Three Activator Protein-1-binding Sites Bound by the Fra-2-JunD Complex Cooperate for the Regulation of Murine Laminin α3A (lama3A) Promoter Activity by Transforming Growth Factor-β*

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Several lines of evidence suggest a role for laminin-5 in skin wound healing. We report here that transforming growth factor-β (TGF-β), which elicits various responses during cutaneous healing, stimulates transcription of the mouse laminin α3A (lama3A) gene. To identify the TGF-β-responsive elements (TGF-β-REs) on the lama3A promoter, we have generated a series of 5′-deletions of the promoter upstream of the β-galactosidase reporter gene. Transient cell transfection assays using mouse PAM212 keratinocytes revealed that TGF-β-REs lie between nucleotides −297 and −54 relative to the transcription start site. Insertion of the TGF-β-RE in front of the unresponsive minimal SV40 promoter conferred TGF-β inducibility. Computer analysis of the promoter sequence identified three canonical activator protein-1 (AP-1) sites located at nucleotides −277 (AP-1A), −125 (AP-1B), and −69 (AP-1C). Site-directed mutagenesis of either the AP-1A or AP-1C site did not drastically alter the basal activity of the lama3A promoter, but reduced TGF-β responsiveness by 50%. Simultaneous mutation of these two AP-1 sites resulted in a 65% decline in the response to TGF-β, suggesting a cooperative contribution of each site to the overall promoter activity. In contrast, mutation of the AP-1B site markedly reduced the basal activity of the lama3A promoter, indicating that this AP-1 site is essential for gene expression. Mobility shift assays demonstrated specific binding of Fra-2 and JunD to the AP-1 sites, suggesting for the first time a possible regulatory function for the Fra-2-JunD AP-1 complex in a basal keratinocyte-specific gene.

Laminin-5 is the major adhesion ligand present in the basement membranes of stratified squamous epithelia (1, 2). In the skin, this adhesive protein is secreted by the basal keratinocytes and colocalize with the anchoring filaments of the lamina lucida of the dermal epidermal junction (3–5). Laminin-5 binds to integrin αβ1 in focal adhesions and interacts with hemidesmosomes via αβ4 to form a stable anchorage complex (6, 7). Laminin-5 is a heterotrimeric glycoprotein composed of the α3A, β3, and γ2 polypeptide chains that are products of different genes. Mutations in the genes encoding laminin α3 (LAMA3), β3 (LAMB3), and γ2 (LAMC2) have been shown to underlie the Herlitz or non-Herlitz forms of junctional epidermolysis bullosa, characterized by blister formation and erosions of the skin and mucosas that frequently lead to neonatal death (8–13).

Several lines of evidence suggest a role for laminin-5 in the re-epithelialization of wound skin repair. Laminin-5 is found at the epidermal-dermal junction at sites and times that coincide with actively migrating or rapidly proliferating basal keratinocytes (14, 15). Moreover, enhancement of laminin-5 transcription is observed at low cell densities in vitro in migrating and proliferating keratinocytes, similar to what happens at the wound edge (15). Although the function of laminin-5 in wound healing remains to be clarified, its major dual contribution would be to allow migration and adhesion of keratinocytes during the wound process. In addition, accumulating data suggest that laminin-5 might be associated with growth and migration of cancer cells (16–19). Recently, cloning of the cDNAs encoding the α3 chain of mouse laminin-5 has identified two distinct polypeptides (α3A and α3B) that derive from a single alternatively spliced gene (20–22). Genomic organization analysis of the murine lama3 gene revealed that the α3A chain is transcribed by an independent internal promoter (21).

In this study, we investigated the transcriptional regulation of the laminin α3A (lama3A) gene by TGF-β. Indeed, it has been shown earlier that TGF-β up-regulates the adhesion protein laminin α3A mRNA level (23). TGF-β, a member of a large superfamily of cytokines, is generally acknowledged to be the cytokine with the broadest range of activities in injured tissue repair and tumor progression (24). It affects nearly every aspect of tissue repair. Indeed, TGF-β is the most potent known stimulator of chemotaxis since it promotes the migration of the majority of cell types that participate in the repair processes. TGF-β regulates the transcription of a wide spectrum of matrix proteins, increasing their production while decreasing their proteolysis and modulating their interactions with cellular integrin receptors (25). Matrix production by keratinocytes is also regulated by TGF-β (26–28).

Using transient transfection, site-directed mutagenesis, and nuclear protein binding assays, we have mapped a TGF-β-responsive region between nt −297 and −54 of the lama3A promoter. Computer analysis of this sequence identified three

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The nucleotide sequence(s) reported in this paper has been submitted to the GenBank™/EBI Data Bank with accession number(s) Y08738.

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1 The abbreviations used are: TGF-β, transforming growth factor-β; TGF-β-RE, TGF-β-responsive element; nt, nucleotide(s); AP-1, activator protein-1.
canonical AP-1 sites. Insertion of this region upstream of the unresponsive minimal SV40 promoter conferred TGF-β inducibility. Site-directed mutagenesis of either AP-1 site suggested a cooperativity among these AP-1 sites in the laminin o3A promoter. Mobility shift assays demonstrated specific binding to the three AP-1 sites. Moreover, antibody supershift analyses have identified JunD and Fra-2 proteins binding to these sites.

EXPERIMENTAL PROCEDURES

Cell Cultures—Mouse PAM212 keratinocytes (kindly provided by Dr. S. H. Yuspa, NCI, National Institutes of Health, Bethesda, MD) were cultured in Eagle’s minimal essential medium supplemented with 10% fetal calf serum (Life Technologies, Inc.).

Plasmid Constructs—The mouse lama3A promoter construct pGalA (21) contains 1 kilobase of genomic lama3A sequence extending upstream from the creation of the transcription initiation site. The deletion panel Δ2 to Δ5.5 was created using the exonuclease III system Erase-a-Base (Promega). The 5′-deletion constructs were confirmed by sequencing and restriction digest analysis. To create ΔSM and ΔSAP, pGalA was digested with EcoRI/MseI, and Smal/ApalI, respectively, blunted with Klenow polymerase I, and religated. The ΔPA20, ΔPA25, ΔPA24, and ΔPA25 constructs were generated by polymerase chain reaction using the oligonucleotides PA20 (sense, 5′-CTTGGCGCTGTCTGCA-3′), PA23 (sense, 5′-TGGGCTTTCTTCGTCATCGC-3′), PA24 (sense, 5′-CTCCTGACCTGCTTATTG-3′), and PA25 (sense, 5′-CACTGCTCTTCTT-3′), and PA25 (sense, 5′-CTTGCAAACTCCTGTTGC-3′), located at Δ244, Δ291, Δ279, Δ265, and Δ21 base pairs, respectively, of the transcription initiation site of murine laminin o3A. These polymerase chain reaction fragments were cloned into pUag, pM)-treated PAM212 cells in Totex lysis buffer (20 mM Hepes, pH 7.9, 350 mM NaCl, 20% glycerol, 1% Nonidet P-40, 1 mM MgCl2, 0.5 mM EDTA, 0.1 mM EGTA, 0.5 mM dithiothreitol, 0.1 mM phenylmethylsulfonyl fluoride, and 0.1% aprotinin) as described (29). Supernatants (15,000 × g, 15-min centrifugation) were collected. An in vitro binding reaction of AP-1 in a total volume of 25 μl was performed by incubation of 5 μg of whole cell extract in a binding buffer containing 10 mM Hapes, pH 7.8, 50 mM KCl, 2 mM dithiothreitol, 1 mM EDTA, 5 mM MgCl2, 10% glycerol.
FIG. 3. Deletion analyses and transcriptional activation of the mouse lama3A gene promoter by TGF-β in transient transfection assays of PAM212 cells. A, full-length and deletion lama3A promoter-reporter constructs were transiently transfected into PAM212 cells and stimulated with 100 pm TGF-β1 for 16–20 h as described under "Experimental Procedures" and as described in the legend of Fig. 2. The numbers on the left indicate the 5'-ends of the constructs relative to the transcription initiation site. The values are the means of triplicates from at least three independent experiments. B, progressive 5'-deletion constructs of ΔSM were transfected as described for A. The AP-1A binding site is underlined. C, -fold induction was calculated by comparing the normalized β-galactosidase (βgal) activities of TGF-β-treated cells and untreated control cells.
RESULTS

TGF-β Stimulates lama3A Transcription—The structure of the murine lama3A promoter and several of its regulatory DNA elements is depicted in Fig. 1. Full-length pGalA, which contains 1 kb of promoter region upstream of the β-galactosidase reporter gene, was transfected into PAM212 cells and examined for responsiveness to TGF-β. A dose-responsive increase in lama3A activity was observed with maximal stimulation (4.5-fold) at 100 pM TGF-β (Fig. 2). A series of 5′-deletions of the lama3A promoter were examined to delineate the minimal region responsive to TGF-β. TGF-β responsiveness was significant (3.0–4.5-fold) for pGalA (nt −1096), Δ2.4M (nt −839), Δ4.2M (nt −619), Δ6.5M (nt −505), and ΔSM (nt −297) constructs, but decreased to 1.5-fold upon deletion from nt −297 to −244 (ΔPA20) (Fig. 3, A and C). This slight induction was lost from nt −244 to −94 (ΔSAP). It therefore appeared that an essential TGF-β-responsive element (TGF-β-RE) was located between nt −297 and −244 of the lama3A promoter. However, since the basal activity drastically decreased for ΔSAP, it remained to be determined whether the loss of stimulation was due to the low basal activity or to the presence of additional sequences allowing secondary TGF-β responsiveness between nt −244 and −94.

Delineation of TGF-β-responsive Elements within the lama3A Promoter—To more precisely map the potential TGF-β-RE that should reside between ΔSM and ΔPA20, additional 5′-deletions of ΔSM constructs were created (Fig. 3, B and C). Similar induction with TGF-β treatment was observed with the ΔSM (nt −297), ΔPA25 (nt −291), and ΔPA24 (nt −279) constructs, whereas a decrease in induction was observed with ΔPA25 (nt −265). This result indicates that a TGF-β-responsive element is located between nt −279 and −265 of the lama3A promoter. Examination of the deleted region that reduced TGF-β responsiveness revealed the presence of one potential AP-1-binding site (Figs. 1 and 3B).

To assess whether the region between nt −279 and −265 was sufficient for activation by TGF-β, four copies of this sequence were linked to a heterologous unresponsiveness SV40 promoter (construct SV-RE4) (Fig. 4). Since no TGF-β induction was observed in SV-RE4, we conclude that the 15-base pair sequence containing AP-1 (nt −279) is necessary but not sufficient to confer TGF-β responsiveness.

As suggested previously, additional TGF-β-RE sequences must reside downstream of the AP-1-binding site. To assess whether the region between nt −297 and the TATA box was sufficient for activation by TGF-β, the MscI/SmaI fragment from pGalA (from nt −297 to −54) was linked to a heterologous SV40 promoter (construct SV-MS). This construct was able to fully restore the TGF-β induction of β-galactosidase transcription in PAM212 cells as compared with ΔSM, whereas no induction was observed with the pGal-promoter vector alone (Fig. 4). Thus, the sequence of this region of the lama3A promoter is sufficient to confer TGF-β responsiveness to a previously non-inducible promoter. Examination of the TGF-β-responsive region indicated the presence of three potential AP-1-binding sites located at nt −277 (AP-1A), −125 (AP-1B), and −69 (AP-1C) (Fig. 1). Site-directed mutagenesis was used to sequentially modify these putative AP-1 sites within the context of the pGalA promoter fragment because this region retains high basal activity and TGF-β responsiveness (Fig. 3A). The mutated constructs were then used in transient transfection experiments in parallel with their wild-type counterparts. As shown in Fig. 5, the mutation of AP-1B (mutB) drastically reduced the promoter activity, whereas mutation of each of the other AP-1 sites (mutA and mutC) still maintained 60% of the pGalA basal activity. However, elimination of each AP-1 site reduced TGF-β responsiveness to half the level seen with the wild-type promoter construct pGalA. Simultaneous mutation of both AP-1A and AP-1C (mutAC) abated by 65% the inducible activity by TGF-β, whereas simultaneous mutations of the three AP-1 sites (mutABC) completely abolished TGF-β responsiveness, as did dual mutants including the AP-1B mutation (mutAB and mutBC) (Fig. 5). These results indicate that the integrity of each AP-1 site of the lama3A promoter is necessary for full transcriptional induction. Furthermore, since half the response to TGF-β is retained within single AP-1 mutants, the full transcriptional induction of the lama3A promoter by TGF-β requires cooperation among the three AP-1 sites.

AP-1 Proteins Bind to the lama3A TGF-β-responsive Element—To confirm the interaction of nuclear proteins with the AP-1 sites, electrophoretic gel mobility shift assays were performed using radiolabeled lama3A TGF-β-RE sequences corresponding to each of the three AP-1 sites and flanking regions, as detailed in Table I. AP-1Am, AP-1Bm, and AP-1Cm are mutants of the AP-1A, AP-1B, and AP-1C sites, respectively. Fig. 6 shows a gel mobility shift experiment in which unstimulated and TGF-β-stimulated mouse keratinocyte total cell ex-
tracts were incubated with ^32^P-labeled AP-1A, AP-1B, or AP-1C oligonucleotides in the absence or presence of excess nonradioactive competitors. Our results indicate that, although these regions bound protein complexes isolated from both control and TGF-ß-treated keratinocytes, TGF-ß treatment induced a significant increase in DNA binding within 1 h for the AP-1A, AP-1B, and AP-1C oligonucleotides (Fig. 6, A–C). Protein binding was specifically competed in a dose-dependent manner by addition of 20- and 50-fold excesses of homologous DNA, but not by a 50-fold excess of the corresponding homologous mutant AP-1 sequence or heterologous Sp1 oligonucleotide competitors. These data indicate that AP-1 complexes bind to each of the three TGF-ß-RE elements of the lama3A promoter. AP-1 binding was specifically competed in a dose-dependent manner by addition of 20- and 50-fold excesses of homologous DNA, but not by a 50-fold excess of the corresponding homologous mutant AP-1 sequence or heterologous Sp1 oligonucleotide competitors. These data indicate that AP-1 complexes bind to each of the three TGF-ß-RE elements of the lama3A promoter. Although the AP-1A and AP-1C oligonucleotides were specifically competed by 20-fold (data not shown) and 50-fold (Fig. 6, A and C, respectively) molar excesses of every AP-1 oligonucleotide, the AP-1B band shift was not displaced by a 50-fold molar excess of either AP-1A or AP-1C competitor (Fig. 6B).

To characterize further the protein complexes binding to the TGF-ß-RE region of the murine lama3A promoter, total cell extracts from untreated and TGF-ß-treated PAM212 cultures were incubated prior to DNA/protein interactions with antibodies specific for each member of both the Jun (c-Jun, JunB, and JunD) and Fos (c-Fos, FosB, Fra-1, and Fra-2) family proteins and visualized by gel mobility shift assay. Since identical results were obtained from untreated and TGF-ß-treated cells, we illustrated the data from treated cells. As shown in Fig. 7, the antibodies against JunD and Fra-2 (and to a much less extent, JunB) induced a supershift of the labeled DNA probes (brackets). These results indicate that JunD and Fra-2 participate in the formation of the complex that binds to the three AP-1 sites of the lama3A promoter.

**DISCUSSION**

This study was designed to investigate the molecular mechanism of lama3A transcriptional induction by TGF-ß. TGF-ß is known to regulate many different gene transcripts of the extracellular matrix, thereby modulating cell adhesion, migration, and proliferation, under both physiological and pathological conditions (24). Our results define three AP-1-binding sites in the mouse lama3A promoter that cooperate to confer TGF-ß responsiveness since (a) their presence is needed in front of unresponsive SV40 promoter sequences to fully restore TGF-ß inducibility; (b) mutations of the AP-1A, AP-1B, and AP-1C sites significantly abate the TGF-ß-promoter transactivation in PAM212 cells; and (c) simultaneous mutations of the three AP-1 sites abolish this transactivation. Furthermore, the AP-1B site is crucial for lama3A promoter activity since mutating its sequence almost completely abolished the basal transcriptional activity of the lama3 promoter. Since the AP-1B site...
is not cross-competed on band shift assays by a 50-fold molar excess of either AP-1A or AP-1C oligonucleotide competitors, the AP-1 protein heterodimer binds the AP-1B site with higher affinity than the two other AP-1 sites. These results suggest that the AP-1B site is preferentially bound by the AP-1 proteins under basal activity and must cooperate with the two other AP-1 sites to allow full transcriptional basal and TGF-β-stimulated activities.

As reviewed recently (32), many promoters of keratinocyte-specific genes contain cis-acting elements that are capable of binding AP-1 heterodimer complexes. In the epidermis, the AP-1 heterodimer serves as an activator of gene expression in all the keratinocyte layers, i.e. keratin K5 in the basal layer; human papillomavirus in the suprabasal compartment; loricrin and profilaggrin in the granular layer; and finally, keratin K1, involucrin, and transglutaminase 1 in the spinous/granular layer (32). Therefore, it is intriguing how the cell coordinately regulates genes through identical DNA elements. Since AP-1 consists of proteins from the Jun and Fos families that associate as homodimers (Jun-Jun) or heterodimers (Fos-Jun), one clue might be the composition of the AP-1 dimers, meaning that a certain combination of Fos-Jun complexes may be necessary to provide different levels of transcriptional activity, depending on the stage of keratinocyte differentiation. It should be noted that laminin α3A transcripts are produced only by proliferating basal keratinocytes in vivo (33) and in vitro (15). We have shown here that the lama3A promoter AP-1 sites are preferentially bound by the Fra-2-JunD complex and that the binding is significantly increased by TGF-β stimulation of PAM212 keratinocytes as compared with untreated cells. Recently, immunohistological studies on Fos/Jun factors have shown that the distribution of AP-1 proteins in the mouse epidermis is compartmentalized in vivo, suggesting that distinct AP-1 complexes act in the various layers of the skin (34). In accordance, Fra-2 and JunD are coexpressed only in the basal layer of mouse skin, but are absent in the spinous (for Fra-2) and granular (for JunD) layers of the epidermis, implying that the particular Fra-2-JunD heterodimer is selectively down-regulated in the early stages of epidermal differentiation (34). All the epidermal genes investigated so far are regulated by different AP-1 family members, i.e. JunB/JunD for HPV18 (35), JunB/Fra-1 and JunD/Fra-1 for involucrin (36), and c-Jun/c-Fos for profilaggrin (37). These keratinocyte genes are ex-

![Fig. 6. Binding of nuclear proteins to the lama3A AP-1-binding sites. A-C, binding of nuclear proteins to the AP-1A, AP-1B, and AP-1C binding sites, respectively. 32P-Labeled oligonucleotides were incubated with nonstimulated (NS) or TGF-β-stimulated total cell extracts in the absence (0x) or presence of a 20- or 50-fold molar excess of unlabeled competitors. none indicates a lane in which the total cell extract was omitted. Arrows indicate the free probe (bottom) and the specific retarded bands (top). For details, refer to Table I and "Experimental Procedures."

![Fig. 7. Identity of nuclear factors that interact with the lama3A promoter AP-1 sites. TGF-β-treated PAM212 total cell extracts were incubated with labeled AP-1A (A) or AP-1B (B) or 32P-labeled AP-1C (C) oligonucleotides in the presence of nonimmune serum (NI) or antibodies against JunD (D), JunB (B), c-Jun (c), c-Fos (c), FosB (B), Fra-1, or Fra-2. The brackets indicate the supershifted complexes.]
pressed in the suprabasal compartments of the epidermis. Since the lama3A gene is expressed exclusively in the basal cells of most stratified epithelia, it will be important to determine the potential role of Fra-2 and JunD in the regulation of basal keratinocyte-specific genes in general and of the lama3A gene in particular.

AP-1 has been shown to be the transcriptional mediator of several TGF-β-responsive genes, including TGF-β itself (40), plasminogen activator inhibitor type-1 (41), c-jun (42), α2(I)-collagen (43), osteocalcin (44), retinoic acid receptor (45), and clusterin (46). However, the nature of the AP-1 complexes that are induced by TGF-β has not been determined, except partially for the α2(I)-collagen promoter, which is bound by c-Jun in keratinocytes and JunB in fibroblasts (47). AP-1-binding sites are not the exclusive cis-acting elements bound in response to TGF-β stimulation; Sp1 has also been reported to participate in the regulation of human α2(I)-collagen (48), p15 (49), and p21 (50) gene expression by TGF-β. In other promoters (51), a TGF-β-responsive consensus sequence has been identified as a nuclear factor 1 binding motif, but the corresponding transcription factors that bind to these sequences remain unidentified.

In conclusion, we have used a combination of techniques to identify the regulatory elements important for the transcriptional induction of the lama3A gene by TGF-β. We have demonstrated a cooperative contribution of three canonical AP-1-binding sites to the stimulation of the promoter activity and that the AP-1B site is essential for basal gene expression. These AP-1-binding sites contain almost exclusively the JunD and Fra-2 proteins, which suggests for the first time a possible regulatory function of the Fra-2-JunAP-1 complex in a basal keratinocyte-specific gene. Our results strongly support the idea that AP-1 proteins play a central role in the transcriptional regulation of epidermal gene expression (32). As for many other genes, the same regulatory elements are involved in both basal and stimulated transcriptional activities. These studies represent the initial steps toward the identification of the signaling pathways involved in TGF-β-mediated transcriptional activation of laminin α3 under physiological and pathological conditions, such as wound healing and carcinogenesis.

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Table I

| Name   | Sequence                                      |
|--------|-----------------------------------------------|
| AP-1A  | 5'-TTCCCCGATCACGACGGCTGCTG-3'                |
| AP-1Am | 5'-TTCCCCGCGTTAAGCAGGGCGAAGG-3'              |
| AP-1B  | 5'-TAGGGGACTGATGTTGGTG-3'                    |
| AP-1Bm | 5'-CCCTCCCTCGGACTGAGTTGTTG-3'                |
| AP-1C   | 5'-CCCGAGACAGCATTTCTCTTTTCTCTGTTAAGGCGCGCGCCGGCCGGAGTGCACGGAGAAG-3' |
| AP-1Cm  | 5'-ATTGGACGGGCGGGCGGGCAG-3'                  |
| Sp1    | 5'-CTTCCCAGATGGGAGGCGAGC-3'                  |

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