HEALTH RESEARCH ABSTRACT SUBMISSIONS #18

Name *	Christopher Pelham
Email *	christopher-pelham@uiowa.edu
Educational Level *	PhD Candidate
If Selected Other	
College *	College of Medicine
Department *	Molecular Physiology & Biophysics
Title of Research *	Smooth Muscle-Specific PPAR Gamma Interference Reveals Cullin-3 as a Regulator of Vascular Function via RhoA/Rho-kinase
Other Authors *	Pimonrat Ketsawatsomkron (Univ. Iowa); Severine Groh (Univ. Iowa); Willem de Lange (Univ. Iowa); Henry Keen (Univ. Iowa); Eric Weatherford (Univ. Iowa); Frank Faraci (Univ. Iowa); Curt Sigmund (Univ. Iowa)
Introduction & Purpose *	Human subjects carrying dominant negative mutations in peroxisome proliferator-activated receptor γ (PPARγ) exhibit early-onset hypertension suggesting it plays a vital role in cardiovascular regulation. We report that smooth muscle-specific expression of dominant negative PPARγ (S-P467L) in transgenic mice causes elevated blood pressure and severe aortic dysfunction via a RhoA/Rho-kinase-dependent mechanism.
Experimental Design *	Genome-wide microarray profiling was used to identify putative vascular smooth muscle-specific PPARγ target genes. PPARγ-dependent pathways in smooth muscle were further interrogated by siRNA-mediated knockdown or pharmacological inhibition in cultured smooth muscle cells or aortic function assays ex vivo.

Results *

Enhanced Rho-kinase activity in S-P467L aorta caused a blunting of nitric oxide-mediated relaxation and hypertension, both of which were corrected by Rho-kinase inhibition. Rho-kinase and RhoA mRNA was unchanged. Rho-kinase activity and the level of RhoA was significantly increased in S-P467L aorta. Gene expression profiling identified RhoBTB1 as a novel PPAR□ target gene. RhoBTB1 interacts with Cullin-3 RING E3 ubiquitin ligase which regulates the turnover of RhoA. Expression of RhoBTB1, Cullin-3 and neddylated-Cullin-3 protein were selectively decreased in S-P467L aorta suggesting a defect in post-translational regulation of RhoA. Consistent with this, siRNA-mediated knockdown of Cullin-3 in aortic smooth muscle cells led to increased RhoA. Inhibition of cullin-RING ligase activity in aortic rings using the Nedd8-activating enzyme inhibitor MLN4924 caused enhanced agonist-mediated contraction that was Rho-kinase-dependent.

Conclusions *	Our results demonstrate that interference with PPARγ in smooth muscle impairs Cullin-3-mediated regulation of RhoA/Rho-kinase signaling and identify Cullin-3 as a novel regulator of vascular function.

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