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Energy Metabolism in the Liver

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Abstract

The liver is an essential metabolic organ, and its metabolic activity is tightly controlled by insulin and other metabolic hormones. Glucose is metabolized into pyruvate through glycolysis in the cytoplasm, and pyruvate is completely oxidized to generate ATP through the TCA cycle and oxidative phosphorylation in the mitochondria. In the fed state, glycolytic products are used to synthesize fatty acids through *de novo* lipogenesis. Long-chain fatty acids are incorporated into triacylglycerol, phospholipids, and cholesterol esters in hepatocytes, and these complex lipids are stored in lipid droplets and membrane structures, or secreted into the circulation as VLDL particles. In the fasted state, the liver secretes glucose through both breakdown of glycogen (glycogenolysis) and *de novo* glucose synthesis (gluconeogenesis). During pronged fasting, hepatic gluconeogenesis is the primary source of endogenous glucose production. Fasting also promotes lipolysis in adipose tissue to release nonesterified fatty acids which are converted into ketone bodies in the liver though mitochondrial β oxidation and ketogenesis. Ketone bodies provide a metabolic fuel for extrahepatic tissues. Liver metabolic processes are tightly regulated by neuronal and hormonal systems. The sympathetic system stimulates, whereas the parasympathetic system suppresses, hepatic gluconeogenesis. Insulin stimulates glycolysis and lipogenesis, but suppresses gluconeogenesis; glucagon counteracts insulin action. Numerous transcription factors and coactivators, including CREB, FOXO1, ChREBP, SREBP, PGC-1α, and CRTC2, control the expression of the enzymes which catalyze the rate-limiting steps of liver metabolic processes, thus controlling liver energy metabolism. Aberrant energy metabolism in the liver promotes insulin resistance, diabetes, and nonalcoholic fatty liver diseases (NAFLD).

Introduction

The liver is a key metabolic organ which governs body energy metabolism. It acts as a hub to metabolically connect to various tissues, including skeletal muscle and adipose tissue. Food is digested in the gastrointestinal (GI) tract, and glucose, fatty acids, and amino acids are absorbed into the bloodstream and transported to the liver through the portal vein circulation system. In the postprandial state, glucose is condensed into glycogen and/or converted into fatty acids or amino acids in the liver. In hepatocytes, free fatty acids are esterified with glycerol-3-phosphate to generate triacylglycerol (TAG). TAG is stored in lipid droplets in hepatocytes or secreted into the circulation as very low-density lipoprotein (VLDL) particles. Amino acids are metabolized to provide energy or used to synthesize proteins, glucose, and/or other bioactive molecules. In the fasted state or during exercise, fuel substrates (e.g. glucose and TAG) are released from the liver into the circulation and metabolized by muscle, adipose tissue, and other extrahepatic tissues. Adipose tissue

produces and releases nonesterified fatty acids (NEFAs) and glycerol via lipolysis. Muscle breaks down glycogen and proteins and releases lactate and alanine. Alanine, lactate, and glycerol are delivered to the liver and used as precursors to synthesize glucose (gluconeogenesis). NEFAs are oxidized in hepatic mitochondria through fatty acid β oxidation and generate ketone bodies (ketogenesis). Liver-generated glucose and ketone bodies provide essential metabolic fuels for extrahepatic tissues during starvation and exercise.

Liver energy metabolism is tightly controlled. Multiple nutrient, hormonal, and neuronal signals have been identified to regulate glucose, lipid, and amino acid metabolism in the liver. Dysfunction of liver signaling and metabolism causes or predisposes to nonalcoholic fatty liver disease (NAFLD) and/or type 2 diabetes.

1. LIVER GLUCOSE METABOLISM

Hepatocytes are the main cell type in the liver (~80%). Blood glucose enters hepatocytes via GLUT2, a plasma membrane glucose transporter. Hepatocyte-specific deletion of *GLUT2* blocks hepatocyte glucose uptake (231). GLUT2 also mediates glucose release from the liver; however, deletion of *GLUT2* does not affect hepatic glucose production in the fasted state (231), suggesting that glucose is able be released from hepatocytes through additional transporters (e.g. GLUT1) or by other mechanisms. Glucose is phosphorylated by glucokinase in hepatocytes to generate glucose 6-phosphate (G6P), leading to a reduction in intracellular glucose concentrations which further increases glucose uptake (Fig. 1). Moreover, G6P is unable to be transported by glucose transporters, so it is retained within hepatocytes. In the fed state, G6P acts as a precursor for glycogen synthesis (Fig. 1). It is also metabolized to generate pyruvate through glycolysis. Pyruvate is channeled into the mitochondria and completely oxidized to generate ATP through the tricarboxylic acid (TCA) cycle (Fig. 1) and oxidative phosphorylation. Alternatively, pyruvate is used to synthesize fatty acids through lipogenesis (Fig. 3). G6P is also metabolized via the pentose phosphate pathway to generate NADPH (Fig. 1). NADPH is required for lipogenesis and biosynthesis of other bioactive molecules. In the fasted state, G6P is transported into the endoplasmic reticulum (ER) and dephosphorylated by glucose-6-phosphatase (G6Pase) to release glucose.

1.1. Glycogen metabolism

In the fed state, glucose enters hepatocytes via GLUT2 and is phosphorylated by glucokinase and used to synthesize glycogen by glycogen synthase (4). In the fasted state, glycogen is hydrolyzed by glycogen phosphorylase to generate glucose (glycogenolysis) (Fig. 1). G6P is a precursor for glycogen synthesis, and it also is an allosteric inhibitor of glycogen phosphorylase and an allosteric activator of glycogen synthase, thus further increasing liver glycogen levels (4). The activity of both glycogen synthase and glycogen phosphorylase is also regulated by posttranslational modifications. Phosphorylation of glycogen synthase, mainly by glycogen synthase kinase 3 (GSK-3), inhibits glycogen synthase activity; in contrast, phosphorylation of glycogen phosphorylase increases its activity. Both glycogen synthase and glycogen phosphorylase are able to be

dephosphorylated by protein phosphatase 1. In the fed state, pancreatic β cells secret insulin in response to an increase in blood glucose, amino acids, and fatty acids. Insulin stimulates glycogen synthase by activating Akt which phosphorylates and inactivates GSK-3, thus increasing glycogen synthesis. Insulin stimulates acetylation of glycogen phosphorylase, which promotes dephosphorylation and inhibition of glycogen phosphorylase by protein phosphatase 1, thus suppressing glycogenolysis (288). Insulin stimulates the expression of glucokinase which increases hepatocyte glucose uptake indirectly by phosphorylating glucose and generating G6P (4). G6P in turn stimulates glycogen synthesis and inhibits glycogenolysis. Additionally, in the fasted state, the GI secretes fibroblast growth factor 15/19 (FGF15/19) which also stimulates glycogen synthesis (112). FGF15/19 stimulates the ERK/RSK pathway by activating its receptors FGFR4 and β-klotho, and activated RSK phosphorylates and inactivates GSK-3, a negative regulator of glycogen synthase (112).

In the fasted state, insulin and FGF15/19 secretion is downregulated, leading to inhibition of glycogen synthase and activation of glycogen phosphorylase. Moreover, glucagon and catecholamines (e.g. epinephrine and norepinephrine), collectively called counterregulatory hormones, are secreted from pancreatic α cells and the adrenal medulla, respectively. These counterregulatory hormones bind to their cognate G protein-coupled receptors and activate protein kinase A (PKA) by increasing intracellular cAMP levels. PKA phosphorylates and activates glycogen phosphorylase directly or indirectly by phosphorylating and activating phosphorylase kinases. Glucagon inhibits acetylation of glycogen phosphorylase, which decreases the ability of protein phosphatase 1 to bind to, dephosphorylate, and inactivate glycogen phosphorylase (288). Glycogen is also able to be hydrolyzed to generate glucose through autophagy in the fasted state (116).

1.2. Gluconeogenesis

During short-term fasting periods, the liver produces and releases glucose mainly through glycogenolysis. During prolonged fasting, glycogen is depleted, and hepatocytes synthesize glucose through gluconeogenesis using lactate, pyruvate, glycerol, and amino acids (Fig. 1). These gluconeogenic substrates are either generated in the liver or delivered to the liver through the circulation from extrahepatic tissues. Lactate is oxidized by lactate dehydrogenase to generate pyruvate. Pyruvate is transported into the mitochondria and converted to oxaloacetate by pyruvate carboxylase (Fig. 1). Oxaloacetate is reduced to malate by mitochondrial malate dehydrogenase, exported into the cytoplasm, and oxidized by cytoplasmic malate dehydrogenase to regenerate oxaloacetate. Cytoplasmic oxaloacetate is converted to phosphoenolpyruvate by cytoplasmic phosphoenolpyruvate carboxylase (PEPCK-C), a key step of gluconeogenesis. Systemic deletion of *PEPCK-C* causes postnatal death within 3 days after birth (233). Mice with hepatocyte-specific deletion of *PEPCK-C* are viable but are unable to produce glucose from lactate and amino acids via gluconeogenesis, leading to accumulation of TCA cycle intermediates in hepatocytes and hepatic steatosis in the fasted state (21). However, liver-specific PEPCK-C knockout mice are able to generate glucose from glycerol and maintain relatively normal blood glucose levels after 24 h of fasting (21, 233). Phosphoenolpyruvate, after multiple biochemical reactions, is converted into fructose 1,6-biphosphate (F1,6P) which is then dephosphorylated by fructose 1,6 bisphosphatase (FBPase) to generate fructose-6-phosphate (F6P). F6P is

converted to G6P, transported into the ER, and dephosphorylated by G6Pase to generate glucose. Dephosphorylation of G6P is a rate-limiting step common for both glycogenolysis and gluconeogenesis. Mice with hepatocyte-specific deletion of *G6Pase* (which encodes the catalytic subunit) develop hyperlipidemia, lactic acidosis, uricemia, and hepatomegaly with glycogen accumulation and hepatic steatosis (175). Glycerol enters into hepatocytes via aquaporin-9 and is phosphorylated by glycerol kinase to generate glycerate-3 phosphate, a precursor for gluconeogenesis (92). Amino acids are converted to α-ketoacids through deamination reactions catalyzed by glutaminase, glutamate dehydrogenase, and/or aminotransferase. The α-ketoacids are further converted to intermediates of the TCA cycle (e.g. pyruvate, oxaloacetate, fumarate, succinyl-CoA, or α-ketoglutarate) which serve as precursors for gluconeogenesis.

1.2.1. Gluconeogenesis is regulated by the availability of gluconeogenic substrates—The rate of gluconeogenesis is determined by both the availability of gluconeogenic substrates and the expression/activation of gluconeogenic enzymes (e.g. PEPCK-C and G6Pase) which control key steps of gluconeogenesis (Fig. 1). During exercise or fasting, skeletal muscles produce pyruvate through glycogenolysis and glycolysis. Pyruvate has two fates. It can be catabolized by mitochondrial pyruvate dehydrogenase complex (PDC) to produce acetyl-CoA, which is then completely oxidized in the TCA cycle (Fig. 1). Alternatively, pyruvate can be converted into lactate, released into the circulation, and utilized by hepatocytes to produce glucose through gluconeogenesis. PDC is phosphorylated and inactivated by pyruvate dehydrogenase kinases (PDKs, 4 isoforms) (Fig. 1), and it is dephosphorylated and activated by pyruvate dehydrogenase phosphatases (93). PDK2 and PDK4 levels are higher in the fasted state and in diabetes (93). Deletion of *PDK4* increases PDC activity, which allows pyruvate to be channeled to the TCA cycle for complete oxidation (95). As a result, pyruvate is not available for gluconeogenesis, leading to hypoglycemia in fasted PDK4 knockout mice (95). Glycerol, which is released from adipose tissue through lipolysis, is also a gluconeogenic substrate. Fatty acid β oxidation is unable to produce gluconeogenic substrates, but it does generate ATP which is required for gluconeogenesis. Prolonged starvation leads to protein degradation and release of amino acids, which are important gluconeogenic substrates.

1.2.2. Gluconeogenesis is regulated by gluconeogenic enzymes—Gluconeogenic enzymes are regulated by posttranslational modifications and/or allosteric regulation. Most liver enzymes, which regulate glycolysis, gluconeogenesis, the TCA cycle, the urea cycle, and fatty acid and glycogen metabolism, are acetylated (292). Acetylation states of these enzymes are regulated by nutrient availability (292). Glucose stimulates acetylation of PEPCK-C by p300, which promotes PEPCK-C ubiquitination and degradation (97). In contrast, cytosolic SIRT2 deacetylates and stabilizes PEPCK-C (97), which may contribute to increased gluconeogenesis in the fasted state. Fructose-2,6-bisphosphate (F-2,6-P2), which is derived from G6P (Fig. 1), binds to FBPase and inhibits the catalytic activity of FBPase, thus inhibiting gluconeogenesis in the fed state (215).

1.2.3. Gluconeogenesis is controlled by multiple transcription factors and coregulators—Hepatic gluconeogenesis is largely controlled in by transcriptional

regulation of the enzymes which catalyze the key reactions of gluconeogenesis. Numerous transcription factors, including CREB, FOXO1, and C/EBPα/β, have been identified to stimulate the expression of PEPCK-C and G6Pase. CREB is a well-documented gluconeogenic transcription factor which is activated by PKA-mediated phosphorylation, and it stimulates the expression of PEPCK-C, G6Pase, and peroxisome proliferator γ-activated receptor coactivator 1-α (PGC-1α) (75). Inhibition of liver CREB, by liver-specific transgenic overexpression of a dominant negative form of CREB, decreases the expression of PEPCK-C, G6Pase, and PGC-1α, leading to reduced hepatic glucose production (HGP) and hypoglycemia (75). Knockdown of CREB in the liver reduces HGP in rodents with type 2 diabetes (52). Hepatocyte-specific deletion of *FOXO1* decreases both glycogenolysis and gluconeogenesis in fasted mice, leading to hypoglycemia (158). Deletion of *C/EBP*α also decreases gluconeogenesis, and the mutant mice die from hypoglycemia within 8 h after birth (261). C/EBPα stimulates the expression of carbamoyl phosphate synthetase-1 (CPS-1) which controls the rate-limiting reaction of the urea cycle; therefore, C/EBPα is able to increase production of gluconeogenic substrates by promoting amino acid catabolism (89, 111). However, hepatocyte-specific deletion of *C/EBP*α does not affect the expression of PEPCK-C and G6Pase, and the mutant mice have normal blood glucose levels (89). These observations suggest that other C/EBP family members may have a compensatory function in the mutant mice, and indeed, deletion of *C/EBPβ* also decreases HGP and blood glucose in mice (144).

Several coactivators have been described to stimulate the expression of PEPCK-C and G6Pase in the liver. Both p300/CBP and cAMP-regulated transcriptional coactivator 2 (CRTC2) binds to CREB and stimulate the expression of PEPCK-C and G6Pase, thus increasing hepatic gluconenogenesis (115, 295). Systemic deletion of *CRTC2* impairs both the expression of liver gluconeogenic genes and the ability of glucagon to stimulate glucose production in hepatocytes (123, 264). PGC-1α is higher in the fasted state and in diabetes (75, 284), and it promotes gluconeogenesis by coactivating HNF-4α (284). Steroid receptor coactivator-1 (SRC-1) coactivates C/EBPα and promotes expression of pyruvate carboxylase and other gluconeogenic genes, and deletion of *SRC-1* results in hypoglycemia (149). SRC-2 stimulates *G6Pase* promoter activity by coactivating retinoid-related orphan receptor α (RORα), and genetic deletion of *SRC-2* results in decreased G6Pase expression and hypoglycemia in fasted mice (38).

1.3. Gluconeogenesis is regulated by metabolic states and the circadian clock

Low energy states under fasting conditions are associated with activation of both SIRT and AMPK family members, whereas high energy states are associated with mTORC1 activation. SIRT, AMPK, and mTORC1 are considered molecular energy sensors. Many gluconeogenic transcriptional regulators are substrates of SIRT1, AMPK and/or TORC1. PGC-1α is acetylated by GCN5, and acetylation decreases the ability of PGC-1α to activate gluconenogenic genes (133). SIRT1 deacetylates PGC-1α, thus increasing its ability to coactivate HNF-4α for gluconeogenesis (216). Knockdown of SIRT1 in the liver decreases hepatic gluconeogenesis in mice with obesity (53, 217). Surprisingly, mice with hepatocyte-specific deletion of *SIRT1* appear to be able to maintain relatively normal blood glucose levels (32, 270). Hepatic gluconeogenesis is even higher in these mice (263). In addition to

deacetylating PGC-1α, SIRT1 also deacetylates CRTC2 during prolonged fasting, leading to degradation of CRTC2 and decreased gluconeogenesis (146). Both SIRT3 and SIRT5 are located in mitochondria, and their activity is higher in the fasted state (69, 179). SIRT3 deacetylates and activates ornithine transcarbmoylase (OTC), a key enzyme of the urea cycle (69). SIRT5 deacetylates and activates CPS-1 (179). Mitochondrial SIRT3 and SIRT5 are able to increase gluconeogenic substrate availability and hepatic gluconeogenesis during starvation by stimulating amino acid catabolism. The LKB1/AMP pathway suppresses hepatic glucose production. AMPK phosphorylates CRTC2 and blocks nuclear translocation of CRTC2, thus inhibiting the ability of CRTC2 to promote hepatic gluconeogenesis (115). Genetic deletion of *AMPKα2* in the liver increases hepatic gluconeogenesis and glucose intolerance (5). Liver-specific deletion of *LKB1* also increases hepatic gluconeogenesis and blood glucose levels (232). S6 kinase, a downstream effector of mTORC1, phosphorylates PGC-1α and inhibits its ability to bind to HNF-4α, thus inhibiting gluconeogenesis (152).

Circadian clock genes have been reported to regulate hepatic gluconeogenesis. Cryptochrome 1 (Cry1) and Cry2 bind to and inhibit glucocorticoid receptors (GR) (121). Glucocorticoids are important counterregulatory hormones and stimulate hepatic gluconeogenesis. Cry1 also inhibits the ability of glucagon, another important counterregulatory hormone, to stimulate HGP by uncoupling glucagon receptors from G α (287). Ubiquitin-specific protease 2 (UPS2) is a clock-regulated gene in the liver, and it increases hepatic gluconeogenesis by stimulating the expression of 11-hydroxysteroid dehydrogenase 1 (HSD1) (168). HSD1 converts inactive glucocorticoids into their active forms.

1.4. Regulation of gluconeogenesis by the ER

The ER is able to both positively and negatively regulate hepatic gluconeogenesis depending on the cellular context and the nature of downstream signaling pathways. CREBH is an ER-membrane protein, and its levels are higher in the fasted state (128). CREBH binds to CRTC2 and promotes the expression of gluconeogenic genes, including PEPCK-C and G6Pase (128). ER stress activates the unfolded protein response (UPR). Three UPR pathways, the protein kinase-like ER kinase (PERK)/elF2α, the inositol-requiring enzyme 1 (IRE1)/XBP1, and the ATF6 pathways, have been extensively characterized (101). The PERK/elF2α pathway stimulates HGP by increasing translation of C/EBPα and C/EBPβ (191). In contrast, XBP1 is able to bind to FOXO1 and target FoxO1 for degradation, thus inhibiting the hepatic gluconeogenesis (296). ATF6 binds to CRTC2 and inhibits the expression of gluconeogenic genes by sequestering CRTC2 from CREB (266). Moreover, chronic activation of the UPR pathways promotes insulin resistance, thus indirectly increasing HGP (101, 193).

1.5. Insulin suppresses hepatic gluconeogenesis

Insulin potently suppresses gluconeogenesis, and hepatocyte-specific deletion of insulin receptors markedly increases hepatic gluconeogenesis in mice, resulting in hyperglycemia and glucose intolerance (165). Insulin resistance is a determinant for the development of type 2 diabetes, and it also contributes to the pathogenesis of NAFLD. Insulin receptors bind to IRS1 and IRS2 and phosphorylate them on tyrosine residues (223, 272). Hepatocyte

growth factor receptor Met is able to form a hybrid complex with insulin receptors in the liver to promote insulin signaling (55). Tyrosine phosphorylated IRS proteins activate the PI 3-kinase/Akt pathway (223, 272). Liver-specific inhibition of either *IRS1* or *IRS2* partially impairs insulin action; deletion of both *IRS1* and *IRS2* in the liver completely blocks hepatic insulin action, resulting in increased hepatic gluconeogenesis, hyperglycemia, and type 2 diabetes (49). Insulin stimulates mTORC2, which phosphorylates Akt at Ser473 and enhances Akt activity (90). Mice with hepatocyte-specific deletion of *rictor*, an essential component of the mTORC2 complex, have higher hepatic gluconeogenesis and develop hyperglycemia and insulin resistance (68). Akt phosphorylates and inactivates FOXO1 in the liver, thus suppressing gluconeogenesis (Fig. 3A) (67, 158, 178, 204). In contrast, MAPK phosphatase-3 (MKP-3) dephosphorylates FOXO1 at pSer256 and promotes nuclear translocation of FOXO1, which activates gluconeogenic genes and increases hyperglycemia (276). FOXO1 activity is also regulated by additional mechanisms. FOXO1 is acetylated on multiple sites by p300/CBP, and acetylation decreases the ability of FOXO1 to bind to the promoters of its target genes (162). FOXO1 interacts with C/EBPα, and these two proteins act cooperatively to promote gluconeogenesis (229). Wnt ligands in the liver are higher in the fasted state, and they increase the expression of PEPCK-C and G6Pase by stimulating the binding of β-catenin to FOXO1; deletion of *β-catenin* impairs HGP (143).

In addition to FOXO1, insulin also stimulates phosphorylation of FOXO3, FOXO4, and FOXO6 by Akt and inhibits their ability to stimulate hepatic gluconeogenesis (67, 105). Insulin stimulates phosphorylation of PGC-1α by Akt and decreases the ability of PGC-1α to activate gluconeogenic genes (Fig. 2A) (138). Insulin still suppresses HGP in mice with liver-specific triple knockout of Akt1, Akt2, and FoxO1 (150), suggesting that insulin is able to suppress HGP by Akt1/2/FOXO1-independent mechanisms. Insulin stimulates activation of SIK2 which phosphorylates CRTC2 and promotes cytoplasmic translocation and degradation of CRTC2, thus suppressing gluconeogenesis in hepatocytes (Fig. 2A) (46). Insulin also stimulates phosphorylation of CBP on Ser^{436} by atypical PKCι/λ, which disrupts the CREB/CBP/CRTC2 complex and inhibits gluconeogenesis (Fig. 2A) (72, 295); however, mice with liver-specific deletion of *CBP* have relatively normal insulin sensitivity, hepatic glucose production, and blood glucose (11).

1.6. Glucagon stimulates hepatic gluconeogenesis

Glucagon is secreted from pancreatic α cells, and glucagon secretion is higher in the fasted state and during exercise (268). Genetic depletion of pancreatic α cells causes glucagon deficiency, resulting in improved glucose tolerance and decreased gluconeogenic gene expression, HGP, and blood glucose in the fasted state (70). Systemic deletion of glucagon receptors decreases blood glucose levels and improves glucose tolerance (62, 196). Glucagon receptor knockout mice resist diet-induced obesity, glucose intolerance, and hepatic steatosis (40). Streptozotocin (STZ)-induced insulin deficiency is associated with increased α cell number and hyperglucagonemia, and deletion of glucagon receptors decreases hepatic gluconeogenesis and fully rescues STZ-induced hyperglycemia and glucose intolerance (129). Silencing of liver glucagon receptors also reduces blood glucose and improves glucose tolerance in *db/db* mice and Zucker diabetic fatty rats (140, 238). Glucagon receptors, members of the G protein-coupled receptor family, activate the Gα-

cAMP-PKA pathway (96). Liver-specific deletion of *G*α results in glucagon resistance, hypoglycemia, and reduced expression of gluconeogenic genes (34). PKA phosphorylates and activates CREB which stimulates hepatic gluconeogenesis (Fig. 2B). CRTC2, a critical CREB coactivator, is phosphorylated by SIK2, and phosphorylated CRTC2 is then translocated from the nucleus to the cytoplasm, ubiquitinated, and degraded (46). PKA promotes dephosphorylation of CRTC2 and inhibits CRTC2 degradation (Fig. 2B) (146). PKA also phosphorylates and activates inositol-1,4,5-triphosphate receptors (IP3Rs), thus increasing the release of Ca^{2+} from the ER into the cytoplasm (Fig. 2B) (265). Ca^{2+} activates calcineurin which in turn dephosphorylates and stabilizes CRTC2, thus promoting gluconeogenesis (265). Glucagon also stimulates acetylation of CRTC2 by p300/CBP, which increases both the stability and gluconeogenic activity of CRTC2 (146).

Aside from stimulating the CREB/CRTC2 pathway, glucagon is able to stimulate gluconeogenesis through additional mechanisms. Glucagon stimulates Ca^{2+} release from the ER in hepatocytes via PKA-mediated phosphorylation of IP3R as described above. Ca^{2+} activates CaMKII which in turn promotes nuclear translocation of FOXO1 (Fig. 2B) (192). Hepatic gluconeogenesis is lower in CaMKIIγ null mice, and liver-specific overexpression of CaMKII increases gluconeogenesis (192). CaMKII activates p38 MAPK which in turn increases nuclear translocation and activity of FOXO1 (192). Activation of the p38 MAPK pathway stimulates HGP (26). FOXO1 is acetylated at multiple sites by p300/CBP, which reduces its ability to bind to the promoters of its target genes (162). Glucagon promotes deacetylation of FOXO1 (166). Glucagon stimulates dephosphorylation and nuclear translocation of HDAC4/5/7 which interact with both HDAC3 and FOXO1 at the promoters of FOXO1 target genes (Fig. 2B), thus allowing HDAC3 to deacetylate and activate FOXO1 (166). Glucagon also stimulates phosphorylation of IRE1α by PKA, and silencing of hepatic IRE1α impairs HGP (155).

1.7. Regulation of gluconeogenesis by growth hormone (GH) and nuclear receptors

GH and glucocorticoids are important counterregulatory hormones. GH stimulates the JAK2/STAT5 pathway (174). STAT5 directly binds to and stimulates the *PEPCK-C* promoter (110). GH also stimulates the expression of PDK4 through STAT5 (109). PDK4 phosphorylates PDC and inhibits PDC activity (94, 95), which blocks TCA cycle-mediated oxidation of pyruvate, thus channeling pyruvate to gluconeogenesis. The gluconeogenic action of GH is negatively regulated by multiple factors, including bile acids and fibroblast growth factor (FGF) 21. Bile acids activate nuclear receptor farnesoid X receptor (FXR) which stimulates the expression of SHP, a transcription repressor (249). SHP in turn inhibits the ability of STAT5 to bind to *PEPCK-C* and *PDK4* promoters (109, 110), thus inhibiting hepatic gluconeogenesis. Liver-specific overexpression of constitutively active FXR decreases blood glucose (290). FGF21 is largely produced and secreted by hepatocytes (9, 85). It decreases STAT5 levels and causes GH resistance in the liver in an autocrine fashion, thus inhibiting GH-stimulated HGP (86).

The glucocorticoid receptor (GR), a member of the nuclear receptor family, resides primarily in the cytoplasm in quiescent cells in a complex with chaperones heat shock protein (HSP) 90 and HSP70 and cochaperones HSP40 and p23 (257). Ligand binding stimulates nuclear

translocation of GR, which activates gluconeogenic genes (273). Hepatocyte-specific deletion of *GR* decreases both the expression of gluconeogenic genes and blood glucose levels in the fasted state and protects against STZ-induced hyperglycemia (190). Knockdown of GR in the liver also inhibits the expression of gluconeogenic genes and reduces hyperglycemia in *db/db* mice (131). HDAC6 dephosphorylates HSP90 and promotes GR-HSP90 complex assembly, and deletion of *HDAC60* blocks ligand-induced nuclear translocation of GR and GR-stimulated expression of gluconeogenic genes *PEPCK-C*, *G6Pase*, *FBPase*, and pyruvate carboxylase in the liver (273). Additional, GR binds to STAT5 as a cofactor to promote GH-stimulated gluconeogenesis (174). GR expression is upregulated in hepatocytes by transcription factor Yin Yang 1 (YY1) which is elevated in the fasted state (151). Knockdown of YY1 in the liver ameliorates hyperglycemia in *db/db* mice (151). The liver X receptor (LXR), another member of the nuclear receptor family which is activated by oxysterols and controls cholesterol homeostasis (23), inhibits the gluconeogenic action of GR by competing for GR binding sites in the promoter of gluconeogenic genes (176). LXR activation also suppresses GR expression in hepatocytes (147). Surprisingly, genetic deletion of *LXRb* has been reported to impair the ability of GR to stimulate the expression of gluconeogenic genes and HGP (197).

1.8. Cytokines regulate hepatic gluconeogenesis

The liver houses many types of immune cells, including Kupffer, NK, NKT, and $CD4^+$ T cells (10, 134, 211). These immune cells as well as hepatocytes secrete numerous cytokines which regulate hepatocyte metabolism in an autocrine/paracrine fashion. Insulin signaling in the hypothalamus stimulates IL-6 production in the liver, and IL6 in turn suppresses gluconeogenesis by activating STAT3 (87). STAT3 directly binds to the promoters of *PEPCK-C* and *G6Pase* and inhibits promoter activity (209). Hepatocyte specific deletion of *STAT3* increases the expression of PEPCK-C, G6Pase, and PGC-1α; conversely, liver-specific overexpression of a constitutively active form of STAT3 decreases HGP and blood glucose levels in diabetic mice (88). IL-13 also stimulates tyrosine phosphorylation of STAT3 in hepatocytes, and genetic deletion of *IL-13* increases hepatic gluconeogenesis (243). IL-13 null mice develop hyperglycemia and glucose intolerance (243). SIRT1 deacetylates STAT3 and inhibits tyrosine phosphorylation of STAT3, thus decreasing the ability of STAT3 to suppress HGP (182). However, chronic inflammation in the liver causes insulin resistance, leading to increased HGP (79). Liver inflammation also increases the ability of glucagon to stimulate HGP (36, 234).

1.9. GI hormones regulate hepatic gluconeogenesis

Several GI hormones, including glucagon-like peptide 1 (GLP-1), have been well established to regulate HGP indirectly by stimulating insulin secretion. GI-derived factors are also able to act directly on hepatocytes. Bile acids stimulate the expression and secretion of FGF15/19 from small intestines by activating FXR (84). Circulating FGF15/19 levels increase after food ingestion (202). FGF15/19 promotes dephosphorylation of CREB and inhibits the ability of CREB to activate *PGC-1*α and *G6Pase* genes, thus suppressing gluconeogenesis (202). Deletion of *FGF19* or its receptor *FGFR4* increases gluconeogenesis and blood glucose levels (202). Circulating serotonin levels are lower in the fed state and markedly increase during chronic fasting due to increased secretion from the gut, (247).

Serotonin directly increases gluconeogenesis in hepatocytes by activating Htr2b receptors (247). Gut-specific deletion of tryptophan hydroxylate 1, which controls a rate-limiting reaction of the serotonin biosynthesis in peripheral tissues, impairs gluconeogenesis and protects against dietary glucose intolerance and insulin resistance (247). Hepatocyte-specific deletion of *Htr2b* also decreases hepatic gluconeogenesis (247).

1.10. Regulation of glycolysis

Hepatocytes have great flexibility in selecting metabolic fuels (glucose and/or fatty acids). Fuel selection is regulated by both nutrient and hormonal signals. Glycolysis is dominant in the fed state in which glucose is abundant. Glycolytic intermediates and products are used to synthesize lipids, amino acids, and other important molecules in addition to be completely oxidized to generate ATP. In the fasted state in which glucose levels are low, hepatocytes switch to fatty acid β oxidation for energy supply.

Glycolytic flux is controlled largely by four kinases: glucokinase (GCK), 6-phosphofructo-1 kinase (PFK), liver pyruvate kinase (L-PK), and PDKs (Fig. 1). The levels and activity of these glycolytic enzymes are lower in the fasted state and increase in the postprandial period (106). LRH-1, a nuclear receptor family member which is activated by several phosphatydylcholine species (127), stimulates GCK expression, and hepatocyte-specific deletion of *LRH-1* decreases GCK levels and glycolysis (189). GCK binds to glucokinase regulatory protein (GKRP) at low glucose concentrations (4). GKRP, which is exclusively expressed in the liver, inhibits GCK activity by sequestering GCK in the nucleus (4). Glucose induces dissociation of GCK from GKRP, allowing GCK to be translocated into the cytoplasm and phosphorylate glucose (4). F-2,6-P2 is a potent allosteric activator of PFK and stimulates glycolysis in hepatocytes (215). F-2,6-P2 also suppresses gluconeogenesis by inhibiting FBPase (215). Both the generation and clearance of F-2,6-P2 is controlled by a single enzyme called bifunctional 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFK-2/FBP-2) (215). In the fed state, both insulin and carbohydrates stimulate the kinase activity of PFK-2/FBP-2 which phosphorylates fructose-6-phosphate, a glycolytic intermediate, to generate F2,6P2 (188). In the fasted state, glucagon stimulates the phosphatase activity of PFK-2/FBP-2 by PKA-mediated phosphorylation, thereby decreasing F2,6P2 levels and glycolysis (188, 215). Glucose activates carbohydrate response element binding protein (ChREBP), also called Williams-Beuren syndrome critical region 14 (WBSCR14) (255). ChREBP binds to the E-box motifs in the *L-PK* promoter and activates L-PK expression in hepatocytes (280). Insulin suppresses the expression of PDK4 (Fig. 2A), a negative regulator of PDC as described above, by inhibiting FOXO1, thus increasing pyruvate consumption and glycolysis (93).

2. LIVER FATTY ACID METABOLISM

When carbohydrates are abundant, the liver not only utilizes glucose as the main metabolic fuel but also converts glucose into fatty acids. Hepatocytes also obtain fatty acids from the bloodstream, which are released from adipose tissue or absorbed from food digestion in the GI. Fatty acids are esterified with glycerol 3-phosphate to generate TAG (Fig. 3) or with cholesterol to produce cholesterol esters. TAG and cholesterol esters are either stored in lipid

droplets within hepatocytes or secreted into the circulation as VLDL particles. Fatty acids are also incorporated into phospholipids, which are an essential component of cell membranes, and the surface layer of lipid droplets, VLDL, and bile particles. In the fasted state, fatty acids are oxidized mainly in the mitochondria to generate energy supply as well as ketone bodies.

2.1. Hepatocyte fatty acid uptake and trafficking

After a meal, dietary fat is digested mainly in the small intestine and absorbed into enterocytes in which fatty acids are resynthesized into TAG and secreted into the gut lymphatic system as chylomicrons. Chylomicrons arrive at the liver through the circulation and release NEFAs through lipolysis which is mainly mediated by lipoprotein lipase (LPL). Transgenic mice with liver-specific overexpression of LPL develop hepatic steatosis and insulin resistance (108). Hepatic CREBH stimulates the expressing of LPL coactivators (e.g Apoa4, Apoa5, and Apoc2) and suppresses the expression of LPL inhibitor Apoc3, thus promoting plasma TAG clearance from the circulation (125). NEFAs enter into hepatocytes mainly through CD36, fatty acid transport protein 2 (FATP4), FATP4, and FATP5. Pregnane X receptor (PXR) activates the expression of CD36 in hepatocytes, increasing hepatocyte fatty acid uptake and TAG levels (294). Aryl hydrocarbon receptor (AhR) activation also increases hepatocyte CD36 expression, fatty acid uptake, and steatosis (126). FATP5 is exclusively expressed in the liver, and deletion of *FATP5* decreases hepatocyte fatty acid uptake and lipid levels in FATP5 null mice (48). FATP2 also mediates liver fatty acid uptake, and knockdown of FATP2 in the liver decreases NEFA uptake and reduces high fat diet (HFD)-induced hepatic steatosis (56). FATP2 and FATP4 reside mainly in peroxisomes and mediate transport of long-chain fatty acids (LCFAs) into peroxisomes (56, 245). FATP2 also has very long-chain acyl-CoA synthetase activity (56, 245). LCFAs are activated and converted to LCFA-CoA by long chain acyl-CoA synthetase (ACSL) [128,129]. Mammals express five ACSL family members (ACSL1 and 3-6) [128,129]. ACSL1 and 5 are highly expressed in the liver (18, 135), and knockdown of ACSL5 decreases lipid levels in cultured hepatocytes (18); however, liver-specific deletion of *ACSL1* does not alter lipid levels in the liver (135). Fatty acid binding proteins (FABPs) bind to both LCFAs and LCFA-CoA and act as intracellular fatty acid chaperones and carriers. Mammals express a single FABP in the liver (L-FABP). L-FABP delivers its bound LCFAs to the nucleus to activate PPARα, a nuclear receptor family member which promotes fatty acid β oxidation (156, 245). Deletion of *L-FABP* decreases hepatocyte fatty acid uptake, suppresses β oxidation, and protects against dietary steatosis (180, 181). A separated study reported that the liver pool of NEFAs and TAG are relatively normal or higher in L-FABP null mice (156). The null mice have a compensatory increase in the expression of sterol carrier protein-2 (SCP-2) which also binds LCFAs (156).

2.2. *De novo* Fatty acid synthesis

The liver is the main organ which converts carbohydrates into fatty acids. Fatty acids are packed into VLDL particles and delivered to adipose tissue and other extrahepatic tissues through the bloodstream.

2.2.1. The hepatic lipogenic programs—Glucose is hydrolyzed into pyruvate through glycolysis. Pyruvate is imported into the mitochondria and metabolized by PDC to generate acetyl-CoA (Fig. 3). Acetyl-CoA is combined with oxaloacetate by citrate synthase to form citrate (Fig. 3). Citrate is exported into the cytoplasm and split into acetyl-CoA and oxaloacetate by ATP-citrate lyase (ACL). Oxaloacetate is reduced to malate which is converted into pyruvate by malic enzyme, releasing NADPH (Fig. 3). Pyruvate is recycled back into the mitochondria and carboxylated by pyruvate carboxylase (PC) to form oxaloacetate which drives continuous citrate synthesis (Fig. 3).

In the cytoplasm, acetyl-CoA is carboxylated by acetyl-CoA carboxylase (ACC) to form malonyl-CoA (Fig. 3). Both malonyl-CoA and NADPH are used as precursors to synthesize palmitic acid (a 16-carbon fatty acid) by fatty acid synthase (FAS). Mammals have two *ACC* genes, *ACC1* and *ACC2* whose products are located in the cytoplasm and mitochondrial outer membrane, respectively. Systemic deletion of *ACC1* causes embryonic death (3). Hepatocyte-specific deletion of *ACC1* decreases the levels of malonyl-CoA, TAG, and *de novo* lipid synthesis (154). However, a separate study has reported that hepatocyte-specific deletion of *ACC1* does not alter malonyl-CoA levels and lipogenesis in the liver, presumably due to a compensatory increase in ACC2 expression (71). Transient inhibition of both ACC1 and ACC2 in the liver decreases levels of hepatic malonyl-CoA and lipogenesis, increases β oxidation, and protects against hepatic steatosis (226). Mice with liver-specific deletion of *FAS* are relatively normal (31), suggesting that fatty acid uptake is sufficient to maintain normal hepatic lipid content in the absence of liver FAS. Surprisingly, after being fed a zero-fat/high carbohydrate diet, mutant mice develop fatty livers and hypoglycemia which are reversed by treatments with PPARα agonists (31). FAS products are believed to serve as endogenous ligands for PPARα and stimulate fatty acid β oxidation in the liver (30, 31).

Palmitic acid is elongated by fatty acyl-CoA elongase (Elovl) family members in the ER to generate LCFAs (>16 carbon-chain) (Fig. 3). Deletion of *Elovl6* protects against hepatic steatosis and liver inflammation in mice fed an atherogenic high fat diet (AHF); conversely, liver-specific overexpression of Elovl6 increases AHF-induced fatty liver and liver fibrosis (161). LCFAs are desaturated by stearoyl-CoA desaturases (SCDs), ER membrane enzymes, to form mono- and poly-unsaturated LCFAs (Fig. 3). Global knockout of SCD1, which catalyzes the synthesis of monounsaturated LCFAs, protects against obesity (39, 184). Hepatocyte-specific deletion of *SCD1* also protects against high carbohydrate diet-induced, but not HFD-induced, obesity and hepatic steatosis (167). SCD1 products, particularly oleate, appear to be important regulators of glucose and lipid metabolism in the liver (167).

2.2.2. Regulation of *de novo* lipogenesis by the availability of lipogenic substrates—Dietary carbohydrates drive lipogenesis. Pyruvate, the main glycolytic product, provides a carbon source for lipogenesis and links glycolysis to lipogenesis. GCK catalyzes the first chemical reaction of glycolysis, and GCK activity is negatively regulated by GCKR. A variant in the *GCKR* gene is associated with hepatic steatosis and hyperglycemia in patients with obesity (225). LRH stimulates GCK expression, and hepatocyte-specific deletion of *LRH-1* decreases GCK levels, glycolysis, and *de novo* lipogenesis in the liver (189). NADPH provides the reducing power for lipogenesis. Malate is metabolized by malic enzyme to generate NADPH. Moreover, glucose catabolism through

the pentose phosphate pathway provides an additional NADPH source for lipogenesis (Fig. 3). Glucose-6-phosphate dehydrogenase and 6-phosphogluconate dehydrogenase, which catalyze the reactions to generate NADPH, are likely to be involved in the regulation of lipogenesis.

2.3. Lipogenesis is controlled by multiple transcription factors and coregulators

Lipogenesis is controlled in a large part through transcriptional regulation of glycolytic genes and lipogenic genes. Numerous transcription regulators have been identified to activate these genes. Many regulators also regulate the expression of additional genes which are involved in the regulation of lipid uptake, trafficking, and/or storage.

2.3.1. ChREBP—ChREBP binds to and activates the *L-PK* promoter in hepatocytes (280). L-PK is a key glycolytic enzyme. ChREBP also stimulates the expression of lipogenic genes, including malic enzyme, *ACL*, *ACC*, *FAS*, *SCD1*, and *Elovls* (82). Systemic deletion of *ChREBP* decreases the expression of these genes, thus inhibiting glycolysis and hepatic lipogenesis, and glucose is then used to synthesize glycogen in the liver in ChREBP null mice (82). Conversely, overexpression of ChREBP in the liver causes hepatic steatosis without concomitant insulin resistance (13). ChREBP levels are elevated in obese mice, and genetic deletion of *ChREBP*, or liver-specific inhibition of ChREBP, decreases hepatic lipogenesis and steatosis in *ob/ob* mice (45, 83).

ChREBP binds to Max-like protein X (Mlx), and the heterodimer acts as a functional transcription factor (244). ChREBP is phosphorylated and inhibited by PKA, and dephosphoralated and activated by PP2A (102). Glucagon stimulates phosphorylation of ChREBP at Ser196 by activating the cAMP/PKA pathway (Fig. 2B), resulting in nuclear export and inactivation of ChREBP in the liver (44, 47). Phosphorylated ChREBP binds to 14-3-3 and is retained in the cytoplasm (163, 222). Glucose is a potent activator of ChREBP. Glucose is oxidized to generate xylulose 5-phosphate through the pentose phosphate pathway. Xylulose 5-phosphate activates PP2A, which dephosphorylates ChREBP, promoting nuclear translocation and activation of ChREBP (99). G6P, a glycolytic intermediate, binds to and activates ChREBP in hepatocytes (47). Additionally, F-2,6-P2, a G6P-drived product, also stimulates nuclear translocation of ChREBP (7). Glucose promotes acetylation of ChREBP on Lys672 by p300, which increases ChREBP activity (17). Additionally, ChREBP binds to and is glycosylated by O-linked β-N-acetylglucosamine transferase (OGT), and O-GlcNacylation of ChREBP increases ChREBP stability (65).

2.3.2. SREBP—The SREBP family members (SREBP-1a, -1c and -2) are master regulators of lipid metabolism (78). Both SREBP-1a and SREBP-1c are encoded by a single gene and have different N-termini; SREBP-2 is encoded by a separate gene (78). Both SREBP-1c and SREBP-2 are abundantly expressed in the liver (78). SREBP1-c activates the genes that control fatty acid and TAG synthesis, and SREBP-2 activates the genes that control cholesterol biosynthesis (78). SREBP-1b promotes both fatty acid and cholesterol synthesis (78).

SREBPs are integral ER membrane proteins. They are translocated to the Golgi and cleaved sequentially by SIP1 and SIP2 proteases to release transcriptionally-active SREBPs (78). ER

stress promotes proteolytic cleavage and activation of SREBP-1c in the liver, increasing lipogenesis (100). Low levels of cholesterol potently stimulate SREBP processes in hepatocytes (78). SREBP precursors bind to Scap which is a cholesterol sensor and required for ER-Golgi transport of SREBPs (78). Hepatocyte-specific deletion of *Scap* markedly decreases hepatic NEFAs, TAG synthesis, and hepatic steatosis in both *ob/ob* mice and mice with diet-induced obesity (169). Inhibition of phosphatidylcholine biosynthesis reduces phosphatidylcholine pools in hepatocytes, which promotes SREBP-1 cleavage and activation (258). Reduction in phosphatidylcholine/phosphatidylethanolamine ratios may cause relocation of S1P and S2P to the ER, increasing proteolytic activation SREBP-1 (258). SREBP activation is also subjected to posttranslational modifications. AMPK phosphorylates SREBP-1c at Ser372 and inhibits proteolytic cleavages and nuclear translocation of SREBP-1c, thus suppressing hepatic lipogenesis (139). SIRT1 deacetylates and inhibits SREBP-1c,suppressing lipogenesis in the liver (200, 259). SREBP activation is inhibited by nuclear translocation of lepin 1 (198). The mTORC1 complex phosphosphorylates lipin 1 and promotes cytoplasmic translocation of lipin 1, thus stimulating SREBP-1 activity and lipogenesis (198). PGC-1β is a coactivator for SREBP family members and simulates liver lipogenesis (141). Knockdown of PGC-1β in the liver decreases the expression of lipogenic genes and ameliorates fructose-induced hepatic steatosis (177).

2.3.3. LXR and FXR—LXR has two isoforms (α and β) in rodents, and each isoform forms heterodimers with the retinoid X receptor (RXR) to activate its target genes (23). LXR is activated by cholesterol metabolites called oxysterols (35, 91). LXR is well known to control reverse cholesterol transport by stimulating the expression of ATP-binding cassette transporter A1 (ABCA1) and ABCG1 (23). It also stimulates *de novo* fatty acid biosynthesis (23). LXR directly binds to the *SREBP1* promoter and increases SREBP-1c expression (214, 228). It also stimulates ChREBP expression (29). Additionally, LXRα directly stimulates expression of PFK-2/FBP-2, which produces F-2,6-P2 to stimulate glycolysis (291). LXR agonists stimulate the expression of lipogenic genes and increase both liver and plasma TAG levels in wild-type, but not LXRα/β double knockout, mice (228).

Farnesoid X receptor (FXR), a nuclear receptor family member which is activated by bile acids, suppresses bile acid synthesis in a negative feedback fashion (23, 237). It stimulates the expression of SHP, a transcription repressor which inhibits the expression of Cyp7a (23, 237). Cyp7a catalyzes hydroxylation of cholesterol, a rate-limiting step of bile acid biosynthesis. FXR also regulates many genes which regulate NEFA and TAG metabolism (157, 199, 237, 249). SHP, the main transcriptional target of FXR, suppresses the ability of LXR to stimulate the expression of lipogenic SREBP-1 (269). FXR binds to and inhibits ChREBP, suppressing both glycolysis and lipogenesis (27). Bile acids stimulate the expression and secretion of FGF15/19 from the GI by activating FXR in enterocytes. FGF15/19 suppresses lipogenesis in the liver (16). FXR knockout mice have higher levels of TAG in both the circulation and the liver (237). FXR is acetylated by p300 and deacetylated by SIRT1, and SIRT1-mediated deacetylation increases FXR activity (103). Obesity is associated with higher levels of FXR acetylation in the liver (103). PGC-1α serves as a coactivator for some FXR target genes (289).

2.3.4. PPARγ and *PPARδ*—The levels PPARγ in the liver are low in normal mice and increase in mice with obesity (170)[184,185]. Hepatic PPARγ stimulates the expression of many genes which control fatty acid uptake, fatty acid trafficking, and TAG biosynthesis in the liver (130). PPARγ also stimulates the expression of Cidec, a lipid droplet protein (160). Hepatocyte-specific deletion of *PPARγ* suppresses the expression of many lipogenic genes and protects against hepatic steatosis in mice fed a HFD (170). Ablation of liver PPARγ ameliorates hepatic steatosis in *ob/ob* as well as in lipoatrophic A-ZIP/F-1 mice (61, 159). Expression of hepatic PPARγ is repressed by the hairy enhancer of split 1 (HES-1) in the liver (74). CREB stimulates the expression of HES-1 which in turn suppresses PPARγ expression and lipogenesis in the fasted state (74); however, a separate study has reported that knockdown of CREB in the liver decreases hepatic lipogenesis in rodents with type 2 diabetes (52). Like PPARγ, PPARδ also activates lipogenic genes, and liver-specific expression of PPARδ increases liver lipid levels in mice (145).

2.4. Insulin stimulates lipogenesis in the liver

Insulin is the primary hormone which stimulates hepatic lipogenesis in the fed state. The PI 3-kinase/Akt pathway is required for both insulin suppression of gluconeogenesis and insulin stimulation of lipogenesis; however, lipogenesis and gluconeogenesis are mediated by two distinct pathways downstream of Akt (136). Insulin stimulates activation of mTORC1 through the PI 3-kinase/Akt pathway, and mTORC1 is required for insulin to stimulate SREBP-1 expression and lipogenesis (Fig. 2A) (136). Akt, particularly Akt 2, stimulates SREBP-1 activation and lipogenesis (260, 283). Inhibition of hepatic Akt by hepatocyte-specific deletion of *rictor* inhibits both glycolysis and lipogenesis (68). Disruption of mTORC1 signaling in the liver, by deleting *Raptor*, prevents dietary hepatic steatosis (198). mTORC1 phosphosphorylates lipin 1 and blocks its ability to suppress SREBP-1 (Fig. 2A) (198). Activation of mTORC1 alone is not sufficient to stimulate lipogensis in the liver (260, 283). Akt suppresses the activity of INSIG2 (Fig. 2A), an ER membrane protein which binds to Scap, blocks the ER-Golgi translocation of SREBPs, and inhibits proteolytic activation of SREBPs (283). Insulin stimulates the expression of SREBP-1, and LXR is involved in mediating insulin action (33, 250). Insulin stimulates phosphorylation of upstream stimulatory factor-1 (USF-1) through DNA-PK (274). USF-1 stimulates expression of FAS and mitochondrial glycerol-3-phosphate acyltransferase (mGPAT); phosphorylation increases acetylation and activation of USF-1 (274). Deletion of USF-1 or USF-2 markedly suppresses carbohydrate-stimulated expression of FAS in the liver during a fasting/feeding transition (28). Additionally, insulin stimulates glycolysis as described before, thus increasing the availability of lipogenic precursors.

2.5. Regulation of lipogenesis by metabolic states, the circadian clock, and ER stress

Hepatic lipogenesis is low in the fasted state and high in the fed state. SIRT1 is activated in the fasted state, and it deacetylates and inhibits lipogenic SREBP-1c (200, 259). Hepatocyte-specific deletion of *SIRT1* exacerbates dietary hepatic steatosis (206). SIRT1 binds to and is inhibited by deleted in breast cancer-1 (DBC1) (107, 293). Fasting decreases DBC1-SIRT1 interaction in the liver, increasing SIRT1 activity (54). Deletion of *DBC1* increases SIRT1 activity in the liver and protects against dietary hepatic steatosis in mice (54). AMPK phosphorylates SREBP-1c at Ser372 and inhibits proteolytic cleavage and nuclear

translocation of SREBP-1c, thus suppressing hepatic lipogenesis (139). In the liver, mTORC1 is inhibited in the fasted state and activated in the fed state (230), and mTORC1 stimulates lipogenesis as described above.

Chronic ER stress promotes hepatic steatosis (219). The PERK/elF2α pathway stimulates both hepatic glucose production and lipogenesis by increasing the translation of C/EBPα and C/EBPβ as well as the expression of PPARγ (191). Liver-specific overexpression of C/EBPβ induces hepatic steatosis (207); conversely, deletion of *C/EBPβ* ameliorates hepatic steatosis in *db/db* mice (227). XBP1 activates the expression of key lipogenic genes in hepatocytes, including SREBP1, DGAT2 and ACC2 (124, 183); however, IRE1α is able to degrade the mRNAs of some lipogenic enzymes, suppressing hepatic lipogenesis (239).

Core circadian genes are involved in hepatic lipid metabolism. Mice with liver-specific deficiency of molecular clock Rev-erbα/β develop hepatic steatosis (20, 59). Genomic recruitment of HDAC3 displays a circadian rhythm and is controlled by circadian clocks, and the rhythmic recruitment of HDAC3 regulates circadian rhythm of hepatic lipogenesis (59). Hepatocyte-specific deletion of *HDAC3*, increases lipogenic gene expression, resulting in hepatic steatosis in mice (113).

2.6. Fatty acid β oxidation and ketogenesis

Liver fatty acid β oxidation is high in the fasted state and low in the fed state. Mitochondrial β oxidation not only provides energy for hepatocytes but also generates ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone) which are exported into the circulation and provide metabolic fuels for extrahepatic tissues during fasting. LCFA-CoA translocation into mitochondria, which is mediated by carnitine palmitoyltransferase 1 (CPT-1), is a rate-limiting step for fatty acid β oxidation. CPT-1 activity is inhibited by malonyl-CoA. Mitochondrial ACC2 generates malonyl-CoA and increases local malonyl-CoA concentrations, thus inhibiting CPT-1 activity and β oxidation (1). Systemic deletion of *ACC2* increases mitochondrial fatty acid β oxidation, leading to lean phenotypes (2). Long-chain acyl-CoA dehydrogenase (LCAD) activity is also regulated through posttranslational modifications. Deletion of LCAD leads to hepatic steatosis and insulin resistance (286).

PPARα is the master regulator of fatty acid β oxidation and promotes fatty acid β oxidation in both the mitochondria and peroxisomes (104). PPARα expression in the liver is higher in the fasted state, and deletion of *PPARα* decreases hepatic fatty acid β oxidation in the fasted state and exacerbates fasting-induced hepatic steatosis, hypoglycemia, hypoketonemia, and hypothermia (104, 132). PPARα is a nuclear receptor family member activated by a subtype of LCFAs and phosphatidylcholines (30). FAS products appear to generate endogenous PPARα ligands in the liver (30, 31). PPARα agonist treatments correct hepatic steatosis and hypoglycemia in mice with liver-specific deletion of *FAS* that are fed a zero-fat, high carbohydrate diet (31). PPARα ligands are able to be inactivated through peroxisomal β oxidation, and deletion of peroxisomal fatty acyl-CoA oxidase increases PPARα activity in the liver (57), and decreases hepatic steatosis and obesity in *ob/ob* mice (80).

Multiple PPARα coactivators have been identified to promote β oxidation in the liver. PGC-1α is a well-characterized PPARα coactivator which promotes β oxidation (256). In the

fasted state, SIRT1 deacetylates PGC-1α and increases its activity (216). SIRT1 also physically interacts with PPARα and promotes PPARα transcriptional activity in the liver (206). Hepatocyte-specific deletion of *SIRT1* decreases the expression of β oxidative genes and β oxidation, increases fasting-induced lipid accumulation in the liver, and exacerbates diet-induced steatosis (206). Hepatic lipin 1, which is higher in the fasted state, binds to both PPARα and PGC-1α in the nucleus and promotes β oxidation (60). In the fed state, insulin stimulates phosphorylation of PGC-1α by Akt, which impairs the ability of PGC-1α to stimulate fatty acid β oxidation (138). Activation of mTORC1 also inhibits PPARα activity, β oxidation, and ketogenesis in the fed state (230). PGC-1α binds to BAF60α, a subunit of the SWI/SNF chromatin-remodeling complex; the PGC-1α/BAF60α complex interacts with PPARα and mediates PPARαactivated expression of β oxidation genes in the liver (137). BAF60α overexpression in the liver increases β oxidation and ameliorates hepatic steatosis in mice with obesity (137). PGC-1β and transducin beta-like 1 (TBL) also serve as PPARα coactivators. Hepatocyte-specific overexpression of PGC-1β increases the expression of β oxidative genes and protects PGC-1β transgenic mice from diet-induced steatosis (12). Knockdown of TBL1 or its partner TBLR1 in the liver inhibits PPARα activity, decreases β oxidation and ketogenesis, and promotes hepatic steatosis (117).

Multiple factors regulate β oxidation through PPARα. Fasting stimulates expression and secretion of FGF21 from the liver (9, 85). Glucagon stimulates FGF21 secretion in both rodents and humans (6, 66). FGF21 stimulates the expression of PGC-1α in the liver in an autocrine/paracrine fashion, thus increasing fatty acid β oxidation (Fig. 2B), TCA flux, and ketogenesis (203). Glucagon also stimulates β oxidation in the liver by a PPARα-dependent mechanism (Fig. 2B) (148). Glucagon deficiency is associated with higher TAG levels in the liver (70). Deletion of glucagon receptors abolishes fasting-stimulated β oxidation in hepatocytes (148). Glucagon secretion increases during exercise, and exercise attenuates hepatic steatosis in mice with dietary obesity (14). Deletion of glucagon receptors abrogates protection against hepatic steatosis by exercise (14). FGF15/19, a GI-derived hormone, inhibits PGC-1α expression and β oxidation in the liver (202).

In addition to PPARα, hepatic PPARβ/δ is believed to act as a plasma free fatty acid sensor and promote hepatic β oxidation in the liver (224). A subset of PPARα target genes, which stimulate fatty acid β oxidation, may also be stimulated by PPARβ/δ in the liver (224). Mitochondrial SIRT3, which is upregulated in the fasted state, deacetylates and activates LCAD in the liver, thus promoting fatty acid β oxidation (76). SIRT3 also deacetylates and activates mitochondrial 3-hydroxy-3-methylglutaryl CoA synthase 2 (HMGCS2), promoting ketogenesis in the fasted state (236). SIRT6 is a nuclear, chromatin-associated protein which promotes resistance to DNA damage and suppresses genomic instability (173). Hepatic SIRT6 is higher in the fasted state, promotes β oxidation, and suppresses glycolysis; liver-specific deletion of *SIRT6* promotes hepatic steatosis (106).

2.7. Liver-extrahepatic tissue crosstalk

The liver has close communications with extrahepatic tissues, including adipose tissue and skeletal muscle. Liver-produced glucose and ketone bodies are delivered to muscle and other extrahepatic tissues and are used as metabolic fuels during fasting and exercise; in return,

skeletal muscle provides the liver with lactate and amino acids which serve as gluconeogenic substrates for hepatocytes to synthesize glucose. Adipose tissue produces NEFAs and glycerol through lipolysis during fasting and exercise. Hepatocytes oxidize fatty acids to generate ketone bodies or pack NEFAs into VLDL particles. Ketone bodies and VLDL are secreted from the liver and utilized by extrahepatic tissues. Glycerol is used by hepatocytes to synthesize glucose or TAG.

2.7.1. Liver-adipose tissue crosstalk—NEFAs released from adipose tissue through lipolysis are the main source for liver TAG pools, and hepatocyte fatty acid uptake provides ~59% of the supply of liver fat in humans with NAFLD (50). In adipocytes, TAG is stored in lipid droplets (LDs) which consist of a neutral lipid core (triacylglycerol and cholesterol esters) covered by a phospholipid monolayer (64). LDs are believed to be generated from the ER and coated with perilipin family proteins, enzymes, and vesicle trafficking proteins. LD proteins, including perilipins, tail interacting protein 47, (TIP47), and adipose differentiation related protein (ADRP), and cell death-inducing DNA fragmentation factor-like effector (CIDE) family members, are involved in the regulation of lipolysis (64, 205). TAG is hydrolyzed mainly by ATGL to release NEFAs and diacylglycerol (DAG) (285). DAG is further hydrolyzed by hormone-sensitive lipase (HSL) to release NEFAs and monoacylglycerol (MAG), and MAG is completely hydrolyzed by MAG lipase (MGL) and generate glycerol and NEFAs (285). HSL is also able to hydrolyze retinyl esters and cholesterol esters (285). CGI-58, an endogenous activator of ATGL, binds to perilipins under basal conditions; catecholamine hormones stimulate phosphorylation of perilipins which releases CGI-58, allowing it to activate ATGL and stimulate lipolysis (63, 122). In contrast to CGI-58, G0S2 binds to and inhibits ATGL (282). Adipocyte-specific deletion of *ATGL* blocks lipolysis and the release of NEFAs, thus reducing β oxidation and ketogenesis in the liver during starvation (275).

Adipose tissue also regulates liver energy metabolism by secreting a variety of adipokines, including adiponectin and cytokines (208). Adiponectin stimulates β oxidation in the liver and improves liver insulin sensitivity (278, 281). IL-6 is able to suppress insulin signaling by stimulating expression of SOCS3 in the liver (221). SOCS3 inhibits insulin signaling by both promoting IRS protein degradation and uncoupling IRS proteins from insulin receptors (218, 253). Adipocyte-specific deletion of *JNK1* decreases secretion of IL-6 by adipose tissue and improves liver insulin sensitivity and hepatic steatosis in mice with dietary obesity (221). C1q/TNF-related protein-12 (CTRP12), an adiponectin-related adipokine secreted mainly from adipocytes, activates the PI 3-kinase/Akt pathway and suppresses hepatic gluconeogenesis (271). FABP4 (also called aP2) is secreted by white adipose tissue, and secretion is higher in the fasted state (25). FABP4 directly stimulates gluconeogenesis in hepatocytes (25). C16:1n7-palmitoleate is secreted by adipose tissue and acts as a lipid hormone to suppress hepatic steatosis (24). Additionally, adipose tissue is able to regulate liver metabolism indirectly by secreting hormones (e.g. leptin) which act on the brain to regulate liver metabolism (172). The liver also regulates the metabolic activity of adipose tissue. FGF21 is an important metabolic hormone secreted mainly from the liver in the fasted state (9, 85). Glucagon stimulates FGF21 secretion in both rodents and humans (6, 66). FGF21 stimulates both lipolysis and the expression and secretion of adiponectin by

adipose tissue (6, 66, 77, 142). GH is secreted from the pituitary gland. It stimulates not only hepatic gluconeogenesis but also adipocyte lipolysis. Liver-specific deletion of GH receptors causes liver GH resistance, resulting in a compensatory increase in the levels of circulating GH which promotes adipocyte lipolysis and hepatic steatosis (58). Liver-specific deletion of *JAK2* or *STAT5* also causes GH resistance in the liver and increases compensatory GH secretion, thus increasing adipocyte lipolysis and hepatic steatosis (42, 240).

2.7.2. Liver-gut crosstalk—The gut is anatomically connected to the liver by the portal vein circulation. Most absorbed nutrients, GI hormones, and GI metabolites are directly delivered to the liver. Some metabolites from gut microbiota are also delivered to the liver via the portal vein circulation (73). These biologically active molecules directly regulate liver glucose and lipid metabolism. The GI also regulates liver metabolism indirectly through the central nervous system (CNS). In response to food ingestion, nutrient signals, encoded by duodenum lipid sensors, are transmitted via intestinal vagal afferent fibers to the nucleus of the solitary tract (NTS) in the hindbrain (262). The NTS in turn suppresses HGP via the hepatic branch of vagus nerve fibers (262). Intestinal cholecystokinin (CCK) activates CCK-A receptors in the intestinal afferent fibers and decreases HGP via the gut-brain-liver axis (37).

2.7.3. Liver-brain crosstalk—The CNS regulates liver energy metabolism directly via both the sympathetic nervous system (SNS) and the parasympathetic nervous system which directly innervate the liver. The neural circuitry in the hypothalamus and the hindbrain regulate the activity of most internal organs, including the liver, and maintains internal homeostasis (242). The SNS promotes HGP and mobilization of metabolic fuels for extrahepatic tissues, whereas the parasympathetic system antagonizes SNS action and inhibits HGP and promotes fuel storage in the liver.

Insulin directly regulates glucose and lipid metabolism in the liver as described above. It also regulates hepatic energy metabolism indirectly by activating insulin receptor signaling in the hypothalamus. Insulin stimulates the PI 3-kinase/Akt pathway in the brain, which in turn causes downregulation of GSK-3β in the liver and increases glycogen synthesis (210). Insulin activates its receptors in hypothalamic neurons and suppresses HGP in a vagus nerve output-dependent manner (185, 187). Hypothalamic insulin signaling promotes production of hepatic IL-6 which in turn activates STAT3 and suppresses gluconeogenesis in the liver (87). AgRP neuron-specific deletion of insulin receptors blocks the ability of central insulin to suppress HGP (114). Leptin, an adipose hormone, also regulates liver energy metabolism in addition to controlling food intake and body weight (172). Central administration of leptin suppresses glycogenolysis, gluconeogenesis, and the expression of G6Pase and PEPCK-C in the liver (19). Leptin, by activating the PI 3-kinase pathway in hypothalamic neurons, suppresses hepatic lipogenesis indirectly by increasing SNS outflow to the liver (267). Hypothalamic neurons are also able to directly sense glucose, amino acids, and lipids, and they suppress HGP by increasing vagal nervous outflow to the liver (119, 120, 186). Injection of leucine into the mediobasal hypothalamus suppresses hepatic glycogenolysis and gluconeogenesis in rats (246). Activation of glucose sensing pathways in the brain also suppresses SCD1 expression, lipogenesis, and VLDL secretion in the liver (118).

The CNS also regulates liver activity indirectly by controlling secretion of various metabolic hormones. Disruption of glutamatergic transmission in the ventromedial hypothalamus by deleting *VGLUT2* in SF1-expressing neurons decreases secretion of glucagon from pancreatic α cells in the fasted state, resulting in a decrease in hepatic gluconeogenesis and blood glucose levels (251). Mice with leptin receptor LepRb deficiency develop obesity, type 2 diabetes, and high levels of circulating insulin and glucagon. Restoration of LepRb specifically in POMC neurons, an important subpopulation of hypothalamic neurons, markedly decreases hyperglucagonemia, leading to reduction in HGP and blood glucose levels (15).

3. OBESITY, NAFLD, AND TYPE 2 DIABETES

The prevalence of obesity has been increasing rapidly, and it is associated with NAFLD and type 2 diabetes. Glucose produced from the liver contributes significantly to hyperglycemia in humans with type 2 diabetes (41, 153, 164). GCK promotes glucose utilization in the liver and inhibits HGP, and GCK activity is lower in Zucker diabetic, obese rats (252). Liver-specific overexpression of GCK decreases HGP and hyperglycemia in these rats (252). Conversely, hepatocyte-specific deletion of *GCK* results in mild hyperglycemia and hyperinsulinemia (201).

Obesity, NAFLD, and type 2 diabetes are associated with insulin resistance. Insulin resistance is a primary causal factor for the pathogenesis of NAFLD and type 2 diabetes. NAFLD is associated with increased gluconeogenesis in humans (248). Multiple factors have been described to induce insulin resistance in the liver. Insulin signaling is negatively regulated by protein phosphatases, including PTP1B and Shp-1. Liver-specific deletion of *PTP1B* enhances insulin signaling in the liver and the ability of insulin to suppress gluconeogenesis, protecting against diet-induced NAFLD (43). Hepatocyte-specific deletion of *Shp1* protects against liver insulin resistance in mice fed a HFD (279). Insulin signaling is negatively regulated by SOCS1 and SOCS3 in the liver (218, 253). Insulin signaling is positively regulated by SH2B1, a SH2 domain-containing adaptor protein which recruits IRS proteins to the insulin receptors (51, 171). Deletion of *SH2B1* results in leptin resistance, insulin resistance, obesity, NAFLD, and type 2 diabetes (171, 212, 213). Systemic insulin resistance is a causal factor for the development of NAFLD, and lipid accumulation in the liver further promotes hepatic insulin resistance, thus forming a vicious cycle. Saturated NEFAs are able to cause insulin resistance by activating TLR4 (235, 241). Fetuin-A, a glycoprotein secreted by the liver, acts as a NEFA carrier in the circulation, and the NEFA-fetuin-A complex binds to TLR4 and promotes inflammation and insulin resistance (195). DAG induces hepatic insulin resistance by activating PKCε which phosphorylates IRS proteins at inhibitory Ser/Thr residues (98). Ceramides promote insulin resistance by inhibiting Akt activation through PP2A and JNK (194). Obesity and NAFLD are associated with ER stress, which promotes insulin resistance, in the liver (193). Proinflammatory cytokines activate the IKKβ and the JNK pathways which inhibit insulin signaling (22, 79). Liver-specific deletion of *IKKβ* improves hepatic insulin sensitivity and reduces hepatic gluconeogenesis in HFD-fed mice and *ob/ob* mice (8). Hepatocyte-specific deletion of *JNK1* results in liver inflammation and steatosis in mice fed a normal chow diet (220). C-reactive protein (CRP), an acute phase protein secreted by the liver, inhibits insulin signaling through

the ERK pathway in primary hepatocytes and inhibits the ability of insulin to suppress HGP in rats (277). Kupffer cells are a major source of cytokines, and depletion of Kupffer cells improves NAFLD and insulin resistance in the liver (81).

In addition to insulin, aberrant counterregulatory hormone signaling and action in the liver also contribute to the progression of type 2 diabetes (254). Silencing of glucagon receptors in the liver reduces blood TAG levels and improves glucose intolerance in both *db/db* mice and Zucker diabetic fatty rats (140, 238). We recently reported that inflammatory pathways enhance the ability of glucagon to stimulate gluconeogenesis, contributing to hyperglycemia and glucose intolerance in mice with obesity (36, 234).

Conclusion

The liver has long been recognized to be an essential metabolic organ. When carbohydrates are abundant during the postprandial phase, the liver converts glucose into glycogen and lipids, which provide metabolic fuels during fasting. In the fasted state, the liver produces and secretes glucose through both glycogenolysis and gluconeogenesis. The liver also converts fatty acids into ketone bodies which provide additional metabolic fuels for extrahepatic tissues during fasting. The metabolic switch between the fasted and fed states in the liver is tightly controlled by neuronal and hormonal systems. Insulin suppresses glucose production and ketogenesis and stimulates glycolysis and lipogenesis in the liver. Insulin resistance is not only a hallmark of type 2 diabetes but also promotes type 2 diabetes progression in obesity. Glucagon counteracts insulin action, and defects in glucagon signaling lead to hypoglycemia. Hepatic energy metabolism is largely controlled at the genomic levels by numerous transcription factors and coregulators. The activity of these nuclear proteins is regulated by insulin, glucagon and other metabolic hormones, which dynamically regulates gluconeogenesis, β oxidation, and lipogenesis in the liver in order to meet a systemic metabolic demand. Dysregulation of these transcription factors and coregulators contributes to NAFLD in obesity. Moreover, systemic insulin resistance promotes NAFLD, and hepatocyte lipid accumulation further impairs insulin action, thus activating the insulin resistance-lipotoxicity vicious cycle which drives NAFLD and/or type 2 diabetes progression.

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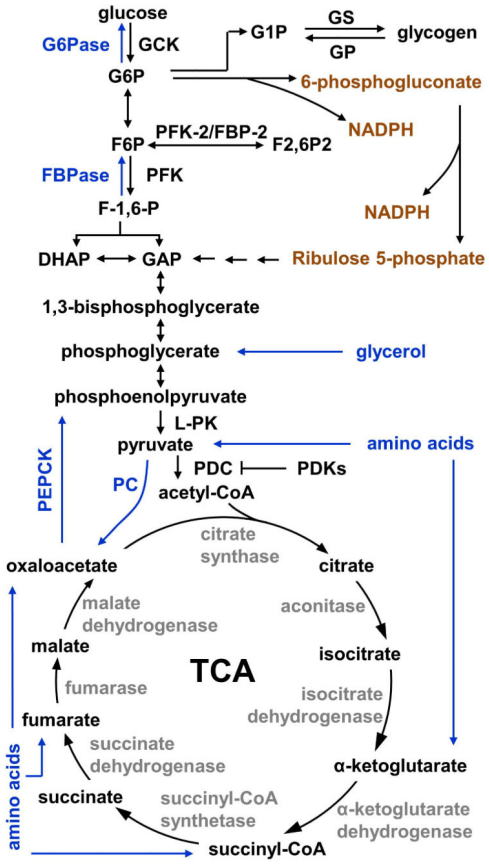

Fig. 1. Glucose metabolism pathways

Gluconeogenic pathways are marked in blue, and the pentose phosphate pathway is marked in orange. GCK: glucokinase; G6Pase: glucose-6-phosphatase; G6P: glucose 1-phosphate; G1P: glucose 1-phosphate; GP: glycogen phosphorylase; GS: glycogen synthase; PFK: 6-phosphofructo-1 kinase; FBPase: fructose 1,6 bisphosphatase; F-1,6-P:; GAP: glyceraldehyde 3-phosphate; DHAP: dihydroxyacetone phosphate; L-PK: liver pyruvate kinase; PC: pyruvate carboxylase; PDC: pyruvate dehydrogenase complex; PDKs: pyruvate dehydrogenase kinases.

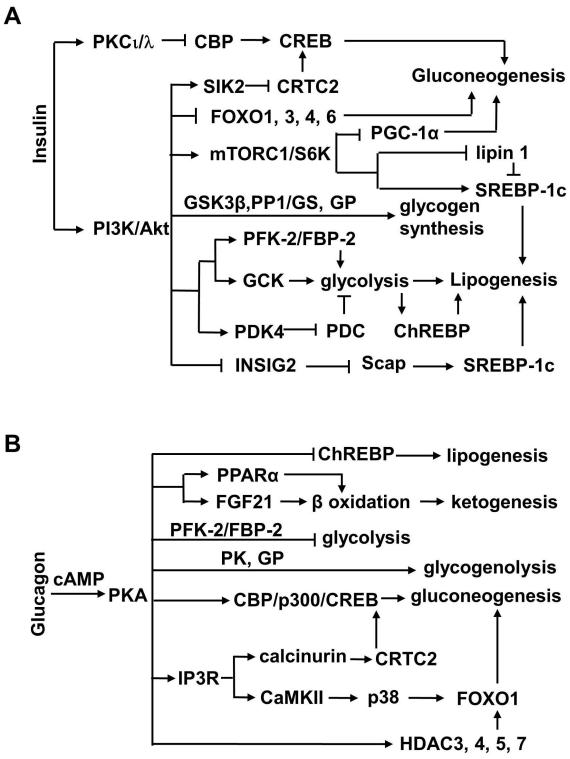

Fig. 2.

Regulation of glucose and fatty acid metabolism by insulin (A) and glucagon (B) in the liver.

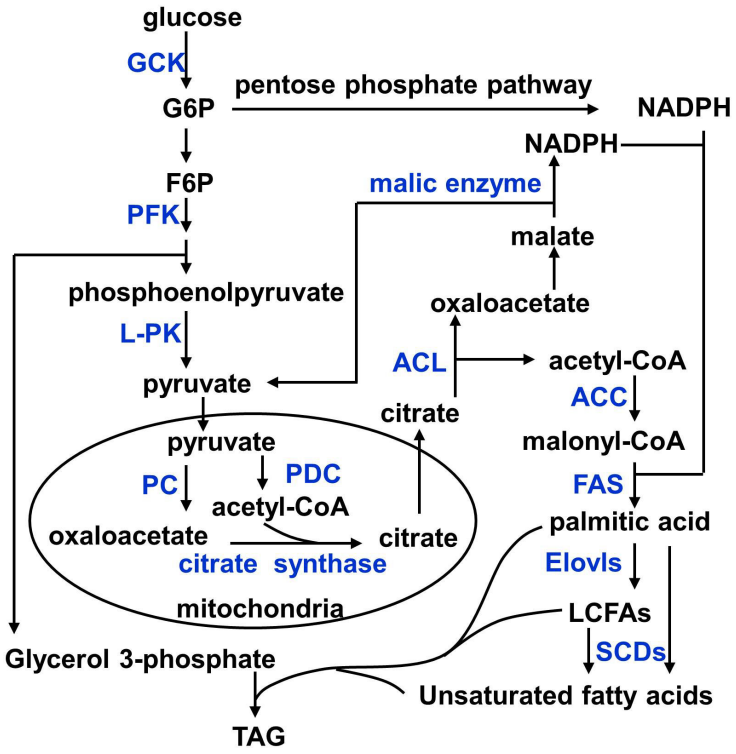

Fig. 3. Lipogenic pathways

Lipogenic enzymes are marked in blue. ACL: ATP-citrate lyase; ACC: acetyl-CoA carboxylase; FAS: fatty acid synthase; Elovls: fatty acyl-CoA elongases; SCDs: stearoyl-CoA desaturases; TAG: triacylglycerol.