Preclinical Development

Chemopreventive Effects of Pioglitazone on Chemically Induced Lung Carcinogenesis in Mice

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Abstract

Pioglitazone [(RS)-5-(4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl)thiazolidine-2,4-dione] is a ligand of nuclear receptor peroxisome proliferator-activated receptor γ that is approved for the treatment of type II diabetes mellitus. Activation of peroxisome proliferator-activated receptor γ has been associated with anticancer activities in a variety of cancer cell lines through inhibition of proliferation and promotion of apoptosis. We examined the effect of pioglitazone on lung cancer development in carcinogen-induced lung adenocarcinoma and squamous cell carcinoma (SCC). When pioglitazone was administered beginning 8 weeks after the first carcinogen treatment when microscopic adenomas already existed, pioglitazone significantly inhibited tumor load (sum of tumor volume per lung in average) by 64% (P < 0.05) in p53wt/wt mice and 50% (P < 0.05) in p53wt/Ala135Val mice in the lung adenocarcinoma model. Delayed administration of pioglitazone caused a limited (35%, P < 0.05) decrease in lung SCC. Induction of apoptosis occurred in both model systems. These data show that pioglitazone significantly inhibited progression of both adenocarcinoma and SCC in the two mouse model systems. Mol Cancer Ther; 9(11): 3074–82. ©2010 AACR.

Introduction

Lung cancer is the leading cause of cancer deaths in men and women in the United States (1). Tobacco smoke exposure has been implicated in 90% of lung cancers, and smokers have a 20-fold greater risk of developing lung cancer compared with lifetime nonsmokers (2). Because the risk of lung cancer remains elevated for years after smoking cessation, additional preventive approaches are needed to reduce the burden of lung cancer (3). Chemoprevention, which seeks to reverse, suppress, prevent, or delay the carcinogenic process either by blocking the development of early lesions or by inhibiting the progression to invasive cancer, offers one such alternative. However, the identification agents with acceptable safety and efficacy profiles to warrant human trials is a challenging task (4).

Since the first report by Wattenberg and Bueding on study of chemoprevention of carcinogen-induced neoplasia in female ICR/Ha mice by Oltipraz (5), there are numerous studies on lung chemoprevention in mouse lung tumor models, and mouse models allow preclinical testing to determine if promising agents warrant clinical chemoprevention trials in humans (as reviewed in refs. 6–10). Transgenic mice carrying a missense p53 mutation (Ala-135-Val) develops a high incidence of lung adenocarcinomas (11), lung squamous cell carcinomas (SCC; ref. 12), head and neck SCC (13), and osteosarcomas and lymphomas (14) when compared with wild-type mice. We have systematically characterized this model for use in chemoprevention studies of lung adenocarcinoma and lung SCC (11, 13, 15–20). Because human lung cancer is composed of multiple histologic subtypes reflecting deregulation of a variety of molecular pathways, identification of chemopreventive agents with broad utility across the diverse lung pathologies is likely to be optimized through the use of multiple models.

The peroxisome proliferator-activated receptor γ (PPARγ), a ligand activated nuclear receptor that is a key regulator of adipogenic differentiation, has recently been identified as a potential target for lung chemoprevention. In a study of male diabetics followed in Veterans Administration hospitals, Govindarajan et al. showed a 33% reduction in lung cancer risk among thiazolidinedione users compared with nonusers (21). Abundant preclinical data are similarly supportive. Activation of PPARγ inhibits multiple aspects of the malignant phenotype, including proliferation, invasiveness, and metastasis (reviewed recently by refs. 22, 23). PPARγ ligands have been shown to inhibit the growth of multiple different cancer cell lines in vitro and in xenograft animal model systems, including cell lines derived from non-small cell lung cancer (NSCLC; refs. 24, 25), breast cancer (26), colon cancer (27), and esophageal SCC (28). Accumulating data also show that PPARγ ligands suppress carcinogenesis in a wide range of rodent model systems,

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including colon (29), liver (30), tongue (25, 31), breast (32), and lung (33) models.

The present study was undertaken to determine the role of the PPARγ ligand pioglitazone in chemoprevention of mouse lung carcinogenesis. Pioglitazone is a member of the thiazolidinedione family of antidiabetic agents that is approved by the U.S. Food and Drug Administration for the treatment of type II diabetes. Its well established and relatively benign toxicity profile makes it a suitable candidate for human studies. In the current study, we used both p53wt/Ala135Val and p53wt/Ala135Val mice to determine if the efficacy of pioglitazone dependent on functional p53 protein. Pioglitazone treatment resulted in significant inhibition of tumor development in lung adenocarcinoma harboring wild-type or mutant p53 and in SCC mouse models, providing further evidence for a potential role of PPARγ ligands in the prevention of lung cancer. In addition, pioglitazone inhibited the growth of NSCLC cell lines in culture and induced transcript accumulation of the proapoptotic PPARγ target, the Cyp-G1 switch 2 (G0S2; ref. 34) in these cell lines.

Materials and Methods

Reagents and animals

Vinyl carbamate and N-nitroso-tris-chloroethylurea (NTCU) were purchased from Toronto Research Chemicals, Inc., aliquoted, and stored at −80°C in total darkness until the time of use. Polyethylene glycol 400 and carboxymethylcellulose were purchased from Sigma. A/J mice were obtained from the Jackson Laboratory. Female NIH Swiss mice were obtained from the Charles River Laboratories. To conduct the animal bioassays, 6-week-old NIH Swiss mice were purchased from the Charles River Laboratories. Mouse lung SCC was scored on serial tissue sections. Tumor volume was calculated using the formula for volume of an ellipsoid: \( V = \frac{4}{3}\pi r^3 \), where \( r \) is radius, \( L \) is length, \( W \) is width, and \( H \) is height (36). Lung tumor development was estimated quantitatively by measuring the number (N), volume (V), and tumor load (sum of V per lung).

Mouse lung SCC model

NTCU skin painting was used to induce lung SCC (12) in female NIH Swiss mice. The mice were randomly distributed among control and treatment groups. At 8 weeks of age, mice received the first dose of NTCU. A 2 cm² area of the interscapular region was shaved and subsequently kept free of hair. A 100-mL drop of 0.03 mol/L NTCU in acetone was applied to the shaved skin, twice a week, with a 3.5-day interval. The treatment was continued for 32 consecutive weeks. Mice were treated with pioglitazone (15 mg/kg body weight) or vehicle by oral gavage beginning 8 weeks following the first dose of NTCU treatment and continuing for the duration of the study. Mice were sacrificed 32 weeks after the first dose of NTCU. Mouse lung SCC was scored on serial tissue sections (5 μm each) of each formalin-fixed lung. One in every 20 sections (100 μm apart) was stained with H&E and examined histologically under a light microscope. All of cross-sectional cuts of bronchiolo were counted on all of the slides. The lesions, including invasive SCC, SCC in situ, and the bronchial hyperplasia/metaplasia, were scored. The criteria for histopathologic examination and scoring were described previously (12).

Immunohistochemical analysis

Antibodies to active caspase-3 and Ki-67 were purchased from Cell Signaling Technology. Briefly, slides were deparaffinized in xylene and rehydrated in gradient ethanol. Antigen retrieval was applied in microwave for 20 minutes with citrate buffer (pH 6.0). After blocking in 10% of normal goat serum in PBS [0.1 mol/L sodium phosphate and 0.15 mol/L sodium chloride (pH 7.4)], primary antibody was diluted in 10% normal goat serum...
and incubated at 4°C overnight. The appropriate secondary biotinylated IgG (1:500) was used followed by avidin-biotin complex method (Vectastain ABC Elite kit, Vector Lab) according to the manufacturer's protocol, and 3,3′-diaminobenzidine (Sigma) was used as chromogen. For negative control, the primary antibody was omitted. Positive stained cells were determined by counting 10 randomly chosen fields per section over tumors.

Statistical analysis

Student’s t test was used to test the differences between the control groups and the treatment groups in the lung adenocarcinoma model. Fisher’s exact test was used to test the differences between the control groups and the treatment groups in the lung SCC model.

Cell culture and in vitro treatment

A549 and H1299 (American Type Culture Collection) NSCLC cells were cultured in RPMI with 10% fetal bovine serum (FBS; Life Technologies) and antibiotics. Cells were treated with DMSO solvent, 15 μg/mL pioglitazone, or 30 μg/mL pioglitazone. DMSO concentration of all treatment groups was 0.2%.

MTS proliferation assay

Cells were seeded onto 12-well tissue culture dishes at a density of 1,000 cells per well. Cells were treated after attachment overnight. Cells were assayed for viable cell numbers in triplicate using the AQueous One Solution Transcription-PCR (Invitrogen). Quantitative reverse transcription-PCR assay was done using the SYBR Green PCR Master Mix (Applied Biosystems). One microliter of cDNA was added to a 25-μL total volume reaction mixture containing water, SYBR Green PCR Master Mix, and primers. Each real-time assay was done in duplicate on a Bio-Rad MyIq machine. Gene β-actin was used as an internal control to compute the relative expression level (ΔΔCT) for each sample. The fold change of gene expression in tumor tissues compared with the paired normal tissues was calculated as 2ΔΔCT, where ΔΔCT = ΔCT normal − ΔCT tumor. One-tailed Student’s t test was carried out to assess the overall statistical significance of the difference in gene expression levels.

Results

Effect of pioglitazone on mouse lung adenocarcinoma

Lung adenocarcinomas were induced by i.p. injection of vinyl carbamate in p53wt/wt or p53wt/Ala135Val at ~7 weeks of age and repeated 1 week later. Treatment with pioglitazone was initiated 8 weeks after initial vinyl carbamate injection and continued for an additional 12 weeks. At 8 weeks, vinyl carbamate–treated mice have multiple small lung adenomas. Vinyl carbamate–treated mice induced an average of eight lung adenomas based on our preliminary study of five mice terminated at 8 weeks after the carcinogen treatment, which is consistent with a previous study (38). Pioglitazone treatment did not cause significant body weight loss compared with vehicle-treated mice. Pioglitazone treatment did not have inhibitory effect on tumor multiplicity of lung adenocarcinomas (Table 1). All mice developed tumors. Lung adenocarcinomas with bronchial invasion were observed in vinyl carbamate–induced lung tumors in p53wt/wt/Ala135Val mice but not in p53wt/wt mice (Fig. 2A), reflecting the large sizes and more advanced histopathology of tumors in these mice. As shown in Fig. 1C and Table 1, pioglitazone

| Table 1. Effect of pioglitazone on vinyl carbamate–induced lung adenocarcinoma development |
|-----------------|-----------------|-----------------|-----------------|
| p53**             | Treatments       | n               | Lung tumor load (sum of tumor volume per lung in average) |
|                  | n ± SD | t test | Load ± SD | t test | Inhibition |
| +/-               | Gavage control  | Vehicle  | 10  | 41.7 ± 3.9 | >0.05 | 26.49 ± 10.43 | 9.55 ± 2.82 | 0.0005 | 63.9% |
| +/-               | Pioglitazone    | 15 mg/kg body weight, gavage | 10  | 42.5 ± 6.9 | >0.05 | 9.49 ± 2.82 | 0.0005 | 63.9% |
| +/-               | Gavage control  | Vehicle  | 9   | 49.7 ± 8.7 | >0.05 | 36.09 ± 17.23 | 0.0069 | 49.6% |
| +/-               | Pioglitazone    | 15 mg/kg body weight, gavage | 19  | 49.4 ± 8.7 | >0.05 | 36.09 ± 17.23 | 0.0069 | 49.6% |

**+/+, wt/wt; +/-, wt/Ala135Val.

†Compared with the p53**/+** controls.
significant inhibited lung tumor load regardless of p53 status. Tumor load was decreased by 63.9% (P = 0.0005) in p53wt/wt mice and 49.6% (P = 0.0069) in p53wt/Ala135Val mice. All lung tumors in pioglitazone-treated mice were adenomas, whereas ~50% of tumors in the control group were adenocarcinomas. These data indicate that pioglitazone was a potent inhibitor for the development of lung adenocarcinomas in mice, both by limiting tumor size and delaying or preventing the conversion from adenoma to adenocarcinoma.

Effect of pioglitazone on mouse lung SCC

Previously, we reported the successful induction of mouse lung SCCs using the organ specific carcinogen NTCU in different strains of mice, including A/J and NIH Swiss (12). The histopathology of the mouse lung SCC is similar to that seen in humans with well-defined pathologic development from normal to bronchiolar hyperplasia, metaplasia, SCC in situ, and SCC (12). Lung SCC was induced with NTCU as described in Materials and Methods, and pioglitazone was administered at a dose of 15 mg/kg body weight beginning 8 weeks after initial carcinogen treatment and continuing for 24 weeks. NTCU induced only bronchiolar hyperplasia in all four mice that were terminated at 8 weeks after the carcinogen administration. Pioglitazone did not cause any symptoms of toxicity or apparent signs of illness nor have any significant effect on body weight for the duration of the study. As shown in Fig. 1D and Table 2, in gavage control NTCU-treated animals, the distributions of lesions are as follows: normal (42.7 ± 3.6%), hyperplasia (34.8 ± 3.4%), metaplasia (4.1 ± 0.8%), and SCC (18.4 ± 1.4%). In animals treated with pioglitazone, the distributions of lesions are normal (52.0 ± 4.1%), hyperplasia (33.1 ± 4.9%), metaplasia (4.7 ± 2.1%), and SCC (12.0 ± 0.6%). Pioglitazone decreased lung SCC by 35% (P < 0.05). At the same time, the percentage of normal lung tissue increased by nearly 24%. This observation indicates that pioglitazone can inhibit the progression of normal lung epithelium to lung SCC.

Immunohistochemical analysis of proliferation and apoptosis in tumors from the lung adenocarcinomas

Immunohistochemical analysis for proliferation using anti-Ki-67 antibody and apoptosis using anti-active caspase-3 antibody were used to determine pioglitazone’s proliferative and apoptotic effects against lung adenocarcinoma. The Ki-67 labeling index was decreased in lung adenocarcinomas from p53wt/wt mice. Approximately 35.7 ± 2.1 Ki-67–positive stained cells per 400× field were...
seen in control tumors and 24.7 ± 2.0 Ki-67-positive stained cells per 400× field were found in pioglitazone-treated tumors, a 31% inhibition (P = 0.0003). However, the inhibitory effect on Ki-67 staining was not seen in lung adenocarcinomas from p53wt/Ala135Val mice. Immunohistochemical staining with anti-caspase-3 antibodies was used to determine the effect of pioglitazone on apoptosis. As shown in Fig. 2, pioglitazone caused a significant increase (P = 5.0E-06) in the number of active caspase-3-positive cells in p53wt/wt mice (10.6 ± 0.93 in control versus 18.3 ± 1.5 in pioglitazone-treated tumors). A similar effect was seen in pioglitazone-treated lung adenocarcinomas of p53wt/Ala135Val mice (14.6 ± 0.94 positive active caspase-3 cells in control versus 20.3 ± 1.18 in pioglitazone-treated tumors).

In NTCU-treated animals, multiple histologic abnormalities, in addition to SCC, coexisted. We therefore analyzed cell proliferation and apoptosis by Ki-67 and active caspase-3 immunohistochemical staining, respectively, in epithelial cells of normal bronchioles, hyperplastic/metaplastic bronchial epithelial cells, and SCC cancer. Although the differences were seen, the antiproliferative effect of pioglitazone was not statistically significant (data not shown). Immunohistochemical staining with active caspase-3 (Fig. 3A–D) indicated that pioglitazone significantly induced apoptosis during lung squamous carcinogenesis (Fig. 3E). In hyperplastic bronchial epithelial cells, there are 0.33 ± 0.07 positive stained active caspase-3 cells 400× field on average in vehicle-fed animals, whereas the positive staining was increased to

Table 2. Effect of pioglitazone on NTCU-induced lung SCC development

<table>
<thead>
<tr>
<th></th>
<th>Normal (%)</th>
<th>Hyperplasia (%)</th>
<th>Metaplasia* (%)</th>
<th>SCC †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>42.7 ± 3.6</td>
<td>34.8 ± 3.4</td>
<td>4.1 ± 0.8</td>
<td>18.4 ± 1.4</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>52.0 ± 4.1</td>
<td>33.1 ± 4.9</td>
<td>4.7 ± 2.1</td>
<td>12.0 ± 0.6</td>
</tr>
</tbody>
</table>

*Combination of metaplasia and dysplasia.
†Combination of SCC in situ and SCC ± SEM.
0.62 ± 0.11 on pioglitazone treatment ($P = 0.016$). A similar result was seen in lung SCC. There are 0.41 ± 0.11 positive stained active caspase-3 cells 400x field on average in lung SCC in vehicle-fed animals. The positive staining doubled to 0.87 ± 0.12 on pioglitazone treatment ($P = 0.008$).

**Effect of pioglitazone on NSCLC cells in culture**

To determine the effect of pioglitazone on the overall growth of NSCLC cells, we did a growth curve analysis of A549 and H1299 cells under treatment with DMSO solvent alone, 15 μg/mL pioglitazone, or 30 μg/mL pioglitazone (Fig. 4A). Cell numbers were assayed by MTS assay, which we have previously shown to correlate closely with viable cell count in these cells (39). Both cell lines exhibited dose-dependent inhibition of growth by pioglitazone over 6 days in culture. To determine the effect of pioglitazone on apoptosis-related PPARγ targets, we did quantitative real-time reverse transcription-PCR. Whereas expression of Bax and Bcl2 were not consistently affected by pioglitazone treatment, G0S2 transcript accumulation was induced in both cell lines (Fig. 4B and C).

**Discussion**

In the current study, the PPARγ ligand pioglitazone was shown to inhibit chemically induced lung carcinogenesis in multiple mouse model systems, including both adenocarcinoma and SCC models. The significant effects were seen primarily on tumor volume, not on tumor multiplicity, in the postinitiation adenocarcinoma model where chemopreventive agent administration was begun when small adenomas already exist. The effect, therefore, was one of inhibition of further growth rather than regression of preexisting lesions. Significantly, pioglitazone reduced lung adenocarcinoma tumor burden by >50% regardless of p53 status, suggesting preservation of efficacy even in the setting of one of the most common mutations in human lung cancer. This is in contrast to the data previously obtained with budesonide, one of the most effective chemopreventive agents in mouse models, whose effect was nearly halved in the setting of a mutated p53 (16). Equally important is the observation that the tumors in p53<sup>wt/Ala135Val</sup> mice treated with pioglitazone were noninvasive adenomas, in contrast to the invasive adenocarcinomas in vehicle-treated wild-type mice. This suggests, in the very least, a significant delay in progression that will need to be confirmed in future studies of longer duration.

In the SCC mouse model, pioglitazone caused a more modest decrease (35%) in carcinoma number, coupled with an increased appearance of normal bronchial tissue suggesting an inhibition of progression of the SCC lesions. The technical difficulties in quantifying tumors in the SCC model render the results more qualitative in nature. However, taking all the data together, these studies describe an effect of pioglitazone across the two most common histologies of NSCLC that constitute more than two-thirds of all human lung cancers (1).
providing a rationale for its further development for lung cancer prevention.

Previous studies have shown that the antitumor effects of PPAR\(\gamma\) ligands are mediated by the inhibition of cell proliferation and induction of apoptosis (24, 26, 27; reviewed in ref. 23). In our studies, proapoptotic effects were demonstrable in both \(p53^{wt/wt}\) and \(p53^{wt/Ala135Val}\) mouse models and in the SCC model. However, pioglitazone inhibited cell proliferation only in lung adenocarcinomas of \(p53^{wt/wt}\) mice, but not in lung adenocarcinomas from \(p53^{wt/Ala135Val}\) mice or in SCC. Whereas inhibition of proliferation seems to be a major mechanism \textit{in vitro}, it may not necessarily be the main mechanism of action of PPAR\(\gamma\) ligands \textit{in vivo}. Rumi et al. (28) reported a marked inhibition of PPAR\(\gamma\) agonists, including pioglitazone, on the growth of esophageal SCC cell lines, which was associated with G1 arrest during cell cycle progression (28). Similarly, Keshamouni et al. showed G0-G1 cell cycle arrest in NSCLC cells treated with the PPAR\(\gamma\) ligand troglitazone in tissue culture (25). However, similar to our current study, Elstner et al. showed induction of apoptosis by troglitazone \textit{in vitro} using MCF7 breast cancer xenografts (26). Furthermore, a recent clinical trial of women with breast cancer treated for 2 to 6 weeks with the PPAR\(\gamma\) ligand rosiglitazone before surgery also failed to show inhibition of proliferation, consistent with our findings in animal models (40). Our findings that pioglitazone treatment of A549 and H1299 cells inhibits cell growth and induces expression of the apoptotic PPAR\(\gamma\) target G0S2 are consistent with these observations and support the notion that the chemopreventive effect of pioglitazone may be mediated through PPAR\(\gamma\)-mediated apoptosis. These results also imply that p53 expression is not necessary for the antiproliferative effects of pioglitazone in NSCLC cells as H1299 cells do not express p53. G0S2 has been found to be frequently methylated in SCC of the lung (41), suggesting that G0S2 may have tumor-suppressive functions in the context of lung SCC. Additional mechanisms, such as induction of differentiation (24, 25, 27), inhibition of invasion, and inhibition of angiogenesis, may also be significant (23).

For a chemopreventive strategy to advance from the preclinical to clinical phase of development, safety and efficacy need to be established. In contrast to rosiglitazone, which has been associated with increased risk of myocardial infarction (42), pioglitazone was found to not be associated with cardiovascular disease in the PROactive study, which directly addressed the effect of
Pioglitazone inhibits mouse lung carcinogenesis

pioglitazone on macrovascular end points in a double-blind randomized placebo-controlled study (43). Concerns have also been raised about the role of PPARy in colon cancer based on the observation in two studies that troglitazone or rosiglitazone treatment of APC$^{Min/+}$ mice results in increased incidence of colon polyps (44, 45). This is in contrast to studies in wild-type mice showing suppression of carcinogen-induced aberrant crypt foci and colon tumors (29) and the observation in humans that loss-of-function somatic mutations occur in a minority of sporadic colon tumors (27). Subsequent studies with mice with heterozygous loss of PPARy showed that they are more sensitive to carcinogen-induced colon tumor formation than wild-type mice and that crossing the PPARy heterozygote mice with APC mutant mice has no effect on the polyp number (46). Taken together, these data show that PPARy can suppress colon carcinogenesis, but only before damage to the APC/β-catenin pathway. Clinical trials and postmarketing experience to date have not revealed any safety signals with regard to colon cancer in human beings.

In summary, our studies of the effect of pioglitazone on lung carcinogenesis using multiple mouse carcinogenesis model systems show a significant delay in progression to invasive cancer and significant reduction in tumor burden in both adenocarcinoma and SCC models. In this study, we used the lung tumor progression model with pioglitazone given 8 to 12 weeks after the carcinogen treatment and continued for the duration of the study. The primary purpose of using lung tumor progression model is to determine the effect of the pioglitazone on the progression of the established lung lesions, because most mice would exhibit multiple small lung adenomas by 8 to 12 weeks. Pioglitazone was given to mice 8 weeks after the carcinogen initiation of the lung tumorigenesis at the time lung tumors had developed (eight tumors per mouse; ref. 35). Pioglitazone seemed to have little effect on reversing established tumors or initiated tumor cells, but it significantly prevented further tumor development of established tumors or initiated tumor cells.

The use of the lung tumor progression model is more clinically relevant because it closely parallels potential clinical trials by exposing individuals with established precancerous lesions. To the best of our knowledge, this is the first time that the oral dose of the PPARy ligand pioglitazone has been shown to be effective for lung cancer prevention in animal models. The consistency of the data across the two most common histologic subtypes of lung cancer and in both wild-type and mutant p53 model systems suggests the potential for broad effects for prevention of multiple subtypes of NSCLC. Whereas induction of apoptosis seems to be involved in this process, further studies will need to address the molecular mechanisms of PPARγ ligand action. However, when combined with the epidemiologic evidence of decreased lung cancer incidence in diabetics taking PPARγ ligands (21), these data provide a sound rationale for testing pioglitazone for lung cancer prevention in clinical trials.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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