Clinical Cancer Research

Molecular Pathways: Fatty Acid Synthase

Suzanne F. Jones and Jeffrey R. Infante

Abstract

Therapies that target tumor metabolism represent a new horizon in anticancer therapies. In particular, cancer cells are dependent on the generation of lipids, which are essential for cell membrane synthesis, modification of proteins, and localization of many oncogenic signal transduction enzymes. Because fatty acids are the building blocks of these important lipids, fatty acid synthase (FASN) emerges as a unique oncologic target. FASN inhibitors are being studied preclinically and beginning to transition to first-in-human trials. Early generation FASN inhibitors have been studied preclinically but were limited by their pharmacologic properties and side-effect profiles. A new generation of molecules, including GSK2194069, JNJ-54302833, IPI-9119, and TVB-2640, are in development, but only TVB-2640 has moved into the clinic. FASN inhibition, either alone or in combination, holds promise as a novel therapeutic approach for patients with cancer. *Clin Cancer Res; 21(24); 5434–8. ©2015 AACR.*

Background

Introduction to lipid metabolism as a target in cancer

It has been long recognized that cancer cells rely heavily on aerobic glycolysis to fuel the high rate of DNA and protein synthesis needed for malignant cell growth, replication, and proliferation (1). Years ago, it was also demonstrated that tumor tissues require a surge in lipid metabolism to accommodate the increased requirement for synthesis of membranes, energy storage, and signaling functions (2, 3). Fatty acids are the major components of these highly important lipids and fatty acid synthase (FASN) is the lone lipogenic enzyme in humans able to synthesize these all important fatty acids *de novo*. Herein, we describe the potential therapeutic implications of inhibiting FASN in cancer patients.

Fatty acid synthase: an integrated target in tumor cell biology

As cancer cells fervently consume glucose, pyruvate is made via the glycolytic pathway. Pyruvate is subsequently fed into the Krebs cycle in the mitochondria to yield ATP (4). One of the by-products of this reaction is acetyl-coenzyme A (CoA); it together with malonyl-CoA becomes the substrates for FASN, which catalyzes the biosynthesis of the fatty acid palmitate in a nicotinamide adenine dinucleotide phosphate–reduced (NADPH)-dependent reaction. Palmitate can then either be conjugated to other proteins or converted to other fatty acids and complex lipids that are vital for (i) lipid synthesis and membrane structures, such as lipid rafts, (ii) protein modification and localization functions, and (iii) receptor localization and signaling of major oncogenic pathways such as the PI3K/AKT/mTOR pathway (Fig. 1).

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doi: 10.1158/1078-0432.CCR-15-0126

The biologic role and physiology of fatty acid synthase

Fatty acids are critical for energy metabolism and are the fundamental components of all cell membrane lipids (1). Interestingly, *de novo* biosynthesis is not the main way adult mammalian tissues fulfill their lipid needs. Free fatty acids (FFA) and lipoproteins are more commonly obtained from the diet via the blood circulation. Interestingly, germline knockout (KO) of *Fasn* is not tolerated with embryos dying preimplantation. Even haploidy, $Fasn^{+/-}$, mice experience a 70% loss of embryos and cannot support embryonic development (5). However, in later development most adult tissues have very little *Fasn* expressed, with the notable exceptions of lactating breast and cycling endometrium (6, 7).

Many adult mouse models show that *Fasn* can often be deleted from many tissues under normal conditions without significant consequence or sequalae. For instance, mice with a liver-specific KO of *Fasn* have only a mild decrease in cholesterol and liver palmitate and a 2-fold increase in liver malonyl-CoA (8). This likely explains why there is minimal phenotypic change from their wild-type counterparts when fed a regular diet. Conversely, if fed a zero-fat diet, then these KO liver mice develop hyperglycemia and, paradoxically, steatosis. Finally, these observed defects can be overcome by restoring normal diet or adding a PPARα agonist.

FASN and cancer

The first association of FASN expression with a malignancy was identified in breast cancer tumors in 1994, formerly described as the antigen OA-519 (9). Since that initial observation, overexpression of FASN has been detected in multiple tumor types, including pancreas, colorectal, ovarian, breast, and prostate cancer (10–15). Interestingly, in many of these reports higher levels of FASN correlate with increasing tumor burden, later stages of disease, and poor prognosis.

A few studies have tried to establish that forcing the expression of *Fasn* above normal levels can drive a malignant phenotype. In one example, *in vitro* ectopic overexpression of *Fasn* in breast cancer cells was shown to enhance lipogenesis along with increased cell growth and proliferation (16). Transgenic expression of *Fasn* in mice showed a significant increase in prostate epithelial neoplasia but this alone was not sufficient enough to result in invasive tumors. Further studies with immortalized

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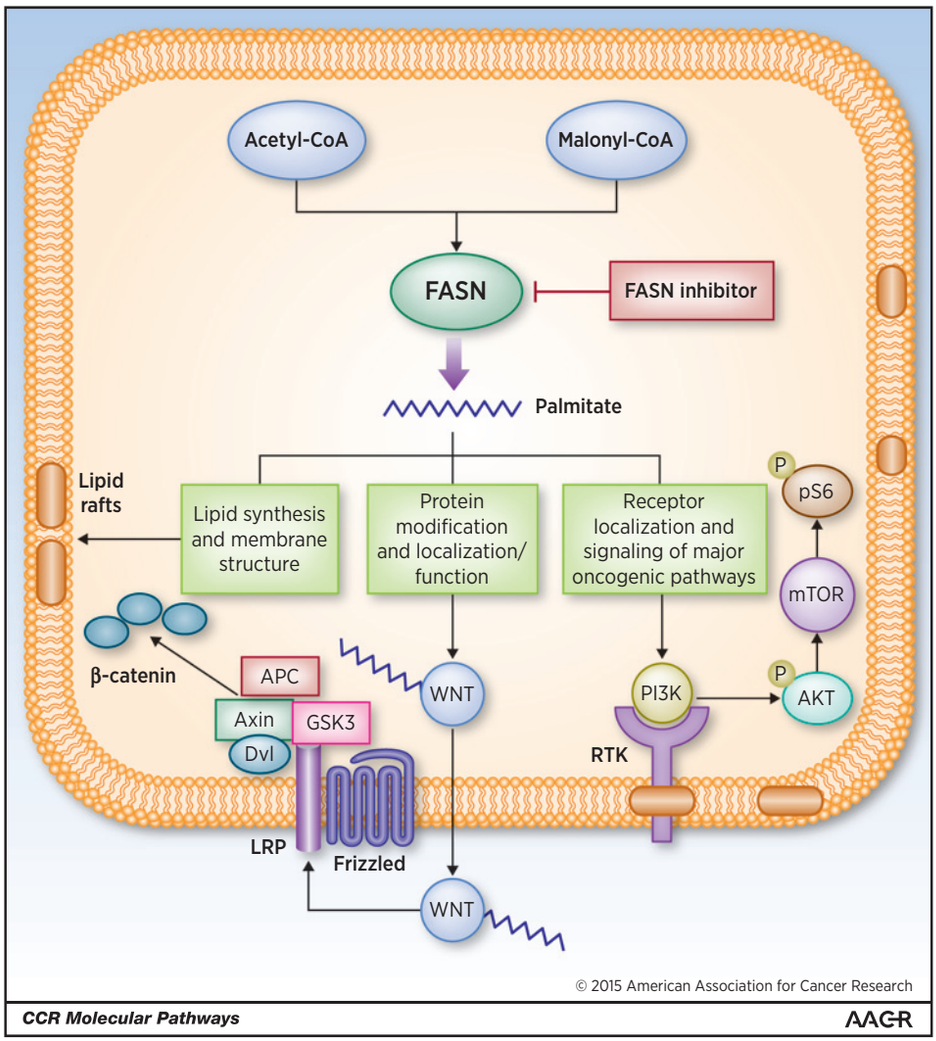

Figure 1.
FASN—integrated target in tumor cell biology. FASN catalyzes the synthesis of palmitate from acetyl-CoA and malonyl-CoA. Palmitate is then converted to other fatty acids/ complex lipids critical for lipid synthesis and membrane structures, protein modification and localization functions, and receptor localization and signaling of major oncogenic signaling pathways.

prostate epithelial cells (iPrEC) suggested that in addition to the *Fasn* expression, coexpression of androgen receptor was required for invasive adenocarcinoma (17). Though these studies do not establish FASN as a true oncogene, one can see the unique association between FASN expression and neoplasia.

Clinical–Translational Advances

Multiple FASN inhibitors are in development and under preclinical evaluation. Unfortunately, there are some limitations to interpreting the effects of FASN inhibition in the different disease models as the early generation of FASN inhibitors, such as cerulenin, C-75, and orlistat, are limited by significant off-target toxicity and tissue distribution. The majority of the evidence suggests FASN inhibition results in cancer cell death by multiple mechanisms, including altering membrane synthesis, protein modification, and interactions with other oncogenic signaling pathways.

Multiple studies support a primary mechanism of action associated with FASN inhibition to be a disruption in membrane synthesis. The current selective molecules in development allosterically inhibit the β-ketoacyl reductase activity of FASN. By blocking the enzymatic activity of FASN, cellular malonyl-CoA increases with a concomitant decrease in phospholipid production. *In vitro* these changes inhibit proliferation of cancer cell lines and alter both metabolic pathway metabolites and mRNA expression of metabolic genes (18). Both cerulenin and C-75 have been studied in liposarcoma models *in vitro*, and as expected the effects could be overcome by the addition of palmitate. siRNA specific for FASN in addition to C-75 resulted in tumor growth regression of 70% and 80%, respectively, in prostate xenograft models as compared with control (19). This tumor growth reduction was associated with a corresponding decrease in FASN expression evaluated by Western blot at the end of treatment ($P < 0.05$). Similarly RNAi expressing plasmids that inhibited FASN-decreased osteosarcoma cell invasion and metastasis *in vitro* (20).

In addition to disrupting lipid membrane synthesis, FASN inhibition can also affect modification of proteins by palmitoylation. This has been most well examined with the Wnt/β-catenin pathway. In one study of 862 cases of human prostate cancer, overexpression of FASN correlated with WNT-1 palmitoylation and stabilization of β-catenin ($P < 0.001$; ref. 21). The palmitate moiety on Wnt is critical for appropriate secretion from the cell and its ability to transduce activation signals to β-catenin

following binding to its cognate receptor. FASN inhibition not only can reduce this important posttranslation modification of these proteins, but also may have more specific effects on the activation of β-catenin alone. By disrupting the classical Wnt/β-catenin pathway, expression of important tumor survival proteins such as c-MYC can be significantly reduced (22).

As a third potential anticancer mechanism, FASN is known to regulate and integrate with other oncogenic signaling pathways, including protein kinase C (PKC), HER2, and the PI3K/AKT/mTOR pathways. In a recent study, investigators used lipidomic analyses to show that in certain tumor cell lines, the inhibition of FASN led to a reduction of specific diacylglycerols (DAG; ref. 23). As DAGs normally stimulate PKC; by reducing their levels, the activity of PKC was reduced ultimately leading to apoptosis of the cells. Conversely, in tumor cells that did not undergo apoptosis in response to FASN inhibition, there was no concomitant reduction in DAGs.

FASN has also been shown to stimulate the activity of HER2 receptor, possibly as a result of enabling assembly of multiprotein signaling complexes at discrete portions of the cellular membrane such as lipid rafts. Either through stimulation of a cellular receptor, such as HER2, or other mechanisms, FASN often increases signaling through the PI3K/AKT/mTOR axis. This becomes a self-amplifying pathway, increasing mTOR activity which in turn increases activity of the transcription factor SREBP-1, leading to an increase in FASN mRNA expression (24).

FASN inhibition in patients

Multiple FASN inhibitors, such as cerulenin, orlistat, C75, C93, and GSK837149A, have demonstrated preclinical antitumor activity in cancer cell lines and xenograft models (4, 25). None of these compounds have been tested in cancer patients due to limitations imparted by their pharmacologic properties or side-effect profiles that would limit their clinical development. A new generation of molecules such as GSK2194069 (26), JNJ-54302833 (27), IPI-9119 (28), and TVB-2640 (29) are in development, but only TVB-2640 has moved into the clinic.

TVB-2640 is the first oral, selective, potent, reversible FASN inhibitor tested clinically. Preliminary results from the first-in-man dose escalation trial demonstrated on-target, reversible skin (including peeling and palmar-plantar erythrodysesthesia) and ophthalmologic (including corneal edema, keratitis, and iritis) toxicities at the highest continuous oral doses administered (29). Pharmacodynamic biomarkers, such as increased serum concentrations of malonyl carnitine and decreased serum concentrations of TG 16:0 palmitate, indicate target engagement following TVB-2640 dosing (30). In this early, first-in-human trial prolonged stable disease has been seen with monotherapy. In addition, when TVB-2640 was given in combination with paclitaxel, a confirmed PR was observed in a patient with peritoneal serous carcinoma as well as prolonged stable disease in both non–small cell lung carcinoma (NSCLC) and breast cancer patients (31).

Future directions

Since the first FASN inhibitors just entered the clinic, there is a paucity of data to support proof of mechanism within tumor cells of patients. Novel biomarker strategies to assess level of FASN inhibition, cell signaling changes, and lipid proteomic alterations will be critical to accelerate the development of this class of drugs. Furthermore, studies enabling a clear patient selection strategy are at the earliest stages of discovery at this time. Without a genomic mutation or tumor-specific fusion protein driving the oncogenic properties inherent to FASN overexpression, as observed with BRAF, ALK, and EGFR (32–34), it remains a challenge to identify and match the best patients to these novel inhibitors. Alternatively, tumor heterogeneity, which remains the Achilles heel of the precision medicine era, may be less of an issue with metabolic agents that broadly affect lipid production.

Although efforts remain ongoing to identify the best monotherapy strategy, there is good rationale supporting a combination development strategy. FASN inhibition accentuates the activity of multiple different cytotoxic chemotherapies, particularly taxanes. Both docetaxel and paclitaxel synergize with FASN inhibitors *in vitro* (35, 36). In addition, a potent synergistic relationship with a combination of paclitaxel and a FASN inhibitor has been demonstrated in xenograft models of NSCLC as well as other tumor types (37). Indeed, the clinical trial of TVB-2640 (ClinicalTrials.gov: NCT02223247) is currently enrolling paclitaxel combination cohorts (29). Furthermore, the addition of a FASN inhibitor was able to restore sensitivity in a number of tumor models in which the cells had become resistant to another chemotherapeutic agent. FASN inhibition can resensitize *in vitro* hepatocellular carcinoma cells known to be taxane resistant (38). Similar results were obtained for cells that had become resistant to doxorubicin (39). These investigators demonstrated that a FASN inhibitor altered the lipid composition of the plasma membrane of these cells allowing doxorubicin to more easily traverse the membrane and regain its antitumor activity (25, 22). Blockade of FASN can also reverse resistance to trastuzumab and lapatinib in HER2-resistant cell lines (4, 40).

In summary, therapies that target tumor metabolism represent a new horizon in anticancer therapies. FASN inhibition represents one of the first strategies in this area, though other metabolism targets, including isocitrate dehydrogenase, glutaminase, and argininase, are already either being tested in patients or making their way toward the clinic (41–44). FASN is uniquely associated with cancer, and preclinical data provide evidence of antitumor activity. The identification of biomarkers to support proof of mechanism and potentially aid in patient selection remains an active area of investigation. FASN inhibition, either alone or in combination, holds promise as a novel therapeutic approach for patients with cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.R. Infante
Development of methodology: J.R. Infante
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.R. Infante
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.R. Infante
Writing, review, and/or revision of the manuscript: S.F. Jones, J.R. Infante
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.R. Infante

Acknowledgments

The authors thank George Kemble, PhD, and Merdad Parsey, MD, PhD, for help with the writing of this article. They also thank Laura DeBusk, PhD, for formatting and editing the article.

Received July 17, 2015; revised September 11, 2015; accepted October 15, 2015; published OnlineFirst October 30, 2015.

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