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SREBP-1c Transcription Factor and Lipid Homeostasis: Clinical Perspective

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Key Words
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Abstract
Insulin has long-term effects on glucose and lipid metabolism through its control on the expression of specific genes. In insulin sensitive tissues and particularly in the liver, the transcription factor sterol regulatory element binding protein-1c (SREBP-1c) transduces the insulin signal. SREBP-1c is a transcription factor which is synthetized as a precursor in the membranes of the endoplasmic reticulum and which requires post-translational modification to yield its transcriptionally active nuclear form. Insulin activates the transcription and the proteolytic maturation of SREBP-1c. SREBP-1c induces the expression of a family of genes involved in glucose utilization and fatty acid synthesis and can be considered as a thrifty gene. Since a high lipid availability is deleterious for insulin sensitivity and secretion, a role for SREBP-1c in dyslipidaemia and type 2 diabetes has been considered in genetic studies and some association demonstrated. Finally, SREBP-1c could also participate to the hepatic steatosis observed in humans and related to alcohol consumption and hyperhomocysteinaemia, two pathologies which are concomitant with a stress of the endoplasmic reticulum and an insulin-independent SREBP-1c activation.

Introduction

Triglyceride storage in adipose tissue is a well-established feature of energy homeostasis. In recent years, it has become apparent that the ectopic accumulation of lipid stores in liver, muscle and pancreatic β-cell is associated with a number of diseases such as insulin resistance, metabolic syndrome and type 2 diabetes. Understanding the regulation of lipid metabolism is thus clearly of clinical importance. In this review, we will address the transcriptional regulation of one pathway of lipid metabolism, namely lipogenesis (endogenous synthesis of lipids) underlying the role of the transcription factor sterol regulatory element binding protein-1c (SREBP-1c) and addressing its potential importance in metabolic diseases.

The Lipogenic Process

Quantitatively, the main form of energy storage is represented by lipids in adipose tissue. The origin of the lipids stored can be either the diet or de novo synthesis from non-lipid substrates (lipogenesis). In mammals, a high and diet-controlled rate of lipogenesis is found mainly in the liver and adipose tissue. In rodents, a high lipogenic capacity is found in both liver and adipose tissue whereas in man, the liver is predominant. Lipogenesis is active in

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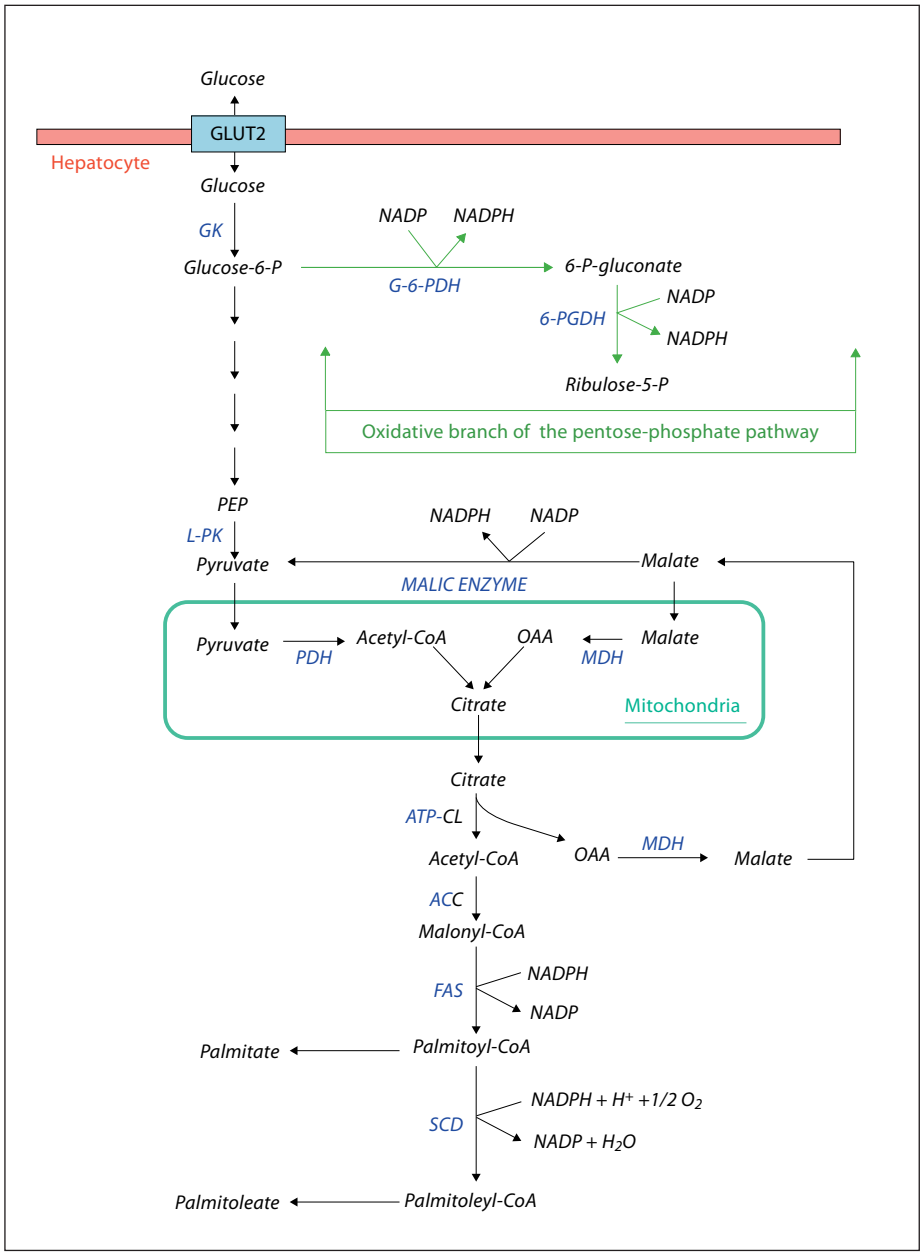

Fig. 1. The lipogenic pathway from glucose in the liver. The abbreviations used are the following: ACC = acetyl-CoA carboxylase; ATP-CL = ATP citrate lyase; FAS = fatty acid synthase; GK = glucokinase; GLUT2 = glucose transporter 2; G-6-PDH = glucose-6-P dehydrogenase; MDH = malate dehydrogenase; OAA = oxaloacetate; PDH = pyruvate dehydrogenase; 6-PG-DH = 6-phosphogluconate dehydrogenase, L-PK = liver pyruvate kinase; PEP = phosphoenolpyruvate; SCD = stearoyl-CoA desaturase.

case of a high carbohydrate supply and glucose is the main substrate of this pathway which is summarized for the liver in figure 1. The enzymes of the glycolytic pathway can be considered as an extended part of lipogenesis, since in the liver the major function of glycolysis is not to provide ATP but to allow the transformation of carbohydrates into fat. In addition, the oxidative branch of the pentose-phosphate pathway which generates the NADPH necessary for the reaction catalysed by fatty acid synthase (FAS) is also important for the lipogenic pathway (fig. 1).

In laboratory rodents, the lipogenic rate is usually high due to the high-carbohydrate, low-fat content of the chow diet. In contrast, in humans hepatic lipogenesis is often considered as negligible since high amounts of lipids are already present in a typical Western diet (35–40% of energy as fat). Recent quantitative analysis using isotopic methods in various nutritional and physiopathological conditions have shown that the fractional contribution of lipogenesis to VLDL triglycerides is 2–5% in normal subjects eating a typical Western diet but that high-carbohydrate, low fat, or simple-sugar enriched diets, obesity, al-

cohol consumption, non-alcoholic fatty liver disease and infectious states can strongly increase this proportion up to 20–30% [1–6].

Long-Term Regulation of Glycolytic/Lipogenic Enzymes

Regulation of the lipogenic flux by the nutritional environment is due to both short- and long-term regulations of enzyme activities. As stated above, we will focus here on the long-term transcriptional regulation of lipogenesis.

The expression of several key glycolytic and lipogenic enzymes is induced by a high-carbohydrate diet in the liver such as glucokinase, acetyl-CoA carboxylase (ACC), FAS, stearoyl-CoA desaturase-1 (SCD-1), glucose-6-phosphate dehydrogenase [reviewed in 7]. For most of these genes involved in glucose carbon utilization, the induction of their mRNA expression by a carbohydrate-rich diet is powerful (from 4 to 25 fold), rapid (in the 1–2 h range) and involves a transcriptional mechanism.

Absorption of a carbohydrate diet is concomitant with increases in the concentration of substrates such as glucose but also with an increase in insulin and a decrease in glucagon. From studies performed on primary cultured cells or cell lines, different kinds of gene regulation have emerged for genes involved in the lipogenic pathway: purely insulin sensitive genes such as hepatic glucokinase which can be induced by a high insulin concentration independently from the presence of glucose and genes which require both an increased insulin and glucose concentration in order to be induced, such as L-pyruvate kinase (L-PK), FAS, ACC, and SCD-1 [reviewed in 7]. Interestingly, glucagon is able to antagonize the effect of insulin and glucose on the expression of glycolytic/lipogenic genes.

Molecular Mechanisms Involved in the Control of Glycolytic/Lipogenic Genes by Insulin: The SREBP-1c Transcription Factor

The SREBP Family of Transcription Factors

A number of studies have shown that insulin action on this family of genes is mediated by a transcription factor called SREBP-1c. SREBP-1c belongs to a family of transcription factors originally involved in the regulation of genes by the cellular availability in cholesterol [8]. Three members of the SREBP family have been described in mammals, SREBP-1a, -1c and -2. SREBP-1a and -1c are encoded by a single gene through the use of alternative transcription start sites and differ by their first exon [9]. Another major difference between the 1a and 1c isoform is their tissue distribution. SREBP-1c is expressed in most of the tissues of mice and human with specially high levels in the liver, white adipose tissue, adrenal gland and brain [10]. SREBP-1c is also expressed in various muscles in adult rats and humans at appreciable levels [11, 12]. By contrast, SREBP-1a is mainly expressed in cell lines and in tissues with a high capacity of cell proliferation such as spleen and intestine [10]. The third member of the family, SREBP-2 is derived from a different gene and presents 50% homology with the SREBP-1 amino acid sequence. The three isoforms have a common structure : (i) an amino-terminal fragment of 480 amino acids which is in fact a transcription factor of the basic domain-helix loop helix, leucine zipper family, (ii) a region of 80 amino acids containing two transmembrane domains separated by 31 amino acids which are in the lumen of the endoplasmic reticulum (ER) and a regulatory C-terminal domain of 590 amino acids. Brown and Goldstein have elegantly unraveled the mechanisms by which the transcriptionally active fragment of SREBP-2 and -1a is liberated [13–15]. When the concentration of cholesterol decreases in the membranes, the precursor form of SREBP-2 and -1a is increased through an enhanced gene transcription. Then this precursor form is cleaved by a complex mechanism involving two proteolytic cleavages catalysed by two distinct proteases (site 1 protease [S1P] and site 2 protease [S2P]), a protein 'sensor' for the cholesterol concentration (SREBP cleavage activating protein [SCAP]) and an anchoring protein (Insig). The mature form migrates inside the nucleus where it activates the promoter of genes involved in cholesterol uptake or in cholesterol synthesis.

Transcriptional Regulation of SREBP-1c

In contrast to SREBP-2 and -1a, SREBP-1c expression and nuclear abundance is not increased in case of low cholesterol availability [16]. In fact, in rodents changes in nutritional status regulate the expression of SREBP-1c in the liver [17], white adipose tissues [18] and skeletal muscles [19, 20]. SREBP-1c expression is depressed during fasting but increases markedly when animals are refed a high carbohydrate diet. In contrast, such manipulations induce only minor effects on the expression of the other SREBP isoforms. Subsequent experiments in isolated adipocytes [18] and hepatocytes [21] showed that the transcription of SREBP-1c is induced by insulin. This induction of SREBP-1c transcription leads to a parallel increase

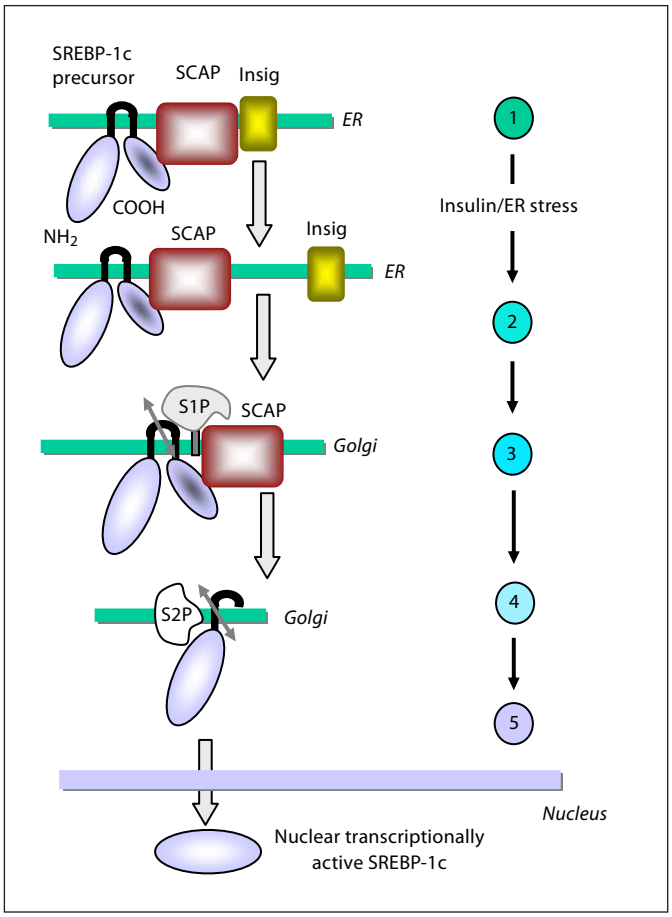

Fig. 2. The SREBP-1c proteolytic activation process. (1) The SREBP-1c/SCAP complex is retained in the endoplasmic reticulum (ER) by its interaction with Insig. (2) Under appropriate signals (insulin, ER stress), the SREBP-1c/SCAP complex migrates to the Golgi where SREBP-1c undergoes two sequential proteolytic cleavage steps by S1P and S2P (diagonal arrows) (3) and (4), yielding the mature active form of SREBP-1c which is translocated into the nucleus (5) and binds to specific response elements on the promoter of its targets genes.

in expression of both the ER membrane-bound precursor and the nuclear mature form of the transcription factor [22]. Insulin also induces the expression of SREBP-1c in adipose tissue and muscles of healthy human patients [11, 23]. The effects of insulin on SREBP-1c transcription are opposed in the liver by glucagon via cAMP [21]. Experiments showing that SREBP-1c mRNA expression is decreased in the livers of streptozotocin (STZ) diabetic rats and near normalized by insulin treatment, confirmed the role of insulin on SREBP-1c transcription in vivo [24]. The effects of insulin on SREBP-1c expression are mediated by a PI(3)-kinase dependent pathway [22, 25]. The downstream effectors remain unclear, with evidence suggesting that both PKB/Akt [25] and PKCλ [26, 27] may be involved. It is likely that SREBP-1c once activated by proteolytic cleavage stimulates its own promoter leading to an amplification of the initial proteolytic signal.

SREBP-1c transcription can also be induced by the activation of Liver X Receptor (LXR) α. LXRα is a nuclear hormone receptor with high hepatic expression that is activated by oxysterols (derivatives of cholesterol) [28, 29]. This transcription factor induces the expression of a range of genes involved in cholesterol efflux and clearance [30]. In addition, in vivo studies have identified a role for LXRα to induce SREBP-1c and lipogenic genes. Animals lacking LXRα exhibit reduced basal expression of SREBP-1c, FAS, ACC and SCD-1 [31, 32]. In contrast, animals fed a high cholesterol diet (a protocol which results in a strong decrease in the activation of SREBP-2 and -1a) or synthetic LXR agonists demonstrate a selective increase in SREBP-1c mRNA and nuclear protein, induced expression of lipogenic target genes and elevated rates of lipogenesis [32–34]. It is believed that LXRα acts as a cholesterol sensor. Consistent with its role, it has been proposed that LXRα induces SREBP-1c in order to generate fatty acids needed for the formation of cholesterol esters, which buffer the free cholesterol concentration [35]. LXRα mediates its induction of SREBP-1c via RXR/LXR DNA-binding sites in the SREBP-1c gene promoter [32, 36].

SREBPs Activation by Proteolytic Cleavage

Following SREBPs mRNA translation, SREBP-2 and -1a precursors are retained in the ER membranes through a tight association with SCAP and a protein of the Insig family [37] (fig. 2). Under the appropriate conditions, SCAP dissociates from Insig and escorts the SREBP precursors from the ER to the Golgi apparatus where two functionally distinct proteases, S1P and S2P, sequentially cleave the precursor protein releasing the mature form of SREBPs in the cytoplasm before its transfer to the nucleus [38]. SREBP processing can be controlled by the cellular sterol content [14]. In the presence of high sterol concentrations, the SREBP-SCAP complex is retained in the ER membranes. When sterol content decreases, the SREBP-SCAP complex moves to the Golgi apparatus where the cleavage takes place.

Interestingly, studies done in vivo have shown that sterol depletion does not regulate the cleavage of the SREBP-1c isoform [16] and recent studies in our laboratory have demonstrated that the SREBP-1c cleavage is

under the control of insulin, in the absence of any variation in sterol concentration [39] (fig. 2). So far, the mechanisms by which insulin acts on SREBP-1c cleavage are not known. But according to recent observations, one could suggest that Insig proteins could be responsible for the differential effects of insulin vs. sterols on the cleavage of the SREBP-1c and -2/1a isoforms. The Insig family is composed of three members: Insig-2a and -2b produced from a single gene by alternative promoters and splicing sites and Insig-1 from a separate gene [15, 40]. Insig-2a and -2b differ in their first non-coding exons, thus they produce the same Insig-2 protein. A major difference between Insig-2a and -2b is their tissue distribution; Insig-2a transcripts are mainly expressed in the liver whereas Insig-2b transcripts are ubiquitous. Interestingly, insulin decreases Insig-2a mRNA expression in the liver while it does not modify Insig-1 mRNA expression [40], suggesting that the following decrease in Insig-2a protein leads specifically to the cleavage of SREBP-1c. Further studies are needed to give a detailed picture of these mechanisms.

Hepatic Target Genes of SREBP-1c

Glucokinase

Hepatic and β-pancreatic glucokinases play a key role in glucose metabolism and β-cell insulin secretion as underlined by the diabetes mellitus associated to glucokinase mutations or by the consequences of tissue specific knock-outs [41, 42]. In addition to short-term regulations, glucokinase is regulated at a transcriptional level. Two different promoters direct glucokinase transcription in the liver or in pancreatic β-cells [42, 43]. The downstream promoter determines the expression of the hepatic glucokinase. In the liver, glucokinase transcription is activated by insulin alone and is repressed by glucagon via cAMP [43, 44].

Using dominant positive and negative forms of SREBP-1c cloned in adenoviral vectors [21, 45], we have shown in cultured hepatocytes that the transcriptional activity of SREBP-1c is absolutely necessary for insulin action on the glucokinase gene expression and that over-expression of the dominant positive form of SREBP-1c mimics the effects of insulin on this gene. In STZ diabetic mice, adenovirus-mediated over-expression of SREBP-1c in the liver resulted in an increase of glucokinase gene expression and activity as well as an increase in the hepatic glycogen content [46], mimicking the effect of an insulin injection. When mouse livers lack all forms of nuclear SREBP (SCAP or S1P deficient mice) the response of the glucokinase gene to refeeding is abolished [47]. The bulk of these studies demonstrated that SREBP-1c is essential for glucokinase expression and that it is a mediator of insulin action.

Lipogenic Genes

The involvement of SREBP-1c in insulin action on genes which require for their full expression both insulin and a high glucose concentration namely L-PK, FAS, ACC was also demonstrated [21, 45]. It must be pointed out that for lipogenic genes, it acts in concert with another transcription factor, namely ChREBP [48].

The importance of SREBP-1c for the expression of lipogenic genes was also demonstrated in vivo by showing that their induction by a high carbohydrate diet was precluded in SREBP-1 knock-out mice [49]. In STZ diabetic mice, adenovirus-mediated over-expression of SREBP-1c in the liver resulted in an increase of lipogenic enzyme expression [46], with an increase of the triglyceride hepatic content and a marked decrease in the hyperglycaemia of diabetic mice mimicking perfectly the effect of an insulin injection [46].

SREBP-1c Target Genes in Non-Hepatic Tissues

Adipose tissue was the first tissue for which an effect of insulin on SREBP-1c transcriptional activity was described and in which FAS promoter was identified as a SREBP-1c target [18]. The action of insulin on SREBP-1c expression in human adipocytes was also demonstrated [11]. Other genes such as the LDL receptor and SCD-1 have been since characterized as SREBP-1c and insulin target genes, as well as the transcription factor CCAAT/enhancer-binding protein β [50] and hexokinase II [51] which is the equivalent of liver glucokinase in terms of glucose metabolism. SREBP-1c has also been implicated in adipose tissue differentiation [52]. However, experiments in which SREBP-1c levels have been manipulated in the adipose tissue of mice have been less clear in elucidating a role for this transcription factor in adipogenesis. Over-expression of SREBP-1c using the adipose-specific aP2 promoter would be expected to promote fat cell development, but instead resulted in the opposite phenotype: lipodystrophy [53]. On the other hand, Horton et al. [54] have shown that over-expression of the SREBP-1a isoform in adipose tissue of mice resulted in hypertrophy of adipocytes. It is thus difficult to conclude at present concerning the in vivo role of SREBP-1c in adipocyte differentiation.

In muscles, SREBP-1c expression and nuclear abundance is also stimulated by insulin [11, 12] and target genes include genes involved in the lipogenic pathway as

well as hexokinase II. Hexokinase II has a major role in terms of insulin-induced glucose utilization since it is the first enzyme of muscle glucose metabolism which thus feeds both glycogen synthesis and glycolysis.

In pancreatic β-cells or in pancreatic β-cell lines, over-expression studies have clearly shown that SREBP-1c controls as in the liver the expression of lipogenic genes [55–58]. At present, whether, the control of SREBP-1c by insulin is similar to the one observed in the liver is not clear.

SREBP-1c: Clinical Perspectives

Insulin Sensitivity and Secretion

In terms of relationship with metabolic diseases, SREBP-1c can be considered from two opposite perspectives. First, as a transcription factor central for the actions of insulin on both carbohydrate and lipid metabolism, a loss of function should ultimately lead to a phenomenon of insulin resistance. Interestingly enough, in SREBP-1c knock out mice there is a tendency for a higher basal plasma glucose when compared to wild type mice and a higher glycaemia during a carbohydrate refeeding period (it must be pointed out that the relatively mild metabolic phenotype in these mice could be due to a partial compensation by the SREBP-1a and -2 isoforms, since the knock-out of both SREBP-1c and -1a isoforms is virtually lethal) [47]. On another hand, SREBP-1c promotes fatty acid synthesis and lipid deposition. Since lipids have been largely implicated in the development of insulin resistance by mechanisms involving substrate competition, antagonism of insulin signalling or lipotoxicity [59], SREBP-1c could also be considered as a factor responsible for insulin resistance. Liver over-expression of SREBP-1c has indeed been described in several models of insulin resistance such as lipodystrophic and ob/ob mice [60], insulin receptor substrate-2 knock out mice [61] and Zucker obese fa/fa rats [62]. Thus a mutation inducing a gain of function for SREBP-1c could also be responsible for insulin resistance. SREBP-1c has been incriminated in the development of human metabolic physiopathology such as obesity, type 2 diabetes, dyslipidaemia, atherosclerosis, global syndrome X and lipodystrophy. In adipose tissue of obese and type 2 diabetic patients, SREBP-1c mRNA expression was found to be decreased in comparison with lean subjects [11, 23, 63–66]. These observations are consistent with DNA microarray studies in animal models showing down-regulation of SREBP-1c in adipose tissue of *ob/ob* mice and obese mice progressing to overt diabetes [67, 68]. The resistance to insulin observed in obesity and type 2 diabetes has been involved in order to explain the diminished SREBP-1c expression observed. Consistent with this hypothesis, weight loss in obese patients, which is associated with an improved insulin-sensitivity, is also concomitant with an increase in SREBP-1c expression in adipose tissue [63–65]. In muscle, SREBP-1c mRNA expression is decreased in type 2 diabetic patients but not in obese patients [11, 23].

Several studies demonstrated that over-expression of SREBP-1c in pancreatic β-cell lines or islets lead to a marked reduction in glucose-stimulated insulin secretion and this was attributed to the concomitant triglyceride accumulation and the subsequent lipotoxicity [56, 57, 69]. In Zucker diabetic fa/fa rats an inappropriately high expression of SREBP-1c and its target lipogenic genes was found in islets inducing increased triglyceride storage that can lead to lipotoxicity and end up in diabetes [62].

SREBP-1c and Hepatic Steatosis

Due to obvious limitations, SREBP-1c mRNA expression in human liver cannot be studied but data in animal models are available. SREBP-1c levels are elevated in the fatty livers of obese, insulin-resistant and hyperinsulinaemic *ob/ob* mice [60, 70]. Despite the profound insulin resistance of the liver concerning glucose production in these mice, SREBP-1c transcription and protein expression is still activated in their liver. This could be explained by the fact that insulin resistance of the glucose producing pathways is due to the down-regulation of the second messenger protein Insulin-Receptor-Substrate-2 (IRS-2) whereas insulin-induced SREBP-1c transcription is dependent on the IRS-1 isoform which is not down-regulated in these mice. Alternatively, SREBP-1c cleavage could be secondary to another signalling pathway. In this respect, a number of studies have invoked an activation of the ER stress pathway. The ER is a specialized organelle that synthesizes secretory and membrane proteins, which are ultimately folded and assembled by chaperones in the ER. Alterations of ER homeostasis such as disturbances in calcium concentration or elevated synthesis of secretory proteins induce an adaptive coordinated response of ER called ER stress or UPR (Unfolded Protein Response) to limit accumulation of unfolded protein. The physiological response to ER stress is regulated by three ER transmembrane proteins, the kinase and endonuclease IRE1 (Inositol Requiring enzyme 1), the PERK kinase and the transcription factor ATF6 [71]. The activation of all three components of the UPR depends on the disso-

ciation of the luminal chaperone BiP/GRP78 from these signalling proteins. Indeed, BiP/GRP78 dissociation from ATF6 results in the transit of ATF6 from the ER to the Golgi where it is cleaved yielding an active transcription factor. The releasing of IRE1 and PERK from BiP/GRP78 also induces their homodimerization, autophosphorylation and activation. Once activated, these three pathways up-regulate the expression of genes encoding proteins involved in the secretory pathway [72]. The ER stress response is also concomitant with the expansion of its membranes, thus increasing its capacity to perform correctly its protein folding functions.

Patients suffering from severe hyperhomocysteinaemia, a pathology characterized by an elevation of plasma homocysteine concentration, present an important risk factor for atherosclerotic arterial disease and develop hepatic steatosis. It has been reported that homocysteine induces an ER stress and that this is concomitant with the activation of SREBP in cultured human hepatocytes and in vascular endothelial cells [73]. Alcohol has been shown to promote an increase in both SREBP-1c expression and its nuclear form [74, 75] as well as ER stress [76]. These mechanisms could partially explain the hepatic steatosis observed in individuals suffering from hyperhomocysteinaemia or drinking alcohol in which a high rate of lipogenesis has been demonstrated. In addition, an ER stress has also been described in the liver of obese mice which are characterized by insulin resistance, high concentration of mature SREBP-1c and a high rate of lipogenesis [77]. It has recently been suggested that in pancreatic β-cells, hyperglycaemia-induced ER stress could activate SREBP-1c [78], thus promoting lipid synthesis and inducing lipotoxicity which could participate in the decrease in insulin secretion observed in type 2 diabetic subjects undergoing episodes of acute hyperglycaemia. The cellular pathways by which an ER stress induces the cleavage of SREBP-1c remain unknown. It can be nevertheless underlined that the S1P and S2P proteases, which are involved in the proteolytic cleavage of SREBPs, are also implicated in the release of ATF6, one of the three ER stress transducers, from the ER membrane.

Interestingly, metformin, one of the most largely used hypoglycaemic drug is able to decrease hepatic lipogenesis [79]. Indeed, in the liver, metformin through its partial mitochondrial uncoupling effect, activates a kinase called AMP-activated protein kinase which is stimulated by a decreased ATP/AMP ratio [79]. When activated, this kinase strongly inhibits the expression of lipogenic enzymes [80] through an inhibition of SREBP-1c transcriptional activity [79]. Metformin could thus theoretically contribute to decrease hepatic steatosis. It must be pointed out however, that the metformin treatment of patients with non-alcoholic fatty liver has yielded controversial results [81].

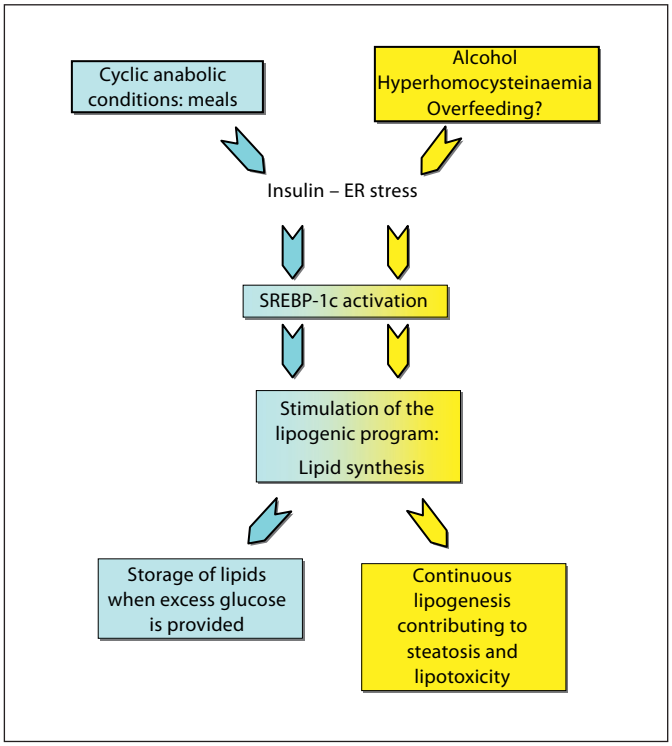

Fig. 3. Summary of the physiological and pathophysiological roles of SREBP-1c.

Genetic Association of SREBP-1 with Metabolic Diseases

Genome scan studies have linked the 17p11 region, comprising the human *SREBP-1* gene locus [9], to plasma leptin concentrations [82], body mass index [83] and type 2 diabetes [84].

An extensive molecular screening of the whole *SREBP-1* gene was performed for Single Nucleotide Polymorphisms (SNPs) detection [85]. By case-control and association studies in large French obese, diabetic, and non-obese non-diabetic cohorts, we have shown that SNPs of the *SREBP-1* gene were associated with obesity and type 2 diabetes. Moreover, SNPs were associated with male-specific hypertriglyceridaemia within the obese group. Laudes et al. [86] identified a common variant linked to type 2 diabetes risk in men and plasma cholesterol level. Previous genetic studies of *SREBP-1* SNPs have

observed modifications in lipid parameters in predominantly male populations [87–89]. Vedie et al. [87] observed that a *SREBP-1* SNP was associated with an atherogenic lipid profile in men at high cardiovascular risk. In a study evaluating fluvastatin treatment, patients demonstrated differentially modified lipid parameters according to *SREBP-1* genotypes [89]. Another study of highly active antiretroviral therapy (HAART) in HIV-1-infected patients showed that *SREBP-1* SNP carriers had a high risk of developing hyperlipoproteinaemia [88]. SREBP-1 related dyslipidaemia seem thus to develop in particular pathophysiological contexts, suggesting that gene-gene and/or gene-environment interactions could be necessary for the phenotype expression. In all the studies described above, no functional data concerning the variants identified were provided. Vernia et al. [90] have described the first SREBP-1 mutation found in a type 2 diabetic patient that modifies the function of the protein, diminishing its DNA binding efficiency and its ability to activate the transcription of target genes. Unfortunately, family data were not available for cohort studies and it is thus difficult to directly relate the observed mutation and the type 2 diabetes of the patient.

Conclusion

SREBP-1c is a transcription factor which responds to insulin and is essential for glucose carbon utilization and storage through the activation of hexokinase expression and the onset of the lipogenic program. It can thus be considered as a gene involved in long-term energy storage (fig. 3) and part of the thrifty gene family.

For reasons which are not entirely clear but which could be related to cellular membrane growth, it is also involved in the ER stress response and the activation of SREBP-1c could explain some of the lipid disorders often associated with ER stress such as steatosis and lipotoxicity (fig. 3).

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