Chapter 10
Transcriptional Regulation of Lipogenesis as a Therapeutic Target for Cancer Treatment

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Abstract A significant increase in lipogenesis is a metabolic hallmark of proliferating tumor cells and is required for oncogenic transformation of epithelial cells. Although most normal cells acquire the bulk of their fatty acids from the circulation, tumor cells synthesize more than 90 % of required lipids de novo. Consistent with an increased demand for lipid synthesis, diverse human cancer cells express high levels of lipogenic enzymes, such as fatty acid synthase (FASN) and stearoyl-CoA desaturase 1 (SCD1). The sterol regulatory element-binding protein 1 (SREBP1) and peroxisome proliferator-activated receptor γ (PPARγ) are master regulators of lipogenesis in diverse organisms. Previous studies have established that FASN and SCD1, the major transcriptional targets of SREBP1 and PPARγ, promote synthesis of fatty acids, which then serve as ligands for PPARγ activation. This review focuses on the potential therapeutic value of these lipogenic transcription factors as targets in cancer treatment.

Keywords Lipogenesis • Transcription factor • Sterol regulatory element-binding protein 1 (SREBP1) • Peroxisome proliferator-activated receptor gamma (PPARγ) • Cancer • Lipid metabolism • Cell proliferation

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10.1 Introduction

Lipogenesis is almost universally upregulated in human cancers [1]. Consistent with an essential role of the sterol regulatory element-binding protein 1 (SREBP1) in sensing and regulating intracellular lipid homeostasis, increased expression of SREBP1 has been detected in colorectal carcinoma, breast and prostate cancer, and hepatocarcinoma [2–5]. Moreover, elevated expression of SREBP1 is closely correlated with malignant transformation, cancer progression, and metastasis for several cancer types, particularly hormone responsive tissue-derived cancers, such as breast and prostate cancers [2, 4, 6, 7]. SREBP1 expression correlates with the expression of *FASN* (encodes fatty acid synthase or FAS) and Ki-67(a nuclear marker for cellular proliferation) in colorectal cancer, suggesting a role for SREBP1 in supporting rapid cellular proliferation [7]. SREBP1 is elevated in clinical prostate cancer samples compared to benign prostatic hypertrophy [3]. Gene expression profiling of hepatocellular carcinoma (HCC) tissue and non-cancerous liver tissue showed increased lipogenic signaling in HCC. ElevatedSREBP1 expression in hepatocellular carcinoma is a known predictor of increased mortality [4, 6]. Overexpression of SREBP1 in human hepatoma HuH7 and Hep3B cells enhanced cellular proliferation and foci formation, while knockdown of SREBP1 in these cells reduced cell replication and anchorage-independent cell growth [6]. A dramatic increase of SREBP1 has been correlated with the progression of prostate cancer towards androgen-independence [3]. Oncogenic transformation of normal breast epithelial cells was accompanied by increased *SREBP1* and *FASN* expression, consistent with the observation of increased SREBP1 levels in human breast cancers [8–10]. Previous studies have established that SREBP1, through induction of *FASN* and subsequent fatty acids production, regulates PPARγ transactivation [11, 12].

Dietary carbohydrates are digested into glucose, the major source of energy for many tissues. Once transported into cells, glucose is converted into pyruvate through glycolysis and subsequently acetyl Co-enzyme A (acetyl-coA), which is then re-engineered into palmitate, the major fatty acid, by Acetyl-coA carboxylase (ACC), the rate-limiting enzyme, and FAS, the major enzyme, both of which are required for fatty acid biosynthesis. Palmitate is further converted into triglycerides for energy storage and phospholipids, the major components of cell membrane. The key steps in lipogenesis in mammalian hepatocytes are summarized in Fig. 10.1. The enzymatic reactions that govern carbohydrate and lipid metabolism, as well as the allosteric regulation of the activities of these enzymes, also known as the "short-term regulation", have been elucidated by many pioneering biochemists during the first half of the twentieth century.

Compared to the short-term quick regulation of the enzymes, however, the transcriptional regulation of the metabolic enzymes in vivo, known as the "long-term regulation" of metabolism, is less well-understood [13]. Since defects in short-term regulation of enzymes are likely detrimental to survival at the cellular or organismal levels, the aberrant regulation of the long-term regulation contributes to a number of major diseases in adults, collectively known as the metabolic syndrome [14–17].

Because of the fundamental importance of FAS, ACC, ACS and SCD1 in regulating lipid metabolism, it is essential to understand the transcriptional regulation of

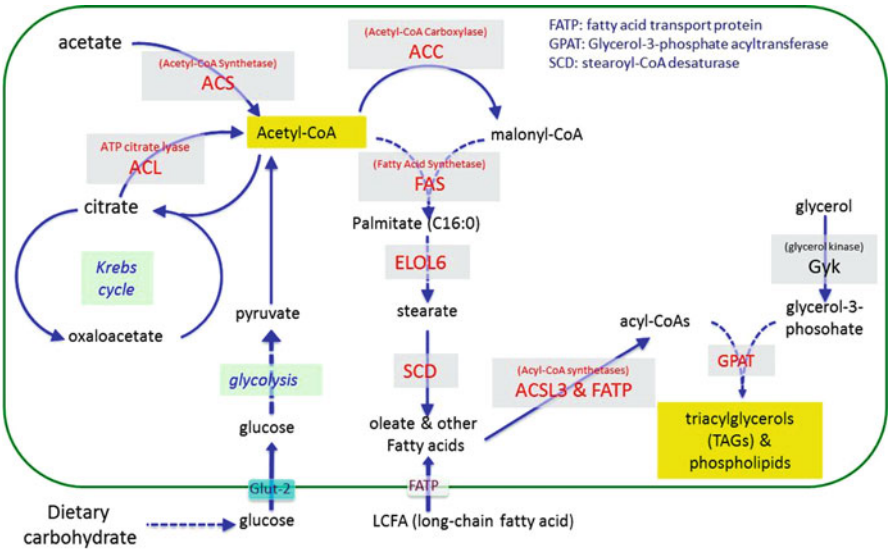

Fig. 10.1 The key biochemical reactions and enzymes involved in de novo lipogenesis in mammalian hepatocytes. This process is highly conserved in evolution. Transcription of many metabolic enzymes in this process is directly regulated by several transcription factors, such as PPARγ, SREBP, ChREBP, and LXR etc.

these enzymes in response to physiological stimuli by key transcription factors, including SREBP, PPARγ, liver X receptor (LXR), and carbohydrate-responsive element-binding protein (ChREBP) [13, 18–20]. In this chapter, we summarize the recent advances in studies linking deregulated lipogenesis in cancers, and then focus on our understanding of SREBPs and PPARγ in regulating lipid homeostasis. Finally, we will discuss potential therapeutic approaches to target lipid metabolism in treating cancer.

10.2 Deregulation of Lipogenic Signaling in Cancer

10.2.1 Elevated FASN Expression and Enhanced De Novo Fatty Acid Synthesis in Cancer

Most normal human tissues preferentially use circulating lipids for synthesis of new structural lipids, and de novo fatty-acid synthesis is normally suppressed due to the low levels of *FASN* expression. In cancer cells, however, fatty-acid supply becomes highly dependent on de novo lipogenesis. Deregulation of de novo fatty-acid synthesis leads to cellular fatty-acid accumulation and affects cellular processes, including signal transduction and gene expression.

FASN over-expression occurs in a variety of human cancers [21–25]. In cancer cells, *FASN* gene expression is upregulated in response to multiple signaling

pathways, including growth factors, steroid hormone receptors such as the estrogen receptor alpha (ERα), androgen receptor (AR) and progesterone receptor (PR), as well as oncoproteins including ErbB2, Ras and Akt [9, 25–30]. In addition to the essential role in cancer cell growth and survival, FAS is involved in other phases of cancer development. FAS over-expression confers resistance to adriamycin and mitoxantrone in breast cancer cells [31] and increased lipogenesis and FAS has been reported to be associated with invasive phenotype and cancer metastasis [24, 27, 32–36]. Elevated expression of *FASN* leads to increased cell proliferation, migration and invasion of prostate cancer cells [27, 32] and FAS inhibition reduces cellular migration and invasiveness [25, 26, 29, 35]. For example, Orlistat, an anti-obesity drug, inhibits FAS function and suppresses endothelial cell proliferation and angiogenesis, suggesting a novel role of FAS in endothelial cell in tumor growth in vivo [37]. It is still unclear how the level and activity of FAS are regulated during tumor progression towards metastasis.

10.2.2 Stearoyl-CoA Desaturase (SCD) and Cancer

SCD is a regulatory enzyme in lipogenesis, catalyzing the rate-limiting step in the de novo synthesis of monounsaturated fatty acids (MUFAs), mainly palmitic and stearic acids. Increased content of the MUFA products, palmitoleic and oleic acids, occurs in a variety of transformed cells and cancers [38–41], suggesting that the high rate of fatty acid synthesis in cancer is coupled to the conversion of saturated fatty acids (SFAs) into MUFAs. Elevated expression and activity of SCD1, the endoplasmic reticulum-resident Δ9 desaturase that converts SFA into MUFA, has been reported in several types of cancers, including colonic and oesophageal carcinoma, liver cancer, and mammary gland tumor [42–45]. SV40-transformed human lung fibroblasts show significantly increased protein and activity levels of SCD1 compared to their parental normal cell line [46]. This is consistent with a model in which a high rate of MUFA synthesis is required for producing membrane lipids in order to sustain the proliferation of transformed cells. Deficiency or inhibition of SCD1 reduces cell proliferation and anchorage-independent growth, and enhances apoptosis in several different cancer cell types [40, 47]. We and others have shown that SCD1 is a transcriptional target of SREBP1 and PPARγ [48–54].

10.3 Cellular Regulation of SREBP1 Function

10.3.1 SREBP1 Signaling in Lipogenesis and Tumorigenesis

SREBPs are a family of transcription factors that control lipid homeostasis by regulating the expression of enzymes required for cholesterol and fatty acids (FAs) synthesis. The three SREBP isoforms, SREBP-1a, SREBP-1c and SREBP-2, have distinct roles in lipid synthesis [55, 56]. In vivo studies using transgenic and

knockout mice suggest that SREBP-1c is involved in FA synthesis and insulin-induced glucose metabolism (particularly in lipogenesis), whereas SREBP-2 is relatively specific in controlling cholesterol synthesis. The SREBP-1a isoform is implicated in regulating both cholesterol and FA pathways [57, 58].

Extensive studies in the past two decades have revealed an elegant paradigm to understand how SREBPs maintain the intracellular lipid and cholesterol homeostasis. SREBP transcription factors are synthesized as inactive precursors bound to the endoplasmic reticulum (ER) membranes and their processing is mainly controlled by cellular sterol content: when sterol level decreases, the precursor undergoes a sequential two-step cleavage process to release the NH2-terminal active domain in the nucleus (designated as the nSREBPs), which then activates SREBP target genes whose products are required for the de novo biosynthesis of cholesterol and FAs [59–66]. The major SREBP targets include FASN [12, 67] and stearoyl-CoA desaturase (SCD) [49–51, 68]. This sterol-sensitive process appears to be a major point of regulation for the SREBP-1a and SREBP-2 isoforms, but not for SREBP-1c. Moreover, the SREBP-1c isoform is mainly regulated at the transcriptional level by insulin. The unique regulation and activation properties of each SREBP isoform facilitate the coordinated regulation of lipid and energy metabolism.

10.3.2 Regulation of the Transcriptional Activity of SREBP1

As summarized above, SREBPs are family of transcription factors that play critical roles in regulating intracellular lipid and cholesterol homeostasis. Using SREBP-1a/-1c as an example, here we focus on the recent advances in our understanding of how SREBP-1 activates lipogenic gene expression and how the transcriptional activity of SREBP is regulated.

10.3.2.1 Transcription Activation by SREBP

In response to cholesterol depletion, the N-terminus of SREBP that contains the transactivation domain and the basic helix-loop-helix leucine zipper (bHLH-Zip) DNA binding domain, is cleaved from its precursor, which is localized in ER and Golgi apparatus, and then translocates to the nucleus and activates the expression of SREBP-target genes [69, 70]. Through the bHLH-Zip DNA-binding domain, the nuclear SREBP fragments bind to the SREBP-target gene promoters that contain either palindromic E-boxes (CAXXTG) or nonpalindromic sterol regulatory elements (SREs) [71].

The transactivation domain of SREBPs can directly interact with transcription coactivators including CBP/p300, PGC-1β, MED14/DRIP150, and MED15/ARC105 [72]. Recruitment of CBP/p300 via the KIX domain of SREBP may alter chromatin structure through the intrinsic histone acetyltransferase activity of CBP/p300, thereby facilitating gene activation [73]. The interaction between PGC-1β and SREBP is required for SREBP-dependent lipogenic gene expression and

contributes to the effect of saturated fat in stimulating hyperlipidemia and atherogenesis [74]. In addition, SREBPs directly interact with the MED14/DRIP150 and the MED15/ARC105 subunits of the Mediator complex in mammals and *C. elegans*, which provides an elegant model to explain how transcription activator SREBPs interact with the general transcription machinery [73, 75–77]. The interactions between SREBP-1c and MED14 or MED15 are weaker than the interactions between SREBP-1a and MED14 or MED15, which may explain why SREBP-1a is more potent than SREBP-1c in activating gene expression [73, 75]. Since the nuclear SREBPs bind to DNA as homo-dimers, it is unclear whether the two transactivation domains of the SREBP homo-dimer can bind to MED14 and MED15 simultaneously.

10.3.2.2 Inactivation of SREBP-Mediated Transcription

Because of the fundamental roles of SREBPs in regulating the expression of lipogenic and cholesterogenic genes, the mechanisms that restrain SREBP transactivation are also important. CDK8, the enzymatic subunit of the Mediator complex, directly phosphorylates a conserved Threonine residue in SREBP (Thr402 in SREBP-1c), thereby promoting nuclear SREBP degradation [78]. Consistent with this model, the mutants of CDK8 and its regulatory partner Cyclin C (CycC) in *Drosophila* larvae, as well as depletion of CDK8 in cultured mammalian cells and mouse liver, display significantly increased expression of SREBP-target genes and dramatic increase of triglyceride accumulation [78]. Feeding and activation of the insulin-signaling pathway can down-regulate CDK8-CycC thus allow the activation of nuclear SRBEP, providing a mechanism for the lipogenic effect of insulin [78]. Together with the previous works on MED14 and MED15 in activating SREBP-dependent gene expression, this recent work on the inhibitory effect of CDK8-CycC on SREBP-regulated de novo lipogenes further highlights the importance of the Mediator complexes in modulating the activation and subsequent degradation of nuclear SREBPs.

Interestingly, GSK3β also negatively regulates SREBP by phosphorylating SREBP-1a at Thr 426 and Ser430 (corresponding to Thr402 and Ser406 in SREBP-1c), thereby providing a docking site for the ubiquitin ligase FBW7 [79–81]. It is still not known whether CDK8 and GSK3β play redundant roles in phosphorylating and thereby promoting SREBP destruction, however, these studies suggest a model to explain how activation of SREBP-dependent transcription is coupled to its degradation. This mechanism is consistent with a general theme by coupling transactivation with their destruction for many transactivators in yeasts and multicellular organisms [82].

Both CDK8 and CycC are amplified, mutated or deleted in a variety of cancers, and CDK8 is identified as an oncoprote in melanoma and colorectal cancers [83]. In addition, the MED12 subunit of the CDK8 module, which is composed of CDK8, CycC, MED12 and MED13, is mutated in prostate cancer, colorectal cancer, and

~70 % of uterine leiomyomas [84–87]. Importantly, MED12, but not MED13, is required for human CDK8 kinase activity [88]. Therefore, although it is still unclear how dysregulation of the CDK8 module contributes to tumorigenesis, it is conceivable that dysregulation of CDK8 submodules may compromise CDK8 activity, thereby potentiating SREBP activity, increasing SREBP target gene expression and promoting lipogenesis in cancer cells. This model may explain the mechanisms underlying aberrantly increased lipogenesis in human cancer cells and provide the rationale for developing pharmaceutical approaches to block de novo lipogenesis in tumor cells.

10.4 Modulation of PPARγ Activation for Cancer Therapeutics

10.4.1 The Function of PPARγ in Lipogenesis

Besides SREBPs, the peroxisome proliferator-activator receptor gamma (PPARγ) also plays a critical role in both lipid metabolism and tumorigenesis. The PPARs are ligand-activated nuclear receptors, which include PPARα, PPARγ and PPAR*δ* [89]. Their modular structure resembles other nuclear hormone receptors with an N-terminal activation function 1 (AF-1), a DNA binding domain, and a C-terminal ligand-binding domain that harbors AF2. PPARγ was initially cloned as a transcription factor involved in adipocyte differentiation. Subsequent studies suggested a broad spectrum of PPARγ functions in lipid metabolism, inflammation, atherogenesis, cell differentiation, as well as tumorigenesis. The endogenous PPARγ ligands include derivatives of fatty acids produced through lipogenesis (Fig. 10.1).

PPARγ regulates lipogenesis and adipocyte differentiation, and ectopic PPARγ expression promotes cell adipogenesis in an NIH 3 T3 cell model [90, 91]. Synthetic PPARγ ligands enhance de novo lipogenesis [92, 93], which was further supported by the genetic evidence that *PPARγ*$^{-/-}$ ES cells and embryonic fibroblasts are resistant to induction of adipogenesis [94, 95]. Aberrant hepatic expression of PPARγ2 stimulates murine hepatic lipogenesis [96, 97]. The screening for PPARγ-regulated genes in mammary epithelial cells, identified that Scd1 (*SCD1*) as a transcriptional target of PPARγ [98]. SCD1 production of unsaturated fatty acids may thereby serve as PPARγ agonist ligands, providing a feedback loop to PPARγ. Reciprocal up-regulation of PPARγ and SREBP-1 has been reported. Ectopic expression of SREBP-1 in pre-adipocyte 3 T3-L1 cells and hepatic cancer HepG2 cells induced endogenous PPARγ mRNA expression [99]. SREBP-1 activation increased the production of lipids as endogenous ligands for PPARγ, which binds to PPARγ and augments the transcriptional activity of PPARγ [11, 12]. PPARγ, upon ligand binding, up-regulates the expression of *INSIG1*, the key regulator in the processing of SREBPs [100].

10.4.2 Contradictory Role of PPARγ in Tumorigenesis

PPARγ has been shown to function either as an oncoprote in, or as a tumor suppressor. PPARγ is expressed in breast, prostate and colonic epithelium and ligand-dependent activation of PPARγ in cell lines derived from these tumors inhibits cellular proliferation [101–105]. Consistent with the role of PPARγ as a tumor suppressor, PPARγ ligand reduced tumorigenesis in the Apc^{Min} model of familial adenomatous polyposis. Carcinogen, N-nitroso-N-methylurea (NMU)-induced mammary tumorigenesis is prevented by PPARγ agonists [106], and 7, 12-dimethylbenz(a)anthracene (DMBA)-induced mammary tumorigenesis was inhibited by troglitazone [107–109]. A chromosomal translocation between PAX8 and PPARγ in follicular thyroid cancer served as a dominant inhibitor of endogenous PPARγ expression [110]. PPARγ expression is reduced in human breast cancers compared with normal breast tissue [111, 112] and PPARγ over expression in tumor cells inhibits cell proliferation in tissue culture [112]. PPARγ levels are reduced in mouse transgenic mammary tumors induced by distinct oncogenes, compared with normal adjacent non tumorous mammary epithelium [111, 112].

In contrast, evidence that PPARγ is an oncogene includes observations that PPARγ ligands promote colonic tumor growth in Apc^{Min} mice when fed a high fat diet [113]. Heterozygous mutations of PPARγ have been detected in 4/55 patients with colon cancer [114]. Although genetic analyses failed to show that PPARγ-deficient mice develop enhanced tumor phenotypes in prostate epithelium induced by the SV40 large-T antigen oncogene [113]. A constitutively active mutant of PPARγ (PγCA) enhanced ErbB2-induced tumor in vivo in immune-competent animals (Fig. 10.2) and in transgenic mice [115]. PγCA promoted ErbB2-induced tumor growth in immune-competent animals. Increased angiogenesis is associated with enhanced tumor growth in vivo [116]. Collectively, these studies suggest cell-type specific functions of PPARγ in the tumor induction versus inhibition.

10.4.3 Can PPARγ Be Targeted to Block the Tumor Growth?

In cell culture, PPARγ expression and/or activation repressed tumor cell growth by inhibiting cell proliferation, promoting apoptotic and autophagic cell death, and inducing terminal differentiation of cancer cells [112, 117, 118]. In whole animal studies, the picture appears more complex, which is consistent with the importance of heterotypic signals in cancer progression, and the presence of PPARγ in a variety of cell types including the inflammatory system. Clinical trials have been undertaken in a variety of tumor types including liposarcomas, prostate, pancreatic, colorectal, breast, thyroid, head and neck cancers, as well as melanoma and leukemia [119]. Overall, PPARγ agonists failed to yield positive clinical outcome in most cancer types. PPARγ is increased in ERα-negative breast cancer, but reduced expression in ERα-positive breast cancers [120]. Breast cancer genetic subtypes

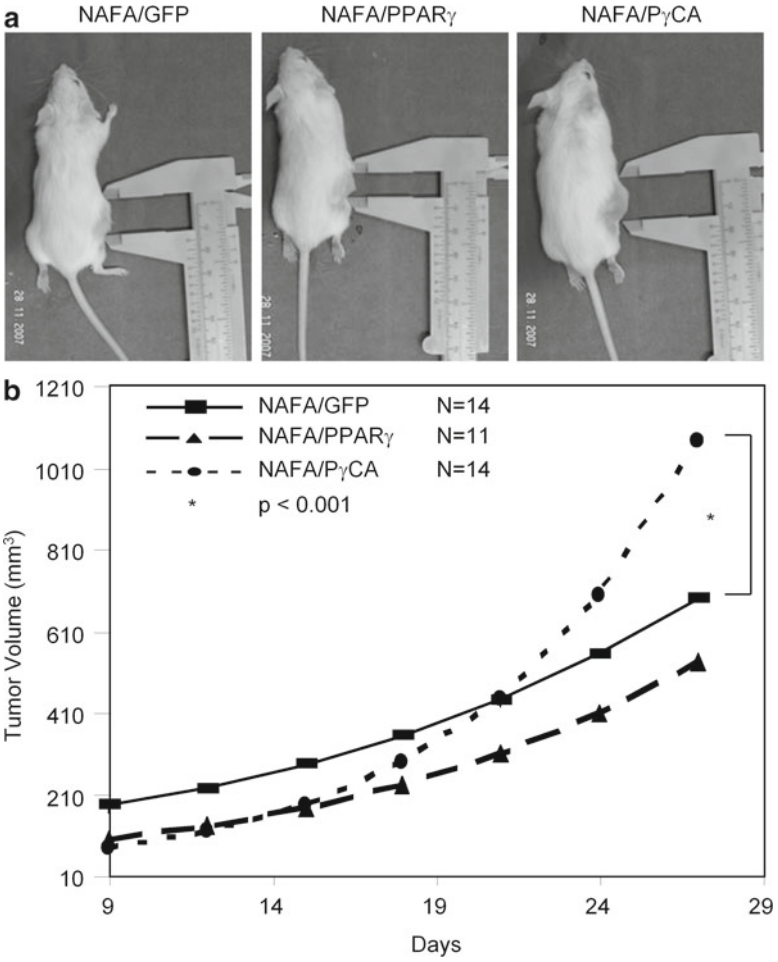

Fig. 10.2 PγCA promotes tumor growth in vivo. (**a**) NAFA cells transduced with MSCV-IRES-GFP vector encoding either PPARγ, PγCA, or empty vector were implanted into FVB by injecting 2×10^6 cells subcutaneously. Tumor growth was measured every 3 days by digital caliper and tumor volume was calculated. (**b**) Tumor volumes were logarithm-transformed and analyzed using a linear mixed model. Separate slope and intercepts were computed for each group (GFP, PPARγ, and PγCA), then compared across groups using a global test followed by pair-wise comparisons via linear contrasts (This figure was reproduced from our previous publication [116])

(Luminal A, Luminal B, Triple negative/basal-like, HER2 subtypes [121–123]) may have different response to PPARγ ligands. Our analysis of *PPARG* gene expression in a combined dataset comprising of over 2,000 breast cancers [124] showed a strong heterogeneous distribution of *PPARG* expression among the subtypes (unpublished data). Consistent with our previous IHC result showing reduced PPARγ expression in breast cancer comparing to normal breast tissue, this analysis demonstrated that the gene expression of *PPARG* was also reduced (data not shown).

The higher *PPARG* expression predicts a better clinical outcome, which again holds the promise that PPARγ could serve as a therapeutic target. Given the variability in PPARγ expression in patient populations, clinical trials using PPARγ expression or function as a companion diagnostic may be warranted.

10.5 Conclusions and Future Directions

Given the importance of lipogenesis in cancer development, targeting lipogenic signaling, particularly lipogenic enzymes, is an attractive strategy. The inhibitors of the rate-limiting or key lipogenic enzymes, including HMGCR, ACC, FASN, and SCD, are summarized in Table 10.1. In addition to inhibiting these lipogenic enzymes, pharmaceutical inhibition of SREBPs and PPARγ, may also be effective.

Taken together, these studies suggest that dysregulated lipogenic signaling in cancer is required for oncogenic transformation, thus targeting the dysregulated lipogenesis in câncer cells may represent an attractive therapeutic approach. Current

Table 10.1 Chemical modulators of lipogenic signaling

Modulator	Targeting molecule/pathway	Mechanism of function	References
Statins	HMG-CoA reductase (HMGCR)/mevalonate pathway	Structural analogs of HMG-CoA reductase, lipid-lowing agent	Review in [125]
Soraphen A	Acetyl CoA carboxylase (ACC)	Interferes with fatty acid elongation	[126, 127]
benzofuranyl alpha-pyrone (TEI-B00422)	Acetyl CoA carboxylase (ACC)	Competitive inhibition of ACC	[128]
5-(tetradecyloxy)-2-furoic acid (TOFA)	Acetyl CoA carboxylase (ACC)	Long chain fatty acid analogues	[129]
CP-640186	Acetyl CoA carboxylase (ACC)	Interacts with ACC	[130]
Cerulenin	Fatty acid synthase (FASN)		[131, 132]
C75	Fatty acid synthase (FASN)	Interacts and inhibits FASN	[133, 134]
C93	Fatty acid synthase (FASN)		[135]
Orlistat	Fatty acid synthase (FASN)		[136]
EGCG	Fatty acid synthase (FASN)		[137]
G28UCM	Fatty acid synthase (FASN)		[138]
GSK837149A	Fatty acid synthase (FASN)	Target the beta-ketoacyl reductase reaction	[139]
MK-8245	Stearoyl-CoA desaturase (SCD)		[140]
Compound 9	Stearoyl-CoA desaturase (SCD)		[141]
Fatostatin (and derivatives)	SREBP-1	Inhibits SREBP-1 processing	[142, 143]
BF175 (and derivatives)	SREBP-1	N.D.	[144]
TZDs	PPARγ	Interacts with and activate PPARγ	[145]

research efforts have been focused on repressing the activity of lipogenic enzymes (such as FASN, HMG-CoA reductase, ACC, ACLY, and SCD). Future studies are required to provide a deeper understanding of the following three major aspects. First, it would be important to understand how alterations in molecular mechanisms of lipogenic signaling occur in cancer. Second, a compendium of metabolic profiling in different cancer types and subtypes may allow for more accurate patient selection for specific lipogenic pathway targeted therapies. Third, it may be important to simultaneously target multiple lipogenic factors rather than a single molecule, to ensure therapy effectiveness.

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