Myogenin and the SWI/SNF ATPase Brg1 Maintain Myogenic Gene Expression at Different Stages of Skeletal Myogenesis*

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Many studies have examined transcriptional regulation during the initiation of skeletal muscle differentiation; however, there is less information regarding transcriptional control during adult myogenesis and during the maintenance of the differentiated state. MyoD and the mammalian SWI/SNF chromatin-remodeling enzymes containing the Brg1 ATPase are necessary to induce myogenesis in cell culture models and in developing embryonic tissue, whereas myogenin and Brg1 are critical for the expression of the late genes that induce terminal muscle differentiation. Here, we demonstrate that myogenin also binds to its own promoter during the late stages of embryonic muscle development. As is the case during embryonic myogenesis, MyoD and Brg1 co-localize to the myogenin promoter in primary adult muscle satellite cells. However, in mature myofibers, myogenin and Brg1 are preferentially co-localized to the myogenin promoter. Thus, the myogenin promoter is occupied by different myogenic factors at different times of myogenesis. The relevance of myogenin in the continued expression from its own promoter is demonstrated in culture, where we show that myogenin and Brg1 are critical for the expression of the late genes that induce terminal muscle differentiation. Finally, we utilized in vivo electroporation to demonstrate that Brg1 is required for the continued production of the myogenin protein in newborn skeletal muscle tissue. These findings strongly suggest that the skeletal muscle phenotype is maintained by myogenin and the continuous activity of Brg1-based SWI/SNF chromatin-remodeling enzymes.

During skeletal muscle differentiation, MyoD plays a critical role in initiating the onset of muscle-specific gene expression in cooperation with the MeF2 family of activators and with the SWI/SNF chromatin-remodeling enzyme, Brg1, which alters chromatin structure at myogenic loci in a manner that facilitates transcription (1, 2). An important target of MyoD is myogenin, a related basic helix-loop-helix myogenic regulatory factor (MRF)2 (3, 4). In addition to MyoD and myogenin, there are two additional members of the basic helix-loop-helix MRF family, Mrf4 and Myf5 (5, 6). Genetic analyses of mice deficient for one or for different combinations of the MRFs have demonstrated that complex relationships exist between members of this family. In particular, there is significant redundancy of function in numerous parameters relating to the initiation of myogenesis (reviewed in Ref. 7). In contrast, gene knock-out analyses indicate that terminal differentiation specifically requires myogenin, as mice deficient for myogenin formed myoblasts but did not develop mature skeletal muscle tissue (8–10). Thus, myogenin is the only MRF that is absolutely required for skeletal muscle differentiation during embryogenesis, and this requirement is manifested not for the initiation of myogenesis but instead for events associated with tissue formation.

Recently, we demonstrated that myogenin, in cooperation with MeF2D and Brg1, directed the expression of myogenic late genes that specify the skeletal muscle phenotype in cell culture and in embryonic tissue (11). We hypothesized that during the time of terminal differentiation and in post-differentiated skeletal muscle, myogenin might also bind to its own promoter and cooperate with Brg1 to regulate its own expression. This idea is further supported by prior cell culture experiments demonstrating that ectopic expression of myogenin in 10T1/2 cells could induce expression from the endogenous myogenin locus by an undefined mechanism (12, 13). Here we provide evidence to support this hypothesis by examining the occupancy and function of myogenin at its own promoter during embryonic and adult skeletal muscle differentiation and in culture and by functionally evaluating the requirement for Brg1 in myogenin expression in differentiated tissue.

EXPERIMENTAL PROCEDURES

Preparation of Mouse Embryonic Tissue—Conditions were identical to those published previously (11).

Nuclei Isolation from Mouse Skeletal Muscle Satellite Cells and Myofibers—Unless noted, all procedures were performed at 4 °C. Skeletal muscle from the upper hind limbs of 4- to 6-week-old C57/BL6 mice was minced to ∼1 mm3 and digested with 110 units/ml collagenase type II (Invitrogen) in phosphate-buffered saline containing 1 mM CaCl2. Samples were incubated at 37 °C for 1 h with agitation (14, 15) and filtered

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The abbreviations used are: MRF, myogenic regulatory factor; ChIP, chromatin immunoprecipitation; GFP, green fluorescent protein.
using a 70-µm cell strainer (352350; BD Biosciences) (16). Flowthrough material was enriched for satellite cells, while material that did not pass through the filter was enriched for myofibers. Aliquots of the separated fractions were taken for RNA isolation; the remainder was pelleted by centrifugation and resuspended in 7 volumes of lysis buffer (10 mM HEPES-KOH, pH 7.3, 10 mM KCl, 5 mM MgCl₂, 0.5 mM dithiothreitol, 0.2 mM phenylmethylsulfonyl fluoride, 3 µg/ml cytochalasin B, 10 µg/ml leupeptin). Following a 30-min incubation at 4 °C, nuclei were released by Dounce homogenization using the A pestle. Nuclei release was checked by Hoechst 33258 staining, and cell debris was removed by centrifugation. Nuclei were first resuspended in 2.5 volumes of 10 STM buffer (5 mM MgCl₂, 10 mM triethanolamine, pH 7.5, 5 mM MgCl₂, 10% sucrose, 10 µg/ml leupeptin) and then 2 volumes of 2.0 M sucrose/10 mM Tris-HCl/5 mM MgCl₂. The samples were overlaid on 750 µl of 2.0 M sucrose/10 mM Tris-HCl/5 mM MgCl₂ in a Beckman ultracentrifuge tube (number 344057) and spun at 116,140 g for 1 h at 4 °C. The pellet was resuspended in 500 µl of lysis buffer +0.1% Nonidet P-40. 1.0% formaldehyde at room temperature was added for 5 min for cross-linking, and, following centrifugation at 13,500 × g, pellets were frozen in liquid nitrogen. Thawed samples were resuspended in lysis buffer and sonicated.

Cell Culture—The B22 cell line inducibly expressing ATPase-deficient, dominant negative Brg1 (17) and retroviral infection (11, 18, 19) was previously described. Cells were cultured for 4 days in the presence of tetracycline (dominant negative Brg1 repressed) or in the absence of tetracycline (dominant negative Brg1 expressed) and were infected at 50% confluence with the indicated retrovirus for 30 h. Low serum differentiation medium was then added (time 0) to induce myogenic differentiation (20). Control samples were mock infected but still subjected to the differentiation protocol.

Quantitative Reverse Transcriptase Polymerase Chain Reaction Analysis—Reverse transcriptase PCR and quantitative PCR conditions were previously described (11). Primers for MyoD, myogenin, desmin, MCK (21), and EF1-α (11) were described. Endogenous myogenin (Fig. 3A) was amplified in the 3′-non-coding region with 5′-CAA GTG TGC ACA TCT GTT CTA GTC TC-3′, 5′-GTA TCA TCA GCA CAG GAG ACC TTG GT-3′. Quantitative PCR reactions shown on agarose gels were stopped in the linear range and visualized using SYBR Green I (Molecular Probes).

Chromatin Immunoprecipitation Assay—Chromatin immunoprecipitation (ChIP) assays were performed as described (11, 22). ChIP PCRs were performed with Qiagen HotStart Taq Master mix using the primer sets described for the myogenin promoter and IgH enhancer (22). Antibodies used include myogenin (sc-576; Santa Cruz) and affinity-purified polyclonal rabbit antibodies raised against glutathione S-transferase fused to full-length MyoD (22) and against glutathione S-transferase fused to a unique portion of Brg1 (17). PCR amplification was quantified using a DNA Engine Opticon system (MJ Research).

Restriction Enzyme Accessibility Assay (REAA)—REAA and detection of restricted DNA by a modified version of ligation-mediated PCR were described previously (11, 22).

RESULTS

Our previous results indicated that at the time of expression in developing embryos, myogenic late genes that specify the skeletal muscle phenotype are predominantly bound by myogenin and Mef2D and that these factors cooperate with the Brg1 chromatin-remodeling enzyme to alter promoter chromatin structure and facilitate late gene expression (11). Though multiple studies have examined the initiation of myogenin expression by MyoD, we recently demonstrated that both MyoD and myogenin could bind to the myogenin promoter in MyoD-differentiated fibroblasts 24 h post-differentiation (22). Therefore, we asked whether myogenin was present at its own promoter in the developing embryo after the point at which MyoD had initiated gene expression.

ChIP analysis of tissue samples at embryonic (E) 10.5 (body with head and internal organs removed), E12.5 (limb buds), and E14.5 (limb muscle) revealed that myogenin binding to the myogenin promoter could be observed at E12.5, with increased binding at E14.5 (Fig. 1). The kinetics of myogenin binding to

![FIGURE 1. Myogenin and Brg1 bind to the myogenin promoter during embryogenesis. ChIP assays for myogenin (left) and Brg1 (right) were performed at the indicated stages of embryonic development. Relative recruitment was defined as the ratio of amplification of the PCR product relative to 1% of input genomic DNA. Values obtained from brain tissue were defined as 1. Quantification represents the average of two independent experiments. Variation between experiments did not exceed 20% for any sample. The IgH enhancer region, which contains an E box that does not bind MyoD, was amplified as control for ChIP specificity.](image)
the myogenin promoter precisely matched those of myogenin binding to late genes (11), suggesting that at the time myogenin binds to genomic sequences in developing tissue, it does not discriminate between the previously inactive late gene loci and the transcriptionally active myogenin locus. Tissue culture studies indicate that Brg1 is essential for the initiation of myogenin transcription (20, 22, 26); as expected, Brg1 was present on the myogenin promoter at each of the embryonic stages examined (Fig. 1). We conclude that myogenin and Brg1 are present on the myogenin promoter at times when skeletal muscle tissue specification is occurring.

Mature skeletal muscle tissue is comprised of differentiated myofibers, which are the functional component of the tissue, and satellite cells, which associate with individual myofibers and are capable of dividing and either fusing with existing myofibers or creating new myofibers. The satellite cell population mediates the formation and repair of skeletal muscle tissue following the completion of development (reviewed in Refs. 27, 28). We separated satellite cells and mature myofibers from mouse hind limb muscles of 4- to 6-week-old mice and then isolated nuclei from the respective cell populations for molecular analyses of factor binding and chromatin accessibility. Nuclei were immediately utilized to isolate total RNA or were treated with cross-linking agents for ChIP analysis (Fig. 2A). Examination of marker gene expression permitted evaluation of the separation protocol. Proteins such as Pax3 and Pax7 are markers of satellite cells (29, 30), whereas the myogenic late gene products MCK and desmin are markers of differentiated skeletal muscle. The expression of these genes was enriched in the expected cell preparations (Fig. 2B).
Prior work revealed that MyoD targets Brg1 to the myogenin promoter during the initiation of myogenesis in tissue culture models for skeletal muscle differentiation (22, 26). ChIP analysis of the myogenin promoter showed that MyoD, not myogenin, bound along with Brg1 in satellite cells, suggesting that these two factors cooperate in the initiation of myogenin expression during adult myogenesis (Fig. 2C). In contrast, myogenin was preferentially associated with its own promoter in mature myofibers (Fig. 2C). These data indicate that myogenin binds to its own promoter in differentiated tissue, consistent with its appearance at times during embryogenesis when terminal differentiation is occurring or has already occurred (Fig. 1). Brg1 was also present on the myogenin promoter in myofibers, consistent with its presence on the promoter during the later stages of embryonic myogenesis.

The data suggest the possibility that activation of the myogenin gene is mediated by MyoD whereas maintenance of myogenin expression may be mediated by myogenin itself. To mechanistically address this possibility, we utilized MyoD-differentiated B22 cells, which are NIH3T3-derived cells that express an ATPase-deficient, dominant negative Brg1 protein in a tetracycline-suppressible manner (17). Previous work using this system demonstrated that MyoD-driven differentiation faithfully recapitulated the events that occur during the activation of myogenic late genes during embryogenesis (11). We previously reported that MyoD binding to the myogenin promoter correlated with the changes in nuclease accessibility at the myogenin locus and activation of myogenin transcription (22). We also noted that both MyoD and myogenin could interact with the myogenin promoter in a Brg1-dependent manner 24 h after the initiation of differentiation (22). ChIP experiments over a time course of MyoD-mediated differentiation confirmed our earlier results and further revealed that as differentiation progressed beyond 24 h, MyoD binding to the promoter diminished whereas myogenin binding was enhanced (Fig. 3A). This apparent transition from MyoD binding to the promoter at the onset of myogenin expression to myogenin binding as the cells completed the differentiation process is similar to the observations made regarding MyoD and myogenin binding to the myogenin promoter in satellite cells and myofibers.

The ChIP data support the idea that myogenin, in combination with Mef2 and Brg1, is activating its own transcription at times subsequent to the initial activation of gene expression by MyoD and Brg1. To directly test this hypothesis, we ectopically expressed MyoD, myogenin, and Mef2D1b, the muscle-specific isoform of the Mef2D protein that is highly induced during myogenesis in vivo (11, 31), alone or in combination, in B22 cells to determine whether the endogenous myogenin gene could be activated. As expected, MyoD stimulated myogenin expression in a Brg1-dependent manner (Fig. 3B). Neither myogenin nor Mef2D1b alone could activate the myogenin gene; however, the combination of myogenin and Mef2D1b, in the presence of functional Brg1, could activate endogenous

![Figure 4](image-url)

**FIGURE 4.** SWI/SNF chromatin-remodeling activity is required for myogenin expression in differentiated skeletal muscle. A, expression vectors encoding dominant negative Brg1 and GFP were introduced directly into mouse hind limb muscle of P2 mice by in vivo electroporation. Thin sections of hind limb skeletal muscle were examined in bright field, were immunostained with anti-myogenin antibody, and were monitored for GFP fluorescence 48 h later. B, control experiments show co-localization of GFP and myogenin in the absence of dominant negative Brg1 (−dnBrg1). Nuclei were visualized by 4',6-diamidino-2-phenylindole. Tissue sections were permeable to 4',6-diamidino-2-phenylindole, so all nuclei in the field are visible. Permeability issues limit the myogenin staining to nuclei at or near the surface of the section. C, quantification of the inhibition of myogenin expression. The number of myogenin-positive nuclei present in GFP fluorescent myofibers were counted in the control electroporation (GFP alone without dnBrg1) and in samples from dnBrg1-electroporated tissue. A total of 400 myogenin-stained nuclei from 16 different sections from both the GFP and GFP + dnBrg1 samples were counted for quantification.
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myogenin expression. Our previous data demonstrated that the combination of myogenin and Mef2D1b did not activate the endogenous MyoD, Myf5, or Mrf4 loci in NIH3T3-based cell lines (Refs. 11, 19 and data not shown). Thus, expression from the endogenous myogenin locus is due solely to the activation potential of myogenin and Mef2D1b. ChIP experiments showed that the mechanism by which myogenin and Mef2D1b mediate myogenin expression is via recruitment of Brg1 to the myogenin promoter (Fig. 3C). The presence of Brg1 then mediated changes in chromatin structure at the myogenin locus, which are reflected as increases in restriction enzyme accessibility at a PvuII site upstream of the myogenin mRNA start site (Fig. 3D). Both MyoD and the combination of myogenin and Mef2D1b could recruit both the functional and ATPase-deficient, dominant negative forms of Brg1 to the promoter, but chromatin accessibility required functional Brg1. Thus, whereas myogenin is not believed to initiate its own expression in vivo, the data indicate that the myogenin protein, in conjunction with Mef2D1b, has the intrinsic ability to activate expression from the endogenous myogenin locus in the absence of MyoD. These data and the differential binding of MyoD and myogenin to the myogenin promoter in satellite cells and myofibers support the conclusion that myogenin and Mef2D1b are responsible for maintaining the expression of myogenin after the onset of myogenesis.

We further note that though the data indicate a role for myogenin in maintaining its own expression, a prior report has shown that the loss of myogenin in postnatal mice does not impact skeletal muscle formation (9). Thus, myogenin is not required to maintain expression from the myogenin locus nor is it required for any skeletal muscle-specific function. These data strongly suggest that there are redundant factors that can compensate for the loss of myogenin during adult myogenesis.

The involvement of the Brg1 SWI/SNF ATPase in the initiation of myogenesis in culture and during embryogenesis is well established (11, 19, 20, 22, 26). The data presented here suggest that Brg1 function is also required in differentiated tissue, but detailed information about the in vivo relevance of Brg1 function in myogenesis in the mouse has been difficult to obtain because knock out of the Brg1 locus results in early embryonic lethality (32). To circumvent this problem, we adapted an in vivo electroporation protocol (24) to directly deliver plasmid DNAs encoding green fluorescent protein (GFP) and a Brg1 allele containing a mutated ATP binding site to differentiated muscle tissue in the hind limb of a postnatal day 2 (P2) mouse. This ATPase-deficient protein has been characterized extensively and acts as a dominant negative by interfering with normal Brg1-dependent functions (17, 25). Tissue isolated 48 h post-electroporation revealed that nuclei showing GFP fluorescence (Fig. 4A, white arrow) did not express myogenin protein. Conversely, nuclei that did not take up plasmid DNA showed no GFP fluorescence but immunostained for myogenin (yellow arrow). Control experiments where GFP alone was electroporated showed that cells expressing GFP also expressed myogenin (Fig. 4B). Quantification of these results revealed that introduction of dominant negative Brg1 inhibited myogenin expression in ~90% of electroporated nuclei (Fig. 4C). The results demonstrate that functional Brg1 is required for expression of myogenin in fully differentiated skeletal muscle tissue. Thus, Brg1 is required for both the initiation and maintenance of myogenin gene expression in vivo.

DISCUSSION

Our earlier work demonstrated that although MyoD was present on myogenic late gene regulatory sequences during embryogenesis prior to activation of these genes, the predominant factors present at the time of late gene expression in the developing tissue were myogenin and Mef2D, along with the chromatin-remodeling enzyme Brg1 (11). We reasoned that if myogenin were being utilized to activate late gene expression during the time of terminal differentiation, it might also activate its own expression both at this time and following the completion of differentiation. Although there have been prior molecular studies examining the regulation of myogenin, we believe this is the first report to explore the relationship between specific MRF occupancy of promoters and the timing of differentiation in primary embryonic and adult tissue.

The data support our hypothesis. ChIP analysis in embryonic tissue shows that myogenin binds the myogenin promoter with the same kinetics it binds to late gene promoters. Further sup-

FIGURE 5. Schematic representation of factor interactions at the myogenin promoter during myogenesis. Genomic DNA is depicted as being nucleosomal. Initiation of myogenin transcription is dependent upon MyoD, the Pbx homeodomain factor, and SWI/SNF chromatin-remodeling enzymes (left panel) (reviewed in Ref. 2). Upon the expression of myogenin, myogenin, Mef2D, and Brg1 localize to the myogenin promoter (right, top panel) to maintain myogenin expression. At the same time, myogenin, Mef2D, and Brg1 also localize to and activate late gene loci, displacing the MyoD and HDAC2 present at these loci prior to late gene expression (11). The schematic representation of these molecules is for illustrative purposes; the relative size of each molecule is not to scale.
port was derived from ChIP studies of adult satellite cells and myofibers, where the myogenin promoter in differentiating satellite cells was occupied by MyoD and the promoter in differentiated myofibers was predominantly bound by myogenin. This implies that when myogenin becomes competent to activate gene expression in the developing embryo or in differentiating adult tissue, there are no structural features associated with the myogenin promoter that distinguish it from the late gene loci.

Based on these and earlier data, we propose that there is a transition in MRF binding during the terminal differentiation stages of embryonic and adult myogenesis. MyoD initially binds to both early and late myogenic genes, but activation of late genes is repressed due to the simultaneous presence of histone deacetylases and possibly other repressive chromatin-modifying enzymes at these loci (11). Following the induction of myogenin and Mef2 family members by MyoD, these factors mediate the transcriptional activation of late genes that specify muscle formation and the continued transcription of early myogenic genes such as myogenin. This model is presented schematically in Fig. 5. Such a model is both similar to and different from the conclusions of previous studies. Prior work comparing the activation domains of MyoD and myogenin in culture led to a model of sequential functions at some genes by MyoD and then myogenin (33). However, genome-wide factor binding studies, where analyzed regulatory sequences were identified as targets of MyoD, myogenin, or both (34, 35), were more recently used to conclude that the myogenic genes identified as targets of both MyoD and myogenin are cooperatively regulated by these MRFs. Although the concept of cooperative regulation could encompass either sequential or simultaneous binding by MyoD and myogenin, we note that the cell culture data shown here and previously (11) demonstrate that myogenin, in the presence of Mef2D, is capable of initiating and maintaining its own transcription and that of the rest of the myogenic genes without cooperative effects by MyoD or any other MRF. Further support for sequential function was recently provided by studies of the E box binding factor HEB, which can heterodimerize with MRFs. That study demonstrated that HEB acted synergistically with MyoD to activate transcription in cell culture, and the presence of SWI/SNF chromatin-remodeling function in culture, and the presence of SWI/SNF subunits on gene regulatory sequences in cultured cells and primary tissue (11, 19, 20, 22, 26) and genetic analysis of a non-enzymatic subunit, Baf60c, revealed a requirement for embryonic myogenesis (38). Here we provide the first in vivo evidence that the SWI/SNF enzymes are required for myogenic gene expression in differentiated muscle tissue. In combination with earlier cell culture studies, we suggest that Brg1 and SWI/SNF enzymes are required continuously throughout every stage of adult and embryonic myogenesis.

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