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REVIEW

Elovl6: a new player in fatty acid metabolism and insulin sensitivity

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Abstract Obesity is a major health problem in industrialized societies often associated with diabetes, insulin resistance, and hepatic steatosis. This review addresses the hypothesis that elongation of long-chain fatty acids family member 6 (Elovl6) has an important role in energy metabolism and insulin sensitivity. Elovl6 is a microsomal enzyme involved in the elongation of saturated and monounsaturated fatty acids with 12, 14, and 16 carbons. Mice with targeted disruption in the gene for Elovl6 (*Elovl6*$^{-/-}$) are resistant to diet-induced insulin resistance despite their hepatosteatosis and obesity being similar to that of the wild-type mice. Protection against diet-induced insulin resistance in *Elovl6*$^{-/-}$ mice is partially due to restoration of hepatic insulin receptor substrate-2 and suppression of hepatic protein kinase C ε, resulting in restoration of Akt phosphorylation. We suggest that inhibition of this elongase could be a new therapeutic approach for the treatment of insulin resistance, diabetes, cardiovascular disease, and other metabolic diseases.

Keywords Energy metabolism · Elovl6 · Fatty acid composition · Insulin resistance · Obesity

Introduction

Insulin resistance, a state of reduced responsiveness to insulin, is associated with obesity and is the major pathogenic indicator of obesity-related diseases. Although major advances have been made in unraveling the underlying defects that cause insulin resistance, many of the pathways and regulators that connect insulin to its downstream metabolic effects are not fully understood. Epidemiological studies have demonstrated that intake of excess carbohydrate and saturated fatty acids results in accumulation of lipid, promoting a lipotoxic state, and evokes insulin resistance in the skeletal muscle, adipose tissue, and liver leading to obesity-related diseases, including the metabolic syndrome [1, 2] highlighting the importance of lipid accumulation in the pathogenesis. Previous studies on acetyl-coenzyme A (CoA) carboxylase, fatty acid synthase (FAS), and stearoyl-CoA desaturase 1 (SCD-1) indicate that endogenous fatty acid synthesis is also crucial for energy metabolism and insulin sensitivity in the liver [3–6]. Recently, we have shown that inhibition of another key lipogenic enzyme, Elovl6, which elongates long-chain saturated and unsaturated fatty acids can modulate insulin resistance in fatty livers, even with concurrent obesity [7]. In this review, we propose the hypothesis that preventing the formation of very long-chain fatty acids and manipulating the fatty acid composition by blocking this enzyme could protect against insulin resistance and obesity-related disorders, and discuss the molecular mechanism of this new paradigm.

Expression and regulation of the *Elovl6* gene

Elovl6 belongs to a highly conserved family of endoplasmic reticulum enzymes involved in the formation of long-chain fatty acids [8, 9]. Functional analysis using expression experiments in cultured cells demonstrated that this enzyme specifically catalyzes the elongation of saturated and

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monounsaturated fatty acids with 12, 14, and 16 carbons, and was the last piece of the puzzle in enzymes responsible for endogenous fatty acid synthesis [10, 11]. In mice, *Elovl6* is expressed at a high level in the adrenal gland, liver, white adipose tissue, brown adipose tissue, brain, testis, and skin, where lipogenesis and steroidogenesis are active [10, 11]. Hepatic expression of the *Elovl6* gene is consistently activated in the liver of transgenic mice overexpressing nuclear sterol regulatory element-binding protein (SREBP)-1a, -1c, or -2 [10, 11]. *Elovl6* mRNA levels in the liver and adipose tissue markedly elevated in a refed state after fasting [11]. Dietary polyunsaturated fatty acids cause a profound suppression of *Elovl6* expression [11]. Hepatic *Elovl6* expression is also highly up-regulated in leptin-deficient *ob*/*ob* mice [11]. Thus, this elongase is a new member of the mammalian lipogenic enzymes regulated by SREBP-1, playing an important role in de novo synthesis of long-chain saturated and monounsaturated fatty acids in conjunction with FAS and SCD-1 (Fig. 1). Promoter analysis of mouse Elovl6 identified two SREBP-binding sites: proximal SRE-1 and distal SRE-2, and Elovl6 is regulated directly and primarily by SREBP-1c [12].

Role of Elovl6 in the development of diet-induced insulin resistance Studies on *Elovl6*$^{-/-}$ mice showed that loss of Elovl6 function increased levels of palmitate (C16:0) and palmitoleate (C16:1*n*−7), but reduced levels of stearate (C18:0) and oleate (C18:1*n*−9), confirming that Elovl6 catalyzes the chain elongation of palmitate to stearate and the elongation of palmitoleate to vaccinate (C18:1*n*−7) *in vivo* [7].

Apart from dramatic alterations in fatty acid composition, the *Elovl6*$^{-/-}$ mice do not differ from wild-type littermates in case of overall lipid concentration of the liver and plasma. The *Elovl6*$^{-/-}$ mice appear grossly normal although slightly leaner than their wild-type littermates. Postprandial plasma levels of insulin and leptin are lower in the *Elovl6*$^{-/-}$ than that in the wild-type mice, while no significant changes are observed in plasma glucose or lipid levels.

On a high-fat, high sucrose (HF-HS) diet, the wild-type and *Elovl6*$^{-/-}$ mice gain body weight and total body fat percentage at similar rates at identical daily food intake. The *Elovl6*$^{-/-}$ mice have a greater tendency to suffer from severe hepatosteatosis than the wild-type mice, as estimated by hepatic triglycerides and cholesterol. In response to diet-induced obesity, the wild-type mice exhibited a robust elevation in plasma insulin levels accompanied by a slight increase in plasma glucose, indicating the emergence of insulin resistance. However, the *Elovl6*$^{-/-}$ mice showed a significant reduction in plasma insulin levels compared to the wild-type mice. Insulin sensitivity, as measured by reduction in plasma glucose levels after insulin administration, was markedly reduced in the wild-type mice with an HF-HS diet, whereas the *Elovl6*$^{-/-}$ mice showed a nearly normal response to insulin. Thus, *Elovl6*$^{-/-}$ mice are resistant to diet-induced insulin resistance, despite their hepatosteatosis and obesity being similar to that of the wild-type mice.

Elovl6 deficiency restores suppressed Akt phosphorylation in the liver, but not in the skeletal muscle and white adipose tissue. Thus, amelioration of whole-body insulin

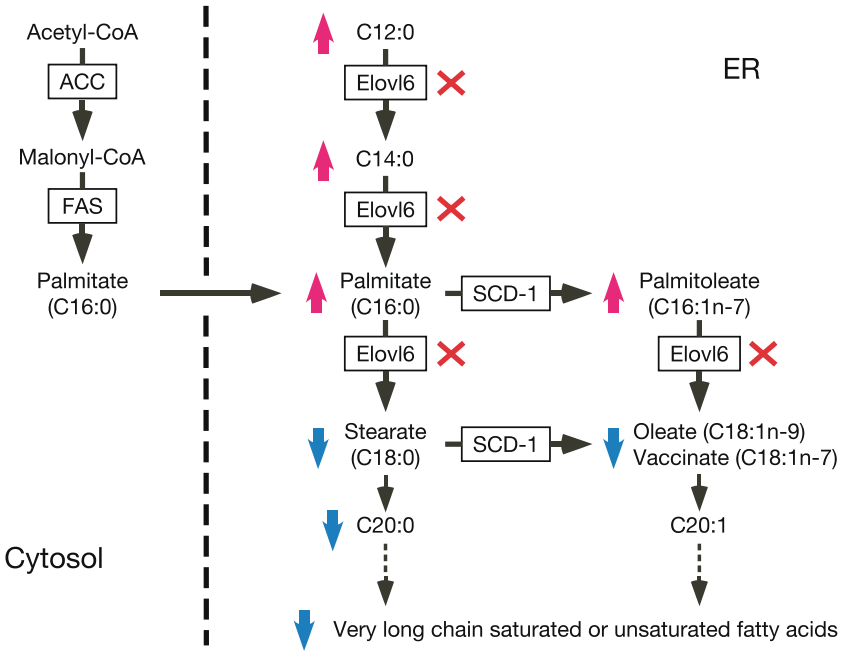

Fig. 1 Role of Elovl6 in mammalian fatty acid synthesis and changes of the fatty acid composition by the Elovl6 deficiency. *ACC* acetyl-CoA carboxylase, *FAS* fatty acid synthase, *ER* endoplasmic reticulum, *SCD*-1 stearoyl-CoA desaturase-1

resistance in the *Elovl6*$^{-/-}$ mice can be attributed to the restoration of hepatic insulin sensitivity. Restoration of Akt phosphorylation is accompanied by increased total and phosphorylated insulin receptor substrate (IRS)-2 protein in the livers of the *Elovl6*$^{-/-}$ mice, whereas phosphorylated insulin receptor and IRS-1 remain suppressed by an HF-HS diet in both genotypes, demonstrating that restoration of insulin signaling is mediated by recovery of the hepatic IRS-2/Akt signaling pathway in *Elovl6*$^{-/-}$ mice (Fig. 2).

Several lines of evidence suggest that lipid metabolites, such as acyl-CoAs, diacylglycerol (DAG), and ceramides, rather than triglycerides themselves, are the determinants of the development of insulin resistance accompanying the accumulation of intracellular lipids [13–15]. DAG accumulation has been reported to be linked to increased protein kinase C epsilon (PKCε) activity and impaired phosphorylation of insulin receptor, IRS-1, and IRS-2 tyrosine by insulin [13, 14]. In the wild-type mice, hepatic DAG content and PKCε activity are significantly increased in the liver in response to an HF-HS diet. However, the livers of *Elovl6*$^{-/-}$ mice contain less DAG and show lower expression of PKC compared with the wild-type mice, indicating that protection against diet-induced insulin resistance in the *Elovl6*$^{-/-}$ mice might be mediated, at least partially, through the DAG/PKCε pathway (Fig. 2).

Role of Elovl6 in regulation of lipogenesis and fatty acid oxidation

In the livers of *Elovl6*$^{-/-}$ mice, how would energy metabolism change with changes in fatty acid composition? An HF-HS diet augmented the hepatic expression of SREBP-1c itself and its target lipogenic enzyme genes, including genes for FAS, Elovl6, SCD-1, and GPAT, in the wild-type mice. The dietary induction of these lipogenic genes is suppressed in the *Elovl6*$^{-/-}$ mice [7]. As we have previously reported, activation of SREBP-1c directly represses IRS-2, the main insulin signal mediator, and causes hepatic insulin resistance [16]. Therefore, suppression of SREBP-1c can contribute to the amelioration of hepatic insulin resistance in the *Elovl6*$^{-/-}$ mice. Consistent with this notion, IRS-2 expression, which is completely suppressed by an HF-HS diet in the wild-type mice, is restored in the liver of *Elovl6*$^{-/-}$ mice (Fig. 2). Meanwhile, genes related to fatty acid oxidation that are regulated by nuclear receptor PPARα, such as carnitine palmitoyltransferase-1, medium-chain acyl-CoA dehydrogenase, acyl-CoA oxidase, and cytochrome *P*450 4a14, are induced by an HF-HS diet in the wild-type mice. However, these oxidation genes, including *PPARα*, are considerably decreased in the *Elovl6*$^{-/-}$ mice, in

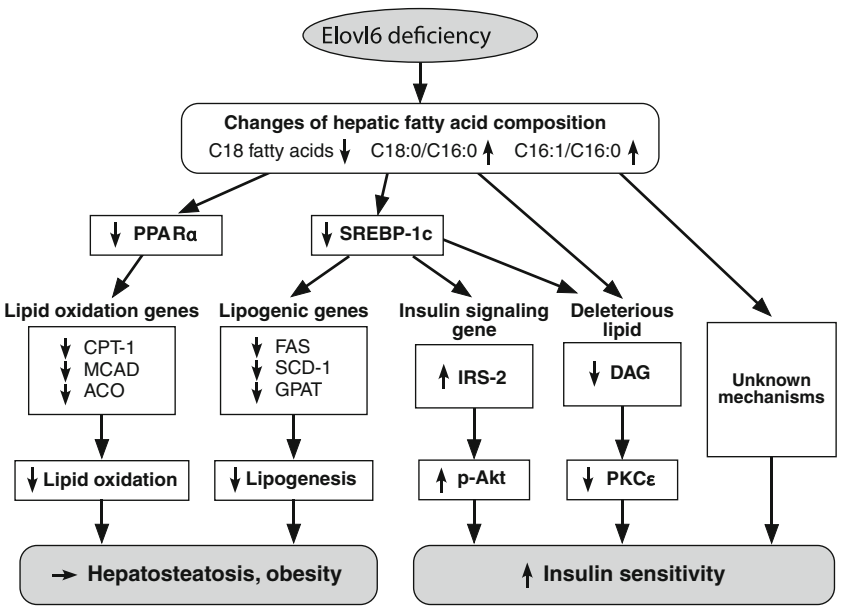

Fig. 2 Absence of Elovl6 improves hepatic insulin sensitivity without amelioration of obesity and hepatosteatosis. *Elovl6* deficiency alters hepatic fatty acid composition; changes in fatty acid chain length (decrease in long-chain fatty acids more than C18) and the ratio of fatty acids (C18:0/C16:0, C16:1/C16:0) could reduce SREBP-1 and PPARα in the liver. Reduction in SREBP-1 leads to decreased fatty acid synthesis via reduction of lipogenic gene expression and increases in IRS-2 level and insulin sensitivity. Reduction in lipogenesis could lead to decreased hepatic diacylglycerol content, which would lead to decreased PKCε activity and increased insulin sensitivity. Unknown mechanisms might include changes in lipid signaling and protein fatty acylation that could improve insulin signaling

contrast to the amelioration of insulin resistance. Thus, *Elovl6* deficiency leads to suppression of both synthesis and degradation of fatty acids by affecting *SREBP-1c* and *PPARα* expression (Fig. 2). The signals generated in the *Elovl6*$^{-/-}$ mice that lead to reduced *SREBP-1c* and *PPARα* expression and consequent reduction in lipid metabolism and increase in insulin sensitivity are currently being studied.

Function of other Elovl enzymes

Elovl family is composed of seven distinct fatty acid elongase subtypes (Elovl1-7) that are present in the mouse, rat, and human genomes. Each elongase has a distinct tissue distribution, and individual enzymes exhibits different fatty acid substrate preferences [8, 9, 17, 18]. Elovl1 (Ssc1) catalyze the condensation of a broad array of saturated and monounsaturated fatty acids up to C24 [19]. Elovl2 (Ssc2) substrates include C20 and C22 PUFAs [19]. Elovl3 (Cig30) and Elovl4 elongate different fatty acids ≤C26 [20, 21]. Elovl5 is involved in the elongation of various PUFAs of C18 and C20 [22]. Elovl7 has not been well characterized. In contrast to other elongases, Elovl6 expression is regulated by many dietary, hormonal, and developmental factors [11, 17, 18]. Consistent with this, Elovl6 is only elongase to connecting with *de novo* lipogenesis.

Deletion of the gene coding for *Elovl* enzymes in mice were reported in *Elovl3*, *Elovl4*, *Elovl5* as well as *Elovl6*. *Elovl3*-null mice displayed a sparse hair coat, the hyperplasia of the sebaceous glands, and increased transepidermal water loss in a water barrier function test due to the decreased level of C22–24 saturated and monounsaturated fatty acids with exceptionally high levels of eicosenoic acid (C20:1) in hair lipids [23]. *Elovl4*$^{-/-}$ mice displayed profound skin atrophy and impaired water insulation function due to lacking ceramides with ω-hydroxy very long-chain fatty acids (≥C28) [24, 25]. *Elovl5*$^{-/-}$ mice demonstrated that decreased elongation of C18:3*n*−6 to C20:3*n*−6 and C18:4*n*−3 to C20:4*n*−3 and that the decreased cellular arachidonic acid (20:4*n*−6) and DHA (22:6*n*−3) concentrations de-represses the activation of SREBP-1c and its target genes involved in fatty acid and triglyceride synthesis, which resulted in the development of hepatic steatosis [26]. It was also reported that adenoviral-mediated induction of Elovl5 activity in livers of mice increased hepatic and plasma levels of 20:3*n*−6 while suppressing hepatic arachidonic acid (20:4*n*−6) and DHA (22:6*n*−3) content. Such alterations in fatty acid profile affect the expression of PPARα-regulated genes and hepatic glucose production during fasting [27]. Elovl5 is abundant in the liver, and the gene expression is controlled by SREBP-1 and PPARα. Examination of the relations between hepatic Elovl5 activity and energy metabolism should provide new findings for the treatment of metabolic disease. These observations suggest that Elovl6 and possibly Elovl5 are involved in central energy metabolism, whereas other Elovl enzymes are involved in regulation of longer and polyunsaturated fatty acids, which is crucial for lipid metabolism in peripheral tissues like skin. Alterations in fatty acid profile as a consequence of *Elovl* gene deletion, as those seen in *Elovl3*, *Elovl4*, *Elovl5,* and *Elovl6* mutant mice, emphasize the importance of these enzymes in maintaining fatty acid homeostasis for proper cellular function and energy metabolism.

New aspects of fatty acid synthesis and insulin resistance

Palmitate has long been thought to be the major detrimental fatty acid in insulin resistance [1]. In the *Elovl6*$^{-/-}$ mice, however, the palmitate levels are increased, but insulin sensitivity is maintained, suggesting that it is the hepatic fatty acid composition, particularly the conversion of palmitate to stearate, which is crucial for insulin sensitivity than simply the accumulation of palmitate.

Recently, Cao et al. reported that the palmitoleate (C16:1*n*−7) is an important signaling lipid hormone newly designated as a "lipokine," stimulating activity of muscle insulin action and influencing fat deposition in the liver [28]. Utilizing quantitative lipidomic analysis, they found that mice lacking FABP4 and FABP5, exhibiting a striking phenotype with strong protection from diet-induced obesity, insulin resistance, and fatty liver disease [29], has a fourfold higher concentration of palmitoleate in plasma, compared to wild-type mice on high-fat diet. The adipose tissue-derived palmitoleate travels to the muscle cells and liver, where it improves cell sensitivity to insulin in muscle and blocks fat accumulation in the liver. Intriguingly, our data from *Elovl6*$^{-/-}$ mice also highlights palmitoleate as a fatty acid potentially responsible for sustained insulin sensitivity. *Elovl6*$^{-/-}$ mice increased liver and, resultantly, plasma palmitoleate level, but skeletal muscle insulin sensitivity and hepatic triglyceride content did not altered, questioning that this particular fatty acid in circulation can simply modify peripheral tissue insulin sensitivity. The precise molecular mechanism that palmitoleate promotes the insulin sensitivity in liver and muscle is yet to be clarified. Further studies of the mice deficient in fatty acids such as FABP, Elovl6, and SCD1 are important for the clarification of this molecular mechanism.

SCD catalyzes the conversion of stearate, the end product of Elovl6, to oleate, the final product of endogenous lipogenesis. The similarity of SCD1 and Elovl6 in ER

localization, gene structures, and the coordinating functions of both proteins implicates that these genes could be derived from a common ancestral gene. Inhibition of *SCD1* expression caused by *Elovl6* deficiency was prominent in mice both normal and HF-HS diet [7]. Mice with global knockout of SCD1 ($SCD1^{-/-}$ mice) show decreased lipogenic gene expression and increased β-oxidation and are protected from diet-induced obesity, hepatic steatosis, and insulin resistance [5]. Liver-specific SCD1 knockout (LKO) mice are protected from high-sucrose, very low-fat diet-induced obesity and hepatic steatosis because of the decreased lipogenic gene expression without the change in the fatty acid β-oxidation gene expression [6]. It is possible that the decrease in *SCD1* expression could partly contribute to the insulin-sensitizing effect of Elovl6 deficiency. However, in contrast to $SCD1^{-/-}$ and LKO mice, $Elovl6^{-/-}$ mice showed sustained obesity, hepatic steatosis, and low fatty acid oxidation in liver, indicating that the mechanisms by which these two enzymes influence insulin sensitivity are not completely convergent.

Amelioration of insulin resistance in obese mice is usually accompanied by loss of fat or body weight caused by decreased food intake, enhanced lipid oxidation, and/or decreased lipogenesis [5, 30–32]. $Elovl6^{-/-}$ mice are unique in that their insulin resistance is improved without amelioration of obesity or hepatosteatosis. These data highlight the importance of tissue fatty acid composition in insulin sensitivity, especially the ratio of C18 to C16 acids, which is controlled by Elovl6 activity. The precise molecular mechanism for this is currently unknown. Distinct effects of different long fatty acids depending upon their extent of desaturation have been generally observed. However, our current studies suggest that the length of fatty acids is also important in energy metabolism and insulin sensitivity. This model aids our understanding of the mechanism by which obesity and obesity-related disorders are sometimes dissociated, and these observations could lead to new therapeutic strategies for diabetes and cardiovascular diseases that target elongase enzymes.

For the treatment and prevention of obesity-related disorders, control of the quantity of lipid accumulating in tissue and blood is important, and thus diet has been the main target. Together with beneficial roles of some pieces of PUFA, the lessons from $Elovl6^{-/-}$ mice suggest that quality aspect of lipids should be more focused for future strategy against cardiovascular diseases.

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