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Emilin-1 controls arterial blood pressure by regulating contractility of vascular smooth muscle cells

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Emilin-1 is a protein of the elastic extracellular matrix (ECM) expressed in interstitial connective tissue and in the cardiovascular system. *Emilin1* null mice display hypotrophic remodeling of the wall of conductance arteries and increased blood pressure. The protein regulates the bioavailability of TGF-β by inhibiting proteolysis of the proTGF-β precursor to LAP/TGF-β, a complex from which the growth factor can be subsequently released for receptor binding. In the absence of Emilin-1, the amount of active TGF-β is increased. As Emilin-1 is expressed in blood vessels starting from early stages of embryonic development to adulthood, a key question concerning the function of the protein is whether the *Emilin1*$^{-/-}$ phenotype is the result of a developmental defect or the function of the protein is required for the regulation of blood pressure and arterial structure also in the adult. The conditional gene targeting procedure chosen to inactivate the *Emilin1* gene in smooth muscle cells (SMCs) of adult mice included the use of floxed *Emilin1* and CreER^{T2} (a tamoxifen inducible *Cre* recombinase) under the control of the smooth muscle myosin heavy chain (*Smmhc*) promoter. Tamoxifen administration induced activity of Cre specifically in vascular and visceral SMCs, as revealed by X-gal staining of tissues from animals with the Rosa26R mutation. When *Emilin1*$^{flox/flox}$ mice carrying the *Smmhc*-CreER^{T2} transgene were given tamoxifen for 7 days, Emilin-1 disappeared completely in 10-12 days from start of treatment. In the same time, blood pressure increased of about 20 mmHg, a level that was stably maintained thereafter.

The myogenic response of second branch meseteric arteries, evaluated using a pressure myograph, was found to be increased in *Emilin1*$^{-/-}$ mice. Additional experiments with aorta and mesenteric artery SMC cultures from control and mutant mice showed that lack of Emilin-1 enhanced phosphorylation of myosin light chain 20 when cells were stimulated with the α1-adrenergic receptor agonists phenylephrine or with angiotensin II. Moreover, basal cytosolic Ca^{2+} levels and calcium transients induced by stimulation with phenylephrine and angiotensin II were increased in SMCs from *Emilin1*$^{-/-}$ mutants. The data suggest that Emilin-1 expression is continuously required for regulation of blood pressure and that the increase of TGF-β activity induced by diminished Emilin-1 stimulates, likely through alteration of intracellular calcium homeostasis, contractility of vascular SMC to mechanical and chemical stimuli with ensuing hypertension.