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Rosiglitazone Inhibits HMC-1 Cell Migration and Adhesion through a Peroxisome Proliferator-Activated Receptor Gamma-Dependent Mechanism

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ABSTRACT

Mast cells play an important role in a variety of inflammatory diseases, particularly asthma and atopy. Peroxisome proliferator-activated receptor gamma (PPARγ) is a member of the large nuclear hormone receptor transcription factor superfamily, and has been recently implicated in the anti-inflammatory response.

To investigate a possible role for PPARγ in human mast cells, we studied the effects of a PPARγ ligand, rosiglitazone (RG), on stem cell factor (SCF)-induced migration and fibronectin-induced adhesion in human mast cell-1(HMC-1) cells.

It was found that HMC-1 cells expressed PPARγ mRNA. RG inhibited SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion, the selective PPARγ antagonist GW9662 prevented the inhibitory effect of RG on HMC-1 cells.

In conclusion, RG inhibits the migration and adhesion of HMC-1 cells by a PPARγ-dependent mechanism.

Keywords: Adhesion; Mast cells; Migration; PPARγ; Rosiglitazone

INTRODUCTION

Mast cells reside in connective tissues and migrate to sites of tissue injury and inflammation, where they presumably play a role in regulating both the inflammatory response and tissue repair.[1] Mast cells mature in peripheral tissues, and committed progenitors are detected only in low numbers in the bone marrow and blood.[2-4] Once recruited to the tissues, the multivalent binding of an antigen to receptor-bound immunoglobulin (Ig) E and the subsequent aggregation of the high-affinity IgE receptor (FcεRI) provide the trigger for the activation of mast cells.

This leads to the secretion of a variety of pro-inflammatory mediators, such as histamine, cytokines and prostaglandin, ultimately resulting in the genesis of the disease process.[5] Therefore, diminishing mast cell recruitment during inflammation may reduce the number of mast cells recruited to the affected tissues, and thereby attenuate the subsequent effect of mast cell activation at these locations.

Peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor that belongs to the

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steroid hormone receptor superfamily, and possesses both a DNA binding domain and ligand binding domain.[6] Endogenous ligands of PPARγ include oxidized fatty acids and prostanoids, while synthetic ligands include the thiazolidinedione (TZD) class of antidiabetic drugs (e.g., ciglitazone and rosiglitazone [RG]).[6] After activation, PPARγ can mediate, via transcriptional regulation, various metabolic processes that influence lipid metabolism, glucose homeostasis, cell differentiation, cancer, inflammation, and the vasculature.[7,8] Many studies, performed in vitro, in animal models, and in humans, have shown that PPARγ agonists have anti-inflammatory properties.[9] Moreover, it has been reported that PPARγ agonists can negatively regulate the activation of various pathways in mouse and human mast cells, such as histamine release and the production of cytokines, including tumor necrosis factor-alpha (TNF-α), interlukin-5 (IL-5) and macrophage inflammatory protein-1α.[10] These data indicate an immunoregulatory effect of PPARγ agonists on mast cells. Additionally, it has been reported that PPARγ ligand, RG can inhibit the migration of dendritic cells from the airway mucosa to the lymph nodes of the thorax.[11] However, whether PPARγ agonists can modulate the migration and adhesion of mast cells is presently unknown. The current study explores the effects of RG on both stem cell factor (S*CF)*-induced human mast cell-1 (HMC-1) cell migration and fibronectin-induced HMC-1 cell adhesion.

MATERIALS AND METHODS

Materials and Cell Culture

Iscove's Modified Dulbecco's Medium (IMDM) and fetal bovine serum (FBS) were obtained from Gibco-BRL (Gaithersburg, MD, USA). Cell culture materials and transwell chambers were obtained from Costar (Corning, NY, USA). RG and GW9662 were purchased from Cayman Chemical (Ann Arbor, MI, USA). 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), dimethylsulphoxide (DMSO) and SCF were purchased from Sigma-Aldrich (St Louis, MO, USA) . The human mast cell line HMC-1 was the kind gift of Dr. Butterfield (Mayo Clinic, Rochester, Minn., USA), and they were maintained at 37°C in a 5% CO2 atmosphere in IMDM supplemented with 10% heat-inactivated fetal bovine serum, penicillin (100 U/ml), and streptomycin (100 μg/ml*).*

Drug Treatment Protocol

GW9662 and RG were dissolved in DMSO and stock solutions of RG (10 mM) and GW9662 (10 mM) were prepared, which were then diluted with IMDM. The selective PPARγ antagonist GW9662 (0.1-1 μM) was added 30 min prior to the addition of RG. Cells were then pretreated with RG (1-10 μM) for 1 h.

MTT Assay

We performed the MTT assay to measure the cell viability. First, 5×10^4 HMC-1 cells in 100 μl of the culture medium were seeded into a 96-well culture plate. RG (1–10 μM) and GW9662 (0.1-1 μM) were added to the individual wells. The plate was then incubated for 24 h at 37°C in a CO_2 incubator. Following the addition of 10 μl of MTT solution (5 mg/ml) in each well, the plate was incubated at 37°C for 4 h in a CO_2 incubator. The formazan crystals that had formed, were then solubilized with 100 μl DMSO by gentle shaking for 15 min. The Absorbance at 570 nm was recorded within 30 min using a microplate reader (Tecan, Clontarf, Australia).

Apoptosis Assay

The effects of RG and GW9662 on the induction of apoptosis in the HMC-1 cell line were examined by flow cytometry with the FITC-Annexin V apoptosis kit (BD Biosciences, San Jose, CA, USA). Cells were treated or not with GW9662 (1 μM) at 37°C for 30 min, and then treated with RG (10 μM) at 37°C for 1 h. After incubation, cells were washed and stained with fluorescein isothiocyanate (FITC)-labeled annexin V (AN) and Propidium Iodide (PI) according to manufacturer's instructions (BD Biosciences). Cells (10^4) were then analyzed by flow cytometry (Epics Altra; Beckman, Seattle, WA), and the AN^-/ PI^-, AN^+/ PI^-, AN^+/ PI^+ populations were enumerated. The three populations determined by FACS analysis, AN^-/ PI^-, AN^+/ PI^-, and AN^+/ PI^+, correspond to live cells, early apoptotic cells, and necrotic cells, respectively.

Transwell Migration Assays

Mast cell migration was examined with a 24-well microchemotaxis assay. Briefly, the lower wells were filled with either 450 μl buffer alone or with buffer that contained SCF (100 ng/ml).[12] The upper wells were filled with either 50 μl of control HMC-1 cells or 50 μl

of treated HMC-1 cells at 5×10^6 cells/ml in IMDM that contained 1% bovine serum albumin and 30 mM HEPES. Cells were allowed to migrate for 5 h, recovered from the lower chamber, and counted using a hemocytometer. The chemotacticindex (CI) was calculated based on the number of cells that had migrated as compared to the control well.

RNA Isolation and Reverse Transcription-Polymerase Chain Reaction (RT-PCR)

Total RNA was extracted from the HMC-1 cells with a total RNA extraction kit (RNeasy mini kit, Tiangen, China) according to the manufacturer's protocol. Each sample of total RNA was reverse transcribed using a random hexamer and a first-strand cDNA synthesis kit (Toyobo, Japan). Synthesized cDNA were amplified with the following specific primers: human PPARγ,[13] sense 5'-TCTCTCCGTAATGGAAGACC-3' and antisense 5'-GCATTATGAGACATCCCC AC-3' (474 bp); GAPDH, sense 5'-GGTGTGAACCATGAGAAGTATGACA-3' and antisense 5'-GTCCTTCCACGATACCAAAGTTGT-3' (121 bp). The PCR reaction mixture contained 1.5 mM $MgCl_2$, 1 µM of each primer, 2.5 U Taq DNA polymerase (Tiangen, China), and 200 µM each of dCTP, dTTP, dGTP, and dATP. The thermocycling parameters were 38 cycles of 94°C for 30 s, 57°C for 1 min, and 72°C for 1 min, followed by 72°C for 7 min for final elongation. Amplified products were visualized by ethidium bromide staining of 2% agarose gels, and were subsequently confirmed by sequencing.

Adhesion Assay

Adhesion assays were carried out in 24-well flat-bottom microtiter culture plates (Costar). Wells were coated overnight at 4°C with 10 ng/ml fibronectin (Sigma-Aldrich). Plates were then gently washed and remaining binding sites were blocked by incubation with 4% BSA in PBS for 1 h at 37°C, followed by washing. HMC-1 cells were treated or not with GW9662 (0.1-1 µM) at 37°C for 30 min, and then treated with RG (1–10 µM) at 37°C for 1 h. The cells were then resuspended at 5×10^4 cells/ml, and 300 µl of the cell suspension was added to each precoated well. Plates were incubated for an additional 90 min at 37°C. Unbound cells were removed by gentle washes with PBS. The remaining cells were counted under a light microscope.

Statistical Analysis of Results

The data are expressed as mean±SD. Statistical differences were analyzed with the use of a Student's t-test for two-group comparisons. The SPSS statistical software package (Version 13.0, Chicago, IL) was used for statistical analysis. Differences with a p value<0.05 were deemed statistically significant.

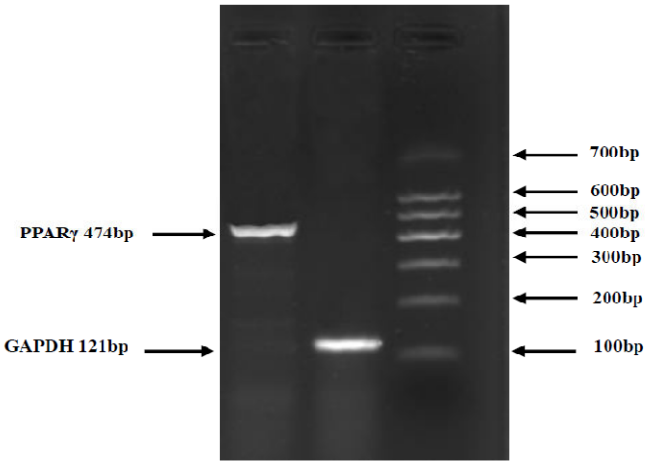

Figure 1. Expression of PPARγ in HMC-1 cells. Total RNA was isolated and reverse transcribed into cDNA. The cDNA was amplified with control primers (GAPDH) or primers specific for PPARγ. Samples without reverse transcriptase were used as negative control for amplification products in all cases.

RESULTS

HMC-1 cells Expressed PPARγ

To test the hypothesis that RG was acting through a PPARγ-dependent pathway, we first determined if HMC-1 cells can express PPARγ. As shown in Figure 1, the HMC-1 cells expressed PPARγ mRNA.

RG and GW9662 Had no Cytotoxic Effect on HMC-1 Cells

Prior to examining the effect of RG and GW9662 on HMC-1 cells, we first examined whether RG and GW9662 affected cell viability. As shown in Figure 2, the survival rate of HMC-1 cells was not altered by treatment with RG at concentrations of 1–10 μM for 24 h, and the survival rate of HMC-1 cells was not altered by treatment with RG at a concentration of 10 μM in the presence of GW9662 at a concentration of 0.1-1 μM. In a short time frame, even in cases where a significant portion of cell population had initiated apoptosis, the total number of cells counted might have been unchanged. Thus, we examined the effect of 5 h incubation with 10 μM of RG or 1 μM of GW9662 on the induction of apoptosis in HMC-1 cells by flow cytometry. Two-color flow cytometric analysis, using AN and PI, could discriminate three populations: viable cells, AN^-/ PI^-; early apoptotic cells, AN^+/ PI^-; and late apoptotic and necrotic cells, AN^+/ PI^+. The percentage of early apoptotic cells in the control population (2.5%) and the cell populations treated with RG or GW9662 (3.3% and 2.6%, respectively) were similar (Figure 3).

RG Inhibited HMC-1 Cell Migration in Response to SCF

Because cell migration is a pivotal step in the inflammatory response, we investigated the change in HMC-1 cell migration after stimulation with the RG. A chemotaxis assay was performed in order to measure the change in HMC-1 cell movement. Different concentrations of RG (1, 3 and 10 μM) were added to cells 1 h prior to the addition of 100 ng/ml of SCF. As shown in Figure 4, RG inhibited the SCF-induced HMC-1 cell migration in a dose-dependent fashion.

RG Inhibition of SCF-Induced HMC-1 Cell Migration was PPARγ-Dependent

To determine whether the effects of RG were dependent on PPARγ activation, the HMC-1 cells were treated with PPARγ antagonist GW9662 (0.1-1 μM) 30 min before RG treatment. As shown in Figure 5, incubation with either 0.3 μM or 1 μM of GW9662 could prevent the inhibitory effect of RG on HMC-1 cell migration, while 0.1 μM of GW9662 had no effect on the inhibition of HMC-1 cell migration by RG. These results indicated that the inhibitory effect of RG on HMC-1 cell migration was PPARγ-dependent.

RG Inhibited Fibronectin-Induced HMC-1 Cell Adhesion

We next examined whether RG modulated HMC-1 cell adhesion to fibronectin, a component of the extracellular matrix. As Fig. 6 shows, fibronectin (100 ng/ml) dramatically induced HMC-1 cell adhesion, with 532±24.576 adherent cells in the fibronectin group and 202±18.083 adherent cells in control group. To investigate the effect of RG on fibronectin-induced HMC-1 cell adhesion, cells were treated with different

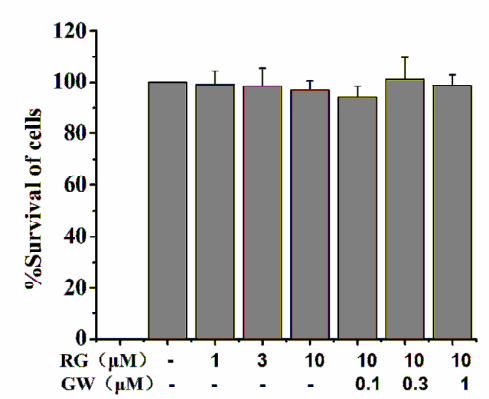

Figure 2. RG and GW9662 had no cytotoxic effect on HMC-1 cells. HMC-1 cells were incubated with RG (1–10 μM) or GW9662 (0.1–1 μM) for 24 h. The survival rate was measured by MTT assay. The data are expressed as the relative ratio to the absorbance of the untreated HMC-1 cells, which was set at 100%. Four replicate measurements are included in each experiment. The data, derived from two independent experiments, are expressed as mean±SD.

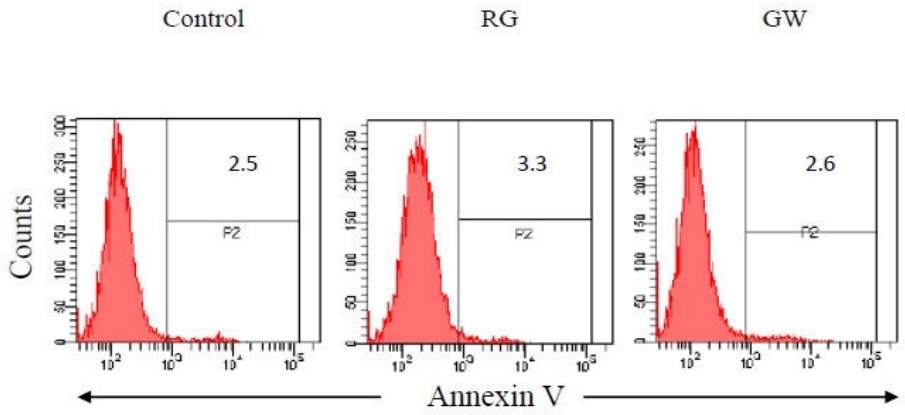

Figure 3. Annexin V apoptosis assay. HMC-1 cells, treated or not with 10 µM RG or 1 µM GW9662 for 1 h, were stained with FITC-labeled annexin V (AN) and Propidium Iodide (PI). The percentage of AN^+/PI^- (early apoptotic) cells is shown. Two independent experiments were carried out, both showing no apoptotic effect of RG or GW9662 treatment on HMC-1 cells.

concentrations of RG (1, 3 and 10 µM) for 1 h before being seeded into fibronectin-precoated wells. As shown in Figure 6, incubation with 3 µM or 10 µM of RG could prevent the fibronectin-induced HMC-1 cell adhesion, while an RG concentration of 1 µM had no effect on the fibronectin-induced HMC-1 cell adhesion.

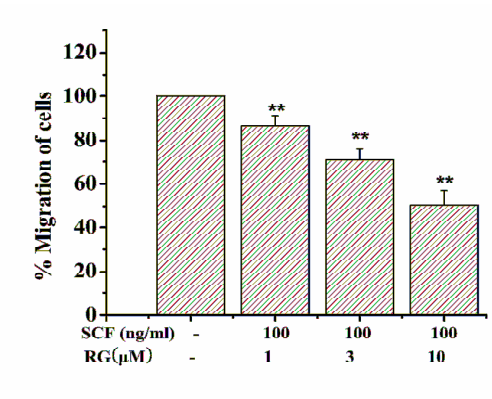

Figure 4. RG inhibited SCF-induced cell migration. HMC-1 cells were pre-incubated in the absence or presence of RG (1–10 µM) for 1 h. The cells were then incubated with 100 ng/ml of SCF in a 24-well microchamber and allowed to migrate for 5 h. The number of cells that migrated in three individual wells was counted under a microscope with a hemocytometer. The data are expressed as mean±SD relative to the negative control, which was set at 100%. **p<0.01 compared with the negative control.

RG Inhibition of Fibronectin-Induced HMC-1 Cell Adhesion was PPARγ-Dependent

To determine whether the inhibition of RG was dependent of PPARγ, the HMC-1 cells were pretreated with PPARγ antagonist GW9662 (0.1-1µM) 30 min

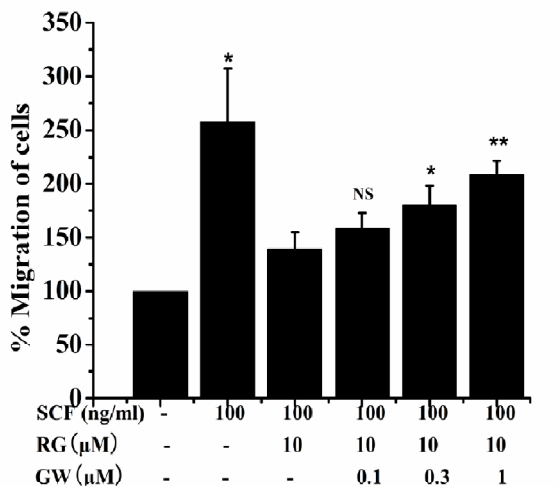

Figure 5. RG inhibition of SCF–induced HMC-1 cell migration is dependent on PPARγ. HMC-1 cells were treated with GW9662 30 min before RG and were allowed to migrate for 5h. The number of cells that migrated was counted in three individual wells under a microscope. The data are expressed as mean±SD relative to the negative control, which was set at 100%. *p<0.05, **p<0.01 and NS (not significant) when compared with the SCF (100ng/ml) and RG (10µM) treatment groups.

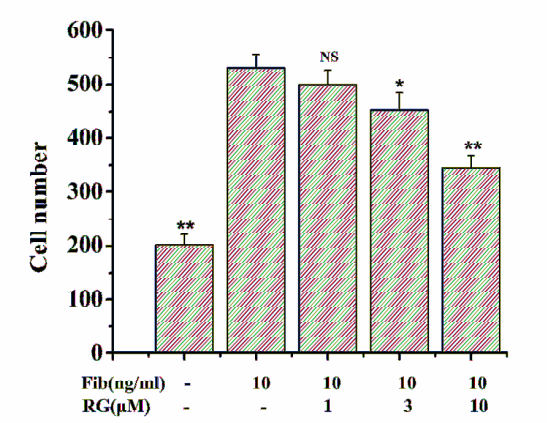

Figure 6. HMC-1 cell adhesion to fibronectin. HMC-1 cells (3×10^4), treated or not with different concentrations of RG (1, 3 and 10 μM) for 1 h, were seeded into 24-well plates, incubated for 1 h, and nonadherent cells were removed by gentle washes with PBS. The remaining cells in three individual wells were counted. The data are expressed as mean±SD. *p<0.05, **p<0.01 and NS (not significant) compared with the fibronectin (10 ng/ml) treatment group.

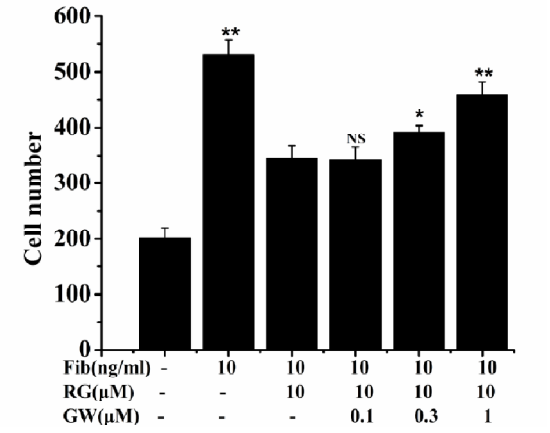

Figure 7. RG inhibition of fibronectin-induced HMC-1cells adhesion was dependent on PPARγ. HMC-1 cells were treated with PPARγ antagonist GW9662 (0.1-1 μM) 30 min prior to RG treatment and were seeded into fibronectin-precoated wells. Plates were incubated an additional 90 min at 37 °C. Unbound cells were removed by gentle washes with PBS. The remaining cells in three individual wells were counted under a light microscope. The data are expressed as mean±SD. *p<0.05, **p<0.01 and NS (not significant) compared with the fibronectin (10ng/ml) and RG (10μM) treatment groups.

before RG treatment. As shown in Figure 7, treatment with 0.3 μM or 1 μM of GW9662 could prevent the inhibition of fibronectin-induced HMC-1 cell adhesion by RG, while the concentration of 0.1 μM of GW9662 treatment was unable to achieve this effect. These results indicated that the inhibition of RG on fibronectin-induced HMC-1 cell adhesion was PPARγ-dependent.

DISCUSSION

PPARγ agonists were initially believed to regulate genes predominantly associated with lipid and glucose metabolism. However, current evidence indicates that PPARγ is present in most cell types (including immune cells, endothelial cells, and neurons) and mediates multiple functions under both physiological and pathological conditions.[14,15] Due to in vivo and in vitro studies performed with different cell types, PPARγ agonists have become a focus of interest because of their anti-inflammatory roles in the immune system. PPARγ agonists can inhibit proinflammatory responses in a variety of cells, including macrophages, dendritic cells, T cells, endothelial cells and vascular smooth muscle cells.[6] Nevertheless, there is little information regarding the role that PPARγ agonists in regulating the migration or adhesion of mast cells, which are important steps in the inflammatory response as well as allergic inflammation. In the current study, we demonstrate that RG, an agonist of PPARγ, can inhibit SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion. Furthermore, we showed that the inhibition was PPARγ-dependent and was not associated with cytotoxicity.

To determine whether RG could be acting through PPARγ to exert its effects, we first determined if HMC-1 cells expressed PPARγ. As shown in Fig. 1, PPARγ was expressed in HMC-1 cells. Sugiyama and his colleagues have also shown that PPARγ was expressed in human cultured mast cells,[13] which was consistent with our results. We then examined whether RG and GW9662 affected cell viability using MTT and flow cytometry. As shown in Fig. 2 and Fig. 3, RG and GW9662 had no cytotoxic effects on HMC-1 cells.

To investigate whether RG affects the migration or adhesion of HMC-1 cells, SCF was employed as a chemotactic factor for HMC-1 cells and fibronectin was utilized to induce HMC-1 cell adhesion. SCF is produced by a variety of cells including endothelial

cells and fibroblasts.[16] Its receptor, c-Kit, is a type III tyrosine kinase broadly expressed on mature mast cells. SCF is a hematopoietic growth factor that promotes survival, proliferation, and differentiation of hematopoietic cells, and is a major chemotactic factor for mast cells.[17] Our results demonstrated that RG inhibits both HMC-1 cell migration in response to SCF (Figure 4) and adhesion in response to fibronectin in a dose-dependent fashion (Figure 6).

The PPARγ-dependence of the effects of RG on SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion was assessed using an antagonist of the PPARγ receptor, GW9662. Our experiments demonstrated that GW9662 (0.3 μM and 1 μM) reversed the inhibitory effect of RG (10 μM) on SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion in a concentration-dependent manner (Figures 5 and 7). These results suggest that RG inhibition on HMC-1 cell migration and adhesion is PPARγ-dependent. In our study, when a low concentration of GW9662 was used (0.1 μM), the treatment had no effect on the inhibition of SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion by RG. However, in a study of thrombin-induced proliferation of HASM, Ward et al. found that incubation with 0.1 μM of GW9662 could reverse the inhibition of the thrombin-induced increase in cell number by 10 μM RG.[18] The difference in the concentration of GW9662 needed to reverse the effect of RG in the study by Ward et al and in our study may be explained by fact that we used a different cell type, a different culture medium and a different measuring method.

To explain how the binding of RG to PPARγ blocks HMC-1 cell migration and adhesion, we considered the following two mechanisms: (1) PPARγ activation induces the transcription of genes; and (2) PPARγ interferes negatively with signal transduction pathways such as NF-kB, AP-1, PI3K and mitogen-activated protein (MAP) kinases, which in turn affects the synthesis of many genes involved in cell function.[19-21] In our study, the inhibitory effect of PPARγ activation by RG on HMC-1 cell migration and adhesion may be linked to its ability to positively or negatively control the expression of genes involved HMC-1 cell motility, such as inflammatory cytokines, chemokines, adhesion molecules, or chemokine receptors. Another possibility is that PPARγ inhibits HMC-1 cell migration and adhesion without a change in gene expression by interfering with intracellular pathways that are directly implicated in cellular movement.

In this study, we showed that RG inhibited HMC-1 cell migration and adhesion. However, there are some limitations of this study that should be noted. First, we only investigated the role of RG, one ligand of PPARγ, on SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion; other ligands of PPARγ, such as pioglitazone and troglitazone, should be utilized to investigate the role of PPARγ on HMC-1 cell migration and adhesion. Second, we only observed the effect of RG on HMC-1 cells in vitro, and whether RG can inhibit the migration and adhesion of mast cells in vivo needs to be clarified. Furthermore, while in this study it was found that the inhibitory effect of RG on HMC-1 cells was PPARγ-dependent, the detailed mechanism how the activation of PPARγ blocks HMC-1 cell migration and adhesion needs be determined in future studies.

Our present study shows that RG can inhibit SCF-induced HMC-1 cell migration and fibronectin-induced HMC-1 cell adhesion, and this inhibition is PPARγ-dependent and is not associated with cytotoxicity.

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