The role of the lipogenic pathway in the development of hepatic steatosis

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Abstract

Non-alcoholic fatty liver disease (NAFLD) represents a wide spectrum of diseases, ranging from simple fatty liver (hepatic steatosis) through steatosis with inflammation and necrosis to cirrhosis. NAFLD, which is strongly associated with obesity, insulin resistance and type 2 diabetes, is now well recognized as being part of the metabolic syndrome. The metabolic pathways leading to the development of hepatic steatosis are multiple, including enhanced non-esterified fatty acid release from adipose tissue (lipolysis), increased de novo fatty acids (lipogenesis) and decreased β-oxidation. Recently, several mouse models have helped to clarify the molecular mechanisms leading to the development of hepatic steatosis in the pathogenesis of NAFLD. This review describes the models that have provided evidence implicating lipogenesis in the development and/or prevention of hepatic steatosis.

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Résumé

Rôle de la lipogenèse dans le développement de la stéatose hépatique

Les maladies métaboliques du foie représentent plusieurs syndromes qui vont de la simple stéatose hépatique à la stéatose hépatique inflammatoire (stéato-hépatite) pouvant évoluer vers la nécrose et même la cirrhose. La stéatose hépatique est très fortement associée à l’obésité, la résistance à l’insuline et le diabète de type 2. Les voies métaboliques, qui peuvent conduire au stockage excessif de lipides dans le foie (principalement des triglycerides), sont multiples et peuvent être liées à une augmentation exacerbée de la lipolyse adipo-cyttaire, une synthèse accrue de la synthèse de novo des acides gras par voie de la lipogenèse ainsi qu’à une réduction conjointe de la β-oxidation des acides gras. Au cours des dernières années, des modèles animaux ont permis une meilleure compréhension des mécanismes moléculaires impliqués dans le développement de la stéatose hépatique. Cette revue présente et discute certains des modèles qui ont permis de révéler l’importance de la voie de la lipogenèse dans l’apparition et/ou la prévention de la stéatose hépatique.

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Keywords: NAFLD; Hepatic steatosis; Lipogenesis; Insulin resistance; Review.

Mots clés : Maladies métaboliques du foie ; Lipogenèse ; Stéatose hépatique ; Résistance à l’insuline ; Revue.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is an increasingly common health concern that is considered to be a component of the metabolic syndrome. Excessive accumulation of triglycerides (TG) in hepatocytes is the hallmark of NAFLD. The spectrum of NAFLD can range from simple fatty liver (hepatic steatosis), with a benign prognosis, to the potentially progressive form of non-alcoholic steatohepatitis (NASH), which can lead to fibrosis and cirrhosis, resulting in increased morbidity and mortality. All features of the metabolic syndrome, including obesity, type 2 diabetes, arterial hypertension and hyperlipidemia (elevated TG levels), are associated with NAFLD/NASH [1,2]. The diagnosis of NAFLD is based clinically on high transaminase levels, a high body mass index (BMI), and ultrasound evidence of fat and features of the metabolic syndrome. Liver biopsies are, however, necessary to determine the presence of NASH and to assess the degree of fibrosis [3]. There is currently no generally accepted treatment...
En général, les graisses stockées dans le tissu adipeux blanc qui flottent à la rate.

(i) Augmentation de la lipolyse des lipides périphériques [notamment par le transport d’acides gras provenant du tube digestif]; (ii) augmentation de la lipolyse des acides gras acétylés [notamment à travers le transport de chylomicrons]; (iii) phagocytose et enfin le stockage par le foie. Cependant, le potentiel des sources de graisses (principalement TG) qui s’accumulent reste largement inconnu. Les sources potentielles d’acides gras à la rate dans le cadre de la NAFLD sont la lipolyse des tissus adipeux périphériques, l’accumulation de graisse dans le foie ou la rate et les acides gras nouvellement fabriqués par le foie à partir de l’apport énergétique.

3. Targeting the lipogenic pathway to prevent hepatic steatosis in mice

De novo fat synthesis (lipogenesis) is the metabolic pathway leading to the conversion of an excess of carbohydrates into fatty acids, which are ultimately esterified with glycerol-3-phosphate to form TG. The activity of the lipogenic pathway is strongly dependent upon nutritional conditions, and it is now clearly established that lipogenic enzyme transcription requires both insulin and glucose to be fully induced [12]. Conditions associated with high rates of lipogenesis, such as a low-fat/high-carbohydrate (LF/HC) diet, hyperglycemia and hyperinsulinemia, are associated with a shift in cellular metabolism from lipid oxidation to TG esterification, thereby increasing the availability of liver TG. The enzymes involved in the synthesis of TG in liver include: (i) glucokinase (GK) [13] and L-pyruvate kinase (L-PK) [14] for glycolysis; (ii) ATP citrate lyase [15], acetyl-CoA carboxylase (ACC) [16] and fatty acid synthase (FAS) [17] for lipogenesis, and long-chain elongase (Elovl6; LCE) [18] and stearoyl-CoA desaturase 1 (SCD1) [19], catalyzing fatty acid elongation and desaturation steps; and (iii) mitochondrial glycerol-3-phosphate acyltransferase (GPAT) and diacylglycerol acyltransferase (DGAT) for TG synthesis [20] (Fig. 1).
Although rodent models of hepatic steatosis and/or insulin resistance do not always perfectly reproduce the human pathology of NAFDL, the use of transgenic, knockout and knockdown mouse models has helped, over the years, to achieve a better understanding of the molecular determinants of NAFDL [21]. Key enzymes of fatty acid synthesis/desaturation/elongation/esterification such as ACC, SCD1, Elovl6, GPAT and DGAT [22-28] have been shown, when knocked down, to reverse many of the metabolic defects associated with hepatic steatosis and/or insulin resistance, indicating that decreased TG synthesis in liver is a potential and interesting target for the treatment of NAFDL. Among them, SCD1 has emerged as a particularly interesting target for the reversal of hepatic steatosis and insulin resistance [29]. SCD1 is a delta-9 fatty acid desaturase that converts saturated fatty acids (SFA) into monounsaturated fatty acids (MUFA), particularly oleate (C18: 1n-9) and palmitoleate (C16: 1n-7). MUFA are major components of membrane phospholipids, TG and cholesterol esters. SCD1-deficient mice [23] or mice treated with SCD1 antisense nucleotides [24] are protected against diet-induced obesity and insulin resistance when fed a high-carbohydrate/high-fat (HC/HF) diet. The protective effect of SCD1 deficiency is attributed to these mice to a combined decrease in lipogenic rates and activation of the β-oxidation pathway, underlying the metabolic link between these two pathways. Indeed, elevated malonyl-CoA concentrations, the metabolic product of lipogenic ACC, inhibit carnitine palmitoyltransferase 1 (CPT-1), the rate-limiting enzyme of β-oxidation, and regulate the transfer of long-chain acyl-CoAs (LCCoAs) from the cytosol into the mitochondria, thereby resulting in a shift from an oxidative to a reesterification pathway [30]. However, it is not clear how SCD1 deficiency affects and/or regulates lipogenic rates in liver. Liver-specific knockout of SCD1 (LKO mice) also protects against diet-induced obesity and hepatic steatosis [31]. Under both short- and long-term conditions, LKO mice exhibit reduced rates of fatty acid synthesis in liver and decreased expression of key genes of the lipogenic pathway (namely, ACC and FAS). Interestingly, hepatic SCD1 deficiency reduces the nuclear content of two key factors—carbohydrate responsive element-binding protein (ChREBP) and sterol regulatory element-binding protein (SREBP-1c) [31]—involved in the transcriptional control of lipogenic gene expression in response to glucose and insulin, respectively, as discussed below (Fig. 1). However, once again, the mechanism by which SCD1 affects the maturation and/or translocation of these two transcription factors is not clear, but could be linked to MUFA concentrations in hepatocytes. Clearly, a better knowledge of the function and/or regulation of the transcription factors involved in the activity of lipogenic enzymes may, in the future, help in the development of potential therapeutic approaches.

4. Transcriptional control of fat synthesis via SREBP-1c, LXR and ChREBP

Lipogenic gene expression is coordinately controlled by key transcriptional regulators: SREBP-1c in response to insulin; and ChREBP in response to glucose [12,32]. Liver X receptors (LXRs) are ligand-activated transcription factors that belong to the nuclear hormone-receptor superfamily [33]. LXRs play a key role in cholesterol and bile acid metabolism, but are also important regulators of the lipogenic pathway, as LXRs are essential for transcriptional control of SREBP-1c by insulin [34-36]. Direct targets of LXR include FAS and SCD1 [27,37]. ChREBP is regulated by glucose at the transcriptional level [38] and was also recently identified as a direct target of LXRs [39,40]. ChREBP is particularly important for the induction of liver pyruvate kinase (L-PK), which is exclusively dependent on glucose [41]. Induction of lipogenic genes (ACC, FAS, SCD1) is under the concerted action of ChREBP, SREBP-1c and LXRs in response to nutritional signals [12,21,36] (Fig. 1).
So far, the relative importance of these transcriptional factors in controlling the synthesis of fat in response to glucose and insulin signals has been difficult to ascertain because they act either independently and/or synergistically to regulate their target genes. We have recently demonstrated that liver-specific inhibition of ChREBP by decreasing the rate of hepatic lipogenesis improved hepatic steatosis and insulin resistance in obese ob/ob mice [42]. These results suggest that ChREBP is a potential therapeutic target and, therefore, accurate knowledge of the mechanisms involved in regulating its expression and activation is crucial for the development of pharmacological approaches in the treatment of metabolic diseases. The mechanism responsible for ChREBP activation at the post-translational level involves an increase in intracellular glucose metabolism [43]. At low glucose concentrations, ChREBP is an inactive phosphorylated cytosolic protein whereas, at high glucose concentrations, ChREBP undergoes dephosphorylation (on Ser-196), and is translocated into the nucleus to activate its target genes [44]. Because this mechanism has only recently been demonstrated with the endogenous protein, the regulation of ChREBP by phosphorylation/dephosphorylation was controversial [45,46]. However, the use of a phospho-specific antibody that we developed, for the first time, a direct correlation between the modulation of Ser-196 phosphorylation and intracellular localization of the endogenous ChREBP protein in liver [40].

5. Is hepatic steatosis always associated with insulin resistance?

As already mentioned in the introduction, the excess accumulation of TG in hepatocytes is the hallmark of NAFLD, which is strongly associated with insulin resistance [2,47]. However, despite the correlation between fatty liver and insulin resistance, it remains unclear whether or not insulin resistance causes the excess accumulation of TG in liver, or whether or not the increase in TG itself or of metabolite intermediates plays a causal role in the development of hepatic or systemic insulin resistance. Recent studies have favored the hypothesis that the accumulation of intrahepatic lipids precedes the state of insulin resistance, although others have shown that hepatic TG per se are not toxic and may, in fact, protect the liver from lipotoxicity by buffering the accumulation of fatty acids [48,49]; this suggests that hepatic steatosis is not necessarily associated with insulin resistance. Indeed, the overexpression of key enzymes of the esterification pathway (such as DGAT2) [50] or blockade of VLDL secretion [51] show a clear dissociation between marked hepatic steatosis and insulin resistance. Recent studies have also shown that the lipid species (length of the carbon chain and/or the degree of saturation) that accumulate in the steatotic liver may not be equally deleterious for hepatic insulin sensitivity [28,31]. Further experiments are needed to better understand how fatty acid composition influences hepatic insulin sensitivity.

6. Conclusion

NAFLD appears to be one of the most frequent causes of liver dysfunction, and its incidence has increased markedly over the years. While the mechanisms involved in the pathogenesis of NAFLD in humans have not been thoroughly investigated, a recent study has reevaluated the contribution of lipogenesis to the development of hepatic steatosis and revealed that the expression of fatty acid metabolism-related genes, such as ACC and FAS, are indeed increased in NAFLD [52] (Fig. 2). Analyses of the expression of lipogenic transcription factors—namely, ChREBP, SREBP-1c and LXR—have revealed that expression levels of LXR are four times greater in the liver of NAFLD patients than in that of controls and was significantly correlated with SREBP-1c, but not ChREBP, levels [53]. In our opinion, more information on the ChREBP contribution to NAFLD in needed, and additional studies of ChREBP activity (nuclear protein content/phosphorylation levels) are also required.
presented here. The research from our laboratory was supported by grants from Alfeldian/Sanofi-Synthelabo, from the Agence Nationale pour la Recherche (ANR-05-PCOD-035-02) and from the Programme National de Recherche sur le Diabète (PNRD-2005).

Conflicts of interest: The authors have none to declare.

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