

057

**PPAR $\gamma$ -DEPENDENT AND -INDEPENDENT INHIBITION  
OF HUMAN CULTURED AIRWAY SMOOTH MUSCLE  
PROLIFERATION AND CYTOKINE RELEASE  
BY ROSIGLITAZONE**

JE WARD, CC TAYLOR, T HARRIS, AG STEWART  
*Department of Pharmacology, University of Melbourne, VIC 3010*

Peroxisome proliferator activated receptor  $\gamma$  (PPAR $\gamma$ ) is a ligand-activated transcription factor that regulates indices of proliferation & inflammation in airway smooth muscle (ASM). Therefore, there is therapeutic potential for PPAR $\gamma$  ligands such as rosiglitazone (RG) to regulate airway wall remodelling & inflammation in asthma. The PPAR $\gamma$  dependence of the modulation of ASM function by RG was examined using the PPAR $\gamma$ -specific, irreversible antagonist, GW 9662 (GW). In ASM from lung transplant recipients, thrombin- (0.3 U/mL) or bFGF- (300 pM) mediated proliferation was assessed by cell enumeration. Supernatant levels of granulocyte macrophage-colony stimulating factor (GM-CSF) & PGE<sub>2</sub> in the presence of IL-1 $\alpha$  (1 ng/mL) were measured by ELISA & RIA, respectively. The PPAR $\gamma$  antagonist, GW, reversed inhibition of thrombin-mediated proliferation by RG (% unstimulated cell number, thrombin 132  $\pm$  2%, + RG (10  $\mu$ M) 98  $\pm$  6%, + RG + GW (1  $\mu$ M) 127  $\pm$  3%,  $n = 6$ ,  $P > 0.05$  *cf* thrombin). However, there was no reversal of the inhibition of bFGF-mediated proliferation (bFGF 146  $\pm$  5%, + RG 102  $\pm$  7%, + RG + GW 110  $\pm$  5%,  $n = 8$ ). GW did not reverse inhibition of IL-1 $\alpha$ -stimulated GM-CSF levels by RG (% IL-1 $\alpha$ -stimulated response, IL-1 $\alpha$  + RG 54  $\pm$  2%, IL-1 $\alpha$  + RG + GW 63  $\pm$  3%,  $n = 6$ ). Rosiglitazone increased IL-1 $\alpha$ -stimulated PGE<sub>2</sub> levels, but GW was unable to prevent this increase (IL-1 $\alpha$  + RG 259  $\pm$  56%, IL-1 $\alpha$  + RG + GW 265  $\pm$  66%,  $n = 6$ ). These data support the conclusion that the PPAR $\gamma$  dependence of the effects of rosiglitazone may be stimulus-dependent.

**Supported by** NHMRC, University of Melbourne Early Career Grant.

**Keywords:** Airway smooth muscle, peroxisome proliferator activated receptor, rosiglitazone, proliferation, cytokine release