Inactivation of serum response factor contributes to decrease vascular muscular tone and arterial stiffness in mice

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Résumé en anglais	RATIONALE: Vascular smooth muscle (SM) cell phenotypic modulation plays an important role in arterial stiffening associated with aging. Serum response factor (SRF) is a major transcription factor regulating SM genes involved in maintenance of the contractile state of vascular SM cells. OBJECTIVE: We investigated whether SRF and its target genes regulate intrinsic SM tone and thereby arterial stiffness. METHODS AND RESULTS: The SRF gene was inactivated SM-specific knockout of SRF (SRF(SMKO)) specifically in vascular SM cells by injection of tamoxifen into adult transgenic mice. Fifteen days later, arterial pressure and carotid thickness were lower in SRF(SMKO) than in control mice. The carotid distensibility/pressure and elastic modulus/wall stress curves showed a greater arterial elasticity in SRF(SMKO) without modification in collagen/elastin ratio. In SRF(SMKO), vasodilation was decreased in aorta and carotid arteries, whereas a decrease in contractile response was found in mesenteric arteries. By contrast, in mice with inducible SRF overexpression, the in vitro contractile response was significantly increased in all arteries. Without endothelium, the contraction was reduced in SRF(SMKO) compared with control aortic rings owing to impairment of the NO pathway. Contractile components (SM-actin and myosin light chain), regulators of the contractile response (myosin light chain kinase, myosin phosphatase target subunit 1, and protein kinase C-potentiated myosin phosphatase inhibitor) and integrins were reduced in SRF(SMKO). CONCLUSIONS: SRF controls vasoconstriction in mesenteric arteries via vascular SM cell phenotypic modulation linked to changes in contractile protein gene expression. SRF-related decreases in vasomotor tone and cell-matrix attachment increase arterial elasticity in large arteries.
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