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Review

A Significant Role of Lipogenic Enzymes in Colorectal Cancer

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Abstract. *In this review, we summarize recent progress regarding the study of the main enzymes of lipid metabolism involved in colorectal cancer development, namely of a) farnesyltransferase (Ftase), a cytosolic enzyme that catalyzes the first step in the protein farnesylation; b) farnesyl diphosphate synthase (FPPS, which yields FPP, a substrate for Ftase; c) fatty acid synthase (FAS), an enzyme required for the conversion of acetyl-CoA and malonyl-CoA to palmitate; and d) lipoprotein lipase (LPL), the crucial enzyme for intravascular catabolism of triglyceride-rich lipoproteins. Alterations in the levels of these enzymes may contribute to a cell growth advantage acquired during the carcinogenic process and to the development of malignancy. We have demonstrated an elevated Ftase activity in human colorectal cancer (CRC), with differences in Ftase activity related to histological grading, tumor location and KRAS mutation status. Moreover, the first evidence of FPPS activity in human CRC was demonstrated by our study, where a higher FPPS activity and mRNA expression was present in cancer rather than in normal mucosa. We also detected a hyperactivation of FAS in colon cancer, related to tumor location, sex and, p53 mutation status. Our data reinforce the role of lipid metabolism in the regulation of cellular metabolic processes and in carcinogenesis. Moreover, our findings suggest that biological factors including sex, gene mutation status, as well as the stratification of patients with colorectal cancer into right- and left-sided subsets may be important in patient selection for targeted therapies. Our studies in vitro demonstrated that FAS might also be a molecular target for the antiproliferative activity of olive oil polyphenols in a metabolically defined subset of patients with colon cancer. Moreover, we detected that the serum levels of FAS in patients with colorectal cancer are associated with tumor stage. Recently, we found a significant reduction in the levels of FAS and another lipogenic enzyme, LPL, in adipose tissue adjacent to tumor lesions, compared to the levels of FAS detected in paired tissue distant from neoplasia in patients with colorectal cancer. The study of metabolic changes in lipogenic enzyme pathways, as well as the determination of the distribution of individual roles within each biochemical pathway provide a rationale for selecting a particular reaction step suitable for therapeutic intervention.*

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Colorectal cancer (CRC) may involve different genetic pathways or different combinations of genetic and biochemical alterations during tumorigenesis (1, 2). An important feature of malignant transformation is the loss of the cholesterol feedback inhibition mechanism that regulates cholesterol synthesis (3). Alterations in biosynthetic processes of the cholesterol pathway and in the levels of enzyme products participating in this biochemical system may contribute to the cell growth advantage acquired during carcinogenesis and to the development of malignancy (4). Several Hydroxy-Methyl-Glutaryl-Coenzyme A (HMGCoA) metabolites, such as farnesyl pyrophosphate (FPP) and geranyl pyrophosphate (GPP) are implicated in oncogene activation and tumorigenesis (4) while the production of isoprenoid intermediates has been found intrinsically enhanced in rapidly proliferating cells (5).

Farnesyltransferase

FPP, serving as a precursor for lipid end-products, is a substrate for protein isoprenylation by farnesyltransferase (Ftase), a cytosolic enzyme that catalyzes the first step of the post-translational modification, "farnesylation" of a number of cellular polypeptides, including RAS (6), the nuclear intermediate filament proteins lamin B (7) and

prelamin A (8), the centromere proteins CENP-E and CENP-F (9), protein tyrosine phosphatases PRL-1, -2 and -3 (10), cyclic GMP phosphodiesterase alpha (11) and others (12-14). Ftase is a heterodimer of α and β subunits. The α subunit appears to be the carrier of its substrate FPP, while the β subunit binds to RAS protein. Ftase has attracted attention because of its role in the processing of RAS proteins, which function as molecular switches linking receptor and non-receptor tyrosine kinase activation to downstream cytoplasmic and nuclear events. Given the role these proteins play in pathways regulating cell survival, proliferation, differentiation and cytoskeletal organization, it seems likely that their altered expression may manifest a markedly abnormal function.

Oncogenic RAS mutations have been identified in ~30% of various human cancers, including CRC, (15). Since the maturation of RAS proteins was originally reported to be dependent on farnesylation (16), Ftase activity inhibition was envisioned as a strategy for interfering with RAS-mediated cell transformation (17-19), although it is now clear that there might also be additional targets (20, 21). The interest in the study of Ftase in tumor growth has been also reinforced by recent experimental observations. Khan *et al*. observed enhanced Ftase activity and mRNA expression in human skin basal carcinoma compared with normal tissue (22); Tanimoto *et al*. found that *Ftase β-subunit* mRNA overexpression in ovarian carcinoma is associated with the *KRAS* mutation (23).

Our study showed an increased Ftase activity in human CRC, showing differences in Ftase activity in relation to histological grading, tumor location and *KRAS* mutation status (24). These findings confirm that Ftase activity may be correlated with more aggressive tumor behavior. Likely, the transformed colonic cells acquire a growth advantage over the non-transformed cells, because the former are capable of utilizing isoprenoid compounds, such as farnesyl, for other important pathways that diverge from the main cholesterogenic route (the *flux diversion hypothesis*) (25).

Therapeutic strategies targeted to the enzymatic activities of the mevalonate pathway are in clinical evaluation. The Ftase inhibitors (FTIs) are currently being investigated in phase I and phase II clinical trials for several solid tumors, including CRC (26-28).

Farnesyl Diphosphate Synthase

FPP is yielded by farnesyl diphosphate synthase (FPPS), which is the pharmacological target of nitrogen-containing biphosphonates, such as alendronate, and pamidronate, potent inhibitors of bone resorption (29). Recent data suggest that, besides inhibiting osteoclast activity, biphosphonate may also have an anticancer action by a pro-apototic and antiproliferative effect on tumor cells (30-32). These effects of biphosphonates have been attributed to different biochemical mechanisms (33), but the most important seems to be the inhibition of FPPS activity (34). This inhibition blocks the biosynthesis of cholesterol with changes in the signaling events which lead to the induction of the caspase cascade and apoptosis (35).

Our previous study provided the first evidence of FPPS activity in human CRC (36). A higher FPPS activity and higher mRNA expression levels has been found in cancer than in normal mucosa. This observation is in agreement with a recent study of Sung *et al*. (37) who detected overexpression of the *FPPS* gene in human hepatocellular carcinoma (HCC), as well as an upregulation of the FPPS protein in about 85% of HCC cases examined. An elevated FPPS expression has been also observed in rat prostate tumor cell lines (38). FPPS seems to be regulated by androgens in rat prostatic cells, suggesting that it likely plays a significant role in androgen action and prostate cancer progression. Furthermore, the demonstration of increased FPPS activity and of an overexpression of its mRNA in CRC, not only clarifies our understanding of colon tumorigenesis, but also contributes to the development of therapeutic targets. In this study, we also investigated the effects of pamidronate on cell growth and apoptosis in a human colon cancer cell line. Cell proliferation inhibition by pamidronate on DLD-1 cells underlines the involvement of FPPS in cell growth and proliferation. The antiproliferative effect of pamidronate observed in this cell line may occur *via* the apoptotic pathway, as the exposure of DLD-1 cells to pamidronate promoted apoptosis. Apoptosis, or programmed cell death, and cell proliferation act concurrently in cancer cells, and often the balance between the two processes determines the net tumor growth rate. In our experiments, the inhibition of cell growth and the apoptotic effects exerted by pamidronate appear to be due to inhibition of FPPS, reinforcing the role of isoprenoids in the regulation of cellular metabolic processes.

Fatty Acid Synthase

Another enzyme known to play an important role in the growth and pathogenesis of colon carcinoma is fatty acid synthase (FAS), a multi-enzyme protein containing domains for acyl-carrier peptide and the seven different catalytic activities required for the conversion of acetyl-CoA and malonyl-CoA to palmitate (39). The expression of FAS is linked to specific functions, such as *de novo* biosynthesis of fatty acids, the conversion and storage of energy in the liver and in the adipose tissue (40), while FAS expression is possibly involved in the regulation of food intake (39, 41). Rapidly proliferating cells and tissues, including proliferative endometrium and some fetal tissues, have high levels of FAS expression (42, 43), which likely support membrane synthesis (44). In most normal human tissuesa, however, FAS is generally expressed at low levels because cells

preferentially use circulating dietary fatty acids for the synthesis of new structural lipids (40). High levels of FAS expression have been found in many types of human cancers, including cancer of the breast, prostate, colon, ovary, thyroid and endometrium (45, 46). In breast epithelial cells, the malignant transformation leads to the up-regulation of FAS and high levels of FAS are associated with poor clinical outcome (47), suggesting a relationship between FAS expression and tumor aggressiveness (48). Several studies have shown that FAS inhibitors suppress mammary carcinogenesis, suggesting that FAS is a promising molecular target for breast cancer chemoprevention (49, 50). FAS is overexpressed at both protein and mRNA levels in prostate carcinoma and its high expression has also been associated with aggressive biological behaviour of tumors (46). Biochemical studies of FAS activity and fatty acid synthesis in colon cancer cells have shown that its levels of expression correlates with the overall activity of the fatty acid synthetic pathway (45, 51, 52).

Our recent study has demonstrated increased FAS activity in colorectal tumors compared with the adjacent normal tissue (53). Our data are in accordance with those of Rhashid *et al*. (39), who demonstrated elevated levels of FAS activity in colorectal neoplasia as compared to adjacent normal mucosa in six surgical specimens of colon. In addition, in our study, we demonstrated that colon tumors on the left side had higher FAS activity than tumors located on the right. A biological difference between proximal and distal colon tumors has also been observed in regard other enzymes, growth factors and multiple genetic alterations (54, 55), underlining the regional biochemical variability of colon neoplastic transformation.

Hyperactivation of FAS seems also to be related to sex in our study. Tumors from male patients had higher levels of FAS activity than tumors from females, suggesting an androgen imprint on FAS activity regulation in cancer tissue from male patients. Sex steroid hormones and growth factors have been demonstrated to up-regulate FAS through SREBPs, which stimulate FAS transcription (46). Several investigations have demonstrated that FAS expression is markedly stimulated by androgens in human prostate cancer cell lines (38) and that an activated androgen signaling pathway in prostate cancer cells contributes to the up-regulation of FAS expression (56, 57). Our findings support the idea that FAS may also be an androgen-regulated enzyme in CRC.

A different behaviour with respect to protein activity was observed for *FAS* mRNA levels of carcinomas when compared to normal adjacent mucosa: higher *FAS* mRNA levels were found in normal colonic tissue compared to cancer tissue. It is possible that the mRNA of the *FAS* gene has an accelerated turnover and degradation in neoplastic compared with normal tissue, or that mRNA modifications in tumor tissue occur at post-transcriptional level.

Recently, important roles for p53 have been recognized in the cellular responses to a variety of metabolic stresses, including hypoxia, acidosis and perturbations of protein synthesis (58). It seems that perturbation of fatty acid synthesis also belongs to the list of metabolic stresses regulated by p53. Changes in FAS activity in colorectal tumors may be modulated by p53, since we have found lower levels of FAS activity in patients carrying the *p53* mutation, even if the difference was not statistically significant. Accumulation of the p53 protein, subsequent to the *p53* gene mutation has been demonstrated to increase the sensitivity of tumor cells to FAS inhibitors (58). The relatively higher FAS activity in tumors with intact p53 function suggests that the p53 protein may be involved in the regulation of FAS in human CRC. Our data, therefore, suggest that biological factors, including sex and gene mutation status, as well as the stratification of patients with CRC into right- and left-sided subsets may be important in patient selection for targeted therapies and for the subsequent assessment of objective therapeutic responses.

Our recent study shows for the first time, to our knowledge, down-regulation of FAS after hydroxytyrosol treatment in the SW620 human CRC cell line (59). Among phenolic compounds of olive oil, oleuropein and hydroxytyrosol are those which give extra-virgin olive oil its bitter, pungent taste, and they possess powerful antioxidant properties *in vitro* (60). As antioxidants, polyphenols may protect cell constituents against oxidative damage and may act as highly effective chemopreventive agents (61-63). Moreover, hydroxytyrosol significantly inhibits the proliferation of SW620 cell, through a pro-apoptotic effect. Exposure to increasing concentrations of hydroxytyrosol also led to a remarkable reduction in the proliferation of HT-29 cells. In these cells, the reduction in cancer cell growth detected after such an exposure seems to be independent of *FAS* gene expression and its enzymatic activity. These findings suggest that FAS might be a molecular target for antiproliferative activity of olive oil polyphenols in a metabolically defined subset of patients with colon cancer. Interestingly our findings demonstrate that the main olive oil polyphenols may induce antiproliferative effects in human CRC cells. These inhibitory effects on cell growth are mediated by FAS in certain human CRC cell types, suggesting that more differentiated and specialized cells are more able to control the expression of genes involved in cell proliferation.

In order to detect the presence of metastasis in CRC, several studies have been carried out in order to improve the prognosis of patients with aggressive disease. Identification of serum protein markers of CRC, together with other markers already known, could help provide such a non-invasive diagnostic screening tool. In a recent study of ours (64) we described for the first time a significant association between circulating levels of FAS and clinical stage CRC. Patients with tumor stage III and IV have significantly higher serum levels of FAS than patients with tumor stage I and II.

The quantitative determination of FAS in the blood might represent a tool to evaluate the aggressiveness during the progression of CRC.

Experiments are currently underway in our laboratory to establish if the measurement of serum FAS might be a rapid and non-invasive test of adequate prognostic/diagnostic accuracy capable of monitoring the effects of antineoplatic treatment. Moreover, it is possible that serum FAS levels could be helpful in identifying and following-up patients with colorectal cancer, when used in combination with other markers, emulating their use in breast and pancreatic cancer (65-68).

Lipoprotein Lipase

Several studies have demonstrated a clear association between obesity and the risk of CRC (69-72). Mature adipocytes seem to influence colon cancer cell proliferation (73). Adipose tissue synthesizes lipoprotein lipase (LPL), the crucial enzyme for intravascular catabolism of triglyceride-rich lipoproteins. Patients with resectable non-small cell lung cancer have higher LPL activity in cancer tissue than in adjacent, apparently healthy, non-cancer lung tissue (74). Moreover, increased LPL activity in non-small cell lung cancer tissue predicts shorter patient survival, independent of standard prognostic factors (73).

The involvement of both LPL and FAS in tumor biology has been widely demonstrated in different studies and regional differences in the expression of these enzymes in visceral adipose tissue collected from patients with CRC might be representative of events which sustain tumor growth.

Therefore, the aim of our recent study was to evaluate LPL and FAS activity and the expression of their genes in adipose tissue adjacent to neoplasia as well as distant from it, in patients with CRC (75). In this study, both LPL and FAS were differentially expressed in the two different regions of adipose tissue. Our findings showed a significant reduction in both *LPL* and *FAS* gene expression and activity in adipose tissue adjacent to tumor lesion compared to those detected in paired tissue distant from the neoplasia. Adipose and colon tissue may affect the enzymatic expression of proteins involved in cell proliferation. The increased demand for long-chain fatty acids by the tumor may lead to adipose atrophy, resulting in alterations of lipid metabolism.

These results underline the influence of the tumor microenvironment on lipid metabolism in adipose tissue, demonstrating a tumor-induced impairment in the formation and lipid-storing capacity of adipose tissue in patients with CRC.

Conclusion

The results presented here demonstrate the extent at which lipogenic enzymes are involved in tumor development and progression. Understanding the distribution of roles within individual biochemical pathways is clearly important and it provides a rationale for selecting a particular reaction step suitable for therapeutic intervention. The molecular mechanisms linking the inhibition of the lipogenic pathway with the induction of cell death in tumor cells remain unclear. More work is needed to conclusively show that inhibition of lipogenesis can be efficacious in the long-term in order to control tumor growth *in vivo*.

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