Smooth muscle specific Rac1 deficiency induces hypertension by preventing p116RIP3-dependent RhoA inhibition

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Résumé en anglais	BACKGROUND: Increasing evidence implicates overactivation of RhoA as a critical component of the pathogenesis of hypertension. Although a substantial body of work has established that Rac1 functions antagonize RhoA in a broad range of physiological processes, the role of Rac1 in the regulation of vascular tone and blood pressure is not fully elucidated. METHODS AND RESULTS: To define the role of Rac1 in vivo in vascular smooth muscle cells (vSMC), we generated smooth muscle (SM)-specific Rac1 knockout mice (SM-Rac1-KO) and performed radiotelemetric blood pressure recordings, contraction measurements in arterial rings, vSMC cultures and biochemical analyses. SM-Rac1-KO mice develop high systolic blood pressure sensitive to Rho kinase inhibition by fasudil. Arteries from SM-Rac1-KO mice are characterized by a defective NO-dependent vasodilation and an overactivation of RhoA/Rho kinase signaling. We provide evidence that Rac1 deletion-induced hypertension is due to an alteration of cGMP signaling resulting from the loss of Rac1-mediated control of type 5 PDE activity. Consequently, cGMP-dependent phosphorylation and binding of RhoA with its inhibitory partner, the phosphatase-RhoA interacting protein (p116(RIP3)), are decreased. CONCLUSIONS: Our data reveal that the depletion of Rac1 in SMC decreases cGMP-dependent p116(RIP3)/RhoA interaction and the subsequent inhibition of RhoA signaling. Thus, we unveil an in vivo role of Rac1 in arterial blood pressure regulation and a new pathway involving p116(RIP3) that contributes to the antagonistic relationship between Rac1 and RhoA in vascular smooth muscle cells and their opposite roles in arterial tone and blood pressure.
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