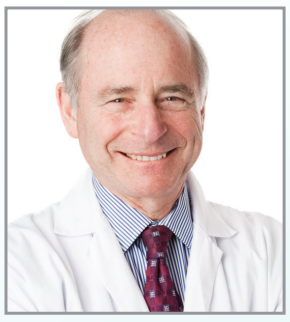
Hôpital général juif
Jewish General Hospital

McGill

Institut Lady Davis de recherches médicales | Lady Davis Institute for Medical Research

PAPER OF THE MONTH • APRIL 2013



Ernesto L. Schiffrin, CM, MD, PhD, FRSC, FRCPC, FACP, FAHA
Physician-in-Chief, Department of Medicine, Jewish General Hospital
Canada Research Chair in Hypertension and Vascular Research, Lady Davis Institute

Pierre Paradis, PhD
Hypertension and Vascular Research,
Lady Davis Institute

Cardiovascular Research

EUROPEAN SOCIETY OF CARDIOLOGY

Protective role of vascular smooth muscle cell PPARγ in angiotensin II-induced vascular disease

Chiara Marchesi, Asia Rehman, Yohann Rautureau, Daniel A. Kasal, Marie Briet, Avshalom Leibowitz, Stefania M.C. Simeone, Talin Ebrahimian, Mario F. Neves, Stefan Offermanns, Frank J. Gonzalez, Pierre Paradis and Ernesto L. Schiffrin

Aims Vascular peroxisome proliferator-activated receptor γ (PPARγ) activation improves vascular remodelling and endothelial function in hypertensive rodents. The goal of this study was to determine that vascular smooth muscle cell (VSMC) PPARγ exerts a vascular protective role beyond its metabolic effects.

Methods and results We generated a model of adult inducible VSMC-specific *Pparγ* inactivation to test the hypothesis that PPAγ counteracts angiotensin (Ang) II-induced vascular remodelling and endothelial dysfunction. Inducible VSMC *Pparγ* knockout mice were generated by crossing *Pparγ* floxed mice with mice expressing a tamoxifen-inducible Cre recombinase *Smooth muscle* (Sm) *myosin heavy chain* promoter control. Eight-to-ten-week-old Sm*Pparγ*–/– and control mice were infused with a nonpressor dose of Ang II for 7 days. Blood pressure was unaffected. Mesenteric arteries showed eutrophic remodelling in Ang II-infused control mice and hypertrophic remodelling in Ang II-infused Sm*Pparγ*–/– mice. Endothelium-dependent relaxation to acetylcholine was reduced in Sm*Pparγ*–/– mice and further impaired by Ang II infusion, and was unaffected by an inhibitor of NO synthase, suggesting a defect of NO-mediated relaxation. Sm*Pparγ* deletion increased the sensitivity to Ang II-induced contraction. Sm*Pparγ*–/– mice exhibited enhanced Ang II-induced vascular NADPH oxidase activity and adhesion molecule ICAM-1 and chemokine monocyte chemotactic protein-1 expression. The antioxidant ***Superoxide dismutase 3*** expression was decreased by Sm*Pparγ* deletion. Ang II infusion increased the expression of *CD3 T-cell co-receptor chain* δ and decreased *Adiponectin* in perivascular adipose tissue of Sm*Pparγ*–/– mice.

Conclusion Inducible *Pparγ* inactivation in VSMCs exacerbated Ang II-induced vascular remodelling and endothelial dysfunction via enhanced vascular oxidative stress and inflammation, revealing the protective role of VSMC PPARγ in angiotensin II-induced vascular injury.

doi: 10.1093/cvr/cvs362