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Role of O-linked N-acetylglucosamine in the homeostasis of metabolic organs, and its potential links with diabetes and its complications

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ABSTRACT

Recent studies using genetically manipulated mouse models have shown the pivotal role of O-linked N-acetylglucosamine modification (O-GlcNAcylation) in the metabolism of multiple organs. The molecular mechanism involves the sensing of glucose flux by the hexosamine biosynthesis pathway, which leads to the adjustment of cellular metabolism to protect against changes in the environment of each organ through O-GlcNAcylation. More recently, not only glucose, but also fluxes of amino acids and fatty acids have been reported to induce O-GlcNAcylation, affecting multiple cellular processes. In this review, we discuss how O-GlcNAcylation maintains homeostasis in organs that are affected by diabetes mellitus: skeletal muscle, adipose tissue, liver and pancreatic β -cells. Furthermore, we discuss the importance of O-GlcNAcylation in the pathogenesis of diabetic complications. By elucidating the molecular mechanisms whereby cellular homeostasis is maintained, despite changes in metabolic flux, these studies might provide new targets for the treatment and prevention of diabetes and its complications.

INTRODUCTION

Diabetes mellitus is rapidly emerging as one of the greatest global health challenges of the 21st century. The International Diabetes Federation estimates that by the year 2030 approximately 578 million, and by the year 2045 approximately 700 million people will have diabetes¹. This epidemic is also expected to trigger a steep rise in the incidences of complications associated with diabetes, such as neuropathy, retinopathy, nephropathy, ischemic heart disease and stroke. Therefore, the development of better treatments and novel prevention strategies for diabetes and its complications is a matter of great urgency. However, to accomplish this goal, a better understanding of the pathogenesis of diabetes and its complications is necessary. Although the underlying cause remains unknown, insulin resistance, metabolic disorders, and hyperglycemia play critical roles in the development of diabetes and its complications^{2,3}. Over the past decade, several groups, including our own, have used genetically manipulated mouse models to investigate the physiological and pathological roles of O-linked N-acetylglucosamine (GlcNAc)

modification (GlcNAcylation) *in vivo*. In this brief review, we discuss recent studies of the role of O-GlcNAcylation in the organs that are most affected by diabetes, which have shed new light on the cellular and molecular mechanisms of diabetes mellitus.

O-GLCNACYLATION AS A NUTRIENT FLUX SENSOR

O-GlcNAcylation is evolutionarily conserved, being present in many species, including *C. elegans*⁴, *Drosophila*⁵, zebrafish⁶, mammals⁷ and plants⁸. O-GlcNAcylation is regulated by two enzymes: O-GlcNAc transferase (Ogt) and O-GlcNAcase (Oga) (Figure 1). Both enzymes are encoded by each single gene, but a number of splice variants are differentially expressed in many tissues, which suggests that they have important regulatory roles in specific tissues⁹. Unlike other glycoproteins, which are expressed on the cell surface or the endomembranes of organelles, O-GlcNAcylation proteins are mostly nuclear, mitochondrial and cytoplasmic (Figure 1). The O-GlcNAc moiety is generally not elongated and is attached as a single moiety to serine or threonine residues, and is removed rapidly, depending on the status of the cell (referred to as O-GlcNAc cycling)¹⁰.

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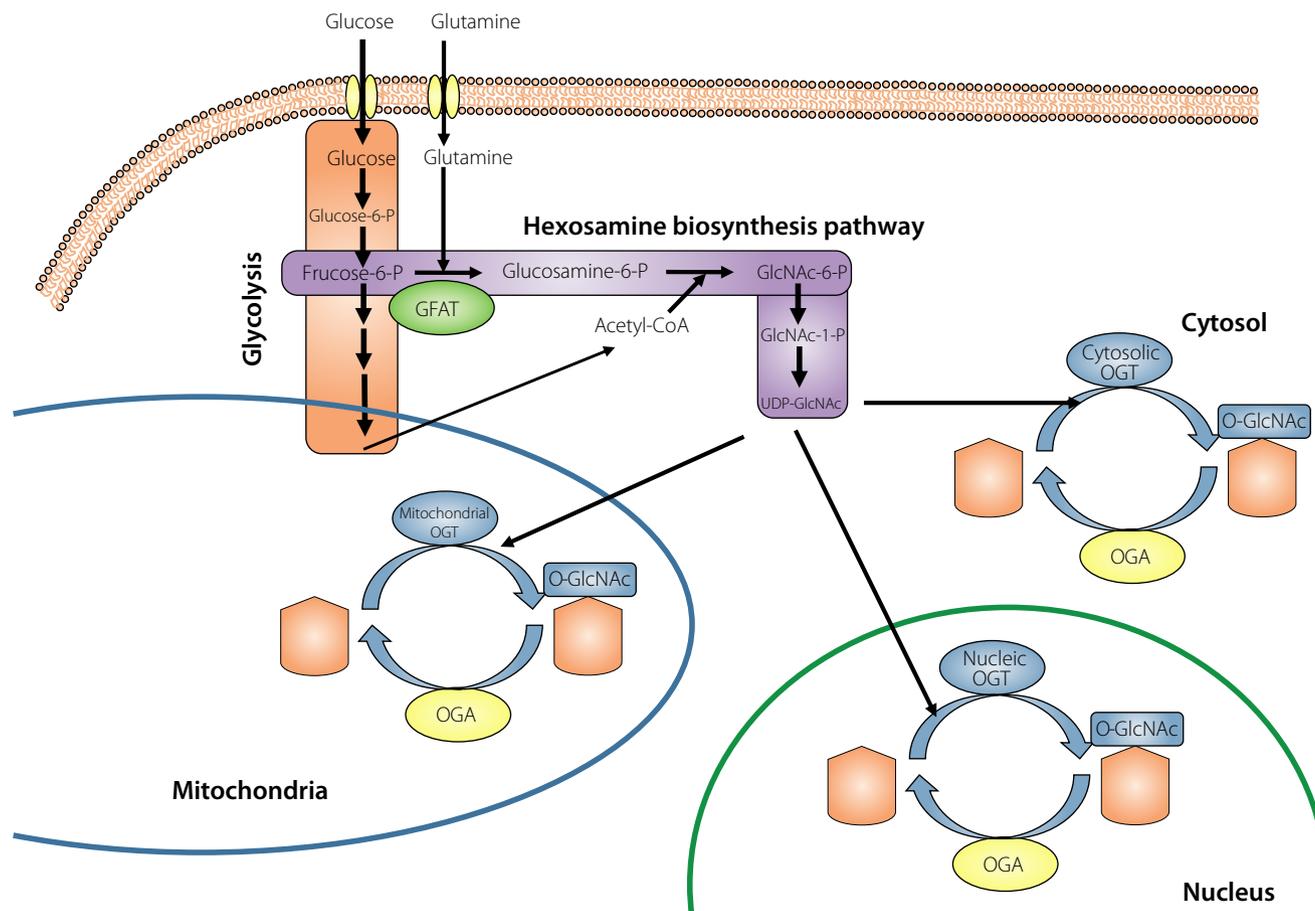


Figure 1 | Link between O-linked N-acetylglucosamine modification (O-GlcNAcylation) and metabolic flux in the regulation of cellular homeostasis. O-GlcNAcylation is determined by two key enzymes: O-GlcNAc transferase (OGT) and O-GlcNAcase (OGA). The activities of these two enzymes and substrate availability in each subcellular fraction determine the level of O-GlcNAcylation of target proteins. Although most glucose enters the glycolytic or pentose phosphate pathways, approximately 1–5% enters the hexosamine biosynthesis pathway, which is a branch of glycolysis. Fructose-6-phosphate and glutamine are converted to glucosamine-6-phosphate (GlcN-6-P) by glutamine:fructose-6-phosphate transferase (GFAT). Acetyl coenzyme A (Acetyl-CoA) then contributes to GlcNAC-6-phosphate (GlcNAC-6-P) synthesis. Uridine diphosphate (UDP)-GlcNAC is produced using UDP and is used by OGT for O-GlcNAcylation.

The hexosamine biosynthesis pathway is a branch of glycolysis, and approximately 1–5% of the glucose flux is used to generate uridine diphosphate-GlcNAC, which is a substrate for Ogt. The generation of glucosamine-6-phosphate from fructose-6-phosphate is the first reaction in the hexosamine biosynthesis pathway, which is catalyzed by glutamine:fructose-6-phosphate transferase, and is considered to be the rate-limiting step¹¹. Hyperglycemia¹², glucosamine infusion¹², glucose transporter overexpression¹³ and glutamine:fructose-6-phosphate transferase overexpression^{14,15}, all of which increase flux through the hexosamine biosynthetic pathway, result in higher intracellular O-GlcNAC concentration. Approximately 4,000 proteins have been predicted to be targets of O-GlcNAcylation¹⁶. Thus, O-GlcNAcylation is a metabolic sensor. The precise mechanisms involved have been effectively summarized in previous reviews⁹.

PANCREATIC β -CELLS: A PRIMARY TARGET IN DIABETES MELLITUS

Pancreatic β -cell failure is a key component of the pathogenesis of diabetes mellitus, because pancreatic islets govern whole-body metabolism, mainly through insulin secretion. β -Cells sense the plasma glucose concentration through the glucose transporter 2–glucokinase–adenosine triphosphate/adenosine monophosphate–adenosine triphosphate sensitive potassium channel– Ca^{2+} influx axis¹⁷. In parallel, a high level of O-GlcNAcylation occurs in the nuclei of β -cells¹⁸, which is consistent with the high expression of Ogt in the pancreas (Figure 2)^{19,20}. During islet development, Ogt – expressed in pancreatic epithelial progenitor cells – plays an important role in cell survival, and thus pancreatogenesis, which is mediated through pancreatic and duodenal homeobox 1 and p53²¹. In adult mice, greater O-GlcNAcylation, induced by glutamine:

fructose-6-aminotransferase overexpression, causes hyperinsulinemia²². In contrast, the disruption of O-GlcNAcylation induces endoplasmic reticulum stress, which results in β -cell failure²³, and analogous effects are induced by the depletion of Ogt in *Drosophila*²⁴. Before β -cell failure, the knockdown of O-GlcNAcylation induces hyperinsulinemia, which suggests a link with the pathogenesis of type 2 diabetes mellitus¹⁸. Streptozotocin is a chemical inducer of diabetes that works through multiple mechanisms. Because it is structurally similar to GlcNAc, streptozotocin is a competitive inhibitor of Oga that increases O-GlcNAcylation²⁵. These findings suggest that GlcNAcylation

might be involved in the molecular mechanisms of glucotoxicity and streptozotocin-induced β -cell failure²⁶. However, further studies are required to fully elucidate the molecular mechanisms of β -cell failure and glucotoxicity, especially in humans.

ADIPOSE TISSUE: A KEY REGULATOR OF WHOLE-BODY HOMEOSTASIS

Adipose tissue stores energy in the form of lipid droplets. It releases free fatty acids and glycerol during fasting, prolonged exercise, and physical stress, but takes up glucose and stores triglyceride in the postprandial phase. The role of O-

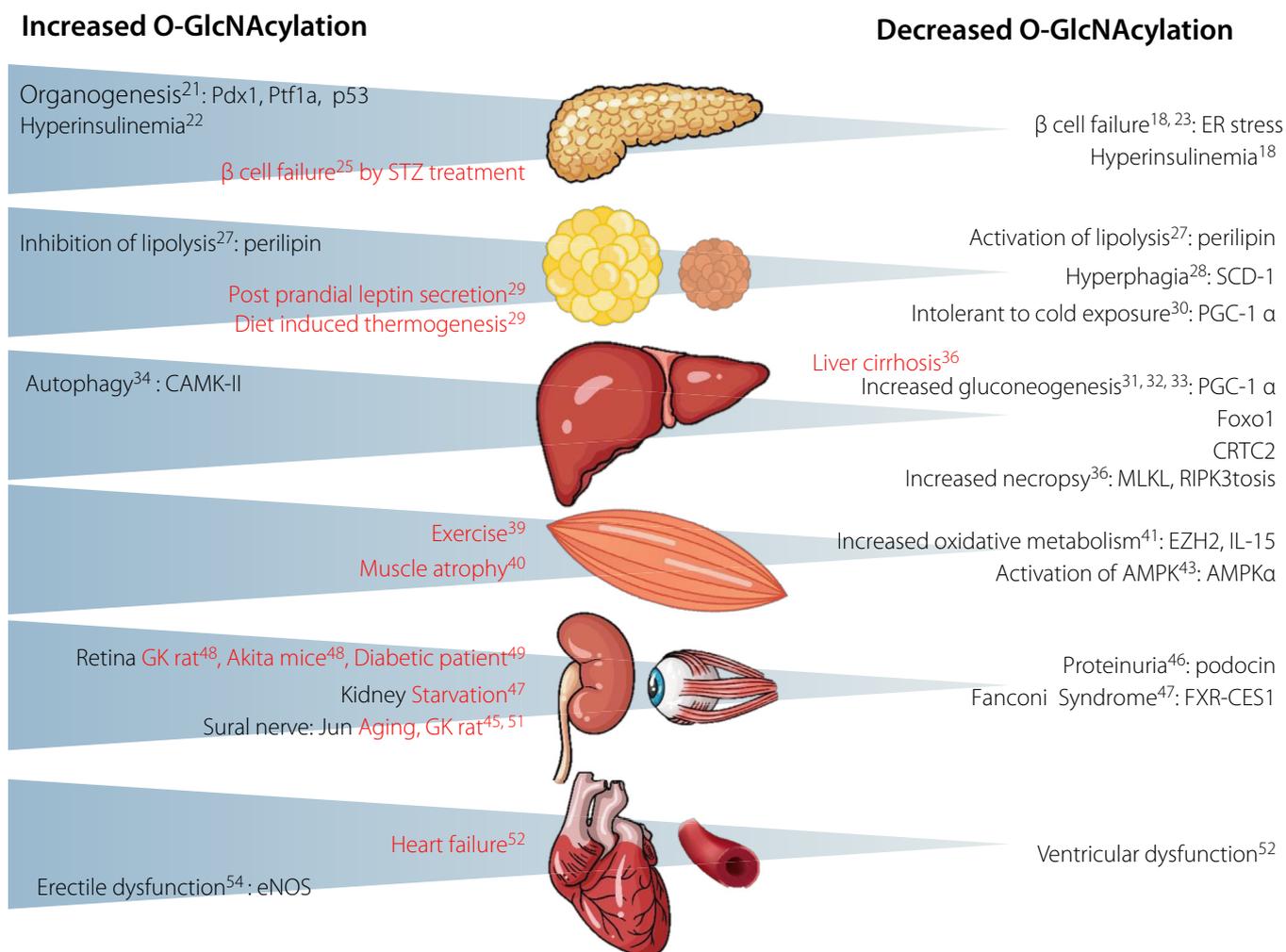


Figure 2 | Role of O-linked N-acetylglucosamine modification (O-GlcNAcylation) in specific organs in diabetes and its complications. Most research has been carried out under extreme conditions in animals with genetically determined organ-specific changes in O-GlcNAcylation. However, O-GlcNAcylation is a finely-tuned system that maintains homeostasis. Thus, relevant symptoms only develop in chronic pathological conditions. In humans and diabetic animal models, there are several states in which O-GlcNAcylation is higher or lower (red characters). AMPK, adenosine monophosphate-activated kinase; CAMK-II, calcium/calmodulin-dependent kinase II; CES1, carboxylesterase 1; CRTC2, cyclic adenosine monophosphate-response element binding protein-regulated transcription coactivator 2; eNOS, endothelial nitric oxide synthase; EZH2, enhancer of zeste homolog 2; Foxo1, forkhead box O1; FXR, Farnesoid X receptor; GK, Goto-Kakizaki; IL-15, interleukin-15; MLKL, mixed lineage kinase domain-like; Pdx1, pancreatic and duodenal homeobox 1; PGC-1 α , peroxisome proliferator-activated receptor-gamma coactivator-1 α ; Ptf1a, pancreas-associated transcription factor 1; RIPK3, receptor interacting serine/threonine kinase 3; SCD-1, stearoyl CoA desaturase; STZ, streptozotocin.

GlcNAcylation in the balance between these processes has been shown by studies of adipose tissue-specific genetic models. An increase in O-GlcNAcylation, induced by overexpression of Ogt in adipose tissue, inhibits lipolysis and promotes diet-induced obesity, whereas the disruption O-GlcNAcylation in adipose tissue by Ogt knockout promotes lipolysis by stimulating perilipin activity by phosphorylation (Figure 2)²⁷. In addition, high O-GlcNAcylation in adipocytes induces hyperphagia by transcriptionally activating genes that mediate de novo lipid desaturation through the accumulation of N-arachidonoyl ethanolamine, an appetite-inducing cannabinoid²⁸. Recently, an elegant study showed that glucose flux has a role in diet-induced thermogenesis in brown adipose tissue, which is mediated through leptin-induced adrenal catecholamine secretion²⁹. In that study, an increase in O-GlcNAcylation in adipose tissue was demonstrated after a meal, and this was shown to play a role in the postprandial increase in plasma leptin concentration and diet-induced thermogenesis.

In addition to diet-induced thermogenesis, O-GlcNAcylation has also been shown to have a significant role in cold-induced thermogenesis, which was established using brown adipose tissue-specific Ogt knockout mice³⁰. Although the brown adipose tissue-specific Ogt knockout mice showed almost no phenotype at 25°C, severe hypothermia was induced by exposure to a 4°C environment. In these mice, low expression of β -oxidation enzymes and uncoupling protein 1 is observed, which is likely to be secondary to low expression of peroxisome proliferator-activated receptor- γ coactivator (PGC)-1 α , a master regulator of mitochondrial biogenesis.

These data suggest that O-GlcNAcylation has two roles in adipose tissue. First, O-GlcNAcylation contributes to diet-induced obesity through perilipin and the CB-1 receptor. Second, it also contributes to thermogenesis, through the leptin-catecholamine pathway post-prandially, and maintains PGC-1 α and uncoupling protein 1 expression, and mitochondrial biogenesis.

ROLE OF O-GLCNACYLATION IN THE LIVER

During starvation, the liver has a central role in the maintenance of plasma glucose through glycogenolysis and gluconeogenesis. Furthermore, the liver generates ketone bodies using free fatty acids derived from adipose tissue. In addition, starvation stimulates autophagy in the liver to provide amino acids for use by other organs. PGC-1 α and Foxo1 together regulate gluconeogenesis², and O-GlcNAcylation of PGC-1 α increases its stability by recruiting host cell factor C³¹ (Figure 2). In addition, greater O-GlcNAcylation of hepatic forkhead box O1 and cyclic adenosine monophosphate-response element binding protein-regulated transcription coactivator 2 increases the expression of phosphoenolpyruvate carboxykinase and glucose 6-phosphatase^{32,33}. O-GlcNAcylation of calcium/calmodulin-dependent kinase II is also involved in the regulation of autophagy in the liver^{34,35}. Furthermore, liver pathology has also been shown to be associated with O-GlcNAcylation. Low O-

GlcNAcylation has been identified in liver biopsy samples from patients with cirrhosis, alongside low expression of Ogt and Oga. Low O-GlcNAcylation is also associated with greater necroptosis, through higher expression of MLKL and RIPK3³⁶. Thus, changes in glucose flux, especially in the portal vein, might affect multiple metabolic pathways in the liver.

ROLE OF O-GLCNACYLATION IN SKELETAL MUSCLE

Skeletal muscle is a major insulin target organ, and plays an essential role in glucose, lipid and amino acid metabolism. In addition to its locomotor function, skeletal muscle serves as a huge protein pool, because it comprises ~40% of body mass in humans³⁷. Although the molecular mechanism underlying insulin resistance remains to be fully established, dysregulation of the insulin signaling cascade is considered to be a key component³⁸. In skeletal muscle, the level of O-GlcNAcylation differs after exercise³⁹ or muscle atrophy (Figure 2)⁴⁰. Recently, the expression of Ogt and Oga was measured in human skeletal muscle, and no differences were found among people with type 2 diabetes, lean individuals and obese individuals⁴¹. However, the disruption of O-GlcNAcylation in skeletal muscle increases the secretion of IL-15, a myokine that regulates whole-body oxidative metabolism⁴², through an effect on enhancer of zeste homolog 2⁴¹. In addition, the disruption of O-GlcNAcylation in skeletal muscle also stimulates adenosine monophosphate kinase- α expression in both muscle-specific Ogt knockout mice and C2C12 myotubes treated with small interfering ribonucleic acid targeting Ogt⁴³.

ROLE OF O-GLCNACYLATION IN DIABETIC COMPLICATIONS

Hyperglycemia is a key feature of diabetes mellitus and a major cause of diabetic complications. In the excellent review by Brownlee, (i) greater flux through the polyol pathway; (ii) the intracellular production of advanced glycation end-product precursors; (iii) PKC activation; and (iv) greater hexosamine pathway activity were proposed as the mechanisms underlying hyperglycemia⁴⁴. Greater O-GlcNAcylation is present in the sciatic nerves, kidneys and liver of diabetic Goto-Kakizaki rats, alongside the morphological changes in these tissues⁴⁵.

Genetic manipulations that alter the level of O-GlcNAcylation have shown its role in diabetic complications (Figure 2). In the kidney, the depletion of O-GlcNAcylation in podocytes causes marked proteinuria because of a reduction in podocin expression, which alters the shape of podocyte foot processes⁴⁶. The proximal renal tube is highly oxidative, and the depletion of O-GlcNAcylation in tubules induces a Fanconi syndrome-like phenotype, which is accompanied by abnormal lipid droplet breakdown and tubular cell damage, mediated through the Farnesoid X receptor-carboxylesterase-1 axis⁴⁷. In addition, greater O-GlcNAcylation is present in renal tubular cells during prolonged fasting and diabetes⁴⁷, which suggests that free fatty acid flux is a stimulus, in contrast to the situation in other tissues.

Greater O-GlcNAcylation is present in the retinas of diabetic Goto-Kakizaki rats, Akita mice, aged animals⁴⁸ and the vitreous humor of patients with proliferative diabetic retinopathy⁴⁹, alongside high Ogt and low Oga expression⁵⁰. Recently, an effect on signal transducer and activator of transcription 3 phosphorylation has also been reported in retinal vascular endothelial cells⁴⁹. However, the role of O-GlcNAcylation in diabetic retinopathy is unknown.

High O-GlcNAcylation has been identified in the sural nerve of diabetic Goto-Kakizaki rats⁴⁵. O-GlcNAcylation promotes peripheral nerve remyelination through AP-1 and the transcription factor Jun⁵¹. Defects in the injury response in Schwann cells might contribute to the pathogenesis of diabetic neuropathy.

In the cardiovascular system, acute injury is associated with greater O-GlcNAcylation in the heart, which seems to be cardioprotective. Disruption of O-GlcNAcylation in the heart causes ventricular dysfunction, but no cardiac hypertrophy⁵². However, a prolonged increase in O-GlcNAcylation, in combination with stress, might have adverse effects⁵³. Greater O-GlcNAcylation is also present in patients with heart failure⁵². Hyperglycemia increases the O-GlcNAcylation of endothelial NO synthase, which results in lower NO production and a consequent impairment in NO-dependent arteriolar dilation⁵⁴. These changes might explain the higher prevalence of diabetic cardiomyopathy, heart failure and diabetic macroangiopathy in patients with diabetes.

CONCLUSION

In summary, recent studies of genetically altered O-GlcNAcylation have provided important new insights into the pathogenesis of diabetes mellitus and its complications. However, the cellular and molecular mechanisms responsible for the changes in metabolism remain to be fully elucidated. Post-translational modification by O-GlcNAcylation is a fine-tuning process that permits cells to maintain homeostasis in the face of environmental changes. Future studies should further characterize this, such that novel strategies can be developed to protect diabetes patients from the development of complications.

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DISCLOSURE

The authors declare no conflict of interest.

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