A Novel EID-1 Family Member, EID-2, Associates with Histone Deacetylases and Inhibits Muscle Differentiation*

Received for publication, December 2, 2002, and in revised form, February 10, 2003

Published, JBC Papers in Press, February 13, 2003, DOI 10.1074/jbc.M212212200

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An EID-1 (E1A-like inhibitor of differentiation-1) inhibits differentiation by blocking the histone acetyltransferase activity of p300. Here we report a novel inhibitor of differentiation exhibiting homology to EID-1, termed EID-2 (EID-1-like inhibitor of differentiation-2). EID-2 inhibited MyoD-dependent transcription and muscle differentiation. Unlike EID-1, EID-2 did not block p300 activity. Interestingly, EID-2 associated with class I histone deacetylases (HDACs). The N-terminal portion of EID-2 was required for the binding to HDACs. This region was also involved in the transcriptional repression and nuclear localization, suggesting the importance of the involvement of HDACs in the EID-2 function. These results indicate a new family of differentiation inhibitors, although there are several differences in the biochemical mechanisms between EID-2 and EID-1.

The terminal differentiation program is regulated both positively and negatively. Among various tissues, skeletal muscle is one of the most well studied in terms of differentiation regulation (1, 2). Several fate-determining transcription factors regulate the expression of tissue-specific proteins. As for skeletal muscle differentiation, ubiquitously expressed basic helix-loop-helix (bHLH) transcription factors such as E proteins heterodimerize with the MyoD family of myogenic bHLH transcription factors, consisting of MyoD, Myf5, myogenin, and MRF4 (2). These heterodimers bind to the canonical E-box (CANNTG) sequences of the promoter regions of muscle-specific genes and up-regulate transcription. Other factors that dimerize with MyoD family proteins are non-bHLH MCM1, agamous, deficiens serum response partner (MADS)-box proteins, myocyte enhancer factors (MEFs). This group consists of MEF2A, -B, -C, and -D (1–3). These tissue-specific transcription factors recruit coactivators such as p300/cAMP-response element binding protein (CBP)-binding protein and P300/CBP-associated factor (PCAF) and then activate transcription (2).

In addition to the above-mentioned positive regulators, several negative regulators for muscle differentiation have been found to date (2). The Id family consists of four members, namely, Id1, -2, -3, and -4 (4). Id proteins are HLH proteins that lack DNA-binding domains. Therefore, they can heterodimerize with bHLH proteins but are unable to bind to DNA (5); hence Id proteins act as dominant negative regulators of bHLH proteins.

Histone deacetylases (HDACs) are known to maintain core histones in a hypoacetylated state, resulting in transcriptional repression. HDACs comprise three classes, namely RPD3-like HDACs (class I), HDAC1-like HDACs (class II), and newly identified SIR2-like HDACs (class III) (6). Both class I and class II HDACs exhibit histone deacetylase activities at the C-terminal portions, but class I HDACs lack an N-terminal extension. Class I HDACs bind to MyoD and repress transcription (7). Class II HDACs bind to MEF2 via its N-terminal MEF2-binding domain and repress transcription (8–11). Class II HDACs are localized to the nuclei of myoblasts and are exported to the cytoplasm with differentiation signals (12, 13).

Recently, we and others (14, 15) identified a novel negative regulator of differentiation, termed EID-1 (E1A-like inhibitor of differentiation-1), as a pRB- and p300-binding protein (14, 15). EID-1 inhibits myogenic differentiation by blocking the histone acetyltransferase (HAT) activity of p300/cAMP-response element binding protein-binding domain (14, 15). This molecule has also been reported as RBP21, which interacts with pRB (16). EID-1 exhibits no homology to known proteins including bHLH factors and HDACs. Functionally, EID-1 exhibits similarity with adenovirus E1A or twist in terms of inhibition of HAT activity (14, 15, 17).

In this study, we identified a new EID-1 family member, termed EID-2 (EID-1-like inhibitor of differentiation-2). EID-2 was mainly expressed in heart, skeletal muscle, kidney, and liver. EID-2 inhibited MyoD-dependent transcription and blocked muscle differentiation in cultured cells like EID-1. However, EID-2 neither bound to p300 nor inhibited p300-dependent transcription. Interestingly, EID-2 associated with class I HDACs. This property was correlated with the ability to repress transcription and its nuclear localization. These results indicate that EID-2 and EID-1 exhibit homology and a similar phenotype but have distinct mechanisms in terms of inhibition of differentiation.

EXPERIMENTAL PROCEDURES

Cell Culture and Transfection—U-2OS osteosarcoma cells and 10T1/2 murine fibroblasts were grown in Dulbecco’s modified Eagle’s medium (Sigma) supplemented with 10% heat-inactivated fetal bovine serum (FBS), 100 units/ml of penicillin, and 100 μg/ml of streptomycin (PSG; Invitrogen). C2C12 murine myoblasts were grown in Dulbecco’s modified Eagle’s medium supplemented with 20% FBS and PSG. To induce differentiation, C2C12 cells were grown in Dulbecco’s modified Eagle’s medium containing 2% horse serum for 3 days once they had become confluent. Transfection was performed with TransIT-LT1 (Mirus) according to the manufacturer’s instructions.

Plasmids—pCMV, pcDNAs, pcDNAs-T7-EID-1, pSG5, pSG5-TetR,
pSG5-TetR-EID-1, pMCK-luciferase (15), pCMV-MyoD (19), 3xGal4-luciferase (20), pCMV-Gal4-p300 (21), pDNA-FLAG-HDAC1, and pME18S-FLAG-HDAC2 (22) were described previously. pRL-SV40-fragments and pGEM-T Easy were purchased from Promega.

EID-2 DNA fragments were generated by the PCR reaction using a fetal brain cDNA library (Clontech) as a template. The 5’-primer (CTATTTCGATGATGAGATAC) was designed as a sense oligonucleotide of the pGAD10 vector, and the 3’-primer (AAGTACGGTGGCAACATACA) was designed as an antisense oligonucleotide whose sequence was obtained from the EST data base of a putative EID-1-related gene.

The PCR product was purified and subcloned into the pGEM-T Easy vector (Promega) and sequenced on both strands. The EID-2 cDNA sequence was deduced by comparing the DNA sequences of multiple overlapping PCR fragments encoding the wild-type EID-2, and its mutants thereof, were obtained by PCR using oligonucleotides that introduced a 5’-BamHI site and a 3’-EcoRI site. To obtain internal deletion mutants, a two-step PCR strategy was used, as described previously (23). The PCR products were restricted with BamHI and EcoRI and then subcloned into pDNA3-T7, pSG5-TetR (15), and DsRed2 (Clontech), which had been linearized with these two enzymes or BglII and EcoRI in case of DsRed2. All of the PCR products were confirmed by DNA sequencing.

**Oligo-capping Method**—To determine the transcriptional start sites for the human EID-2 gene, we used the oligo-capping method described previously (24). In brief, mRNA was purified from HepG2 human hepatocellular carcinoma cell lines followed by exchanging of the cap structure with the adaptor oligonucleotide and reverse transcription. The cDNA was amplified by nested PCR using a sense primer of the adaptor sequence and an antisense primer of EID-2 open reading frame. The first primer set was as follows: 1st sense adaptor oligo, ATGAGCATC-GAGTTCGGCCTTGC; 1st antisense EID-2-F, TTCCCGTGTCTCGACCTGG; 2nd sense adaptor oligo, AGCATGAGTGGCCTTGGTTC; 2nd antisense EID-2-G, TGGCTCGCCGCCGCCTTCACC. The PCR fragment was ligated into the pGEM-T Easy vector and then sequenced on both strands.

**Northern Blot Analysis**—Northern blotting was performed with a multiple tissue northern blot (Clontech) and detected with a digoxigenin-labeled probe (Roche Molecular Biochemicals) according to the manufacturer’s instructions. The EID-2 DNA probe was generated with the PCR DIG labeling mix (Roche Molecular Biochemicals) using a sense primer, GGTGGCGGCCGCCAGCCAG, and an antisense primer, TTCCCGTGTCTCGACCTGG. The PCR product was flanked by nucleotides 162 and 392 of the human fetal brain cDNA, hereafter called EID-2. All of them contain ATG in-frame with the stop codon. The deduced polypeptides consist of 236 amino acids, and homology to EID-1 was observed in both the N and C termini (Fig. 1A). Neither of the six clones had an in-frame stop codon upstream of ATG. Then we used the oligo-capping method (24) to determine the transcriptional start site, as described under “Experimental Procedures.” We obtained a cDNA containing 5 additional nucleotides upstream of ATG of EID-2 (data not shown). There was no additional ATG in this portion, supporting that the EID-2 sequence contains the full-length open reading frame.

The 5’-end of the EID-2 mRNA, which exists in the C-terminal of EID-1, was detected by means of a mammalian two-hybrid assay (data not shown). We showed previously (14, 15) that EID-1 had a potential transcriptional domain because of its p300-binding property. To determine whether EID-2 has a similar property to EID-1 in terms of activation of transcription as a fusion protein with a heterologous DNA-binding domain, EID-2 was fused to the DNA-binding domain of the TetR, followed by scoring the ability to activate or repress transcription from the luciferase reporter plasmid. Surprisingly, although TetR-EID-1 caused an increase in reporter activity (Fig. 2A, left panel) (15), TetR-EID-2 caused a modest but reproducible decrease in reporter activity (Fig. 2A, right panel). In agreement with this result, EID-2 did not bind to p300 in vivo, as determined by means of a mammalian two-hybrid assay (data not shown).
Previous reports showed that EID-1 blocked the HAT activity of p300, which caused inhibition of p300-mediated transcription (14, 15). To determine whether EID-2 can block p300-mediated transcription like EID-1, U-2OS cells were transfected with a reporter plasmid containing Gal4-DNA-binding sites and a plasmid encoding Gal4 fused to the full-length p300 in the presence of a plasmid encoding EID-1 or EID-2. EID-1 inhibited transactivation by p300, whereas EID-2 had no effect on p300-mediated transcription (Fig. 2B). These results suggest that EID-1 and EID-2 have distinct mechanisms as to transcriptional repression.

**The N-terminal Portion of EID-2 Is Involved in the Inhibition of MyoD-dependent Transactivation**—EID-1 inhibits transcription by certain fate-determining proteins such as MyoD (14, 15). To determine whether EID-2 inhibits the activities of such proteins, 10T1/2 murine fibroblasts were transfected with a plasmid encoding EID-1 or EID-2, along with a MyoD expression plasmid and a luciferase reporter plasmid containing the MCK promoter. As determined by a luciferase assay, both EID-1 and EID-2 inhibited the MyoD-dependent transactivation (Fig. 3B).

We tried to determine which region is responsible for the
transrepression activity. As shown in Fig. 1, EID-2 and EID-1 exhibit similarities in three distinct portions, namely, one N-terminal and two C-terminal regions. To this end we produced various truncation mutants lacking either the N terminus or C terminus, as well as an internal deletion mutant lacking the central alanine-rich region (Fig. 3A). All of the EID-2 mutant proteins in these studies were produced at comparable levels, as determined by immunoblot analyses (data not shown). The wild-type EID-2 inhibited MyoD-dependent transcription, and the various C-terminal truncation mutants and the internal deletion mutant still retained the same inhibitory property. In contrast, all of the N-terminal deletion mutants in this assay showed impaired transrepression ability (Fig. 3B). These results indicated that the N-terminal portion of EID-2 is involved in the inhibitory function as to MyoD-dependent transcription.

**EID-2 Inhibits Muscle Differentiation of Cultured Cells**

As shown in Fig. 4, EID-2 inhibits muscle differentiation. A, stable C2C12 clones producing T7-EID-2, as well as an empty vector transfectant, were grown under conditions that are (2% horse serum) or are not (20% FBS) permissive for differentiation. Cell extracts were prepared and immunoblotted for the indicated proteins. B, microscopic appearance of C2C12 myoblasts expressing a low level of EID-2 protein (d, e, and f), a high level of EID-2 protein (g, h, and i), and the empty vector (a, b, and c). Cells were induced to differentiate in DM for 3 days (c, f, and i) or maintained in GM at 50% (a, d, and g) or 100% (b, e, and h) confluency. C, stable C2C12 clones producing T7-EID-2, as well as an empty vector transfectant, were grown under conditions that are (2% horse serum) or are not (20% FBS) permissive for differentiation. Cell cycle profiles were determined by FACS analyses. The x-axis in d, h, and i is a log scale to highlight the sub-G1 population.
EID-1 inhibits muscle differentiation of cultured cells, C2C12 myoblasts were stably transfected with EID-2 DNA so as to produce the wild-type EID-2 protein in the next set of experiments. Totally, five clones with lower expression and three clones with higher expression were obtained. The protein levels of ectopically produced EID-2 in representative clones (clones 8 and 15 for lower and higher expression, respectively) were determined by immunoblotting (Fig. 4A). It is noteworthy that the EID-2 protein levels were not changing during the course of differentiation. In contrast, the EID-1 protein level decreased with differentiation signal because of protein degradation via the ubiquitin-proteasome pathway (15).

Both the low and high expressing clones were analyzed for myotube formation (Fig. 4B). There were almost no microscopic difference between the clones in both sparse and confluent cultures in growth medium (GM) (Fig. 4B, a, b, d, e, g, and h). However, the clones transfected with an empty vector formed myotubes (Fig. 4B, c) upon a shift to differentiation medium (DM) and expressed markers of muscle differentiation (Fig. 4A, lane 2), whereas the clones producing lower level of wild-type EID-2 did not (Fig. 4, A, lane 4 and B, f). The higher expression clones exhibited marked cell death upon a shift to DM (Fig. 4, B, i and C, l). These results indicated that EID-2 had a similar phenotype to EID-1, that is, inhibition of muscle differentiation, when it was ectopically expressed in myoblasts, even though EID-2 did not have the ability to inhibit p300-mediated transactivation (Fig. 2B).

EID-2 Does Not Inhibit Cell Cycle Arrest with Differentiation Signal—Terminal differentiation and cell cycle arrest are closely related. Therefore, we determined the cell cycle profiles of C2C12 myoblasts expressing different levels of EID-2. Both in sparse and confluent cultures in GM, there was almost no difference between the clones with empty vector and EID-2-expressing cells in terms of the cell cycle profiles (Fig. 4C, a, b, e, f, i, and j). After incubation in DM for 3 days, the G1/G0 population of each clone exhibited no difference (Fig. 4C, c, g, and h). Note that only a few cells of both the vector transfectant and the lower expresser of EID-2 (clone 8) exhibited cell death (Fig. 4C, c, d, g, and h); however, for the higher expresser of EID-2 (clone 15), the number of dead cells increased dramatically (Fig. 4C, h and l).

N-terminal Portion of EID-2 Is Required for Nuclear Localization—As transcriptional regulation occurs mainly in the nucleus, we next asked whether EID-2 was localized in the nucleus or the cytoplasm. We transfected U-2OS cells with plasmids encoding red fluorescent protein (DsRed2) or fusion proteins of EID-2 and its mutants (Fig. 5). DsRed2 itself was localized both in the nucleus and the cytoplasm (Fig. 5, a). The fusion protein of wild-type EID-2 to DsRed2 was localized exclusively in the nucleus; however, the fusion protein of the N-terminal deletion mutant, EID-2 (33–236), was localized exclusively in the cytoplasm (Fig. 5, a and c). On the other hand, the fusion proteins of C-terminal deletion mutants still remained in the nucleus (data not shown). Therefore, the N terminus of EID-2 was required for nuclear localization.

EID-2 Binds to Class I HDACs in Vivo—Previous reports described that HDACs are involved in muscle differentiation (7–11). The data that EID-2 had a potential transcriptional repression domain prompted us to examine a possible interaction between EID-2 and HDACs. To determine whether EID-2 can bind to class I HDACs, U-2OS cells were cotransfected with plasmids encoding T7 epitope-tagged EID-2, or mutants thereof, along with a plasmid encoding FLAG epitope-tagged HDAC1 or HDAC2. HDAC binding to EID-2 was scored by means of anti-T7 immunoblot analysis of anti-FLAG immunoprecipitates (Fig. 6A). The wild-type and C-terminal deletion mutants of EID-2 interacted with both HDAC1 and HDAC2 in vivo, whereas the N-terminal deletion mutants of EID-2 (33–236, 47–236, 101–236) did not (Fig. 5A) (data not shown). Next we examined whether the transcriptional repression by EID-2 was recovered by treatment with an HDAC inhibitor, TSA. As shown in Fig. 6B, TSA treatment recovered the EID-2-mediated transcriptional repression in a dose-dependent manner. This result supported that HDAC activity may be involved in the transrepression activity of EID-2.

**DISCUSSION**

In this study, we identified a novel inhibitor of differentiation, EID-2, which exhibited homology to EID-1. EID-1 and EID-2 showed no homology to any other known proteins. Neither of them exhibited the characteristic structures of the known negative regulators of muscle differentiation. Thus EID-1 and EID-2 comprise a novel family of inhibitors of differentiation with distinct functions from those of known negative regulators of differentiation.

In terms of subcellular localization of proteins, the wild-type EID-2 was localized exclusively in the nucleus, whereas the EID-2 mutant lacking N-terminal 32 amino acids was localized in the cytoplasm. Because the cytoplasmic localization of the mutant protein was not affected by the treatment with leptomycin B, an inhibitor of nuclear export, we speculated that the mutant protein was not able to enter the nucleus, suggesting the existence of the nuclear localization signal in the N-terminal portion of EID-2. In contrast, wild-type EID-1 was localized...
mainly in the cytoplasm (27). However, when the cells were treated with leptomycin B, EID-1 was found in the nucleus. These data suggested that EID-1 was originally localized in the nucleus and exported rapidly to the cytoplasm (27). Interestingly, the EID-1 mutant lacking C-terminal 30 amino acids was localized in the nucleus even without leptomycin B treatment. These data indicated the difference between EID-2 and EID-1 as to the subcellular localization.

A fusion protein comprising EID-2 and a heterologous DNA-binding domain exhibited transcriptional repression instead of the activation in the case of EID-1, which reflects its p300-binding ability (15). EID-1 inhibited transcription caused by fate-determining transcription factors such as MyoD by blocking the HAT activity of p300. This inhibitory effect on HAT was mediated by both the C-terminal p300-binding domain and the middle acidic clusters of EID-1 (15). EID-2 also inhibited MyoD-dependent transactivation. However, EID-2 neither bound to p300 nor blocked p300-dependent transcription. Deletion analyses showed that the N-terminal region of EID-2 was involved in the inhibition of MyoD-mediated transcription. Interestingly, both the N-terminal portion of EID-1 and the C-terminal region of EID-2 were dispensable for the inhibitory function as to transcriptional repression. Thus the mechanisms of transrepression and differentiation inhibition of EID-2 may be distinct from those of EID-1.

EID-2 interacted with HDACs, which have an opposite effect on transcription to p300. The N-terminal region of EID-2 was necessary for this interaction. EID-1 interacted with p300 via its C-terminal region but not with HDACs, and EID-2 interacted with HDACs via its N-terminal region but not with p300, despite these two putative family proteins exhibited homology in both the N and C termini. The data that the transrepression activity of EID-2 was alleviated by TSA treatment supported the physiological importance of the interaction between EID-2 and HDACs.

Like EID-1, EID-2 blocked myogenic differentiation of cultured cells when stably introduced into murine C2C12 myoblasts (Fig. 4). A previous report (26) indicated that cell cycle arrest and differentiation could be separated, although they are closely linked. Our results support this observation and suggest that EID-2 mainly causes inhibition of differentiation but not cell cycle progression, which was also observed in the case of EID-1 (15). In addition to inhibiting differentiation, EID-2 induced cell death when the protein level was high (Fig. 4). It remains to be clarified whether this phenomenon is physiologically relevant.

As for the mechanism of the inhibition of differentiation by EID-2, the N-terminal 32 amino acids were important not only for the nuclear localization and the transcriptional repression but also HDAC binding. Because HDACs are the inhibitors of muscle differentiation (7), nuclear EID-2 may be associated with HDACs, and the resultant complex may inhibit transcription involved in muscle differentiation. Further biochemical and biological studies will elucidate the link between the role of EID-2 in muscle differentiation and the functions of HDACs.

Acknowledgments—We thank Bill Kaelin, Bill Sellers, Shoumo Bhattacharya, Steve Grossman, and Takayuki Yamada for providing the plasmids. We also thank Sumio Sugano and Yutaka Suzuki for providing the cDNAs and Hidenori Ichijo for helpful suggestion.

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J. Biol. Chem. 2003, 278:17060-17065.
doi: 10.1074/jbc.M212212200 originally published online February 13, 2003

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