RhoBTB1 is a Novel Gene Protecting Against Hypertension

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Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand activated transcription factor regulating metabolic and vascular function. We previously reported that mice (S-DN) expressing dominant-negative PPARγ in smooth muscle cells (SMC) are hypertensive, exhibit impaired vascular relaxation and enhanced contraction, and display reduced expression of a novel PPARγ target gene, RhoBTB1. We hypothesized that RhoBTB1 may play a protective role in vascular function that is disrupted in S-DN mice and in other models of hypertension. We generated double transgenic mice (termed R+) with tamoxifen-inducible, Cre-dependent expression of RhoBTB1 in SMC. R+ mice were crossed with S-DN to produce mice (S-DN/R+) in which tamoxifen-treatment (75 mg/kg, ip, 5 days) restored RhoBTB1 expression in aorta to normal. Thoracic aorta and basilar artery from S-DN showed impaired acetylcholine (ACh)-induced endothelial-dependent relaxation, which was reversed by replacement of RhoBTB1 in SMC (thoracic aorta, 43.3±4.4 vs 74.2±1.1%, $p<0.01$, basilar artery, 19.9±6.7 vs 48.1±12.3%, $p<0.05$, n=6). Aorta from S-DN mice also displayed severely decreased sodium nitroprusside (SNP)-induced endothelial-independent relaxation with a right-shifted dose-response, which was also reversed in tamoxifen-treated S-DN/R+ mice ($p<0.01$, n=6). Importantly, replacement of RhoBTB1 also reversed the hypertensive phenotype observed in S-DN mice (Radiotelemetry SBP, 135.9±3.9 vs 123.7±3.0 mmHg, $p<0.05$, n=4). To examine if overexpression of RhoBTB1 in SMC has a protective effect on other hypertensive models, Ang-II (490 ng/min/kg) was infused in tamoxifen treated R+ mice for 2 wks. RhoBTB1 expression prevented Ang-II-induced impairment of ACh relaxation in basilar artery (17.0±8.6 in control mice vs 40.7±5.3 % in R+ mice, $p<0.05$, n=4) and decreased SBP (166.0±7.2 in control mice vs 133.3±5.1 mmHg in R+ mice, $p<0.05$, n=4). We conclude that a) loss of RhoBTB1 function explains the vascular dysfunction and hypertension observed in response to interference with PPARγ in smooth muscle, and b) RhoBTB1 in SMC has an anti-hypertensive effect and facilitates vasodilatation.

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