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Control of smooth muscle development by the myocardin family of transcriptional coactivators

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Differentiation of smooth muscle cells (SMCs) is accompanied by the transcriptional activation of an array of muscle-specific genes that confer the unique contractile and physiologic properties of this muscle cell type. The majority of smooth muscle genes are controlled by serum response factor (SRF), a widely expressed transcription factor that also regulates genes involved in cell proliferation. Myocardin and myocardin-related transcription factors (MRTFs) interact with SRF and potently stimulate SRF-dependent transcription. Gain- and loss-of-function experiments have shown myocardin to be sufficient and necessary for SMC differentiation. SMCs are highly plastic and can switch between differentiated and proliferative states in response to extracellular cues. Suppression of SMC differentiation by growth factor signaling is mediated, at least in part, by the displacement of myocardin from SRF by growth factor-dependent ternary complex factors. The association of SRF with myocardin and MRTFs provides a molecular basis for the activation of SMC genes by SRF and the responsiveness of the smooth muscle differentiation program to growth factor signaling.

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SRF serum response factor
TAD transcription activation domain
TCF ternary complex factor

Introduction

Smooth muscle cells (SMCs) are required for the formation and function of the cardiovascular, respiratory, genitourinary, and gastrointestinal systems. In contrast to cardiac and skeletal muscle cells, which undergo terminal differentiation, SMCs are highly plastic and can modulate their phenotypes between proliferative and differentiated states in response to extracellular cues [1]. Abnormalities in vascular SMC differentiation are responsible for a variety of disorders, including atherosclerosis, asthma, vascular restenosis following angioplasty, and hypertension.

Serum response factor (SRF) is a widely expressed transcription factor required for smooth muscle (SM) gene expression and differentiation [2]. Paradoxically, SRF also regulates genes involved in cell proliferation, which opposes the SM differentiation program. The recent discovery of myocardin and myocardin-related transcription factors (MRTFs), which act as SRF coactivators [3,4], has revealed a mechanism for the activation of SMC genes and a molecular basis for suppression of SMC differentiation by growth factor signals. In this review, we discuss the roles of the myocardin family in the control of SM differentiation and signal-dependent gene expression.

Diversity of smooth muscle cells

SMCs express a set of contractile proteins that are distinct from those expressed in skeletal and cardiac muscles [1]. Genes that are activated during SM differentiation include those encoding SM-myosin heavy chain, SM α -actin, SM22, SM-myosin light chain kinase, and calponin. Certain of these genes are expressed transiently in developing cardiac and skeletal muscle cell lineages during embryogenesis, whereas others are specific to the SMC.

SMCs are highly heterogeneous and arise throughout the embryo from multiple types of progenitors [1]. SMCs of the dorsal aorta and large elastic arteries are derived from mesenchyme of the lateral mesoderm and from neural crest cells, whereas coronary artery SMCs originate from proepicardial cells that migrate over the surface of the heart and undergo an epithelial to mesenchymal transformation. Arterial and venous SMCs, as well as different types of visceral SMCs within internal organs, display

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Abbreviations

ANF atrial natriuretic factor
CRP cysteine-rich LIM domain protein
HOP homeodomain-only protein
MADS MCM1, Agamous, Deficiens, serum response factor
MAL megakaryocytic leukemia
MAP mitogen activated protein
MKL megakaryoblastic leukemia
MEF2 myocyte enhancer factor-2
MRTF myocardin-related transcription factor
NTD N-terminal domain
SAP SAF-A/B, Acinus, PIAS
SM smooth muscle
SMC smooth muscle cell

remarkably diverse phenotypes with respect to their growth and functional properties and patterns of gene expression. The molecular basis for this heterogeneity has yet to be defined, although mutational analyses of native and artificial SM gene promoters point to the involvement of SRF in establishing such diversity [5–7].

Regulation of smooth muscle cell gene expression by SRF

Nearly every SMC gene analyzed to date has been found to be controlled by SRF (reviewed in [1,2]), a widely expressed MADS (MCM1, Agamous, Deficiens, SRF) box transcription factor first identified as a serum-responsive activator of the *c-fos* promoter [8]. SRF binds as a homodimer to a consensus sequence CC(A/T)₆GG, known as a CArG box or serum response element. Whereas the *c-fos* promoter contains a single CArG box, most SM genes contain two or more CArG boxes, which act cooperatively to promote transcription [5,6,9,10]. CArG boxes also contribute to the expression of many cardiac and skeletal muscle genes [11,12]. There are also examples of SM genes that are SRF-independent [13,14]. Whether such genes are regulated indirectly by SRF, through subordinate SRF-dependent transcription factors remains to be determined.

The requisite role of SRF in SM gene expression has been demonstrated by the ability of dominant negative SRF mutants to prevent SMC differentiation [15]. However, although necessary, SRF is not sufficient to activate SM genes. These findings led to the notion that SRF acted together with other cofactors to activate the SM gene program. The formation of SM-specific protein complexes on CArG boxes supports such a model [16].

SRF cofactors

SRF, like other MADS box proteins, has a propensity to associate with other transcription factors, providing for combinatorial control of SRF target genes [17]. Ternary complex factors (TCFs) of the ETS-domain family, including Elk-1, SAP-1a and NET/SAP-2/Erp, were among the first SRF cofactors identified [18]. These TCFs interact with the MADS box of SRF through a short hydrophobic stretch known as a B-box. Stable association of TCFs with SRF also requires an ETS binding site (GGAA/T) immediately adjacent to the CArG box. The association of TCFs with SRF on DNA is triggered by MAP kinase phosphorylation of their C termini, which un masks the B-box and provides for signal-dependent activation of specific SRF target genes, such as *c-fos*. SRF also associates with several homeodomain transcription factors, including phox/Mhox, Nkx2.5, and homeodomain-only protein (HOP), as well as with GATA4 and myocyte enhancer factor-2 (MEF2) [19–24], affording additional possibilities for target gene specific-modulation of SRF activity.

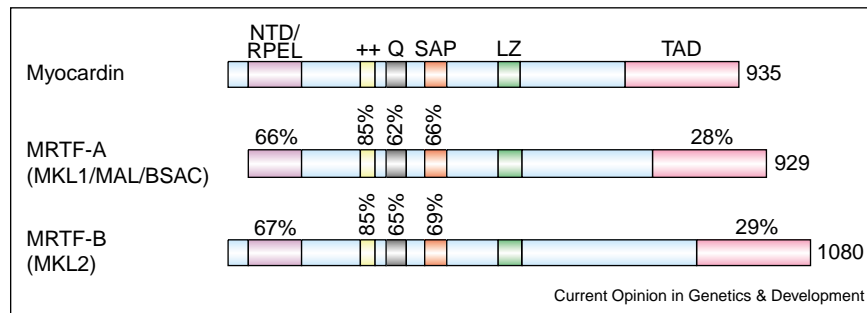
The cysteine-rich LIM-only proteins, CRP1 and CRP2, have also been shown to function as a link between SRF and SMC gene expression. CRP1 and CRP2 strongly enhance SRF-mediated SM gene expression, and dominant negative mutants of those proteins block SMC differentiation [25]. CRP1 and CRP2 apparently enhance SRF DNA-binding activity. Interestingly, the *CRP1* gene itself is regulated by SRF, suggesting that CRP1 acts within a positive amplification loop to promote its own expression [26]. The ability of CRP proteins to shuttle between the cytoplasm and nucleus suggests their potential role in transmission of intracellular signals to SRF.

The myocardin family of transcriptional coactivators

Myocardin was discovered in an *in silico* screen for novel genes expressed specifically in the heart [3]. Myocardin stimulates SRF activity by forming a ternary complex with SRF on DNA and providing its strong transcriptional activation domain (TAD) to SRF, which otherwise is a very weak activator of transcription. Myocardin preferentially activates promoters containing two or more CArG boxes, an observation consistent with the known cooperativity of CArG boxes associated with muscle genes. However, there are dramatic differences in responsiveness of SRF-dependent promoters to myocardin that cannot be accounted for simply by the number of CArG boxes or their affinity for SRF. How the positions and flanking sequences of CArG boxes contribute to responsiveness to myocardin remain to be determined. Transcriptional activation by myocardin is also exquisitely sensitive to the level of SRF, such that even subtle increases in SRF expression can result in suppression of myocardin activity, presumably through a ‘quelching’ mechanism in which excess SRF titrates myocardin away from SRF target genes [3].

Two additional members of the myocardin family, referred to as MRTF-A (MAL, MKL1, BSAC) and MRTF-B (MKL2) have also been identified (Figure 1) [3,4,27–29]. The gene encoding human MRTF-A (MAL/MKL1) is translocated in acute megakaryocytic leukemia, creating an oncogenic fusion protein with a novel protein called One-twenty-two (OTT)/RBM15 (RNA binding protein motif protein 15) [27,28]. The RBM15–MKL1 fusion protein displays heightened transcriptional activity toward the growth factor-inducible *c-fos* and *Egr1* promoters, but its ability to activate SM genes is comparable to that of the wild-type MKL1 protein [30]. Why this fusion protein shows enhanced activity toward growth-associated SRF target genes is unclear, but such activity could account for its leukemogenic effects. The specific target genes of the MRTF–SRF complex responsible for oncogenesis also remain to be determined. MRTF-A was also identified in a screen for genes that protect against tumor necrosis factor-induced cell death, and named BSAC [29].

Figure 1



Schematic diagrams of myocardin and MRTFs. Structural domains of myocardin and MRTFs are shown. ++, basic region; Q, glutamine-rich region. The percent identity between different domains is shown.

Whereas there are three genes encoding myocardin family members in mammals, there appear to be four such genes in *Xenopus* and puffer-fish (*Fugu rubripes*) (D Wang, EN Olson, unpublished; Krieg *et al.*, personal communication). A single myocardin-related gene exists in *Drosophila*. The product of this gene, called DMRTF, stimulates activity of *Drosophila* SRF and is required for the formation of terminal regions of the tracheal system, a primitive organ comprised of branching tubes involved in gaseous exchange that functions analogously to a vertebrate vascular system (Z Han, EN Olson, unpublished). It is fascinating, in this regard, that the molecular partnership of myocardin and SRF has apparently been evolutionarily conserved to regulate the development of branching tubular networks involved in exchange of oxygen and nutrients.

Structural features of myocardin proteins

Myocardin belongs to the SAP (SAF-A/B, Acinus, PIAS) family of proteins, which play diverse roles in chromatin remodeling, transcriptional control, and fragmentation of DNA during apoptosis [31]. The 35-amino acid SAP domain has been predicted to adopt a helix-linker-helix structure with the potential to bind to DNA. The SAP domain of SAF-A binds to A/T rich genomic DNA associated with the nuclear matrix, the so-called nuclear matrix attachment region. Similarly, the SAP domain in myocardin is required for the association of myocardin with A/T rich DNA (Z Wang, E Olson, unpublished). Interestingly, deletion of the SAP domain of myocardin abolishes the ability to activate the *atrial natriuretic factor* (*ANF*) gene, a marker of the cardiac stress response, without affecting the activation of the *SM22* gene [3]. This finding suggests that the SAP domain of myocardin may discriminate between SRF target genes, possibly by differential association with additional factors.

Myocardin and MRTFs contain a conserved N-terminal domain (Figures 1 and 2) composed of RPEL repeats that have been implicated in Rho-dependent nuclear import of MRTF-A/MAL [32^{••}]. Deletion of the N-terminal

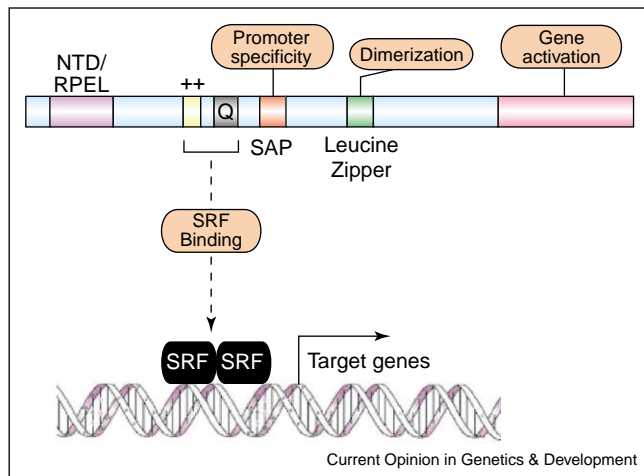
domain of myocardin or MRTFs enhances the transcriptional activity of the proteins. The basic domain of myocardin family proteins has been shown to mediate nuclear localization as well as SRF interaction [3], and a leucine zipper-like domain mediates homo- or heterodimerization among myocardin family members [3,4[•], 32^{••},33]. Dimerization may provide a mechanism for interlinking myocardin or MRTF/SRF complexes bound at different CArG boxes within the control regions of SM genes.

The transcriptional activity of myocardin is mediated by a TAD at the C terminus of the protein [3]. Even though the amino acid sequences of the TADs are only 30% identical among myocardin and MRTFs, they are functionally interchangeable (S Li, Z Wang, EN Olson, unpublished). The TADs of myocardin and MRTFs can also be replaced with the VP16 TAD, indicating that this domain does not confer specificity with respect to target gene activation [3]. Recent studies demonstrate that the TAD of myocardin is associated with the transcriptional coactivator p300, a histone acetyl transferase, raising the possibility that myocardin may govern chromatin structure of SRF target genes, a key step in activation of the SM differentiation program [34,35].

Expression patterns of myocardin and MRTFs

During mouse embryogenesis, myocardin expression is first detected in cardiac precursor cells within the cardiac crescent at ~E7.5 and, thereafter, is maintained in cardiac myocytes in the atrial and ventricular chambers of the heart until adulthood [3]. In addition, myocardin is expressed in a subset of vascular and visceral smooth muscle cell types. Expression is especially robust in visceral SMCs of the stomach, bladder, and intestine, where myocardin expression precedes expression of smooth muscle genes such as *SM22*. It should be noted, however, that myocardin is not expressed in all developing SMC types and there is a curious disparity between the timing of myocardin and its target genes in SMCs of

Figure 2



Functional domains of myocardin. Myocardin contains an NTD/RPEL domain. A related domain in MAL has been shown to regulate nuclear import. A segment of the protein including the basic and Q-rich domains mediates interaction of myocardin with SRF homodimers. The SAP domain is required for activation of a subset of SRF target genes, suggesting it confers promoter specificity. The leucine zipper mediates homodimerization or heterodimerization of myocardin with MRTFs. The transcription activation domain at the C terminus is required for gene activation.

the dorsal aorta [3,37]. These observations suggest the existence of myocardin-independent mechanisms for activation of SM gene expression. Whether MRTFs are responsible for SM gene expression in the absence of myocardin remains to be determined. Myocardin is not expressed in skeletal muscle cells, despite the requirement of CArG boxes for expression of numerous skeletal muscle structural genes. MRTF-A and -B are expressed ubiquitously during embryogenesis and in adulthood [4], suggesting that those factors might be involved in other biological processes in addition to muscle cell differentiation.

Myocardin is necessary and sufficient for smooth muscle cell differentiation

Cardiac gene expression can be blocked in *Xenopus* embryos by injection of mRNA encoding a dominant negative mouse myocardin mutant into a ventral blastomere fated to form heart [3]. Similarly, expression of dominant negative myocardin in the P19CL6 teratocarcinoma cell line inhibits cardiogenesis [52]. While such studies suggest an essential role for myocardin in cardiogenesis, it is conceivable that a dominant negative myocardin mutant could simply perturb SRF activity and thereby block cardiogenesis through a nonspecific mechanism unrelated to the function of the wild-type protein. Consistent with the conclusion that myocardin acts as a regulator of cardiac gene expression in *Xenopus*, a *Xenopus* homologue of mouse myocardin has been shown

by RNA interference experiments be required for heart development (E Small, D Wang, E Olson, P Kreig, unpublished). Conversely, mis-expression of myocardin in *Xenopus* embryos by mRNA injection results in ectopic activation of cardiac genes. Moreover, transgenic frogs that express myocardin in spinal cord neurons under control of the neural-specific β -tubulin promoter display cardiac gene expression in the spinal cord. Myocardin has also been shown to be sufficient to activate cardiac gene expression in *Xenopus* animal caps *in vitro*. Although the above experiments demonstrate the sufficiency of myocardin to activate cardiac gene expression, it appears that only a subset of cardiac genes are activated, suggesting that additional factors might be needed for activation of the entire cardiac phenotype.

In contrast to the ability of myocardin to activate cardiac gene expression in *Xenopus* embryos and animal caps, ectopic overexpression of myocardin in cultured mammalian fibroblasts is unable to activate cardiac gene expression. Instead, myocardin activates SMC genes in this assay [36–39,40]. Similarly, forced expression of myocardin in ES cells is also sufficient to activate smooth, but not cardiac, muscle gene expression [37]. MRTF-A is as effective as myocardin in inducing SM gene expression in transfected fibroblasts [38], which seems paradoxical given that MRTF-A is expressed in a wide range of cell types that do not express SM genes. Perhaps the activation of SM genes by MRTF-A requires a threshold of expression above that of the endogenous level or perhaps MRTF-A activity is repressed in non-muscle cell types *in vivo*. Whereas myocardin (and MRTFs) can activate endogenous SM genes in transfected fibroblasts or ES cells, it is unclear whether this reflects the stable conversion of such cells to an SM phenotype or simply the direct activation of specific SM target genes for SRF.

Further evidence for the role of myocardin and MRTFs in SMC differentiation comes from the finding that dominant negative myocardin or MRTF mutants or interfering mRNA for myocardin prevent differentiation of SMCs [38,39]. Similarly, dominant negative MKL has also been shown to block differentiation of the C2C12 skeletal muscle cell line *in vitro* [41], suggesting that these factors are required for SRF-dependent activation of skeletal muscle genes, as well.

Why does myocardin activate cardiac genes in some settings and SM genes in others? We favor the possibility that the myogenic activity of myocardin is influenced by other factors and signaling mechanisms. In the complex milieu of a *Xenopus* embryo, there may be additional transcription factors and signaling events that are permissive for cardiac gene expression. Perhaps these influences are missing in the context of mammalian tissue culture transfection assays. Alternatively, or in addition,

mammalian fibroblasts may express negative regulators of cardiogenesis. In this regard, prior studies have shown that the cardiac phenotype is recessive and can be silenced in heterokaryons between cardiomyocytes and fibroblasts [42]. It has also been reported that myocardin can activate expression of the cardiac-specific *ANF* gene in transfected skeletal muscle cells [36^{*}]. Whether transcription factors expressed in skeletal muscle cells can provide partial support for a cardiac phenotype remains to be determined.

A key question is whether SRF is an obligate partner for myocardin. Support for this conclusion has been provided by transfection assays in SRF null ES cells in which myocardin is unable to activate either endogenous SM genes or SRF-dependent reporters [4^{*},37^{*}]. Supplementation with exogenous SRF restores myocardin activity in such cells. Moreover, only the DNA binding domain of SRF is required for restoration of myocardin-dependent transcription in SRF null ES cells [37^{*}], reinforcing the conclusion that the interaction of myocardin with this region of SRF is necessary and sufficient to activate SRF target genes. Of course, these results do not rule out the possibility that myocardin might also associate with other transcription factors on SRF-independent genes.

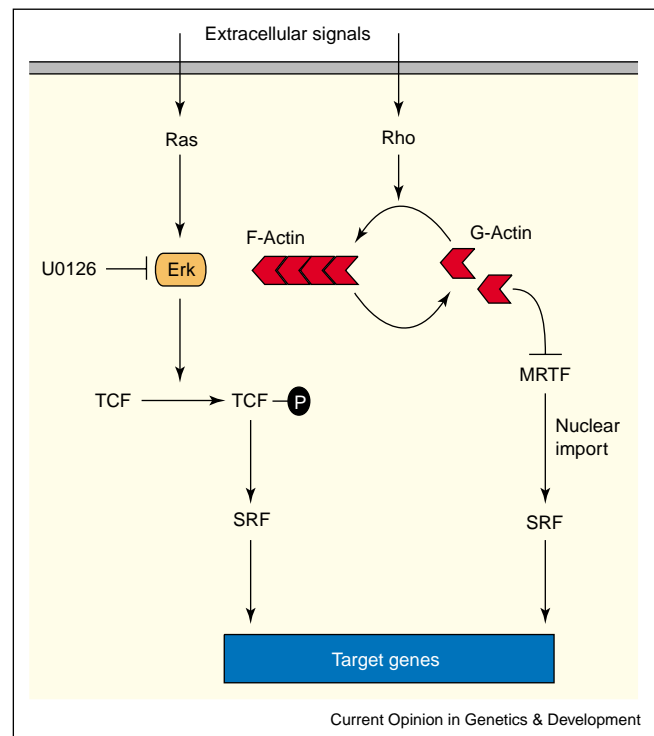
Surprisingly, cardiac development is seemingly unperturbed in myocardin knock out mice, which die at ~E11.5 from a lack of vascular SMCs [43^{*}]. As both MRTF-A and -B are also expressed in the embryonic heart during mouse development, they are likely to compensate for the absence of myocardin function. Mice lacking *MRTF-A* are viable, whereas a deletion of *MRTF-B* results in early embryonic lethality [44]. Creation of mice with compound mutations in the *myocardin* and *MRTF* genes will address this issue.

An interesting area that remains to be explored is the potential role of myocardin and MRTFs in cardiac hypertrophy. Numerous stress signals lead to hypertrophic growth of the heart, which is accompanied by the activation of SRF-dependent transcription. It is notable in this regard that forced expression of SRF in the heart is sufficient to induce hypertrophic cardiomyopathy [45]. Moreover, recent studies have reported that myocardin expression is upregulated in failing human hearts [46], which may account for the changes in SRF-dependent gene expression in this setting.

Signaling pathways leading to SRF

Serum and purified growth factors stimulate SRF activity via two independent pathways, one dependent on phosphorylation of TCFs by a MAP kinase cascade, the other dependent on Rho signaling and actin dynamics [47] (Figure 3). Dominant negative MRTF mutants or inhibition of MRTF-A/B expression with RNA interference has been shown to specifically inhibit SRF-dependent acti-

Figure 3



Parallel signaling pathways leading to SRF activation. Growth factor signaling activates Ras/MAP kinase cascades that culminate with ERKs and phosphorylation of TCFs. Phospho-TCFs are recruited by SRF to specific SRF binding sites. Rho signaling promotes actin treadmilling. G-actin inhibits the activity of MRTF by sequestering it in the cytoplasm. Actin polymerization releases MRTF for nuclear import.

vation of the *c-fos* promoter in response to serum and RhoA, whereas TCF-mediated activation was unaffected by the loss of MRTF activity [30^{*}]. Inhibition of both MRTF-A and -B was required for maximal suppression of RhoA-dependent activation of SRF, suggesting that these factors act redundantly.

Miralles *et al.* showed that MAL (MRTF-A) is sequestered in the cytoplasm of serum-starved fibroblasts and undergoes serum-dependent nuclear import through a mechanism dependent on RhoA signaling [32^{**}]. The N-terminal RPEL motifs are required for signal-dependent nuclear import and associate indirectly with G-actin. As there is no evidence for the direct interaction of actin with the RPEL motif of MAL, yet G-actin clearly represses nuclear import of MAL and can be immunoprecipitated with MAL, there must be one or more intermediary proteins that link actin to MAL. Identification of such proteins represents an important issue for the future. These findings point to MRTFs as a key link between Rho-actin signaling and SRF-dependent transcription. In contrast to MRTFs, which undergo signal-dependent nuclear import, myocardin is localized

constitutively to the nucleus [3], which appears to reflect an insensitivity of its N-terminal domain to actin dynamics. MRTFs have also been shown to undergo signal-dependent changes in phosphorylation [32^{••}]. The specific phosphorylation sites and their potential contributions to SRF-dependent transcription remain to be defined.

Consistent with the stimulatory effect of Rho signaling on SRF activity, differentiation of SMCs is enhanced by activators of Rho signaling and actin polymerization [48]. Recent studies suggest that the dependency of SM differentiation on Rho signaling reflects a requisite role of MRTFs in this process [33].

Antagonists of myocardin/MRTF activity

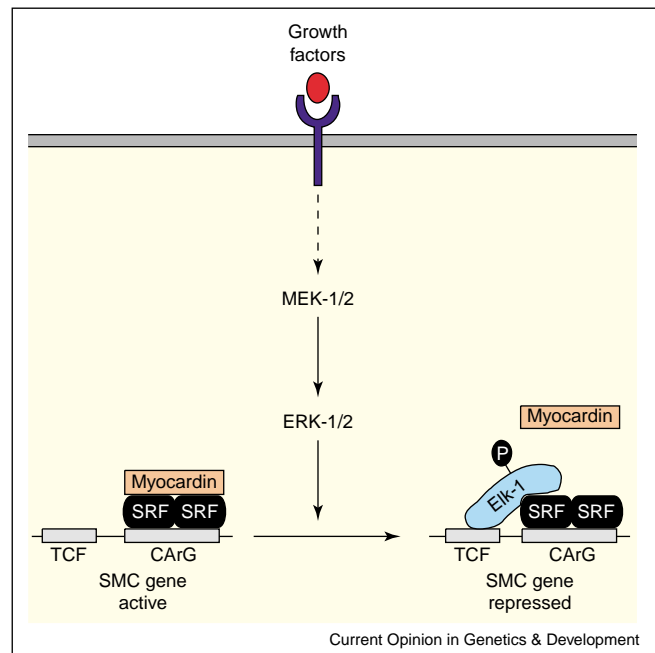
In principle, repressors of SRF activity should antagonize the activity of myocardin and MRTFs. There are multiple mechanisms through which such antagonism can occur. The small homeodomain-only protein HOP has been shown to suppress SRF activity by interfering with the ability of SRF to bind DNA. Accordingly, HOP can suppress myocardin-dependent activation of SRF [23,24]. Similarly, GATA transcription factors act as powerful repressors of SRF activity by multiple mechanisms [49].

Switch between differentiation and proliferation of smooth muscle cells

How SRF selects between muscle-specific and growth-regulated genes is not fully understood. Any proposed mechanism for the activation of SM gene transcription must account for the ability of growth factor signals to reversibly suppress the differentiation program. In this regard, the reversible association of myocardin with SRF appears to provide a mechanism for plasticity of SM phenotypes [50[•]].

Many, but not all, SM genes contain TCF binding sites near adjacent CArG boxes. In SMCs, myocardin and TCFs have been shown to associate with SRF within native chromatin in a mutually exclusive and signal-dependent manner [50[•]]. Interestingly, myocardin and MRTFs contain a short hydrophobic stretch of amino acids with the potential to adopt a secondary structure similar to that of the TCF B-box, which mediates SRF binding [50[•]]. Moreover, Elk-1 and myocardin bind to the same docking site on SRF; their binding is mutually exclusive such that association of myocardin with SRF activates SM-specific gene expression whereas formation of a TCF/SRF complex represses SM gene expression and activates cell growth gene expression [50[•]] (Figure 4). It seems paradoxical that Elk-1 can activate growth factor inducible genes such as *c-fos*, yet it inhibits expression of SM gene targets of myocardin. One explanation for this observation may be that Elk-1 (and other TCFs) is a relatively weak transcriptional activator compared to myocardin. Thus, its displacement of myocardin from

Figure 4



A model for the opposing roles of myocardin and TCFs in the control of SMC genes. Growth factor signaling activates MEK-1/2, which activates ERK-1/2, which phosphorylates TCFs, such as Elk-1. Phospho-Elk-1 is recruited to a subset of SMC genes where it can displace myocardin with consequent down-regulation of transcription.

SRF would be expected to result in a diminution in expression of myocardin target genes. Since TCF sites are not contained in all SMC gene promoters, additional mechanisms must also exist for negatively regulating myocardin activity under conditions of SMC phenotypic modulation.

Mutation of the TCF site in the *SM22* promoter renders the gene insensitive to the repressive effects of serum or PDGF [50[•]]. Moreover, a promoter lacking the TCF site continues to be expressed in the embryonic heart *in vivo* for several days after expression of the wild-type promoter has been down-regulated. These findings suggest that competition between TCFs and myocardin is important for the normal developmental control of SM gene expression in the developing heart *in vivo*.

Conclusions and questions for the future

The discovery of myocardin and MRTFs has provided new models and mechanisms to account for the seemingly paradoxical roles of SRF in the control of cell proliferation and myogenesis, and has raised many intriguing questions for the future. For example, how is the expression of myocardin controlled within the earliest progenitors of the cardiac and SM lineages? What are the functions of MRTFs *in vivo* and to what extent are they redundant with myocardin? How do myocardin and MRTFs

contribute to the heterogeneity of SMCs? What are the transcriptional targets of myocardin/MRTFs in different cell types, and how do these coactivators discriminate between genes involved in cell proliferation, myogenesis, and other cellular functions. Do myocardin and MRTFs associate with transcription factors in addition to SRF? How are the activities of myocardin and MRTFs regulated in response to extracellular signaling, and how do MRTFs sense changes in actin dynamics? Myocardin and MRTFs do not associate with MEF2, a MADS box transcription factor that binds a similar site to SRF and associates with cell type-restricted and signal-responsive cofactors to control the expression of muscle and growth factor-regulated genes. The similarities in mechanism of action of SRF and MEF2 raise the possibility that cofactors analogous to the myocardin family may also modulate MEF2 activity. Given the central roles of SRF in the control of cell migration, adhesion, and cytoskeletal dynamics [51], it is likely that myocardin and MRTFs will be intimately involved in these processes. Finally, in light of the involvement of SRF in many pathological states, it will be of interest to further explore the potential contributions of myocardin and MRTFs to disease pathologies.

Update

Following submission of this review, the following publications [53*–55*] provided further insight into the functions of the myocardin family.

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