Composition and Function of AP-1 Transcription Complexes during Muscle Cell Differentiation*

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The role of activating protein-1 (AP-1) in muscle cells is currently equivocal. While some studies propose that AP-1 is inhibitory for myogenesis, others implicate a positive role in this process. We tested whether this variation may be due to different properties of the AP-1 subunit composition in differentiating cells. Using Western analysis we show that c-Jun, Fra-2, and JunD are expressed throughout the time course of differentiation. Phosphatase assays indicate that JunD and Fra-2 are phosphorylated in muscle cells and that at least two isoforms of each are expressed in muscle cells. Electro-photoric mobility shift assays combined with antibody supershifts indicate the appearance of Fra-2 as a major component of the AP-1 DNA binding complex in differentiating cells. In this context it appears that Fra-2 heterodimerizes with c-Jun and JunD. Studying the c-jun enhancer in reporter gene assays we observed that the muscle transcription factors MEF2A and MyoD can contribute to robust transcriptional activation of the c-jun enhancer. In differentiating muscle cells mutation of the MEF2 site reduces transactivation of the c-jun enhancer and MEF2A is the predominant MEF2 isoform binding to this cis element. Transcriptional activation of an AP-1 site containing reporter gene (TRE-Luc) is enhanced under differentiation conditions compared with growth conditions in C2C12 muscle cells. Further studies indicate that Fra-2 containing AP-1 complexes can transactivate the MyoD enhancer/promoter. Thus, an AP-1 complex containing Fra-2 and c-Jun or JunD is consistent with muscle differentiation, indicating that AP-1 function during myogenesis is dependent on its subunit composition.

The activating protein-1 (AP-1)* transcription complex is intrinsically involved in diverse cellular processes such as transformation, apoptosis, proliferation, and differentiation (1). The diverse cellular responses to AP-1 activity may, in part, be mediated by the specific subunit composition of the AP-1 complex. This complex is a dimer of the Jun and Fos proto-oncogene families that binds to a cis element termed the TRE (12-O-tetradecanoylphorbol-13-acetate response element) with the consensus 5’-TGAC/GTCA-3’ (1). AP-1 is thus formed by a dimeric association between Jun (c-Jun, JunB, and JunD) and Fos (c-Fos, FosB, Fra-1, and Fra-2) family proteins or a subset of ATF proteins. Therefore, a primary issue in understanding AP-1 activity concerns the functional properties of the different AP-1 dimer combinations. For example, in mouse fibroblasts JunD has an antiproliferative role, whereas c-Jun promotes S-phase entry and proliferation (2, 3). Furthermore, the role of AP-1 in apoptosis is complex, dependent on the cellular context, and while c-Jun appears to be pro-apoptotic, JunD protects cells from senescence and apoptosis (4). Since AP-1 components are differentially expressed during development and in different tissues, it is likely that heterogeneous AP-1 complexes fulfill distinct roles in cells of different lineage. This idea is supported by gene targeting experiments in which c-Fos →/- mice have impaired bone development but are viable (5), c-jun and junB knock-outs are lethal (6–8) and targeted disruption of the junD gene results in specific defects in male reproductive function (9). The importance of AP-1 composition for specific biological responses is also exemplified in cellular transformation of NIH 3T3 by Ras; JunD is down-regulated in contrast to c-Jun levels, which increase. Overexpression of JunD also antagonizes transformation. The Jun proteins are responsive to an array of stimuli such as UV irradiation, cytokines, oxidative stress, and growth factors (1, 10–13). At least some of these signals are mediated by activation of the JNK/SAPK kinase cascade (13–16). Thus, the specific AP-1 dimer composition and also the targeting of these components by cellular signaling pathways provide the cell with complex machinery to modulate genes bearing this TRE element. Additional studies to clarify the function of specific AP-1 dimers in different cell types are therefore paramount to understanding the biology of AP-1 function in vivo, both during development and also in the adult.

The process of muscle differentiation has proved to be a powerful model for studying mechanisms of tissue-specific transcriptional control (17, 18). The identification and extensive characterization of the basic helix-loop-helix myogenic regulatory factors (MRFs) and the myocyte enhancer factor 2 (MEF2) transcription factors have led to the establishment of a paradigm for the regulation of tissue specific gene expression (17, 18). In contrast, the physiological role for AP-1 during myogenesis is not well defined. Initial studies showed that c-Jun represses myogenesis due to a direct physical antagonism of the activity of the MRF family members, MyoD and myogenin (19–21). However, one hallmark of these studies was that the effects on myogenesis were dependent on high levels of c-Jun overexpression from retroviral vectors, possibly implying that the mechanism of inhibition was through competition with...
the MRFs for a limiting factor such as CBP/p300. Moreover, mice expressing an H-2K-v-Jun transgene develop malignant sarcomas that contain focal areas of skeletal muscle (22). These observations are consistent with the idea that expression of v-Jun in transgenic tumors is compatible with skeletal muscle differentiation.

Since these studies, the full complexity of AP-1 has been documented, and it is possible that c-Jun overexpression in these earlier investigations disturbed the requirement for precise balance of AP-1 components in the cells. This idea is supported by observations that AP-1 components can be detected in differentiating myogenic cells, and some of the MRF gene promoters and certain muscle structural genes contain TRE elements. Thus, co-expression of AP-1 proteins with myogenic and structural proteins is compatible with a positive role for physiological levels of AP-1 in myogenic differentiation (23–28).

Here, we report that the subunit structure of the AP-1 complex undergoes a transition from a “proliferation”- to “differentiation”-specific, Fra-2-containing complex during myogenesis. Also, the transcriptional control of the c-Jun gene promoter becomes partially under the control of muscle specific transcription complexes during differentiation. These data highlight the complex role of heterogeneous AP-1 complexes in the context of muscle cell differentiation.

**EXPERIMENTAL PROCEDURES**

**Cell Culture**—HeLa and COS cells were grown in Dulbecco’s modified Eagle’s medium (DMEM) with 10% fetal bovine serum (FBS) on plastic dishes. C2C12 cells and primary rat myoblasts were grown in DMEM + 10% FBS on gelatin-coated plastic dishes. To induce differentiation of the C2C12 myoblasts or primary rat myoblasts, the medium was changed to DMEM + 5% horse serum (as described previously (29, 30)). For primary myoblast cultures, one litter of neonatal rat pups was processed using standard procedures of trypsin/collagenase dissociation and preplating to deplete fibroblasts.

**Immunoprecipitations and Immunoblotting**—Equal amounts of protein per lane, as determined by Bradford assay, were resolved on sodium dodecyl sulfate (SDS)-polyacrylamide gel (PAGE). Resolved proteins were electrophoretically transferred to Nitroplus nitrocellulose type membranes (Micron Separations) for immunoblotting. Membranes were stained with Ponceau S to check for equivalent transfer and then washed with transfer membrane (Micron Separations). Membranes were stained with reagent (PerkinElmer Life Sciences) was used to detect secondary antibody with its peptide competitor prior to inclusion in the binding reaction. For the immunogold shift analysis, where appropriate, 1 μl of antisera or preimmune serum was added to the incubation reaction. Where appropriate, antibody peptide competition was carried out by preincubating the antibody with its peptide competitor prior to inclusion in the binding reaction.

**Transcriptional Response Assays**—For the reporter assays, the appropriate reporter gene (see figure legends for details) was transfected into C2C12 myoblasts and COS or HeLa cells, which were at 60% confluence, with the calcium phosphate co-precipitation technique. Each plate was transfected with 5 μg of the appropriate luciferase reporter construct, and 2 μg of PSV β-galactosidase, which served as an internal control for transfection efficiency. For the overexpression studies, 2.5 μg of pMT2-MEF2A and/or 6 μg of pMT2-MoYoD, or the pMT2 vector alone as a control, were transfected into the cells. Twenty-four hours later the medium was changed to DMEM + 5% horse serum. For HeLa and COS cell transfections, fresh DMEM + 10% FBS was added 48 h after the calcium phosphate precipitate was added. The cells were then collected 24 or 48 h after the medium was changed. The reporter gene constructs used were the following: pLuc, which contains −225 to +150 of the c-jun enhancer/promoter upstream of a basal promoter-luciferase gene (pGL2); pJSX Luc, containing −225 to +150 of the c-jun enhancer/promoter (the same as pJSXLuc except for two point mutations in the MEF2 site, which inhibit MEF2 binding); pC6 contains −225 to +150 of the c-jun enhancer/promoter upstream of a basal promoter-luciferase gene (this contains the same regulatory elements as pJSX Luc except that a later generation luciferase reporter gene was used as the backbone-pGL3); pJTX (same as the wild type pJC6 apart from a point mutation in the AP-1 binding site); pJC90Fluc, which contains −80 to +150 of the c-jun enhancer, containing only the MEF2 and jun1 site, upstream of −53 to +42 of the c-fos promoter; pPOLuc, which contains −53 to +42 of the c-fos promoter; and TATA Luc, which contains a TATA box upstream of the luciferase reporter gene. A TRE-Luc reporter gene (1.5 μg) and 0.5 μg of PSV β-galactosidase were transfected into myogenic cells under growth and differentiation conditions as an indicator of AP-1 activity. For these experiments, C2C12 cells were plated in gelatin-coated six-well plates at a density of 2 × 105 cells/well. One day after plating, fresh FBS was added to the growth condition prior to transfection. For the differentiation condition, 5% HS was added prior to transfection. On the day following the transfection, the medium was changed to fresh 5% horse serum for the differentiation condition. For the growth condition, the cells were trypsinized and divided between two wells prior to adding fresh 10% FBS. The cells in both conditions were harvested 2 days after the transfection, and normalized luciferase activity was determined. For the MyoD enhancer assays, we used a luciferase reporter gene downstream of either the 2.5-kb MyoD promoter region or the 2.5-kb promoter region with the 258-base pair core enhancer upstream (27). 2 μg of the reporter genes were transfected along with 2 μg of the pCMV c-Jun, pCMV JunD, or pCMV Fra-2 expression vectors. The cell extracts were prepared, and luciferase activity was determined as described by the manufacturer (Promega).

**RESULTS**

**Expression of AP-1 Family Members during Myogenesis**—We initially tested the expression of various AP-1 subunits in cultured muscle cells. We found that both myoblasts and myotubes express c-Jun, JunD, and Fra-2 (Fig. 1A). MyoD expression was monitored in each immunoblot as an internal control. Throughout the time course of differentiation, the expression of c-Jun, JunD, and Fra-2 was maintained. There were some fluctuations in the absolute levels of c-Jun, JunD, and Fra-2 by 120 h in differentiation medium, but these were minor (Fig. 1A). Thus, we observed an appreciable expression of AP-1 factors throughout the time course of myogenesis differentiation.

We observed at least two immunoreactive Fra-2 and JunD bands in the Western analysis, indicating the possibility of post-translational modification of these proteins by cellular signaling pathways during differentiation (Fig. 1A). Immunoprecipitation of JunD and Fra-2 followed by phosphatase treatment indicated that the major isoforms of both proteins were altered in their mobility in SDS-PAGE, indicating that they are phosphorylated in muscle cells (Fig. 1B). A number of signaling pathway-activated kinases are known to target AP-1 proteins.

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The underlined nucleotides conform to the consensus sequence of the MEF2 site and AP-1 site, respectively. For the immunogold shift analysis, where appropriate, 1 μl of antisera or preimmune serum was added to the incubation reaction. Where appropriate, antibody peptide competition was carried out by preincubating the antibody with its peptide competitor prior to inclusion in the binding reaction.
having both negative and positive effects on AP-1 activity. Therefore, the precise implications of these modifications for AP-1 activity in myogenic cells requires further investigation. Even though the mobility of the JunD and Fra2 bands was altered by phosphatase treatment, at least two immunoreactive bands were still observed for each protein after phosphatase treatment (Fig. 1B). This indicates that these protein isoforms could result from alternative splicing or another type of modification.

**Heterogeneous Composition of AP-1 DNA Binding Complexes in Proliferating Myoblasts and Differentiated Myotubes**—A major level of control for AP-1 is at the level of heterodimer formation and DNA binding activity; therefore we next assessed the contribution of the different AP-1 family members to AP-1 DNA binding complexes in myoblasts and myotubes. Since the similar molecular weight of the AP-1 proteins gives rise to similar sized DNA binding complexes, it is not possible to discern heterogeneous complex composition by the mobility of the binding complex alone. Therefore, to analyze AP-1 complex composition, we used electrophoretic mobility shift assay analysis coupled with specific antibodies against the AP-1 proteins. Fig. 2 indicates that in differentiating C2C12 myotubes the predominant dimer combination indicated by the immuno-

gel shift analysis was a Fra-2-containing complex, since nearly all of the AP-1 complex was eliminated by antibodies directed against Fra-2. (Fig. 2B, lane 7). Since both c-Jun and JunD were also in the complex (Fig. 2B, lanes 4 and 5), it is likely that the complex is comprised of c-Jun:Fra-2 and JunD:Fra-2 heterodimers. In myoblasts, in contrast to myotubes, there was virtually no Fra-2 in the complex (Fig. 2A, lane 7), although c-Jun and JunD are also components of the AP-1 complex (Fig. 2A, lanes 4 and 5). Since c-Fos is expressed at high levels in proliferating myoblasts (24), it is likely that the Jun partner in myoblasts is c-Fos. However, we were unable to test this adequately due to the paucity of good c-Fos antibodies that work in electrophoretic mobility shift assay supershift analysis. Since Fra-2 is a major part of the myotube AP-1 complex, we conclude that the major AP-1 complex in differentiating myotubes is a JunD:Fra-2 or c-Jun:Fra-2 heterodimer.

**Control of the c-Jun Promoter in Myogenic Cells**—Our studies indicate that c-Jun expression is maintained in differentiating myogenic cells despite the loss of growth factor signaling, which normally regulates c-Jun transcription (32). Therefore, we went on to analyze the c-jun enhancer/promoter in muscle cells to discern whether muscle-specific transcriptional regulators could contribute to its activation in the absence of "prolif-
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**Composition of the AP-1 DNA binding complex in myoblasts and myotubes.** Extracts made from myoblasts or myotubes were analyzed for the composition of AP-1 complexes. Where indicated the extracts were preincubated with antibodies directed against c-Jun, JunD, or Fra-2. In some cases the antibody was also preincubated with a neutralizing peptide (pep.) inhibitor to indicate antibody specificity. 50X refers to the inclusion of a 50-fold molar excess of unlabeled AP-1 competitor in the binding reaction.

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**AP-1 Activity in Myogenic Cells and Activation of the MyoD Promoter—A role for AP-1 in muscle differentiation is supported by recent observations that the MyoD and Myf5 promoters contain AP-1 elements (27, 23). We therefore tested what effect different AP-1 components have on the MyoD enhancer/promoter region. We studied the 2.5-kb MyoD promoter or the promoter plus the 258-bp core enhancer that has recently been described (27) to determine whether AP-1 components could transactivate these regions in transcriptional response assays. These experiments indicated that Fra-2-containing AP-1 complexes could activate transcription through the MyoD promoter region that contains an AP-1 site (Fig. 5A), although this requires further clarification by detailed promoter analysis. Finally, we used an AP-1 site containing luciferase reporter gene (TRE-Luc) to indicate the activity of AP-1 in C2C12 muscle cells.
cells under growth and differentiation conditions. In these studies (Fig. 5B) we observed that despite the withdrawal of serum in differentiation conditions, we could still see activation of the TRE-Luc reporter gene, and the level of activation was greater than in growth conditions. This, therefore, indicates that AP-1 activity is maintained and potentiated under differentiation conditions in myogenic cells.

DISCUSSION

Here we present data pertaining to the expression and activity of AP-1 in myogenic cells. AP-1 activity in differentiating muscle cells raises the possibility, contrary to previous ideas, that it may play a positive role during myogenesis. Since the AP-1 complex in proliferating myoblasts is distinct from that of terminally differentiated myotubes, differentiation-specific changes in AP-1 composition may reflect dynamic changes in the activation of AP-1 target genes in these cells. In differentiating muscle cells the predominant AP-1 complex consists of a heterodimer comprised of Fra-2 complexed with c-Jun or JunD. The increased level of Fra-2 in the myotube AP-1 complex is correlated with cell cycle withdrawal and the activation of muscle gene expression. Thus, these data suggest that a different set of AP-1 target genes may be activated by heterogeneous AP-1 complexes during differentiation. It is likely that there are a multitude of AP-1 target genes in muscle, but one notable target could be MRF family members. Here we show that Fra-2-containing AP-1 complexes can transactivate the MyoD core enhancer. Although the functional implications of changes in the AP-1 subunit composition are incompletely un-
understood at this point, it is clear that the AP-1 complex in differentiating muscle cells is distinct from that in proliferating myoblasts.

An important level of regulation of AP-1 occurs through controlling its activity and concentration within the cell (1). For example, the activity of c-Jun and Fra-2 is regulated through phosphorylation (14, 36, 37). In response to various stressors such as UV, heat, or TNF-α, c-Jun is phosphorylated on Ser 63 and, more prominently, Ser 73 in its activation domain by the JNKs (14, 16). This phosphorylated c-Jun can then interact with co-activators CBP/p300 to increase transactivation of target genes. The abundance of c-Jun is also regulated at the level of protein stability. The half-life of c-Jun is 90 min, and degradation of c-Jun has been shown to be mediated by the ubiquitin pathway (36). However, phosphorylation of c-Jun by the JNKs decreases c-Jun ubiquitination and increases its stability (36). Less is known concerning the regulation of Fra-2 by phosphorylation, but the present study indicates that both JunD and Fra-2 are modified by phosphorylation in myogenic cells. The implications of this post-translational regulation of Fra-2 and JunD during myogenesis is thus of considerable interest.

Activation of c-jun transcription through the c-jun enhancer/promoter is elevated in growing HeLa cells. We attribute this to the various sites in the enhancer, i.e., NF-jun, jun1, jun2, SP1, and the CAAT box, which are bound by various transcription factor complexes. However, endogenous MEF2 proteins in HeLa do not contribute to this activation, since the c-jun enhancer, which contains a mutated MEF2 binding site, has the same activity as the wild type enhancer when it is transfected. Therefore in HeLa cells, the basal levels of c-jun transcription do not depend on the MEF2 site. In contrast to the minimal role played in proliferating cells, we show that the MEF2 site in the c-jun enhancer is an important regulatory element in myogenic cells, since a mutated MEF2 site in the c-jun enhancer leads to a considerable diminution of reporter activity during differentiation. The residual enhancer activity remaining when the MEF2 site is mutated is due to the contribution from the other transcription factor binding sites or possibly as yet unknown cis elements in the c-jun enhancer.

Previous studies have suggested that a putative AP-1/CRE element at −342 to −322 of the MyoD promoter is a negative regulator of MyoD expression (38). This element is not a classical AP-1 site but fits the consensus as a cAMP-responsive element. Previous studies suggest the involvement of AP-1 in the regulation of this element. However, even though c-Jun and c-Fos were implicated in negative control of the MyoD promoter through this element, it is not yet known what the role of a different AP-1 dimer combination could be. Our initial studies with overexpression of Fra-2 indicate that it can activate the 2.5-kb MyoD promoter containing this element, thus supporting the notion that there could be differential regulation through this element depending on the specific AP-1 dimer binding there. Additional studies of the MyoD gene have indicated the presence of a consensus AP-1 site in the middle of a region referred to as the MyoD core enhancer, which is located.
20 kb away from the transcriptional start site (27). Thus, further studies dissecting the role of AP-1 dimer combinations on the MyoD promoter may be important in determining the control of MyoD expression.

Considering our data, along with those of others, we propose a testable model (Fig. 6) for the inclusion of specific AP-1 complexes in the MyoD promoter. We also show data indicating that AP-1 may play a role in the myogenic cascade.

Several studies in the early nineties suggested that AP-1 is a possible explanation, based on evidence presented by others. We therefore propose that physiological levels of an AP-1 complex consisting of a JunD/Fra-2 or a c-Jun/Fra-2 heterodimer is consistent with, and not antagonistic to, myogenic differentiation. We also show data indicating that AP-1 may play a role in the full activation of MyoD expression due to direct effects on the MyoD promoter. These data implicate specific AP-1 subunits in the positive control of muscle differentiation.

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