn decrease *PPARG*

expression (Costa et al., 2011). Apparently, resveratrol was also found to promote Akt pathway, which also alleviate insulin resistance (Brasnyó et al., 2011; Chen et al., 2015). Such unspecific effect might be the reason on the balance activity of FoxO1 in displaying its activity as cell survival gene and hyperglycemic-related critical gene. Comparable effect was also displayed in Xanthigen, a diet product derived from pomegranate seed and brown seaweed which contain puniceic acid and fucoxanthin. Administration of Xanthigen increases the activity of SIRT1 and AMPK and down-regulates *PPARG*. However, Xanthigen also stimulate insulin signaling and promote Akt-dependent phosphorylation of FoxO1 (Lai et al., 2012). Additionally, compound W2476 also manages to dephosphorylate FoxO1 at Ser319 and promotes FoxO1 association with (carbohydrate response element-binding protein (ChREBP). However, the activity to alleviate diabetes was rather due to subsequent repression of thioredoxin-interacting protein (TXNIP) (Zhong et al., 2021).

It is clear that there is a large gap in the treatment of diabetes by targeting FoxO1. One concept by promoting FoxO1 activity is directed toward wound healing and cell longevity point of view on the treatment of diabetes. In general, blocking FoxO1 activity shows more decisive conclusion to reduce high plasma glucose and alleviate insulin resistance. However, long-term study must be done on FoxO1 inhibitor, for example, its effect on the cell survival in hyperglycemic condition. Additionally, chronic study must also be done in which promoting cell survival by activating FoxO1 will not induce insulin resistance. For example, curcumin is famously known to disrupt Akt pathway for anticancer activity (Choi et al., 2008), which might also promote insulin resistance.

Furthermore, the chemical structures of various drugs that target or directly bind to FoxO1 protein (Table 2) seem very diverse ranging from small molecules, which freely rotate to cyclic aliphatic and/or aromatic. Many drugs that were found to modulate (activate / inhibit) FoxO1 were subjected rather from its effect for blood glucose-lowering activity or from its impact on FoxO1 transcriptional activity. As such, it might happen that the modulation of FoxO1 activity can be not due to direct interaction to FoxO1 but rather via binding to other macromolecule(s) that further modify FoxO1 activity. One example about the predicted binding modes was found rather only by molecular docking (Abuzenadah et al., 2018) to the previously established crystal of the free structures that only contain the DNA-binding domain of FoxO1 (Brent et al., 2008). The reported binding modes might not reflect the real binding sites to the whole FoxO1 protein. Moreover, results extracted by molecular docking without support from biophysical and structural studies are uncertain.

Biophysical assays to proof the binding of the ligands to FoxO1 protein seem scarce (Table 2). Out of all studied articles, compound AS1842856 was screened by mass spectrometry that indicates direct binding (Nagashima et al., 2010). While AS1842856 inhibitory activity is selective to FoxO1, carbenoxolone was also proven to directly bind to the DNA-binding domain, however, of various FoxO proteins by fluorescence titration assay (Salcher et al., 2020). One example about complementation of molecular docking with biophysical studies can be found in a study that screen natural products which selects one compound called tanzawaic acid D which also hints that the $\Delta G_{\text{binding}}$ obtained from molecular docking cannot be interpreted directly into the experimentally obtained K_d (Sun et al., 2017). Therefore, the need to establish high-resolution structure for ligand-FoxO1 interaction cannot be evaded which is still absent to this date for better rational drug design and more specific protein targeting.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

The studies conducted in this article do not involve human participants or animals.

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REVIEW

4

The role of FoxO1 and its modulation with small molecules in the development of diabetes mellitus: A review

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Abstract

Diabetes mellitus type 2 (T2D) is one of the metabolic disorders suffered by a global human being. Certain factors, such as lifestyle and heredity, can increase a person's tendency for T2D. Various genes and proteins play a role in the development of insulin resistance and ultimately diabetes in which one central protein that is discussed in this review is FoxO1. In this review, we regard FoxO1 activation as detrimental, promote high plasma glucose level, and induce insulin resistance. Indeed, many contrasting studies arise since FoxO1 is an important protein to alleviate oxidative stress and promote cell survival, for example, also by preventing hyperglycemic-induced cell death. Inter-relation to PPAR γ , another important protein in metabolism, is also discussed. Ultimately, we discussed contrasting approaches of targeting FoxO1 to combat diabetes mellitus by small molecules.

KEYWORDS

Akt pathway, diabetes, FoxO1, modulators, small molecules

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1 | INTRODUCTION

Diabetes mellitus, known as diabetes, is a metabolic disease characterized by high blood sugar. This disease is one of the ten diseases with the world's highest lethality rate. International Diabetes Federation counted that 463 million people have diabetes. This number will continue to increase, and it is estimated that in 2045, diabetes mellitus sufferers will increase of up to 51% and reach 700 million people. In general, diabetes consists of several types, namely type 1 diabetes mellitus (T1D), type 2 diabetes mellitus (T2D), and gestational diabetes mellitus (GDM). Globally, T2D is a type of diabetes that accounts for 85–95% of diabetes mellitus sufferers. Most countries show that diabetes increases along with rapid socio-cultural development such as urbanization, changing dietary patterns, to decreasing physical activity followed by unhealthy lifestyles (Goryakin et al., 2017). Without an

effective management program, the number of diabetes mellitus sufferers will continue to increase.

Our previous literature study (Nathanael et al., 2020) showed that several gene expressions changed when animal models, cell culture, or epidemiological study applied a diet with a high carbohydrate or MSG. However, such study is a comprehensive study in which no central genes which may become determining factor(s) in the formation of T2D are concluded. This study focuses on two central proteins which are very much related to the insulin signaling pathway (Akt/Protein kinase B(PKB) and mitogen-activated protein kinase (MAPK) pathway), forkhead box protein 1 (FoxO1) and peroxisome proliferator-activated receptor gamma (PPAR γ). Study compared *FoxO1* expression in average (non-obese) conditions and obesity with mild insulin resistance, in which *FoxO1* expression was found to increase in obese conditions and even higher when sustaining a combination of obesity with

acute insulin resistance relative to the non-obese group (Battiprolu et al., 2012). It was shown that *FoxO1* overexpression or gain-of-function studies increased blood sugar levels, which led to impaired insulin, glucose tolerance, and other various metabolic disorder such as obesity, glucose intolerance, hyperphagia, and impaired insulin secretion (Qu et al., 2006; Zhang et al., 2006). Other positive results also supported that *FoxO1* knockdown or knock-out can decrease blood sugar levels and increase insulin sensitivity and shows rescue of diabetes (Alharbi et al., 2018; Altomonte et al., 2003; Dong et al., 2008; Matsumoto et al., 2007; Nakae et al., 2002; Samuel et al., 2006). High expression of *PPARG* in pancreatic β -cell can be associated with a high-glucose profile (Hogh et al., 2014; Kanda et al., 2009). Additionally, mice lack *PPARG* result in hypotension, insulin resistance, and other metabolic-related disorder (Duan et al., 2007; Greenstein et al., 2017; Norris et al., 2003; Odegaard et al., 2007).

Those correlation experiments mentioned above can be the basis for the involvement of the *FoxO1* gene in body weight regulation and carbohydrate metabolism. Its inter-relation, several genes which regulate and are regulated by those two genes are discussed. Moreover, several small molecule ligands which have been reported to regulate the activity of two genes directly/indirectly will be discussed and mainly subjected to alleviate diabetes progression.

2 | REGULATION OF FoxO1: RELATION TO AKT SIGNALING AND REGULATION

2.1 | FoxO1 and Akt signaling pathway

When insulin is released by β -cell, it binds to a receptor known as insulin receptor (InsR). This receptor plays a vital role in a series of biochemical pathways such as carbohydrate and lipid metabolism. The abundance of this gene variant in humans is predominantly found in liver tissue, skeletal muscle, adipose tissue, and placenta (Benecke et al., 1992; Escribano et al., 2017). Binding of insulin to its receptor activates several insulin receptor substrate (IRS) proteins in which two proteins, IRS1 and IRS2, exert down-regulation activity toward various FoxO proteins, particularly focussing on FoxO1. The later was reported to give more dominant activity in various cells while IRS1 is mostly exerts its activity in skeletal muscle. Further signaling pathway activates the p110 α subunit of phosphoinositide-3-kinase (PI3K) and to Akt/Protein kinase B (Guo et al., 2006). As transcription factor, FoxO1 displays most of its activity in nucleus. This signaling promotes phosphorylation of FoxO1 by Akt, resulting in

an ejection of FoxO1 to cytoplasm and subsequently degraded by ubiquitin-mediated proteasome degradation (Huang & Tindall, 2011; Matsuzaki et al., 2003). Indeed, inactivation of Akt by a protein phosphatase 2A (PP2A) prevents FoxO1 deactivation and results in insulin resistance (Beg et al., 2016). Activated FoxO1, for example, in liver, promotes gluconeogenesis through activation of several genes such as *glucose-6-phosphatase (G6Pase)* and *phosphoenolpyruvate carboxykinase (PEPCK)*, which also confers an insulin resistance phenomenon by the inability of insulin to suppress glucose production (Nakae et al., 2001a).

Insulin receptor correlation with the onset diabetes was not consistent. One study proved that overexpression of *InsR* in diabetic mice significantly reduced body weight, alleviated hyperphagia, and improved blood sugar level compared to diabetes control although other growth parameters were compromised (Sasaki et al., 2015). The particular study also reported no improvement on insulin sensitivity. In contrast, other study explained that overexpressed *InsR* increased insulin sensitivity so that glucose transport and glycogen synthesis run effectively and reduce blood sugar (Besic et al., 2015; Kosaki et al., 1995). Moreover, prolonged insulin stimulation in *IRS1*^{-/-} mouse embryo fibroblasts (MEF) apparently failed to degrade FoxO1 in which IRS2 level itself was reduced (Guo et al., 2006). Additionally, FoxO1 activation can in turn give feedback by deactivating IRS1 by serine phosphorylation which promote the vicious cycle of metabolic disorder. Inactivation of FoxO1 reduced IRS2 level, but not IRS1 which plays more dominant role in metabolism (Battiprolu et al., 2012; Zhang, Li, et al., 2012). The negative impact of FoxO1 related to insulin sensitivity on another central protein such as *PPARG* (Armoni et al., 2006; Dowell et al., 2003) and thus toward more downstream protein such as glucose transporter type 4 (GLUT4) activity (Armoni et al., 2007; Gonzalez et al., 2011) proofs that FoxO1 is a central protein that can modulate whole Akt signaling pathway. General overview on the action of insulin via Akt signaling to modulate FoxO1 activity and its downstream effect can be seen in Figure 1.

Modulating FoxO1 requires a delicate approach in which FoxO1 activation itself is one mechanism to alleviate oxidative stress and promote wound healing by activating various antioxidant-related proteins such as manganese superoxide dismutase (MnSOD) (Kitamura et al., 2005; Mohseni et al., 2021; Yun et al., 2014). One mechanism to protect cells from oxidative stress includes induced apoptosis (Ning et al., 2015; Shen et al., 2012; Weng et al., 2016). Additionally, active FoxO1 itself is responsible for the expression of insulin receptor, thus creating self-feedback loop (Puig & Tjian, 2005).

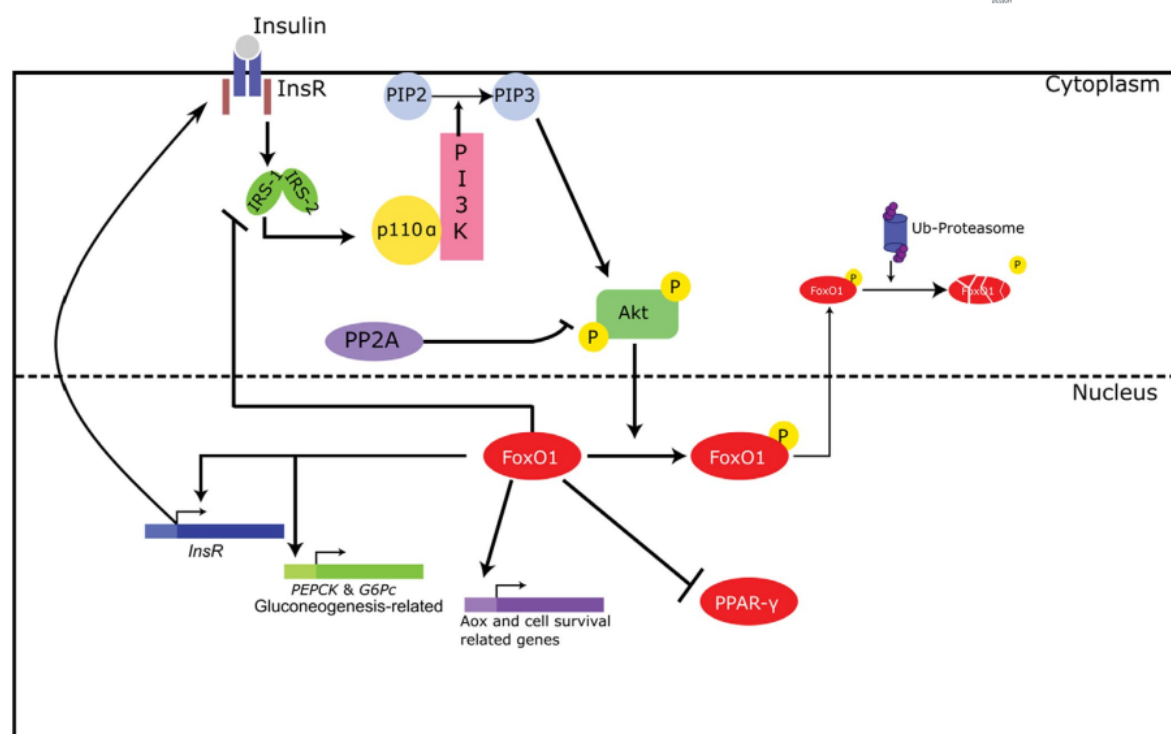


FIGURE 1 Overview of FoxO1 signaling pathway related to insulin response to Akt signaling cascade. InsR, insulin receptor; IRS, insulin receptor substrate; PI3K, phosphoinositide-3-kinase; PIP, phosphatidylinositol phosphate; PP2A, protein phosphatase 2A; FoxO1, forkhead box protein O1; Ub, ubiquitin; *PEPCK*, phosphoenolpyruvate carboxykinase-encoded gene; *G6Pc*, glucose-6-phosphatase-encoded genes; PPAR- γ , peroxisome proliferator-activated receptor gamma

2.2 | Regulation of FoxO1 activity through post-translational modification

Although the basic concepts regarding FoxO1 regulation are that insulin activates cascades which ultimately deregulate FoxO1 activation through phosphorylation by Akt (Protein Kinase B), distinct phosphorylation sites by other protein kinase, various protein modification such as acetylation also plays a role on FoxO1 activity. Phosphorylation by Akt at S256, followed by T24 and S319 which seems Akt-independent, ultimately promotes degradation of FoxO1 by ubiquitination (Accili & Arden, 2004; Biggs et al., 1999; Guo, 2013; Matsuzaki et al., 2003; Nakae et al., 2001a, 2001b; Rena et al., 1999). However, its degradation is apparently regulated by 14-3-3 protein, in which 14-3-3 protein binding to the FoxO1 is promoted by phosphorylation, exporting FoxO1 out from the nucleus while subsequently protects FoxO1 from ubiquitin-mediated degradation (Saline et al., 2019; Tzivion et al., 2011). Other phosphorylation site is recently identified in S276 by protein kinase A (PKA), which is induced by glucagon (Wu et al., 2018). In contrast, phosphorylation of FoxO1 by MST-1 hinders binding of 14-3-3 protein

toward phosphorylated FoxO1 at S212, thereby promoting nuclear localization and in turns can be dephosphorylated and activated in nucleus by PP2A (Lehtinen et al., 2006; Yan et al., 2008; Yuan et al., 2009) which promotes FoxO1-mediated cell death and modulates longevity. Additionally, FoxO1 can be activated through phosphorylation by AMP-activated protein kinase (AMPK) although with a preference to FoxO3 (Greer et al., 2007, 2009).

FoxO1 can be modified by acetylation through CREB-binding protein (CBP)/p300 which can reduce its activity as transcription factor and promotes degradation through phosphorylation (Matsuzaki et al., 2005). On the contrary, FoxO1 can also be deacetylated by sirtuin (SIRT) proteins, both SIRT1 and SIRT2. It is generally known that deacetylation of lysine increase the amount of positive charge of the protein, thereby creating a condition of nuclear trapping and promoting the binding to the DNA although the degree of the effect is dependent on the acetylation of the protein DNA-binding interface (Matsuzaki et al., 2005). As such, the consensus is deacetylation of FoxO1 by sirtuin protein positively regulates FoxO1 activity as transcription factor, thereby further promoting gluconeogenesis in which in long terms may promotes diabetic condition,

for example, by repressing PPARG (Wang & Tong, 2009). On the contrary, FoxO1 is also related to the expression of genes, which seems to be important for the protection from cell death due to oxidative stress. Increased activity of FoxO1 by SIRT1 deacetylation apparently reduces the effect of diabetic nephropathy by autophagy (Xu et al., 2019, 2020).

Acetylation dynamic effects are rather conflicting and seem to be quite dependent on genes and cells, level of acetylation and acetylated protein and closely related to alleviating oxidative stress and promoting cell longevity (Brunet et al., 2004; Motta et al., 2004). One example in muscle cells was that *SIRT1* overexpression reduced FoxO1 activity and results in the protection and muscle atrophy (Lee & Goldberg, 2013). Acetylation of FoxO1 also creates a site competition for subsequent ubiquitination (Kitamura et al., 2005). It is worth to be mentioned that sirtuin itself asserts its effect to lots of protein, which are critical to metabolism and survival. Dynamics of FoxO1 acetylation is well discussed by Daitoku et al. (2011).

FoxO1 expression can be regulated by methylation both in protein and mRNA level. Methylation of FoxO1 in position K273 by G9a (known as euchromatic histone-lysine-N-methyltransferase) promotes its recruitment to S-phase kinase-associated protein-2 (SKP2), an E3 ubiquitin ligase and its degradation (Chae et al., 2019). In contrast, methylation at arginine position 248 and 250 by protein arginine N-methyltransferase 1 (PRMT1) turns out to block Akt binding to FoxO1, hinders its degradation, and subsequently promotes its activation. Methylation by PRMT1 can be promoted by oxidative stress and resulted in the FoxO1-mediated cell death (Yamagata et al., 2008). Methylation of *FoxO1* mRNA by m(Altomonte et al., 2003) A methyltransferase possibly by METTL3 (methyltransferase 3) and its demethylation by fat mass and obesity-associated protein (FTO) affects the dynamic of its translation, in which the later promotes FoxO1 production (Dominissini et al., 2012; Peng et al., 2019). Additionally, FoxO1 can be glycosylated by N-acetylglucosamine via O-linked β -N-acetylglucosamine transferase (OGT), which apparently increased its activity for gluconeogenesis (Kuo et al., 2008a, 2008b). O-glycosylation of FoxO1 by glucosamine can also be induced by high-glucose intake and apparently leads to an increase of hepatic *G6Pase* expression, thereby releasing glucose into blood circulation and creating a vicious cycle of glucotoxicity. The effect of glycosylation can also be found in mutant FoxO1 protein in which the phosphorylation sites are mutated by alanine, which hints to an independent regulation from phosphorylation. Overview of post-translational modifications of FoxO1 and its impact on FoxO1 activity is summarized in Figure 2 and Table 1.

2.3 | PPARG (Peroxisome proliferator-activated receptor gamma)

Peroxisome proliferator-activated receptor (PPAR) is a group of transcription factors and attached to PPAR response element (PPRE). PPAR itself comprises of PPARG, PPARG, and PPARG/B. PPARG and PPARG/B play a role in adipogenesis, while PPARG- α is involved in lipolysis. PPARG agonists, such as thiazolidinedione (TZD) or chiglitazar, are believed to improve glucose tolerance and obesity (Li et al., 2006). PPARG has three isoforms and mainly distributed in different tissues. Isoforms 2 and 3 are mainly expressed in adipose, and isoform two is usually found in the obese subject. Its activity is heavily dependent on various ligands, growth factors, protein complexes, and modifications on the protein.

The importance of PPARG can be extracted from several animal and transgenic studies. A high-glucose profile also showed overexpression of *PPARG* pancreatic β -cell-specific (Hogh et al., 2014). Meanwhile, mice lack PPARG result in hypotension, insulin resistance, and higher plasma-free fatty acid (Duan et al., 2007; Norris et al., 2003; Odegaard et al., 2007). Mice with PPARG deficient in adipose-specific bone marrow and liver-specific suffer from hepatomegaly and steatosis (Greenstein et al., 2017; He et al., 2003; Kanda et al., 2009). Furthermore, agonists applied to mice with obesity and insulin resistance have better results in improving conditions.

It is of note that PPARG signaling is also interrelated to adipogenesis and development of cancer. This is due to the signaling via MAPK-ERK kinase (MEK) pathway, which is related to cell division. In this case, phosphorylation of PPARG by MAPK/ERK (and janus kinases) inhibits its activity, which induces its export toward cytoplasm and its degradation by proteasome (Burgermeister & Seger, 2007; Kaplan et al., 2010) (Figure 3a). It is phosphorylated at position S84 in which its mutation to alanine increases the transcriptional activity of this protein (Adams et al., 1997). In mice, mutation S112A that inhibits PPARG phosphorylation indeed promotes weight gain but also manages to alleviate insulin resistance (Rangwala et al., 2003). PPARG exerts its activity by activating glucose transporter expression, mainly *GLUT4* which further stimulate glucose uptake (Liao et al., 2007; Michael et al., 2001; Wu et al., 1998). It is to be noted that PPARG activities depend on the bound ligands. Some contrasting studies were reported in which activation of PPARG inhibits *GLUT4* transcription in skeletal muscle cells (Miura et al., 2003) while PPARG knockout mice displayed better insulin sensitivity (Kubota et al., 1999; Miles et al., 2000). It turns out that retinoid X receptor (RXR) acted as ligands to

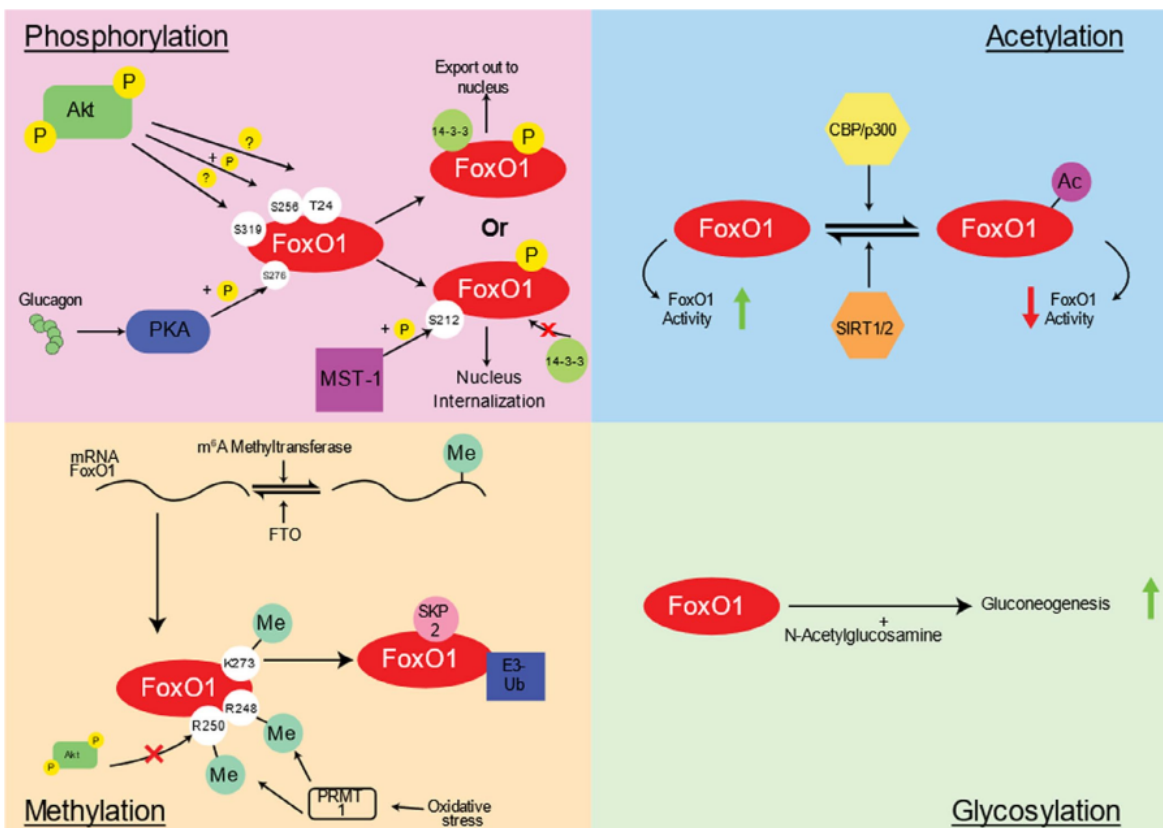


FIGURE 2 Various post-translational modification on FoxO1 protein / mRNA regulates its activity and response. PKA, protein kinase A; CBP, CREB-binding protein; SIRT, sirtuin; FTO, fat mass and obesity-associated protein; PRMT1, protein arginine N-methyltransferase 1

unphosphorylated S112 PPARG which suppress GLUT4 transcriptional activity while combination of PPARG agonist such as rosiglitazone displays the opposite phenotype (Armoni et al., 2003).

2.4 | PPARG entanglement with FoxO1 signaling

FoxO1 and PPARG itself are interrelated and also center proteins which bridges and can modulate or be modulated Akt and MAPK signaling that affects the activity of GLUT4 which is downstream of the insulin signaling pathway (Liao et al., 2007; Wu et al., 1998). Early reports about FoxO1 relationship with PPARG are quite contrasting (Daitoku et al., 2003; Dowell et al., 2003). However, further studies showed that FoxO1 reported to repress PPARG2 isoform production through binding to IRS promoter (Armoni et al., 2006) or direct inhibition (Fan et al., 2009). This would indicate that both proteins modulate cell sensitivity toward insulin in the order of PPARG

ligand-dependent activity. PPARG also displays crosstalk toward insulin signaling directly, in which administration of thiazolidinediones as PPARG agonist managed to increase *IRS2* gene expression (Smith et al., 2001). PPARG itself can possibly indirectly modulate FoxO1 by its interrelation to SIRT1. Apparently, PPARG is negatively modulated by SIRT1 in which SIRT1 can act as corepressor of PPARG in the promoter (Picard et al., 2004) or through the dynamic of acetylation by SIRT1 (Han et al., 2010). Interestingly, SIRT1 itself can also be back regulated by PPARG by reducing SIRT1 transcription level, thereby creating self-loop regulation (Han et al., 2010).

It is to be noted that the activities of both proteins are quite dependent on the type of the cells. One well studied that link FoxO1 and PPARG is in the kidney through Klotho protein (Figure 3b), a protein related to alleviating oxidative stress and nephropathy mostly in streptozotocin-induced or db/db diabetic rat/mice models (Asai et al., 2012; Cheng et al., 2010; Kim et al., 2016; Takenaka et al., 2019). Klotho protein managed to protect kidney from further destruction through

TABLE 1 Summary of post-translational modification of FoxO1 and its impact on FoxO1 activity

Post-translational modification	Modifying protein	Residues	Remarks
Phosphorylation	Akt	S256	Further phosphorylation which seems Akt-independent is at T24 and S319, promotes ejection of FoxO1 from nucleus, and subsequently degrades by proteasome in conjunction with ubiquitinylation
	PKA	S276	Induced by glucagon, promotes FoxO1 degradation
	MST-1	S212	Promotes nuclear localization and prevents FoxO1 ubiquitin-mediated degradation
	AMPK	–	Activate FoxO1
Dephosphorylation	PP2A	–	Dephosphorylate phosphate groups that have been added by various phosphate-modifying proteins; activate FoxO1
Ubiquitinylation	Ubiquitin	–	In conjunction usually with Akt-mediated phosphorylation to promote degradation of FoxO1 by proteasome
Acetylation	CBP/p300	–	Reduces FoxO1 activity
Deacetylation	SIRT1, SIRT2	Unknown lysine residue	Increase the activity of FoxO1, f.e. promotes gluconeogenesis but also protects cells from oxidative stress-related cell death
Methylation	G9a	K273	Promotes FoxO1 ubiquitin-mediated degradation
	PRMT1	R248 R250	Blocks Akt-mediated phosphorylation, promotes FoxO1 activity
	METTL3	adenine residue in FoxO1 mRNA	Decrease FoxO1 mRNA translation
Demethylation	FTO	adenine residue in FoxO1 mRNA	Increase FoxO1 translation
Glycosylation	OGT	unknown but different than Akt modification site	Modified with glucosamine, increase FoxO1 activity to promote gluconeogenesis

^aProtein abbreviations are given in the text.

its inhibition of MAPK and RelA, a protein related to the activation of inflammatory protein nuclear factor kappa-light-chain enhancer of activated B cells (NF- κ B) (Zhao et al., 2011). It is known although FoxO1 is positively related to the onset of diabetes, FoxO1 activity also protects cell from oxidative stress via activating various antioxidant enzymes or induced apoptosis and autophagy as described above. This indicates that PPARG indirectly activates FoxO1 activity by preventing its phosphorylation in kidney through klotho protein (Kuro-o, 2008; Yamamoto et al., 2005; Zhang et al., 2008). It is also true then overexpression of *Klotho* in transgenic mice displays moderate resistant to insulin (Utsugi et al., 2000).

To summarize, FoxO1 and PPARG as a regulatory protein play a critical factor in modulating expression and activation of protein both downstream and upstream of the signaling pathway. While GLUT4 localization on the membrane, for example in muscle tissue,

can also be a biomarker to detect abnormality in the metabolism, aberrant *FoxO1* and *PPARG* expression, especially high level of FoxO1 protein, can be a good indicator for the onset of diabetes and other metabolic disorder.

2.5 | Chemical biology: Modulating FoxO1 activity by small molecules

One study made an opinion that targeting the expression or transient inactivation of FoxO1 by selective ligand may indeed be a promising technique for diabetes therapy and/or detection (Zhang, Li, et al., 2012). FoxO1 inhibitor such as AS1842856 remains a tool for molecular and chemical biologist for *in vitro* and *in vivo* study (Nagashima et al., 2010; Tanaka et al., 2010). It proves to be challenging to directly use FoxO1 inhibitor as drug since inhibition of FoxO1 can also induced cell death. Designing or derivating

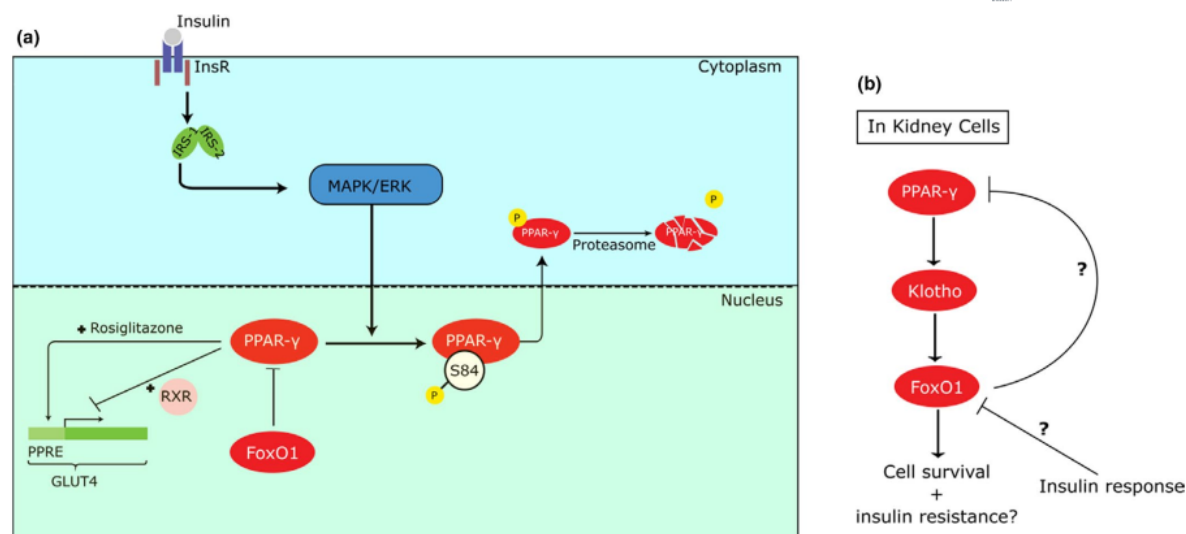


FIGURE 3 (a) Overview of PPAR signaling cascade, its relation to insulin response via MAPK/ERK pathway and interdependence to FoxO1. (b) Interrelation of FoxO1 and PPAR model in kidney cells through klotho protein. MAPK/ERK, mitogen-activated protein kinase/extracellular signal-regulated kinases; RXR, retinoid X receptor; PPRE, PPAR response element; GLUT4, glucose transporter type 4

inhibiting ligands for specific binding on FoxO1 may open new therapeutic FoxO1 inhibitor ligands strategy to combat diabetes.

On the contrary, many PPAR agonists (and antagonists) have been developed for drugs as PPAR is heavily dependent on ligands. Many reviews have discussed and compiled PPAR ligands (Lamers et al., 2012; Takada & Makishima, 2020). Those include also various metabolites natural products (Grygiel-Górniak, 2014; Wang et al., 2014) and a study about structure to function correlation study (Peng et al., 2010). Trends between agonists and antagonists are also mixture and conflicting, for example in the case of anticancer drug antagonist GW9662 that manage to covalently binds to PPAR (Leesnitzer et al., 2002). GW9962 was reported to inhibit growth of breast tumor cells and reporting that rosiglitazone (PPAR agonist) cannot reverse the antagonist effect given by GW9962, and thus, the effects are independent from PPAR activation (Seargent et al., 2004). Meanwhile, recent paper using bladder cancer said otherwise (Lv et al., 2019) in which PPAR activation inhibits Akt signaling pathway and thus detrimental to cancer cells. On the contrary, various ligands from the same class (thiazolidinediones) were reported to not affect Akt expression but increase *IRS2* expression (Smith et al., 2001). Diverse effects can arise due to the multiple binding sites or structural arrangement upon ligand binding (Hughes et al., 2014; Sheu et al., 2005). Further discussion of PPAR ligands is out of the scope of this review. Excluding this topic, it is to be reminded that targeting

PPAR for the modulation of Akt and ERK signaling pathway directly or indirectly (using rapamycin) can be one strategy to combat metabolic disorder (Goetze et al., 2002; Kim & Chen, 2004).

2.6 | Small molecules modulated FoxO1 activities

Treating diabetes by targeting FoxO1 activity must be taken with great caution since FoxO1 is a central protein which regulates various metabolic processes, cell division, and longevity. Two big approaches are reported in various paper, which can also be biased on constructing the method to proof their initial hypothesis. A nice review that also includes various small molecules modulating FoxO1 activity is written by Calissi et al. (2021). Indeed, various ligands discussed in the aforesaid review act rather as anticancer drug. We focus our discussion on the ligands, which are relevant for diabetes treatment (Table 2).

Two common FoxO1 inhibitors that have been used in many studies are AS1842856 (Nagashima et al., 2010) and AS1708727 (Tanaka et al., 2010). Both small molecules proved to improve blood glucose level in db/db mice model by possibly inhibiting gluconeogenesis by PEPCK due to the inactivation of FoxO1. AS1842856 is also shown to selectively bind to FoxO1, but not the S256-phosphorylated one and shows considerably lower inhibition activity to FoxO3 and FoxO4. Antihypertriglyceridemia effects are also displayed by

TABLE 2 Structural formula of reported small molecules that exert antidiabetic activity through modulation of FoxO1 activity in this study

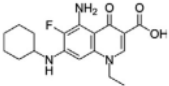
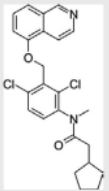

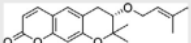
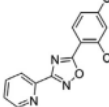
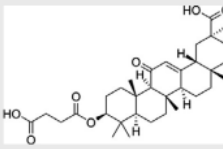
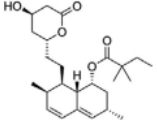
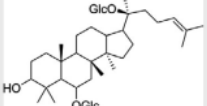
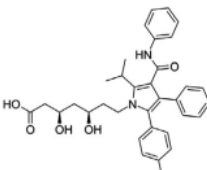
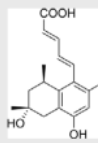
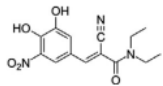

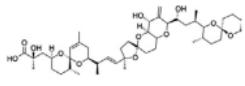
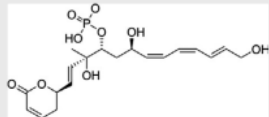
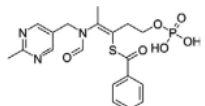
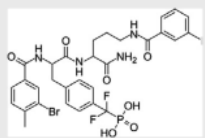
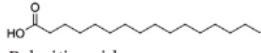
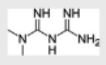
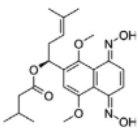
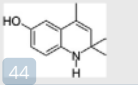
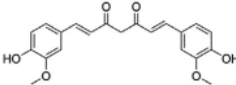
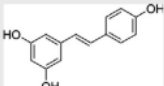
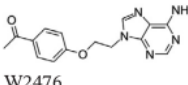
Chemical	Effect	Remarks	Concentration-dependent parameters	References
 AS1842856	Binds and inactivates FoxO1	Direct binding	IC ₅₀ by reporter gene assay to insulin response element = 0.03 μM. IC ₅₀ for FoxO3 and FoxO4 is above 1 μM	Nagashima et al. (2010)
 AS1708727	Inactivates FoxO1	Unknown	EC ₅₀ = 0.48 μM for FoxO1 one-hybrid assay and 0.1 μM for reporter gene assay to insulin response element DNA	Tanaka et al. (2010)
 Valproic acid	Inhibits FoxO1 activity	Unknown	Observed from animal treatment methods	Khan et al. (2016)
 Decursinol derivative (compound 2b)	FoxO1 inhibitor	Unknown	Compound 2b exhibits ~40% of FoxO1 activity at 100 μM	Joo et al. (2019)
 JY-2	FoxO protein inhibitor	Unknown	IC ₅₀ for FoxO1 transcriptional activity = 22 μM	Choi et al. (2021)
 Carbenoxolone	FoxO proteins binder, including FoxO1 but mainly FoxO3	Direct binding	Found to directly bind to FoxO3 (K _d = 53.4 nM) but can also quench fluorophore completely at 10 μM	Salcher et al. (2020)
 Simvastatin	Activates Akt thereby promotes FoxO1 phosphorylation	Unknown	Observed from animal treatment methods	Wu et al. (2008)
 Rg1	Activates Akt and promotes FoxO1 phosphorylation	Unknown	Observed from animal treatment methods	Liu et al. (2017)
 Atorvastatin	Activates Akt thereby promotes FoxO1 phosphorylation	Indirectly modulates FoxO1	Unknown, observed from incubating human umbilical vein endothelial cells with 1 μM atorvastatin	Park et al. (2018)

TABLE 2 (Continued)

Chemical	Effect	Remarks	Concentration-dependent parameters	References
 Hydroxylated tanzawaic acid D	Putative FoxO1 binder	Direct binding	Direct binding with $K_d = 37$ nM	Sun et al. (2017)
 Entacapone	Competitively inhibits FTO thereby increases FoxO1 mRNA methylation and inhibit transcription	Direct binding to FTO	$IC_{50} = 3.5$ μ M	Peng et al. (2019)
 Docosahexanoic acid	Reduce transcriptional level of FoxO1	Unknown	Observed from animal treatment methods	Chen et al. (2012)
 Okadaic acid	PP2A inhibitor, prevents FoxO1 dephosphorylation	Direct PP2A inhibitor	$K_i = 30$ – 40 μ M	Takai et al. (1992)
 Fostriecin	PP2A inhibitor, more potent toward type 2A than type 1	Direct PP2A inhibitor	$IC_{50} = 3.2$ nM	Walsh et al. (1997)
 Benfotiamine	PP2A inhibitor	Indirectly inhibit PP2A activity	Unknown	Du et al. (2010)
 Compound 7	Selective PTP-MEG2 inhibitor than other protein tyrosine phosphatase types	Competitive inhibitor	$IC_{50} = 75$ nM; $K_i = 34$ nM	Zhang, Liu, et al. (2012)
 Palmitic acid	Induces insulin resistance, indirectly inhibits phosphorylation of FoxO1	Unknown, seems to be indirect modulation mode	Unknown, but cells were incubated with 750 μ M of palmitate for 24 h	Kumar & Tikoo, 2015)
 Metformin	Alleviates oxidative stress and increase cell survival through FoxO1 activation	Unknown	Unknown, various animal- and cells-based techniques were used rather to detect FoxO1 signaling pathway	Xu et al. (2019), Wang et al. (2018), Kalender et al. (2010), Zhou et al. (2001), Ren, Shao, et al. (2020)

(Continues)

TABLE 2 (Continued)

Chemical	Effect	Remarks	Concentration-dependent parameters	References
 DMAKO-05	Inhibits Akt phosphorylation and its signaling	Unknown	Unknown, but cells were treated with a concentration of 10 μM	Yang et al. (2016)
 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol	Antioxidant activity through FoxO1 activation	Unknown	Observed from animal treatment methods	Kryl'skii et al. (2021)
 Curcumin	Activates SIRT-FoxO1 but also Akt	Unknown	Unknown	Ren, Zhang, et al. (2020)
 Resveratrol	Activates SIRT1 and AMPK, indirectly promotes FoxO1 activity. Other reports include the activation of Akt pathway	Indirect modulation	Activates SIRT1 in vitro with a working concentration of 200 μM . As low as 1 μM can be used in a cell-based studies. Other mode concentration parameters are unknown	Borra et al. (2005), Chen et al. (2009), Costa et al. (2011)
 W2476	Dephosphorylate FoxO1, activating FoxO1 and subsequently repressing TXNIP	Unknown	Unknown, but cells were incubated with a concentration of 20 μM	Zhong et al. (2021)

these two ligands. Similar activity is displayed by valproic acid, a drug usually subjected to treat neuronal disorders (Khan et al., 2016), planar decursinol derivatives particularly named compound **2b** (Joo et al., 2019), and a non-planar aromatic heterocyclic compound named JY-2 (Choi et al., 2021). It is particularly intriguing that JY-2 is also the same compound that exhibits allosteric inhibition toward metabotropic glutamate receptor subtype 5 (mGluR5) (Raboisson et al., 2012). The IC_{50} to mGluR5 was found to be 10-fold lower than to FoxO1 although the difference in values might also be due to different kind of assays. An old ligand, carbenoxolone, which is initially reported as 11β -hydroxysteroid dehydrogenase inhibitor apparently also exerted antidiabetic activity (Andrews et al., 2003; Walker et al., 1995). It is recently reported that carbenoxolone can also bind to the several FoxO class protein DNA-binding domain including FoxO1 (Salcher et al., 2020) in which the main study is for FoxO3 inhibitors. While valproic acid might not interfere directly with FoxO1, the decursinol derivative, compound JY-2, and carbenoxolone intriguingly inhibits FoxO1 in concentration-dependent manner although both compounds have different electron distribution in the ring systems (chemical structures are provided in Table 2). Clearly, the binding

modes, intermolecular interactions between ligand and protein, and possibly the binding sites as well might not be similar and cannot be easily generalized for rational drug design. Another approach may also activate Akt which increase FoxO1 phosphorylation and its degradation, for example by various drugs that combat high lipid level such as simvastatin and even natural products such as Rg1, a saponin ginsenoside from *Panax ginseng* (Liu et al., 2017; Wu et al., 2008). In addition to activating Akt, atorvastatin enhances FoxO1 degradation by promoting the binding of SKP2 (Park et al., 2018).

Similar results in inhibiting hepatic glucose production by reducing FoxO1 activity were reported as well in a small compounds library screening study (Langlet et al., 2017). Moreover, various natural products derived from marine organism exert FoxO1 DNA-binding domain binder as well in which the largest affinity ($>10^7 \text{ M}^{-1}$) is displayed by hydroxylated tanzawaic acid D by fluorescence titration assay in the presence of DNA as competitor (Sun et al., 2017). Additionally, metabolite such as docosahexaenoic acid (DHA) also reduces the transcriptional level of FoxO1 (Chen et al., 2012).

Indirectly, FoxO1 can also be down-regulated by inhibiting FTO with entacapone by preventing adenine demethylation of FoxO1 mRNA (Peng et al., 2019, 2020).

Entacapone was found to act as competing substrates for FTO with IC_{50} of 3.5 μ M in which the hydroxyl groups bound to the phenyl seem important for inhibitory activity as also has been proven by crystal structure (PDB 6AK4). Insulin resistance and high-glucose-related drawbacks can also be alleviated by blocking PP2A, which hinders Akt activity (Galbo et al., 2011). Small molecules that are known to inhibit PP2A activities are okadaic acid, fostriecin, and benfotiamine (Cheng & Li, 2020; Du et al., 2010; Takai et al., 1992; Walsh et al., 1997). Similar FoxO1 inhibition activity is also shown by synthetic compound **7** that was found to competitively inhibit PTPN9 (protein tyrosine phosphatase non-receptor type 9/PTP-MEG2), which again in turn reduce the dephosphorylation of FoxO1 and promotes its destruction (Zhang, Liu, et al., 2012). This compound **7** is found to bind specifically to PTPN9 in particular in terms of inhibition constant and not the other protein tyrosine phosphatases (PTPs) protein. In opposite, palmitate rather induces insulin resistance not only by inhibiting the phosphorylation of Akt but also potentially through modification of mTOR activity (Kumar & Tikoo, 2015).

Opposite polar point of view is also proposed in which activating FoxO1 prevent diabetes-induced cell death. For example, metformin itself is a very common diabetes drug to improve insulin resistance conditions (Giannarelli et al., 2003). Metformin promotes the activation of FoxO1 via activation of AMPK, promoting deacetylation by SIRT1 or inhibition mTOR kinase (both mTORC1 and mTORC2) which in turn also inhibits Akt to promote longevity of cells and relieve oxidative stress (Kalender et al., 2010; Ren, Shao, et al., 2020; Wang et al., 2018; Xu et al., 2019, 2020; Zhou et al., 2001). Inhibition of Akt phosphorylation is also shown by shikonin derivative DMAKO-05 (Yang et al., 2016).

Similar to metformin result in alleviating oxidative stress through FoxO1 activation are 2,2,4-trimethyl-1,2-dihydroquinolin-6-ol (Kryl'skii et al., 2021) and curcumin (Ren, Zhang, et al., 2020). However, two contradicting results were reported in curcumin study in which curcumin managed to activate not only SIRT-FoxO1 pathways but also Akt in which phosphorylated FoxO1 by Akt is subsequently destroyed by proteasome. Specific discussion can also be directed to SIRT1-binder using natural product. It is also clear that SIRT1 promotes deacetylation of FoxO1, thereby activating its axis. In that case, resveratrol, a stilbenoid phenolic compound, activates SIRT1 (Borra et al., 2005) or AMPK (Yun et al., 2014) and subsequently FoxO1 which alleviates oxidative stress and promotes wound healing in various diabetes mice model such as with STZ treatment or db/db model (Chen et al., 2009; Huang et al., 2019; Kitada et al., 2011; Wu et al., 2012) and in turn decrease *PPARG*

expression (Costa et al., 2011). Apparently, resveratrol was also found to promote Akt pathway, which also alleviate insulin resistance (Brasnyó et al., 2011; Chen et al., 2015). Such unspecific effect might be the reason on the balance activity of FoxO1 in displaying its activity as cell survival gene and hyperglycemic-related critical gene. Comparable effect was also displayed in Xanthigen, a diet product derived from pomegranate seed and brown seaweed which contain puniceic acid and fucoxanthin. Administration of Xanthigen increases the activity of SIRT1 and AMPK and down-regulates *PPARG*. However, Xanthigen also stimulate insulin signaling and promote Akt-dependent phosphorylation of FoxO1 (Lai et al., 2012). Additionally, compound W2476 also manages to dephosphorylate FoxO1 at Ser319 and promotes FoxO1 association with (carbohydrate response element-binding protein (ChREBP). However, the activity to alleviate diabetes was rather due to subsequent repression of thioredoxin-interacting protein (TXNIP) (Zhong et al., 2021).

It is clear that there is a large gap in the treatment of diabetes by targeting FoxO1. One concept by promoting FoxO1 activity is directed toward wound healing and cell longevity point of view on the treatment of diabetes. In general, blocking FoxO1 activity shows more decisive conclusion to reduce high plasma glucose and alleviate insulin resistance. However, long-term study must be done on FoxO1 inhibitor, for example, its effect on the cell survival in hyperglycemic condition. Additionally, chronic study must also be done in which promoting cell survival by activating FoxO1 will not induce insulin resistance. For example, curcumin is famously known to disrupt Akt pathway for anticancer activity (Choi et al., 2008), which might also promote insulin resistance.

Furthermore, the chemical structures of various drugs that target or directly bind to FoxO1 protein (Table 2) seem very diverse ranging from small molecules, which freely rotate to cyclic aliphatic and/or aromatic. Many drugs that were found to modulate (activate / inhibit) FoxO1 were subjected rather from its effect for blood glucose-lowering activity or from its impact on FoxO1 transcriptional activity. As such, it might happen that the modulation of FoxO1 activity can be not due to direct interaction to FoxO1 but rather via binding to other macromolecule(s) that further modify FoxO1 activity. One example about the predicted binding modes was found rather only by molecular docking (Abuzenadah et al., 2018) to the previously established crystal of the free structures that only contain the DNA-binding domain of FoxO1 (Brent et al., 2008). The reported binding modes might not reflect the real binding sites to the whole FoxO1 protein. Moreover, results extracted by molecular docking without support from biophysical and structural studies are uncertain.

Biophysical assays to proof the binding of the ligands to FoxO1 protein seem scarce (Table 2). Out of all studied articles, compound AS1842856 was screened by mass spectrometry that indicates direct binding (Nagashima et al., 2010). While AS1842856 inhibitory activity is selective to FoxO1, carbenoxolone was also proven to directly bind to the DNA-binding domain, however, of various FoxO proteins by fluorescence titration assay (Salcher et al., 2020). One example about complementation of molecular docking with biophysical studies can be found in a study that screen natural products which selects one compound called tanzawaic acid D which also hints that the $\Delta G_{\text{binding}}$ obtained from molecular docking cannot be interpreted directly into the experimentally obtained K_d (Sun et al., 2017). Therefore, the need to establish high-resolution structure for ligand-FoxO1 interaction cannot be evaded which is still absent to this date for better rational drug design and more specific protein targeting.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL

The studies conducted in this article do not involve human participants or animals.

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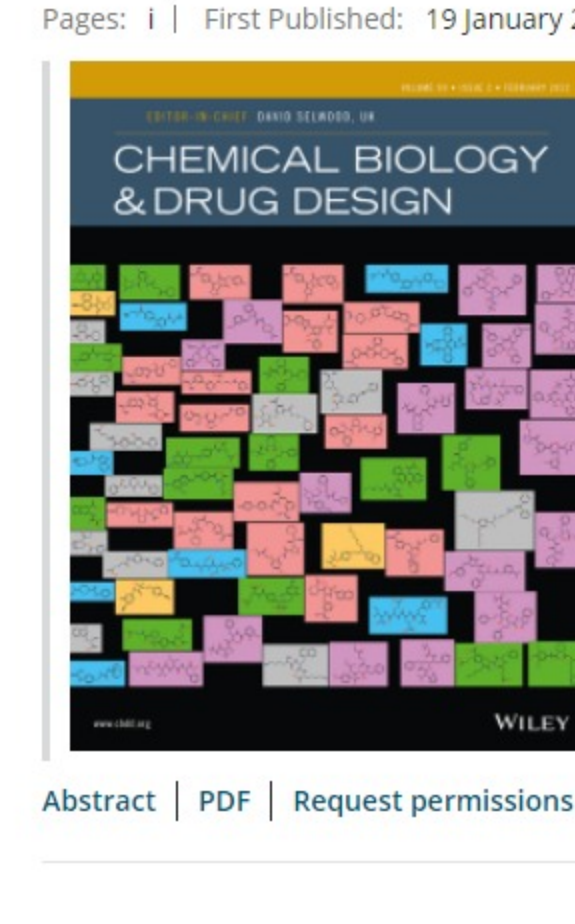
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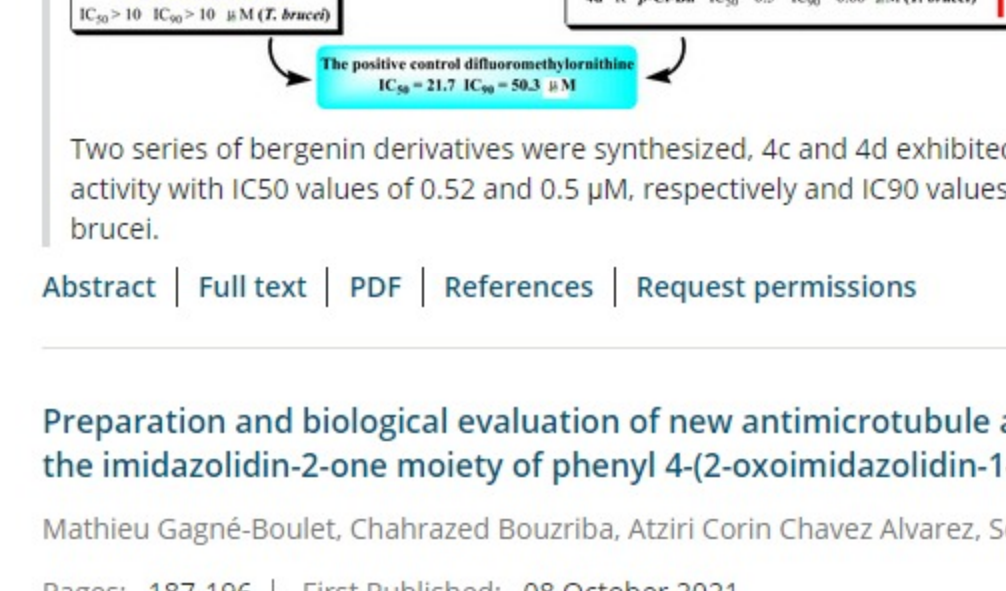
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Seham S. El-Hawary, Rabab Mohammed, Sameh AbouZid, Mohamed A. Zaki, Zeinab Y. Ali, Ahlam Elwekeel, Heba A. H. Elshemy

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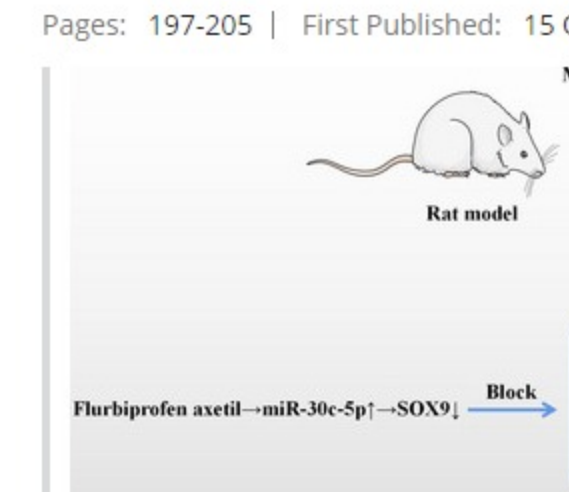
Two series of bergenin derivatives were synthesized. 4c and 4d exhibited potent antitrypanosomal activity with IC50 values of 0.52 and 0.5 μM, respectively and IC90 values of 0.66 μM against T. brucei.

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Mathieu Gagné-Boulet, Chahrazed Bouzriba, Atziri Corin Chavez Alvarez, Sébastien Fortin

Pages: 187-196 | First Published: 08 October 2021



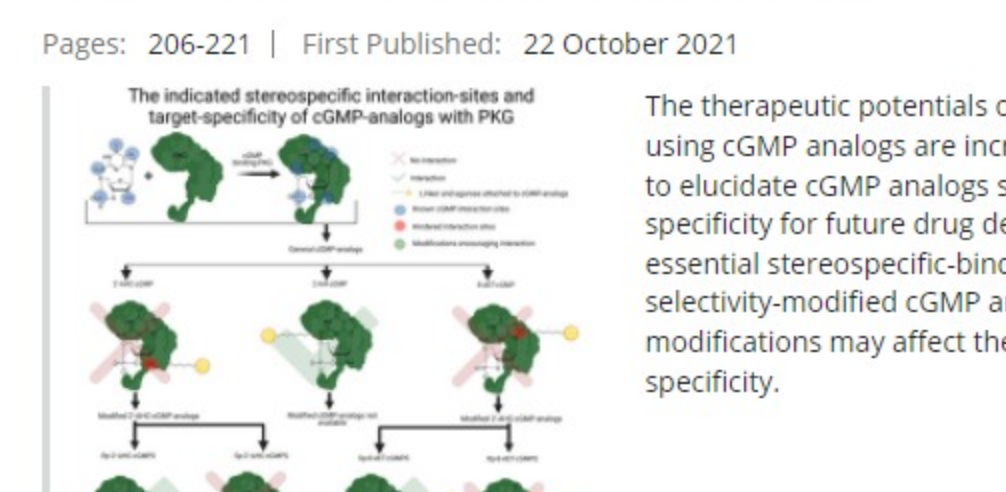
We report the synthesis and biological evaluation of 32 novel molecules named phenyl 4-(2-dioximidazolidin-1-yl)benzenesulfonates (PID-SOs) and ethyl 2-(3-(4-(phenoxysulfonylphenyl)ureido)acetates (EPA-SOs). The most potent compounds were PID-SOs (16–18) exhibit antiproliferative activity in the nanomolar to low micromolar range (0.066–0.9 μM), arrest the cell cycle progression in G2/M phase and interact with the colchicine-binding site leading to microtubule disruption.

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Flurbiprofen axetil protects against cerebral ischemia/reperfusion injury via regulating miR-30c-5p and SOX9

Bangkun Yang, Ying Nie, Lesheng Wang, Wenping Xiong

Pages: 197-205 | First Published: 15 October 2021



In a rat model, flurbiprofen axetil exerts the neuroprotective effects in cerebral ischemia/reperfusion injury, inhibiting the inflammatory response and oxidative stress, via inducing the expression of miR-30c-5p, and repressing the expression of SOX9.

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The stereospecific interaction sites and target specificity of cGMP analogs in mouse cortex

Michel Rasmussen, Charlotte Welinder, Frank Schwede, Per Ekström

Pages: 206-221 | First Published: 22 October 2021



The therapeutic potentials of the cGMP-signaling system using cGMP analogs are increasing, and there is a need to elucidate cGMP analogs stereospecificity and target specificity for future drug design. Here, we show essential stereospecific-binding sites of general and selectivity-modified cGMP analogs and how such modifications may affect the cGMP analogs target specificity.

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Identification of an AXL kinase inhibitor in triple-negative breast cancer by structure-based virtual screening and bioactivity test

Pei Li, Yuzhen Niu, Shuyan Li, Xuyu Zu, Maoyu Xiao, Liyang Yin, Jianbo Feng, Jun He, Yingying Shen

Pages: 222-232 | First Published: 22 October 2021



(1) The structure-based virtual screening and bioassay test were used to identify a compound Y041-5921 (IC50 = 6.069 μM for AXL kinase and IC50 = 4.1 μM for MDA-MB-231 cell line). (2) Y041-5921 could significantly inhibit the proliferation and invasion of the TNBC cells and the toxicity of Y041-5921 to normal immortalized breast epithelial cells was far lower than that of commonly used clinical chemotherapy drugs. (3) The key residues whose energy contribution mainly comes from non-polar solvation interaction (such as Ala565, Lys567, Met598, Leu620, Pro621, Met623, Lys624, Arg676, Asn677 and Met679) were identified.

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Specific delivering of RNAi using Spike's aptamer-functionalized lipid nanoparticles for targeting SARS-CoV-2: A strong anti-Covid drug in a clinical case study

Haidar Saify Nablalbad, Massoume Amini, Servet Demirdas

Pages: 233-246 | First Published: 29 October 2021



LNPs functionalized with 35 μM Aptamer and containing 30 nM RNAi/ml of cell culture had the best anti-viral activity. Clinical case study confirms treatment of 2019-nCoV infection through inhalation of Aptamer-LNPs-RNAL.

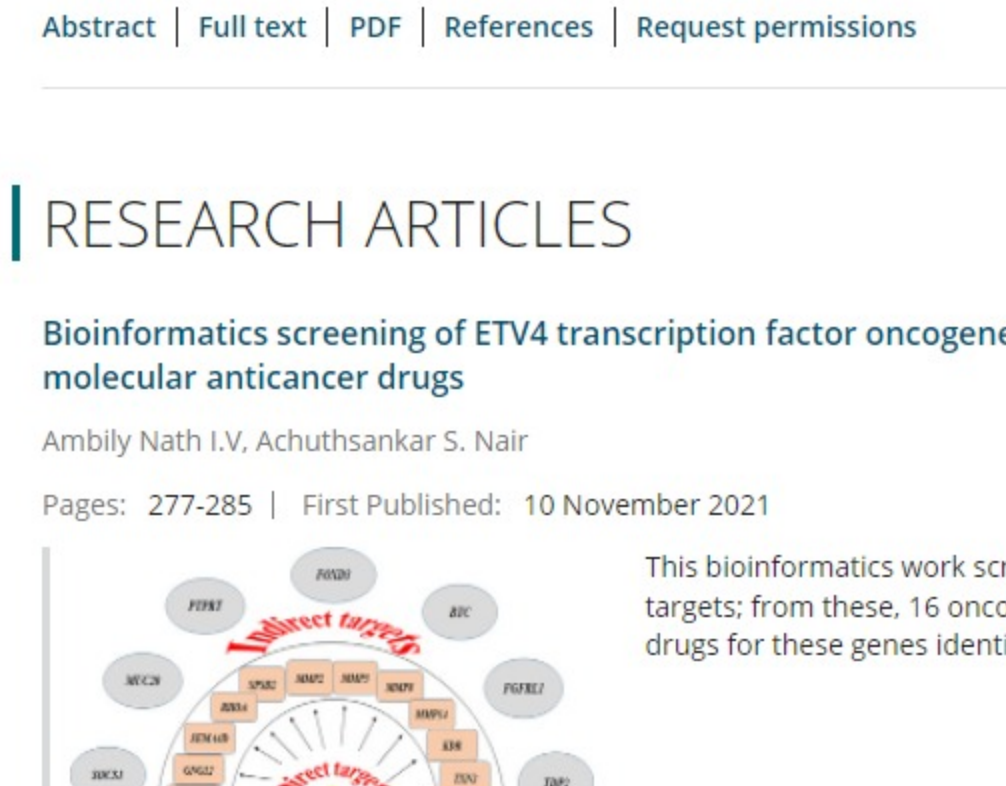
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REVIEW

A comprehensive review on glucokinase activators: Promising agents for the treatment of Type 2 diabetes

Ramasamy Thilagavathi, Maryam Sadat Hosseini-Zare, Manokaran Malini, Chelliah Selvam

Pages: 247-263 | First Published: 29 October 2021



2-D interaction diagram with crucial interactions between glucokinase and glucokinase activator.

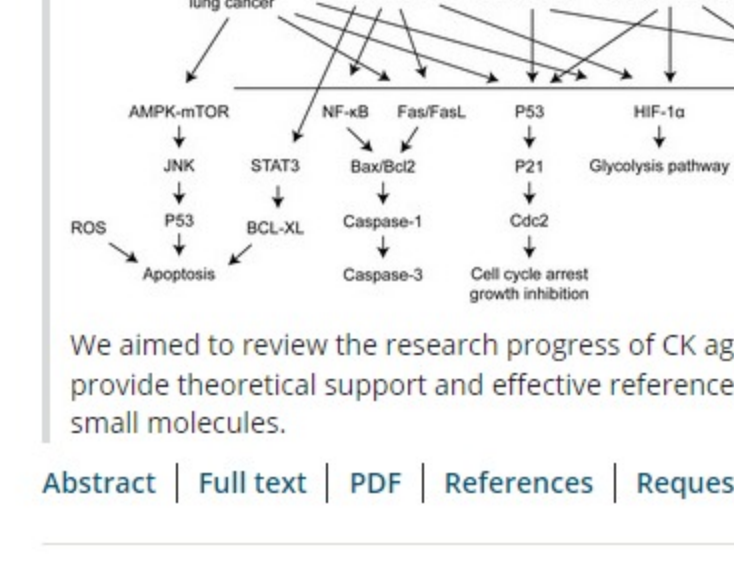
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RESEARCH ARTICLE

Inhibition of BACE1 and amyloid β aggregation by polyketide from Streptomyces sp.

Masashi Yokoya, Keyo Nakai, Miki Kawashima, Sanae Kurakado, Natchanun Sirimangkalakitti, Yoshihiro Kino, Takashi Sugita, Shinya Kimura, Masamichi Yamanaka, Naoki Saito

Pages: 264-276 | First Published: 10 November 2021



To discover lead compounds for the treatment of Alzheimer's disease, we investigated EtOAc extracts of 142 strains of Streptomyces sp. cultures. We focused on Streptomyces sp. RD 063311 and found five polyketides from the extracts, including a new compound 1, and demonstrated that KS-619-1 inhibits both Aβ aggregation and BACE1.

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Bioinformatics articles

Bioinformatics screening of ETV4 transcription factor oncogenes and identifying small-molecular anticancer drugs

Ambily Nath I.V, Achuthsankar S, Nair

Pages: 277-285 | First Published: 10 November 2021



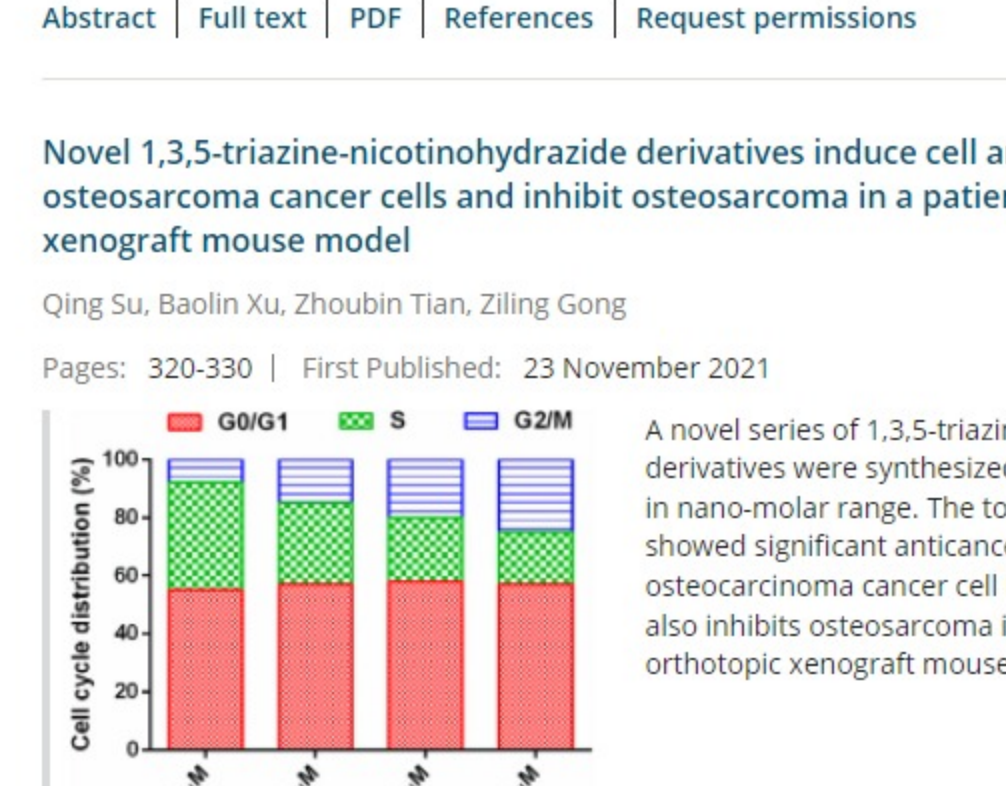
This bioinformatics work screened 23 direct ETV4 targets, from these, 16 oncogenes listed and anticancer drugs for these genes identified.

Abstract | Full text | PDF | References | Request permissions

Anticancer properties and pharmaceutical applications of ginsenoside compound K: A review

Li Zhou, Zhong-Kun Li, Cong-Yuan Li, Yue-Qin Liang, Fan Yang

Pages: 286-300 | First Published: 18 November 2021



We aimed to review the research progress of CK against cancer in the past decade, which might provide theoretical support and effective reference for further research on the medicinal value of small molecules.

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1*H*-1,2,3-triazole embedded Isatin-Benzaldehyde-bis(heteronuclearhydrazones): design, synthesis, antimicrobial, and cytotoxic evaluation

Bhavni Sharma, Sumit Kumar, Preeti, Matt D. Johansen, Laurent Kremer, Vipani Kumar

Pages: 301-307 | First Published: 16 November 2021



Isatin-benzaldehyde-bis(heteronuclear hydrazones) were synthesized and evaluated as anti-microbials. The introduction of isoniazid improved the activity and reduced cytotoxicity. The most promising and non-cytotoxic conjugates 14c and 14e exhibited MIC99 0.36 μg/ml. The most potent conjugate demonstrated a selectivity index > 277.

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Systematic identification of activity cliffs with dual-atom replacements and their rationalization on the basis of single-atom replacement analogs and X-ray structures

Huabin Hu, Jürgen Bajorath

Pages: 308-319 | First Published: 22 November 2021



Shown is an analog quartet assembled to aid in the rationalization of potency differences (ΔpPOT) as a consequence of dual-atom replacements.

Abstract | Full text | PDF | References | Request permissions

Novel 1,3,5-triazine-nicotinohydrazide derivatives induce cell-arrest and apoptosis in osteosarcoma cancer cells and inhibit osteosarcoma in a patient-derived orthotopic xenograft mouse model

Qing Su, Baolin Xu, Zhoubin Tian, Ziling Gong

Pages: 320-330 | First Published: 23 November 2021



A novel series of 1,3,5-triazine-nicotinohydrazide derivatives were synthesized as potent inhibitor of CDK9 in nano-molar range. The top-ranked molecule (5k) showed significant anticancer activity against human osteosarcoma cancer cell line (MG-63). In MTT assay, it also inhibits osteosarcoma in a patient-derived orthotopic xenograft mouse model.

Abstract | Full text | PDF | References | Request permissions

Information-theoretic approach in allometric scaling relations of DNA and proteins

Yekban Adiguzel

Pages: 331-343 | First Published: 02 December 2021

Information-theoretic approach applied in allometric scaling relations' studies for the first time for relating the sizes of genes and proteins.

Abstract | Full text | PDF | References | Request permissions

REVIEW

The role of FoxO1 and its modulation with small molecules in the development of diabetes mellitus: A review

Joshua Nathanael, Putu Suardana, Yoanes Maria Vianney, Sulistyono Emantoko Dwi Putra

Pages: 344-361 | First Published: 03 December 2021

FoxO1 is a critical gene in cell that can also contribute to the onset and severity of diabetes. Small molecules manage to modulate FoxO1 activity directly or indirectly. Conflicting results of up- or down-regulating FoxO1 with ligands were reported to similarly alleviate diabetic symptoms.

Abstract | Full text | PDF | References | Request permissions

RESEARCH ARTICLE

Hydroxamates as a potent skeleton for the development of metallo-β-lactamase inhibitors

Jia-Zhu Chigan, Jia-Qi Li, Huan-Huan Ding, Yin-Sui Xu, Lu Liu, Cheng Chen, Ke-Wu Yang

Pages: 362-372 | First Published: 03 December 2021

The hydroxamate derivatives exhibited potent and selective inhibition against metallo-β-lactamases IMP-1 and NDM-1 with IC50 values of 0.10 and 0.23 μM, and covalently and irreversibly bind to IMP-1.

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Literature Review

The role of FoxO1 and its modulation with small molecules in the development of diabetes mellitus: A review

December 2021 · Chemical Biology & Drug Design 99(8)

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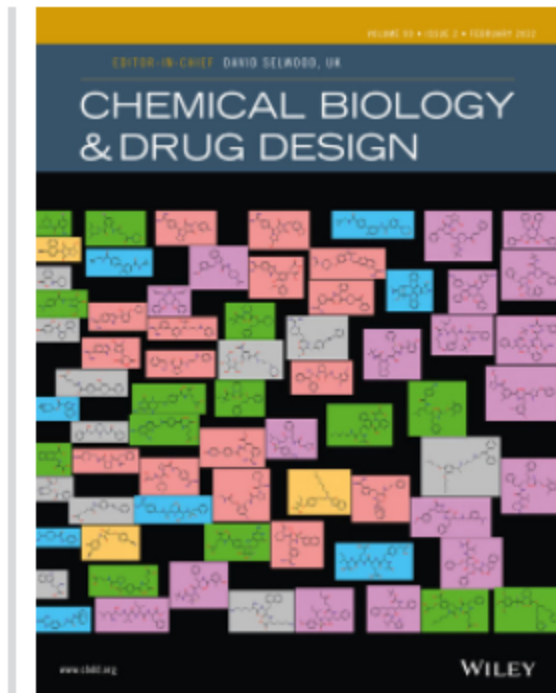


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