review

Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol

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Abstract **The lipid composition of cellular membranes is regulated to maintain membrane fluidity. A key enzyme involved in this process is the membrane-bound stearoyl-CoA desaturase (SCD) which is the rate-limiting enzyme in the cellular synthesis of monounsaturated fatty acids from saturated fatty acids. A proper ratio of saturated to monounsaturated fatty acids contributes to membrane fluidity. Alterations in this ratio have been implicated in various disease states including cardiovascular disease, obesity, non-insulin-dependent diabetes mellitus, hypertension, neurological diseases, immune disorders, and cancer. The regulation of stearoyl-CoA desaturase is therefore of considerable physiological importance and its activity is sensitive to dietary changes, hormonal imbalance, developmental processes, temperature changes, metals, alcohol, peroxisomal proliferators, and phenolic compounds. Two mouse and rat SCD genes (SCD1 and SCD2) and a single human SCD gene have been cloned and characterized. In the past several years we have studied the dietary influences on the genetic expression of the mouse stearoyl-CoA desaturase. The expression of the mouse SCD genes is regulated by polyunsaturated fatty acids and cholesterol at the levels of transcription and mRNA stability. Promoter elements that are responsible for the polyunsaturated fatty acid repression colocalize with the promoter elements for SREBP-mediated regulation of the SCD genes. It is the goal of this review to provide an overview of the genetic regulation of the stearoyl-CoA desaturase in response to dietary polyunsaturated fatty acids and cholesterol.**—Ntambi, J. M. **Regulation of stearoyl-CoA desaturase by polyunsaturated fatty acids and cholesterol.** ***J. Lipid Res.*** **1999.** 40: **1549–1558.**

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STEAROYL-CoA DESATURASE: WHAT DOES IT DO?

It has been recognized that irrespective of diet, the major storage fatty acids in human adipose tissue are oleate and palmitoleate (1). Why this is the case has not been satisfactorily addressed. There appears to be a number of answers at different levels, i.e., special physico-chemical properties of oleic acid at body temperature, its effects on membrane fluidity, a readily available energy source, and the constraints of the intermediary metabolism of carbohydrates and fats. During the de novo synthesis of fatty acids, the fatty acid synthase enzyme stops at palmitate but the end product of the pathway is usually oleic acid. Stearate is too insoluble to be stored (2). High carbohydrate feeding also leads to high levels of palmitoleate as seen in neonates (2). Adipose fatty acid composition of monounsaturated fatty acids is considered to reflect dietary intake (3) but it is not an exact mirror suggesting the requirement of de novo biosynthesis of the monounsaturated fatty acids in addition to the dietary sources.

A critical committed step in the biosynthesis of monounsaturated fatty acids is the introduction of the first *cis*-double bond in the Δ9 position (between carbons 9 and 10). This oxidative reaction is catalyzed by the iron-containing, microsomal enzyme stearoyl-CoA desaturase (SCD) and involves cytochrome b_5, NADH (P)-cytochrome b_5 reductase, and molecular oxygen (**Fig. 1**). Although the insertion of a double bond occurs in a spectrum of methylene-interrupted fatty acyl-CoA substrates including *trans*-11 octadecenoic acid (4), the preferred substrates are palmitoyl- and stearoyl-CoA, which are converted into palmitoleoyl- and oleoyl-CoA, respectively (5–8). Overall, Δ9 desaturase affects the fatty acid composition of phospholipids and triglycerides. Effects on phospholipid composition are important in the maintenance of membrane fluidity and alterations have been implicated in a variety of disease states (6). Two mouse and rat genes (SCD1 and SCD2) and a single human SCD gene have been cloned and characterized (9–12). Other SCD cDNAs and genes have been isolated from different species including yeast (13), ovine (14), and hamster (15), and the regulation of their expression is currently being studied by several research groups. The two mouse genes have been shown to

Abbreviations: SCD, stearoyl-CoA desaturase; SREBP, sterol regulatory element binding protein; C/EBP, CCAAT enhancer binding protein; PPRE, peroxisome proliferator response element; PUFA-RE, polyunsaturated fatty acid response element; PUFA-BP, polyunsaturated fatty acid binding protein; VLDL, very low density lipoprotein; LXRα, nuclear oxysterol receptor; RXR, retinoic X receptor.

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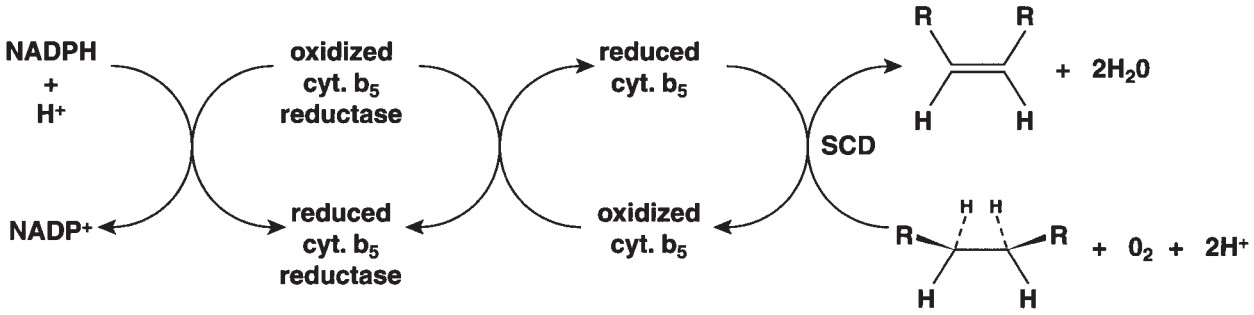

Fig. 1. The pathway of electron transfer in the desaturation of fatty acids by stearoyl-CoA desaturase.

be regulated differently in different tissues, presenting a unique model to study tissue-specific gene expression. The tissue distribution and the dietary alteration of the mouse and rat SCD1 mRNA differ markedly from that of SCD2, being constitutive in adipose tissue, and are markedly induced in liver in response to feeding a high carbohydrate diet (9, 10, 16). Like SCD2, SCD1 mRNA is expressed to a lesser extent in kidney, spleen, heart, and lung in response to a high carbohydrate diet. The SCD2 expression in brain is induced during the development of neonatal mice (17) and down-regulated during the development of mouse lymphocytes (18). The reason for having two SCD isoforms is not known but could be related to the substrate specificities of the two isomers and their regulation through tissue-specific expression. Although certain regions of the promoter of the two mouse genes differ markedly, there is one region with high nucleotide sequence homology. The sequence between −201 to −54 in the SCD2 gene is 77% identical to the sequence between −472 to −325 in the SCD1 gene (**Fig. 2**). The regulatory elements responsible for polyunsaturated fatty acid and cholesterol regulation of the SCD genes are contained in the sequences within the conserved region. In the past several years we have studied the genetic regulation of the mouse stearoyl-CoA desaturase by dietary and hormonal factors and also during fat cell differentiation. This review will focus on our current understanding of the genetic regulation of the stearoyl-CoA desaturase in response to dietary polyunsaturated fatty acids and cholesterol.

INFLUENCE OF DIETARY FAT ON STEAROYL-CoA DESATURASE IN DISEASE STATES

Oleic acid and palmitoleic acid are the major monounsaturated fatty acids in fat depots and membrane phospholipids. These fatty acids are synthesized by the stearoyl-CoA desaturase. The ratio of stearic acid to oleic acid is one of the factors influencing membrane fluidity and cell–cell interaction (6). Abnormal alteration of this ratio has been shown to play a role in several physiological and disease states including diabetes, cardiovascular disease, obesity, hypertension, neurological diseases, immune disorders, cancer, and aging (19–36).

SCD was viewed as a lipogenic enzyme not only for its key role in the biosynthesis of monounsaturated fatty acids but also for its pattern of regulation by diet and insulin. SCD activity was decreased in rat liver during starvation and diabetes and was rapidly induced to high levels upon refeeding high carbohydrate diets or upon insulin

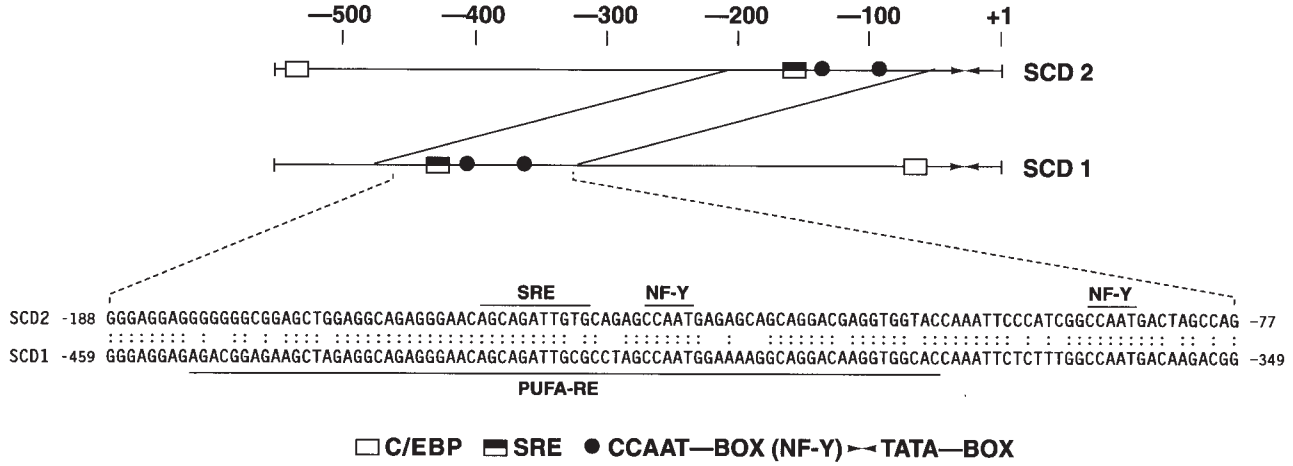

Fig. 2. Organization of the mouse SCD1 and SCD2 promoters and the nucleotide sequence similarity of the 110-bp segment in the 5′-flanking region of the mouse SCD2 and SCD1 genes. SRE, sterol regulatory element; NF-Y, CCAAT-binding factor or nuclear factor Y binding site; C/EBP, CCAAT enhancer binding protein sequence.

administration (37–39). Diets rich in saturated fatty acids or cholesterol also induced desaturase activity in rat liver (40–42). On the other hand, dietary polyunsaturated fatty acids (PUFAs) such as linoleic acid (18:2n–6) diminished SCD activity (43).

The consequences of regulating the stearoyl-CoA desaturase by PUFAs and cholesterol may be relevant to lipoprotein metabolism. Liver and adipose cell metabolic homeostasis could be dependent on SCD for several reasons. The majority of de novo synthesis of fatty acids in liver is directed toward triglyceride synthesis and secretion (25). The hepatic packaging and secretion of very low density lipoprotein (VLDL) requires synthesis of apolipoprotein B-100 (apoB-100) as well as sufficient amounts of oleic acid which would either come from the diet or from synthesis by SCD (25). Oleic acid is the preferred substrate for acyl-CoA cholesterol acyltransferase, the enzyme responsible for esterification of cholesterol. This esterification prevents the toxic accumulation of free cholesterol in liver and increases the availability of esterified cholesterol for export in the form of VLDL. Repression of SCD activity by PUFAs could lower the amount of cholesterol transported from the liver to the peripheral tissues by limiting the availability of oleic acid or fatty acids in general. Indeed PUFAs mainly of the n–3 series have been shown to exhibit beneficial effects by decreasing plasma lipids and lipoproteins (23). On the other hand, induction of SCD activity by saturated fatty acids and cholesterol would increase plasma lipids and lipoproteins thus leading to cardiovascular disease.

SCD activity has also been shown to be elevated in the adipose tissue of various animal models of obesity (26) and a positive correlation between SCD activity in skeletal muscle and the percentage of body weight has been recently reported in human subjects (27). Mice that lack the obese gene (ob) are characterized by a 5-fold higher deposition of body fat than their lean counterparts. The only consistent change in the fatty acid composition, however, is an increase in palmitoleic acid (16:1n–7) as a result of increased SCD activity (28). In type II diabetes, SCD levels are increased, presumably in response to increased levels of plasma insulin (28).

The regulation of the SCD activity may also affect cancer growth. There is accumulating evidence supporting the hypothesis that a change in C18 fatty acid saturation is important in cancer promotion (29, 30). The higher level of oleic acid in malignant cells accounts for increased membrane fluidity. In general, increased membrane fluidity leads to increased cell metabolism and also higher division rates, features characteristic of cancer cells (29). Stearic acid delays the appearance of spontaneous mammary tumors in mice and growth of carcinogen-induced mammary tumors in rats (30). Stearic acid also inhibits mammary carcinogenesis in vivo (31). On the other hand, increased oleic acid has been reported to be associated with colorectal and mammary tumors (29) and increases malignant cell growth in vitro (31). Thus, one possible mechanism of the anti-cancer activity of certain classes of fatty acids such as sterculic acid and thia fatty acids is to alter the ratio of saturated to monounsaturated fatty acids by reducing SCD activity (32, 33).

Essential fatty acids (EFAs) are required for normal function of mammalian tissues and the lack of EFAs in the diet causes a human and animal disease known as essential fatty acid deficiency (34). In skin it is manifested as a severe scaly lesion accompanied by chronic epidermal hyperproliferation, abnormal differentiation, and abnormal cutaneous barrier function (34). These symptoms are accompanied by the relative abundance of the monounsaturated fatty acids, mainly oleate and palmitoleate, suggesting an increase in SCD activity (34). The severity of the symptoms is lessened upon treatment with linoleic acid, which reduces the levels of C18:1 and C16:1 presumably by reducing SCD activity. Other studies using the human skin model have shown that all-*trans* retinoic acid stimulates the growth of EFA-supplemented keratinocytes while increasing the levels of C16:1 in cells (35), suggesting a role of all-*trans* retinoic acid in the regulation of the SCD in skin diseases.

Regulation of oleic acid synthesis by SCD in the peripheral nervous system has been linked to myelin synthesis (36). During mouse postnatal development, the total SCD activity measured in sciatic nerve homogenates is high and the proportion of oleate rises in sciatic nerve during the first 3 weeks of development. However, this rise in SCD activity and oleate levels does not occur in the demyelinating mutant mouse trembler (36). Oleate is the major fatty acid in the peripheral nervous system (PNS) myelin, comprising between 35 and 45% of the fatty acids of sciatic nerves. Repression of expression of SCD in the PNS could therefore lead to demyelination, a serious neurological disorder.

Immune tissues are susceptible to changes in proliferation and differentiation in response to PUFA. Previous studies have shown stearic acid to be a potent inhibitor of T-lymphocyte proliferation and function (44). The susceptibility of T-lymphocytes to stearate is due to their unique deficiency in SCD activity (44). By contrast, stearate levels do not affect B-lymphocytes because they express an SCD isoform that converts stearate to oleate. Such a fundamental difference between B- and T-lymphocytes indicates a cell type-specific expression with regard to SCD. PUFAs have been shown to repress the expression of the desaturase activity in B-lymphocytes reducing the levels of C18:1 (44). The repression of SCD and subsequent decrease in oleate composition of the lymphocyte membrane could affect B-lymphocyte function.

Thus there is substantial evidence linking SCD activity to a wide range of disorders including obesity, diabetes, cardiovascular disease, skin disease, neurological disorders, and cancer. However, causal relationships between SCD activity and these various disease states remain unclear. Many mechanisms may exist for regulating the activity of SCD by fatty acids and cholesterol in different disease states. Some evidence has been provided that some PUFAs such as sterculic acid and thia fatty acids directly inhibit the SCD activity (32, 33). However, studies of liver, lymphocyte, brain, and adipocytes indicate that the effects

of PUFAs and cholesterol on SCD activity are at the level of gene expression (6, 9, 10, 18, 36, 42, 44–47, 54).

DIETARY n–6 AND n–3 POLYUNSATURATED FATTY ACIDS REPRESS SCD GENE EXPRESSION

In 1978, Jeffcoat and James (43) reported a 60% decrease in hepatic SCD enzyme activity of rats fed a diet containing 60% linoleic acid. This change in enzyme activity we now know is due to altered gene expression (46, 48–54). Two mouse SCD genes (SCD1 and SCD2) are well characterized and are being studied in response to dietary and hormonal changes. At the moment it is not clear why two SCD isoforms exist in the mouse and rat. Under normal dietary conditions the hepatic SCD1 mRNA levels are low. However, when the mice are fed a fat-free high-carbohydrate diet, the SCD1 mRNA is induced about 50-fold (16, 48, 54). This induction is caused by either insulin or carbohydrate (47). The SCD2 gene is not expressed under either dietary condition. The induction of the SCD1 mRNA by a fat-free diet suggested that a fat component present in the chow diet represses the expression of the SCD1 gene in liver. The fat component that represses hepatic SCD1 gene expression has been established to be PUFAs of the n–3 and n–6 series. Thus, when the fat-free diet is supplemented with various triglycerides containing linoleic (18:2n–6), arachidonic (20:4n–6), and linolenic (18:3n–3) acids, SCD1 mRNA expression is repressed whereas triglycerides containing saturated (i.e., C18:0 and C16:0) and monounsaturated fatty acids (C16:1 and C18:1) have very little effect (16). Similar results have been obtained with primary hepatocytes (46). The degree of desaturation was related to repression as 20:4n–6 was more potent than 18:2n–6. In general, as shown in several other studies (55), long chain PUFAs [e.g., 18:2n–6, 18:3n–3, 18:3n–6, 20:4n–6, 20:5n–3, 22:6n–3] repress the expression of the genes that encode lipogenic enzymes including SCD1. The basic requirement for a dietary fatty acid to inhibit expression of lipogenic genes had been proposed to be that it should contain 18 carbons and possess at least 2 conjugated double bonds in the 9 and 12 positions (56). However, recently we have found that the *trans*10, *cis*12 isomer of conjugated linoleic acid also represses SCD mRNA expression in liver (53) but this fatty acid does not contain a double bond at position 9. It contains double bonds at positions 6 and 8 from the ω-carbon. The only double bond position that conjugated linoleic acid and other polyunsaturated fatty acids share is at position 6. The inhibitory effects that conjugated linoleic acid and other polyunsaturated fatty acids have on the expression of the SCD1 mRNA levels may be related to the position and orientation of just one of the double bonds present in all these fatty acids. This information could become important in determining the structure of the polyunsaturated fatty acids that inhibit gene expression.

In adipose tissue of lean and obese Zucker rats, Jones et al. (26) observed a 75% decrease in SCD1 mRNA when both groups were fed a diet high in polyunsaturated fatty acids relative to a control diet. Interestingly, the SCD1 mRNA content was much higher in obese rats compared to normal rats both with and without PUFA supplementation (26). Similar results have been obtained with tissue culture systems as well (26, 52). In the 3T3-L1 adipocyte cell line, arachidonic acid decreased SCD1 mRNA expression in a dose-dependent manner (80% maximum repression), as did linoleic, linolenic, and eicosapentaenoic EPA acids (52). Inhibiting eicosanoid synthesis did not prevent the PUFA suppression of SCD1 gene expression in adipocytes, suggesting that the oxidative metabolism of arachidonic acid to eicosanoids is not involved in the arachidonic acid-mediated decrease of SCD1 mRNA expression in 3T3-L1 adipocytes (52). Furthermore, as indicated above, the desaturase gene expression is repressed by a range of PUFAs, some of which do not give rise to eicosonoids, suggesting that repression of SCD mRNA expression is PUFA-specific.

The regulation of SCD gene expression by PUFAs has also been observed in other tissue types such as brain and the immune tissues. In the brain of neonatal mice, SCD2 mRNA expression is increased in response to feeding diets rich in 18:2n–6 (17). It was suggested that the induction of SCD2 serves to provide oleic acid for the synthesis of myelin (17). In contrast, SCD2 expression in the adult animal is constitutive and not influenced by dietary PUFAs (10, 17). In various lymphoid cells SCD2 mRNA expression is inhibited by 20:4n–6 (18, 44, 45). Stearic acid (18:0) is a potent inhibitor of T-lymphocyte proliferation and function because, in contrast to B-lymphocytes, T-lymphocytes do not express the SCD2 gene (18). However, immature thymocytes and some T-lymphocyte-derived cell lines do express SCD2 mRNA consistent with a developmental down-regulation of the SCD gene within the thymus. SCD1 gene expression, on the other hand, is not detected in any of the lymphoid cells. Such a fundamental difference between B- and T-lymphocytes indicates a cell-type specific gene expression with regard to SCD gene expression. As in adipocytes, the inhibitory effect of 20:4n–6 on SCD2 mRNA expression in B-lymphocytes was independent of arachidonic acid metabolism by either the lipooxygenase or cyclooxygenase pathway. By using protein synthesis inhibitors it was shown that the arachidonic acid-mediated effects on SCD2 mRNA expression were independent of new protein synthesis (45).

The list of tissues in which PUFAs regulate the expression of the SCD genes continues to grow indicating that PUFA action on the SCD genes is much more widespread than originally thought. The differential effects of PUFAs on gene expression may explain the numerous beneficial as well as detrimental effects attributed to various dietary fats in different tissues.

MECHANISMS OF POLYUNSATURATED FATTY ACID CONTROL OF SCD GENE EXPRESSION

A. Transcriptional control

The molecular mechanisms by which PUFAs regulate SCD gene expression in different tissues are still poorly

understood, although progress has been made in the last few years. PUFA-mediated suppression of SCD1 expression in liver and primary hepatocytes and of SCD2 expression in lymphocytes was shown to be largely due to a decrease in their rates of gene transcription (16, 45, 46, 48–51, 54, 57). Therefore, many recent studies have been predicated on the hypothesis that a *cis*-acting PUFA responsive element (PUFA-RE) exists in the promoters of SCD genes to which a transcription factor binds, thus blocking transcription. Using deletion analysis, we localized the SCD1 and SCD2 PUFA-REs to a 60 bp region in each of their promoters (57). This is the only region of high sequence homology within the promoters of the two SCD genes as depicted in Fig. 2. The PUFA-RE of the rat S14 and pyruvate kinase genes have also been mapped (55, 56, 58, 59) and were found to share homologous sequences. However, these PUFA-REs are not homologous to those of SCD1 or SCD2.

PUFAs are known to activate nuclear transcription factors termed peroxisome proliferator-activated receptors (PPARs) and have, therefore, been hypothesized to be the endogenous activators of this receptor (56). Both peroxisome proliferators and PUFA (56, 60) repress lipogenic genes, such as S14 and fatty acid synthase. However, the PUFA suppression of these genes does not require peroxisome proliferator activator receptors (61, 62). Peroxisome proliferators and polyunsaturated fatty acids in adipocytes (63, 64) also repress the GLUT4 gene expression. It was speculated that the PUFA-RE in the GLUT4 gene is related to the peroxisome proliferator responsive element (PPRE). We hypothesized that PUFA-activated PPAR, along with its heterodimeric partner retinoic acid X receptor (RXR), might repress SCD1 gene transcription. Unexpectedly, our studies (49) on the effects of peroxisome proliferators on SCD1 gene expression showed that PUFA and peroxisome proliferators had opposing effects on the SCD1 mRNA levels in mouse liver. Unlike the S14 and fatty acid synthase genes, peroxisome proliferators induced the expression of the SCD gene. In addition, transient transfection experiments localized the SCD1 PPRE to an area of the SCD1 promoter that is distinct from the PUFA-RE (49). This indicates that different mechanisms account for the transcriptional regulation of the SCD1 gene by peroxisome proliferators and PUFA and suggests the existence of a putative PUFA binding protein (54).

The search for a PUFA-specific transcription factor for SCD gene repression has now become a major focus in our laboratory. We demonstrated the binding of nuclear proteins to the PUFA-RE of the SCD1 and SCD2 genes by DNA mobility shift analysis (57). Two of the proteins that bind to specific regions within the PUFA-RE of the SCD genes have been identified by Tabor and coworkers (65) and they are the sterol regulatory element binding proteins (SREBPs) and the CCAAT-binding factor/nuclear factor Y or NF-Y. While the expression vectors containing the cDNAs corresponding to SREBP-1 and SREBP-2 activate the expression of the SCD genes both in vitro and in vivo (65, 66–69), the SREBPs do not by themselves seem to directly mediate PUFA repression of the SCD genes (see below). Our current model indicates that PUFAs bind to a putative PUFA-binding protein (PUFA-BP) and repression of transcription occurs upon the binding of the PUFA-BP to the PUFA-RE of the SCD genes (**Fig. 3**). Crosstalk between the putative PUFA binding protein and the SREBP or NFY-1 is also suggested.

B. Post-transcriptional control

Studies on the SCD genes in mature adipocytes and in yeast have shown that the effect of PUFA on these genes could be at the level of mRNA stability (52, 70). When added to cultures of fully differentiated 3T3-L1 adipocytes, arachidonic acid decreased the SCD1 mRNA half-life from 8 h to 4 h (52). By contrast, oleic acid and stearic acid did not affect SCD1 mRNA stability. Therefore, this response is unique to PUFAs. Arachidonic acid also decreased the stability of the SCD2 transcript (A. Sessler and J. M. Ntambi, unpublished results). Although transcriptional regulation could not be completely ruled out, changes in transcriptional rates were not detected, suggesting that transcriptional regulation does not play a significant role in PUFA suppression of adipocyte SCD gene expression in mature adipocytes (52). The observed reduction in enzyme activity (60%) could be completely accounted for by decreases in SCD1 mRNA levels (80%). Thus, there appeared to be no additional down-regulation occurring post-translationally. Therefore, in contrast to what occurs in hepatocytes, changes in mRNA stability are the major determinant of SCD1 mRNA abundance in adipocytes in response to PUFA.

Destabilization of SCD mRNA in adipocytes may be regulated through mRNA sequences in the 3′-untranslated region (UTR). The mouse, rat, and human SCD cDNAs contain an unusually long 3′-UTR (9–12, 71). The role of such a long 3′-noncoding stretch is currently unknown, though it contains several structural motifs (e.g., AUUUA) characteristic of mRNA destabilization sequences (52). Four of these sequences are clustered close to the 3′-end of the coding region. Because these AU-rich elements (ARE) play active roles in the selective degradation of several mRNAs in response to various factors, these sequences could be possible targets of PUFA effects on SCD1 and SCD2 mRNA in adipocytes. In yeast, PUFAs act through sequences in the 5′-UTRs to decrease the OLE1 mRNA stability (70). Northern blot analysis shows that the human SCD gene gives rise to two mRNA transcripts of 3.9 and 5.2 kb which arise as a consequence of the two polyadenlyation signals, indicating that the two differently expressed transcripts encode the same SCD polypeptide (12). The function of the polyadenylation is not known but could be in addition to the transcriptional control, a means by which the two transcripts differ in stability or translatability thus allowing for rapid and efficient changes in cellular environment (12).

The work on SCD gene regulation by PUFA in adipocytes suggests that PUFA regulate SCD gene expression through different mechanisms in different tissue types, the reasons for which are not yet understood. However, SCD gene provides a good model to study the effects of

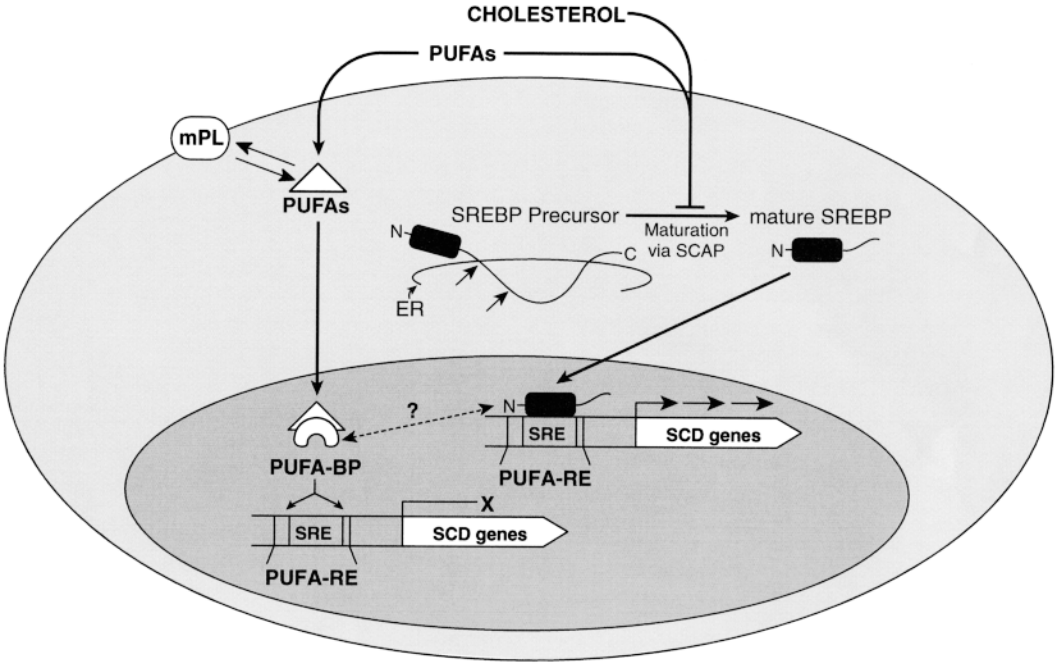

Fig. 3. Pathways of SCD regulation by PUFA and cholesterol. PUFA and cholesterol repress the maturation of the sterol regulatory element binding protein (SREBP) via the SREBP cleavage-activating protein (SCAP) that would otherwise translocate from the endoplasmic reticulum (ER) into the nucleus to activate the transcription of the SCD genes by binding to the sterol regulatory element (SRE). PUFAs either from the diet or membrane phospholipid (mPL) independently bind the putative binding protein (PUFA-BP) and the PUFA and PUFA-BP complex represses transcription of the SCD genes by binding to the polyunsaturated fatty acid response element (PUFA-RE). Crosstalk between the two pathways is designated by the dashed arrow.

PUFA on mRNA stability. The ongoing search in our lab and others for possible protein mediators that destabilize SCD1 mRNA should provide further definition to the molecular basis of PUFA regulation of lipogenic gene expression.

CHOLESTEROL AS A REGULATOR OF SCD GENE EXPRESSION

Nearly two decades ago, Chin and Chang (72) demonstrated that there was an increase in the SCD enzyme activity when Chinese hamster ovary cells were incubated with lipid-depleted media. They noted that the desaturase activity was reduced when the medium was supplemented with cholesterol. Subsequently, mutants were isolated that failed to induce enzymes involved in both cholesterol and monounsaturated fatty acid biosynthesis. Revertants were able to synthesize both cholesterol and monounsaturated fatty acids concomitantly. Using differential display techniques to identify genes that are transcriptionally activated by sterol regulatory element binding proteins (SREBPs), Tabor et al. (65) recloned the SCD2 cDNA from Chinese hamster ovary cells and demonstrated that the SCD2 mRNA expression is repressed in these cells when cultured in the presence of cholesterol. These in vitro studies using the Chinese hamster ovary cells showed that, like PUFAs, cholesterol represses the expression of the SCD genes and enzyme activities.

There are in vivo rat studies, however, that show that contrary to results in vitro, high levels of cholesterol can induce SCD gene expression. In one study, feeding rats with various diets supplemented with cholesterol increased SCD enzyme activity and SCD mRNA levels in liver (40–42). The increase in SCD enzyme activity correlated with increased synthesis of oleic acid and its enhanced incorporation into cholesteryl esters. Another study considered the expression of the SCD mRNA in LXRα receptor knockout mice (73). LXRα is the oxysterol receptor that mediates regulation of gene expression by cholesterol or its metabolites (73, 74). Mice lacking LXRα receptor expressed low levels of SCD mRNA in the presence or absence of cholesterol feeding while the wild-type animals fed 2% cholesterol had their SCD mRNA levels up-regulated 4-fold (72). As expected, the mRNA levels corresponding to several enzymes involved in cholesterol biosynthesis were up-regulated in the LXRα knockout animals and down-regulated in the wild-type animals upon cholesterol feeding. These in vivo studies would be consistent with the possibility that the liver, when challenged with excess cholesterol, increases SCD activity in order to provide oleoyl-CoA as a substrate for cholesterol esterification and storage to package into VLDL for secretion and transport to other tissues. As esterified cholesterol does not down-regulate the LDL receptor, the liver can continue cholesterol uptake and prevent hypercholesterolemia. It is not clear from the in vivo studies whether cholesterol or its metabolites induce the transcription of the SCD1 through the LXRα or indirectly

through the regulation of the SREBPs. It is not known whether the induction of SCD gene expression by cholesterol is liver-specific or occurs in other tissues as well.

There are other studies that support cholesterol's regulation of SCD expression in vivo. Female mice express higher levels of SCD mRNA than male mice (75). The underlying mechanistic basis for the higher levels of expression of SCD1 gene in female mice is unknown but it could be due to differences in levels of hormones such as estrogen and testosterone which are synthesized from cholesterol. Estrogen administration causes a remarkable increase of plasma lipids in mice and of VLDL in avian species (76). Androgens stimulate the expression of the stearoyl-CoA desaturase in the sebaceous glands of hamsters (77). Estrogen has also been shown to induce SCD activity in rooster liver (78) but whether this occurs at the level of gene expression has not been established. Several peroxisome proliferators induce SCD activity differently in males than in females and this difference has been shown to be due to higher levels of testosterone in males (79). Thus, the differences in SCD1 gene expression may aid our understanding of how certain gender-related diseases such as cancer, diabetes, obesity, and heart disease are influenced by dietary fat lipid saturation and steroid hormones.

TRANSCRIPTIONAL REGULATION OF SCD GENES BY STEROL REGULATORY ELEMENT BINDING PROTEINS (SREBPs)

Transcriptional activation of genes containing sterol responsive element (SRE) is known to be under the regulation of sterols through modulation of the proteolytic maturation of the sterol responsive element binding proteins (SREBP-1 and SREBP-2) (80, 81). The SREBPs are inserted into the membrane of the endoplasmic reticulum envelope in a wide variety of tissues. In sterol-deficient cells, proteolytic cleavage of SREBPs releases their N-terminal mature forms from the membrane, enabling them to enter the nucleus, where they bind to the SREs and activate genes involved in cholesterol, triglyceride, and fatty acid biosynthesis (66–69). In the presence of sterols, the proteolytic process is inhibited and the transcription of the genes is reduced because little SREBP is available to activate their transcription.

Tabor and coworkers (65) showed that the transcription of the mouse SCD2 is regulated in response to alterations in either levels of sterols or the levels of nuclear SREBP/ADD1. Increased expression/nuclear localization of SREBP-1 and SREBP-2 after incubation of cells in sterol-depleted medium was sufficient to enhance transcription of the SCD2 gene and resulted in increased SCD2 mRNA levels. The observation that hepatic SCD1 and SCD2 mRNA levels were induced in transgenic mice that overexpress SREBP-1 and SREBP-2 (67–70), leading to increased synthesis of monounsaturated fatty acids, is consistent with the direct transcriptional activation of the SCD1 promoter by SREBPs. The in vivo experiments with LXRα knockout mice alluded to above suggest that LXRα is involved in the activation of SCD gene transcription by cholesterol or its metabolites. This is similar to the activation of the gene encoding cholesterol 7α-hydroxylase, a rate-limiting enzyme in bile acid biosynthesis (74). In the LXRα knockout mouse it was also shown that SREBP-1 mRNA and protein levels are reduced and that SREBP-1 mRNA was induced only in wild-type animals fed 2% cholesterol in their diets, suggesting that cholesterol regulates the expression of SREBP through LXRα. If this is the case, then the in vivo experiments would imply that LXRα indirectly regulates the SCD expression by controlling SREBP-1 expression. This phenomenon would be consistent with studies of the transgenic mice expressing a constitutively active form of SREBP-1 in which fatty acid-synthesizing enzymes are dramatically elevated resulting in a fatty liver phenotype (67). These studies would also be consistent with the in vitro results that show activation of the SCD gene expression by SREBPs.

A novel sequence in the PUFA-RE of the SCD2 gene that functions as an SRE has been identified (65). This sequence (5′AGCAGATTGTG3′), shown to bind purified SREBP, is distinct from previously described SREs. It does not contain the direct repeat nor does it contain a functional E-box (65), but within its vicinity are two CCAAT boxes for the binding of NF-Y (Fig. 2). SREBP and NF-Y have been shown to dimerize in the activation of the sterol-dependent transcription of several sterol-regulated genes (81–84) and it is more than likely that both transcription factors are required in cholesterol regulation of the SCD genes.

PUFAs and oleic acid have been shown to reduce the expression of promoters with sterol regulatory elements by inhibiting the proteolytic maturation of SREBP (85, 86). These studies suggest that the SREBP participates in the repression of the SCD gene transcription by PUFA. In addition, oleic acid has been shown to potentiate the maturation of SREBP by sterols in CHO-K1 cells (86). However, oleic acid could not reduce the transcription of the SCD genes both in vivo and in vitro (16, 45, 57). Thus, SREBP maturation does not seem to exhibit the selectivity required to explain PUFA control of SCD gene transcription. Transfection of the SCD2 promoter constructs containing the PUFA-RE linked to a reporter gene in HepG2 cells results in repression of reporter gene expression in the presence of cholesterol and PUFAs (65). However, the SREBP or the NF-Y elements on their own do not mediate PUFA repression in a heterologous context (57) but PUFA repression is observed only when the entire 60 bp PUFA-RE is used in a heterologous context (57). Therefore, although there are indications that SREBP maturation as well as binding of the SREBP and NF-Y to the PUFA-RE are involved in PUFA repression, there is strong evidence for the existence of an SREBP-independent mechanism involving a putative PUFA-binding protein (Fig. 3) through which PUFAs repress SCD gene expression. Crosstalk could exist between the SREBP, NF-Y, and the putative PUFA binding protein. More research is required in this area to resolve this issue.

CONCLUSION AND FUTURE DIRECTION

Research in the past few years has confirmed the importance of PUFAs and cholesterol as universal cellular regulators. The discovery that lipids can affect gene transcription, and thus modulate the cell's metabolic state, is essential to our understanding of responses to dietary changes. Both PUFAs and cholesterol can control the synthesis of monounsaturated fatty acids in liver by regulating the expression of the SCD genes. PUFAs regulate expression of SCD in other tissues as well. Whether cholesterol regulates SCD gene expression in tissues other than the liver needs further investigation. The role of SREBP in mediating the action of cholesterol is well established through several elegant studies but its role in the regulation of gene expression by PUFA needs more study. It is very interesting that the SCD PUFA-RE and SRE overlap, but our current understanding of SCD gene expression suggests an SREBP-independent pathway of PUFA repression of gene expression. Several lipogenic genes such as FAS and S14 are also regulated by PUFA and cholesterol but the regulation of the SCD gene assumes greater importance when we consider the multitude of human diseases in which abnormal synthesis of monounsaturated fatty acids is a factor. Further elucidation of the mechanisms by which PUFA and cholesterol alter cellular monounsaturated fatty acids is therefore needed to understand the impact of SCD gene regulation in various human disease states.

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