Concomitant Suppression of Hyperlipidemia and Intestinal Polyp Formation in Apc-deficient Mice by Peroxisome Proliferator-activated Receptor Ligands

Naoko Niho, Mami Takahashi, Tomohiro Kitamura, Yutaka Shoji, Masaki Itoh, Tetsuo Noda, Takashi Sugimura, and Keiji Wakabayashi

Cancer Prevention Division, National Cancer Center Research Institute, Tokyo 104-0045 [N. N., M. T., T. K., Y. S., T. S., K. W.]; Cell Biology Department, Cancer Institute, Tokyo 170-8455 [M. I., T. N.]; Oncology Department, Jikei University School of Medicine, Tokyo 105-8461 [M. I.]; and The Core Research for Evolutional Science and Technology Program, Japan Science and Technology Corporation, Kawaguchi 332-0012 [T. J. N.]

ABSTRACT

Epidemiological studies have shown a positive association of colon cancer with hyperlipidemia. Furthermore, signaling generated by peroxisome proliferator-activated receptor (PPAR) α and γ ligands, suggested to be candidate tumor preventive agents, has been shown to lower serum triglyceride levels. In the present study, we assessed hyperlipidemia in Apc-deficient mice, model animals for human familial adenomatous polyposis, and examined the effects of pioglitazone and bezafibrate, respectively, PPARγ and PPARα agonists, on both hyperlipidemia and intestinal polyp formation. Serum lipid levels in Apc1309 mice and Min mice from 6 to 15 weeks of age were measured. Although serum levels of triglyceride and cholesterol were low in both Apc1309 and wild-type mice at 6 weeks, triglycerides were elevated 10-fold in Apc1309 mice by the age of 12 weeks but not in their wild-type counterparts. Cholesterol was also increased significantly, and marked centrilobular-restricted steatosis was observed in the livers of aged Apc1309 mice. Similar findings were observed for Min mice at 15 weeks of age. Moreover, lipoprotein lipase mRNA levels in the liver and small intestine of Apc1309 and Min mice were demonstrated to be lower than those in wild-type mice. Treatment of Apc1309 mice with 100 and 200 ppm pioglitazone or bezafibrate for 6 weeks of age caused dose-dependent reduction in serum triglycerides and cholesterol, along with reduction in the numbers of intestinal polyps to 67% of the control value. The present study clearly demonstrated a hyperlipidemic state in Apc gene-deficient mice and a potential of PPARα and PPARγ ligands to suppress both hyperlipidemia and polyp formation. Hyperlipidemia in these mice may thus be associated with their intestinal lesion development.

INTRODUCTION

The risk of colon cancer appears to be elevated by a high fat diet (1), and epidemiological studies have shown a clear association with serum triglycerides and cholesterol (2, 5). It has been reported that reduction of cholesterol levels by HMG-CoA reductase inhibitors can suppress colon carcinogenesis (4). A decrease in levels of triglycerides, total cholesterol, and FFAs. As a possible cause, we found decreases of LPL mRNA levels in the liver and small intestine. We also investigated the effects of 100 or 200 ppm of pioglitazone and bezafibrate in the diet on both hyperlipidemia and intestinal polyposis in Apc1309 mice and demonstrated concomitant reduction in both. On the basis of these results for Apc gene-deficient mice, possible involvement of hyperlipidemia in intestinal polyp formation is proposed.
tions for 1 week. Three to five mice were housed per plastic cage, with sterilized softwood chips as bedding, in a barrier-sustained animal room, air-conditioned at 24 ± 2°C and 55% humidity, on a 12-h light/dark cycle. Body weights and food consumption were measured weekly. The PPARγ ligand pioglitazone [1:5:5:4-2-(5-ethyl-2-pyridyl)ethoxy]benzyl[(thiazolidine-2,4-dione monohydrochloride] was kindly provided by Takeda Chemical Industries, Ltd. (Osaka, Japan), and the PPARα ligand bezafibrate [2-[4-(2-[4-chlorobenzamido]ethyl)phenoxyl]-2-methylpropanoic acid] was purchased from Sigma Chemical (St. Louis, MO). These compounds were well mixed with powdered basal diet AIN-76A (CLEA Japan) at concentrations of 100 and 200 ppm.

Experimental Design. To assess change in serum lipid levels with aging, female Apc<sup>1309</sup> and wild-type mice were randomly divided into four groups, each consisting of five animals, and fed a basal diet from 5 to 12 weeks of age. For comparison, female Min mice were randomly divided into three groups, each consisting of three or four mice, and fed a basal diet from 5 to 15 weeks of age. To investigate the effects of pioglitazone and bezafibrate on both hyperlipidemia and intestinal polyps, 6–10 male Apc<sup>1309</sup> mice were given 0 (control), 100 or 200 ppm pioglitazone, or bezafibrate in the diet for 6 weeks, starting from 6 weeks of age. The doses were selected according to the results of a previous study, in which 100 ppm pioglitazone and bezafibrate in the diet suppressed formation of dextran sodium sulfate/AOM-induced ACF (18).

Food and water were available ad libitum. At the sacrifice time points, animals were anesthetized with ether, and blood samples were collected from the abdominal aorta. Various serum parameters, including triglycerides, total cholesterol, and FFAs, were measured, as reported previously (27–29). Livers were removed, fixed in 10% phosphate-buffered formalin (pH 7.4), and embedded in paraffin. Sections were prepared and stained with H&E for assessment of histopathological features. The experimental protocol was approved by the Institutional Ethics Review Committee for animal experimentation.

Intestinal Polyp Assesment. The intestinal tract was removed and divided into four sections, the colon and three segments of small intestine: (a) the duodenum (~4 cm in length; proximal) and the (b) proximal (middle) and (c) distal halves of the remainder (distal). All were opened longitudinally and fixed flat between sheets of filter paper in 10% phosphate-buffered formalin. The numbers and sizes of polyps as well as their distribution in the intestine were determined with a stereoscopic microscope, as described previously (30).

RT-PCR Analysis. Samples of normal and polyp tissue from small intestine and liver of mice (n = 3–4 each) were quickly deep frozen in liquid nitrogen and stored at −80°C. Total RNA was isolated using Isogen (Nippon Gene, Tokyo, Japan); then RNA was purified with DNase (Invitrogen, Leek, the Netherlands) according to the manufacturer’s instructions. cDNA was synthesized with 3 μg of total RNA in a final volume of 20 μl using an Omniscript RT Kit (Qiagen GmbH, Hilden, Germany) and an oligo(dT) primer. PCR amplification of 1 μl of cDNA was carried out in a final volume of 10 μl with a Perkin-Elmer GeneAmp PCR System 9600 (Perkin-Elmer Applied Biosystems, Foster City, CA) or an MJ Research PTC-200 DNA Engine (MJ Research, Inc., Waltham, MA), using a HotStarTaq (Qiagen). As an internal control to confirm the integrity of the isolated mRNA, β-actin (5’-primer: AACACCCCGAGCATCCAG, 3’-primer: CGCTCAGGAGGACCAATGA) was used. PCR was performed with specific primers for mice LPL (31), acyl-CoA oxidase (32), very long-chain acyl-CoA synthetase (33), carnitine palmitoyl transferase I (34), FAS (31), acyl-CoA carboxylase (31), stearoyl-CoA desaturase-1 (31), phosphoenolpyruvate carboxykinase (35), apolipoprotein A-I (apo-A-I) (31) and apolipoprotein C-III (apo-C-III) (5’: TCTTGGCCTCCTGCATGCT, 3’: TGGAGTTGGTTGGCTTCCAG). Cycling conditions were as follows: 94°C for 20 s, 57.8°C for 30 s, and 72°C for 30 s cycles (except 40 cycles for FAS and acetyl-CoA carboxylase and 25 cycles for β-actin) after an initial step of 95°C for 15 min. A final elongation step of 72°C for 10 min completed the PCR. The products were then analyzed by 2% agarose gel electrophoresis.

Immunohistochemistry. Expression and localization of PPARγ and PPARα in the small intestine were examined with rabbit polyclonal antibodies against each antigen using an avidin biotin complex method. Briefly, paraffin-embedded sections were deparaffinized and pretreated by heating in a microwave oven in 10 mM citrate buffer at pH 6.0 for 20 min. Nonspecific endogenous peroxidase activity was blocked by exposure to 0.5% hydrogen peroxide in methanol for 15 min, and masking was conducted with 5% normal goat serum in PBS containing 0.5% casein for 30 min. Incubation with anti-PPARγ (clone H-100; Santa Cruz Biotechnology, Santa Cruz, CA) and anti-PPARα (clone H-98; Santa Cruz Biotechnology) was performed at 4°C, overnight. This step was followed by sequential incubation with biotin-labeled goat anti-rabbit IgG and avidin-biotin complex reagents (Vector Laboratories, Burlingame, CA).

Statistical Analysis. The data for blood biochemistry and poly formation are expressed as mean ± SE, and their statistical analysis was performed with Student’s t test. P < 0.05 were considered to be significant.

RESULTS

Elevation of Serum Lipid Levels in Apc Gene-deficient Mice. Changes of serum lipid levels with ages were determined in female Apc<sup>1309</sup> and wild-type mice. No significant differences were evident at 6 weeks of age. However, triglyceride levels were dramatically increased in Apc<sup>1309</sup> mice thereafter (Fig. 1A), the average value at 12 weeks of age (618.2 ± 161.5 mg/dl) being almost 10 times higher than that at 6 weeks (72.0 ± 2.6 mg/dl). No such increase was observed in their wild-type counterparts. Total cholesterol in Apc<sup>1309</sup> mice also significantly increased between 6 and 12 weeks of age (Fig. 1B), from 87.0 ± 3.2 mg/dl to 162.4 ± 33.0 mg/dl in contrast to the 70.2 ± 8.8 mg/dl to 79.6 ± 13.7 mg/dl found for the wild type. Significant changes in FFA levels also occurred with age (Fig. 1C). Serum lipid levels in male Apc<sup>1309</sup> mice aged 12 weeks were almost the same as those in female Apc<sup>1309</sup> mice at the same age (Fig. 2, A–C). Histopathologically, centrilobular-restricted steatosis was observed in the livers of all Apc<sup>1309</sup> mice at 12 weeks of age, with numerous microvesicular fatty droplets in the cytoplasm of parenchymal cells (data not shown). Steatosis observed in Apc<sup>1309</sup> mice was confirmed by staining frozen sections with Oil Red O. Wild-type mice exhibited no fatty change. The above observations indicate that Apc<sup>1309</sup> mice develop hyperlipidemia as they age, the severity not differing between males and females.

In Min mice, triglyceride and FFA levels also increased dramatically with age (Fig. 1, D–F). Values for triglycerides in the serum of female Min mice at 8 and 15 weeks of age were 40.3 ± 6.2 and 377.3 ± 136.1 mg/dl, those for total cholesterol were 83.7 ± 6.3 and 107.8 ± 15.6 mg/dl, and those for FFAs were 1.0 ± 0.1 and 3.1 ± 0.4 mEq/liter, respectively. Histopathologically, centrilobular-restricted...
steatosis was apparent in the livers of the mice aged 15 weeks (data not shown).

Other serum biological parameters, such as glucose, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and alkaline phosphatase, did not differ between groups of Apc-deficient mice, of either Apc<sup>1309</sup> or Min strains, and wild-type mice at 6–15 weeks of age (data not shown).

**Depression of Serum Lipid Levels in Apc<sup>1309</sup> Mice by Pioglitazone and Bezafibrate.** Administration of pioglitazone or bezafibrate did not affect food intake or behavior of Apc<sup>1309</sup> mice. Final body weights in the 100 and 200 ppm pioglitazone-treated group were increased to 113–115% of those in the basal diet group, and those in bezafibrate-treated groups to 118–122%. Serum levels of triglycerides at 12 weeks of age decreased dose dependently, being reduced 44 and 50% by 100 and 200 ppm of pioglitazone, respectively (Fig. 2A). The levels of total cholesterol were also decreased by 15 and 28%, respectively, and administration of pioglitazone caused a 27% decrease in FFA levels in both 100 and 200 ppm groups, although significance was not attained (Fig. 2, B and C). Administration of bezafibrate reduced serum levels of triglycerides, dose dependently, by 30 and 55% (P < 0.05) at 100 and 200 ppm, respectively (Fig. 2D). The levels of total cholesterol and FFA showed a tendency for decrease by 6–18% (Fig. 2, E and F). The severity of hepatic steatosis was clearly decreased in Apc<sup>1309</sup> mice after treatment with pioglitazone and bezafibrate at doses of 100 and 200 ppm (data not shown).

**Suppression of Intestinal Polyp Formation in Apc<sup>1309</sup> Mice by Pioglitazone and Bezafibrate.** A suppressive effect of pioglitazone and bezafibrate on intestinal polyp development was also found. Most polyps were located in the small intestine, with only a few apparent in the colon of control and pioglitazone or bezafibrate-treated animals (Table 1). The total numbers of polyps in the groups treated with pioglitazone at 100 and 200 ppm were reduced to 67% (P < 0.05) of the value for the control group, in both cases. The numbers of polyps in the distal parts of the small intestine in Apc<sup>1309</sup> mice fed diet containing 100 ppm pioglitazone were 64% (P < 0.05) of the control values, and those in the proximal and middle parts of the small intestine in the mice treated with 200 ppm pioglitazone were 58% (P < 0.05) and 61% (P < 0.01), respectively. Dietary administration of 100 and 200 ppm bezafibrate reduced the total numbers of polyps to 87 and 75% (P < 0.05), respectively, of the value for the control group. The numbers of polyps in the proximal, middle, and distal parts of the small intestine in Apc<sup>1309</sup> mice treated with 100 and 200 ppm bezafibrate were reduced to 73–96% of the control values, respectively, although these values were not statistically significant.

The size distribution of intestinal polyps in the basal diet and pioglitazone or bezafibrate-treated groups was investigated. Treatment with 100 and 200 ppm pioglitazone reduced the numbers of polyps measuring ≥1 and ≥0.5 mm in diameter, respectively (Fig. 3A). On the other hand, 100 and 200 ppm bezafibrate reduced the numbers of polyps, especially 0.5–1.5 mm in diameter (Fig. 3B).

**Alterations of Metabolic Enzyme mRNA Expression in the Liver and Small Intestine of Apc-deficient Mice.** To approach the mechanisms of how heterozygous mutations in the mouse Apc gene lead to dramatic changes in serum lipids, especially triglycerides, with age, we investigated liver and small intestine expression levels of mRNAs encoding metabolic enzymes involved in hydrolysis of triglycerides, lipogenesis, β-oxidation, and glucose homeostasis. In the liver and small intestine of Apc<sup>1309</sup> mice at 6, 8, and 12 weeks of age, there was no obvious variation in their mRNA levels for the lipogenic genes, including FAS and stearoyl-CoA desaturase-1; β-oxidation genes, including acyl-CoA oxidase and carnitine palmitoyl transferase 1; and gluconeogenesis genes, including phosphoenolpyruvate carboxykinase, as compared with the wild-type counterparts. Similarly, the expression levels for these genes were not different between Min and wild-type mice at any age. On the other hand, the liver mRNA levels for LPL, which catalyze the hydrolysis of triglycerides in lipoprotein particles into fatty acids and monoacylglycerol (17), were clearly lowered in Apc<sup>1309</sup> mice at 6, 8, and 12 and in Min mice at 8, 11, and 15 weeks of age, and the degree of decrease was the most evident at 12 and 15 weeks of age, respectively (Fig. 4A). A similar shift was also evident for the small intestinal mRNA level (Fig. 4B). Between normal mucosa and polyp tissue of Apc<sup>1309</sup> mice, there were no differences in LPL mRNA levels. We also measured both apoA-I and apoC-III, which are pivotal in metabolism of high-density lipo-

### Table 1 Data for intestinal polyps in Apc<sup>1309</sup> mice treated with PPAR ligands<sup>a</sup>

<table>
<thead>
<tr>
<th>Polyp location</th>
<th>Pioglitazone (ppm)</th>
<th>Bezafibrate (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 (10&lt;sup&gt;b&lt;/sup&gt;)</td>
<td>100 (8)</td>
</tr>
<tr>
<td>Proximal small intestine</td>
<td>9.5 ± 1.1&lt;sup&gt;c&lt;/sup&gt;</td>
<td>5.8 ± 1.6</td>
</tr>
<tr>
<td>Middle small intestine</td>
<td>15.7 ± 1.1</td>
<td>11.4 ± 2.1</td>
</tr>
<tr>
<td>Distal small intestine</td>
<td>10.9 ± 1.2</td>
<td>7.0 ± 1.3&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Colon</td>
<td>0.6 ± 0.2</td>
<td>0.5 ± 0.3</td>
</tr>
<tr>
<td>Total</td>
<td>36.7 ± 2.7</td>
<td>24.6 ± 4.4&lt;sup&gt;e&lt;/sup&gt;</td>
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<sup>a</sup> Mice were fed the basal diet or a diet containing 100 or 200 ppm of PPAR ligand for 6 weeks.

<sup>b</sup> Numbers in parenthesis are the numbers of animals examined.

<sup>c</sup> Number of polyps per mouse.

<sup>d</sup> Data are means ± SE.

<sup>e</sup> Versus the basal diet group: P < 0.05.

<sup>f</sup> Versus the basal diet group: P < 0.01.
proteins and very low-density lipoproteins, respectively, but hepatic values for mRNAs were similar in all mouse strains, independent of the age. Administration of 100 and 200 ppm pioglitazone or bezafibrate raised the hepatic mRNA levels of LPL in Apc1309 mice (Fig. 5, A and B). A similar up-regulation was also evident for the small intestinal mRNA levels, although the degree of elevation was small (data not shown).

Fig. 3. Effects of pioglitazone (A) and bezafibrate (B) on size distribution of intestinal polyps in Apc1309 mice. Apc1309 mice were fed basal diet (closed box) or diet containing 100 ppm (open box) or 200 ppm (cross-hatched box) pioglitazone or bezafibrate for 6 weeks. Polyps were grouped at intervals of 0.5 mm according to their diameters. The number of polyps/mouse in each size class is expressed as the means; bars, SE.

Fig. 4. Decrease of LPL mRNA expression in the liver and small intestine of Apc1309 and Min mice. A, RT-PCR analysis of LPL mRNA expression in the liver of Apc1309 mice at 12 weeks of age and Min mice at 15 weeks of age. Wild-type mice for comparison were the same ages in each case. B, RT-PCR analysis of LPL mRNA expression in the normal mucosa (N) and polyp (P) of small intestine of Apc1309 and wild-type mice at 12 weeks of age. Data are representative of three separate experiments.

PPARγ and PPARα Expression in Small Intestinal Polyps. The presence of PPARγ in the small intestines of female Apc1309 mice at 12 weeks of age was immunohistochemically confirmed in polyp epithelium and normal crypt epithelial cells. Diffuse staining of PPARγ of epithelial cells of polyps and the bases of crypts was evident in the cytoplasm and nuclei (data not shown). Localization and staining intensity of PPARγ in small intestinal epithelium of the wild-type mice was the same as in normal epithelium in Apc1309 mice. The expression pattern of PPARα was also similar to that for PPARγ. In the case of Min mice at 15 weeks of age, the localization and staining intensity of PPARγ and PPARα in small intestinal epithelium were also the same as in Apc1309 mice. Control sections without primary antibodies showed no staining. Administration of pioglitazone or bezafibrate did not significantly alter the expression or localization of PPARγ and PPARα in polyps and normal mucosa of Apc1309 mice when compared with the nontreated group.

DISCUSSION

The present study clearly demonstrated a hyperlipidemic state in two strains of FAP model mice. The levels of serum lipids, especially triglycerides, were thus dramatically increased with age in both Apc1309 and Min cases, with marked centrilobular-restricted steatosis observed in the livers. Moreover, LPL mRNA levels in the livers and small intestines of these mice were markedly lower than those of wild-type mice. Administration of the PPARγ ligand, pioglitazone, or the PPARα ligand, bezafibrate, reduced both the serum level of triglycerides and intestinal polyp formation in the Apc1309 mice. The mRNA levels of LPL in the liver and small intestine were increased by pioglitazone or bezafibrate. It is therefore speculated that low levels of LPL mRNA expression may be associated with hyperlipidemia in Apc1309 and Min mice and involved in intestinal polyp development.

It has been reported that there are no accompanying increases in serum triglycerides and total cholesterol in rats with colon tumors induced by 1,2-dimethylhydrazine (36). We also confirmed no changes of serum lipid levels in C57BL/6 mice with colon tumors induced by AOM (data not shown). Therefore, tumor development itself may not cause hyperlipidemia. The deficiency in the Apc gene may be related not only to development of intestinal polyps but also to hyperlipidemia via decreased LPL gene expression. Inactivation of normal Apc function leads to accumulation of β-catenin and activation of the Wnt signaling pathway, in which the complex of β-catenin and the T-cell factor acts as a transcriptional factor. Thus far, c-myc, cyclin
D1, matrilysin, MDR1, gastrin, Id2, and PPARδ have been identified as target genes of Wnt signaling relevant to carcinogenesis (37–40). At present, the biological relationship between Apc deficiency and severe hyperlipidemic state is uncertain, but a report has been published that Wnt signaling maintains preadipocytes in an undifferentiated state through inhibition of the adipogenic transcription factors, CCAAT/enhancer binding protein α, and PPARγ (41). Moreover, transcriptional induction of the LPL gene has been reported to be mediated through binding of PPAR-retinoid X receptor heterodimers to the functional PPRE sequence in the LPL gene promoter (17). LPL catalyzes the rate-limiting step for clearance of triglycerides from the blood (17), and decrease of LPL mRNA levels results in elevation of serum lipid levels. Regarding lipid lowering drugs, fibrates predominantly affect liver LPL production through activation of PPARα (17). Moreover, the present study clearly showed that pioglitazone, as well as bezafibrate, raises the hepatic mRNA levels of LPL. It is therefore speculated that both PPARα and the retinoid X receptor. Thus, PPARγ may act as a suppressor of the Wnt pathway, and the decreases of polyp numbers in Apc1309 mice by pioglitazone in the present study might be resulted from such suppression. Ginrun et al. (42) also reported no difference in the number of colon tumors between Apc+/+ and Apc−/− mice at 65 weeks of age. However, the authors did not mention the serum lipid levels of these animals. Moreover, in contrast to Apc1309 and Min mice, the incidence and multiplicity of intestinal polyps in Apc+1638N, Pparγ−/−, and Apc+/+ mice at 63 weeks of age were very small (24). It is therefore speculated that the change of lipid metabolism in Apc-deficient mice may differ between strains, associated with the severity of polyp formation. A hyperlipidemic state could enhance the growth of intestinal polyps, and improvement of hyperlipidemia by treatment with PPAR ligands might thus reduce their size in Apc1309 mice. Furthermore, it has been reported that indomethacin, a nonsteroidal anti-inflammatory drug and cyclooxygenase inhibitor that suppresses intestinal polyp development in Min mice (43), can activate PPARα and γ in vitro (44). The relation between Apc deficiency and changes of lipid metabolism with age and the influence of hyperlipidemia on intestinal polyp development are now under detailed investigation in our laboratory.

It has been reported that polyp formation in the colon of the Min mice is enhanced by 2000 ppm or 150 mg/kg troglitazone, whereas that in the small intestine is not affected (19, 20). In the present study, such promotion of colon polyp formation was not observed in Apc1309 mice treated with 100 and 200 ppm pioglitazone. Indeed, a clear suppressive effect on small intestinal polyp development was evident in these groups. Chemically induced ACF formation in the rat colon has also been shown to be suppressed by treatment with 100 ppm troglitazone and 100 ppm pioglitazone (18). Our preliminary study with a wide range of pioglitazone doses (50, 100, 200, 400, 800, and 1600 ppm in diet) in Apc1309 mice confirmed that small intestinal polyp development was suppressed at doses of 100 and 200 ppm and that the numbers of polyp in the colon and the small intestine were not increased up to 1600 ppm. It has been reported that low doses of PPARγ ligands are tumor promotive, whereas they are tumor suppressive at higher levels in breast cancer cells (45). Dose response effects of pioglitazone across a wide range on intestinal polyp formation in Min mice are also now under investigation in our laboratory.

In conclusion, the present study demonstrated that the PPAR ligands, pioglitazone and bezafibrate, have the potential to suppress both hyperlipidemia and polyp formation in Apc gene knockout mice. It is very important to now elucidate the mechanisms underlying the hypertriglyceridemia in FAP model mice and the roles of PPARγ and/or PPARα in intestinal polyp development.

REFERENCES


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