SRF Function in Vascular Smooth Muscle
When Less is More?
Blanca Camoretti-Mercado, Nickolai O. Dulin, Julian Solway

The transcription factor serum response factor (SRF) controls the expression of genes involved in promoting the proliferation and differentiation of muscle and nonmuscle cells. In this issue, Kaplan-Albuquerque et al report that depletion of SRF from cultured vascular smooth muscle cells (VSMC) through RNA interference blocks expression of SM-specific proteins as expected, but surprisingly also promotes cell migration and proliferation. If confirmed, these unforeseen effects of SRF could have important mechanistic implications for pathological conditions involving abnormal VSMC proliferation and migration.

SRF binds to the 10-bp CArG motif found in the regulatory regions of several muscle-specific genes and also located in the serum response elements of mitogen-inducible gene promoters. In smooth muscle cells, 2 families of SRF-interacting coactivators, myocardin/MKL and p62TCF, bind to the same region of SRF in a mutually exclusive manner and so induce either smooth muscle–specific gene expression or early response gene expression, respectively. Growth signals negatively affect SM gene expression by inducing the displacement of myocardin from SRF by Elk-1, a ternary complex factor (TCF). Because VSMC cells are not terminally differentiated, they undergo phenotypic shift in response to mitogenic stimulation (such as platelet-derived growth factor [PDGF] treatment), resulting in both increased proliferation and suppression of smooth muscle contractile markers. On the other hand, exposure to constrictor agents promotes a phenotype characterized by augmented accumulation of contractile proteins and mRNA transcripts. Thus, current understanding is that SRF can promote either differentiation or proliferation of VSMC, depending on the physiological environment.

New findings presented by Kaplan-Albuquerque et al show that SRF-depleted embryonic and adult rat VSMC exhibit greater unstimulated and PDGF-stimulated proliferation rates than do wild-type myocytes. Importantly, this abnormality was rescued by artificial reexpression of SRF. Thus, whereas SRF undoubtedly promotes differentiation of VSMC, it also appears to repress VSMC proliferation under these circumstances. Curiously, no such repression was found in serum-fed myocytes.

These observations are not easy to reconcile with current knowledge. Perhaps answers will emerge from genome-wide profiling of SRF-deficient cells. The authors suggest that changes in expression of GADD-45α, c-Jun, versican, or C/EBPα individually or in combination may affect the growth properties of SRF-deficient cells. Interestingly, c-Jun was upregulated in SRF-deficient VSMC in Kaplan-Albuquerque’s study, but conversely c-Jun can repress SRF activity and repress SM-actin promoter activation, demonstrating complex cross-talk between proliferation and differentiation pathways. Other important questions raised from this study include: (1) why does SRF repress proliferation induced by PDGF, but not by serum, and (2) what is then the importance of serum-induced SRF activity in cell function?

Studies of the role of SRF in cell adhesion, spreading, and migration were lacking until very recently. The importance of SRF activity for building a robust actin cytoskeleton in embryonic and adult migrating cells of insects and mammals is now established. Knockdown of SRF in endothelial cells impaired VEGF-induced cell migration. Furthermore, ectopic expression of SRF in VSMC, or within the bowel epithelium and musculature of an animal model of gastric ulcer, accelerated cell migration and healing. In sharp contrast, Kaplan-Albuquerque et al report that SRF depletion enhances the migration of VSMC, suggesting that SRF activity can under some circumstances also repress migration. Whether this property is the outcome of a perturbed cytoskeleton or altered extracellular matrix deposition or both needs further investigation. If this observation is confirmed, then understanding the underlying mechanism could conceivably shed light into other crucial processes such as cell branching, outgrowth, and metastasis.

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References

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