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SREBPs: Metabolic Integrators in Physiology and Metabolism

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Abstract

Recent advances have significantly increased our understanding of how sterol regulatory element binding proteins (SREBPs) are regulated at the transcriptional and post-transcriptional levels in response to cellular signaling. The phosphatidyl inositol-3-kinase (PI3K) and SREBP pathways intersect at multiple points and recent insights demonstrate the importance of tight regulation of the PI3K pathway for regulating SREBPs in the adaptation to fluctuating dietary calorie load in the mammalian liver. Additionally, genetic and genome-wide approaches highlight new functions for SREBPs in connecting lipid metabolism with other cellular processes where lipid pathway flux affects physiologic or pathophysiologic adaptation, such as cancer, steatosis and innate immunity. This review focuses on recent advances and new roles for mammalian SREBPs in physiology and metabolism.

Introduction

The Sterol Regulatory Element-Binding Proteins (SREBPs) comprise a subclass of basic-helix–loop–helix–leucine zipper (bHLH-LZ) transcription factors that are conserved from fission yeast to man, and regulate expression of genes required to maintain cellular lipid homeostasis (1). In mammals, there are two SREBP genes,SREBP-1 and -2, that express three major SREBP proteins. Most data suggest that the two SREBP-1 isoforms -1a and - 1c primarily regulate fatty acid metabolism and that SREBP-2 is the main regulator of cholesterol metabolism (2). However, significant overlap exists in the pathways and processes regulated by the individual SREBPs. Additionally, recent studies from seemingly diverse areas suggest that regulation of lipid metabolism through SREBPs is fundamental to many physiologic and pathophysiologic processes (1). The current review attempts to assimilate these recent findings into a model that proposes SREBPs have evolved to exploit the cell's ability to dynamically adapt to changes in requirements for lipid pathway flux that arise as a consequence of physiological conditions that challenge cell growth and survival.

Regulation of mammalian SREBP gene expression

The three mammalian SREBPs differ in their tissue distribution and responses to regulatory cues. SREBP-1a and -1c are encoded from different promoters that drive expression of overlapping transcripts from the same gene, distinguished only by their unique 5' terminal

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exons. The singular SREBP-2 isoform is encoded from a different gene (1). The SREBP transcriptional activation domain is located at the extreme amino-terminus and the longer SREBP-1a isoform has a potent transcriptional activation domain whereas the shorter SREBP-1c isoform has a much weaker activation domain. SREBP-2 has a strong activation domain similar to that of SREBP-1a.

SREBP-1c is the predominant isoform in most adult non-dividing metabolic tissues such as liver and adipose. The SREBP-1c promoter is autoregulated by SREBPs (3) and stimulated by both liver X receptor (LXR) and insulin signaling. Interestingly, LXR binding to a DR-4 binding site required for both responses (4, 5). Strong evidence in support of this model was revealed when endogenous LXR agonists were depleted by over-expressing the enzyme SULT2B1b sulfotransferase, which adds sulfate groups to sterol substrates making them unable to bind to and activate LXR (Glossary). As expected, in the presence of excess SULT2B1b, activation of the SREBP-1c promoter by endogenous LXR agonists was lost. However, SREBP-1c stimulation by insulin was also eliminated, suggesting that the nuclear receptor LXR plays a key role in the insulin dependent stimulation of SREBP-1c (6).

SREBP-1a mRNA is expressed at very high levels in cells of the immune system and its promoter is activated by NFkB (Glossary) in macrophages, as part of the proinflammatory phase of the innate immune response (7). The SREBP-2 gene promoter is both auto-regulated and stimulated by thyroid hormone (8) (9). Thyroid hormone receptor (TR) regulation of SREBP-2 provides a mechanism that may explain the low expression of LDL receptor and the hypercholesterolemia that is associated with low systemic thyroid hormone levels and hypothyroidism in humans (9).

Interestingly, expression of SREBP-2 mRNA, but not SREBP-1, is regulated by insulin in the hypothalamus (10) and following streptozotocin injection to induce diabetes, SREBP-2 levels in the hypothalamus are also reduced. Furthermore, direct addition of insulin increases SREBP-2 and its target genes in primary cultures of neurons and glial cells (10). The reasons for the differential effects of insulin on SREBP-1c and SREBP-2 in the liver vs. hypothalamus, respectively, remain to be determined.

The microRNA miR-33a is encoded within an intron of the SREBP-2 gene (11–15). Sequence prediction analysis and mechanistic studies together demonstrated that miR-33a targets the mRNAs encoding for ABCA1 and ABCG1 (Glossary), both of which are ATP dependent membrane cholesterol transporter proteins that control cellular cholesterol efflux. This observation indicates that miR-33a balances intracellular cholesterol by functioning together with the co-expressed SREBP-2. Because SREBP-2 mRNA is regulated by insulin in the brain where miR-33a is expressed at relatively high levels (12), this may be another metabolic response where miR-33a regulation of cholesterol efflux may have significant physiological effects (10).

A highly related mircroRNA, miR-33b, is encoded within an intron of the human SREBP-1 gene, but this is not conserved in rodents (13, 16). This suggests miR-33b expression is subject to regulation by mechanisms that influence both SREBP-1a and -1c in different human tissues. miR-33's have also been shown to regulate fatty acid oxidation and glucose metabolism indicating that these micro RNAs may have a broader role in regulating metabolism(15, 16).

Modulation of SREBP activity

SREBPs exist as membrane bound precursor proteins. An elaborate membrane-trafficking/ proteolytic pathway releases the soluble and nuclear-targeted SREBPs from the membrane (Fig. 1, Box 1. Ref. (1)). The maturation mechanism was defined for sterol dependent

regulation of both SREBP-1 and -2 in response to sterol pathway flux, in cultured cells (17). SREBP-1 processing is also preferentially regulated in cultured cell systems by unsaturated fatty acids, which fits mechanistically with its preferred role in fatty acid metabolism (18). Studies employing knockout and transgenic expression of wild type and mutant SREBP pathway components have confirmed the fundamental aspects of the membrane-trafficking mechanism for SREBP regulation (2, 19–25).

Differential Nuclear Accumulation of SREBP-1 vs. SREBP-2 In Vivo

Nuclear accumulation of SREBP-1 vs SREBP-2 in animal liver can be uncoupled through dietary manipulation. Hepatic nuclear SREBP-2 levels are increased by feeding the combination of a statin, which inhibits HMG CoA reductase activity and reduces hepatic cholesterol synthesis, along with either ezetimibe or a bile acid sequestrant such as cholestid, both of which interfere with cholesterol absorption directly or indirectly, respectively (26, 27). Under these conditions, SREBP-2 levels are robustly induced but SREBP-1 nuclear accumulation is reduced, likely because the diet limits production of endogenous LXR agonists, which are potent activators of SREBP-1c gene expression. On the other hand, hepatic nuclear accumulation of SREBP-1c is dramatically enhanced when mice are fed a high carbohydrate diet following a period of food withdrawal (26, 28). Under these conditions, SREBP-2 nuclear levels are not consistently affected. Differential accumulation of SREBP-1 vs SREBP-2 under the different dietary conditions discussed above is consistent with each performing a preferred metabolic function in lipogenesis vs. cholesterolgenesis in the liver respectively. A comparison of the genome-wide binding profiles for SREBP-1 vs SREBP-2 in hepatic chromatin revealed that only 11.7 % of their binding sites overlap and the nearest genes associated with the common binding sites are mostly associated with lipid metabolism (29). These results provide unbiased and comprehensive evidence that the SREBP-1 and 2 have overlapping but distinct functions as well.

SREBP Regulation by Intracellular Signaling Pathways

A number of studies have reported that additional regulatory signals such as insulin and growth factors, the unfolded protein response (UPR), and altered intracellular K+ also regulate transcription and/or post-transcriptional maturation/stability of SREBPs (30–32). There has been significant investigation of the signaling pathways involved in the UPR and growth factor responses and recent advances are discussed in the following sections.

SREBPs and the PI3 kinase pathway

In the liver, insulin signaling through phosphatidylinositol 3-kinase (PI3K) and AKT, results in activation of both SREBP-1c gene expression and accumulation of SREBP-1 nuclear protein (Fig. 1; refs. (31 Li, 2010 #1961, 33–35), and there is general consensus that insulin affects SREBP-1 at multiple levels. The molecular mechanisms which need further interrogation (Fig. 1) are thoroughly discussed in an earlier review (36).

However, it should be emphasized that when analyzing the effects of PI3K on the production of native-nuclear SREBP, one needs to determine whether the observed effects are through changes in SREBP gene expression, protein maturation, or protein stability. In fact, many times the effects are likely a combination of all three. It should be noted that this careful analysis should be applied to any study involving SREBP regulation. This ambiguity was highlighted in an original report demonstrating that the LXR dependent increase in nuclear SREBP-1c is also matched by a similar increase in SREBP-1c gene expression (5). Here, the authors were cautious about implicating LXR in SREBP-1 processing, because the increase in SREBP-1 gene expression would alter the concentration of the precursor

substrate. This could alter the equilibrium distribution of the precursor vs. the mature-nuclear form without a necessary change in the kinetics of processing. Thus, conclusions that SREBP maturation is specifically targeted where SREBP gene expression changes also occur (or are not evaluated) need to be taken with caution, even if levels of the larger precursor form appear unchanged.

In hepatocytes and several other cell systems, PI3 kinase effects on SREBP-1 are predominantly mediated through AKT and the mammalian target of rapamycin complex 1 (mTORC1, Fig. 1). This conclusion is based on studies that show SREBP-1 expression and lipogenesis are both blocked by the mTORC1 inhibitor, rapamycin (37, 38). Genetic studies that inactivate different components of the PI3 kinase pathway also support and extend these conclusions. The tuberous sclerosis protein complex (TSC) functions at a critical step in the AKT signaling pathway (Fig. 1) and is composed of two proteins, hamartin and tuberin, that are encoded by the TSC1 and TSC2 genes respectively (39). TSC1 forms a complex with and stabilizes TSC2, a GTPase-activating protein for the Rheb GTPase. Rheb functions as a positive activator of TORC1, thus TSC is a negative regulator of TORC1 in the AKT pathway (Fig. 1) and genetic inactivation of either TSC1 or 2 results in constitutive Rheb activation of TORC1.

To evaluate the effects of constitutive mTORC1 on cellular physiology, Tsc1 null mouse embryo fibroblasts (MEFs) were interrogated with chemical inhibitors and siRNA knockdown of other critical AKT pathway components. The results revealed that a major role for mTORC1 signaling is to regulate lipogenesis through SREBP-1 (40). This study showed that lipogenesis and expression of mature SREBP-1 protein not only depends on TORC1 signaling but SREBP-1 nuclear accumulation requires also the TORC1 downstream target p70 S6 kinase (p70S6K) as well. Another study using primary rat hepatocytes showed that rapamycin inhibits SREBP-1c gene induction by insulin but inhibition of p70 S6 kinase with the chemical inhibitor LYS6K2 has no effect on SREBP-1c gene induction (37). Taken together, these studies are consistent with PI3kinase regulating both SREBP-1c gene expression and protein maturation, with a specific role of p70S6K in regulating SREBP-1 protein maturation.

An additional important part of the AKT regulatory pathway was revealed through studies using more complete mTOR kinase inhibitors than rapamycin. Lipin 1, a phosphatidic acid phosphatase (PAP), was shown to play a prominent role in the mTORC1 mediated regulation of SREBP activity which is not inhibited by rapamycin Fig. 1, and (41)). Lipin 1 also augments the coactivator function of PGC-1α in stimulating fatty acid oxidation through PPARα (42). Although Lipin 1 was previously shown to be phosphorylated by TORC1 (43), Peterson et al. (41) demonstrated that TORC1 phosphorylation results in cytoplasmic localization of Lipin-1 whereas inhibition of TORC1 results in unphosphorylated nuclear Lipin 1. Remarkably, nuclear Lipin 1 is also associated with a decrease in nuclear levels of both SREBP-1 and SREBP-2 (Fig. 1). Additionally, when the TORC1 phosphorylation sites in Lipin 1 are changed to alanines, the mutant Lipin 1 inhibits transcriptional activation via a constitutively nuclear-targeted SREBP, suggesting that Lipin 1 acts directly in the nucleus on the mature transcription factor. Although the inhibitory effect requires the intact PAP enzyme active site, the exact mechanism remains to be established. Interestingly, Lipin 1 gene expression is also regulated directly by SREBP, which might provide a feedback regulatory mechanism over nuclear SREBP levels (44, 45).

SREBPs, AKT signaling and Steatosis

Excess triglyceride accumulation in the liver or hepatic steatosis develops when there is an imbalance of liver fatty acid metabolism. Simplistically, this could result from alterations in synthesis, oxidation, or secretion of fatty acids (46). One potential mechanism is elevated

lipogenesis driven by high SREBP-1c nuclear levels (47). In fact, SREBP-1c is responsible for steatosis that develops in both the leptin deficient Ob/Ob mice (48, 49) and in wild type mice fed a lard based high fat diet (49). Interestingly, in both cases the increase in SREBP-1c expression and hepatic steatosis is prevented by a liver-specific knockout of AKT2, providing *in vivo* evidence for the importance of AKT in hepatic SREBP regulation and lipid accumulation (49).

Continued activation of SREBP-1c due to elevated insulin signaling in these and other models of insulin resistance, forms the basis of the paradox of "mixed insulin resistance" where insulin activation of SREBP-1c and lipogenesis is maintained, whereas insulin dependent suppression of hepatic glucose production, through inhibiting FoxO1 nuclear localization, is impaired (50). The apparent inconsistency is suggested after comparison with a mouse containing a liver specific deletion of the insulin receptor, which results in complete hepatic insulin resistance. In this setting, insulin stimulation of lipogenesis is lost and the mice fail to develop hepatic steatosis (51). Thus, paradoxically the mixed insulin resistant state is more hepatotoxic.

To evaluate the effects of constitutive activation of mTORC1 in the liver *in vivo*, Yecies et al. (52) developed a mouse model with a hepatic deletion of Tsc1, which results in constitutive high levels of hepatic TORC1 activity. These mice were unexpectedly protected from high fat diet induced steatosis. Careful analysis revealed two distinct effects of insulin signaling on SREBP-1; one that is dependent on mTORC1 and one that is AKT dependent but rapamycin resistant (Fig. 1). In the Tsc1 mutant mice, the constitutively active mTORC1 is predicted to result in feedback suppression of insulin signaling (53–55), and would limit signaling through a PI3 kinase pathway branch downstream of AKT, that is required for SREBP-1 activation but not affected by rapamycin.

Expression of the Insig 2a isoform in mouse liver is high when insulin signaling is low, and expression is repressed by insulin (56). Because elevated Insig levels results in reduced mature SREBP protein, the model further suggests the rapamycin insensitive branch of the AKT pathway inhibits Insig2 gene expression, which would limit SREBP protein maturation (Box 1). Because rapamycin does not completely inhibit mTORC1 (41), it is possible that Insig2 regulation may be mTORC1 dependent, and studies with newer more complete inhibitors of TORC1 (57) will be useful for evaluating this possibility.

In the Tsc1 knockout studies, mRNA expression of both Insig2 and SREBP-1c were evaluated as AKT pathway readouts and the model posits that Insig2 repression by insulin/AKT results in increased SREBP-1c protein, which increases expression of SREBP-1c mRNA through autoregulation. While the data strongly support a role for Insig2, there are still aspects of the mechanism that need to be defined, because the refeeding dependent activation of SREBP-1c gene expression still occurs in an SREBP-1 knockout mouse, where the truncated-nonfunctional SREBP-1 RNA is still robustly regulated by the fasting/refeeding response (25). It is possible that SREBP-2 may compensate because it is over-expressed in the SREBP-1 knockout and is also regulated by Insig2 (58).

A similar protection from diet-induced steatosis is observed in a mouse line with a liver specific deletion of raptor, a key mTORC1 complex component. Raptor deletion apparently eliminates all mTORC1 activity (41). This phenotype is consistent with mTORC1 activating SREBP-1 and the lipogenic program, in response to nutrient overload. The protective effect on hepatic lipids is reversed by knockdown of Lipin 1 expression, which, as mentioned above, regulates nuclear SREBP levels. While this is consistent with the reduced lipid accumulation resulting from Lipin 1 dependent suppression of SREBP-1c mediated lipogenesis, an earlier study (42) showed that Lipin 1 also stimulates fatty acid oxidation,

which occurs predominantly under conditions where mTORC1 signaling is low. Thus, the effects on lipid accumulation could be explained, at least in part, by Lipin 1's known role to increasing fatty acid oxidation.

A comparison of the Tsc1 and raptor knockout studies presents an apparent conundrum; how could inactivation of key regulatory proteins that have opposite effects on the activation of mTORC1 both protect against diet induced steatosis? Mechanistically, the direct effect of mTORC1 on SREBP-1 dependent lipogenesis likely explains the results from the raptor knockout, whereas the mTORC1 dependent feedback regulation of AKT (Fig. 1) provides an explanation for steatosis protection in the Tsc1 knockout. In fact, a comparison of AKT activation supports this interpretation, because the raptor knockout line that is fed a high fat diet, exhibits elevated levels of active-phosphorylated AKT, whereas in the Tsc1 knockout, AKT activation is reduced, an observation consistent with feedback suppression of AKT by the constitutively active mTORC1. Thus, a tightly regulated PI3K signaling pathway is essential to maintaining hepatic lipid homeostasis and these results demonstrate that when the regulatory system is altered, the physiologic result depends on the specific step that is affected and how it changes the dynamics of the regulatory circuitry.

SREBPs, AKT, Lipogenesis, and Cancer

Because of its fundamental role in controlling cell growth, the PI3K pathway is also intimately linked to cell transformation, and PI3K pathway inhibitors represent fertile territory for developing anti-cancer drugs. Historically, there have been numerous reports that the multi-functional fatty acid synthase (FAS) enzyme, which is the major enzyme converting acetyl CoA into fatty acids, is over- expressed in a diverse array of human tumors and transformed cell lines (59, 60). In fact, many of the original reports occurred long before FAS was recognized as a SREBP-1 target gene (61). The connection between PI3K and FAS in cancer, is likely through SREBP-1 activation of FAS expression, and has been reviewed before (36).

One recent example using glioblastoma as a model is particularly noteworthy in this regard, because SREBP-1 activation was proposed as an important part of the transformation mechanism (62). Glioblastomas represent a therapeutically challenging and aggressive form of cancer, with high levels of epidermal growth factor receptor (EGFR) signaling, which feeds into the PI3K pathway. EGFR driven glioblastomas are resistant to treatment with the mTORC1 inhibitor rapamycin (63), although, as mentioned above, rapamycin does not eliminate all mTORC1 signaling (41). Guo et al (62) showed that SREBP-1 activation through PI3K/AKT in glioblastomas is resistant to rapamycin but sensitive to EGFR antagonists and synthetic AKT inhibitors (62). When the proteolytic maturation of SREBPs is prevented by the addition of 25-OH cholesterol or when FAS is directly inhibited by a chemical inhibitor C75, growth of the PI3K dependent glioblastoma cells is inhibited in culture, and similar treatments reduce the size of tumors explanted into mice. The resistance to rapamycin but requirement for SREBP and FAS is possibly explained by the incomplete effects of rapamycin as an mTORC1 inhibitor. There may be a role for Lipin 1 here because its effect on SREBPs is rapamycin resistant but mTORC1 dependent (41).

The results of Guo et al (62) are remarkable, because both the cultured cells and tumor explants were in environments where there was a plentiful supply of exogenous fatty acids, indicating that activation of endogenous fatty acid synthesis through mTORC1/SREBP-1 plays an important role in the growth effects of PI3K/AKT. The studies suggest that drug resistant nuclear accumulation of SREBP-1 may provide at least a partial explanation for rapamycin resistant tumors (63), and indicate that new complete mTORC1 inhibitors will be more therapeutically useful (57). Importantly, these results also strongly suggest SREBP-1 is a key cellular target of mTORC1 activity in cancer.

SREBPs, UPR, Autophagy and Steatosis

Induction of the unfolded protein response (UPR) or ER stress increasing Insig degradation and activates SREBP maturation, in cultured cells (32). There is additional strong evidence for significant overlap in the activation of multiple UPR responses and the SREBP pathway (1). However, the UPR can lead to steatosis independently of SREBP-1 activation pathways. Indeed, when an ER stress response is elicited by tunicamycin injection into mice, steatosis develops even though SREBP-1c expression rapidly decline to very low levels and remain low (64). In this case, the lipid accumulation after tunicamycin challenge is not due to increased lipogenesis but seemingly to either defective lipoprotein secretion and/or reduced fatty acid oxidation. It is also possible that steatosis develops because autophagy dependent lipid droplet turnover is inhibited. This specialized form of autophagy that was recently uncovered is referred to as lipophagy (65). Interestingly, steatosis developed when autophagy pathway components were inactivated. Additionally, in this study lipid droplet turnover and autophagy markers were reduced in genetic or dietary models of obesity in mice, while markers of ER stress were elevated (66).

A direct connection between the regulation of intracellular cholesterol metabolism and autophagy was uncovered when a genome-wide ChIP-sequencing analysis revealed that SREBP-2 occupies the promoters of several genes involved in autophagy (29). When SREBP-2 levels were reduced by siRNA, autophagosome formation and triglyceride mobilization were impaired in serum depleted cultured cells (29). These results form the basis of a hypothesis that SREBP-2 activates genes involved to provide the cell with lipids from three sources: *de novo* biosynthesis, lipoprotein uptake, and lipid droplet mobilization through lipophagy. The questions that still remain are whether SREBP-1 can also regulate lipophagy, and whether SREBP regulation of lipophagy has any influence on the development of clinically relevant disorders of lipid metabolism such as obesity related steatosis and atherosclerosis.

SREBPs and Innate Immunity

Previous studies in fibroblasts suggested that SREBPs are activated during phagocytosis (67) and after exposure to a bacterial pore-forming toxin (30). Since fibroblasts are not the primary cell types in the body to undergo phagocytosis or respond to initial encounters with invading pathogens, this indicates the regulatory connections are fundamental cellular adaptive responses.

Recent studies in more *in vivo* relevant cell-types have demonstrated that individual SREBPs are essential for protective responses. Indeed, SREBP-1a was shown to play a crucial role in the proinflammatory response in macrophages (7). Here, a mouse with a whole-body deficiency of SREBP-1a (SREBP-1aDF) was instrumental in showing that SREBP-1a specifically activates expression of the gene encoding Nlrp1a (Glossary), a nucleotide oligomerization domain and leucine rich repeat receptor family member (NOD/LRR), which is predicted to function as a component of the inflammasome (68). The inflammasome is a protein complex assembled from pro-Caspase 1 monomers that accelerates their auto-activation and cleavage of proinflammatory cytokines including proIL-1β, IL-18 and IL-33 into their active secreted forms (Glossary). The role of SREBP-1a in stimulating expression of a key inflammasome subunit predicts that the SREBP-1aDF mice should have a compromised pro-inflammatory response. Indeed, SREBP-1aDF mice are protected from toxic shock that results from hyper-proinflammatory signaling and are also more susceptible to infection from *S. typhimurium*, when a normal proinflammatory response is essential to ward off infection (7).. Experiments in bone marrow macrophages confirmed the inflammasome defect in SREBP-1aDF mice (Fig. 2). SREBP-1a was also shown to be a proinflammatory gene directly, because its expression is

activated through NF-kB binding to its proximal promoter, in response to lipopolysacharide (LPS) challenge. Interestingly, rapamycin has been used widely for its anti-inflammatory and general immunosuppressant properties (69, 70). Because rapamycin would be predicted to decrease SREBP-1, it is likely that at least part of the mechanism for its anti-inflammatory actions is through inhibition of SREBP-1.

A global analysis of gene expression following infection of macrophages by cytomegalovirus (CMV), showed that expression of a cluster of genes involved in cholesterol biosynthesis was specifically reduced (71). This was accompanied by a significant reduction in the levels of both SREBP-2 mRNA and mature protein. Further studies revealed that SREBP-2 was down-regulated through a secreted type I interferon response (Fig. 2). This is a unique mechanism by which macrophages prevent a productive infection by CMV, and possibly other pathogens, where the cell shuts down synthesis of lipid precursors that are essential for pathogen maturation.

There is a switch in lipid synthesis pathways from one favoring sterols to fatty acids, that occurs during differentiation of monocytes into macrophages (72). Along with the lipid synthetic shift, the differentiation was accompanied by an increase in SREBP-1 target gene expression and a compsensatory decrease in SREBP-2 target genes of cholesterol production. Additionally, when a siRNA against SREBP-1 was added during the differentiation process, macrophage differentiation was inhibited. Phagocytosis was also inhibited but because macrophage differentiation was reduced, it was not possible to discern whether SREBP-1 was required only for differentiation or whether it also plays a direct role in phagocytosis. The physiologic reason for the shift from favoring SREBP-2 dependent cholesterol synthesis to SREBP-1 dependent fatty acid synthesis is not clear, but may be related to a potential need for altered membrane structure and a decreased ratio of cholesterol to phospholipid in the membrane that may be required for optimal phagocytosis in the mature macrophage.

Concluding Remarks

Recent studies demonstrate that AKT signaling and SREBP activation pathways are interconnected at multiple levels which makes teasing out the contribution from regulatory input at each point of intersection difficult to assess (Fig. 1). This is made even more challenging by the demonstration that SREBPs are directly phosphorylated by AMP kinase (73), which also impinges directly on the AKT pathway (74) and could indirectly affect SREBPs as well. Feeding studies in knockout mice indicate that inhibition and constitutive activation of mTORC1 can have similar ultimate effects on hepatic SREBPs and lipid metabolism. This highlights the necessity for careful mechanistic evaluation along with the *in vivo* studies to reveal the contributions from the different pathway derived signals, how they affect different steps of the SREBP activation pathway and how each influences key physiologic and pathophysiologic processes where SREBPs may function prominently. Because mTORC1 is also regulated directly by nutrient signaling directly, this opens up another pathway whereby SREBP-1 levels respond to the growth needs of the cell.

Additional recent studies have also uncovered roles for SREBPs in key responses of the innate immune system in macrophages. When taken together with reports that SREBPs have evolved to respond to low oxygen in *S. pombe* (75), and dietary bitter toxins in the mammalian gut (76), these studies suggest a model where SREBPs might function as “metabolic integrators” to adapt to extracellular environmental conditions by initiating the intracellular physiologic responses required for optimal cell growth and survival (Fig. 3).

Box 1: Membrane Directed pathway for regulating SREBP nuclear localization (1)

Precursor SREBPs are held in a hairpin configuration in the ER membrane with the amino-terminal transcription factor domain and carboxyl-terminal regulatory domain on the cytoplasmic face of the membrane (Figure 1). The SREBP carboxyl domain interacts with the carboxyl terminal WWD repeat domain of the polytopic SREBP cleavage activated protein (SCAP). SCAP interacts with the insulin induced protein (Insig; green in Fig. 1) only when cholesterol levels are replete and cholesterol binds directly to the sterol sensing domain in SCAP. The SCAP-Insig interaction keeps the SCAP-SREBP complex in the ER. As cholesterol levels fall and cholesterol dissociates from SCAP, the SCAP no longer binds Insig and the SCAP-SREBP complex is transported to the Golgi apparatus where cleavage by site 1 protease (S1P) is closely followed by cleavage and membrane release by site 2 protease (S2P). Once soluble, the mature SREBP enters the nucleus and binds as a dimer to SREBP sites (SRE) within promoters of its target genes.

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Glossary

LXR	liver-X-receptor is a nuclear receptor that forms obligate heterodimer with retinoid-X-receptor and stimulates genes of lipid and glucose metabolism in response to binding oxysterol agonists within its ligand binding domain.
SULT2B1b	an enzyme that attaches sulfate groups to sterol substrates changing their function
NFkB	nuclear factor kappa beta is a highly-regulated and pivotal transcription factor that is present as a latent form in the cytoplasm. The integration of many cellular stress and survival pathways impinge on NF-kB, altering its ability to translocate to the nucleus where it activates gene expression.
ABCA1 and ABCG1	ATP-binding cassette membrane transporters that use ATP hydrolysis to drive cholesterol efflux from the cell.
PI3K/AKT/ mTOR	Are three critical kinases in an intracellular signaling pathway that relay signals from the cell surface and intracellular sources, to modulate cellular growth and metabolism
UPR	unfolded protein response sometimes referred to as endoplasmic reticulum “ER” stress. The cellular response initiated in the ER when the folding of nascent polypeptides cannot match the protein synthetic rate.
FoxO1	Transcription factor whose cellular location changes from the nucleus to the cytoplasm after phosphorylation directly by AKT. It activates genes that regulate cell cycle and growth in many cells, and glucose production in the liver.
p70S6K1	After direct phosphorylation by TORC1, this 70KDa kinase is activated to phosphorylate ribosomal protein S6 to enhance protein translation.
Lipin	gene mutated in fld mouse. Functions as a metabolic enzyme that converts phosphatidic acid into diacylglycerol. Also functions as a

	transcriptional coactivator for PPARα/PGC-1 in liver and accelerates turnover of nuclear SREBPs. Direct phosphorylation by TORC1 results in cytoplasmic localization of lipin and SREBP nuclear stabilization.
Caspase 1	A member of the Caspase cysteine-dependent aspartate-specific proteases that plays a key role in inflammation by converting pro IL-1β and related molecules into the active cytokine forms.
Nlrp1a	Member of the NACHT, LRR, PYD repeat containing family of proteins. Interacts with Caspase 1 through its caspase recruitment domain (CARD) to allow caspase 1 auto-activation.
TLR4	Toll-like receptor 4 is a member of the TLR family of cell surface receptors and relays signals to intracellular signaling pathways after interaction with lipid components of bacterial surfaces.

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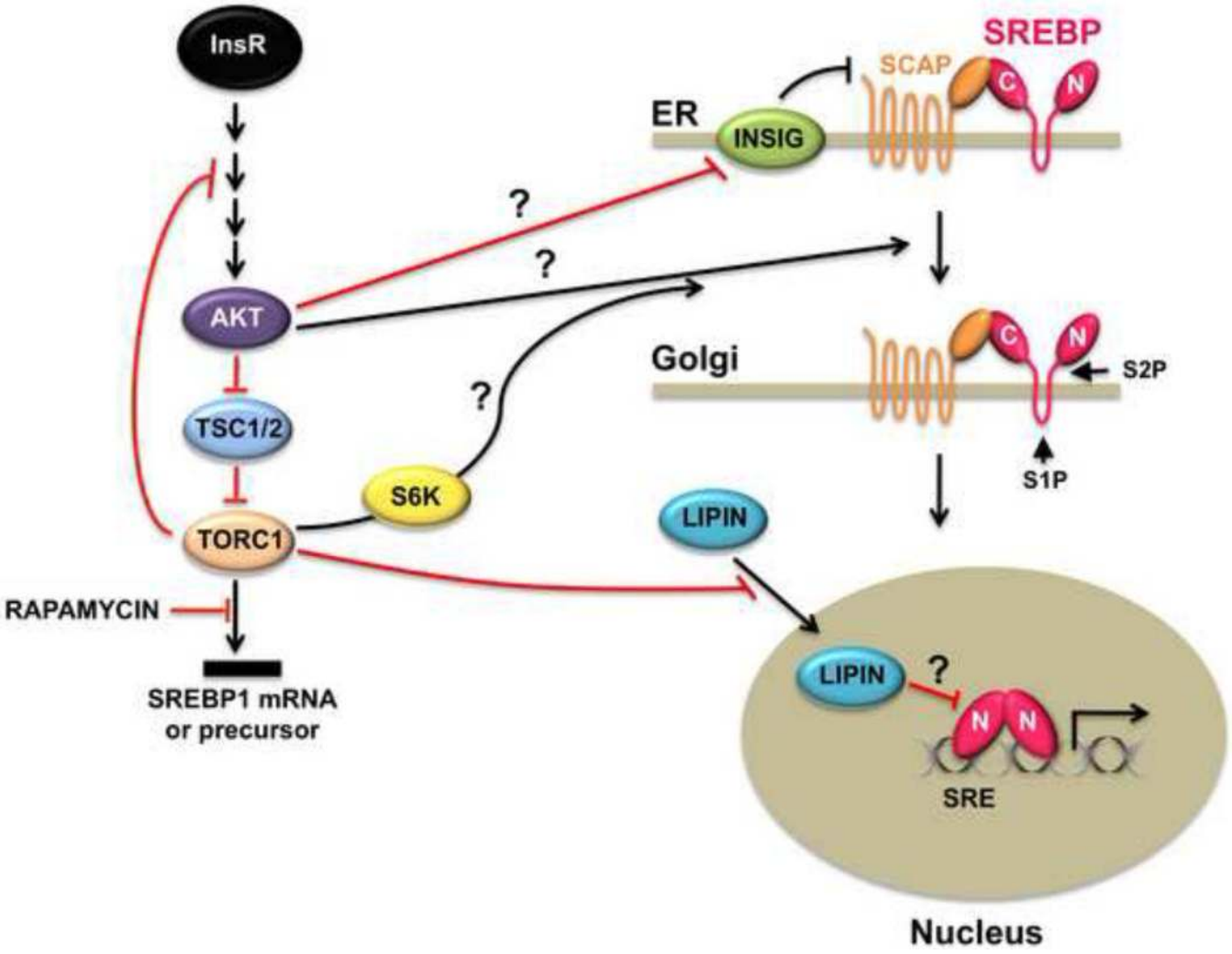

Figure 1.

Model for SREBP regulated maturation. The precursor SREBP is embedded in the ER membrane in a complex with SCAP, and Insig interacts with SCAP (bound to cholesterol) and retains the SCAP/SREBP complex in the ER. Low sterol conditions result in dissociation of cholesterol from SCAP disrupting the SCAP-Insig interaction which leads to SCAP/SREBP transit through the COP II vesicle transport system to the golgi apparatus. There, SREBPs are cleaved sequentially by the S1P/S2P enzymes, the mature SREBP amino terminal fragment (N) is released and rapidly enters the nucleus where it activates target genes. Insulin/growth factor signaling (InsR) through AKT affects SREBP maturation, as shown by the arrows. Red and black arrows indicate inhibitory and stimulatory actions. The question marks indicate the mechanism for the effects still need to be defined. Torc1 feedback inhibition of InsR signaling is also shown.

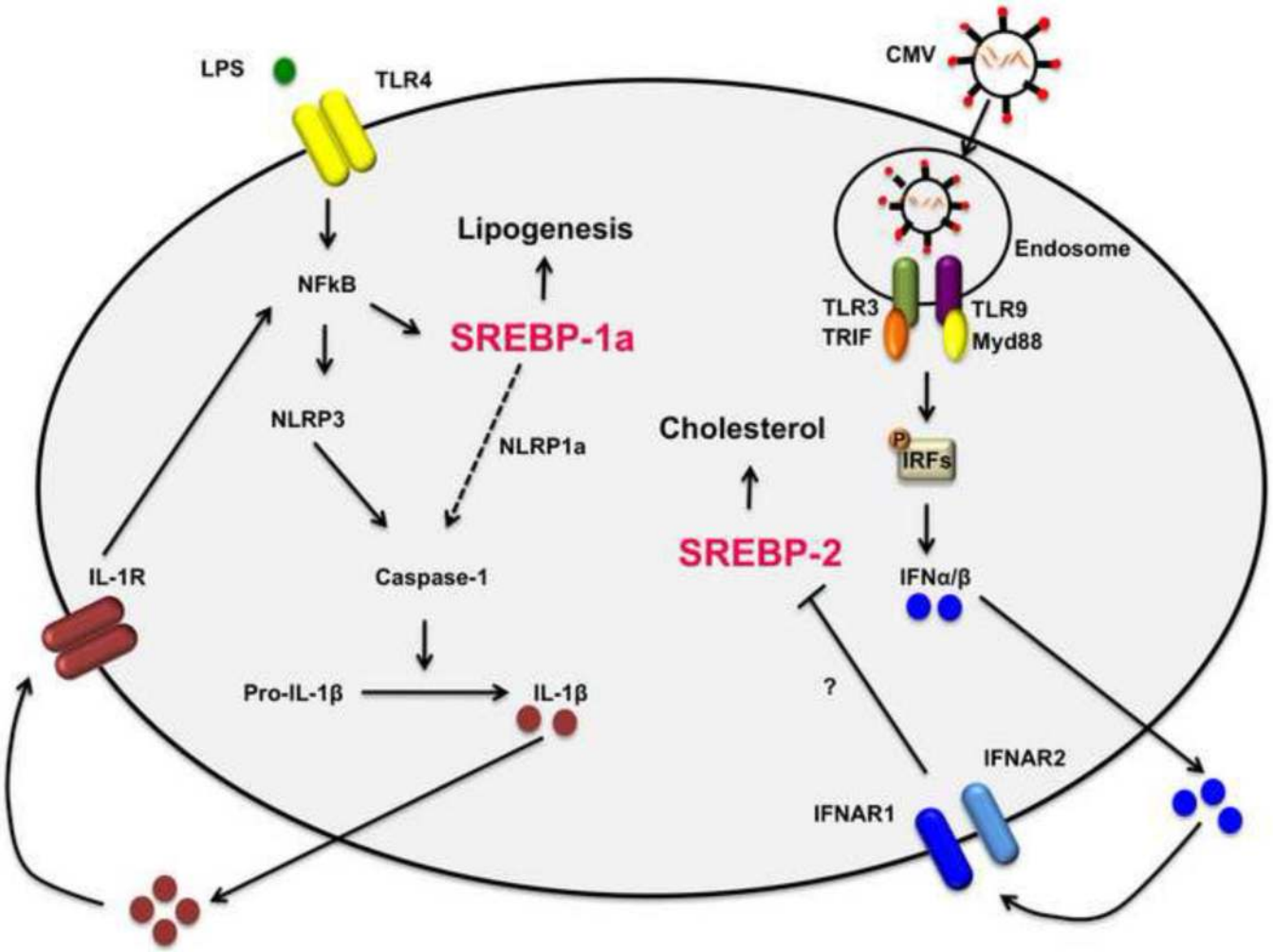

Figure 2.
SREBPs in the innate immune response. The pathway whereby SREBP-1a is regulated by TLR4 signaling and stimulates Caspase-1 activity and IL-1β secretion is shown on the left. The involvement of interferon signaling (IRF) in regulating SREBP-2 is shown on the right. Both pathways are discussed in the text.

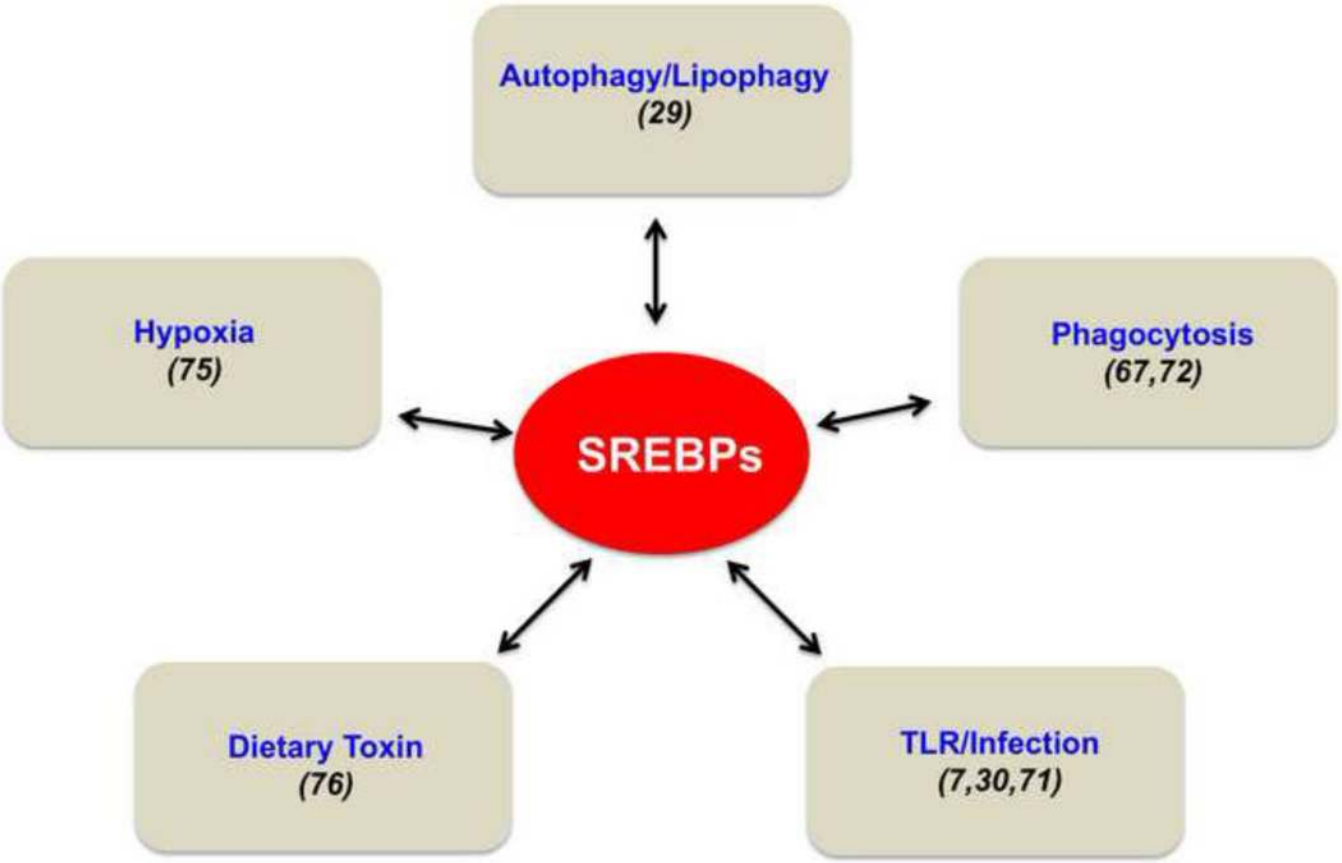

Figure 3.
SREBPs as "Metabolic Integrators". The figure highlights the studies that document the central role that SREBPs play in connecting together diverse physiologic processes.