PPARG: A New Independent Marker for Colorectal Cancer Survival

Colorectal cancer represents one of the most common cancers in the United States, with >150,000 new cases reported each year. Epidemiologic evidence has demonstrated a link between dietary fat and obesity and an increased risk of colorectal cancer. About a dozen years ago, it was shown that lipid derived molecules could activate the nuclear receptor peroxisome proliferator-activated receptor (PPARG) and induce differentiation. The link between dietary fat and colorectal cancer prompted a significant interest in a potential role of PPARG in colon cancer. Although studies have shown that PPARG is expressed in colon-derived tumors and normal colonic mucosa, the consequence of this on patient outcome is unclear. In this issue of GASTROENTEROLOGY, Ogino et al demonstrate, using 2 large, prospective, cohort-based studies, that the expression of PPARG in tumors is associated with increased survival compared with PPARG-negative tumors (Figure).

PPARG is a member of the nuclear receptor superfamily of ligand activated transcription factors. Ligand activation of PPARG induces it to heterodimerize with the retinoid X receptor and directly regulate gene expression. In addition, PPARG activation has been shown to repress proinflammatory genes via transrepression and transcriptional squelching. Although a central role for PPARG has been demonstrated in adipocyte differentiation and as a target for antidiabetic therapy, subsequent studies have shown that PPARG plays an important role in regulating the growth of a number of different cancers, including colorectal cancer. Importantly, the thiazolidinediones (TZDs) class of antidiabetic drugs have been shown to be high affinity ligands for PPARG. Two of these TZDs, pioglitazone and rosiglitazone, are currently approved for use in the United States for the treatment of...
Given the availability of these compounds, PPARG is attractive as a target in cancer therapy.

PPARG is present at high levels in both normal and malignant colon tissues. Activation of PPARG in human colon cancer cells with TZDs decreases growth both in vitro and in vivo. Paradoxically, it has been demonstrated that activation of PPARG actually increases colonic polyps in the Apc min mouse model of colon carcinogenesis. Several years ago, the Spiegelman laboratory used a genetic approach to address the role of PPARG in colorectal cancer. Using PPARG heterozygous mice, they demonstrated a decreased latency to onset of polyp formation and increased incidence of colon carcinogenesis compared with wild-type mice after treatment with a colon-specific carcinogen. These data demonstrate that PPARG is a tumor suppressor gene in the colon.

Given the potential role of PPARG to function as tumor suppressor, a small clinical trial in advanced colorectal cancer was carried out using the PPARG ligand Rezulin (which has since been removed from the market). No difference in disease progression or survival was observed. Another study followed >80,000 men taking TZDs and other drugs for control of their diabetes. The data demonstrate that the use of PPARG ligands was associated with a decrease in lung, prostate, and colon cancer incidence. A more recent study found that TZD use among diabetics was associated with a significantly reduced risk of colorectal cancer.

These studies suggest that PPARG ligands may not be effective as a single agent in advanced cancer, but may be able to prevent tumorigenesis. However, the question remains as to the consequence of PPARG in colorectal tumors. Two previous studies investigated the role of PPARG expression on patient survival. Owing perhaps in part to the small sample size, neither of these studies found an association between PPARG expression and patient outcome.

In the current study by Ogino et al., the authors used patient samples and data from the large Nurses Health Study and Health Professionals Follow Up Study. The Nurses Health Study represents 121,700 women followed since 1976 and the Health Professionals Follow Up Study represents 51,500 men followed since 1986. From these patients, the authors were able to obtain medical records and tumors samples from 470 patients with stage I-IV colorectal cancer that included information of patient mortality. This represents a large study group from which strong, statistically based conclusions could be achieved, something lacking in the previous studies.

Immunohistochemistry for PPARG was performed on the 470 tumor samples. PPARG was expressed in 102 tumor cases compared with 268 PPARG-negative cases. Kaplan–Meier analysis demonstrated that patients with tumors expressing PPARG had a greater 5-year overall survival rate than patients with tumors that were PPARG negative (83% vs 71%, respectively). Using univariate analysis or taking into account other potential indicators of patient outcome using multivariate analysis, patients with PPARG positive tumors showed a significant reduction in overall risk of mortality (hazard ratios, 0.55 and
0.43, respectively). The authors also investigated colorectal cancer–specific death and found a significant reduction in risk mortality. Similar to the smaller studies, Ogino et al, six investigated whether a number of clinical factors (age, gender, family history, year of diagnosis, tumor stage or grade) were playing a modifying effect on the association between PPARG expression and patient survival. These variables did not seem to modify the effect of PPARG on survival.

Although previous studies examined a small number of potentially modifying factors, Ogino et al took into account a number of expanded clinical and molecular parameters associated with colorectal cancer progression and mortality. This is important because studies have shown that PPARG interacts with a number of oncogenic and tumor suppressor pathways that may be modifying the effect of PPARG expression on survival. Mutations of the oncogenes KRAS, BRAF, and PI3KCA did not seem to be associated with a modifying effect. In addition, expression of the cycle regulators p53, p21, p27, and cyclin D1 also did not seem to be having a modifying effect.

Genetic and epigenetic alterations play an important role in cancer because they represent molecular changes to the tumor and are related to patient survival. These include microsatellite instability, CpG island methylator phenotype, and LINE1 hypomethylation. Again, these pathways did not seem to be modifying the association of PPARG expression and survival. Finally, because PPARG regulates multiple metabolic pathways, the authors investigated whether metabolic parameters that are associated with colon tumorigenesis modify the PPARG effect. These include FASN, PI3KCA, and COX2. In addition, obesity is associated with increased colorectal cancer incidence and mortality. Given the connection between PPARG and fat development, the authors also examined the effect of body mass index. Again, no modifying effect was observed on PPARG expression and patient survival.

Several possible mechanisms may explain the increased survival in patients with tumors expressing PPARG. Increased inflammation and inflammatory pathways have been shown to be negatively associated with tumor progress and patient survival. Studies have shown that PPARG exerts anti-inflammatory effects in multiple tissue types. Furthermore, studies have shown that some of the tumor-suppressive effects of PPARG are mediated via the anti-inflammatory effects of PPARG. Therefore, increased PPARG expression may be associated with decreased inflammation and would thus be predicted to result in a more indolent tumor. It would be of interest for future studies to determine if inflammatory markers were indeed reduced in the tumors expressing PPARG.

Another possible mechanism that may explain the increased survival of patients with tumors expressing PPARG is response of tumors to chemotherapy. Although the authors did not have access to data on patient therapy, it is unlikely that differences in therapy would be observed based on PPARG status. However, recent studies demonstrate that PPARG can potentiate the effects of a variety of chemotherapeutic drugs. Therefore, the presence of PPARG in the tumor would sensitize the tumor to the chemotherapeutic agents and increase patient survival. It would be useful if future studies could identify whether there are differences in the response of patients with PPARG-positive tumors to chemotherapy.

These data also suggest possible therapeutic interventions. A previous phase II clinical trial in advanced colon cancer demonstrated that PPARG ligands did not alter patient progression or survival. The results of the study by Ogino et al suggest a possible explanation for the lack of a response in the previous study. Of the 470 samples evaluated in this study, only 22% were positive for PPARG, whereas the vast majority (78%) were PPARG negative. Therefore, the lack of response in the previous study may reflect an absence of PPARG in the tumors. This suggests that perhaps subsequent studies should examine patient tumor PPARG status in conjunction with treatment with PPARG agonists. This is even more relevant in light of the recent work showing how PPARG agonists can increase the sensitivity of tumors to chemotherapeutic drugs. Patients could be stratified based on whether their tumors express PPARG. Patients with PPARG-negative tumors would receive standard chemotherapy, whereas patients with tumors expressing PPARG would receive standard chemotherapy in combination with PPARG ligand therapy.

Most of the studies on the role of PPARG have shown it plays an anticancer role. Although this study does not address the role of PPARG in the development of colorectal cancer, it provides strong data that PPARG expression in tumors is associated with increased survival. Additional variables not examined in these studies could be playing a modifying role on PPARG expression and survival. However, the use of a large number of different factors and detection using different assays supports the finding that PPARG is also an independent marker of patient survival in colorectal cancer. Future studies, such as those suggested, should hopefully determine whether this finding could be used to improve the treatment of patients with colorectal cancer and increase patient survival.

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Conflicts of interest
The authors disclose no conflicts.

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