Pharmacological inhibitors of Fatty Acid Synthase (FASN)--catalyzed endogenous fatty acid biogenesis: a new family of anti-cancer agents?


Source

Department of Medicine, Evanston Northwestern Healthcare Research Institute, Evanston, IL 60201, USA. r-lupu@northwestern.edu

Abstract

The expression and activity of Fatty Acid Synthase (FASN; the sole enzyme capable of the reductive de novo synthesis of long-chain fatty acids from acetyl-CoA, malonyl-CoA, and nicotinamide adenine dinucleotide phosphate -NADPH-) is extremely low in nearly all nonmalignant adult tissues, whereas it is significantly up-regulated or activated in many cancer types, thus creating the potential for a large therapeutic index. Since the pioneering observation that inhibition of FASN activity by the mycotoxin cerulenin preferentially kills cancer cells and retards the growth of tumors in xenografts models, numerous in vitro and in vivo studies have confirmed the potential of FASN as a target for antineoplastic intervention. Other FASN inhibitors such as the cerulenin derivative C75, the beta-lactone orlistat, the green tea polyphenol epigallocatechin-3-gallate (EGCG) and other naturally occurring flavonoids (i.e., luteolin, quercetin, and kaempferol), as well as the antibiotic triclosan, have been identified and have been shown to limit cancer cell growth by inducing apoptotic cell death. Though the exact mode of action of these FASN inhibitors is under discussion, it has been revealed that depletion of end-product fatty acids, toxic intracellular accumulation of supra-physiological concentrations of the FASN substrate malonyl-CoA and/or limited membrane synthesis and/or functioning by altered production of phospholipids partitioning into detergent-resistant membrane microdomains (lipid raft-aggregates), can explain, at least in part, the cytostatic, cytotoxic as well as the apoptotic effects occurring upon pharmacological inhibition of FASN activity in cancer cells. Moreover, several cancer-associated molecular features including nonfunctioning p53, overexpression of the Her-2/neu (erbB-2) oncogene, and hyperactivation of the PI-3'K down-stream effector protein kinase B (AKT), appear to determine an exacerbated sensitivity to FASN inhibition-induced cancer cell death. Although few of these inhibitors are expected to be "exclusively" selective for FASN, the potential of FASN as a target for antineoplastic intervention has eventually been confirmed by RNA interference (RNAi)-knockdown of FASN. Certainly, future studies should definitely
elucidate the ultimate biochemical link between FASN inhibition and cancer cell death. Although the combination of FASN structural complexity and until recently the lack of X-ray crystallography data of mammalian FASN created a significant challenge in the exploitation of FASN as a valuable target for drug development, it is hoped that the improvement in the selectivity and potency of forthcoming novel FASN-targeted small molecule inhibitors by taking advantage, for instance, of the recent 4.5 Å resolution X-ray crystallographic map of mammalian FASN, will direct the foundation of a new family of chemotherapeutic agents in cancer history.

PMID:17168665