ChREBP, a Transcriptional Regulator of Glucose and Lipid Metabolism

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Abstract

Dysregulations in hepatic lipid synthesis are often associated with obesity and type 2 diabetes, and therefore a perfect understanding of the regulation of this metabolic pathway appears essential to identify potential therapeutic targets. Recently, the transcription factor ChREBP (carbohydrate-responsive element-binding protein) has emerged as a major mediator of glucose action on lipogenic gene expression and as a key determinant of lipid synthesis in vivo. Indeed, liver-specific inhibition of ChREBP improves hepatic steatosis and insulin resistance in obese *ob/ob* mice. Since ChREBP cellular localization is a determinant of its functional activity, a better knowledge of the mechanisms involved in regulating its nucleo-cytoplasmic shuttling and/or its post-translational activation is crucial in both physiology and physiopathology. Here, we review some of the studies that have begun to elucidate the regulation and function of this key transcription factor in liver.

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VLDL: very-low-density lipoprotein

TG: triglyceride

GK: glucokinase

L-PK: liver-pyruvate kinase

SCD-1: stearoyl-CoA desaturase-1

ACC: acetyl-CoA carboxylase

INTRODUCTION

In mammals, the liver is crucial for maintaining overall energy homeostasis and for the conversion of carbohydrate into fat (**Figure 1**). The absorption of a high-carbohydrate diet induces several metabolic events aimed at decreasing endogenous glucose production by the liver and increasing glucose uptake and storage in the form of glycogen. When glucose is delivered into the portal vein in large quantities and hepatic glycogen concentrations are restored, glucose is converted in the liver into lipids (through de novo lipogenesis), which are exported as very-low-density lipoprotein (VLDL) and ultimately stored as triglycerides (TGs) in adipose tissue. The activity of the metabolic pathways leading to the synthesis of lipids in liver is strongly dependent upon the nutritional conditions. Indeed, a diet rich in carbohydrates stimulates the glycolytic and lipogenic pathways (**Figure 1**), whereas starvation or a diet rich in lipids decreases their activity. The genes encoding enzymes involved in these pathways include glucokinase (GK) (24), L-pyruvate kinase (L-PK) (55) for glycolysis, ATP citrate lyase (11), stearoyl-CoA desaturase (SCD-1) (43), acetyl CoA carboxylase (ACC) (29), and fatty acid synthase (FAS) (30) for lipogenesis (**Figure 1**). Most of these enzymes are acutely regulated by post-translational and allosteric mechanisms but are also controlled on a long-term basis by a modulation of their transcription rate. Indeed, it is now clear that glycolytic and lipogenic gene transcription requires both insulin and a high glucose concentration to be fully induced (14).

The absorption of carbohydrate in the diet leads to changes in glucose concentrations but is also concomitant with changes in the concentrations of pancreatic hormones, insulin, and glucagon. The transcriptional effect of insulin, long thought to be the main inductor of glycolytic and lipogenic gene transcription, is mediated by sterol regulatory element binding protein-1c (SREBP-1c), a transcription factor of the basic-helix-loop-helix-leucine zipper (bHLH/LZ) transcription factor family. SREBP-1c induces lipogenic genes by its capacity to bind to a sterol regulatory element (SRE) present in the promoter sequence of its target genes (2, 32, 38). SREBP-1c itself is regulated by changes in the nutritional status in liver of rodents (20), and in vitro studies in isolated hepatocytes have demonstrated that the transcription of SREBP-1c is induced by insulin and inhibited by glucagon (13). Transgenic mice that overexpress

SREBP-1c in the liver have increased mRNA of most lipogenic genes (50) and develop liver steatosis. Although it is clear that SREBP-1c plays a major role in the long-term control of glucose and lipid homeostasis by insulin, SREBP-1c activity alone does not appear to fully account for the stimulation of glycolytic and lipogenic gene expression in response to carbohydrate diet. In fact, SREBP-1c gene deletion in mice only results in a 50% reduction in fatty acid synthesis (34). In addition, overexpression of a constitutive active form of SREBP-1c in hepatocytes lacking GK (i.e., the enzyme that catalyzes the first step of glucose metabolism in liver) does not allow for a full induction of glycolytic and lipogenic gene expression by glucose and insulin (9).

Although it is clear that increased metabolism through GK is required to initiate glucose signaling, the intracellular mechanism and/or the transcription factor of the glucose-signaling pathway until recently was not fully understood (15, 56). Glucose- or carbohydrate-response elements (ChoREs) that mediate the transcriptional response of glucose have been identified in the promoters of most lipogenic genes through promoter-mapping analysis (48, 49). This element is composed of two E-box (CACGTG) or E-box-like sequences separated by 5 bp. The presence of E-box motifs in these response elements suggests that a bHLH protein family member recognizes the ChoRE and mediates the response to glucose. The recent discovery of a glucose-responsive bHLH/LZ transcription factor, named carbohydrate responsive element-binding protein (ChREBP) (60), has helped explain the mechanism whereby glucose affects gene transcription. This review examines the studies that have helped elucidate the function and regulation of this fascinating transcription factor in liver. We also discuss the recent implication of ChREBP in the physiopathology of hepatic steatosis and insulin resistance.

ChREBP PLAYS A CENTRAL ROLE IN GLUCOSE SIGNALING

Identification and Function of ChREBP in Liver

In 2001, using affinity chromatography and mass spectrometry, K. Uyeda's group (60) purified a large protein (864 amino acids and Mr = 94,600) that contains several domains, including a nuclear localization signal (NLS) near the N-terminus, polyproline domains, a basic loop-helix-leucine-zipper (b/HLH/Zip), and a leucine-zipper-like (Zip-like) domain (**Figure 2**). This protein, ChREBP, was soon identified as the long-sought glucose-responsive transcription factor. Indeed, when overexpressed in primary culture of hepatocytes, ChREBP induces the activation of an L-PK reporter construct (31). Studies from our laboratory later determined, and for the first time in a physiological context, that ChREBP mediates the transcriptional effect of glucose on both glycolytic (L-PK) and lipogenic (ACC, FAS) gene expression (9). We used small interfering RNA (siRNA) to selectively inhibit ChREBP expression in mouse hepatocytes. When cells were transfected with the ChREBP siRNA, the effect of high glucose concentrations (25 mM) on L-PK, ACC, and FAS gene expression was no longer observed (9). Chromatin immunoprecipitation analysis was later used to confirm that ChREBP directly binds to the promoter sequences of these genes (23).

ChREBP does not homodimerize or bind to the ChoRE as a homodimer (37, 52). Using the yeast two-hybrid system, Towle and coworkers (52) identified a bHLH/LZ protein, Mlx (Max-like protein X) that interacts with the bHLH/LZ domain of ChREBP (**Figure 2**). Mlx is a member of the Myc/Max/Mad family of transcription factors that can serve as a common interaction partner of a transcription factor network (41). The evidence that Mlx is the functional partner of ChREBP was demonstrated using an

FAS: fatty acid synthase

SREBP-1c: sterol regulatory element-binding protein-1c

bHLH/LZ: basic/helix-loop-helix/leucine zipper

SRE: sterol regulatory element

ChoRE: carbohydrate-responsive element

ChREBP: carbohydrate-responsive element-binding protein

Mlx: Max-like protein X

PKA: cAMP-dependant protein kinase

adenovirus expressing a dominant negative form of Mlx (37). The inhibition of Mlx directly interferes with the endogenous ChREBP/Mlx complex and abrogates the glucose response of the ACC reporter gene in primary cultures of hepatocytes (37). This glucose response, however, can be partially restored when ChREBP is overexpressed. The fact that this rescue only occurs at high glucose concentrations of recombinant ChREBP adenovirus suggests that sufficient ChREBP needs to be provided in the cell in order to titrate out the dominant negative effect of Mlx. Over the past three years, Towle's laboratory (35–37, 52) has explored in detail the regulatory domains of the ChREBP and/or Mlx proteins. According to a recent model proposed by Ma et al. (36), two ChREBP-Mlx heterodimers would bind to the two E boxes of the ChoRE to provide a transcriptional complex necessary for glucose regulation. The authors used a ChREBP/Mlx structural model followed by specific mutation experiments to identify three critical residues (F164, I166, and K170) within the Mlx loop that play a crucial role in the binding of the ChREBP/Mlx complex to the ChoRE (35). Therefore, it appears that the Mlx loop region, but not the loop region of ChREBP, is determinant for mediating the response of glucose. Mlx has a significantly longer loop domain than that of most other bHLH/LZ proteins, potentially allowing it to interact across the interface between heterodimer pairs. Therefore, it is possible that other proteins, via interactions involving the Mlx loop, could assist the binding of the ChREBP/Mlx complex to the ChoRE.

Regulation of ChREBP by Translocation and Phosphorylation-Dephosphorylation

ChREBP gene expression is induced by glucose in liver both in vitro (primary cultures of hepatocytes) and in vivo (9), but there are post-translational modifications that allow for a rapid activation of ChREBP. By transfecting a ChREBP-GFP fusion protein in primary cultures of hepatocytes, Uyeda and coworkers (31) first demonstrated that this transcription factor is rapidly translocated from the cytosol into the nucleus in response to high glucose concentrations (27.5 mM). We later confirmed these findings and showed that the endogenous ChREBP protein is indeed addressed into the nucleus in response to high glucose concentrations in primary cultures of mouse hepatocytes and in response to a high-carbohydrate diet in liver of mice (8). Although never demonstrated on the endogenous protein, the mechanism responsible for ChREBP nuclear translocation is thought to involve the dephosphorylation of serine residue 196 (Ser-196), target of cAMP-dependent protein kinase (PKA) and located near the NLS (**Figure 2**). According to the current model, under basal conditions (i.e., low glucose concentrations) ChREBP is phosphorylated on Ser-196 and localized in the cytosol. Under high glucose concentrations, protein phosphatase 2A (PP2A) is selectively activated by xylulose 5-phosphate (X5P), an intermediate of the nonoxidative branch of the pentose phosphate pathway, dephosphorylates ChREBP on this particular residue, and allows for its translocation in the nucleus (28) (**Figure 3**). However, because the importance of the PP2A-mediated dephosphorylation of Ser-196 in controlling the translocation process of ChREBP remains to be demonstrated in a physiological context, our laboratory has recently developed a phospho-specific antibody directed against ChREBP residue Ser-196.

Once in the nucleus, ChREBP undergoes a second PP2A-mediated dephosphorylation on residue Threonine 666 (Thr-666) that permits its binding to its ChoRE binding site and hence the transcriptional activation of its target genes (**Figure 3**). Lange and coworkers (58) have observed that the phosphorylation status of the endogenous ChREBP protein (using an in-gel phosphoprotein assay) is decreased under conditions of increased glucose flux through hepatic GK. The fact that

the overexpression of GK and the lower phosphorylation state of ChREBP were correlated to a 1.5-fold increase in X5P concentrations seems in agreement with the model initially proposed by Uyeda and colleagues (58). Although there is no doubt that ChREBP is a phosphoprotein, the fact that its activity is activated by dephosphorylation has brought some controversy. Studies from the laboratories of Towle and Chan have strongly challenged these concepts and have suggested that dephosphorylation is not responsible for the activation of ChREBP. The first insight came from the observation that although global phosphorylation of the endogenous ChREBP protein was increased under cAMP conditions, it did not change when hepatocytes were switched from low to high glucose concentrations (54). In addition, mutants of ChREBP, in which one or several of the proposed PKA phosphorylation sites are lacking (including Ser-196 and Thr666), retain the ability to respond to high glucose concentrations (54). More importantly, preventing PKA-mediated phosphorylation at these residues did not create a constitutive active form of ChREBP under low glucose concentrations (54). Taken together, these studies suggest that the post-translational regulation of ChREBP is complex and that mechanisms other than PKA phosphorylation may be required to mediate the glucose activation of ChREBP.

An alternative mechanism to the regulation of ChREBP by phosphorylation/dephosphorylation was also recently proposed (33). Using a structure-function analysis, Li et al. (33) identified within the ChREBP protein sequence a glucose-sensing module composed of a low-glucose inhibitory domain as well as a glucose-response activation conserved element. The specific inhibition of the transactivation activity of the glucose-response activation conserved element by the low-glucose inhibitory domain would confer the inactivity to ChREBP, this inhibition being modulated under high glucose concentrations. Therefore, according to this model, the glucose responsiveness of ChREBP would occur by an intramolecular mechanism independent of a regulation by phosphorylation or dephosphorylation. An interesting finding of this study is that a mutant of ChREBP deleted of its first 197 amino acids behaves as a constitutive active isoform of ChREBP, being transcriptionally active even at low glucose concentrations (33). This region does not contain the Ser-196, thereby excluding a regulatory role for this residue in ChREBP activation. It should be noted, however, that these studies were performed in INS-1-derived 832/13 cells and not in hepatocytes (33). Therefore, the possibility that the activation of ChREBP differs depending on its site of expression should not be excluded.

Finally, as mentioned above, ChREBP interacts with a functional partner, Mlx, to mediate the transcriptional glucose response of its target genes. Although the functional relevance of Mlx is now well established, several questions concerning its regulation remain unaddressed. To our knowledge, nothing is known about the regulation of Mlx by glucose (either transcriptional or post-translational). For example, it would be interesting to determine whether Mlx, like ChREBP, undergoes a nuclear translocation in response to glucose and in which cell compartment (cytosol or nucleus) the association between these two transcription factors occurs (**Figure 3**).

ROLE OF ChREBP IN THE PHYSIOPATHOLOGY OF HEPATIC STEATOSIS AND INSULIN RESISTANCE

Global Inactivation of ChREBP in Vivo

Only a few studies have addressed the role of ChREBP under either physiological or physiopathological conditions in vivo. Global ChREBP gene knockout mice (ChREBP$^{-/-}$) were generated in 2004 by Uyeda's laboratory, and the analysis of these mice has revealed the role of ChREBP in the control of glucose and lipid homeostasis (21). ChREBP$^{-/-}$ mice

NAFLD: nonalcoholic fatty liver disease

have impaired glycolytic and lipogenic pathways in liver and exhibit glucose and insulin intolerance (21). Although this study demonstrates the tight control exerted by ChREBP on hepatic lipogenesis in vivo, the tissue distribution of ChREBP makes the analysis of the phenotype complex. Indeed, the effect on glucose tolerance and insulin sensitivity cannot exclusively be attributed to the inactivation of ChREBP in liver, since this transcription factor is also expressed in other tissues that greatly contribute to the control of glucose homeostasis (i.e., skeletal muscles, white adipose tissue, brain, and pancreatic β cells) (**Figure 4**). In addition, the fact that ChREBP$^{-/-}$ mice also show reduced fat pads suggests that ChREBP may play a role in the development and/or function of this tissue. This hypothesis is confirmed by the fact that ChREBP expression is induced during 3T3-L1 preadipocyte differentiation (18). More research clearly is needed to determine the tissue-specific contribution of ChREBP in controlling the phenotypes observed in ChREBP$^{-/-}$ mice (**Figure 4**).

Finally, an unpredicted phenotype of the ChREBP$^{-/-}$ mice is their marked intolerance to fructose. In fact, the exclusive consumption of a diet enriched in fructose leads to premature death in these mice (21). The increase in fructose consumption in Western countries over the past 10–20 years has been linked with a rise in obesity and metabolic disorders. In rodents, fructose stimulates lipogenesis, leading to hepatic and extrahepatic insulin resistance as well as dyslipidemia (57). The cellular and/or molecular mechanisms leading to these deleterious metabolic effects remain largely unknown, but are associated with production of reactive oxygen species and activation of cellular stress pathways, engaging in particular the c-jun N-terminal kinase (57). An interesting finding is that administration of a high-sucrose diet (in which 68% of energy comes from sucrose) leads to higher hepatic concentrations of X5P than do standard diets (in which 68% of energy comes from cornstarch). This indicates that high-sucrose diets are highly lipogenic and stimulate the lipogenic pathway, at least in part, through the specific activation of ChREBP in liver. Nevertheless, further studies are required to delineate the deleterious effects of fructose in ChREBP$^{-/-}$ mice.

Molecular Mechanisms Leading to Hepatic Steatosis

The emergence of ChREBP in the control of lipogenic gene expression in liver prompted us to address its role in the physiopathology of hepatic steatosis. Indeed, fatty acids utilized for the synthesis of TG in liver are available from the plasma nonesterified fatty acid pool as well as from fatty acids newly synthesized through hepatic de novo lipogenesis. TGs can then be stored as lipid droplets within the hepatocytes or secreted into the blood as VLDLs; they can also be hydrolyzed and the fatty acids channeled toward β oxidation. Excessive accumulation of TG is one the main characteristics of hepatic steatosis, a pathological pattern that is now considered as a component of the metabolic syndrome (39) (**Figure 5**). Nonalcoholic fatty liver disease (NAFLD) is emerging as the most common chronic liver disease in the Western countries. NAFLD, which describes a large spectrum of liver histopathological features including simple steatosis, nonalcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma (5), is associated, in the vast majority of the cases, with obesity, insulin resistance, and type 2 diabetes. Therefore, with the epidemics of obesity and type 2 diabetes, NAFLD has become an important public health issue.

Although the molecular mechanism leading to the development of hepatic steatosis is complex, animal models have brought important information for the understanding of hepatic steatosis. For example, mice invalidated for the nuclear receptor PPARα develop steatosis during fasting, which illustrates the crucial role of β oxidation for the removal of fatty acids in the liver (17). Furthermore, a

deficiency in choline (which is essential for the export of triglycerides as VLDL) results in the development of a "fatty liver." Hepatic steatosis is also particularly developed in rodent models of obesity, such as *ob/ob* mice, *db/db* mice, and Zucker obese rats, in which an exaggerated lipogenesis has been observed in liver (3). Previously, transcription factors SREBP-1c (51, 59) and PPARγ (the PPARγ2 isoform) have been shown to contribute to the high rates of lipogenesis in livers of these mice (47). When *ob/ob* mice are crossed with either SREBP-1c knockout mice (51) or liver-specific knockout mice of PPARγ2 (40), they show a significant improvement in their hepatic steatosis but not of their overall insulin resistance. We thought that ChREBP, given its importance in the control of lipogenesis, could represent a good candidate to explain the development of the fatty liver phenotype of *ob/ob* mice (**Figure 5**).

Liver-Specific Inhibition of ChREBP in *ob/ob* Mice

We first established a possible molecular link between ChREBP and hepatic steatosis in *ob/ob* mice by determining that ChREBP gene expression and nuclear protein content were markedly increased in livers of these mice (7). We next took the approach of shRNA in vivo (through an adenoviral expression) to specifically inhibit the expression of ChREBP in liver. Our study demonstrated that ChREBP knockdown, both under short-term (two days) and long-term (seven days) conditions, significantly improves the fatty liver phenotype of *ob/ob* mice by decreasing rates of lipogenesis, thereby decreasing hepatic fat accumulation. As expected, the liver-specific inhibition of ChREBP not only markedly affected the expression of ACC and FAS, but also that of SCD-1, the rate-limiting enzyme catalyzing the conversion of saturated long-chain fatty acids into monounsaturated fatty acids, which are the major components of TG (12). Several recent studies have addressed the role of SCD-1 in the development of obesity and insulin resistance (16, 25). The inhibition of SCD-1 using antisense oligonucleotide inhibition (targeting both liver and adipose tissues) has been shown to prevent many of the high-fat-diet metabolic complications, including hepatic steatosis and postprandial hyperglycemia (16, 25). In these studies, the protective effect of SCD-1 on hepatic steatosis was attributed to a combined decrease in SREBP-1c gene expression (i.e., reduced lipogenic rates) and to the up-regulation of L-carnitine palmitoyl transferase I (L-CPT-I) gene expression (i.e., activation of the β-oxidation pathway). Since we did not observe any alteration in SREBP-1c mature protein content in livers of shChREBP RNA-treated *ob/ob* mice, we attributed the improvement of the fatty liver phenotype exclusively to ChREBP knockdown (7). Clearly, more studies are needed to determine the exact contribution of SREBP-1c and ChREBP in controlling fatty acid synthesis.

Interestingly, ChREBP knockdown not only affected the rate of de novo lipogenesis but also had consequences on β oxidation. Lipogenesis and β oxidation are directly correlated because malonyl-CoA, the allosteric inhibitor of CPT-1 (the rate-limiting enzyme of β oxidation) is synthesized by the lipogenic enzyme ACC. The fact that both ACC1 and ACC2 protein content was significantly lower in liver of fasted ChREBP-deficient mice probably led to a constitutive activation of L-CPT1 activity in liver. The significant decrease in malonyl-CoA concentrations and the increase in plasma β hydroxybutyrate levels measured in fasted mice support this hypothesis. Therefore, the coordinate modulation in fatty acid synthesis and oxidation in liver led to overall improvement of lipid homeostasis in ChREBP-deficient mice. Our study is in agreement with the fact that ACC2 gene knockout is also associated with increased rates of β oxidation in liver, leading to the improvement of overall lipid homeostasis in these mice (1).

Interestingly, our study also shows that ChREBP is not only required for the

G6P: glucose 6-phosphate

carbohydrate-induced transcriptional activation of enzymes involved in de novo fatty synthesis but also in TG synthesis, since gene expression was significantly decreased after shChREBP RNA treatment in *ob/ob* mice. Therefore, ChREBP appears to act as a central modulator of fatty acid concentrations in liver by transcriptionally controlling most of the lipogenic program (ACC, FAS, SCD-1), TG synthesis (at the level of glyceraldehyde 3-phosphate acyltransferase), and potentially VLDL export (R. Dentin & C. Postic, unpublished observations).

Improvement in Overall Glucose Tolerance and Insulin Sensitivity After ChREBP Knockdown

Excessive accumulation of hepatic fatty acids in liver is known to lead to deleterious effects on insulin signaling. In agreement with this concept, by markedly preventing fat accumulation in liver, ChREBP knockdown also significantly restored insulin sensitivity in liver. Although the phosphorylation by insulin of Akt, ERK1, ERK2, and Foxo1 was markedly decreased in liver of control *ob/ob* mice, ChREBP knockdown resulted in a significant improvement of insulin signaling in liver of treated *ob/ob* mice as evidenced by the restoration of Akt, ERK1, ERK2, and Foxo1 phosphorylation by insulin (7). Since the phosphorylation of Foxo1 by Akt inhibits its ability to activate gluconeogenesis (46), we hypothesized that restored Foxo1 phosphorylation may lead to an efficient inhibition of gluconeogenic genes in liver of Ad-shChREBP treated *ob/ob* mice. Indeed, after Ad-shChREBP treatment, glucose 6-phosphatase and phosphoenol pyruvate carboxykinase mRNA levels were significantly decreased in livers of *ob/ob* mice, demonstrating that the liver-specific inhibition of ChREBP was associated with a normalization of hepatic insulin signaling in treated *ob/ob* mice.

Interestingly, insulin sensitivity was restored not only in liver but also in skeletal muscles and adipose tissue, in which we also observed a significant improvement in Akt phosphorylation in response to the insulin bolus (7). As a result, glycogen content was restored to control levels in skeletal muscles from shChREBP RNA-treated *ob/ob* mice. Skeletal muscle is known to play a determinant role in the physiopathology of insulin-resistance, and defects in glycogen synthesis have been particularly implicated in the development of the pathogenesis (45). The beneficial effect of ChREBP knockdown was apparent on overall glucose tolerance and insulin sensitivity, with a significant improvement in hyperlipidemia, hyperglycemia, and hyperinsulinemia.

Our findings were also corroborated with the study of Uyeda and coworkers (22) in which the importance of ChREBP in the development of obesity and type 2 diabetes was addressed by intercrossing ChREBP-deficient mice with *ob/ob* mice (*ob/ob*-ChREBP$^{-/-}$ mice). Similar to what we observed, fat accumulation was prevented in liver of these mice, and their hyperlipidemic phenotype was significantly improved (22). An interesting role for ChREBP in the control of appetite was also uncovered by this study. ChREBP gene expression was reported in the brain, a tissue in which this transcription factor could play a role in the sensing of glucose (21) (**Figure 4**). Because of leptin deficiency, *ob/ob* mice are hyperphagic. Interestingly, food consumption was significantly reduced in *ob/ob*-ChREBP$^{-/-}$ mice and was associated with a 30% decrease in the expression of the appetite-stimulating neuropeptide AgRP. Whether ChREBP directly controls food intake or indirectly controls it through AgRP expression needs to be further addressed.

It should be noted that our study (7) and the study of Uyeda and coworkers (22) only addressed the role of ChREBP in the physiopathology of obesity and insulin resistance in the *ob/ob* mouse model. The limitation of this model, as mentioned above, is the fact that *ob/ob* mice are obese and

insulin resistant because of genetic deficiency of leptin. A model of diet-induced obesity in C57BL/6J mice would better address the role of ChREBP in a leptin-deficiency independent context. Nevertheless, these studies (7, 22) provide strong support for an important role of ChREBP in insulin resistance and diabetes associated with genetic obesity, and they suggest that ChREBP may represent a potential therapeutic target for the treatment of fatty liver disease and insulin resistance in the future.

PROTECTIVE EFFECT OF POLYUNSATURATED FATTY ACIDS: A ROLE FOR ChREBP

From a therapeutic point of view, dietary polyunsaturated fatty acids (PUFAs), which are potent negative regulators of lipogenesis, were previously shown to ameliorate not only hepatic steatosis of *ob/ob* mice but also notably to attenuate their insulin resistance. PUFAs are potent inhibitors of hepatic glycolysis and de novo lipogenesis, through the inhibition of genes involved in glucose utilization and lipid synthesis, including L-PK, FAS, and ACC. By regulating this pathway, PUFAs promote a shift from fatty acid synthesis and storage to oxidation (26). The positive effects of PUFA on hepatic steatosis are at least partially mediated by SREBP-1c because PUFAs markedly decrease the mature form of SREBP-1c in liver of *ob/ob* mice (**Figure 6**). However, since it has been previously reported that disruption of SREBP-1c in *ob/ob* mice does not influence their state of insulin resistance, we can speculate that ChREBP may be responsible for insulin sensitization by PUFA. Indeed, we have recently shown that ChREBP is central for the coordinated inhibition of glycolytic and lipogenic genes by PUFA (8). PUFA [linoleate (C18:2), eicosapentaenoic acid (C20:5), and docosahexaenoic acid (C22:6)] suppresses ChREBP activity by increasing its mRNA decay and by altering ChREBP protein translocation from the cytosol to the nucleus both in primary cultures of hepatocytes and in liver in vivo. The PUFA-mediated alteration in ChREBP translocation is the result of a decrease in glucose metabolism (i.e., an inhibition of the activities of GK and G6PDH, the rate-limiting enzyme of the pentose phosphate pathway) (8) (**Figures 1** and **6**). It remains to be determined whether PUFAs also exert a transcriptional effect on ChREBP gene expression. In the case of SREBP-1c, one of the mechanisms by which PUFAs suppress its gene transcription is through liver X receptor (LXR). PUFAs, by displacing oxysterol from LXR, antagonize the transactivation of LXR, at least in HEK293 cells (44). The recent observation that LXR transcriptionally regulates ChREBP gene expression (4) in liver may suggest that the inhibitory effect of PUFA on ChREBP occurs in an LXR-dependent manner.

PUFA: polyunsaturated fatty acid

LXR: liver X receptor

CONCLUSIONS AND PERSPECTIVES

Dysregulations in hepatic lipid synthesis are often associated with obesity and type 2 diabetes and, therefore, a perfect understanding of this metabolic pathway is essential in both physiology and physiopathology. With the discovery of ChREBP, our understanding of the long-term regulation of glucose and lipid metabolism in liver has recently made considerable progress. ChREBP deficiency overcomes the fatty liver phenotype and improves glucose tolerance and insulin resistance in *ob/ob* mice, suggesting that a reduction of ChREBP activity may have beneficial effect in the treatment of metabolic diseases associated with hyperglycemia and dyslipidemia. So far, the concept that de novo lipogenesis contributes to hepatic steatosis was only based on studies performed in rodents. Recent studies have shown that lipogenesis contributes significantly to TG synthesis in humans and that this metabolic pathway is increased in individuals with obesity and insulin resistance (10). Therefore, the implication of ChREBP in the development of hepatic steatosis

in human disease remains to be clearly addressed.

Since ChREBP cellular localization is a key determinant of its functional activity, a better knowledge of the mechanisms involved in regulating its nucleo-cytoplasmic shuttling and/or its post-translation regulation will be crucial in the future to develop novel therapeutic approaches for the study of diseases characterized by dysregulations of glucose and/or lipid metabolism. Indeed, although ChREBP is translocated in the nucleus under high glucose and insulin concentrations in cultured hepatocytes, it is in contrast retained in the cytosol in the presence of PUFAs, well-known inhibitors of lipogenesis. However, the exact mechanisms and/or potentially novel proteic partners involved in the sequestration of ChREBP under nutritional and hormonal conditions remain largely unknown.

In addition, the recent observations on ChREBP function suggest that the physiological roles of ChREBP may be broader and may not be limited to liver (**Figure 4**). The function of ChREBP in white adipose tissue may be of particular interest from a therapeutic point of view. The fact that troglitazone induces ChREBP gene expression during 3T3-L1 preadipocyte differentiation is an interesting observation that suggests that ChREBP may be directly regulated by thiazolidinediones or indirectly regulated through PPARγ (18). Nevertheless, the thiazolidinedione-mediated induction of ChREBP in adipose tissue may represent a way to decrease the hyperglycemic phenotype in diabetic patients.

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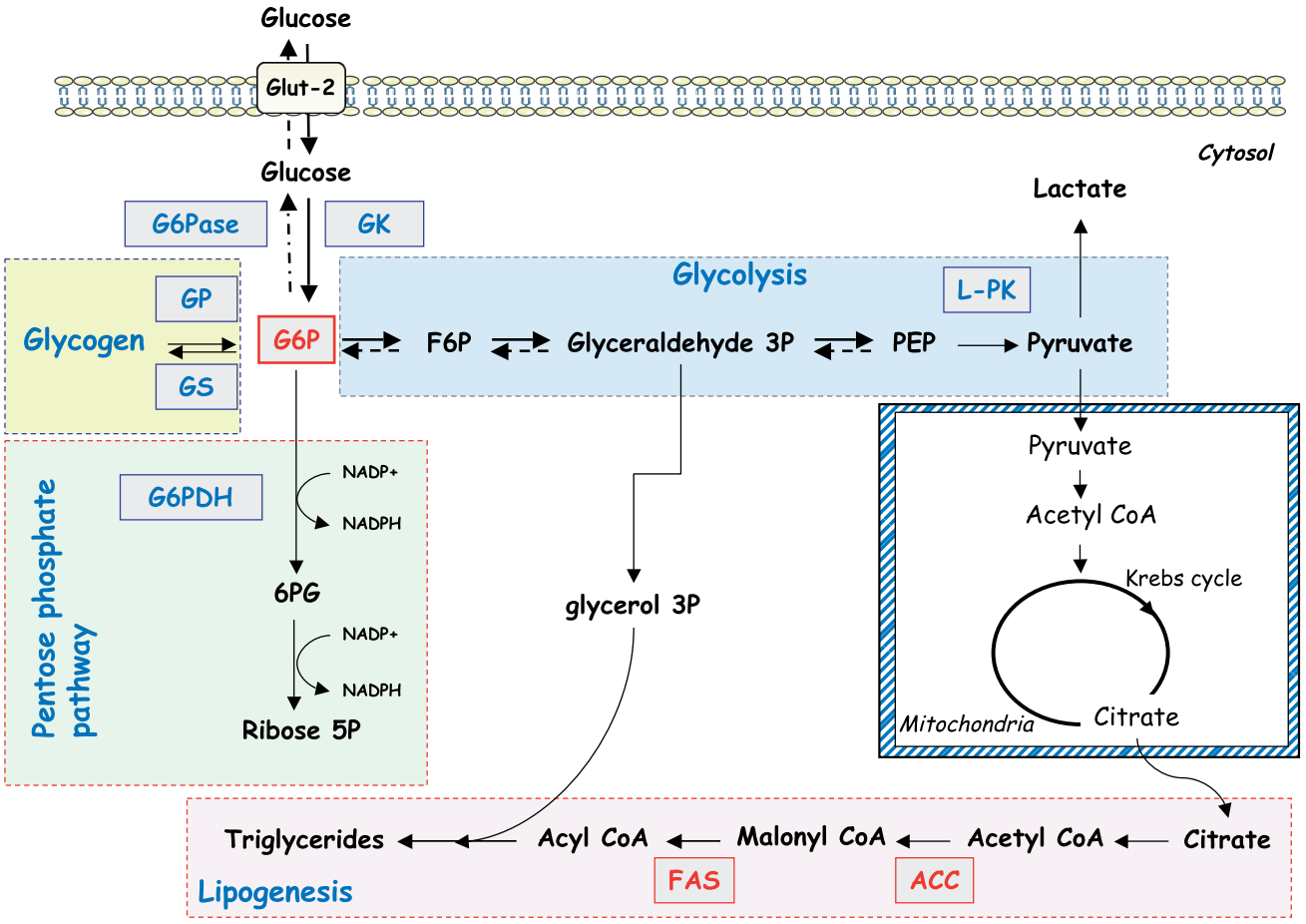

Figure 1

Metabolic pathways leading to the synthesis of triglycerides in liver. Abbreviations: ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; F6P, fructose 6-phosphate; GK, glucokinase; G6P, glucose 6-phosphate; G6Pase, glucose 6-phosphatase; G6PDH, glucose 6-phosphate dehydrogenase; GP, glycogen phosphorylase; GS, glycogen synthase, L-PK, liver-pyruvate kinase; PEP, phosphoenol pyruvate; TG, triglycerides; X5P, xylulose 5-phosphate.

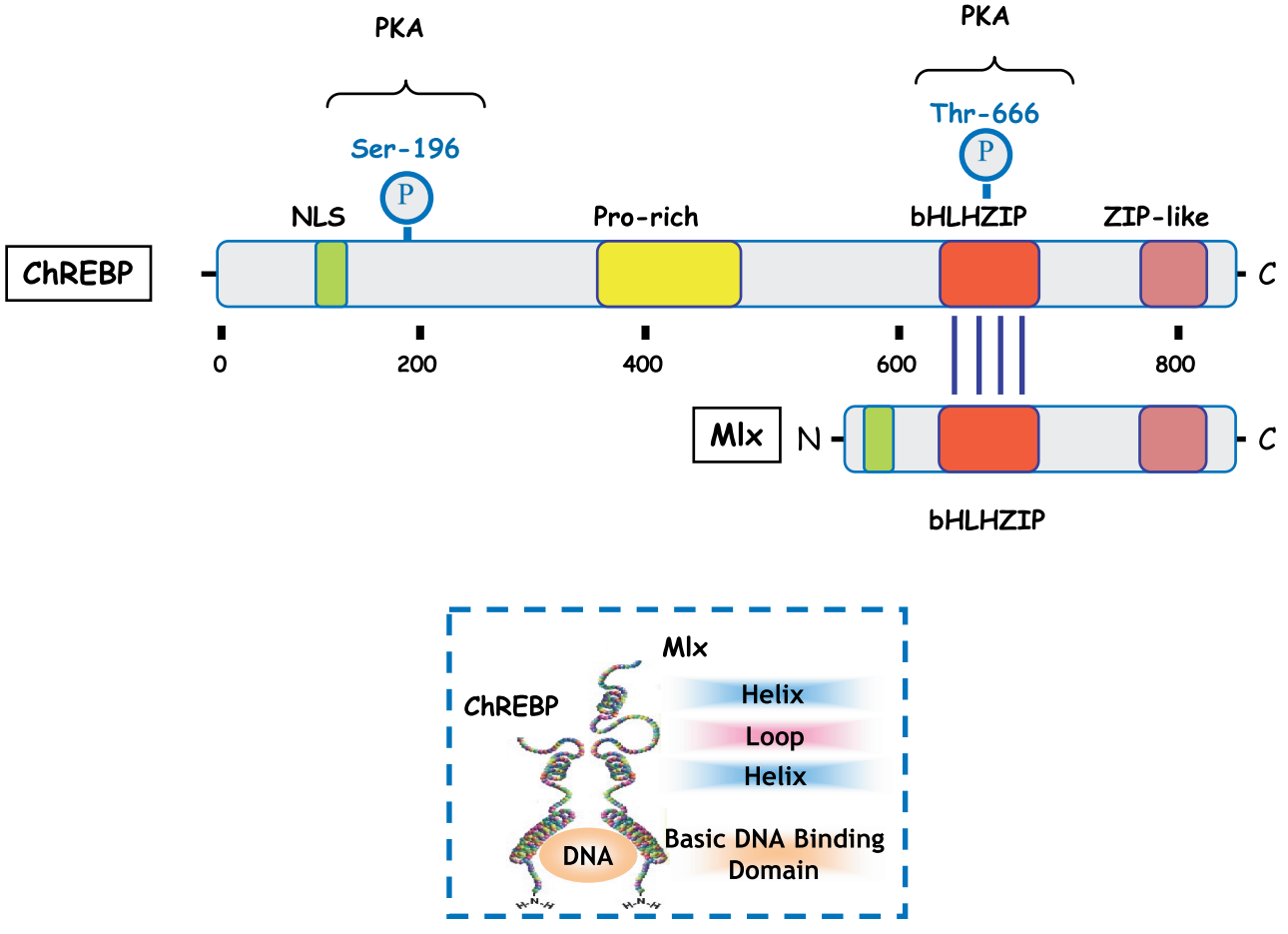

Figure 2

ChREBP and Mlx protein structures. Abbreviations: bHLH/LZ, basic loop-helix-leucine-zipper; ChREBP, carbohydrate-responsive element-binding protein; Mlx, Max-like protein X; NLS, nuclear localization signal; PKA, cAMP-dependent protein kinase.

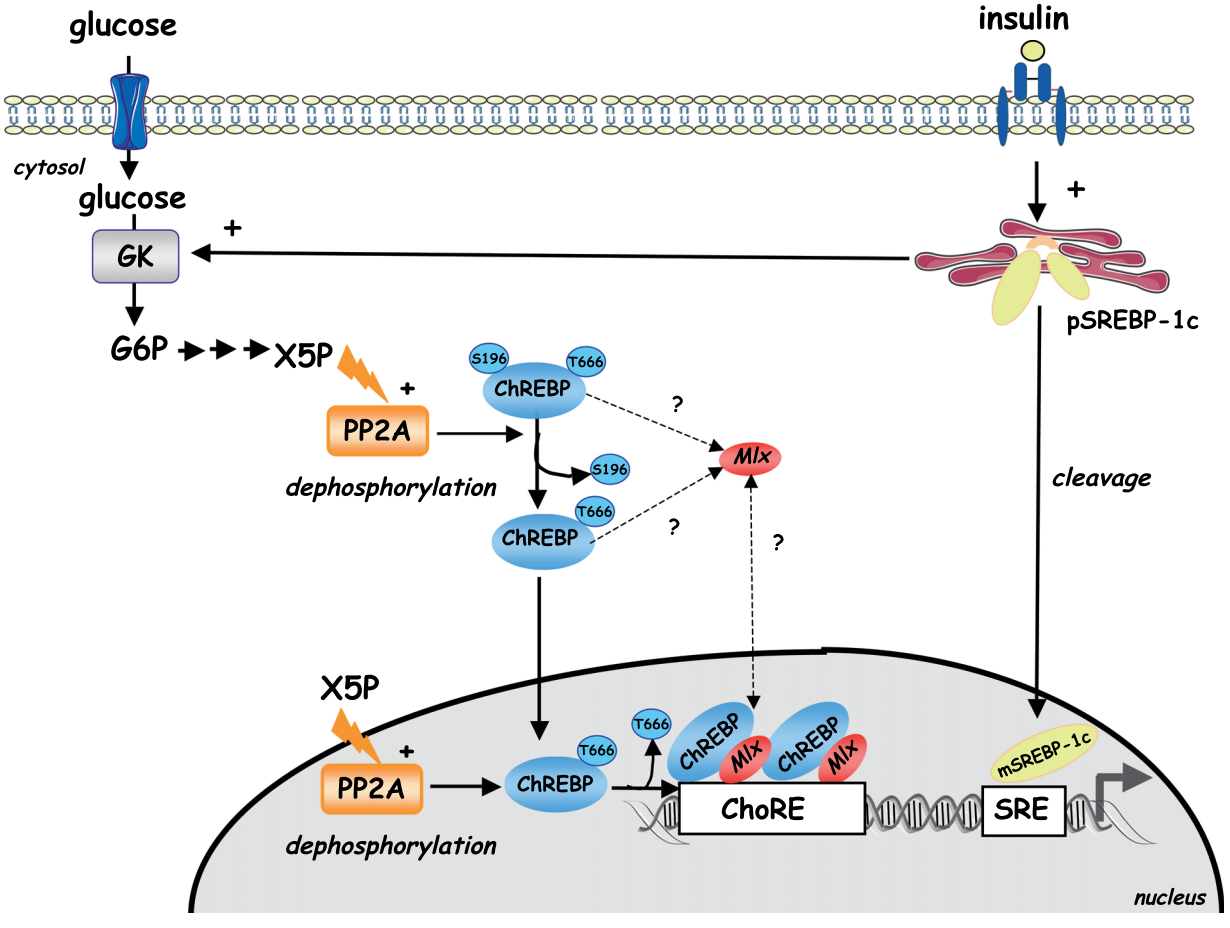

Figure 3

Transcriptional activation of glycolytic and lipogenic genes by ChREBP/Mlx and SREBP-1c in liver. Abbreviations: ChoRE, carbohydrate-responsive element; ChREBP, carbohydrate-responsive element-binding protein; GK, glucokinase; G6P, glucose 6-phosphate; Mlx, Max-like protein X; PP2A, protein phosphatase 2A; SRE, sterol regulatory element; SREBP-1c, sterol regulatory element-binding protein-1c; X5P, xylulose 5-phosphate.

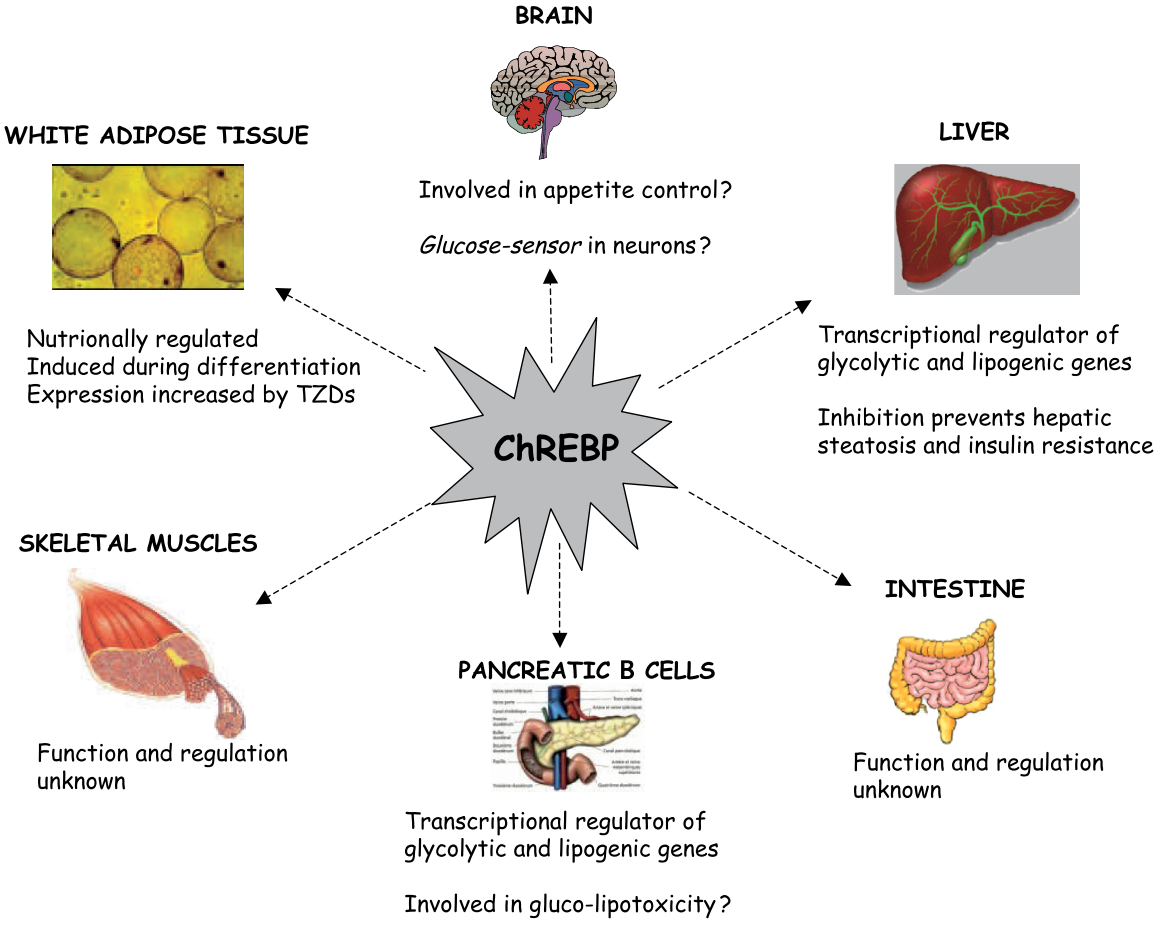

Figure 4

The multiple functions of carbohydrate-responsive element-binding protein (ChREBP). The metabolic and physiological roles of ChREBP may not be limited to the liver. In fact, the function of this transcription may be broader and of particular interest in other sites of expression, including white adipose tissue, brain, and pancreatic β cells (6).

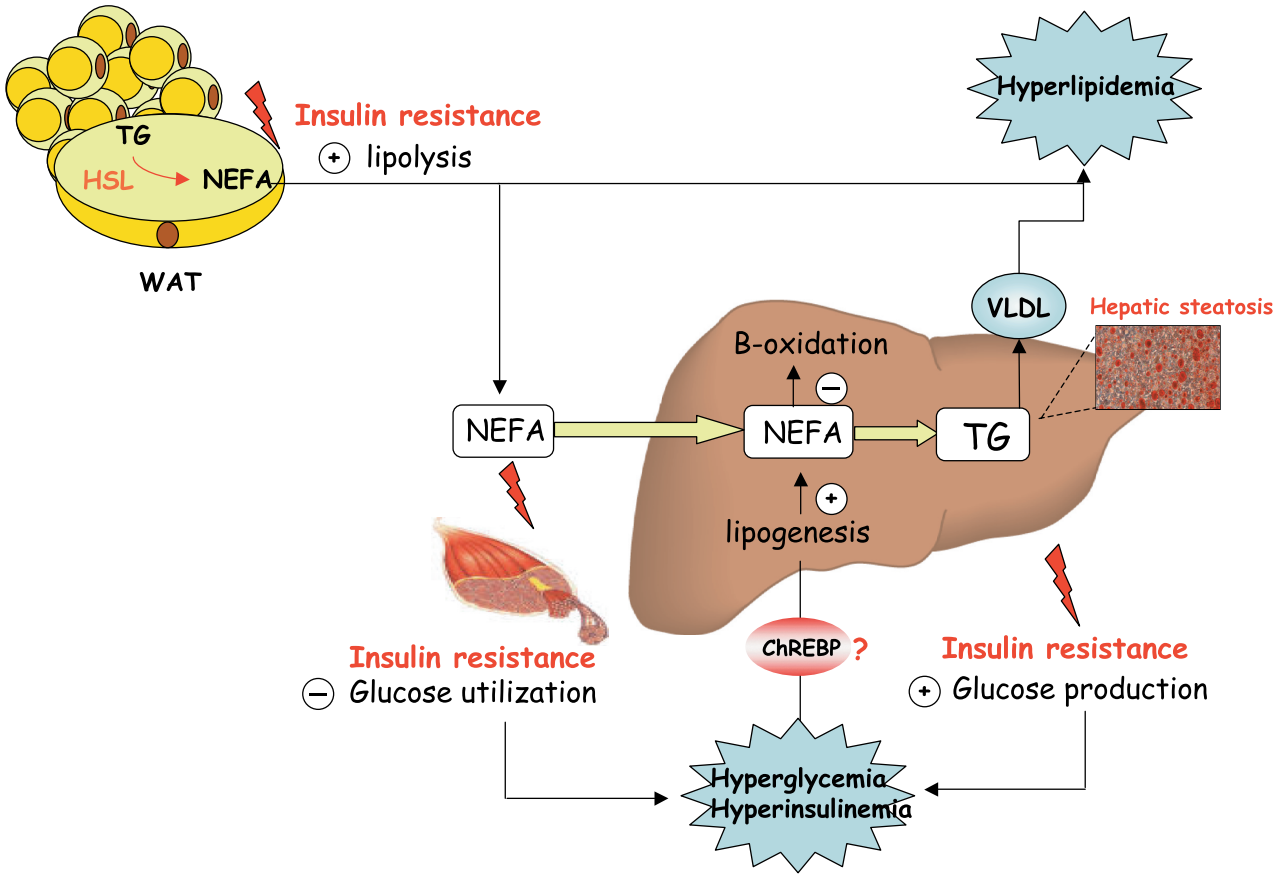

Figure 5

Metabolic defects leading to the development of hepatic steatosis and insulin resistance. Different sources of fatty acids contribute to the development of fatty liver. Under conditions of insulin resistance, insulin does not efficiently suppress lipolysis in the adipose tissue; therefore, peripheral fats stored in adipose tissue flow to the liver by way of plasma nonesterified fatty acids (NEFAs). Because of the circulating NEFAs, skeletal muscles become insulin resistant, and glucose utilization is reduced in this tissue. In addition, the combination of elevated plasma concentrations of glucose and insulin promotes de novo lipid synthesis and impairs β oxidation, thereby participating in the development of hepatic steatosis. The intrahepatic accumulation also has deleterious effects on insulin signaling in liver. Hepatic glucose production is exacerbated, leading to the development of the hyperglycemic phenotype. Recent studies have shown that hepatic lipogenesis contributes significantly to triglyceride (TG) synthesis in humans and that this metabolic pathway is increased in individuals with obesity and insulin resistance (10). Although the molecular mechanisms leading to excess fatty acid accumulation in insulin-resistant states have not been clearly resolved, recent studies have established that alterations in carbohydrate-responsive element-binding protein (ChREBP) expression can be correlated to the physiopathology of hepatic steatosis in genetically obese *ob/ob* mice (7, 22).

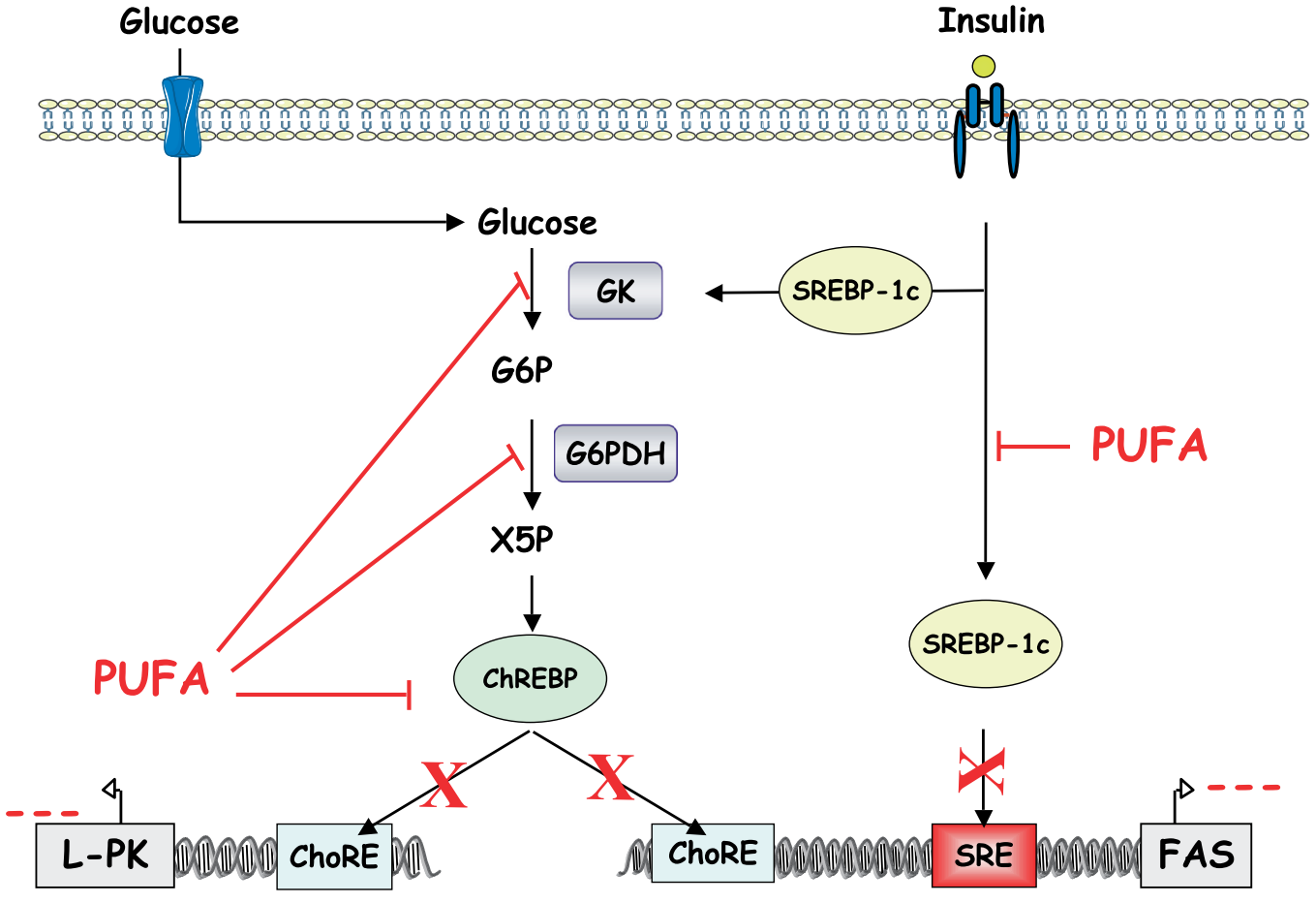

Figure 6

Inhibitory effect of PUFA on ChREBP and SREBP-1c expression and activation. Polyunsaturated fatty acids (PUFA) are potent inhibitors of hepatic glycolysis and de novo lipogenesis, through the inhibition of genes involved in glucose utilization and lipid synthesis, including L-PK, FAS, and ACC. With the identification of the transcription factor SREBP-1c, the molecular mechanism responsible for the PUFA inhibition of lipogenic genes has made important progress. Indeed, PUFA inhibit SREBP-1 gene transcription, enhance SREBP-1c mRNA turnover and interfere with the proteolytic processing of SREBP-1c protein (27). However, the PUFA-mediated suppression of L-PK gene expression cannot be directly attributed to SREBP-1c since L-PK expression is not subjected to SREBP-1c regulation (53) and its promoter does not contain a sterol regulatory element-binding site (SRE) (42). We have recently demonstrated that PUFA suppress ChREBP activity by increasing ChREBP mRNA decay and by altering ChREBP protein translocation from the cytosol to the nucleus, independently of an activation of the AMP-activated protein kinase (AMPK), previously shown to regulate ChREBP activity (8). In the presence of PUFA, ChREBP is retained in the cytosol through the specific inhibition of GK and G6PDH activities, two key enzymes of glycolysis and of the pentose phosphate pathway, respectively.

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Errata

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