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Review

Sterol regulatory element-binding proteins (SREBPs): transcriptional regulators of lipid synthetic genes

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Abstract

Roles of sterol regulatory element-binding proteins (SREBPs) have been established as lipid synthetic transcription factors especially for cholesterol and fatty acid synthesis. SREBPs have unique characteristics. Firstly, they are membrane-bound proteins and the N-terminal active portions enter nucleus to activate their target genes after proteolytic cleavage, which requires sterol-sensing molecule, SREBP-activating protein (SCAP) and is crucial for sterol-regulation. Secondly, they bind and activate sterol-regulatory (SREs) containing promoters as well as some E-boxes, which makes SREBPs eligible to regulate a wide range of lipid genes. Finally, three isoforms, SREBP-1a, –1c, and –2 have different roles in lipid synthesis. In vivo studies using transgenic and knockout mice suggest that SREBP-1 seems to be involved in energy metabolism including fatty acid and glucose/insulin metabolism, whereas SREBP-2 is specific to cholesterol synthesis. Future studies will be focused on understanding molecular mechanisms sensing cellular sterol and energy states where SREBPs are deeply involved.

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1. Introduction

Cholesterol and fatty acids are primary components of cellular membranes. Growing cells need to synthesize both cholesterol and fatty acids according to their demand for growth. In the differentiated tissues such as liver and endocrine organs, cholesterol biosynthetic pathway is linked to synthesis of bile acids and steroid hormones, respectively. Synthesis for fatty acids and triglycerides, often referred to as lipogenesis, is an energy storage system specialized to lipogenic organs such as liver and adipose tissues. In contrast to cholesterol synthesis, which is tightly regulated by a feedback system to maintain cellular cholesterol levels, fatty acid synthesis is driven primarily by the availability of carbohydrates and the actions of hormones such as insulin (reviewed in [1, 2]). Both pathways are nutritionally controlled at the transcriptional level. Recent evidence suggests that despite these different patterns of regulation, both biosynthetic pathways are controlled by a common family of transcription factors designated sterol regulatory element binding proteins (SREBPs) (reviewed in [3]). In this review, we focus on recent progress in understanding the molecular basis on physiological functions of SREBPs which have now been established as global lipid synthetic regulators.

2. Molecular aspects of SREBPs

2.1. Structure of SREBPs (Fig. 1)

SREBPs were purified as nuclear factors that bind to the sterol regulatory element (SRE) common to LDL receptor and HMG CoA synthase genes [4,5]. Cloning and sequence of SREBP genes revealed their unique aspect as membrane-bound transcription factors (6). SREBPs are

structurally composed of four domains with two membrane-spanning regions. Both amino- and carboxyl-terminal portions of the proteins project into the cytoplasm. The N-terminal domain of approximately 480 amino acids is a basic-helix-loop-helix leucine zipper (bHLHZip) protein and a functionally active portion as a transcription factor. This segment begins with an acidic transactivation domain that clusters acidic residues. When this segment is deleted in transfection studies, the proteins retain the ability to bind to the relevant DNA sequence, but they lose their ability to activate transcription [7]. The acidic NH_2-terminal sequence is followed by a glycine, serine, proline, and glutamine rich region whose function is unknown. These sequences are followed by the bHLH-Zip domain. SREBPs are believed to form a homodimer to bind to an SRE. What makes SREBPs a unique membrane-bound transcription factor is the subsequent sequence consisting of a hydrophobic membrane-spanning sequence, a hydrophilic loop region, a second membrane-spanning sequence, and a long carboxyl-terminal region. SREBP forms a complex with WD domain of SREBP cleavage activating protein (SCAP) through this carboxyl-terminal region (Fig. 2). Therefore, this region of SREBP should be involved in sterol-regulation, and thus is named a carboxyl regulatory domain [8,9].

2.2. Cleavage of SREBPs for activation (Fig. 2)

Unlike other members of this class, SREBPs are produced as membrane-bound precursors that require cleavage by a two-step proteolytic process in order to release their amino-terminal bHLH-Zip-containing domain (nuclear SREBP) into the nucleus to activate their target genes [10,11]. Molecular mechanisms for cleavage of SREBPs in sterol regulation have been elegantly and extensively analyzed by Goldstein and Brown [3,12–14]. Upon sterol deprivation, the membrane-bound SREBP precursor protein undergoes a sequential two-step cleavage process to release the amino-terminal portion SREBP [10,11]. This nuclear SREBP, then enters the nucleus and activates the transcription of genes involved in cholesterol and fatty acid synthesis by binding to sterol regulatory elements (SREs) or to palindromic sequences called E-boxes within their promoter regions. SREBP precursor and SCAP form a complex on the rough endoplasmic reticulum (ER) membrane [9]. SCAP is a multiple membrane-spanning protein containing a consensus sequence for a sterol-sensing domain which is shared by HMG CoA reductase, Niemann-Pick C1 disease gene product (NPC1), and Patched [8,15]. Therefore, SCAP has been suggested to function as a cholesterol sensor. SCAP is prerequisite for cleavage of SREBPs [16,17]. When sterol is depleted, the SREBP-SCAP complex targets to golgi where site-1 and site-2 proteases await. Site-1

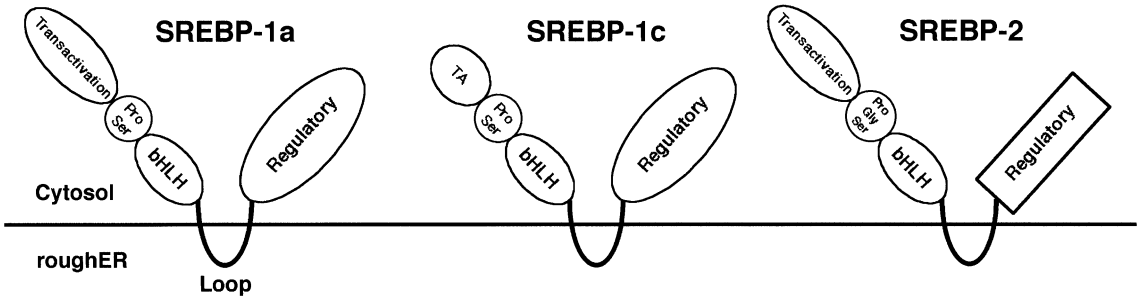

Fig. 1. Domain structure of SREBP family.

protease, activated by auto-catalysis, cleaves SREBP at the loop region, followed by the second cleavage in the first membrane spanning region by site-2 protease to liberate the N-terminal of SREBP [16,18–21]. Importin β is involved in this nuclear transport of SREBP [22]. The SCAP presumably goes back to rough ER to meet another SREBP molecule. When sterol is abundant, SREBP-SCAP complex is retained at the rough ER and no cleavage occurs. Therefore, cellular sterol regulation entirely depends upon the sterol-sensing and cleavage system. The molecular mechanism of this sterol-sensing system is currently a most intriguing enigma. Some oxysterols such as 25-OH cholesterol efficiently inhibit this sterol-regulated, inter-organella trafficking of the SREBP-SCAP complex. It is a tempting speculation that an unknown sterol sensor protein which could be an acceptor of oxysterol might bind to the sterol sensing domain of SCAP to make the complex retain to rough ER.

In contrast to this sterol regulation, sterol-independent cleavage of SREBP has been also suggested. Caspase-3 (CPP32) can cleave SREBP to liberate nuclear forms in apoptosis [23].

TNF-alpha involving neutral shpingomyelinase and ceramide, is also known to activate SREBP, presumably through the same cleavage process [24,25]. Physiological relevance of this sterol-independent cleavage is currently unknown.

In another report, unsaturated fatty acids mediate regulate cleavage of SREBP-1, but not SREBP-2 [26]. These data might open up a new regulation of fatty acid metabolism mediated by SREBP-1 at the cleavage level in contrast to sterol regulation by SREBP-2. The key to the understanding of this distinct regulation by SREBP-1 and-2 is the lipid sensing mechanism of SCAP.

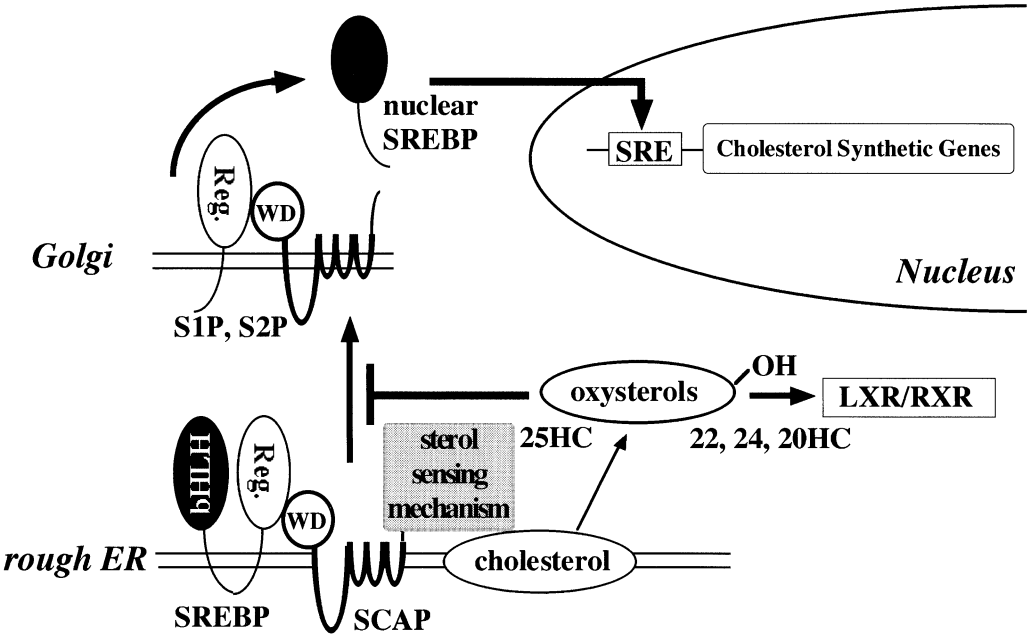

Fig. 2. SREBP-SCAP trafficking and sterol regulation.

2.3. SRE and E-box: DNA binding sites of SREBPs

After entry into nucleus, nuclear SREBP binds to the specific DNA sequence in the promoters of its target genes. The *cis*-elements are named as sterol regulatory elements (SREs) because they were identified as regulatory elements common to HMG CoA synthase and reductase and LDL receptor gene promoters. The original SRE sequence was ATCACCCCAC [4]. In the initial mutational analysis, SRE was thought to be tightly strict to the original sequence with a permissive diversity of only a couple of bases [4].

Another unique feature of SREBPs is that they can bind to and activate classic palindromic E-boxes (CAXXTG) containing promoters as well as nonpalindromic sterol regulatory elements (SREs) [27]. In the screening of SREBP binding sites from random DNA sequences, ADD1, a rat homologue picked up ATCACGTGAT most preferably [27]. The tyrosine residue in the basic region of SREBPs where regular bHLH proteins have an ariginine residue, is a key to this dual binding specificity of SREBPs [27]. Mutant SREBPs where ariginine was substituted for the tyrosine lost a binding specificity to the SRE, but retains to the E boxes [27]. Presumably, this dual binding specificity makes SREBPs eligible to have a broad spectrum of target genes covering both cholesterogenic and lipogenic genes. The 2.3 A resolution co-crystal structure of the DNA-binding portion of SREBP-1a bound to an SRE revealed a quasi-symmetric homodimer with an asymmetric DNA-protein interface [28]. Our recent data on binding specificity of SREBP to SRE and E-box indicate that SREBPs have higher affinity and lower capacity for SRE than E-box [110].

2.4. Target genes of SREBPs

The current list of SREBP target genes is shown in Table 1. Basically, they are all involved in lipid synthesis and roughly categorized as cholesterol synthetic genes and lipogenic enzyme genes. Genes involved in cholesterol synthesis contain SRE(s) which are identical or relatively similar to the original SRE sequence found in the LDL receptor gene. Meanwhile, sequences of SREBP binding and activation sites in lipogenic genes vary considerably and are tentatively designated SRE-like sequences [29].

2.5. Cofactors for SREBPs

In the neighboring (usually 15 bases around the SRE) sequence of SREBP target gene promoters, NF-Y site or Sp1 site is usually found [5,30–59]. NF-Y and Sp1 directly bind to SREBP and seem involved in recruitment of basic transcription machinery including CBP (58). Transactivation domains of SREBP-1a and -2 binds to CBP, but SREBP-1c does not (58).

In some SREBP target genes, SREBP activation of gene expression can be negatively regulated by Yin Yang-1 zinc finger transcription factor (YY1). YY1 can repress SREBP activation of HMG CoA synthase, FPP synthase, and LDL receptor genes by displacing NF-Y, which is essential for SREBP activation of these genes [49,60]. Another mechanism is also proposed in YY1 repression of HDL receptor (SRBI) and steroidogenic acute regulatory protein (StAR) genes: YY1 binds to SREBP-1a with a high affinity and interferes SREBP binding to the SREs in these genes [61,62]. These transfection studies suggest involvement of YY1 in SREBP gene regulation, but physiological relevance of YY1 in this context needs to be tested in vivo.

2.6. Repression of genes through SRE

SREBPs are basically thought to activate their target genes. However, there are some reports that SREBPs play a role in repression of SRE-containing genes such as microsomal transfer protein (MTP) [63] and caveolin [39]. MTP and caveolin are involved in regulating cellular cholesterol content by assembly and secretion of lipoproteins, and cholesterol efflux, respectively. Therefore, repression of these genes by SREBPs could be a part of sterol regulation. Binding to SREBP site and displacing some other positive regulators specific to these genes can be a possible mechanism of their SREBP repression.

Table 1
Genes activated by SREBPs[a]

Gene	SRE promoter sequence	Reference
Cholesterol metabolism		
LDL receptor	ATCACCCCAC	[101]
HMG CoA synthase	CTCACCCCAC	[102]
	GCCACCCTAC	
HMG CoA reductase	ACCGCACCAT	[103]
	CTCTCACCAC	
Farnesyl diphosphate synthase	CTCACACGAG	[34]
Squalene synthase	ATCACGCCAG	[104]
	CTAGTGTGAG	
SREBP-2	ATCACCCCAC	[35]
Lanosterol 14α-demethylase (Cyp51)	ATCACCTCAG	[105]
Fatty acid metabolism		
Acetyl CoA carboxylase	CCAT - - - - TCAC	[38]
Fatty acid synthase	GCCACGCCAC	[106]
	GTCAGCCCAT	
Stearoyl CoA desaturase-1 and 2	AGCAGATTGTG	[50,107]
AcylCoA binding protein (Diazepam)	CTCGCCCGAG	[107]
SREBP1	CTCACCCGAG	[55]
ATP citrate lyase	TCAGGCTAG	[54,56]
Malic enzyme	TCACCCGTCGGTG	[110]
PPAR gamma	ATCACTTGAG	[98]
Acetyl CoA synthease	ATTCATGTGACAT	[111]
	ATCACTCCAC	
Triglyceride synthesis		
Glycerol-3-phosphate acyltransferase	CTCAGCCTAG	[37]
	CTCACCCCAG	
	GACACCCCAG	
Plasma lipoprotein metabolism		
Lipoprotein lipase	CTCCCCCCAA	[108]
HDL receptor (SRBI)	GCCACCTGCA	[52]

[a] Other genes whose promoters are involved in SREBP binding includes StARP [62], CETP [109], and neutral cholesterol ester hydrolase, [44]. In contrast, MTP [63], caveolin [39] are reported to be repressed by SREBPs.

3. Isoforms of SREBP family

3.1. SREBP-1a,-1c, and -2 (Fig. 1)

To date, three SREBPs have been identified; SREBP-1a and SREBP-1c produced from a single gene through the use of alternate promoters, and SREBP-2 from a separate gene [6,64–66]. SREBP-1a and -1c are identical except the NH2-terminal transactivation domains. The rat homologue of SREBP-1c, named ADD1, was cloned independently as a protein which binds to E-boxes, and presumably promotes adipocyte differentiation [67]. All actively growing cultured cells so far studied produce predominantly SREBP-1a and SREBP-2, whereas most organs including liver from adult animals predominantly synthesize SREBP-1c and SREBP-2 [68]. Consistent with high similarity between N-terminal portions of the isoforms, all three SREBPs are capable of activating each of the known target genes, although with differing efficiencies (discussed later). SRBP-1c is weaker than SREBP-1a and SREBP-2 due to its shorter transactivation domain [69,70]. The caboxyl-terminal regulatory domains of SREBP-1 and -2 are relatively less conserved as compared to other portions of SREBPs, suggesting some difference between SREBP-1 and -2 in a sterol regulation manner.

3.2. Differences among SREBP isoforms in target DNA specificity

As discussed later, various lines of evidence from in vivo studies suggested that SREBP-1 is more active for lipogenic genes whereas SREBP-2 is more specific to cholesterogenic genes [69–74]. Generally, cholesterogenic genes contain classic SREs in their promoters while SREBP binding sites in the promoters of lipogenic genes vary including E-boxes. Consistently, our recent transfection studies indicated that SREBP-1a, -1c and -2 have a different specificity for activation of SRE-containing promoters and E-box containing promoters [110]. In summary, SREBP-1a and -2 are equally active for SRE-reporter gene (SRE-luciferase) whereas SREBP-1c is essentially inactive. In contrast, SREBP-1a and -1c are active for E-box while SREBP-2 is inactive. All SREBP isoforms can bind and activate SRE-like sequences in lipogenic gene promoters, although with different efficiencies. These different activities of SREBP isoforms for target DNAs can partially explain their different in vivo functions.

4. In vivo functions of SREBPs

4.1. SREBP transgenic mice

To gain insight into the distinct roles of each SREBP isoform in vivo, transgenic mice that overexpress truncated, active nuclear forms of human SREBP-1a, -1c, or-2 in the liver, were produced and characterized [69,74]. The different SREBP-overexpressing transgenic animals showed different patterns of increase in hepatic synthesis and accumulation of cholesterol and/or fatty acids. These data suggest that the SREBP-1c is more selective in activating fatty acid biosynthetic genes while SREBP-2 is more specific for controlling cholesterol biosynthesis. Overexpression of nuclear SREBP-1a profoundly activated both cholesterol

and fatty acid synthetic genes, resulting in the most striking phenotype of a huge fatty liver with the accumulation of large amounts of triglycerides and cholesteryl esters [71]. Very similar phenotypic changes in the liver were observed in transgenic mice overexpressing dominant positive type of mutated SCAP [75]. Induction of a whole battery of lipogenic genes in this transgenic mouse liver was the first observation that SREBP-1 could be involved in lipogenic genes.

4.2. SREBP knockout mice [72]

SREBP1 knockout mice were partially embryonic lethal (70–90% of expected number of homozygotes). They die at day 10.5–11.5 (p.c.). The cause of their lethality remains unknown. Livers in surviving homozygote at ad labium showed a significant decrease in fatty acid synthesis with a trend in decreases in mRNA levels of fatty acid synthetic genes. Unexpectedly, SREBP-1 deficient mice showed increased mRNA levels in cholesterol synthetic enzyme genes, accompanying a significant increase in cholesterol synthesis. This was due to activation of SREBP-2 to compensate for the absence of SREBP-1 for an unknown endpoint at the expense of overshooting cholesterol synthesis. SREBP2 knockout mice were completely lethal at the day earlier than 8 (p.c.). SREBP-1 could not compensate for absence of SREBP-2, presumably due to its different way of regulation.

4.3. Nutritional regulation of lipogenic enzyme genes by SREBP-1

The first evidence of different regulation of SREBP-1 and -2 emerged from in vivo study with HMG CoA reductase inhibitor (lovastatin) and bile acid lesin (Colestipol) [76]. When hamsters were put on a diet containing these anti-hypercholesterolemic drugs which deplete cholesterol in the liver, the nuclear SREBP-2 protein was upregulated to restore hepatic cholesterol content as sterol regulation. In contrast, mRNA, precursor, and nuclear protein levels of SREBP-1 were decreased, suggesting that in vivo regulation of SREBP-1 was not in a sterol-regulatory manner.

Lipogenic enzymes, which are involved in energy storage through synthesis of fatty acids and triglycerides, are coordinately regulated at the transcriptional level during different metabolic states [1,2]. Recent in vivo studies demonstrated that SREBP-1c plays a crucial role in the dietary regulation of most hepatic lipogenic genes; these include studies of the effects of over-expression of SREBP-1 on hepatic lipogenic gene expression as described [69,72] and physiological changes of SREBP-1c protein in normal mice after dietary manipulation,such as placement on high carbohydrate diets, polyunsaturated fatty acid-enriched diets, and fasting-refeeding regimens [77–81] The similar coordinated changes in SREBP-1c and lipogenic gene expression upon fasting and refeeding were also observed in adipose tissue [82]. Finally, we established a role of SREBP-1 in nutritional regulation of lipogenic genes by showing a severely impaired nutritional induction of lipogenic gene expression in SREBP-1-null mice [73]. Previous reports on the regulation of SREBP-1c have all demonstrated the induction to be at the mRNA level. Up-regulation of hepatic SREBP-1 mRNA was observed in rodent livers on a fasting-refeeding regimen, a chronic high carbohydrate diet, and in primary hepatocytes with a high glucose medium [80,81,83,84]. In contrast, down-regulation of SREBP-1c was observed in livers from fasted rodents, insulin-

depleted diabetic rats with streptzotocin treatment, and from mice on a diet containing polyunsaturated fatty acids [77–81,85].

4.4. The effects of insulin/glucose on SREBP-1 expression

It is known that both glucose and insulin are required for the production of fatty acids via the induction of hepatic lipogenic enzymes. Several lines of evidence suggest that the roles of glucose and insulin in this action are mediated by induction of SREBP-1c. In support of a role for SREBP-1 in the induction of lipogenic genes by insulin, different groups have shown that SREBP-1c is up-regulated by insulin in vivo and in primary hepatocyte cultures [85–87]. These observations raised a possibility that SREBP-1c could be a metabolic mediator of insulin effect in the liver [88]. It is interesting to explore the relationship insulin-receptor signaling and SREBP-1c induction. PI3 kinase inhibitors decrease nuclear and precursor SREBP-1c proteins [84]. In contrast, we and other groups showed that glucose can induce SREBP-1c expression [83,84]. It has been shown that glucose must be metabolized for this effect on lipogenic gene induction and that insulin could only be permissive to this glucose action [89,90]. Further studies are required to clarify the mechanism by which insulin/glucose induces SREBP-1c expression.

5. Promoter analysis of SREBP-1c (Fig. 3)

5.1. Presence of SRE and oxysterol-inducible region in SREBP-1c promoter

Transcriptional regulation of lipogenic enzymes is controlled by the amount of SREBP-1c mRNA. This notion prompted us to analyze the promoter of SREBP-1c to understand the regulation of SREBP-1c itself, and thus, that of lipogenic enzymes [55]. A cluster of putative binding sites of several transcription factors composed of NF-Y site, E-box, sterol-regulatory element, and Sp1 site were located at −90 bp of the SREBP-1c promoter. Luciferase reporter gene and gel shift assays indicated that the NF-Y site and the SRE in the SRE complex are responsible for SREBP activation. This implicates an autoloop production of SREBP-1c through the SRE complex,

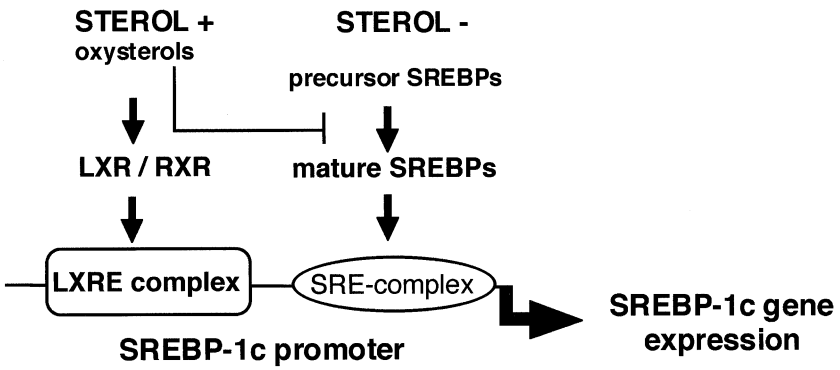

Fig. 3. Activation of SREBP-1c promoter.

possibly leading to an overshoot phenomenon in induction of SREBP-1c and its downstream genes in the livers of refed mice [81]. We also found another region that is upregulated by oxysterols upstream of the SRE complex. This region was identified as LXR/RXR binding site later (next section). The presence of the SRE complex and a sterol-inducible region in the same promoter suggests a novel regulatory link between cholesterol and fatty acid synthesis (Fig. 3).

5.2. LXR/RXR activation of SREBP-1c: a new link between cholesterol and fatty acid regulation

We took an expression cloning strategy to seek a factor that activates SREBP-1c promoter [91]. We cloned and identified LXR α and β as strong activators of SREBP-1c promoter [91]. Deletion and mutation analysis on the SREBP-1c promoter identify two sets of new LXR binding sites (LXR elements) which are very similar to an LXRE which has been recently identified in ATP binding cassette (ABC1) gene promoter [92–94]. Either LXR, RXR, or their respective ligands can synergistically activate SREBP-1c promoter. Recent reports on the effects of pharmacological LXR ligands and mice deficient in LXR α, β or both also indicated that LXR/RXR activated SREBP-1c expression [95,96]. Both group observed that this activation of SREBP-1c by LXR/RXR is accompanied by a substantial increase in nuclear SREBP-1c, leading to activation of its target lipogenic genes [95]. LXR has been recently established as an oxysterol receptor and plays a key role in dealing with an excess amount of free cholesterol in the cells by enhancing cholesterol efflux or bile acid synthesis. Since SREBP-1c can activate fatty acid synthesis, activation of SREBP-1c by the oxysterol receptor could be another cellular adaptation for excess cholesterol by enhancing formation of cholesterol esters. This might suggests a new link between cholesterol and fatty acid metabolism. As shown in Fig. 3, SREBP-1c promoter can be activated regardless of sterols, ensuring lipogenesis or cholesterol ester formation.

6. ADD1/SREBP-1c in adipogenesis

SREBP-1c was also cloned as a transcription factor for genes involved in adipogenesis, and designated adipocyte determination and differentiation factor 1 (ADD1) [67]. ADD1/SREBP-1c has been suggested to be involved in adipogenesis by activating PPAR gamma, a master gene for adipogenesis [97]. It was reported that ADD1 activates promoters of PPAR gamma 1 and 3, and directly induces transcription of PPAR gamma [98]. More interestingly, ADD1 induces production or secretion of some lipid molecule which can be a ligand for PPAR gamma [99]. This lipid molecule could be an endogenous ligand for PPAR gamma and a key for adipogenesis. However, the role of ADD1/SREBP-1c in adipogenesis and lipogenesis in adipose tissue seems to be very complex and not straightforward. SREBP-1 knockout mice have slightly less fat, but adipogenesis and lipogenesis were grossly abnormal, although it could be explained by a compensatory activation of SREBP-2 [72,73]. Overexpression of nuclear SREBP-1c in a fat-specific manner using aP2 promoter in transgenic mice impaired adipose tissue differentiation, causing decreased amount of fat and severe insulin resistance and hyperinsulinemia [100]. These apparently opposing observations lead us to speculate that timing and amount of ADD1/SREBP-1c expression might be important for adipogenesis.

7. Transcriptional regulation of lipid synthesis by SREBP-2 and -1c in the liver (Fig. 4)

Fig. 4 depicts a current diagram for different functions of SREBP-2 and SREBP-1c in the regulation of lipid synthesis in the liver. Both SREBP-2 and -1c are subjected to the cleavage-system by SCAP, S1P, and S2P. If SCAP is disrupted, no cleavage of SREBP-1 or -2 occurs in the cultured cells [17], suggesting that there is no other cleavage system at least in the cultured system. Then, in the presence of sufficient amount of cholesterol, is lipogenesis shut down because cleavage of SREBP-1 is cancelled? Our recent findings using a well-differentiated liver cell line showed that cleavage of SREBP-1 was less sensitive to sterol-suppression than SREBP-2, suggesting that SREBP-1 could have a chance to liberate its active form into nucleus even in the presence of sterols to activate lipogenic genes by increasing its own amount [84]. In another report, unsaturated fatty acids mediate and regulate cleavage of SREBP-1, but not SREBP-2 [26]. These data might open up a new regulation of fatty acid metabolism mediated by SREBP-1 in contrast to sterol regulation by SREBP-2. The key to an understanding of this distinct regulation by SREBP-1 and-2 is the lipid sensing mechanism of SCAP. Through these complex ways of SREBP regulation at different levels, SREBP-2 controls cholesterol synthesis at the cleavage system, whereas SREBP-1c regulates lipogenesis mainly by changing SREBP-1c mRNA level.

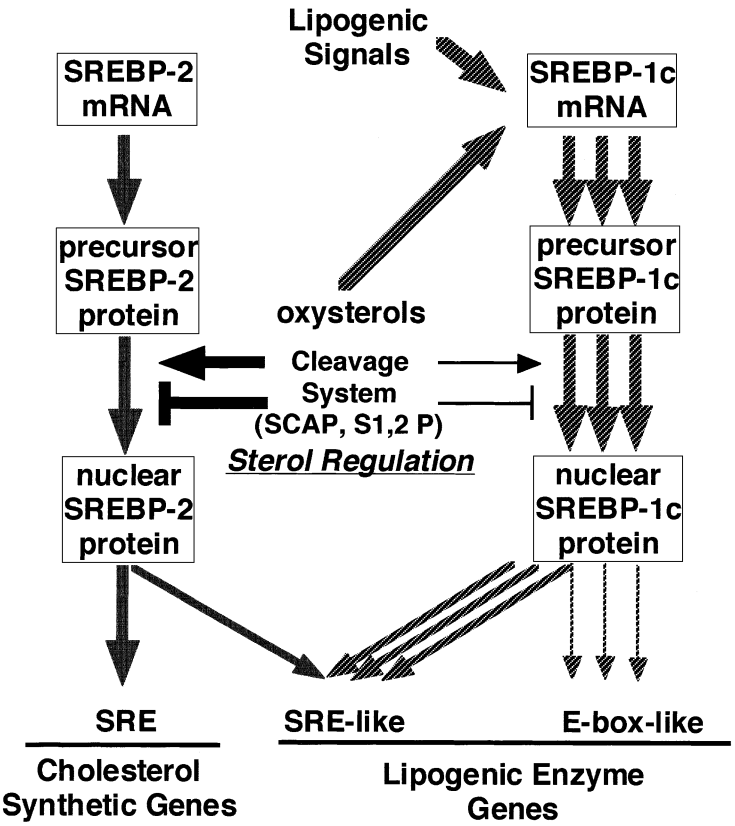

Fig. 4. Different regulations of lipid synthetic genes by SREBP-2 and -1c in the liver.

8. Future aspects of SREBPs; crosstalk of transcription factors for lipid metabolism

The list of SREBP target genes is expanding. More detailed analysis on unknown target genes using DNA microarray or DNA chip technology will help our understanding of SREBP functions. It is necessary to elucidate a sterol-sensing system and identify signaling molecules for cellular cholesterol amount. The SCAP–SREBP-2 complex should play a key role in this mechanism. Identification of energy sensing molecules is another interesting topic. SREBP-1 should be involved in this mechanism and play a role as a mediator for energy storage.

Recent progress in the studies on transcriptional regulation of cholesterol and fatty acid metabolism unveiled several key players; SREBP-2 for cholesterol synthesis, LXR/RXR for cholesterol catabolism, SREBP-1 for fatty acid synthesis, and PPARα for fatty acid degradation. These factors might interact with each other to exert their own functions more efficiently. For instance, nutritional regulation of SREBP-1c and PPARα are reciprocal and the effects of polyunsaturated fatty acids on these are opposite. LXR/RXR activates SREBP-1c, suggesting oxysterol involvement in fatty acid metabolism. Cholesterol and energy metabolism may be regulated in a complex manner by mutual interaction of these transcription factors. Future studies on SREBPs should be focused on the crosstalk of these lipid transcription factors.

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