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A cysteine-rich LIM-only protein mediates regulation of smooth muscle-specific gene expression by cGMP-dependent protein kinase

Tong Zhang, Shunhui Zhuang, Darren E Casteel and Renate B Pilz*

Address: Department of Medicine University of California, San Diego, La Jolla, CA 92093

Email: Renate B Pilz* - rpilz@ucsd.edu

* Corresponding author

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Vascular smooth muscle cells can reversibly change from a differentiated, contractile to a de-differentiated, synthetic phenotype; de-differentiation correlates with decreased expression of smooth muscle (SM)-specific genes and loss of cGMP-dependent protein kinase (PKG), and transfection of PKG into de-differentiated cells restores defective SM-specific gene expression through unknown mechanisms [1]. We now show that siRNA-mediated down-regulation or pharmacologic inhibition of PKG reduced SM-specific gene expression in differentiated vascular SM cells, and provide a mechanism for cGMP/PKG regulation of SM-specific genes involving the cysteine-rich LIM-only protein CRP4. PKG associated with CRP4 and phosphorylated the protein in intact cells. We found that CRP4 had no intrinsic transcriptional activity, but it synergistically enhanced activation of the SM-∀-actin promoter by serum response factor and GATA6. Similar to other CRP family members, CRP4 may act as an adaptor protein. CRP4 co-expression with serum response factor and GATA6 was required for cGMP/PKG stimulation of the SM-∀-actin promoter; a phosphorylation-deficient mutant CRP4 and a CRP4 deletion mutant deficient in PKG binding did not support cGMP/PKG stimulation of the promoter. In the presence of wild type, but not mutant, CRP4 (and GATA6), cGMP/PKG enhanced the binding of serum response factor to a probe encoding the distal SM-∀-actin promoter CArG element. Chromatin immunoprecipitation assays showed that CRP4 and SRF associated with the CArG elements of endogenous SM-specific genes in intact cells. In the presence of CRP4, cGMP/PKG increased serum response factor- and GATA6-dependent expression of endogenous SM-specific genes in pluripotent embryonal 10T1/2 cells. These findings suggest that CRP4 mediates cGMP/PKG stimulation of SM-specific gene expression and support an important role of PKG in regulating the phenotype of vascular SM cells.

References

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