Obesity is associated with infiltration of macrophages into adipose tissue. Adipose macrophages may contribute to an elevated inflammatory status by secreting a variety of proinflammatory mediators, including tumor necrosis factor α and interleukin-6 (IL-6). Recent data suggest that during diet-induced obesity the phenotype of adipose-resident macrophages changes from alternatively activated macrophages toward a more classical and pro-inflammatory phenotype. Here, we explore the effect of peroxisome proliferator-activated receptor γ activation on obesity-induced inflammation in 129Sv mice fed a high fat diet for 20 weeks. High fat feeding increased bodyweight gain, adipose tissue mass, and liver triglycerides. Rosiglitazone treatment further increased adipose mass, reduced liver triglycerides, and changed adipose tissue morphology toward smaller adipocytes. Surprisingly, rosiglitazone remarkably increased the number of macrophages in adipose tissue, as shown by immunohistochemical analysis and quantification of macrophage marker genes CD68 and F4/80+. In adipose tissue, markers for classically activated macrophages including IL-18 were down-regulated, whereas markers characteristic for alternatively activated macrophages (arginase 1, IL-10) were up-regulated by rosiglitazone. Importantly, conditioned media from rosiglitazone-treated alternatively activated macrophages neutralized the inflammatory status by secreting a variety of proinflammatory mediators such as IL-10, IL-1 receptor antagonist, and arginase I (9).

The global prevalence rate of obesity is rising steadily (1). Obesity is linked to several metabolic disturbances that greatly increase morbidity risk, which are collected in the metabolic syndrome and include hypertension, dyslipidemia, and insulin resistance (2). Each serves as an independent risk factor for atherosclerosis and associated coronary heart disease. Although the overall negative impact of obesity and metabolic syndrome on morbidity is evident, it has been very difficult to get a handle on why some individuals are obese seemingly without any damaging consequences for health, whereas others are afflicted by a range of metabolic abnormalities. Clearly, our understanding of the chain of events that leads to metabolic syndrome, although growing, is still remarkably scarce. Recent studies suggest an important role for inflammatory processes. Indeed, it has been found that obesity is associated with a state of chronic low grade inflammation which is likely caused by adipocyte hypertrophy together with infiltration of macrophages into adipose tissue (3). As a result, the secretion of pro-inflammatory mediators such as tumor necrosis factor α and IL-6 from adipose tissue is increased, leading to disruption of normal homeostatic control of metabolism either locally or systemically (4–6). Why macrophages infiltrate adipose tissue during obesity is currently unclear, although it has been suggested that macrophage localization and infiltration is strongly linked to adipose cell death (7). More recently, it has been proposed that adipose tissue resident macrophages itself undergo phenotypic changes during obesity. In adipose tissue of mice rendered obese by high fat feeding, macrophages appear to be mainly activated according to “classical activation,” whereas macrophages present in adipose tissue of lean mice are “alternatively activated” (8). Classically activated macrophages express high levels of pro-inflammatory mediators including tumor necrosis factor α, which may contribute to insulin resistance. In contrast, alternatively activated macrophages are considered anti-inflammatory by expressing genes such as IL-10, IL-1 receptor antagonist, and arginase I (9).

The peroxisome proliferator-activated receptor γ is a ligand-activated transcription factor and member of the superfamily of nuclear receptors. It regulates gene transcription by binding to specific DNA sequences in target genes, leading to chromatin remodeling and activation of gene transcription. PPARγ serves as the molecular target for an important class of anti-diabetic drugs.

The abbreviations used are: IL, interleukin; PPAR, peroxisome proliferator-activated receptor; qPCR, quantitative PCR; LFD, low fat diet; HFD, high fat diet; FCS, fetal calf serum.
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TABLE 1
Primer sequences used for qPCR

| Gene        | Forward primer              | Reverse primer          |
|-------------|-----------------------------|-------------------------|
| 36B4        | AGGCGCTTCTTCGACGGAAAGACA    | GGCGACAGGCTGCTGGAGCAC   |
| UCP1        | TCTCCATTACCGCCTGGATGTTT     | CCAATGACCGCTTCTGGAGTC   |
| CPT-1b      | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| CD36        | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Adiponectin | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Glut4       | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| CD68        | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| F4/80+      | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Cycin A2    | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Cycin B     | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Clec7a      | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Arginase 1  | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| IL-10       | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| sIL-1ra     | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| IL-18       | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| MCP-1       | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| MSR1        | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| SAA3        | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Fibr-B      | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| IL-6        | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |
| Leptin      | GAGCACTGCCTGGATGTTT         | CACGATACAGGAGAGAGC      |

—Sv129 male mice were purchased at The Jackson Laboratory (Bar Harbor, ME). Male mice received a low fat diet (LFD) or low fat diet (HFD) for 21 weeks, providing 10 or 45% energy percent in the form of triglycerides (D12450B or D12451, Research Diets, New Brunswick, NJ).

The aim of the present study was to examine the effect of rosiglitazone on macrophage infiltration in Sv129 mice rendered obese by chronic feeding of a high fat diet. Our data indicate that short term rosiglitazone treatment increases infiltration of alternatively activated macrophages in adipose tissue.

MATERIALS AND METHODS

Animal Study—Sv129 male mice were purchased at The Jackson Laboratory (Bar Harbor, ME). Male mice received a low fat diet (LFD) or low fat diet (HFD) for 21 weeks, providing 10 or 45% energy percent in the form of triglycerides (D12450B or D12451, Research Diets, New Brunswick, NJ). The lard component in these diets was replaced by palm oil. In the last week of diet intervention, half of the mice receiving the HFD were switched to HFD supplemented with rosiglitazone (0.01% w/w). At the end of the feeding experiment, blood was collected in EDTA-coated tubes and centrifuged at 10,000 × g to collect plasma. Liver and epididymal white adipose tissue were dissected, weighed, and immediately frozen in liquid nitrogen. The animal experiments were approved by the animal experimentation committee of Wageningen University.

Microarray Analysis, RNA Isolation, and Quality Control—Total RNA was isolated from adipose tissue or 3T3-L1 adipocytes using TRIzol reagent (Invitrogen) according to the manufacturer’s instructions. Concentrations and purity of RNA samples were determined on a NanoDrop ND-1000 spectrophotometer (Isogen, Maarssen, The Netherlands). RNA integrity was checked on an Agilent 2100 bioanalyzer (Agilent Technologies, Amsterdam, the Netherlands) with 6000 Nano Chips.

Pooled RNA samples from five mice per experimental group were used for microarray analysis. Samples were hybridized on Affymetrix GeneChip Mouse Genome 430A arrays. Expression levels were calculated applying the multi-chip modified gamma model for oligonucleotide signal (multi-mgMOS) (20) and a remapped Gene Chip Description (CDF) File (21). Detailed descriptions of the applied methods are available on request. Microarray data were submitted to the NCBI gene expression and hybridization array data repository. The assigned GEO accession number is GSE11295.

Ingenuity Pathway Analysis (Ingenuity Systems, Redwood City, CA) was used to identify the most significantly changed cellular pathways using input criteria of a relative fold change above 2 or below −2 and a p value similar to or below 0.001.

Real-time PCR—1 µg of RNA was used for reverse transcription using the iScript cDNA Synthesis Kit (Bio-Rad). Real-time PCR was done with platinum Taq polymerase (Invitrogen) and SYBR Green using an iCycler PCR machine (Bio-Rad). Melting curve analysis was included to assure a single PCR product was primed by polyunsaturated fatty acids and fatty acid-derived molecules. The expression of PPARγ is highest in adipose tissues, where it plays a pivotal role in the adipocyte differentiation and lipid storage (10, 11). PPARγ is also relatively well expressed in macrophages. Target genes of PPARγ identified so far include fatty acid-binding protein 4, GLUT4, glycogen synthase 2, glycerol-3-phosphate dehydrogenase, lipoprotein lipase, glyceral kinase, and aquaporin 7 (12, 13).

As mentioned above, PPARγ is the molecular target for the insulin-sensitizing thiazolidinediones, which effectively lower plasma glucose and insulin levels by promoting insulin sensitivity and, thus, stimulating glucose uptake. Thiazolidinediones also reduce plasma free fatty acid concentrations, although this effect is mainly evident in rodents (14, 15).

In addition to its role in adipocyte differentiation and glucose metabolism, PPARγ also has potent anti-inflammatory activity. Treatment of mice with rosiglitazone causes a significant decrease in expression of numerous inflammatory mediators, including tumor necrosis factor α and IL-6 (16). In adipose tissue, induction of adipocyte differentiation by PPARγ is paralleled by the appearance of smaller adipocytes (17), which may partially account for the inhibitory effect of PPARγ on inflammatory gene expression (18). Furthermore, it has been suggested that PPARγ may suppress inflammation associated with diet-induced obesity by lowering the number of macrophages present in adipose tissue (5, 19).

The aim of the present study was to examine the effect of rosiglitazone on macrophage infiltration in Sv129 mice rendered obese by chronic feeding of a high fat diet. Our data indicate that short term rosiglitazone treatment increases infiltration of alternatively activated macrophages in adipose tissue.
formed. The primers used are listed in Table 1. The mRNA expression of all genes reported was normalized to 36B4 gene expression.

Histology/Immunohistochemistry—For detection of macrophages/monocytes, an F4/80+ antibody (Serotec, Oxford, UK) was used. Sections were preincubated with 20% normal goat serum followed by overnight incubation at 4 °C with the primary antibody diluted 1:50 in phosphate-buffered saline, 1% bovine serum albumin. After incubation with the primary antibody, a goat anti-rat IgG conjugated to horseradish peroxidase (Serotec) was used as a secondary antibody. Visualization of the complex was done using 3,3′-diaminobenzidine for 5 min. Negative controls were used by omitting the primary antibody. Hematoxylin and eosin staining of sections was done using standard protocols. The percentage of F4/80+ cells was assessed using digital image analysis. Microscopic images were formed. The primers used are listed in Table 1. The mRNA expression of all genes reported was normalized to 36B4 gene expression.

RESULTS

Rosiglitazone Treatment of Obese Mice Increases Adipose Mass Together with Up-regulation of PPARγ Target Genes—Sv129 mice were fed a LFD or HFD for 20 weeks. Although energy intake was similar (Fig. 1A), mice on HFD showed a significantly higher bodyweight gain compared with mice on LFD (Fig. 1B). Adipose tissue weight at the end of the study was also significantly higher in the HFD animals (Fig. 1D). One week of rosiglitazone treatment of mice fed the HFD further increased adipose tissue weight (Fig. 1D) and plasma leptin concentrations (Fig. 1E). HFD also significantly increased plasma insulin (Fig. 1F), suggesting development of insulin resistance as well as liver triglycerides (Fig. 1G), which were reversed by rosiglitazone. The increase in adipose tissue weight and decrease in liver triglyceride content strongly suggests redistribution of liver fat toward white adipose tissue after rosiglitazone treatment. Rosiglitazone also caused a marked increase in the expression of several PPARγ target genes in adipose tissue including UCP-1 and CPT-1b (Fig. 1H). In line with previous data, an overall change in adipocyte size was observed after rosiglitazone treatment resulting in the appearance of smaller adipocytes (Fig. 1I and J).

Rosiglitazone Treatment Promotes Macrophage Infiltration—Besides an increase in adipose mass, rosiglitazone treatment promoted formation of clusters of cells surrounding adipocytes, as revealed by 4′,6-diamidino-2-phenylindole nuclear staining, suggesting the presence of cell aggregates (Fig. 2A).
The clusters of cells strongly resembled so-called Crown-like structures that are formed by aggregated macrophages in adipose tissue of obese mice (7). To analyze if more macrophages were present in adipose tissue after rosiglitazone treatment, immunohistochemical staining using the specific macrophage marker F4/80 was performed. As shown in Fig. 2B, rosiglitazone increased F4/80 staining, suggesting more macrophages were present. These results were corroborated by quantitative analysis of the number of macrophages present in adipose tissue (Fig. 2C) and gene expression analysis of F4/80 and CD68, another macrophage specific gene (Fig. 2D). In agreement with an increased macrophage content, expression of MCP-1 was up-regulated by rosiglitazone in total adipose tissue (Fig. 2D). These data suggest that short term rosiglitazone treatment stimulates macrophage infiltration in adipose tissue of obese mice. Noticeably, plasma concentrations of MCP-1 were not elevated after rosiglitazone treatment and even showed a tendency toward a decrease (data not shown), suggesting that MCP-1 expression is increased only locally.

To examine the effect of rosiglitazone and the increased abundance of macrophages on global adipose gene expression, microarray analysis was performed in animals fed HFD with or without rosiglitazone. As expected, rosiglitazone significantly changed genes involved in lipid metabolism and energy production (Fig. 3). More surprisingly, cell cycle, tissue morphology, and connective tissue development were significantly altered after rosiglitazone treatment, suggesting changes in adipose tissue structure and composition.

Rosiglitazone Increases Adipose Abundance of Alternatively Activated Macrophages—Macrophages can either be activated by T helper 1-type responses via interferon γ and by alternative activation via T helper 2-type cytokines. The latter response, which is stimulated by IL-4 and IL-13, elicits a macrophage phenotype connected with tissue repair and remodeling and blockade of inflammation (9). To investigate the effects of rosiglitazone on adipose tissue macrophage polarization, the expression of several macrophage markers was determined in adipose tissue (Fig. 4). Strikingly, adipose expression of sIL-1ra, Clec7a, arginase 1, MSR1, and IL-10, which are markers characteristic of alternatively activated macrophages (9, 22, 23), were all significantly increased by rosiglitazone treatment. In contrast,
expression of IL-18, a cytokine linked to the classical activation of macrophages via T helper 1 type responses (24), was decreased by rosiglitazone. Expression levels of fibrinogen, serum amyloid A3, and IL-6 were also down-regulated by rosiglitazone, although the latter failed to reach statistical significance. Rosiglitazone did not alter adipose expression levels of CD11c, suggesting no change in the number of pro-inflammatory classically polarized macrophages (8).

To investigate whether the changes in total adipose tissue gene expression were specific for the stromal vascular fraction containing adipose tissue macrophages, adipose tissue from was fractionated into stromal vascular cells and adipocytes. As expected, leptin was predominantly expressed in the adipocyte fraction (Fig. 5A). In the stromal vascular fraction, rosiglitazone significantly up-regulated expression of arginase I and sIL-1ra (Fig. 5B). In contrast, rosiglitazone down-regulated expression of IL-18. Thus, changes in expression of markers genes observed in stromal vascular cells mirrored those in white adipose tissue. Taken together, these data suggest that rosiglitazone increases the presence of alternatively activated macrophages in adipose tissue.

It has been reported that alternatively activated macrophages stimulate cell proliferation (9). As mentioned above, global analysis of gene expression by microarray indicated that rosiglitazone altered expression of genes related to cell cycle, proliferation, and tissue morphology (Fig. 3). Therefore, we analyzed expression levels of cyclin A2 and cyclin B in total white adipose tissue. Remarkably, expression of both genes was significantly
more pronounced induction was observed using conditioned medium from macrophages treated with both IL-4 and rosiglitazone. The effect was accompanied by a significant increase in expression of adipogenic marker genes (Fig. 6B). These data suggest that rosiglitazone may deactivate the inhibitory effect of macrophages on adipocyte differentiation via a mechanism involving alternatively activated macrophages.

**DISCUSSION**

Obesity is associated with the infiltration of macrophages into adipose tissue, which may contribute to an elevated inflammatory status by secreting a variety of pro-inflammatory mediators, including tumor necrosis factor α and IL-6. MCP-1 has been identified as an important chemo-attractant responsible for the recruitment of macrophages into adipose tissue (6, 25). Previous studies suggest that PPARγ may counteract obesity-induced inflammation in adipose tissue via several mechanisms (26) including down-regulation of chemo-attractant and pro-inflammatory genes (5), apoptosis of adipose-resident macrophages (19), and changing the morphology of adipose tissue toward smaller adipocytes (27). In contrast to previous studies, in our study treatment with rosiglitazone was associated with a marked increase in the number of macrophages present in adipose tissue, as evidenced by (immuno)histological staining and measurement of expression of macrophages markers genes. In support of these data, we found that rosiglitazone increased expression of MCP-1 in adipose tissue leading to an influx of monocytes and macrophages. This is in contrast to previously reported data showing a reduction of MCP-1 expression in adipocytes after PPARγ activation (28). However, results in this study were obtained using isolated human whole adipose tissue. In addition, activation of PPARγ might have differential effects in obese versus lean animals. Whereas treatment of lean mice with rosiglitazone might reduce MCP-1 expression, short term PPARγ activation in obese animals might lead to increased MCP-1 expression and an influx of macrophages. These macrophages are possibly involved in remodeling of adipose tissue to accommodate the PPARγ-dependent influx of triglycerides originating from other tissues.

Recently, it was reported that obesity leads to polarization of adipose-resident macrophages toward a M1 phenotype. M1-polarized macrophages secrete higher levels of pro-inflammatory genes and likely contribute to obesity-induced inflammation (8). The increased expression of arginase I and sIL-1ra and decreased expression of IL-18 in rosiglitazone-treated animals is indicative of re-polarization of adipose macrophages toward an M2 phenotype. In contrast to our results, MCP-1 has been reported to mainly attract M1-polarized macrophages (29). Nevertheless, it has been suggested that M1 and M2 macrophages can switch from one phenotype to another (9). The increased adipose expression of MCP-1 after rosiglitazone treatment might indeed lead to a higher influx of M1 macrophages. However, the local environment created by the activation of PPARγ might induce a switch from M1- to toward M2-activated macrophages after infiltration of the adipose tissue. In as much as M2 or alternatively activated macrophages possess mainly anti-inflammatory properties, the switch in macro-

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**FIGURE 5. Rosiglitazone increases the expression of markers for alternatively activated macrophages in the stromal vascular fraction of mice fed a HFD.**

*Panel A:* Selective expression of leptin in the adipocyte fraction of white adipose tissue. In the rosiglitazone-induced changes in expression of marker genes for alternatively activated macrophages in the stromal vascular fraction of mice fed a HFD, as determined by qPCR. Gene expression levels in HFD-fed animals were set at 1. Error bars represent S.E. Differences were evaluated using Student’s t test. *, p < 0.05; **, p < 0.01; ***, p < 0.001.

*Panel B:* Increased expression of arginase I and sIL-1ra with rosiglitazone treatment, as determined by qPCR. Gene expression levels in LFD-fed animals were set at 1. Error bars represent S.E. Differences were evaluated using Student’s t test. *, p < 0.05; **, p < 0.01; ***, p < 0.001.

*Panel C:* Roiglitazone increased expression of cyclin A2 and B, which are involved in the DNA replication phase after rosiglitazone treatment, as determined by qPCR. Gene expression levels in LFD-fed animals were set at 1. Error bars represent S.E. Differences were evaluated using Student’s t test. *, p < 0.05; **, p < 0.01; ***, p < 0.001.
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A

B

FIGURE 6. Conditioned medium from IL-4- and rosiglitazone-treated macrophages deactivates the inhibitory effect of macrophages on adipogenesis. A, representative Oil Red O staining of 3T3-L1 adipocytes after 6 days of differentiation. During differentiation, 3T3-L1 cells were incubated with conditioned media from RAW264.7 cells treated with vehicle, IL-4, rosiglitazone, or IL-4 and rosiglitazone. B, expression of adipogenic marker genes, as determined by qPCR. Control, medium from untreated RAW264.7 macrophages; IL-4, medium from IL-4-treated RAW264.7 macrophages; Rosi, medium from rosiglitazone-treated RAW264.7 macrophages; IL-4 + Rosi, medium from IL-4- and rosiglitazone-treated RAW264.7 macrophages. Gene expression levels from 3T3-L1 cells treated with medium from untreated RAW264.7 macrophages were set at 1. Error bars represent S.E. Differences were evaluated using a Students t test. *p < 0.05 (**), p < 0.01 (**), and p < 0.005 (***) compared with 3T3 adipocytes treated with control-conditioned medium.

phage phenotype may be partially responsible for the suppression of inflammatory gene expression by rosiglitazone.

It can be hypothesized that changes in macrophage population may contribute to PPARγ-dependent remodeling and expansion of adipose tissue. Alternatively activated macrophages have been linked to tissue repair and cell proliferation. Indeed, co-culture experiments have shown that alternatively activated macrophages can positively influence proliferation of neighboring cells (30). According to our data, rosiglitazone altered expression of genes related to cell cycle, proliferation, and tissue morphology, including cyclin A2 and cyclin B. The increase in cell cycle-related genes in the result of increased numbers of alternatively activated macrophages in adipose tissue rather than direct stimulation of gene expression by PPARγ.

Interestingly, we observed that conditioned medium from alternatively activated macrophages treated with rosiglitazone neutralized the inhibitory effect of conditioned medium from untreated macrophages on 3T3-L1 adipogenesis. Accordingly, it suggests that the rosiglitazone-induced switch from classical to alternatively activated macrophages may underlie the effects of rosiglitazone on adipose tissue remodeling and growth.

PPARγ is well expressed in adipocytes and macrophages. From our study it is not possible to derive any conclusions regarding the role of macrophages versus adipocyte PPARγ in mediating the effect of rosiglitazone on total macrophage abundance as well as on macrophage polarization. While this manuscript was in preparation, two reports were published addressing the role of macrophage PPARγ in the development of obesity-induced inflammation and insulin resistance using macrophage-specific PPARγ knock-out mice (31, 32). However, after HFD feeding the macrophage-specific PPARγ knock-out mice became more obese, fewer macrophages were present in adipose tissue (31). Supporting our data, expression of markers of alternatively activated macrophages in adipose tissue was strongly decreased in animals lacking PPARγ in macrophages, which likely accounted for the increase in inflammatory gene expression, including IL-6 and Nos2. Importantly, the absence of PPARγ in macrophages aggravated insulin resistance, especially after HFD. These data suggest that macrophage PPARγ plays a major role in determining macrophage polarization in adipose tissue, thereby suppressing production of inflammatory mediators as well as in mediating the effect of thiazolidinediones on insulin sensitivity.

In contrast with previous data showing a decrease in adipose tissue macrophage content after long term rosiglitazone treatment due to apoptosis (19), our data suggest that short term treatment increases the adipose presence of alternatively activated macrophages. Future studies should address the effects of short versus long term rosiglitazone treatment. Whereas short term exposure to rosiglitazone induces macrophage infiltration, longer treatment might eventually lead to apoptosis of macrophages after successful PPARγ-dependent adipose tissue remodeling and expansion.

In conclusion, we show that short term PPARγ activation in the context of HFD-induced obesity promotes macrophage infiltration into adipose tissue while simultaneously reducing inflammatory gene expression. The majority of the newly recruited macrophages is alternatively activated and may play an important role in PPARγ-dependent adipose tissue remodeling and expansion.

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