Title	Adrenomedullin suppresses migration inhibitory factor production and cytokine response of rat macrophages to lipopolysaccharide
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CVS-21 Do you know your mice? A lesson from SM22alpha knockout mice

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Introduction: SM22alpha is a 22-kD smooth muscle cell (SMC) lineage restricted protein that physically associates with cytoskeletal actin filament bundles in contractile SMCs. To examine the function of SM22alpha, gene targeting as used to generate SM22alpha -deficient ($SM22^{-/-LacZ}$) mice.
Method: The gene targeting strategy employed resulted in insertion of the bacterial LacZ reporter gene at the SM22alpha initiation codon permitting precise analysis of the temporal and spatial pattern of SM22alpha transcriptional activation in the developing mouse. Multidisciplinary approach was taken to characterize the SM22alpha knockout mice from the ultrastructual organization to whole animal cardiovascular physiology.
Results: Northern and Western blot analyses confirmed that the gene targeting strategy resulted in a null mutation. Histological analysis of $SM22^{+/-LacZ}$ embryos revealed detectable beta-galactosidase activity in the unturned E8.0 embryo in the layer of cells surrounding the paired dorsal aortae concomitant with its expression in the primitive heart tube, cephalic mesenchyme and yolk sac vasculature. Subsequently, during postnatal development, beta-galactosidase activity was observed exclusively in arterial, venous and visceral SMCs. SM22alpha -deficient mice are viable and fertile. Their blood pressure and heart rate do not differ significantly from their control SM22alpha $^{+/-}$ and SM22alpha $^{+/+}$ littermates. Cardiac echocardiography revealed preserved systolic function and no significant differences in chamber sizes. The vasculature and SMC-containing tissues of SM22alpha-deficient mice develop normally and appear histologically similar to those of their control littermates. Deconvolution microscopy confirms the colocalization of SM22alpha to actin filaments. However, electron microscopy revealed a subtle ultra structural defect in the actin filament organization.
Conclusion: Taken together, these data demonstrate that SM22alpha is not required for basal homeostatic functions mediated by vascular and visceral SMCs in the developing mouse. These data also suggest that signalling pathways that regulate SMC specification and differentiation from local mesenchyme are activated earlier in the angiogenic program than previously recognized.

CVS-22 Adrenomedullin suppresses migration inhibitory factor production and cytokine response of rat macrophages to lipopolysaccharide

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Introduction: Adrenomedullin (AM) is a vasorelaxant peptide that is also involved in inflammation. Macrophage migration inhibitory factor (MIF) is released from pituitary and macrophages and is an important regulator of inflammation. We investigated the interaction between AM and MIF in cultured rat macrophages.
Method: Rat macrophages (NR8383) were activated by LPS in the absence and presence of AM at 1ng/mL to 1μg/mL. MIF, TNF-alpha, IL-6 and IL-1beta were measured by ELISA at 0, 1, 3, 6, and 24-hours. The effect of AM on cytokine response from resting macrophages was determined from cell cultures containing RPMI medium and AM alone.
Results: AM increased release of MIF from resting macrophage dose-dependently in the first hour by 36.3 % to 75.7 % (compared to control with no AM) while further production in subsequent 24 hours was not significantly affected by the presence of AM. For LPS-stimulated macrophages, AM also increased MIF secretion dose-dependently in the first hour by 13.5% to 35.4% (compared to control containing LPS but no AM), but reduced further production of MIF by 22.6±6.8% at 24 hours. The suppressive effect was observed even at 1 ng/mL of AM. The presence of AM also reduced the production of TNF-alpha, IL-6 and IL-1beta from LPS-stimulated cells by 66%, 49 % and 30 % respectively.
Conclusion: Our results suggest that AM modulates cytokine secretion from rat macrophages and may have a regulatory role in inflammation.