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REVIEW

# Hepatic glucose sensing and integrative pathways in the liver

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**Abstract** The hepatic glucose-sensing system is a functional network of enzymes and transcription factors that is critical for the maintenance of energy homeostasis and systemic glycemia. Here we review the recent literature on its components and metabolic actions. Glucokinase (GCK) is generally considered as the initial postprandial glucose-sensing component, which acts as the gatekeeper for hepatic glucose metabolism and provides metabolites that activate the transcription factor carbohydrate response element binding protein (ChREBP). Recently, liver receptor homolog 1 (LRH-1) has emerged as an upstream regulator of the central GCK–ChREBP axis, with a critical role in the integration of hepatic intermediary metabolism in response to glucose. Evidence is also accumulating that *O*-linked β-*N*-acetylglucosaminylation (*O*-GlcNAcylation) and acetylation can act as glucose-sensitive modifications that may contribute to hepatic glucose sensing by targeting regulatory proteins and the epigenome. Further elucidation of the components and functional roles of the hepatic glucose-sensing system may contribute to the future treatment of liver diseases associated with deregulated glucose sensors.

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**Abbreviations**

| | |
|---|---|
| Acetyl-CoA | Acetyl-coenzyme A |
| ACL | ATP citrate lyase |
| ChoRE | Carbohydrate response element |
| ChREBP | Carbohydrate response element binding protein |
| CREB | Cyclic AMP-responsive element binding protein |
| CRTC2 | cAMP-regulated transcriptional co-activator 2 |
| F2 | 6bisP, fructose-2,6-bisphosphate |
| F6P | Fructose-6-phosphate |
| FOXA2 | Forkhead box protein A2 |
| FOXO1 | Forkhead box protein O1 |
| FXR | Farnesoid x receptor |
| G6P | Glucose-6-phosphate |
| G6Pc | Glucose-6-phosphatase |
| G6Pt | Glucose-6-phosphate transporter |
| GCK | Glucokinase |
| GCKR | GCK regulatory protein |
| GLUT | Glucose transporter |
| GSD-1 | Glycogen storage disease type 1 |
| HDAC | Histone deacetylase |
| HIF-1 | Hypoxia-inducible factor 1 |
| HK | Hexokinase |
| HNF-4 | Hepatocyte nuclear factor 4 |
| KAT | Lysine acetyltransferase |
| KLF-6 | Kruppel-like factor 6 |
| LRH-1 | Liver receptor homolog 1 |
| LXR | Liver x receptor |
| Mlx | Max-like protein X |

| | |
|---|---|
| MLXIP | Mlx interacting protein |
| MLXIPL | Max-like protein X interacting protein-like |
| OGA | *O*-GlcNAcase |
| *O*-GlcNAcylation | *O*-linked β-*N*-acetylglucosaminylation |
| OGT | *O*-GlcNAc transferase |
| PGC-1α | Peroxisome proliferator-activated receptor gamma coactivator 1-alpha |
| PPARγ | Peroxisome proliferator activated receptor gamma |
| SREBP-1c | Sterol regulatory binding protein-1c |
| T2D | Type 2 diabetes |
| TCA | Tricarboxylic acid |
| TCFE3 | Transcription factor E3 |
| UDP-GlcNAc | UDP-*N*-acetylglucosamine |
| UTP | Uridine triphosphate |
| X5P | Xylulose-5-phosphate |

## Introduction

Glucose is a simple sugar carbohydrate that serves as a fundamental fuel for most species and provides precursors for biomolecule synthesis. In order to control metabolism, differentiation, and growth, cells possess evolutionary conserved glucose-sensitive signaling pathways [1]. These glucose-sensing systems ensure efficient adaptation to changes in environmental glucose availability in unicellular organisms and allow for homeostatic maintenance of internal glucose pools in multicellular organisms. In higher species, the internal pool is represented by glucose circulating in the bloodstream. From here, glucose is further distributed to different tissues and organs to meet local needs.

The liver plays a central role in metabolic homeostasis by coordinating the breakdown, synthesis, storage, and redistribution of nutrients. Hepatocytes possess multiple nutrient-sensing systems that interact to modulate biochemical pathways in order to accommodate systemic fuel requirements and availability. These systems enable the body to maintain its functions during periods of feeding and fasting and upon excessive energy demands such as exercise. Blood glucose concentrations fluctuate during the feeding and fasting cycles [2], and one of the liver's primary functions is to maintain blood glucose concentrations within a physiological range [3]. Hepatocytes are among the few cell types that possess the ability to both consume and produce glucose [4]. Glycemic control, which is coordinated by both extrahepatic and intrahepatic factors, is hence the result of a balancing act between these two processes. Most reviews have focused on extrahepatic glucose-sensing systems such as hormonal regulation by insulin and glucagon [3, 5, 6]. In contrast, this review will provide an overview of the regulatory components within the liver that are activated by glucose metabolites in response to glucose availability. We provide an overview of these regulatory components and discuss the role of this intrahepatic glucose-sensing system in health and disease.

## Hepatic glucose metabolism

The concentration of glucose in the blood is a primary determinant of glucose availability to the liver. During the postprandial phase, which in humans lasts about 2 h after the intake of a meal, blood glucose levels rise and approximately 10–25 % of ingested glucose is taken up by hepatocytes [7–10]. Facilitated transport of glucose across cellular membranes is mediated by members of the glucose transporter (GLUT) family [11]. GLUT2 is the major glucose transporter in the hepatocytes [11, 12] and its physiological role has been studied extensively [13–15]. GLUT2 is also expressed in pancreatic islets, intestine, kidney, and brain [11, 12]. The rate of GLUT2-mediated glucose transport into the liver is high and only saturates at glucose concentrations above 30 mM [11] allowing efficient glucose transport and extremely rapid equilibration of glucose across the hepatocyte membrane [16]. Once in the cytoplasm, glucose is phosphorylated to glucose-6-phosphate (G6P) by glucokinase (GCK; also known as hexokinase IV) [17, 18]. G6P lies at the crossroads of different biochemical pathways and has multiple biochemical fates. Elevated G6P synthesis allosterically activates glycogen synthase while inhibiting glycogen phosphorylase [19–21]. G6P is also oxidized for energy supply via glycolysis, which involves several steps including the production of fructose-6-phosphate (F6P) and triose phosphates. The pentose phosphate pathway represents a third route of G6P utilization that involves the production of ribose-5-phosphate, an intermediate of nucleotide synthesis, and the biological reductant NADPH. Excess pentose phosphates can ultimately enter the glycolytic pathway by their conversion into F6P and triose phosphates. Pyruvate produced by glycolysis is transported into the mitochondria, where it is decarboxylated to acetyl-coenzyme A (acetyl-CoA), which subsequently enters the tricarboxylic acid (TCA) cycle, a central metabolic hub that is involved in both energy production and biomolecule synthesis. To keep TCA cycle intermediates at a constant level, reactions that extract TCA metabolites for biosynthesis (cataplerotic reactions) are balanced by those that replenish TCA intermediates (anaplerotic reactions) [22]. In the TCA cycle, acetyl-CoA becomes further metabolized to generate reducing equivalents used for ATP production through oxidative phosphorylation. The TCA cycle intermediates also serve as precursors for non-essential amino acids, which serve as substrates for protein

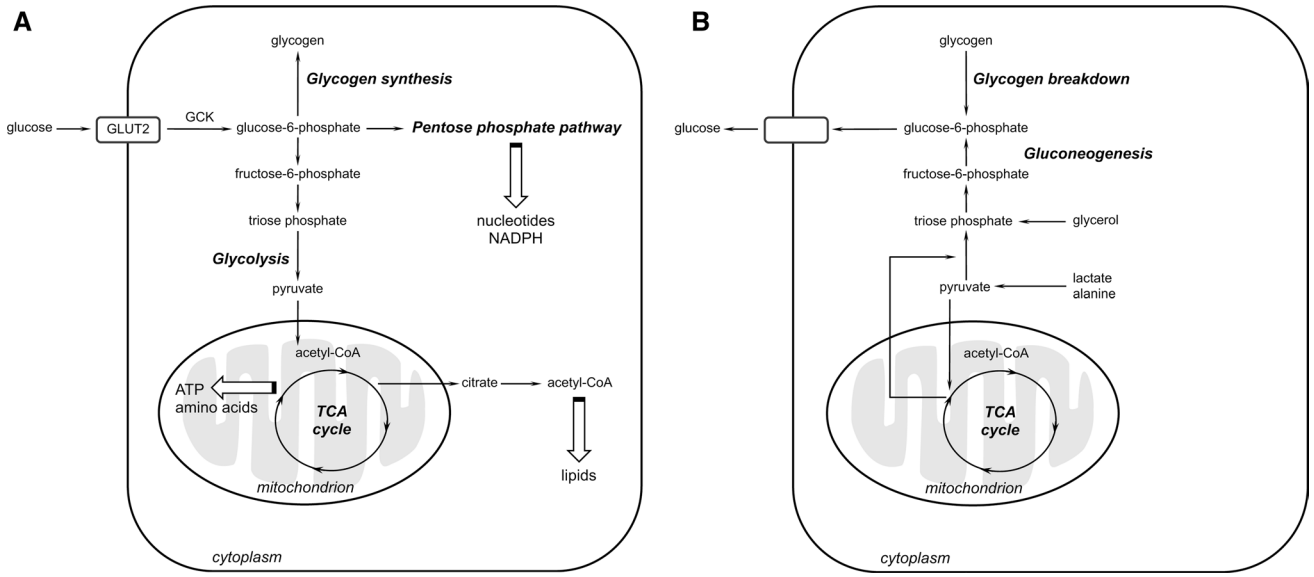


**Fig. 1** Pathways of hepatic glucose metabolism. **a** Simplified scheme depicting the major biochemical pathways activated during postprandial glucose consumption and storage. **b** Simplified scheme depicting the major biochemical pathways activated during postabsorptive glucose production. Glycerol, lactate, and alanine are used as gluconeogenic substrates upon their conversion into triose phosphate and pyruvate. *Acetyl-CoA* acetyl-coenzyme A, *GCK* glucokinase, *GLUT2* glucose transporter 2, *TCA* tricarboxylic acid

synthesis. Citrate produced in the TCA cycle is partly shuttled from the mitochondria into the cytosol where it is converted into oxaloacetate and acetyl-CoA, the latter of which can be used as a substrate for lipid synthesis. These hepatic glucose oxidation and storage pathways are summarized in Fig. 1a.

Hepatic glucose uptake and metabolism decrease as soon as the intestinal absorption of glucose is completed. During this period, which is often referred to as the postabsorptive phase, most tissues reduce their glucose consumption by switching to alternate energy sources. Endogenous glucose production by the liver now represents the major route of glucose supply to the bloodstream. The maintenance of glucose homeostasis is particularly important for cells that partly or fully rely on glucose as energetic substrate such as neurons and erythrocytes. The liver contributes to endogenous glucose production via two G6P-generating pathways. In the initial postabsorptive phase, hepatic G6P is derived from glycogen breakdown while gluconeogenesis becomes the major source of G6P after prolonged fasting. G6P generated through glycogen breakdown and gluconeogenesis is first translocated from the cytosol into the endoplasmic reticulum by the glucose-6-phosphate transporter (G6Pt; also known as SLC37A4), and subsequently dephosphorylated into glucose by glucose-6-phosphatase (G6Pc). Glucose is finally released into the bloodstream, presumably through the concerted action of GLUT2 and a membrane traffic-based mechanism [13, 14, 23]. These glucose-production pathways in the liver are summarized in Fig. 1b.

## Postprandial glucose sensing in the liver

When blood glucose concentrations rise, hepatic glucose sensors induce adaptive responses to shift the balance toward hepatic glucose consumption and storage. GLUT2 is a high-capacity glucose transporter that allows glucose to flow into hepatocytes in response to increasing glycemia [11]. However, its activity does not appear to be critical for postprandial glucose sensing in the liver, as was recently reported [13]. In this study, hepatic GLUT2 deficiency did not result in major perturbations in hepatic glucose metabolism in fed and refed mice, suggesting that alternate mechanisms compensate for the reduction in glucose transport. GCK, on the contrary, is a major component of the hepatic glucose-sensing system. By converting glucose into G6P, GCK catalyzes the first step of intrahepatic glucose metabolism [17]. In contrast to hexokinases (HKs) I-II, GCK exhibits low affinity for glucose, is not feedback-inhibited by its product G6P [17, 24], and its activity increases sigmoidal with increasing glycemia [18, 25]. High glucose concentrations furthermore inhibit the interaction of GCK with its regulatory protein (GCKR), hence promoting the translocation of free GCK to the cytoplasm where it can access glucose and convert it into G6P [26]. GCK consequently acts as a glucose-sensitive enzyme that remains active over a wide range of glucose concentrations and enables hepatocytes to efficiently trap glucose in response to glycemic fluctuations. Lack of hepatic GCK expression in mice perturbs intrahepatic glucose metabolism [27, 28] while overexpression of GCK, but not HK-I, markedly

induces glycogen storage and glycolysis in hepatocytes [29, 30]. These fundamental differences of GCK versus HK-mediated G6P synthesis illustrate the unique role of hepatocytes as compared to other cells.

Further downstream metabolism of G6P generates metabolites that act as signaling molecules to regulate the activity of enzymes within seconds to minutes after hepatic glucose exposure [19, 20, 31–35]. Glucose-mediated control of gene transcription in hepatocytes translates into adaptive responses on longer timescales, i.e., within a timeframe of minutes to hours [36–38]. The expression of many glucose-sensitive genes is regulated by the carbohydrate response element binding protein (ChREBP; also known as Mondo B or Max-like protein X interacting protein-like, MLXIPL) [39, 40], a transcription factor that recognizes conserved carbohydrate response elements (ChoREs) in gene promoters [41, 42]. ChREBP is a member of the Mondo family, which forms heterodimers with Max-like protein X (Mlx) to induce transcriptional responses [43–48]. Mondo-Mlx-dependent glucose sensing is evolutionary conserved among worms, flies, and vertebrates [49–55]. ChREBP has been identified as the major mediator of ChoRE-dependent gene transcription in the liver [40, 48], while its paralog MondoA (or Mlx interacting protein, MLXIP) has been proposed to act predominantly in extrahepatic tissue [45, 56]. However, a recent study showed that MondoA also regulates transcription of specific glucose-responsive genes in hepatocytes [49]. ChREBP is best-known for its effects on the expression of enzymes involved in glycolysis and fatty acid synthesis [57]. In addition, ChREBP suppresses sirtuin 1, thereby likely reducing PGC-1α-dependent gluconeogenesis under glucose abundant conditions [58]. Somewhat counter-intuitively, ChREBP also induces G6Pc expression, a response that may serve to maintain the intracellular G6P homeostasis [59]. ChIP-seq analysis indicated that ChREBP not only regulates metabolism, but also targets genes related to transport, development, and cell motility [39].

Several studies have shown that hepatic ChREBP activation requires GCK-dependent glucose metabolism [28, 60]. Early work showed that the pentose phosphate pathway intermediate xylulose-5-phosphate (X5P) induces ChREBP dephosphorylation, thereby promoting its nuclear translocation and transcriptional activity [61]. However, this model has been challenged, based on the finding that pentose phosphate pathway inhibition leads to a decrease rather than an increase in ChREBP activity [62, 63]. Instead, G6P was suggested to be the major signaling metabolite responsible for ChREBP activation [62, 63]. Finally, fructose-2,6-bisphosphate (F2,6bisP), another glucose metabolite, has also been proposed to induce ChREBP-mediated transcription in hepatocytes [49, 64]. The mechanisms through which these three glucose derivatives act remain to be resolved, but likely involve changes in allosteric regulation and post-translational modifications [53, 65, 66]. In this respect, it should be noted that ChREBP activity is increased by acetylation and *O*-linked β-*N*-acetylglucosaminylation (*O*-GlcNAcylation) [67, 68], two enzyme-catalyzed post-translational modifications that use glucose metabolites as substrates, as will be discussed in more detail below [69–71]. The fact that several independent glucose metabolites (X5P, G6P, F2,6bisP, acetyl-CoA, and *O*-GlcNAc) activate hepatic ChREBP illustrates the unique glucose-sensing ability of this transcription factor in hepatocytes [57]. A recent study furthermore showed that glucose promotes the binding of full-length ChREBP-α to a ChoRE located in an alternative promoter region of the *Chrebp* gene thereby inducing transcription of a potent, short ChREBP isoform (ChREBP-β) [72]. Future work should identify the specific glucose-dependent pathways that induce and activate these different isoforms in hepatocytes, and reveal whether ChREBP-α and ChREBP-β regulate different target genes.

## Regulation of the central hepatic glucose-sensing axis

The GCK–ChREBP axis can be considered as the central glucose-sensing system in the liver. Because GCK acts as a gatekeeper for hepatic glucose metabolism and ChREBP activation [60, 73], regulation of its expression and activity will significantly impact hepatic glucose sensing. Interestingly, glucose increases GCKR expression while it inhibits GCK transcription in cultured hepatocytes [59]. However, in vivo GCK expression is induced in response to an oral glucose load [60]. Because insulin is a major regulator of GCK expression in the liver [31], the discrepancy between these findings can be explained by the lack of a concomitant insulin-mediated GCK transcription under in vitro conditions [74]. The mechanistic basis of insulin-dependent GCK induction is incompletely understood [31, 75]. Several transcription factors, i.e., hepatocyte nuclear factor 4 (HNF-4), hypoxia-inducible factor 1 (HIF-1), sterol regulatory binding protein-1c (SREBP-1c), liver x receptor (LXR), peroxisome proliferator activated receptor gamma (PPARγ), Kruppel-like factor 6 (KLF-6) and transcription factor E3 (TCFE3) have been shown to control hepatic GCK transcription [60, 76–82]. Studies from our laboratory have indicated that the nuclear receptor liver receptor homolog 1 (LRH-1) coordinates multiple aspects of hepatic intermediary metabolism by regulating GCK-dependent G6P synthesis [60, 83]. While initially identified as a transcriptional regulator of cholesterol and bile salt homeostasis [84, 85], LRH-1 has recently emerged as

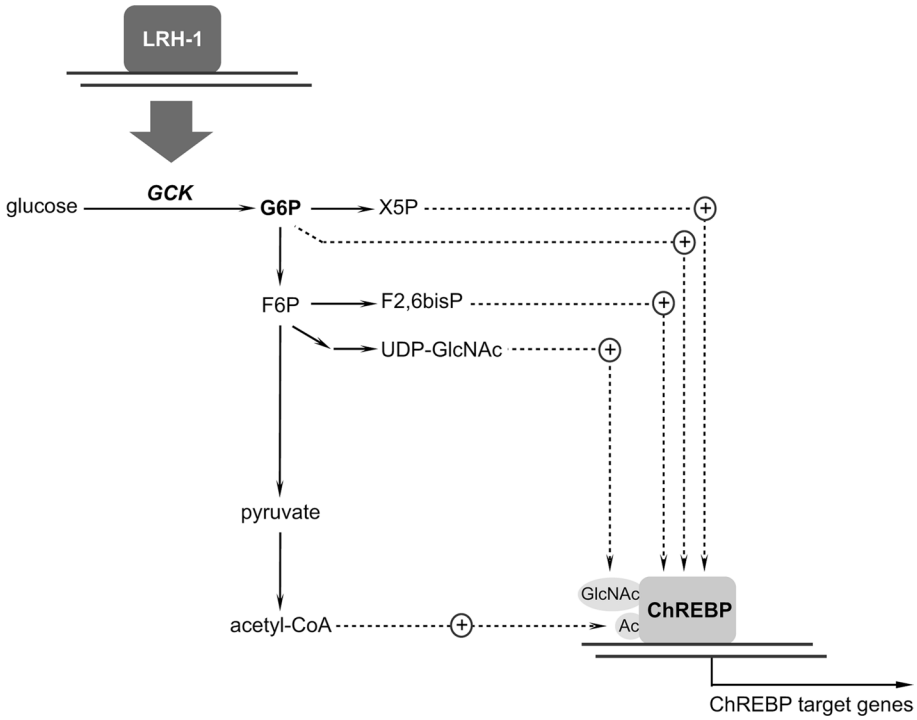


**Fig. 2** LRH-1 is an upstream regulator of the central glucose-sensing system in the liver. ChREBP activation requires GCK-dependent synthesis of glucose metabolites. Because LRH-1 is a transcriptional regulator of GCK, it impacts postprandial G6P synthesis and ChREBP activity. *Acetyl-CoA* acetyl-coenzyme A, *ChREBP* carbohydrate response element binding protein, *F2,6bisP* fructose-2,6-bisphosphate, *F6P* fructose-6-phosphate, *G6P* glucose-6-phosphate, *GCK* glucokinase, *LRH-1* liver receptor homolog 1, *UDP-GlcNAc* UDP-*N*-acetylglucosamine, *X5P* xylulose-5-phosphate

a key integrator of hepatic glucose and fatty acid metabolism [60, 83, 86, 87]. LRH-1 contributes to basal GCK expression under fed and fasted conditions and its activity is not dependent on glucose. This was based on the finding that ectopic LRH-1 expression is sufficient to induce *Gck* expression in hepatoma cells, and that increasing glycemia fails to amplify LRH-1-mediated transcription [60]. Hepatic LRH-1 deficiency significantly perturbed the hepatic response to feeding, as illustrated by delayed glycogen synthesis, as well as reduced ChREBP expression and activity, which resulted in a strong attenuation of glycolysis and de novo fatty acid synthesis upon refeeding [60]. Importantly, these perturbations occurred secondary to reduced GCK activity, as GCK reconstitution restored ChREBP target gene expression in hepatocyte-specific LRH-1 knockout mice [60]. LRH-1-dependent glucose sensing in the liver also affected systemic glucose homeostasis. In liver-specific LRH-1 knockout mice impaired GCK-mediated glucose consumption triggered the pancreas to release more insulin, leading to elevated insulin levels and increased glucose disposal [60]. These findings place LRH-1 upstream of the central glucose-sensing system in the liver (Fig. 2).

Similar functions have been attributed to LXR. Although LXR has been identified as a transcriptional regulator of both GCK and ChREBP [76, 88–92], its deficiency does not impair the hepatic response to carbohydrate refeeding or ChREBP activity [93, 94]. Further work will be necessary to establish whether LXR is essentially required for postprandial glucose sensing in the liver.

## Glucose-sensitive modifications as potential glucose sensors in the liver

Post-translational modifications of regulatory proteins allow for adaptive responses to a variety of metabolic cues [95, 96]. Interestingly, some post-translational modifications are closely linked to glucose metabolism and target metabolic enzymes, components of cellular signal transduction pathways as well as transcription factors and their co-regulators (reviewed in [97, 98]). These modifications are typically enzyme-catalyzed, but can also occur through non-enzymatic interaction between metabolites and proteins. Although enzyme-mediated transfer of glucose metabolites has been investigated most intensively, a very recent study has identified a glucose-sensitive and enzyme-independent post-translational modification that controls hepatocyte function [99]. It is now also increasingly recognized that glucose metabolism can induce epigenetic changes through glucose-dependent post-translational modification of histone proteins (reviewed in [96, 100–102]). Because the composition of the histone code determines the degree of chromatin condensation, glucose-dependent modification of histones may alter the accessibility for transcription factors and regulatory enzymes that may ultimately translate into changes in transcriptional activity. In this section, we will discus two enzyme-mediated glucose-sensitive post-translational modifications that target regulatory proteins and epigenome, and may as such contribute to glucose sensing in the liver. The metabolic origins, enzymatics, and hepatic

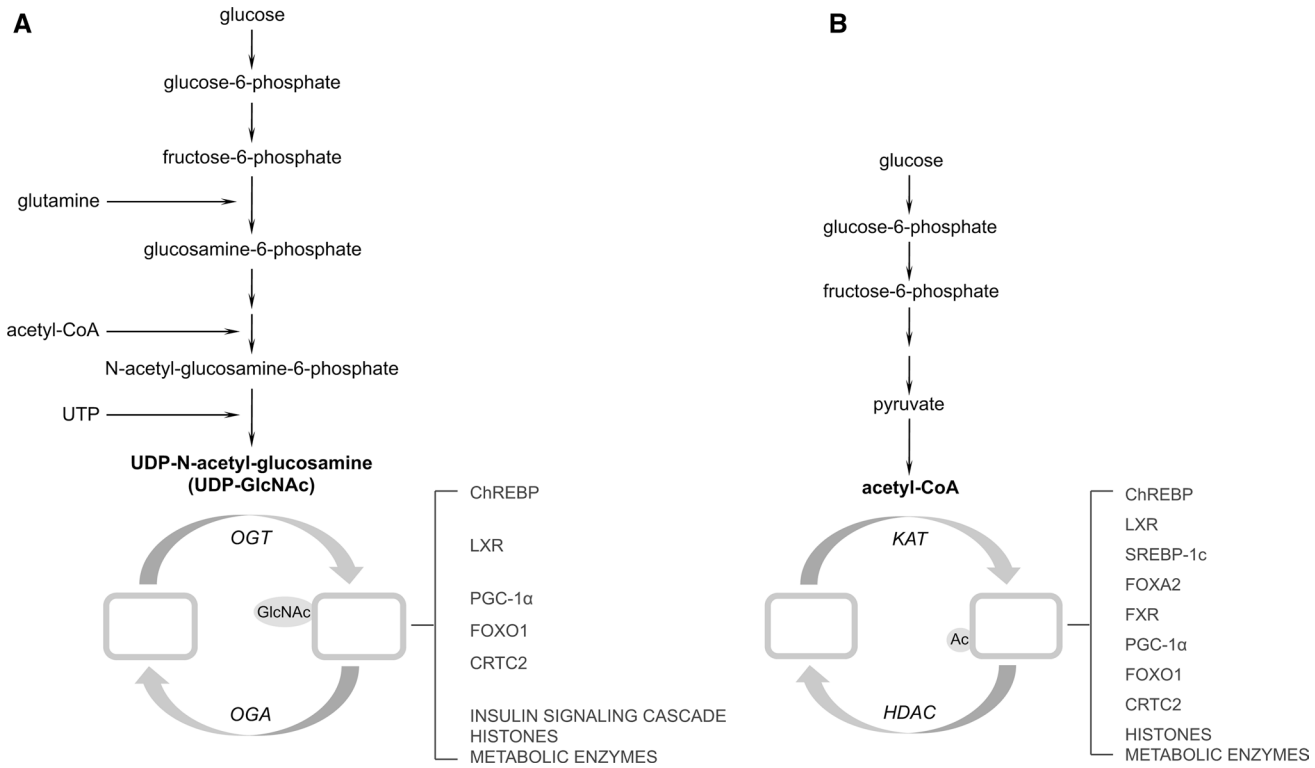


**Fig. 3** Working model depicting the metabolic origins, enzymatics, and targets of glucose-sensitive post-translational modifications in the liver. **a** The hexosamine biosynthesis pathway uses F6P, glutamine, and UTP for *O*-linked β-*N*-acetylglucosaminylation. **b** Glycolysis can link glucose metabolism to acetylation. *Acetyl-CoA* acetyl-coenzyme A, *ChREBP* carbohydrate response element binding protein, *CRTC2* cAMP-regulated transcriptional co-activator 2, *FOXA2* forkhead box protein A2, *FOXO1* forkhead box protein O1, *F6P* fructose-6-phosphate, *FXR* farnesoid x receptor, *HDAC* histone deacetylase, *KAT* lysine acetyltransferases, *LXR* liver x receptor, *OGA* *O*-GlcNAcase, *OGT* *O*-GlcNAc transferase, *PGC-1α* peroxisome proliferator-activated receptor gamma coactivator 1-alpha, *SREBP-1c* sterol regulatory element binding protein-1c, *TCA* tricarboxylic acid, *UTP* uridine triphosphate

targets of these post-translational modifications are summarized in Fig. 3.

*O*-GlcNAcylation of serine and threonine residues is a modification that occurs in the cytoplasm, nucleus, and mitochondria [103]. The substrate, UDP-*N*-acetylglucosamine (UDP-GlcNAc), is generated by the hexosamine biosynthesis pathway, a branch of hepatic glucose metabolism that uses F6P, glutamine, acetyl-CoA, and uridine triphosphate (UTP) [104]. The addition and removal of UDP-GlcNAc is catalyzed by two enzymes. *O*-GlcNAc transferase (OGT) mediates the addition of UDP-GlcNAc to target proteins while *O*-GlcNAcase (OGA) catalyzes its removal [105, 106]. Both OGT and OGA are encoded by single genes that are alternatively spliced in mammals, and the different isoforms are located in separate subcellular compartments [105, 107–110]. Their activities are regulated by protein–protein interactions and post-translational modifications including *O*-GlcNAcylation, however this domain is as yet largely unexplored [111]. *O*-GlcNAcylation is considered as a unique glucose-sensitive post-translational modification [112] and has wide-ranging effects on transcription, protein activity, and stability as well as on epigenetic and genomic imprinting (reviewed in [113]). In hepatocytes, *O*-GlcNAcylation has mainly been studied in relation to its role in metabolism. Recent work has shown that hepatic OGT is required to maintain circadian control of glucose homeostasis by regulating the clock system in the liver [114, 115]. OGT also targets metabolic transcriptional regulators such as LXR [90] and cAMP-regulated transcriptional co-activator 2 (CRTC2), a coregulator of the gluconeogenic transcription factor cyclic AMP-responsive element binding protein (CREB) [116]. Moreover, the activity of two other key gluconeogenic regulators, i.e., forkhead box protein O (FOXO1) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), is regulated by *O*-GlcNAcylation [117–119]. Another key finding is that OGT modifies multiple nodes of the insulin signaling pathway [108, 120]. Interestingly, under normoglycemic conditions *O*-GlcNAcylation contributes to insulin signaling [121], while it induces insulin resistance when chronically activated [120]. Although these studies point to a general role for *O*-GlcNAcylation in regulating glucose homeostasis, strong evidence for a more specific role in glucose-sensing stems from the fact

that *O*-GlcNAcylation activates hepatic ChREBP [68]. Finally, it should be mentioned that despite the fact that *O*-GlcNAcylation is emerging as a histone-modifying post-translational modification [122], there is currently no evidence that *O*-GlcNAcylation also contributes to hepatic glucose sensing via epigenetic regulation. As methodologies for high-throughput *O*-GlcNAc profiling are emerging [123, 124], more insight into the hepatic targets of *O*-GlcNAcylation and its potential contribution to hepatic glucose sensing is expected in the near future.

Acetylation is another post-translational modification that potentially reflects glucose availability. This modification involves the enzymatic transfer of acetyl-CoA, and is facilitated by lysine acetyltransferases (KATs) [125]. These enzymes act on the lysine residues of both histones and non-histone proteins in different cellular compartments. The reverse reaction is mediated by deacetylases, which can be divided into four classes. Class I, II, and IV deacetylases are considered as the classical histone deacetylases (HDACs). Class III deacetylases, better known as sirtuins, are structurally unrelated to HDACs. HDACs and sirtuins are localized in the mitochondria or cytoplasm, and are able to shuttle between the nucleus and the cytosol [126–129]. High-throughput analysis of human liver biopsies and liver cells has shown that many metabolic enzymes are acetylated [69, 130], either to modulate their activities or to direct them towards proteosomal or lysosomal degradation [131, 132]. Moreover, the activity of several transcriptional regulators of hepatic metabolism including ChREBP, LXR, CRTC2, PGC-1α, FOXO1, SREBP-1c, forkhead box protein A2 (FOXA2), and farnesoid x receptor (FXR), is known to be modified by acetylation [67, 133–140], in some cases in coordination with phosphorylation [134, 141]. Studies in yeast and mammalian cell cultures have shown that histone acetylation is dependent on subcellular acetyl-CoA concentrations [142–146]. Notably, glucose was shown to promote histone acetylation via ATP citrate lyase (ACL), the enzyme that generates acetyl-CoA from TCA-derived citrate in mammalian cell lines [142]. The existence of a similar mechanism in hepatocytes challenged with glucose would point to a glucose-sensing role of histone acetylation in liver but needs to be confirmed. The observation that both histones [147] and non-histone proteins [130] are dynamically acetylated in response to feeding/fasting cycles is also suggestive of glucose-dependent acetylation in liver. Moreover, it has been reported that hepatic acetyl-CoA levels increase upon short-term refeeding as compared to fasted conditions [148]. It should however be noted that besides being produced by decarboxylation of glycolytic pyruvate, hepatic acetyl-CoA can also be derived from fatty acid oxidation and amino acid metabolism. A dedicated analysis of acetylation profiles in glucose-challenged hepatocytes is therefore warranted to establish the impact of glucose metabolism on protein acetylation, as well as the potential contribution of protein acetylation to glucose sensing in the liver.

## Metabolic liver diseases associated with aberrant glucose sensing

Glucose sensors enable the liver to respond to dynamic changes in glucose availability. However, when these sensors are chronically activated, they may predispose to the development of liver diseases.

During poorly controlled diabetes, the liver is frequently exposed to hyperglycemic episodes. In type 2 diabetes (T2D), GCK is constitutively active and GCK flux is increased secondary to elevated glucose concentrations [149, 150]. This leads to sustained activation of glucose sensors in the liver. For example, the hexosamine biosynthesis pathway normally accounts for less than 5 % of the hepatic glucose flux, yet its activity is markedly increased by hyperglycemia [151, 152]. Aberrant glucose sensing in T2D results in triglyceride accumulation and excessive glucose production in the liver [116, 153]. While triglyceride accumulation contributes to the development of liver steatosis, increased hepatic glucose output leads to a further increase in glycemia.

A clear association exists between hepatic steatosis and the pathogenesis of T2D, cardiovascular disease, and steatohepatitis [154]. It is, however, increasingly recognized that, up to a certain threshold, the accumulation of triglycerides may serve as a buffering system that would actually protect the liver against metabolic dysfunction [154]. In mice, ChREBP plays a key role in the development of hepatic steatosis in T2D [153], and hepatic ChREBP function is perturbed in obese and (pre-)diabetic subjects [155, 156]. Interestingly, a recent study revealed that ChREBP overexpression protects against diet-induced glucose intolerance and insulin resistance [157]. This finding indicates that under conditions of dietary fat overload, ChREBP-mediated lipogenesis likely contributes to a metabolically benign state by promoting mono-unsaturated fatty acid synthesis [154, 157]. It was furthermore shown that diabetic steatosis is associated with ChREBP hyperacetylation [67] and that hepatic lipid accumulation can be prevented when ChREBP *O*-GlcNAcylation is reduced [68]. Increased *O*-GlcNAcylation also contributes to uncontrolled hepatic glucose production under diabetic conditions. T2D is associated with increased *O*-GlcNAcylation levels of the gluconeogenic co-regulator CRTC2 and removal of *O*-GlcNAc from CRTC2 normalizes glycemia in diabetic mice [116]. Whether sustained CRTC2 acetylation levels also promote hepatic glucose production in diabetics remains to be established. Likewise, it is as yet unknown whether

aberrant acetylation and *O*-GlcNAcylation of the gluconeogenic regulators FOXO1 and PGC-1α [117–119, 135, 158] directly contribute to hyperglycemia in T2D.

Glucose sensors may also become deregulated by inherited loss-of-function mutations in enzymes that regulate intrahepatic glucose metabolism. An example of such an "inborn error of metabolism" is Glycogen Storage Disease type 1 (GSD-1) [159] which is caused by loss of either G6Pc or G6Pt activity [160–162]. The primary consequences of perturbed hepatic G6Pase activity in GSD-1 are hypoglycemia and the accumulation of G6P in the liver [163–165]. In addition, GSD-1 is characterized by excessive glycogen and lipid storage in the liver [163, 165–167] as well as hyperlipidemia [165, 167–170]. Interestingly, GSD-1 is associated with a ChREBP-dependent increase in de novo fatty acid synthesis [163, 167, 170]. Combined, these observations indicate that sustained activation of hepatic glucose sensors by extrahepatic (diabetes) or intrahepatic (GSD-1) changes in glucose homeostasis predisposes to development of hepatic steatosis [171].

Another consequence of both T2D and GSD-1 is the increased incidence of liver tumorigenesis [172–175]. Although steatosis has been proposed as a predisposing factor for liver cancer [176, 177], altered metabolism may be the actual driving force for tumor development. It is well known that tumors require specific metabolic adaptations to support the bioenergetic and biosynthetic demands of growth and proliferation [178]. More specifically, a switch to non-oxidative glucose metabolism combined with a predominant anabolic role of the TCA cycle are considered as major hallmarks of cancer metabolism [179]. T2D and GSD-1 are characterized by a high flux from hepatic G6P towards glycolysis and lipid- and nucleotide biosynthesis. The exact mechanisms by which these metabolic adaptations confer a preneoplastic status to hepatocytes and direct them towards tumorigenesis are incompletely understood [165, 172, 179]. Glucose sensors likely play an important role here. In support of this hypothesis, ChREBP mediates the switch towards pro-oncogenic metabolism in proliferating cells [180]. Moreover, ChREBP functionally interacts with the pro-oncogenic transcription factor c-Myc, which is critical for ChREBP-dependent glucose sensing in the liver [45, 181, 182]. Because mouse models of T2D and GSD-1 exhibit increased hepatic ChREBP activity [153, 163], ChREBP may play a key role in the pathophysiology of liver tumor development in these diseased states. The potential existence of such a mechanism urges for the exploration of a potential oncogenic role of hepatic LRH-1, a potent upstream regulator of the GCK–ChREBP axis in the liver ([60] and Fig. 2) and a key player in the development of colorectal, breast and pancreatic cancers [183–185]. Finally, acetylation and *O*-GlcNAcylation have recently emerged as critical modifiers of the activity of metabolic enzymes as well as of oncogenes and tumor suppressors in cancer cells [123, 186–190]. These glucose-sensing post-translational modifications may therefore direct hepatocytes towards a pro-oncogenic state under conditions of excessive hepatic glucose metabolism [142, 191, 192].

## Conclusions and future directions

Hepatic glucose sensing is critical for an adequate postprandial response and the maintenance of glycemic control. However, it may also contribute to liver pathology under conditions of excessive intrahepatic glucose metabolism. Research in the past years has identified GCK–ChREBP as the central glucose-sensing system in the liver. Further exploration of the mechanisms by which different glucose metabolites activate hepatic ChREBP, and the function of the different ChREBP isoforms are required to unravel the mechanistic basis of the glucose-sensing axis. In addition, it remains to be established whether ChREBP's paralog MondoA, which can be activated by G6P and F2,6bisP [49, 56], also contributes to postprandial glucose sensing in the liver.

Because LRH-1 has recently emerged as a potent upstream regulator of the GCK–ChREBP axis, modulation of its activity may provide opportunities for the treatment of diseases that are characterized by aberrant hepatic glucose sensing. LRH-1 transcriptional activity can be modified by post-translational modifications or by agonists/antagonist binding, and depends on its interaction with co-regulators [83, 183, 193–204]. Detailed insight into these processes is therefore needed to define strategies that target LRH-1-dependent glucose sensing.

Finally, dedicated studies are required to uncover the exact role of *O*-GlcNAcylation and acetylation in hepatic glucose sensing. Systematic analysis of glucose-dependent responses in the absence of OGT or KAT activity will establish to what extent, and via which mechanisms these post-translational modifications contribute to glucose-sensing system in the liver. Moreover, there is extensive crosstalk between post-translational modifications, and different combinations of post-translational modifications on a single target may lead to distinct biological outcomes [112, 205]. Future research will likely uncover novel interplays between GlcNAcylation/acetylation and other post-translational modifications including protein ubiquitination and methylation (reviewed in [206, 207]). Such crosstalk may in turn unveil unexpected functions and consequences of chronically activated hepatic glucose sensors that go beyond metabolism.

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