EBioMedicine 2 (2015) 778–779

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

A Fatty Acid Synthase Inhibitor Shows New Anticancer Mechanisms

Maria J. Bueno[a], Ramon Colomer[a,b,*]

[a] Breast Cancer Clinical Research Unit, Spanish National Cancer Research Center (CNIO), Madrid, Spain
[b] Medical Oncology Division, Hospital Universitario La Princesa, Madrid, Spain

The pharmacological modulation of proteins and molecules related to cancer is an important goal for translational science. Fatty acid synthase (FASN) is a complex dimeric protein that converts acetyl-CoA and malonyl-CoA into palmitic acid in a NADPH-dependent reaction in mammalian cells (Maier et al., 2006). Many cancers present a strong FASN expression and high enzymatic activity, and in recent years FASN has emerged as a relevant anticancer target. So far, several compounds have been reported to inhibit the enzymatic activity of FASN and to have an effect on the growth of malignant cells. Some of these compounds exhibit pharmacological limitations or induce weight loss, preventing their development as systemic drugs. In this issue of *EBioMedicine*, Ventura et al. report the characterization of the anti-tumor activity of TVB-3166, a potent and orally available FASN inhibitor that may provide a novel approach for cancer therapy (Ventura et al., 2015). The authors observed that FASN inhibition with TVB-3166 was able to induce apoptosis, to inhibit anchorage-independent cell growth under lipid-rich conditions, and to inhibit *in vivo* xenograft tumor growth in a dose-dependent manner without affecting non-cancer cells.

FASN plays a critical role in a number of metabolic functions by catalyzing the terminal steps in the synthesis of long-chain saturated fatty acids. There is a strong FASN expression and high enzymatic activity in many cancers especially in carcinomas (Sebastiani et al., 2006), while FASN is expressed at low levels in most normal tissues, except the liver, adipose tissue, and lactating mammary gland (Sul and Wang, 1998), suggesting that cancer cells are more dependent on *de novo* palmitate synthesis catalyzed by FASN than normal cells (Menendez and Lupu, 2007). Palmitate and palmitate-derived lipids are essential components in cancer cell proliferation and survival as they provide energy metabolism and storage, membrane biosynthesis, and architecture and protein localization and activity. The well-documented upregulation of FASN in many human cancers as well as its association with poor clinical outcome (Witkiewicz et al., 2008) both strengthen the hypothesis that FASN is involved in the development, maintenance, and enhancement of the malignant phenotype. Interestingly, increased FASN expression has also been observed in some pre-neoplastic lesions and increases with tumor progression, supporting the hypothesis that the early up-regulation of FASN in precursor lesions might represent an obligatory metabolic acquisition that provides growth and survival advantages through multiple mechanisms.

In the report by Ventura et al., the evidence for a role of FASN as a therapeutic target comes from both *in vitro* and *in vivo* models of human cancers. The authors found that pharmacological inhibition of FASN using TVB-3166 causes an increase in apoptosis in breast and prostate cancer cell lines. Interestingly, this response is not observed in non-cancer cells. These findings are consistent with previous reports that also used other FASN inhibitors (Brusselmans et al., 2003; Puig et al., 2009). The authors describe here unreported mechanisms of action including alteration on lipid raft architecture, palmitoylated protein localization disruption and inhibition of signal transduction through the PI3K-AKT-mTOR and ß-catenin pathways. The effect of TVB-3166 on lipid raft architecture was examined using immuno-fluorescent confocal microscopy to check palmitoylated protein localization. The data reveal that FASN inhibition disrupts lipid raft distribution in the membranes, altering the localization of raft-associated proteins such as N-Ras, inhibits multiple signal transduction pathways including PI3K-AKT-mTPOR and B-catenin, and modulating the expression of several genes in metabolic, proliferation and apoptosis pathways.

In addition to *in vitro* experiments, Ventura et al. also present important results using *in vivo* models. The authors show that FASN inhibition has anti-tumor activities in biologically diverse preclinical tumor models, including those expressing mutant K-Ras, ErbB2, c-Met, and PTEN. These results are globally in agreement with previous publication in which treatments with siRNA or chemical inhibitors of FASN have been shown to decrease tumor size in animal models of various types of cancers (De Schrijver et al., 2003; Puig et al, 2011). Finally, the authors performed both genetic and expression analyses and found that FASN inhibition modulates genes involved in lipid synthesis, signal transduction, cell cycle and apoptosis pathways. It may be very relevant for future development that those pathways were not affected in non-cancer cells.

In conclusion, the results from this report show the potency, selectivity, reversible mechanism of action and *in vivo* availability of the FASN inhibitor TVB-3166, differentiating it from earlier FASN inhibitors such as C75 or cerulenin. The authors found that TVB-3166 modulates lipid synthesis, signal transduction, cell cycle and apoptosis pathways in both *in vitro* cell culture and *in vivo* tumor xenograft models. These results represent an important step in discovering the multiple mechanisms of action of FASN and pave the way for the identification of biomarkers with potential utility as predictive factors.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.06.020.
* Corresponding author at: Medical Oncology Division, Hospital Universitario La Princesa, c/ Diego de Leon 62, planta 9, 28006 Madrid, Spain.

http://dx.doi.org/10.1016/j.ebiom.2015.08.023

Conflict of Interest Statement

The authors declare no conflict of interest.

References

Brusselmans, K., De Schrijver, E., Heyns, W., Verhoeven, G., Swinnen, J.V., 2003. Epigallocatechin-3-gallate is a potent natural inhibitor of fatty acid synthase in intact cells and selectively induces apoptosis in prostate cancer cells. Int. J. Cancer 106, 856–862.

De Schrijver, E., Brusselmans, K., Heyns, W., Verhoeven, G., Swinnen, J.V., 2003. RNA interference-mediated silencing of the fatty acid synthase gene attenuates growth and induces morphological changes and apoptosis of LNCaP prostate cancer cells. Cancer Res. 63, 3799–3804.

Maier, T., Jenni, S., Ban, N., 2006. Architecture of mammalian fatty acid synthase at 4.5 A resolution. Science 311, 1258–1262.

Menendez, J.A., Lupu, R., 2007. Fatty acid synthase and the lipogenic phenotype in cancer pathogenesis. Nat. Rev. Cancer 7, 763–777.

Puig, T., Turrado, C., Benhamu, B., Aguilar, H., Relat, J., Ortega-Gutierrez, S., Casals, G., Marrero, P.F., Urruticoechea, A., Haro, D., et al., 2009. Novel inhibitors of fatty acid synthase with anticancer activity. Clin. Cancer Res. 15, 7608–7615.

Puig, T., Aguilar, H., Cufí, S., Oliveras, G., Turrado, C., Ortega-Gutiérrez, S., Benhamú, B., López-Rodríguez, M.L., Urruticoechea, A., Colomer, R., 2011. A novel inhibitor of fatty acid synthase shows activity against HER2 + breast cancer xenografts and is active in anti-HER2 drug-resistant cell lines. Breast Cancer Res. 13 (6), R131.

Sebastiani, V., Botti, C., Di Tondo, U., Visca, P., Pizzuti, L., Santeusanio, G., Alo, P.L., 2006. Tissue microarray analysis of FAS, Bcl-2, Bcl-x, ER, PgR, Hsp60, p53 and Her2-neu in breast carcinoma. Anticancer Res. 26, 2983–2987.

Sul, H.S., Wang, D., 1998. Nutritional and hormonal regulation of enzymes in fat synthesis: studies of fatty acid synthase and mitochondrial glycerol-3-phosphate acyltransferase gene transcription. Annu. Rev. Nutr. 18, 331–351.

Ventura, R., Mordec, K., Waszczuk, J., Wang, Z., Lai, J., Fridlib, M., Johnson, R., Hu, L., Buckley, D., Kemble, G., Heuer, T.S., 2015. Inhibition of de novo palmitate synthesis by fatty acid synthase induces apoptosis in tumor cells by remodeling cell membranes, inhibiting signaling pathways, and reprogramming. Gene Expr. (EBIOM-D-15-00026R2).

Witkiewicz, A.K., Nguyen, K.H., Dasgupta, A., Kennedy, E.P., Yeo, C.J., Lisanti, M.P., Brody, J.R., 2008. Co-expression of fatty acid synthase and caveolin-1 in pancreatic ductal adenocarcinoma: implications for tumor progression and clinical outcome. Cell Cycle 7, 3021–3025.