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Fatty Acid Synthase: A Metabolic Oncogene in Prostate Cancer?

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Abstract In 1920, Warburg suggested that tumors consistently rely on anaerobic pathways to convert glucose to ATP even in the presence of abundant oxygen [Warberg, 1956] despite the fact that it is less efficient for energy supply than aerobic glycolysis. The reasons for this remain obscure to date. More often than not, the microenvironment of solid tumors contains regions of poor oxygenation and high acidity. In this context hypoxia can act in an epigenetic fashion, inducing changes in gene expression and in metabolism for survival. It is reasonable to assume that only the tumor cells capable of developing an unusual tolerance to limiting oxygen availability and to the acidosis resulting from excessive lactate production, can survive. In addition to the striking changes that occur in glucose metabolism, studies in human cancer patients suggest that there is often also an increase in free fatty acid turnover, oxidation and clearance [Legaspi et al., 1987; Hyltander et al., 1991]. For instance, a lipid mobilizing factor produced by tumor cells appears to be responsible for the increase in whole body fatty acid oxidation [Russell and Tisdale, 2002]. Fatty acids synthesis in tumor tissues also occurs at very high rates, as first demonstrated more than half a century ago [Medes et al., 1953]. Importantly, ^{14}C glucose studies have shown that in tumor cells almost all fatty acids derive from de novo synthesis despite adequate nutritional supply [Sabine and Abraham, 1967; Ookhtens et al., 1984; Weiss et al., 1986]. In addition, tumors overexpressing fatty acid synthase (FAS), the enzyme responsible for de novo synthesis of fatty acids, display aggressive biologic behavior compared to those tumors with normal FAS levels, suggesting that FAS overexpression confers a selective growth advantage. Here, we will review the roles that FAS plays in important cellular processes such as apoptosis and proliferation. In addition, speculations on the putative role of FAS in the altered metabolic pathways of prostate cancer cells will be explored. Because of the frequent overexpression of this enzyme prostate cancer, FAS constitutes a therapeutic target in this disease. J. Cell. Biochem. 91: 47–53, 2004.

Key words: fatty acid synthase; prostate cancer; metabolism

BRIEF BIOCHEMICAL NOTIONS OF LIPID METABOLISM AND FATTY ACID SYNTHESIS

Fatty acid synthase (FAS) is a 250–270 kDa cytosolic protein that functions as a homodimer. In addition, a second gene, located on a different chromosome, encodes a mitochondrial FAS which transfers exclusively malonyl moieties to the mitochondrial holo-acyl carrier proteins [Zhang et al., 2003]. This enzyme may thus play an important role in mitochondrial function, particularly as it relates to apoptosis. FAS, which catalyzes the synthesis of palmitate from the condensation of malonyl-CoA and acetyl-CoA, also plays an important role in energy homeostasis by converting excess carbon intake into fatty acids for storage. When necessary, these provide energy via β-oxidation [Kuhajda, 2000]. Since diet supplies most fatty acids, endogenous synthesis is minimal. Consequently, FAS is expressed at low to undetectable levels in most normal human tissues. In contrast, FAS is overexpressed in a large number of human cancers despite high levels of ambient fatty acids.

Antonella Baron and Toshiro Migita contributed equally to this work.

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For all these reasons, FAS has recently been the subject of intense scrutiny, particularly because of the selective tumor cells cytotoxicity that results from FAS targeting [Pizer et al., 1996a,b].

FAS EXPRESSION IN PROSTATE CANCER

Despite its apparently marginal physiologic role under normal conditions, FAS is overexpressed at both protein and mRNA level in prostate carcinoma [Epstein et al., 1995; Shurbaji et al., 1996; Swinnen et al., 2000; Bull et al., 2001; Dhanasekaran et al., 2001; Welsh et al., 2001; Swinnen et al., 2002; Rossi et al., 2003]. Its high expression has also been associated with aggressive biologic behavior [Epstein et al., 1995]. Interestingly, the highest levels of FAS expression are found in androgen-independent (AI) bone metastases [Rossi et al., 2003].

FAS REGULATION

Androgen-dependent transcriptional FAS regulation through steroid regulatory element binding proteins (SREBPs) has been established in prostate cancer cell lines [Swinnen et al., 1997; Swinnen et al., 2000; Heemers et al., 2001; Yang et al., 2002]. However, FAS overexpression has been demonstrated in the AI setting as well [Myers et al., 2001; Pizer et al., 2001]. We have recently demonstrated a strong correlation between the expression of FAS and that of its transcriptional regulator SREBP-1 in both primary and metastatic, AI human tumors analyzed by oligonucleotide arrays [Rossi et al., 2003]. The increase in FAS expression in AI prostate cancers metastatic to bone, taken together with concomitant SREBP overexpression in the same cases, suggests an AI but androgen receptor-dependent transcriptional mechanism for the induction of FAS overexpression in this setting. Previous studies in animal models also demonstrate that FAS is overexpressed in AI tumors. In the CWR22 model of prostatic adenocarcinoma, FAS protein expression, tumor size and proliferation rate were decreased after castration and returned to normal with androgen replenishment [Myers et al., 2001]. Importantly however, tumors in castrated mice, which relapsed after a long latency, displayed high levels of FAS protein. Since growth inhibition by FAS inhibitors has been achieved in some AI prostatic cancer xenografts [Pizer et al., 2001], FAS may be an attractive drug target in both androgen-dependent and independent disease.

Interestingly, in a subset of prostate cancer cases, FAS mRNA and protein levels are discordant, suggesting non-transcriptional regulation of this enzyme as well [Rossi et al., 2003]. In addition, it has been shown that FAS is regulated by the ubiquitin-proteasome pathway in yeast [Egner et al., 1993] and our data suggest that this may be the case in mammalian cells as well [Graner et al., unpublished observations].

FAS OVEREXPRESSION MAY AFFECT SIGNAL TRANSDUCTION PATHWAYS BY ALTERING MEMBRANE PHOSPHOLIPID COMPOSITION

Many functional properties of cellular membranes are influenced by the relative fatty acids composition within phospholipids. FAS has been shown to play a major role in the synthesis of phospholipids partitioning into detergent-resistant membrane microdomains [Swinnen et al., 2003]. These are raft-aggregates implicated in key cellular processes including signal transduction, intracellular trafficking, cell polarization, and cell migration. In addition, the products of FAS myristate and palmitate are involved in the myristoylation and palmitoylation of cellular and viral proteins for membrane targeting [Chirala et al., 2003]. It is easy to predict then, that alterations in membrane lipid composition that may occur as a result of FAS overexpression can have profound effects on many cellular processes such as signal transduction pathways.

Activation of the phosphatidylinositol 3′-kinase (PI3K) pathway occurs in the late phases of human prostate cancers [McMenamin et al., 1999]. In turn, PI3K activation increases FAS transcription at least in part through the activation of SREBPs in prostate cancer cell lines [Van de Sande et al., 2002]. Importantly, in breast epithelial cells, Her-2-neu stimulates the FAS promoter through a PI3K-dependent pathway and mediates increased fatty acid synthesis, while pharmacological inhibition of FAS preferentially induced apoptosis of HER2-overexpressing breast epithelial cells [Kumar-Sinha et al., 2003]. Forced expression of Her-2-neu in androgen-dependent prostate cancer cells activates the androgen receptor and confers AI growth to these cells [Craft et al., 1999]. We had previously determined that the expression

of Her-2-neu in prostate cancer increases with progression towards androgen independence [Signoretti et al., 2000] being highest, as is the case for FAS, in prostate cancer metastatic to bone. Thus, the oncogenic effects of PI3K activation may be mediated, at least in part, via the induction of FAS expression. Furthermore, it is known that insulin up-regulates FAS and fatty acid synthesis in normal liver [Paulauskis and Sul, 1989]. Insulin-like growth factor, known to be up-regulated in blood plasma of patients at risk of prostate cancer [Chan et al., 2002], may be responsible for the activation of the PI3K pathway and in turn, for the induction of FAS.

FAS AND TUMOR CELL PROLIFERATION

It is possible that the synthesis of fatty acids is required for the biogenesis of cellular membranes in rapidly dividing tumor cells. Very long chain fatty acids, generated from the stearate and palmitate precursors (in turn generated by FAS) are required for cell division [Hannun and Obeid, 2002]. FAS inhibition has been shown to decrease DNA synthesis and not to allow cells to progress into S-phase [Pizer et al., 1998]. It has thus been proposed that the link between FAS and DNA replication may be a result of the need for de novo synthesis of membrane phospholipids necessary when cells divide. In fact, Apolipoprotein E, which is a major regulator of phospholipid metabolism, is up-regulated in the group of tumors with high FAS protein [Lomnitski et al., 1999; Igbavboa et al., 2002; Rossi et al., 2003], while estrogens down-regulate serum levels of Apolipoprotein E in prostate cancer patients [Usui et al., 2002]. Thus, the abundance of fatty acids in cancers overexpressing FAS may affect proliferation either by providing a larger pool of available substrates for membrane synthesis during cell division or by affecting membranous second messengers in pathways critical to cell replication.

FAS AND APOPTOSIS

FAS inhibitors, such as C75 and the mycotoxin cerulenin, as well as RNA interference of FAS message, result in apoptosis of cancer cells [Kuhajda, 2000; De Schrijver et al., 2003] and decrease the size of prostate cancer xenographs that overexpress the enzyme [Pizer et al., 2001]. Thus, FAS overexpression is likely not just associated with the dysregulation of the lipogenic pathways in cancer cells, but plays an important role in survival as well. The means by which FAS inhibition leads to apoptosis is still not clear although several mechanisms have been invoked. Malonyl-CoA, which accumulates after treatment with cerulenin or C75, may mediate, at least in part, the cytotoxicity resulting from FAS inhibition [Pizer et al., 2000; De Schrijver et al., 2003]. FAS-mediated cytotoxicity may also be metabolic in origin, through the inhibition of fatty acid β-oxidation [Thupari et al., 2001]. Finally, cellular damage may result from the direct activation of apoptotic pathways. In fact, FAS inhibition results in the release of cytochrome c, caspase activation and apoptosis without affecting mitochondrial membrane permeabilization [Heiligtag et al., 2002].

Pro-apoptotic genes such as tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) were found overexpressed by gene expression profiling in tumors with low FAS protein level [Rossi et al., 2003]. TRAIL, whose transcripts have been previously detected in human prostate [Nesterov et al., 2002; Deeb et al., 2003], is capable of inducing apoptosis through the caspase cascade in a variety of cancer cells in vitro, including prostate AI cancer cell lines [Ng et al., 2002] and prostate normal epithelial cells [Secker-Walker et al., 1998; Vizirianakis et al., 1999; Ayton et al., 2001].

The decision between apoptosis and growth arrest after FAS inhibition may be influenced by p53 function. In fact, the perturbation of fatty acid synthesis belongs to the list of metabolic stress responses regulated by p53 [Li et al., 2001]. However, Heiligtag et al. [2002] have shown that the apoptotic response to cerulenin is mediated both by the overexpression of the pro-apoptotic Bax, which occurs in a p53-independent manner despite its purported p53-regulated transcription, and by a rapid mitochondrial release of cytochrome c in both p53 wild-type and mutant lines. In turn, release of cytochrome c in the cytosol results in the activation of caspases 3 and 9 [Heiligtag et al., 2002].

The fact that FAS overexpression protects cancer cells from apoptosis is thus well established. Whether this is purely an effect on the mitochondrial apoptotic pathway or a metabolic effect however, remains to be elucidated. Interestingly, links between apoptosis and meta-

bolic pathways are beginning to emerge. The survival effect of activated Akt is dependent on the availability of glucose [Downward, 2003]. Importantly, Danial et al. [2003] have shown that the pro-apoptotic protein BAD is complexed in the mitochondria with glucokinase. They also demonstrate interdependence of glucose metabolism and apoptotic pathways. Akin to FAS, glucokinase is an enzyme that functions principally in the liver to drive glycogen synthesis.

How FAS, when overexpressed, prevents apoptosis in cancer cells remains a poorly understood phenomenon. It will be of paramount importance to unveil putative links between lipid metabolic or catabolic pathways and mitochondrial function as it relates to apoptosis.

IS FAS OVERXPRESSION AN INDICATION OF ALTERED CANCER CELL METABOLISM?

With the discovery and the confirmation of the altered expression of FAS in different types of tumors, the de novo synthesis of fatty acid appears to be an important process required by many transformed cells for growth and survival. Is it then possible that the most important role played by FAS is indeed the synthesis of fatty acids for energy while the effects on proliferation and apoptosis lie downstream of altered metabolic pathways?

Data supporting a metabolic role of FAS include epidemiologic findings and direct measurements of fatty acid metabolism in tumor patients. Dietary fatty acids in humans appear to be risk factors for prostate cancer, even adjusting for energy intake [Giovannucci et al., 1993]. In addition, studies in human cancer patients suggest that there is often an increase in free fatty acid turnover, oxidation, and clearance [Legaspi et al., 1987; Hyltander et al., 1991]. Recently, α-methylacyl CoA racemase (AMACR), an enzyme that converts fatty acids to (S)isomers prior to β-oxidation [Jiang et al., 2001; Luo et al., 2002; Rubin et al., 2002], was found to be expressed at high levels in most prostate cancer but not in non-transformed prostate epithelium. This is also indicative of an enhanced β-oxidative pathway in tumors. β-oxidation of fatty acids generates hydrogen peroxide, a potential source of oxidative damage [Tamatani et al., 1999; Wanders et al., 2001] suggesting a role in prostate cancer initiation by de-regulated catabolism of fatty acids.

The paradox to be resolved in order to embrace the catabolic theory for FAS overexpression in prostate cancer, i.e., the enhanced synthesis of fatty acids and their subsequent breakdown by β-oxidation, is that the simultaneous synthesis and breakdown of fatty acids as an energy source appears to be a futile, if not a wasteful cycle. However, bearing in mind the predominantly anaerobic glycolysis that occurs in cancer cells, it is possible that acetyl-CoA forms in excess from surplus lactate and pyruvate, and that the synthesis of fatty acids by mitochondria is enhanced. This would accomplish both a reduction in lactic acidosis and the storage of fatty acids to be utilized as energy source, as needed.

An alternative and extremely attractive theory to explain FAS overexpression in prostate cancer has been put forth by Hochachka et al. [2002]. They compared the defense mechanisms developed by lower animals with unusual tolerance to limiting oxygen availability, to those utilized by prostate cancer cells. In both instances, excessive lactate is produced by anaerobic glycolysis. This, in turn, limits the respiratory chain and results in limited oxidizing power. Interestingly, both lower animals tolerant to hypoxia and prostate cancer cells favor synthesis and chain elongation of fatty acids because they supply oxidizing power for key oxidative steps. Thus, overexpression and enhanced activity of FAS would result in a significant improvement in redox balance despite hypoxic conditions.

MODELS AND TECHNIQUES TO EXPLORE THE ROLE OF FAS IN PROSTATE CANCER

The hypotheses outlined above need to be explored and thoroughly investigated. Techniques such as gas chromatography–mass spectrometry, resonant electron capture mass spectrometry, and electrospray HPLC can be adopted today to refine the classical and mostly abandoned investigation of lipid metabolism in tumors [Kasumov et al., 2002; McCue et al., 2002]. Deuterized precursor of fatty acid may be utilized using resonant electron capture mass spectrometry [Lin and Salem, 2002; Voinov et al., 2002] to trace the fate of fatty acids synthesized by FAS in human prostate cancer cells and in animal models of prostate cancer such as the TRAMP and MPAKT models [Kaplan-Lefko et al., 2003; Majumder et al.,

2003]. Pflug et al. [2003] have shown that FAS overexpression plays an important role in prostate tumorigenesis in the TRAMP model. In addition, FAS inhibition resulted in both a decrease in FAS enzymatic activity and cell death. Metabolic profiling of these experimental tumors as well as in human prostate cancers may prove invaluable for the definition of the role FAS plays in prostate cancer cell survival.

CONCLUSIONS

In the age of gene expression profiling and proteomics, a dimension too often ignored has been the metabolism of tumors. It is clear that lipid metabolism is altered in prostate cancer and that interfering with FAS has detrimental effects on prostate tumor cell survival. However, the precise biochemical pathways linking apoptosis, proliferation with fatty acid synthesis, and breakdown are yet to be elucidated. We speculate that utilizing novel, powerful techniques to study lipid metabolism in cancer cell lines and animal models of prostate cancer will give us important insights into connections between metabolism and these key cellular processes. Metabolic profiling of tumors will be an invaluable adjunct to gene expression profiling or proteomics in the characterization of prostate cancer.

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