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SREBPs: regulators of cholesterol/lipids as therapeutic targets in metabolic disorders, cancers and viral diseases

SREBPs control genes involved in cholesterol/lipid metabolism, membrane synthesis and fat storage. Aberrant SREBP activities have been linked to conditions associated with metabolic syndrome, including insulin resistance, obesity, elevated circulating LDL-C and triglycerides, and nonalcoholic fatty liver diseases. In addition, SREBPs have been implicated in cancer cell proliferation and enveloped viral replication through regulation of membrane synthesis. Therapeutic approaches to block SREBP functions linked to disease states may act through potentiation of SREBP negative regulators such as AMP-activated kinase or the sirtuin, SIRT1, or by inhibiting the proteolytic maturation into the active transcription factor forms. Additionally, cofunctional miRNAs embedded within the SREBP genomic loci (*miR-33a/b*) may also serve as novel therapeutic targets to ameliorate cardiometabolic diseases. Taken together, aberrant SREBP-linked activities could represent important targets of therapies to limit lipid/cholesterol synthesis or membrane production in metabolic diseases, cancer progression and viral pathogenesis.

KEYWORDS: AMPK • cholesterol membrane production • lipid • metabolic syndrome
• *miR-33a/b* • mTOR • SREBP

The ability to store excess calories as lipids has provided an evolutionarily selected advantage, allowing organisms to survive during periods of food limitation. In western societies, however, the combination of increased caloric intake with a sedentary lifestyle has resulted in metabolic imbalances that contribute to a host of related conditions such as circulating cholesterol/lipid abnormalities, obesity, insulin resistance and nonalcoholic fatty liver disease (NAFLD). These metabolism-related disorders are important risk factors for the development of more severe diseases, including Type 2 diabetes, nonalcoholic steatohepatitis and coronary artery disease/atherosclerosis, which are taking a rapidly increasing toll on human health worldwide [1,2]. While changes in diet and exercise are important lifestyle modifications used to counter metabolism-related disorders, they are difficult to adhere to, and additional therapeutic tools are urgently needed. There is, therefore, keen interest in unraveling the molecular underpinnings of metabolic control to find new and more effective therapeutic avenues to combat the rise in diseases associated with aberrant lipid metabolism.

At the most basic level, lipid homeostasis is a product of the balance between dietary intake, *de novo* production and degradation/utilization. Lipid production depends on the levels of acetyl-CoA, which is produced by the tricarboxylic acid

cycle. Acetyl-CoA is used as the starting point to generate the array of fatty acids incorporated into triglycerides, phospholipids and sphingolipids [3]. These complex lipids provide energy storage and are components of cellular membranes, as well as being signaling molecules. Acetyl-CoA also serves as the basic building block for the synthesis of cholesterol through the mevalonate pathway [4]. A key enzyme in this biosynthetic cascade is HMG-CoA reductase (HMG-CR), which is the target of the cholesterol-lowering statins [4]. Many of the enzymes, cellular binding proteins and import/export factors involved in the production and trafficking of cholesterol, fatty acids and other lipids are transcriptionally controlled by the SREBP family of transcription factors (**Figure 1**) [5]. This special report will discuss recent advances in our understanding of the key roles played by SREBPs in the regulation of cholesterol/lipid homeostasis and metabolism in relation to human disease, and highlight the therapeutic potential of targeting SREBPs, as well as miRNAs associated with the SREBP-encoding genes in the treatment of metabolic disorders, cancers and viral diseases.

The SREBP transcription factors, metabolism & disease

SREBPs are transcription factors that bind as dimers to cognate DNA sequences in the

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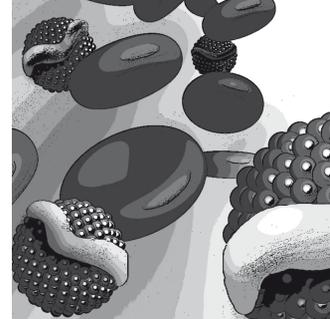
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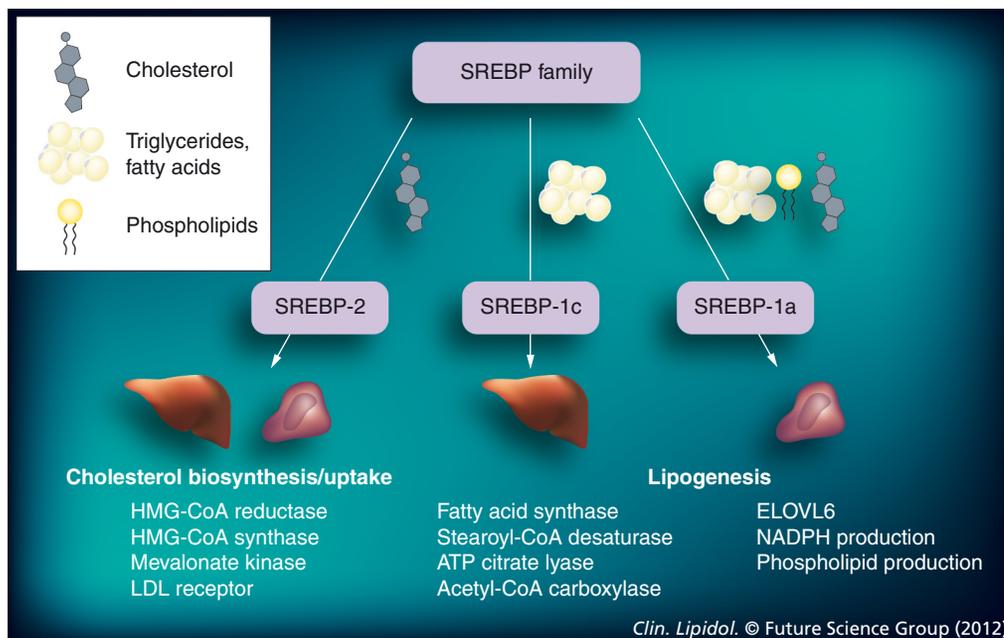


Figure 1. Members of the SREBP family of transcription factors, their preferred classes of target genes and predominant expression patterns. SREBP-2 is expressed ubiquitously and is also important in the liver for regulation of cholesterol homeostasis genes. SREBP-1c is expressed in the liver and regulates lipid homeostasis in response to insulin and oxysterols. SREBP-1a controls a broad range of SREBP targets, but may primarily affect production of fatty acids, triglycerides, phospholipids and cholesterol in most growing cells.

promoter regions of target genes. There are three isoforms in mammals: SREBP-1a and -1c, which are produced from the *SREBF1* gene through alternative promoter usage and splicing, and SREBP-2, which is encoded by the *SREBF2* gene. SREBP-1a/c primarily control genes involved in fatty acid, phospholipid and triglyceride production in addition to cholesterol, whereas SREBP-2 preferentially regulates genes responsible for cholesterol synthesis and uptake. SREBPs are controlled at multiple levels, such as the regulation of mRNA expression, cellular localization or post-transcriptional modification by nutrient-dependent signaling pathways (e.g., insulin), as well as end-product feedback mechanisms by cholesterol and other lipids (**Figure 1**) (reviewed in [6]). The complexity of this regulatory network intimately links cholesterol biosynthesis and lipogenesis to pathways for cellular growth, nutrient sensing and energy homeostasis, but also permits the inappropriate regulation of SREBP activity in a variety of disease states. Excess SREBP activity can contribute to elevated circulating cholesterol and triglycerides, and increased lipid accumulation in tissues such as liver and adipose; thus, SREBP-dependent physiological changes are key to pathologies associated with metabolic syndrome (MetS) such as obesity,

NAFLD, insulin resistance and cardiovascular disease [7]. Many of the products of SREBP-regulated genes are also building blocks for cellular membranes [8], and SREBP-1 activity can be increased via a feedback loop responding to low levels of the membrane phospholipid phosphatidylcholine [9]. In addition to its roles in metabolic pathways, membrane production links SREBP function to cancer development, as increased production is required for unlimited growth, and also to the replication of viruses that require cellular membranes to form their envelopes [10,11]. Thus, the cholesterologenic and lipogenic functions of SREBPs can contribute to multiple disease states, and therapeutic tools for modulating SREBP activities could impact not just metabolic disorders, but also cancers or viral-related diseases.

Targeting of SREBPs for the treatment of MetS

MetS is a complex disorder that can include insulin resistance, elevated plasma LDL:HDL ratios, increased circulating triglycerides, NAFLD, obesity and hypertension [12]. Many of these conditions appear to be functionally linked. For example, insulin resistance associated with obesity and hepatosteatosis promotes additional lipid storage, setting up a vicious

cycle of lipid accumulation and increased insulin resistance that may ultimately result in the development of Type 2 diabetes [13]. In addition, increases in cellular lipids in liver tissue, adipose tissue or in atherosclerotic plaques also promote inflammatory responses that may exacerbate cardiometabolic diseases [14]. Therefore, targeting SREBP-dependent increases in fat or cholesterol accumulation may serve as an attractive strategy for the treatment of MetS.

Several therapeutics in current or proposed regimens for treating conditions associated with MetS indirectly impact SREBP activity. For example, the antidiabetic drug metformin promotes the activity of AMPK, a critical sensor of cellular metabolic status (Figure 2). AMPK is a critical sensor of low cellular energy states, and acts as a molecular switch by phosphorylating a number of factors involved in lipid/energy metabolism to inhibit cholesterol/lipid biosynthesis and fat storage and promote increased energy consumption when ATP levels are low. These include factors involved in stimulation of mitochondrial biogenesis and activation of fatty acid β -oxidation, such as the transcriptional coactivator PGC1 α , thereby promoting lipid degradation and energy utilization [15]. In addition, AMPK directly phosphorylates and inhibits acetyl-CoA carboxylase and HMG-CR, rate-limiting enzymes in fatty acid and cholesterol

biosynthesis, respectively, that are key transcriptional targets of SREBPs [16]. Recent evidence has also implicated AMPK as a direct regulator of SREBPs [17–20]. For example, AMPK interacts with and phosphorylates SREBP-1c and -2, inhibiting activation of SREBPs through proteolytic maturation and nuclear translocation. The inhibitory effects of AMPK on SREBPs can be further stimulated by small-molecule activators of AMPK such as metformin, AICAR and polyphenols (e.g., S17834) (Figure 3) [18,20]. Indeed, AMPK activators were found to protect diet-induced, insulin-resistant LDL receptor-deficient mice against hyperlipidemia and fatty liver disease [17]. Blocking SREBP-1c and SREBP-2 processing in this manner also abrogates auto-activation at the *SREBF1* and *SREBF2* promoters [17]. However, these regulatory relationships are complex and may not be completely conserved between rodent and human physiology, as clinical trials assessing metformin's ability to improve hepatic steatosis are yielding inconsistent results [21]. AMPK also inhibits mTOR signaling [22–24], which is a central mediator of PI3K/AKT-dependent activation of SREBPs (discussed in more detail below). Thus, by activating AMPK, metformin and other AMPK activators exert potent effects on SREBPs at multiple levels by impacting SREBP mRNA expression,

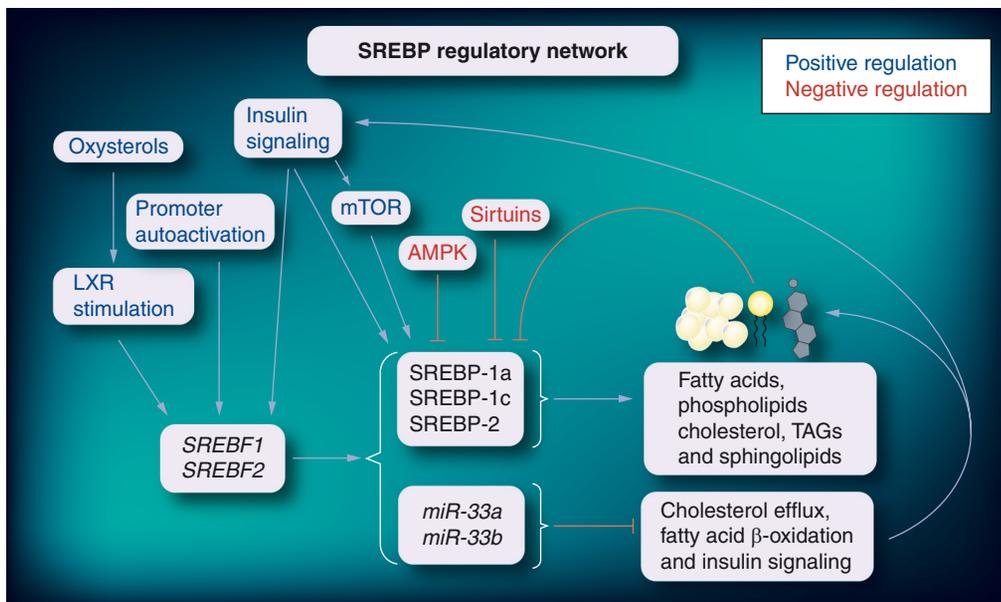


Figure 2. SREBPs and the intronic miRNAs *miR-33a/b* are controlled by feeding/fasting cues, growth factor signaling pathways and by end-product inhibition (e.g., cholesterol). Some pathways, such as LXR stimulation, affect expression of the *SREBF1* locus, whereas others (mTOR, AMPK and SIRT1) exert their effects on the transcriptional activities of SREBP-1 or -2. Insulin signaling is a critical regulator because it may affect SREBP at multiple levels. TAG: Triacylglyceride.

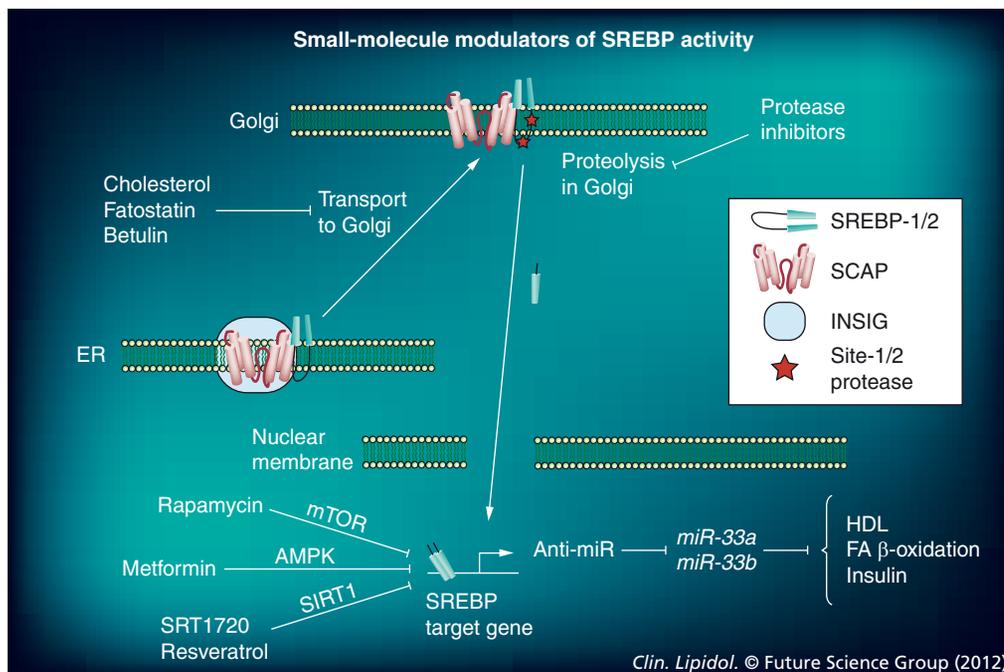


Figure 3. Small-molecule modulators of SREBP activity affect a variety of steps in SREBP processing or its transcriptional activity. Cholesterol, cholesterol analogs or other structurally unrelated compounds may globally block SREBPs by inhibiting processing of the inactive precursor. Protease inhibitors may inhibit SREBP processing, but may also affect additional factors. Small molecules affecting metabolic regulators such as mTOR, AMPK or SIRT1 may impinge on the transcriptional activity of SREBPs. Antisense oligonucleotides directed against *miR-33a* and/or *miR-33b* may increase the expression of targets impacting HDL biogenesis, FA β -oxidation and insulin signaling.
ER: Endoplasmic reticulum; FA: Fatty acid.

proteolytic processing, transcriptional activity, as well as the function of downstream targets of SREBP activation, thereby efficiently blocking lipogenesis and cholesterol synthesis.

Members of the NAD⁺-dependent sirtuin family of deacetylases regulate broad cellular responses to low energy supply by removing regulatory acetyl groups from a large array of mitochondrial and nuclear proteins involved in metabolic control, as well as through epigenetic control of metabolic gene expression programs by chromatin deacetylation [25]. For example, the mammalian sirtuin, SIRT1, directly deacetylates several transcriptional activators and coactivators in stress response or metabolic control pathways such as FOXO proteins, PPARs and PGCs [26]. Through activation of these factors, the cell becomes primed to respond to energy stress and shift metabolic potential toward fatty acid β -oxidation and consumption of stored energy. SIRT1 can also block cholesterol synthesis/lipogenesis by directly inhibiting SREBPs (Figures 2 & 3) [27,28]. By deacetylating SREBP-1 or -2, SIRT1 promotes ubiquitination and proteasomal degradation of the transcriptionally active, nuclear

forms of SREBPs. Pharmacological activators of SIRT1, including the polyphenol resveratrol and more potent synthetic compounds such as SRT1720, may achieve their effects, at least in part, through blocking *de novo* SREBP-dependent lipogenesis [28,29]. Studies from multiple groups have outlined the complex crosstalk between SIRT1 and AMPK that extends from reciprocal regulatory interactions to additional controversies regarding the specificity of action of polyphenols, such as resveratrol, which have been reported to activate both sirtuins and AMPK [16,30,31]. Although these questions are beyond the scope of this article, it is clear that both AMPK and SIRT1 can exert direct effects on SREBPs, and that therapies stimulating their activities impact SREBP-dependent cholesterologenic and lipogenic functions.

Involvement & targeting of SREBPs in cancers

The capacity of cancer cells for unlimited growth requires alteration of normal metabolism [32]. Cancer cells must assure the production of building blocks for continual division, increasing

protein synthesis, DNA replication and *de novo* fatty acid/lipid synthesis for membrane production. Many types of solid tumors also appear to shift energy production to aerobic glycolysis (Warburg effect) [32], which is also associated with increased lipogenesis. A number of studies have shown that elevated lipogenesis in cancer is linked to upregulation of fatty acid synthase (FASN), a multisubunit enzyme that produces the fatty acid palmitate from acetyl-CoA and malonyl-CoA [33]. Palmitate may be elongated or desaturated by a series of enzymes as the starting point for the production of the complex array of fatty acids that are incorporated into phospholipids, sphingolipids and triglycerides, or serving roles in cellular signaling [34]. FASN is normally expressed at low levels in adults, as much of the palmitate is obtained through the diet; however, increased *FASN* transcription occurs in a broad spectrum of cancers, and is associated with more aggressive malignancies and increased mortality [33]. Although multiple mechanisms for elevated *FASN* expression may exist, increased SREBP-1c activity may be an important contributing factor [19,33,35]. SREBP-1c levels and activity are normally under the strict control of nutritional signals; however, deregulation of growth factor receptor signaling pathways with major roles in cell proliferation and cell survival (e.g., EGFR/HER2/Neu) may promote SREBP-1c-dependent activation of *FASN* gene expression [10,33]. Thus, as is the case in the context of insulin resistance in MetS, changes in gene expression associated with elevated SREBP-1c activity may occur outside normal nutritional control and contribute to cancer pathologies [17].

The PI3K/AKT and mTOR (mammalian target of rapamycin) signaling networks are critical coordinators of nutritional state and cellular proliferation [36]. Importantly, pharmacological inhibitors of several kinases in these linked pathways are being developed as anticancer agents [37]. The effects of PI3K/AKT signaling on SREBPs are complex, and occur at multiple levels (Figure 2) [10,38]. The AKT kinases respond to upstream signals from the insulin receptor or other growth factor-responsive pathways and phosphorylate multiple targets that act together to promote lipogenesis and energy storage [10]. Two of these AKT targets, GSK3 β and the mTOR complex mTORC1, also regulate SREBPs. GSK3 β is inhibited by AKT, and has multiple roles in metabolic control, including inhibition of glycogen storage [39]. Importantly, phosphorylation by GSK3 β

promotes the ubiquitination and degradation of the transcriptionally active form of SREBP-1; thus, inhibition of GSK3 β by AKT allows a more robust lipogenic transcriptional activation program [40,41]. mTORC1 also responds to stimulation from AKT and not only regulates canonical pathways such as protein synthesis and cell size, but can also profoundly affect cell survival, response to stress and aging [36]. Previously, studies had linked AKT, mTORC1 and SREBP by showing that AKT-dependent lipogenesis required both mTORC1 and SREBP [42]. While the mTORC1 inhibitor rapamycin does block SREBP-dependent transcriptional increases upon insulin or AKT stimulation (Figure 3) [42,43], other studies suggested that mTORC1 might also affect SREBP processing independently of rapamycin [44]. Recently, the mechanistic details of this pathway have been worked out in more detail. Using mice deficient in mTORC1 signaling, Yecies *et al.* found that mTORC1 requires other aspects of AKT signaling to activate SREBP-1c and show that AKT suppresses expression of *Insig2a*, an endoplasmic reticulum (ER)-associated inhibitor of SREBP processing [45]. In addition, mTORC1 controls the subcellular localization of Lipin1, a multifunctional protein that acts both as a phosphatidic acid phosphatase and as a nuclear transcriptional coactivator. The inhibitory effect of mTORC1 antagonists on SREBP-dependent elevation in cholesterol and lipids in western-type diet-fed mice requires Lipin1 [46], providing additional functional details of the link between mTORC1 and SREBPs. Interestingly, the interaction between mTOR, Lipin1 and SREBP was initially discovered in a screen comparing phenotypes of more potent mTOR inhibitors with rapamycin. Taken together, it is clear that therapeutics targeting the mTOR pathway directly or indirectly (e.g., by AMPK activators) impact SREBP-dependent functions at multiple points *in vivo*.

Both the complexity and clinical relevance of these pathways are illustrated in two recent studies by Guo and colleagues, who show that glioblastomas activate SREBP-1 downstream of AKT and the EGF receptor, and that this dramatically increases *FASN* transcription [47]. While activation of SREBP-1 in these tumors is resistant to the mTOR inhibitor rapamycin, the authors did not further examine the link to mTORC1 signaling, and it remains possible that survival of glioblastoma cells dependent on SREBP-1 and its lipogenic target genes may be

inhibited by newer, more effective mTORC1 inhibitors. In another study, Guo *et al.* showed that the direct AMPK activator AICAR is also a strong inhibitor of EGF receptor/AKT-dependent glioblastoma proliferation/survival, and that SREBPs and their target genes are required downstream of this signaling pathway [47]. Thus, therapeutic targeting of SREBP-1, or its regulatory network, may block the growth of certain types of cancer.

SREBPs in viral pathogenesis

Viral replication depends on subversion of the host cell's metabolic processes. Although mechanisms of nucleotide or protein synthesis have been most widely studied, enveloped viruses must also ensure adequate membrane production, and most mammalian viruses activate the PI3K/AKT pathway to promote lipid synthesis [48]. It is therefore perhaps not surprising that some viruses target SREBP for activation (e.g., hepatitis C virus [HCV] and HIV) or that cellular defenses may downregulate SREBP activity to attenuate viral replication [49,50]. SREBPs appear tightly linked to HCV pathogenesis; HCV causes hepatosteatosis in many cases and can target SREBP activity by stimulating PI3K/AKT signaling [51] and by increasing expression of the SREBP-1c protein [51]. Although different subtypes of HCV appear to have distinct mechanisms of inducing steatosis, HCV infection increases the severity of liver damage in patients with metabolic disorders [50]. Failure to respond to traditional antiviral therapies, such as ribavirin or IFN, has been associated with insulin resistance [52,53]. Recently, therapeutics such as metformin and statins that target upstream or downstream aspects of the SREBP regulatory network have been used in combination with antiviral therapy, with promising but mixed results [49–52]. Fluvastatin, in concert with IFN, has been found to inhibit HCV replication *in vitro*; however, fluvastatin as a single-agent therapy showed only short-term effects on HCV titers in patients [54,55]. Some studies have found that metformin, in combination with IFN or the antiviral ribavirin, decreased viral titers along with insulin resistance [56]; however, this result was not confirmed in other independent trials [57]. Further studies are clearly warranted to determine the molecular mechanism of SREBP activation during viral infections, and to explore therapeutic targeting of the SREBP regulatory network in antiviral therapies.

Blocking SREBP maturation with small-molecule inhibitors

Transcription factors such as SREBPs may be difficult to directly target with small-molecule inhibitors; however, the complex cytoplasmic maturation of SREBPs provides a window to access druggable targets. Newly translated SREBPs are inserted into the ER membrane, where they are stored in association with a chaperone complex, SCAP (SREBP-cleavage activating protein) and INSIG [6]. The interaction of cholesterol with SCAP results in stabilization of the interaction with the INSIG tether in the ER, blocking transport of SREBPs to the Golgi for proteolytic maturation [58–60]. When cellular cholesterol levels are low, INSIG fails to block SCAP interactions with the COPII transport machinery, allowing SREBP and SCAP to traffic to the Golgi where two proteases, Site-1 (S1P) and Site-2 (S2P), release the transcriptionally active N-terminal portion from the transmembrane domain [6]. Because SREBP/SCAP/INSIG complexes have evolved as exquisite sensors of cholesterol, sterol analogs were initially developed, and showed promise in blocking SREBP processing, and in reducing circulating LDL-C and triglycerides in rodents [61]. However, the mechanism of action of these drugs may be complex [62], and oxysterol derivatives may have unintended effects on activation of the nuclear hormone receptor LXR, which can also promote SREBP-1c expression [63]. Interestingly, recent screens for novel compounds regulating SREBPs uncovered two promising small-molecule candidates that are structurally unrelated to sterols; fatostatin and betulin (**Figure 3**) [64,65]. Fatostatin interacts with SCAP and inhibits SREBP processing [64], and can improve lipid homeostasis in hyperlipidemic *ob/ob* mice. Betulin, derived from birch bark, also inhibits SREBP processing and, importantly, decreases atherosclerotic plaque formation in *LDLR^{-/-}* mice [65]. Although in early stages of development, these molecules could represent promising leads for therapeutics interfering with SREBP-dependent lipogenesis.

Another class of small molecules that may affect SREBP-dependent functions are protease inhibitors designed as antiviral therapies (**Figure 3**). For example, nelfinavir, a HIV protease inhibitor, also can inhibit S1 and S2 proteases [66]. This results in decreased SREBP processing/maturation, but additionally affects the ER stress effector ATF-6, which also depends on S1P and S2P for activation. Nelfinavir has

potent effects in cell culture, significantly reducing liposarcomacancer cell proliferation and survival; however, this is likely due to combined effects on SREBP and ATF-6. While the S1 and S2 proteases are accessible as targets for small molecules, their multifunctional nature is likely to generate additional unintended effects, thus these therapies may have limited utility.

Micromanaging the SREBP network

The loci encoding SREBPs are complex. SREBP-1a and -1c are transcribed from *SREBF1*; the isoforms differ in the transactivation domain due to differential promoter usage and alternative splicing [67]. SREBP-2 is produced from *SREBF2*, a distinct locus. In humans, both loci also harbor miRNAs (*miR-33a/b*), which cooperate with SREBP-1a/c and SREBP-2 to increase intracellular levels of cholesterol, fatty acids and triglycerides (Figure 2) [68–72]. Thus, therapeutics that target the maturation or activity of SREBP as a transcription factor may not affect these additional critical regulators within the *SREBF* loci. Recently, our group, along with several others have found that *miR-33a*, located in an intron of *SREBF2*, can cooperate with SREBP-2 to raise cellular cholesterol levels by inhibiting expression of the ABCA1 and ABCG1 cholesterol efflux transporters [68–72]. Antisense approaches have been used to block *miR-33a* function in mice, resulting in significant increases in HDL, the ‘good’ cholesterol, and an associated

decrease in atherosclerosis (Figure 3) [70–73]. The *SREBF1* gene in humans (but not in rodents) harbors *miR-33b*, which can inhibit AMPK α 1 and parts of the fatty acid β -oxidation process and thus promote increases in fatty acid/triglyceride levels [68,74,75]. Effective technologies for disrupting miRNA function *in vivo* are being developed [76,77], and antisense-based targeting *miR-33a/b* function in humans could represent an attractive approach to therapeutic modulation of HDL-C and triglycerides in MetS, and to decrease atherosclerosis.

Conclusion

Because SREBPs support the gene expression networks producing cholesterol, fatty acids, triglycerides and membrane lipids their activity is critical in diseases of metabolic function, such as obesity, NAFLD and cardiovascular disease, as well as in diseases that require overproduction of cellular building blocks, as in cancer and viral pathogenesis. Present therapies targeting SREBP-regulatory factors are used to treat MetS and are being tested for use in anticancer or antiviral therapies. Small molecules directly targeting SREBP processing or *miR-33a/b* are also attractive targets for blocking SREBP-associated activities.

Future perspective

Therapeutics that directly target SREBPs or the SREBP-regulatory network controlled by

Executive summary

The SREBP transcription factors, metabolism & disease

- SREBPs control expression of genes for production of cholesterol and other lipids.
- SREBPs are functionally linked to metabolic diseases, unrestricted cell proliferation/cancer and viral pathogenesis.

Targeting of SREBPs for the treatment of metabolic syndrome

- Therapeutically targeting SREBP is attractive for combating metabolic syndrome.
- Current therapies such as metformin (which may directly affect AMPK), sirtuin activators (e.g., resveratrol and SRT1720) or mTOR inhibitors (e.g., rapamycin) indirectly affect SREBP function.

Involvement & targeting of SREBPs in cancers

- Key SREBP-1 target genes, such as *FASN*, are dysregulated in many cancers.
- SREBPs support cell growth downstream of AKT and mTOR signaling pathways.

SREBPs in viral pathogenesis

- Enveloped viruses such as hepatitis C virus and HIV may activate SREBPs to ensure adequate membrane production.
- Therapies used to treat metabolic syndrome (metformin) are being tested as anti-viral agents.

Blocking SREBP maturation with small-molecule inhibitors

- Cholesterol mimetics tested as SREBP inhibitors may also have unintended effects on other metabolic regulators (LXR nuclear hormone receptors).
- Other small-molecule inhibitors, fatostatin and betulin, block SREBP processing and may inhibit excess lipogenesis.

Micromanaging the SREBP network

- miRNAs within the *SREBP* loci, *miR-33a/b*, cooperate with SREBPs to increase cellular cholesterol and lipid levels.
- Targeting *miR-33a/b* *in vivo* may be an effective therapy to limit SREBP function in metabolic diseases.

miR-33a/b may soon emerge as clinical tools to ameliorate circulating cholesterol and triglyceride abnormalities, and associated pathologies such as insulin resistance, NAFLD, obesity and atherosclerosis. Used alone, or in combination with therapies aimed at other metabolic regulators (e.g., AMPK), such compounds may also be efficacious for 'nonmetabolic' applications such as anticancer or antiviral therapy.

Financial & competing interests disclosure

AM Näär has patents pending on the treatment of cholesterol/lipid disorders using miR-33a/b antisense oligonucleotides. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. No writing assistance was utilized in the production of this manuscript.

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▪▪ of considerable interest

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