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Myocardin Dominant Driver of the Smooth Muscle Cell Contractile Phenotype

Michael S. Parmacek
University of Pennsylvania Cardiovascular Institute, Philadelphia.

A distinguishing feature of the smooth muscle cell (SMC) lineage is its remarkable plasticity required for maintenance and adaptation of the cardiovascular system. The biological properties of SMCs are ultimately determined by the orchestrated expression of genes encoding contractile and cytoskeletal proteins, intracellular enzymes, and cell surface ligands and receptors (for review see[1,2]). In the postnatal vasculature, medial SMCs exit the cell cycle and assume a "contractile" phenotype required for regulation of vascular tone.[3,4] However, in response to vascular injury, SMCs reenter the cell cycle, downregulate expression of contractile proteins, and assume a "synthetic" phenotype resembling a fibroblast.[3,4] The modulation of vascular SMC phenotype has been implicated in the pathogenesis of vascular proliferative syndromes including atherosclerosis, restenosis, pulmonary hypertension, and transplant arteriopathy (for review see[5]). Myocardin (*Myocd*) is a recently discovered SMC-restricted transcriptional coactivator that physically associates with the MADS box transcription factor, SRF, to synergistically activate transcription of genes encoding SMC-restricted cytoskeletal and contractile proteins.[6] Forced expression of myocardin transactivates multiple SMC-restricted transcriptional regulatory elements.[6-8] Remarkably, forced expression of myocardin in embryonic stem (ES) cells induces expression of multiple endogenous SMC genes including SM22α, SM-MyHC, and SM-α-actin.[7] In response to vascular injury, extrinsic cues and intracellular signals converge on myocardin/SRF complexes ultimately regulating and modulating vascular SMC phenotype (for review see[9,10]). Mice harboring a null mutation in the myocardin gene survive only to embryonic day (E)10.5 and exhibit obvious defects in the embryonic and extraembryonic vasculature including a block in SMC differentiation.[11] In addition, mice in which the *Myocd* gene was selectively ablated in neural crest-derived SMCs exhibit patent ductus arteriosus (PDA) and neonatal lethality resulting from a cell autonomous block in vascular SMC differentiation.[12] Taken together, these data demonstrate that myocardin promotes SMC differentiation and the contractile SMC phenotype.

A recent report from Miano and colleagues challenges accepted lineage relationships that define and distinguish the SMC and skeletal muscle cell lineages.[13] Cell lineage fate mapping studies revealed that the *Myocd* gene is expressed transiently in skeletal muscle progenitor cells located within the dermamyotome of the somite and that skeletal muscle cells arise from these myocardin-expressing skeletal muscle progenitor cells.[13] In skeletal muscle progenitors, myocardin functions as a transcriptional repressor inhibiting expression or activity of the bHLH myogenic regulatory factors, myogenin and MyoD. The molecular basis of myocardin-induced transcriptional repression is complex involving both HDAC-regulated transcriptional repression of bHLH myogenic regulatory factors, as well as protein–protein interactions that abolish MyoD binding to DNA and the capacity of MyoD to physically associate with MEF2

Correspondence to Michael S. Parmacek, MD, Division of Cardiovascular Medicine, Department of Medicine, University of Pennsylvania School of Medicine, 9035 Gates Pavilion, 3400 Spruce St., Philadelphia, PA 19104. E-mail Michael.parmacek@uphs.upenn.edu.

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None.

and synergistically activate transcription.[13] These data raise the intriguing possibility that skeletal muscle cells and a subpopulation of mesodermally-derived smooth muscle cells arise from a common progenitor pool. Consistent with this possibility, clonal analysis in mice revealed that some embryonic aortic SMCs arise from the dermamyotome of somites.[14] Alternatively, myocardin may be transiently expressed in skeletal muscle progenitors, but this population of cells may be distinct from some, or all, SMC and pericyte progenitors located within the somite.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Long and colleagues follow-up and extend the findings in this important study. They now report that adenoviral-mediated expression of myocardin in BC_3H1 skeletal muscle cells induces expression of SMC and cardiac genes while suppressing expression of a subset of skeletal muscle genes.[15] Ad-Myocd–transduced BC_3H1 cells assume a spindle-like morphology and decrease their rate of proliferation, resembling contractile SMCs in the vessel wall. Myocardin-transduced BC_3H1 cells exhibit slow rhythmic SMC-like contractions when stimulated with contractile agonists. As such, these data demonstrate that myocardin acts in a dominant fashion inducing not only expression of genes encoding SRF-dependent contractile proteins, but also adoption of contractile properties resembling those observed in bona fide SMCs.

These data raise the intriguing question of whether myocardin functions in a dominant fashion as a “master-regulator” of the SMC lineage in a manner analogous to that of basic helix-loop-helix (bHLH) skeletal myogenic regulatory factors including MyoD (for review see[16]). However, multiple questions must be addressed before one may reasonably conclude that myocardin acts as a “master-regulator” of the SMC lineage. First, it remains unclear why skeletal muscle progenitors residing in the dermamyotome that express myocardin are not irreversibly driven to the SMC fate. If myocardin autoregulates its own expression,[17] what is the molecular basis for extinction of myocardin expression in skeletal muscle progenitor cells? Second, it remains to be determined whether forced expression of myocardin induces nonskeletal muscle cell lines to assume a SMC contractile phenotype. Does overexpression of myocardin in cardiac myocytes cause these cells to transdifferentiate into SMCs? What about nonmuscle cell lineages? Third, unlike bHLH skeletal myogenic regulatory factors, which function by binding directly to cis-acting regulatory elements encoded within the genome, myocardin functions exclusively as a transcriptional coactivator. It is generally believed that transcriptional coactivators evolved primarily to transduce extrinsic stimuli and developmental cues thereby extending and modulating information encoded within the genome required for cellular adaptation (for review see[18]). Consistent with its role as a transcriptional coactivator, vascular injury induces repression of myocardin-induced activation of SMC-restricted genes thereby modulating vascular SMC phenotype.[3,4]

Elucidation of the developmental programs that regulate cell fate decisions and differentiation of the smooth muscle cell lineage(s) is fundamentally important at a basic level and relevant to understanding the pathogenesis of common forms of vascular disease. The demonstration that myocardin acts in a dominant fashion repressing the skeletal muscle phenotype and promoting the contractile smooth muscle cell phenotype raises fundamental questions in existing paradigms of muscle cell development.[13,15] Recently, human kindreds were identified with familial thoracic aneurysms and dissections (TAAD) caused by mutations in the *SM-myosin heavy chain* (*Myh11*) and *SM-α-actin* (*Acta2*) genes, respectively.[19,20] Each of these genes is regulated directly by myocardin in the postnatal vasculature confirming that myocardin-regulated transcriptional targets are directly involved in human diseases affecting the cardiovascular system.[12] Further study examining the genetic and epigenetic mechanisms that underlie SMC differentiation promises to inform future therapies for common cardiovascular diseases as well as potential regenerative therapies.

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