Fatty acid synthase as a potential therapeutic target in cancer

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Abstract

Fatty acid synthase (FASN) is a key enzyme involved in neoplastic lipogenesis. Overexpression of FASN is common in many cancers, and accumulating evidence suggests that it is a metabolic oncogene with an important role in tumor growth and survival, making it an attractive target for cancer therapy. Early small-molecule FASN inhibitors such as cerulenin, C75 and orlistat have been shown to induce apoptosis in several cancer cell lines and to induce tumor growth delay in several cancer xenograft models but their mechanism is still not well understood. These molecules suffer from pharmacological limitations and weight loss as a side effect that prevent their development as systemic drugs. Several potent inhibitors have recently been reported that may help to unravel and exploit the full potential of FASN as a target for cancer therapy in the near future. Furthermore, novel sources of FASN inhibitors, such as green tea and dietary soy, make both dietary manipulation and chemoprevention potential alternative modes of therapy in the future.

Keywords

C75; cancer; ERBB-2; fatty acid synthase; MAPK; PI3K/AKT; SREBP-1

Fatty acid synthase (FASN) is a key bio synthetic enzyme involved in lipogenesis and the production of long-chain fatty acids from acetyl-coenzyme A (CoA) and malonyl-CoA. Uptake of glucose into cancer cells leads to the production of pyruvate via the glycolytic pathway. Pyruvate is utilized to produce ATP via the Krebs cycle in the mitochondria; in

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turn, acetyl-CoA, one of the products, acts as a substrate for neoplastic lipogenesis (Figure 1). Normal cells (except liver and adipose tissue) have low levels of expression and activity of FASN, which is tightly regulated by diet, hormones and growth factors (reviewed in [1]). However, in rapidly proliferating cancer cells, fatty acids can be synthesized de novo in order to provide lipids for membrane formation and energy production via β-oxidation and lipid modification of proteins. As such, FASN is highly expressed in many cancers, including prostate, ovarian, breast, endometrial, thyroid, colorectal, bladder, lung, thyroid, oral, tongue, esophageal, hepatocellular, pancreatic and gastric carcinomas, as well as malignant melanoma, mesothelioma, nephroblastoma and retinoblastoma, soft tissue sarcoma (reviewed in [1–7]), gastrointestinal stromal tumor [8], Paget’s disease of the vulva [9] and multiple myeloma [10]. Interestingly, increased FASN expression has also been observed in some benign and pre-invasive lesions of prostate, breast, lung, stomach, colon (aberrant crypt foci) and cutaneous nevi [2,11–14].

Elevated expression of FASN has been linked to poor prognosis and reduced disease-free survival in many cancer types [15–19]. In addition, several reports have demonstrated that FASN plays an important role in tumor cell development and survival, with siRNA knockdown or pharmacological inhibition of FASN resulting in apoptosis of cancer cells and prolonged survival of xenograft tumors [20–23]. Overexpression studies in immortalized non-transformed human prostate epithelial cells and in transgenic mice have demonstrated that FASN is a bona fide oncogene in prostate cancer [24], and similarly in breast cancer, fatty acid biosynthesis induces a cancer-like phenotype in noncancerous epithelial cells that is dependent on HER1/HER2 signaling [25]. A potential mechanism of FASN onco-genicity may involve cytoplasmic stabilization of β-catenin with palmitoylation of Wnt-1 and subsequent activation of the WNT/β-catenin pathway [26]. In this article, we focus on the mechanisms of FASN regulation in cancer and discuss recent updates on the potential of FASN as a therapeutic target in cancer treatment.

### Regulation of FASN in cancer

The regulation of FASN expression in cancer is complex and involves transcriptional and post-translational control acting in concert with several microenvironmental influences (reviewed in [1,3,27]; Figure 2). Growth factor receptors, such as ERBB-2 and EGF receptor, interact and activate downstream PI3K/AKT and MAPK signaling pathways with subsequent transcriptional activation of FASN expression (loss of PTEN in prostate cancer tissue may also activate AKT thereby indirectly regulating FASN levels) [28]. Similarly, aberrant activation of AKT and MAPK can occur in hormonally sensitive organs (breast, endometrium, ovary and prostate) through activation of sex hormone receptors by estrogen, progesterone and androgen. Mutual crosstalk between upstream regulators: growth factors, sex hormones and their corresponding receptors, may also occur, amplifying FASN overexpression [27]. FASN, in turn, may activate the tyrosine kinase growth factor receptor as evidenced in human breast epithelial cells [25], thereby setting up an auto-regulatory loop. Ultimately, both the AKT and MAPK transduction pathways regulate FASN expression through the modulation of expression of sterol regulatory element-binding protein (SREBP)-1c, which binds to regulatory elements in the FASN promoter. Proto-oncogene FB1-I (Pokemon), a transcription factor of the bric-à-brac tramtrack broad complex/pox viruses and zinc fingers (BTB/POZ) domain family, interacts directly with SREBP-1c through its DNA-binding domain to synergistically activate the transcription of FASN (Figure 2) [29]. This is accomplished by acting on the proximal GC box and SRE/E box.

S14 is a lipogenesis-related nuclear protein that is overexpressed in most breast cancers. A recent study demonstrated that SREBP-1c drives S14 gene expression in breast cancer cells,
and progesterone magnifies that effect via an indirect mechanism. This supports the prediction, based on \(S14\) gene amplification and overexpression in breast tumors, that \(S14\) augments breast cancer cell growth and survival [30]. These effects are mediated through FASN expression. D’Erchia et al. report that the \(FASN\) gene is a conserved target of the p53 family throughout evolution; CEP-1, the \(Caenorhabditis\) \(elegans\) p53 homolog, is able to bind the two p53 family responsive elements identified in the worm \(fasn-1\) gene. Moreover, by comparing wild-type and CEP-1 knockout worms, they demonstrated that \(fasn-1\) expression is modulated by CEP-1 \(in\) \(vivo\) [31].

Overexpression and copy number gain of the \(FASN\) gene has been previously demonstrated in prostate cancer and related to distinct molecular signatures [16,32]. Using immunohistochemistry and FISH analysis in paraffin-embedded tissue microarrays, Shah et al. observed gene copy gain in 24% of all prostate adenocarcinoma specimens examined, with concurrent increased FASN protein expression. These findings suggest that \(FASN\) gene copy number increases may be involved in the resultant increase in FASN protein expression observed and indicate that potentially alternate post-translational mechanisms of FASN regulation exist in cancer [32]. Similarly, ubiquitin-specific protease 2a (USP2a), a pre-proteosomal deubiquininating enzyme, may interact with and stabilize FASN through the removal of ubiquitin [21]. USP2a is androgen regulated and overexpressed in prostate cancer; its functional inactivation results in decreased FASN protein and enhanced apoptosis. Thus, the isopeptidase USP2a plays a critical role in prostate cancer cell survival through FASN stabilization. An alternate mechanism of regulation may occur via mTOR-mediated translational induction in breast cancer cells overexpressing HER2. Yoon et al. found that SK-BR-3 and BT-474 breast cancer cells that overexpress HER2 also express higher levels of FASN, compared with MCF-7 and MDA-MB-231 breast cancer cells, in which HER2 expression is low. The induction of FASN in BT-474 cells was not mediated by the activation of SREBP-1c. Exogenous HER2 expression in MDA-MB-231 cells induced the expression of FASN, and the HER2-mediated increase in FASN was inhibited by both LY294002 (a PI3K inhibitor) and rapamycin (a mTOR inhibitor). In addition, the activation of mTOR by the overexpression of Ras homolog enriched in brain (RHEB) in MDA-MB-231 cells increased the synthetic rates of FASN. On the other hand, FASN was reduced in BT-474 cells by blockade of the mTOR signaling pathway [33].

As stated earlier, microenvironmental stresses also have a role to play in regulating FASN expression. Oliveras-Ferraros et al. found that extracellular levels of FASN are dependent on the metabolic state of the cell, whereby AMPK, in response to increasing AMP:ATP ratios, leads to extracellular FASN release and a restoration of the cellular energy state [34]. Aminomimidazole carboxamide ribonucleotide (AICAR), an AMPK-activating drug, by stimulating an elevation of the AMP:ATP ratio in breast cancer cells, leads to a dose- and time-dependent augmentation of extracellular FASN levels. Conversely, siRNA blockade of AMPK attenuated the release of FASN. Furuta et al. demonstrated that FASN is significantly upregulated by hypoxia in human breast cancer cell lines [35]. They also found that hypoxia significantly upregulated SREBP-1c via phosphorylation of AKT followed by activation of HIF1. Moreover, results of reporter assay and chromatin immunoprecipitation analysis indicate that SREBP-1c is strongly bound to the SREBP-binding site/E-box sequence on the FASN promoter under hypoxia. In their xenograft mouse model, FASN was strongly expressed in the hypoxic regions of the tumor. In addition, immunohistochemical analyses of human breast tumor specimens indicated that the expressions of both FASN and SREBP-1c were co-localized within hypoxic regions. Furthermore, they found that hypoxia-induced chemo resistance to cyclophosphamide was partially blocked by a combination of FASN inhibitor and cyclophosphamide, which has obvious therapeutic implications [35]. Separately, transient transfection studies performed using a 178-bp \(FASN\) promoter fragment
harboring a complex SREBP-binding site was used to demonstrate that extracellular acidosis may act in an epigenetic fashion to induce changes in the transcriptional activation of FASN gene in breast cancer cells [36]. Interestingly, this stimulatory effect is equally mimicked by well-characterized oncogenic stimuli such as Her2/neu [36].

**Structure of FASN**

Recently, the crystal structure and catalytically active sites of FASN have been delineated. FASN is made up of a paired multifunctional poly peptide with seven catalytic domains that include an acyl-carrier protein (ACP). These domains (in linear order from the carboxy terminus) are: thioesterase, ACP, β-ketoacyl reductase, enoyl reductase, β-hydroxyacyl dehydratase, acetyl/malonyl-CoA transferase and β-ketoacyl synthase. There are two additional non enzymatic domains: a pseudoketoreductase; and a peripheral pseudomethyltransferase, which is probably a remnant of an ancestral methyltransferase domain maintained in some related polyketide synthases [37]. Initial work by Maier et al. resolved the 4.5-Å crystal structure of intact porcine FASN [38]; while, later, the crystal structure of mammalian FASN at 3.2-Å resolution, covering five catalytic domains, was determined (however, the flexibly tethered terminal ACP and thioesterase domains remain unresolved) [37]. Earlier work helped identify the active sites and the inter-relationships of the domain sites by biochemical methods [39–42]. A significant step forward was the determination of the crystal structure of the thioesterase domain from human FASN in complex with the orlistat ligand [43]. Importantly, natural product inhibitors of the ketoreductase domain and small-molecule inhibitors of the β-ketoacyl synthase and thioesterase domains have been described as having anti-oncogenic properties.

**FASN as a potential drug target in cancer therapy**

Fatty acid synthase is an attractive potential target for cancer therapy. As described in the previous sections, FASN is selectively overexpressed in many types of cancer, and these elevated levels have been linked to poor prognosis. RNAi knockdown experiments have shown that multiple cancer cell lines depend on FASN for proliferation and survival. To date, several compounds are known to inhibit FASN. These include cerulenin, C75, orlistat, C93 and naturally occurring polyphenols. Figure 3 outlines the structures of reported FASN inhibitors, and Box 1 is a summary of all compounds that inhibit FASN as outlined in this article.

Cerulenin and C75, both early small-molecule FASN inhibitors, have demonstrated significant antitumor activity. Cerulenin was isolated from Cephalosporium caerulens; it contains an epoxy group that reacts with the ketoacyl synthase domain of FASN [44]. It was one of the first compounds to be found to inhibit FASN in breast cancer cell lines, inducing programmed cell death, and to delay disease progression in a xenograft model of ovarian cancer; its cytotoxic effects are dependent on the level of FASN activity [45,46]. C75 was designed after cerulenin to overcome its chemical instability [47]. C75 is a weak, irreversible inhibitor of FASN that interacts with the β-ketoacyl synthase, the enoyl reductase and the thioesterase domains [48]. C75 showed tumor growth inhibition in a xenograft breast cancer model [23] and chemopreventive activity for mammary cancer in neu-N transgenic mice [49]. Recently, more potent analogs of C75 have been designed as FASN inhibitors [50]. Both cerulenin and C75 have been shown to cause profound effects on food intake and bodyweight in mice that could be limiting in the development of cancer therapy [51]. Weight loss seems to occur through the activation of mitochondrial fatty acid oxidation via the stimulation of carnitine palmitoyltransferase I and, furthermore, through the inducement of anorexia via the inhibition of production of neuropeptide Y within the hypothalamus [51,52]. This effect has been proposed to be mediated by brain FASN, which,
with PPARα, would constitute an integrative sensory module controlling energy balance and feeding behavior [53]. As a result of these effects, FASN has also been considered as a potential target for the treatment of obesity [54].

Several natural plant-derived polyphenols have been shown to inhibit FASN, including epigallocatechin-3-gallate (EGCG) and the flavonoids luteolin, taxifolin, kaempferol, quercetin and apigenin [55–57]. One of the best characterized polyphenol FASN inhibitors is EGCG, a natural component of green tea. EGCG is a high micromolar time-dependent inhibitor of FASN ketoacyl reductase domain [58]. Although EGCG is a promiscuous inhibitor targeting multiple signaling pathways [59], its apoptosis-inducing effect seems to correlate with its activity at FASN [60]. Another compound, luteolin, has the greatest effect on lipogenesis of the polyphenols and inhibits FASN directly. It has structural homology to PI3K inhibitors and has strong antioxidant activity [56]. Recently, more potent analogs of EGCG have been developed and have been shown to inhibit tumor growth in a breast cancer xenograft model [61].

Orlistat is a US FDA-approved pancreatic lipase inhibitor, originally developed as an anti-obesity drug, and is a potent inhibitor of FASN. Kridel et al. first identified orlistat in a proteomic screen for prostate cancer-specific enzymes as a potent FASN inhibitor showing antiproliferative activity against several prostate cancer cell lines in vitro, as well as tumor growth inhibition in a xenograft prostate cancer model [22]. Orlistat is an irreversible inhibitor forming a covalent adduct with the active serine of FASN thioesterase domain as shown in a recently published co-crystal structure [43]. In addition to the original report, orlistat has shown modest anticancer activity in a few in vivo models. Inhibition of tumor FASN activity by orlistat reduces prostate tumor growth in mice xenografts and, at a high concentration, reduces proliferation and promotes apoptosis in the mouse metastatic melanoma cell line B16-F10 (helping reduce the number of mediastinal lymph node metastases) and HER2-overexpressing breast cancer cell lines [22,62,63]. Further evidence indicates that orlistat can accelerate tumor cell apoptosis in culture at high concentrations and increase survival rates somewhat in gastric tumor-bearing mice in vivo [64]. However, orlistat suffers from several limitations hampering its development as a systemic drug: low cell permeability, low solubility, lack of selectivity [65], poor oral bioavailability and poor metabolic stability [66]. Several orlistat analogs have been developed in an attempt to improve on these limitations [67–70].

C93 (or FAS93), a synthetic FASN inhibitor designed after the bacterial FabB inhibitor thiolactomycin, was recently developed as part of an effort to overcome C75’s lack of potency and side effects [71]. C93 has shown some significant tumor growth delay in non-small-cell lung cancer xenograft models and ovarian cancer xenograft models, as well as some chemopreventive effects in chemically induced lung tumors [72–74]. Importantly, C93 did not cause anorexia and weight loss in treated animals [72]. C247 belongs to the same class of compounds as C93 and has also demonstrated efficacy in a transgenic model of breast cancer with no weight-loss side effects [49,71,75]. Recently, the team that developed FAS93 reported a new orally available FASN inhibitor, FAS31. FAS31 showed tumor reduction in ovarian cancer xenograft models with no effect on bodyweight. In preliminary toxicity studies, FAS31 showed no observable toxicity to normal tissues in the rat or mouse [76]. Unfortunately, C93, C247 and FAS31 structures have not been released yet.

As a testimony to the interest in FASN as a therapeutic target, several recent reports describe new potent FASN inhibitors identified through high-throughput screening or medicinal chemistry programs. For example, a research group at Merck developed a series of 3-aryl-4-hydroxyquinolin-2(1H)-one derivatives while another research group at AstraZeneca developed a series of bisamide derivatives as FASN inhibitors [77,201]. Both groups
obtained compounds with activities in the low nanomolar range in their respective FASN biochemical assays but did not report any data regarding cellular or in vivo activity. The dibenzenesulfonamide urea GSK837149A was identified as a low, nanomolar FASN inhibitor by high-throughput screening at GlaxoSmithKline. Biochemical studies showed that GSK837149A is a reversible inhibitor of the FASN β-ketoacyl reductase domain, but its poor cell permeability prevented the study of its mechanism in cells [78]. A systematic screening of 250,000 natural product extracts led to the isolation of platensimycin as a potent inhibitor of bacterial FabF/B with a broad-spectrum Gram-positive antibacterial activity [79]. Platensimycin has also been claimed to potently inhibit mammalian FASN in a biochemical assay, but to our knowledge, no studies in cancer cell lines have been reported [202].

Mechanism of action of FASN inhibitors

The mode of action of several small-molecule FASN inhibitors is not fully understood. Their study can be hampered by their lack of potency, selectivity or cell permeability [48,59,65,78]. FASN inhibition initiates selective apoptosis of cancer cells both in vivo and in vitro, which may involve accumulation of toxic intermediary metabolite malonyl-CoA with reduction of both membrane synthesis and phospholipid function leading to both cytostatic and cytotoxic effects [23,80]. Indeed, recent evidence suggests that malonyl-CoA decarboxylase inhibition may be a potential novel target for cancer treatment [81]. Inhibition of FASN has been shown to induce endoplasmic reticulum stress in tumor cells [82], and a further mechanism of action may involve cooperation with endoplasmic reticulum stress inducers to enhance apoptosis [83]. In addition, ceramide accumulation following siRNA inhibition of FASN may have cytotoxic effects leading to tumor cell death in breast cancer cells (which can be rescued with inhibition of ceramide synthesis) [84]. Focusing on specific compounds, cerulenin has been shown to interfere with DNA replication and both p53 accumulation and mitochondrial-mediated apoptosis appear to have important roles in tumor-cell death [85–87]. C75 has similar effects with rapid malonyl-CoA and p53 accumulation. Similarly, in a subset of papillary thyroid carcinomas, FASN inhibition with C75 induces growth arrest and promotes apoptosis via activation of the mitochondrial arm of the apoptotic pathway with subsequent activation of the caspase cascade [88]. Orlistat appears to have cell cycle effects, inducing G1/S arrest, leads to dysregulation of Skp2 with resultant p27kip1 accumulation and activation of the retinoblastoma pathway [89]. Furthermore, it prevents endothelial cell proliferation and importantly inhibits human neovascularization in ex vivo assays, suggesting it maybe useful as an antiangiogenic drug. These effects are mediated through prevention of VEGF receptor appearance on the endothelial cell surface [90]. Knowles et al. have shown that inhibition of FASN, by either knockdown with siRNA or inhibition with the small-molecule drug orlistat, leads to activation of the receptor-mediated apoptotic cascade (caspase-8-mediated) and ultimately to cell death. The unique apoptotic effect of FASN inhibition results from negative regulation of the mTOR pathway via stress response gene DDIT4 (DNA damage-inducible transcript 4) [91].

Several oncogenic signaling pathways are affected by FASN inhibition.

Recent evidence suggests interaction between FASN and ErbB systems in ovarian cancer cells and that interference with FASN and ErbB abrogates their oncogenicity [92]. Furthermore, C75 reduces HER2 expression in breast cancer cells [93]. This has the potential to be exploited therapeutically both in breast and ovarian cancer treatment, whereby FASN inhibition with C75 can sensitize tumor cells against anti-ErbB drugs (e.g., pelitinib, canertinib, erlotinib, cetuximab, matuzumab and trastuzumab). It seems that AKT is crucial for ErbB/FASN interaction, and several studies indicate a connection between
FASN inhibition and the PI3K pathway. High-level expression of FASN in prostate cancer is linked to activation and nuclear localization of AKT and PI3K inhibition synergizes with FASN siRNA to induce prostate tumor cell apoptosis [28,94]. Furthermore, positive-feedback regulation between AKT activation and FASN expression in ovarian cancer cells has been demonstrated and, indeed, inhibition of the PI3K/AKT pathway sensitizes breast cancer cells to cerulenin-induced cell death [95,96]. Similarly, the mode of action of C93 potentially may be mediated through the AKT signaling pathway or through AMPK [73,74]. Incidentally, FASN inhibition drives the synthesis of phospholipid partitioning into detergent-resistant membrane microdomains or lipid rafts that are associated with these signaling complexes and pathways, highlighting a functional link between FASN inhibitors and these signaling pathways [97].

**FASN & multidrug resistance**

Multidrug resistance is a significant problem in cancer chemotherapy and, importantly, FASN overexpression seems to be a recently identified mechanism of multidrug resistance in cancer. Liu et al. identified that ectopic overexpression of FASN induced drug resistance in breast cancer cell lines MCF7 and MDA-MB-468; use of orlistat sensitized these cells to anticancer therapy. The proposed mechanism is FASN overexpression may lead to a decrease in drug-induced apoptosis due to an overproduction of palmitic acid [98]. This phenomenon of FASN-induced drug resistance may be exploited therapeutically through the use of FASN inhibitors solely or in combination with other chemo-therapeutic agents. For example, FASN blockade can induce a synergistic chemosensitization of breast cancer cells to microtubule-interfering agents, such as docetaxel, paclitaxel and vinorelbine. Furthermore, cerulenin and 5-fluorouracil display a schedule-dependent synergistic interaction, leading to an enhancement of the efficacy of antimetabolite treatment in breast carcinoma cells [99]. Indeed, pharmacological blockade of FASN reverses autoresistance to trastuzumab by transcriptionally inhibiting HER2 ‘super expression’ occurring in high-dose trastuzumab-conditioned SKBR3/Tzb100 breast cancer cells [100]. Interestingly, disruption of crosstalk between the fatty acid synthesis and proteasome pathways in prostate cancer cell lines can enhance unfolded protein response signaling and cell death [101]. FASN inhibition may also have an anti-angiogenic role, as orlistat has been found to suppress endothelial cell proliferation in vivo [90].

**Conclusion**

Fatty acid synthase appears to play a key role in tumor initiation and propagation for many malignancies and, as such, represents an attractive target for cancer treatment. Further improvements in developing and identifying novel FASN inhibitors, as well as identifying the patients who may benefit most from them, will potentially offer more effective treatment strategies.

**Future perspective**

Over the last 15 years, FASN has emerged as an attractive target for cancer therapy. Early small-molecule FASN inhibitors like cerulenin, C75 and orlistat have been shown to induce apoptosis in several cancer cell lines and tumor-growth delay in several cancer xenograft models but their mechanism is still not well understood. These molecules suffer from selectivity, metabolic and pharmacologic limitations that hamper their use in preclinical and clinical settings. Several new potent inhibitors recently reported in the scientific and patent literature testify to the activity in the field and may help unravel and exploit the full potential of FASN as a target for cancer therapy in the near future.
Overexpression of FASN in many preinvasive lesions indicates the potential utility of FASN inhibitors for chemoprevention [12–14,102]. Dietary manipulation may become a real possibility: green tea catechin inhibits FASN without stimulating crosactivation of fatty acid oxidation and inducing weight loss [103,104]. In addition, Xiao et al. found that dietary soy protein inhibits DNA damage and cell survival of colon epithelial cells through attenuated expression of FASN and decreasing circulating insulin levels [105]. The anti-oncogenic effects of the main olive oil monounsaturated fatty acid oleic acid (18:1n-9) which is found in the Mediterranean diet has also been demonstrated [106]. Oleic-acid treatment efficiently blocks FASN activity and down regulates protein expression, which directly leads to an accumulation of FASN substrate malonyl-CoA suppressing HER2 expression.

Moving forward, if sufficiently tolerable FASN inhibitors become widely available, further work will be needed to identify patients in whom FASN inhibition is most likely to be beneficial so that they can be selected for FASN inhibitor trials. Recent work from epidemiological studies suggests an interaction between obesity and the impact of FASN, such that FASN’s deleterious effects on survival seem to be most pronounced in obese patients. Specifically, Ogino et al. observed that increased FASN expression in colon cancer tumors was associated with increased mortality in those with a high BMI but not those with a low BMI [15]. Similarly, unpublished data from the Physician’s Health Study and Health Professionals Follow-up Study suggest that increased FASN expression in prostate cancer tumors is associated with increased prostate-cancer-specific mortality in men with a high BMI but not those with a low BMI [Nguyen et al., Unpublished Data]. Taken together, this epidemiological evidence raises the possibility that men who are obese and whose tumors express high levels of FASN may have the most to gain from FASN inhibition, and should be selected first for FASN inhibitor trials as they become available.

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Bibliography

- of interest
- of considerable interest


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**Patents**


### Box 1

Potential fatty acid synthase inhibitors

**Small-molecule inhibitors**

- Cerulenin
- C75
- Orlistat
- C93 (FAS93)
- FAS31
- C247
- GSK837149A
- Platensimycin
- Merck 3-aryl-4-hydroxyquinolin-2(1H)-one scaffold
- AstraZeneca bisamide scaffold

**Naturally occurring polyphenols**

- Epigallocatechin
- Luteolin
- Taxifolin
- Kaempferol
- Quercetin
- Apigenin

**Dietary compounds**

- Catechin
- Soy protein
- Monounsaturated fatty acid oleic acid (18:1n-9)
Executive summary

**Regulation of fatty acid synthase in cancer**

- The regulation of fatty acid synthase (FASN) expression in cancer is complex. This may involve transcriptional control from growth factors or steroid hormones and post-translational control from elements such as deubiquitinating enzymes. Microenvironmental factors such as hypoxia may also exert a regulatory influence.

**FASN as a potential drug target in cancer therapy**

- Over the last 15 years, FASN has emerged as an attractive potential target for cancer therapy.
- Early small-molecule inhibitors of FASN include cerulenin, C75 and orlistat.
- The mode of action of these compounds is not entirely understood but may involve fatty acid depletion.
- Therapeutic use of these compounds has been limited due to their poor pharmacologic or pharmaceutical properties and to their effect on feeding behavior.
- Recently developed FASN inhibitors such as C93, FAS31, 3-aryl-4-hydroxyquinolin-2(1H)-one derivatives or bisamide derivatives reported herein may offer new opportunities to access FASN inhibitors with greater efficacy and reduced side effects.
- FASN overexpression has a role in drug resistance, which can be exploited therapeutically with FASN inhibitors.
- Novel sources of FASN inhibitors, such as green tea and dietary soy, make both dietary manipulation and chemoprevention potential alternative modes of therapy in the future.
- Obese patients whose tumors overexpress FASN may have the most to gain from FASN inhibition and could be ideal candidates for FASN trials as more tolerable compounds are made available.
Figure 1. Fatty acid biosynthesis in malignancy
Glucose is taken up into cells and is converted into pyruvate via anaerobic glycolysis. Pyruvate in turn is converted into citrate in the mitochondria via Krebs cycle to generate ATP. Excess citrate is metabolized to acetyl-CoA, which enters the lipogenesis pathway, ultimately leading to production of long-chain acyl-CoA.
ACACA: Acetyl co-enzyme A carboxylase; ACLY: ATP citrate lyase; ACS: Acyl co-enzyme A synthetase; CoA: Co-enzyme A; FASN: Fatty acid synthase; NADPH: Nicotinamide adenine dinucleotide phosphate.
Figure 2. Regulation of fatty acid synthase expression in malignancy
Once growth factor or steroid hormone receptors are activated by their corresponding ligand
this leads to downstream activation of the PI3K/AKT or MAPK pathways. Both
transduction pathways regulate FASN expression through modulation of expression of
SREBP-1c and FBI-1, which binds to regulatory elements in the FASN promoter.
FASN: Fatty acid synthase; FBI-1: Pokemon; GF: Growth factor; GFR: Growth factor
receptor; SR: Steroid Hormone receptor; SREBP-1c: Sterol regulatory element-binding
protein 1c.
Figure 3. Fatty acid synthase inhibitors
(A) Cerulenin. (B) C75. (C) Orlistat. (D) GSK837149A. (E) AstraZeneca bisamide scaffold. (F) Merck hydroxyquinolin-2(1H)-one scaffold. (G) Platensimycin. (H) Epigallocatechin gallate analog.